A New and Efficient Route to 3-Amino-2-azetidinones via Zinc Enolates of N,N-Disubstituted Glycine Esters

Fred H. van der Steen, Henk Kleijn, Johann T. B. H. Jastrzebski, and Gerard van Koten*

Debye Research Institute, Department of Metal-Mediated Synthesis, University of Utrecht, Padualaan 8, 3584 CH Utrecht, The Netherlands

Received January 30, 1991

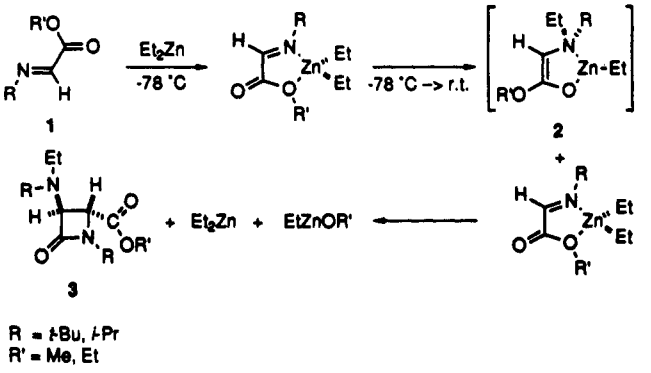
This report describes novel and efficient "one-pot" syntheses of 1-unsubstituted-3-amino-4-substituted-2-azetidinones (8 and 9) involving the in situ preparation of lithium and particularly zinc enolates (5 and 6, respectively) of N,N-disubstituted glycine esters (4) and subsequent reactions of these enolates with (simple) imines (7). Lithium enolates 5 only react with activated imines that are N-substituted with an electron-withdrawing group (e.g. aryl, trialkylsilyl), affording *cis*-3-amino-2-azetidinones in excellent yields with moderate to good stereoselectivity (de 68–92%). Zinc enolates 6 are more generally applicable since they react with activated imines as well as unactivated imines (e.g. those which are N-substituted with an electron-donating group such as alkyl) to afford 3-amino-2-azetidinones in excellent yields. The trans diastereoselectivity of the zinc-mediated enolate–imine condensation can be tuned by changing the steric and electronic properties of the substituents of the reagents (i.e. both enolate and imine), as well as the solvent polarity. The observed stereoselectivities are explained in terms of two highly ordered transition states, consisting of a *Z*-zinc ester enolate and an *E*-imine. Protection of the amino function of the metal enolates as a 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane ring affords 2-azetidinone products that can be easily deprotected to provide a free 3-amino function. In this way, *trans*-1-benzyl-3-(protected amino)-4-methyl-2-azetidinone (9a) and *trans*-3-(protected amino)-4-[(trimethylsilyl)ethynyl]-2-azetidinone (9g), key intermediates in the synthesis of Aztreonam (and 9g for bicyclic β-lactam antibiotics as well), have been prepared in excellent yields (98 and 93%, respectively) with a high diastereoselectivity (de 82 and 94%, respectively). Furthermore, depending on the reactivity of imines 7, our method is also applicable using a catalytic amount (10 mol %) of $ZnCl_2$.

Introduction

Since the discovery of the antibiotic activity of penicillin, thienamycin, and, more recently, monobactams, much attention has been given to the development of efficient and selective procedures for their preparation.[1] Although, the condensation of Reformatsky-type reagents (i.e. zinc ester enolates) and imines to afford 2-azetidinones was first reported by Gilman and Speeter in 1943,[2] the development of the ester enolate–imine condensation route to 2-azetidinones has been slow. When the use of metal enolates became a standard synthetic procedure, the condensation of metal ester enolates with substrates containing an imino functionality appeared to be a very useful methodology for the construction of the 2-azetidinone ring.[3,4] Since the reaction of a Reformatsky reagent with an imine proceeds without any stereoselectivity,[5] in most studies zinc was replaced by other metals (e.g. lithium, tin, zirconium, titanium, boron, aluminum, and magnesium) in order to gain stereochemical control of the reaction. This was not always successful, and in only a few of these studies was attention paid to the role of the metal cation in controlling the chemo- and stereoselectivity of such reactions.

We became interested in the ester enolate–imine condensation after we discovered that the reactions of Et_2Zn with α-imino esters selectively afford *trans*-3-amino-2-azetidinones in quantitative yields (Scheme I).[6a] These 2-azetidinones are most likely formed via intermediate zinc enolates (2), which result from a regioselective, intramolecular transfer of an ethyl group from zinc to the coordinated imino nitrogen in an initial diethylzinc–α–imino ester complex.[6b,c] These zinc enolates react rapidly, by an aldol-like C–C bond formation reaction, with the imino function of complexed α-imino ester to give aldolates that undergo elimination of ethylzinc alkoxide and ring closure to yield *trans*-1-alkyl-3-(dialkylamino)-4-(alkoxycarbonyl)-2-azetidinones (3). This route to 2-azetidinones is not generally applicable. Firstly, it allows only a limited set of substituents, because only primary alkyl groups can be transferred with high regioselectivity from zinc to the imino nitrogen of the complexed α-imino esters to form the intermediate zinc enolates 2.[6] Secondly, these enolates cannot be isolated because of their immediate reaction with α-imino esters (complexed to Et_2Zn) and therefore only

Scheme I



R = *t*-Bu, *i*-Pr
R' = Me, Et

(1) (a) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Ed.; Academic Press: New York, 1982; Vols 1-3. (b) Koppel, G. A. In *Small Ring Heterocycles—Azetidines, β-Lactams, Diazetidines and Diaziridines*; Hassner, A., Ed.; Wiley: New York, 1982. (c) Dürckheimer, W.; Blumbach, J.; Lattrel, R.; Scheunemann, K. H. *Angew. Chem.* **1985**, *97*, 183.

(2) Gilman, H.; Speeter, M. *J. Am. Chem. Soc.* **1943**, *65*, 2255.

(3) For recent literature reviews of the ester enolate–imine condensation: (a) Brown, M. J. *Heterocycles* **1989**, *29*, 2225. (b) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447. (c) van der Steen, F. H.; van Koten, G. *Tetrahedron*. In press.

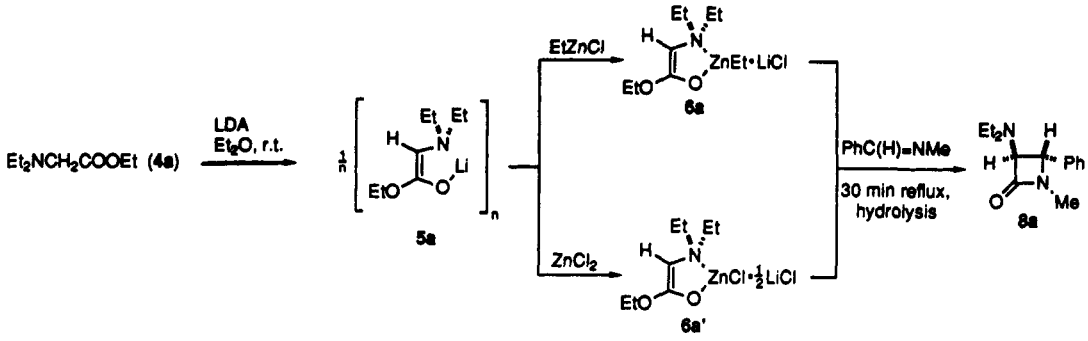
(4) Georg, G. I. In *Studies in Natural Product Chemistry*; Rahman, A-ur, Ed.; Elsevier Science: Amsterdam, 1988; Vol. 2.

(5) (a) Dardoize, F.; Moreau, J. L.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1973**, 1668. (b) Dardoize, F.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1974**, 939.

(6) (a) van Vliet, M. R. P.; Jastrzebski, J. T. B. H.; Klaver, W. J.; Goubitz, K.; van Koten, G. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 132. (b) van Vliet, M. R. P. Ph.D. Thesis, Amsterdam, 1987. (c) van Vliet, M. R. P.; van Koten, G.; Buysingh, P.; Jastrzebski, J. T. B. H.; Spek, A. L. *Organometallics* **1987**, *6*, 537. (d) van Koten, G.; Vrieze, K. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 129.

0022-3263/91/1956-5147$02.50/0

Scheme II



2-azetidinones 3, with an ester function at the 4-position of the 2-azetidinone ring, are accessible. However, these results reveal the basic concept for a highly efficient and stereoselective route to 3-amino-2-azetidinones employing zinc ester enolates and imines.

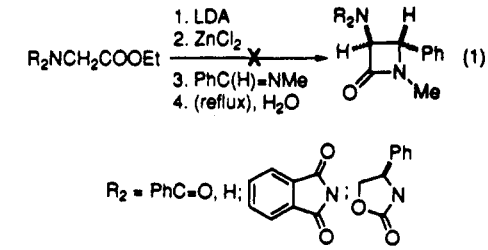
We successfully developed this concept by independently preparing zinc enolates of N,N-disubstituted glycine esters by transmetalation of the lithium enolates with $ZnCl_2$ (or any other suitable ionic zinc compound, e.g. $ZnBr_2$, EtZnCl, ROZnCl) and by their further in situ reaction with imines to afford 2-azetidinones in high yields. The preliminary results of our research have been reported in several communications and patents.[7] In this paper we present detailed results concerning the synthesis of simple 3-amino-2-azetidinones via zinc enolates of N,N-disubstituted glycine esters and put forward a rationale for the role that the metal cation, solvent, and substituents play in the reactions of α-amino zinc ester enolates with imines.

Results

Synthesis of Zinc Enolates of N,N-Disubstituted Glycine Esters. Zinc ester enolates can be prepared by several methods: (i) reaction of activated zinc with an α-bromo ester (Reformatsky),[8a,b] (ii) reaction of EtZnN-(*i*-Pr)$_2$ with an ester,[8c] or (iii) transmetalation of a preformed alkali metal ester enolate with a suitable zinc salt,[8d] e.g. $ZnCl_2$ or EtZnCl. We have chosen the latter method to obtain ester enolates containing a donor α-amino function, as is present in readily available N,N-disubstituted glycine esters (4). These esters can be easily converted to alkali metal enolates (5) by deprotonation with an amide base (e.g., LDA, LTMP, NaHMDS, LiHMDS). Direct deprotonation of esters 4 with EtZnN(*i*-Pr)$_2$ affords pure ethylzinc enolates (2),[9a-c] but this method is synthetically less convenient. Detailed studies of the properties and structural features of the zinc enolates of esters 4 have been published separately.[9b,c]

Thus, deprotonation of **4a** with LDA affords **5a** in high yield.[10] Transmetalation with either EtZnCl or $ZnCl_2$ then affords the ethylzinc enolate **6a** or chlorozinc enolate **6a'**, respectively, that can be isolated as stable white solids. Reaction of benzene solutions of **6a** and **6a'** with *N*-benzylidene-*N*-methylamine (**7a**) (80 °C, 30 min) affords *trans*-1-methyl-3-(diethylamino)-4-phenyl-2-azetidinone (**8a**) in 95 and 98% yield, respectively (see Scheme II). The high yield and trans stereoselectivity of these reactions encouraged us to further explore the reactions of α-amino zinc ester enolates with imines.

Synthesis of 1-Unsubstituted-3-amino-4-substituted-2-azetidinones. In order to obtain 3-amino-2-azetidinones of pharmaceutical interest, e.g. intermediates for Aztreonam and other monobactam antibiotics, the amino function of the starting glycine esters 4 has to be protected with easily removable groups; this allows the introduction of appropriate side chains in later stages of the syntheses of β-lactam antibiotics. Protection of the amino function as an amide, e.g. benzoyl, phthaloyl, or (4*R*)-4-phenyl-2-oxazolidinone, did not give satisfactory results; with imine **7a** the enolates of these protected esters formed no 2-azetidinone product (eq 1).



We therefore shifted our attention to *N*,*N*-bis(trimethylsilyl)glycine ethyl ester (**4b**) and 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane-1-acetic acid ethyl ester (**4b'**) because not only do these esters have more in common with *N*,*N*-dialkyl-substituted glycine esters but also, since the silyl–nitrogen bond is very susceptible to hydrolysis, deprotection of the 2-azetidinone products affords a free 3-amino function. Aldol reactions of the lithium enolate of **4b** with aldehydes,[11] and some reactions of the lithium enolate of **4b'** with activated imines to afford predominantly *cis*-2-azetidinones have been reported.[12] To our knowledge nothing is known about reactions of the

(7) (a) Jastrzebski, J. T. B. H.; van der Steen, F. H.; van Koten, G. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 516. (b) van der Steen, F. H.; Jastrzebski, J. T. B. H.; van Koten, G. *Tetrahedron Lett.* **1988**, *29*, 2467. (c) van der Steen, F. H.; Kleijn, H.; Jastrzebski, J. T. B. H.; van Koten, G. *Tetrahedron Lett.* **1989**, *30*, 765. (d) van der Steen, F. H.; Kleijn, H.; Spek, A. L.; van Koten, G. *J. Chem. Soc., Chem. Commun.* **1990**, 503.

(8) (a) Gaudemar, M. *Organometallic Rev. A* **1972**, *8*, 184. (b) Fürstner, A. *Synthesis* **1989**, 573. (c) For an example of deprotonation of a ketone with EtZnN(*i*-Pr)$_2$, see: Hansen, M. H.; Bartlett, P. A.; Heathcock, C. H. *Organometallics* **1987**, *6*, 2069. (d) Dekker, J.; Schouten, A.; Budzelaar, P. H. M.; Boersma, J.; van der Kerk, G. J. M.; Spek, A. L.; Duisenberg, A. J. M. *J. Organomet. Chem.* **1987**, *320*, 1.

(9) (a) Whereas EtZnN(*i*-Pr)$_2$ only partly deprotonates 2,2-dimethylpentanone,[8c] glycine esters 4 are completely deprotonated because the presence of the α-amino nitrogen, which through intramolecular coordination to zinc, causes the protonation/deprotonation equilibrium to shift competely to the side of the product enolates.[9b,c] (b) van der Steen, F. H.; Boersma, J.; Spek, A. L.; van Koten, G. *J. Organomet. Chem.* **1990**, *390*, C21. (c) van der Steen, F. H.; Boersma, J.; Spek, A. L.; van Koten, G. *Organometallics* **1991**, *10*, 2467. (d) van der Steen, F. H.; van Mier, G. P. M.; Spek, A. L.; Kroon, J.; van Koten, G. *J. Am. Chem. Soc.* **1991**, *113*, 5742.

(10) Jastrzebski, J. T. B. H.; van Koten, G.; van de Mieroop, W. F. *Inorg. Chim. Acta* **1988**, *142*, 169.

(11) Rühlmann, K.; Kaufmann, K. D.; Ickert, K. *Z. Chem.* **1970**, *10*, 393.

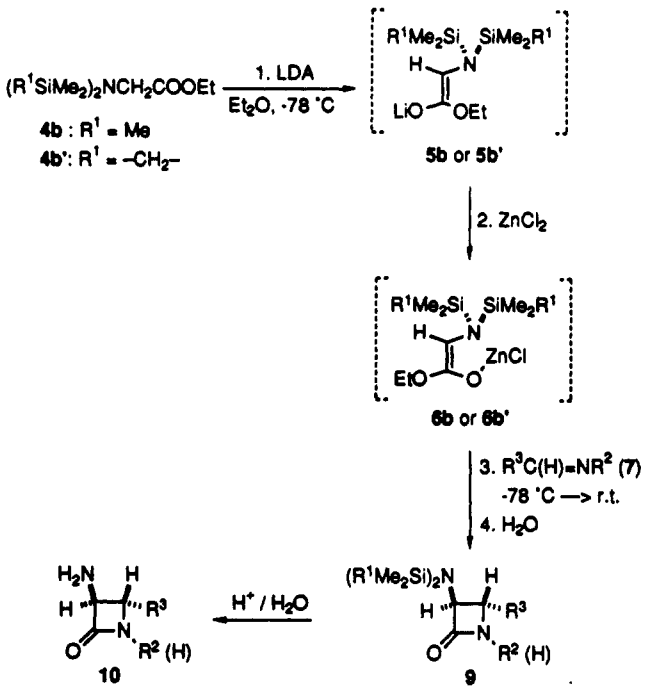
(12) (a) Overman, L. E.; Osawa, T. *J. Am. Chem. Soc.* **1985**, *107*, 1698. (b) Andreoli, P.; Cainelli, G.; Contento, M.; Giacomini, D.; Martelli, G.; Panunzio, M. *Tetrahedron Lett.* **1986**, *27*, 1695. (c) Burnett, D. A.; Hart, D. J.; Liu, J. *J. Org. Chem.* **1986**, *51*, 1930.

Table I. "One-Pot" Preparation of 3-(Protected)amino-2-azetidinones (9)

entry	compd	R^1, R^1	R^2	R^3	yield,[a] %	cis/trans ratio[b]
1	9a	$-(CH_2)_2-$	CH_2Ph	Me	98	9:91
2	9b	$-(CH_2)_2-$	Me	Ph	97	8:92
3	9c	Me, Me	Me	Ph	75	<1:>99[c]
4	9d	$-(CH_2)_2-$	*t*-Bu	Ph	≈10[d]	-
5	9e	$-(CH_2)_2-$	$SiMe_3$/H[e]	Ph	96	14:86
6	9f	Me, Me	$SiMe_3$/H[e]	Ph	70	<1:>99[c]
7	9g	$-(CH_2)_2-$	$SiMe_3$/H[e]	C≡CSiMe$_3$	93	3:97

[a] Yields of the isolated crude products. [b] Determined by ^{1}H NMR integration of the characteristic proton signals of the crude products. [c] Cis isomer not detected with ^{1}H NMR spectroscopy. [d] In the ^{1}H NMR spectrum of the isolated material the presence of a small amount of *trans*-**9d** could be identified. [e] Replaced by a proton upon hydrolysis.

Scheme III



corresponding zinc enolates.

We have now carried out reactions of thermolabile[13] (lithium) and zinc enolates of esters **4b** and **4b'** with imines at −78 °C to afford 3-amino-2-azetidinones in a facile "one-pot" procedure (Scheme III): (i) addition of *n*-BuLi to a solution of *i*-Pr_2NH in diethyl ether, (ii) addition of 1 equiv of ester **4b** or **4b'**, (iii) addition of 1 equiv of *anhydrous* $ZnCl_2$,[15] (iv) addition of 1 equiv of an appropriate imine and then stirring until the reaction is completed, (v) aqueous workup to remove the inorganic salts and isolation of the products by extraction. The crude products were purified by either crystallization or flash chromatography.

Following this procedure, several *trans*-1-(unsubstituted)-3-(protected amino)-4-substituted-2-azetidinones (**9**) have been prepared in high yields (see Table I), though surprisingly the yield of 2-azetidinone **9d** was low (entry 4). The yields of 2-azetidinones **9c** and **9f** starting from ester **4b** are lower than the yields of **9b** and **9e** starting from **4b'**. This is most likely caused by the lower stability of the intermediate enolates **5b** and **6b** compared to enolates **5b'** and **6b'**. The yields of **9c** and **9f** appear to depend on the period between addition of $ZnCl_2$ (to form the zinc enolate) and subsequent addition of imine. A short period (5 min) leads to reasonable yields (70–75%), whereas a longer period (1 h) invariably results in low yields (<25%). Such an effect was not observed for the reactions starting from **4b'**, and we think that enolates **5b'** and **6b'** are slightly stabilized due to a favorable entropy effect of the 1-aza-2,5-disilacyclopentane ring.

The diastereoselectivity of the reactions of zinc enolates **6b** and **6b'** with simple imines **7** is good to excellent (de 72–99%). Although the reactions of zinc enolate **6b** show a slightly better stereoselectivity than those of zinc enolate **6b'**, for practical purposes it is advisable to start from glycine ester **4b'**, which is more readily available than **4b** and which usually provides higher yields of the 2-azetidinone products.

The polarity of the solvent has a marked influence on the stereoselectivity of the reactions. In polar solvents, more of the *cis*-2-azetidinones **9** are formed. For example, reaction of **6b'** with **7a** in THF afforded 2-azetidinone **9b** in 90% yield (cis:trans ratio = 60:40). This solvent effect was not further pursued for reactions of zinc enolates **6b** and **6b'** but will be discussed for reactions of zinc enolates of N,N-disubstituted glycine esters **4** (vide infra).

The protecting silyl substituents on the amino nitrogen are easily removed by acid-catalyzed hydrolysis to afford 3-amino-2-azetidinones (**10**) in high yields (Scheme III). *trans*-2-Azetidinones **10a** and **10g**, which may serve as intermediates for the synthesis of known β-lactam antibiotics, can be prepared in high yields with an excellent diastereoselectivity. The 1-benzyl group in **10a** is readily removed by reductive cleavage with sodium or lithium in

Table II. Synthesis of 2-Azetidinone 9b Using a Catalytic Amount of Zinc Dichloride

entry	y (equiv)	yield[a] (%)	cis/trans ratio[b]
1	2.0	65	10:90
2	1.0	98	8:92
3	0.5	95	4:96
4	0.25	99	2:98
5	0.1	80	2:98
6	0.0	0	-

[a] Yields of the isolated crude product. [b] Determined by ^{1}H NMR integration of the characteristic proton signals of the crude product.

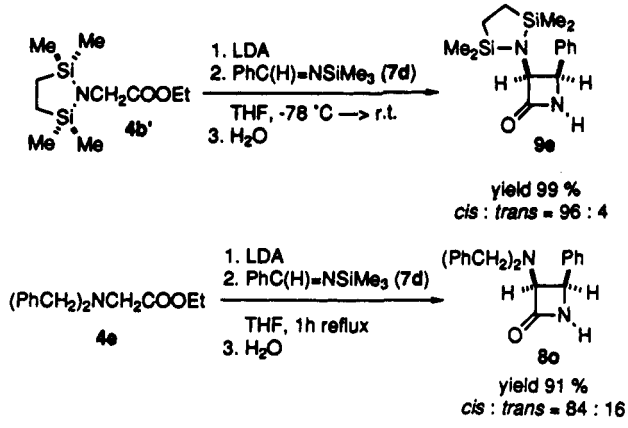
(13) The stability of zinc enolates of N,N-disubstituted glycine esters is correlated to the strength of the intramolecular Zn–N coordination bond.[9b] Because of the delocalization of electron density by the two silyl substituents on the amino nitrogen atom in these enolates the Lewis basicity of this nitrogen is low. Therefore the stabilizing effect of the intramoleceular Zn–N coordination will be minimal and consequently self-condensation of the enolates (ref 14) is likely.

(14) (a) Vaughan, W. R.; Bernstein, S. C.; Lorber, M. E. *J. Org. Chem.* **1965**, *30*, 1790. (b) Vaughan, W. R.; Knoes, H. P. *J. Org. Chem.* **1970**, *35*, 2394. (c) Sullivan, D. F.; Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 2038.

(15) It is important to use absolutely dry $ZnCl_2$, otherwise lower yields and a different stereoselectivity of the reactions will result. Therefore either commercially available $ZnCl_2$ was dehydrated with refluxing $SOCl_2$[6b] or, even better, $ZnCl_2$ was prepared in a dry and oxygen-free nitrogen atmosphere from dry HCl and metallic zinc in diethyl ether, according to a modified procedure of Hamilton and Butler (see the Experimental Section).[16b] The classic method of fusing commercially available $ZnCl_2$ under high vacuum[6b] does not produce material of acceptable quality.

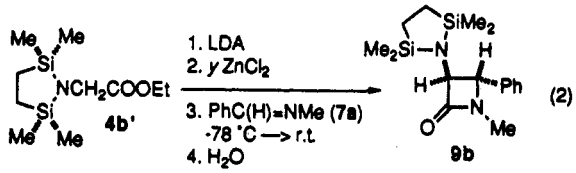
(16) (a) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1972**, *95*, 3310. (b) Hamilton, R. T.; Butler, J. A. V. *J. Chem. Soc.* **1932**, 2283.

Scheme IV



liquid NH_3/THF,[17] affording a key intermediate in the synthesis of Aztreonam. The 4-[(trimethylsilyl)ethynyl] group of **10g** can be easily converted to an acetoxy group by known chemistry.[18] This acetoxy group can be readily displaced by a wide variety of nucleophiles, and numerous syntheses of monocyclic and bicyclic β-lactam antibiotics starting from 4-acetoxy-2-azetidinones are known.[3,4]

Synthesis of 1-Unsubstituted-3-amino-2-azetidinones with a Catalytic Amount of Added Zinc Dichloride. For practical reasons (less waste material, easier workup, lower cost, etc.) it would be more attractive if the present reactions could be performed using a catalytic amount of $ZnCl_2$. Therefore the reaction of the lithium enolate **5b'** derived from **4b'** with imine **7a** was carried out in the presence of varying amounts of $ZnCl_2$ (eq 2). These experiments provide some quite remarkable results (see Table II). When 2 equiv of $ZnCl_2$ is added the yield of



9b is considerably lower while the stereoselectivity of the reaction is only slightly lower (entry 1) than in the stoichiometric standard reaction (entry 2). When less than 1 equiv of $ZnCl_2$ is added, the yields of **9b** remain high and the stereoselectivity of the reaction even improves (entries 3 and 4). Even with only 10 mol % of $ZnCl_2$ the yield of **9b** is still 80% (entry 5), the slightly lower yield being the result of a slow decomposition of the lithium enolate **5b'**. Without $ZnCl_2$ no 2-azetidinone **9b** is formed, indicating that the zinc enolate **6b'** is more reactive toward imines that the corresponding lithium enolate **5b'**.

When the reactions were followed by ^1H NMR spectroscopy, several interesting aspects were uncovered. At −78 °C a fast reaction affords 2-azetidinone **9b** in amounts, which correspond well with the amount of zinc-bound chlorine atoms initially available in solution. There is no further reaction at −78 °C (8 h). However, when the reaction mixture is warmed up to room temperature a slow reaction to 2-azetidinone **9b** occurs (see Discussion).

Further experiments have been carried out to determine whether the process using a catalytic amount of $ZnCl_2$ is generally applicable. First, we examined a few reactions of the lithium enolate **5b'** with imines **7**, because catalytic reactions of zinc enolates **6** may be obscured by competitive reactions of lithium enolate **5b'** with **7**. As expected, lithium enolates **5** of glycine esters **4** do react with activated imines **7** to selectively afford *cis*-2-azetidinones **9** in excellent yields (see Scheme IV). Hence, the use of catalytic amounts of $ZnCl_2$ in the synthesis of *trans*-2-azetidinones is limited to unreactive imines, i.e. *N*-alkyl-substituted ones, that afford 1-alkyl-3-amino-2-azetidinones, which are of little pharmaceutical value but are academically interesting. Therefore, for these catalytic reactions only a few combinations of glycine esters **4** and imines **7** were tested (see Scheme V). Reaction of lithium enolate **5b'** with imine **7b** in the presence of 0.25 equiv of $ZnCl_2$ affords *trans*-2-azetidinone **9a** in 90% yield. Reaction of lithium enolate **5a** with **7a** in the presence of 0.25 equiv of $ZnCl_2$ is not catalytic when performed in benzene (only 25% of 2-azetidinone **8a** is formed after 16 h of reflux), but in THF this reaction leads to **8a** in 91% yield. Also in this case, the use of a catalytic amount of $ZnCl_2$ resulted in the enhancement of the trans stereoselectivity (cis:trans ratio = 27:73) compared with the nonstereoselective stoichiometric reaction (cis:trans ratio = 58:42; entry 4 of Table IV).

Scheme V

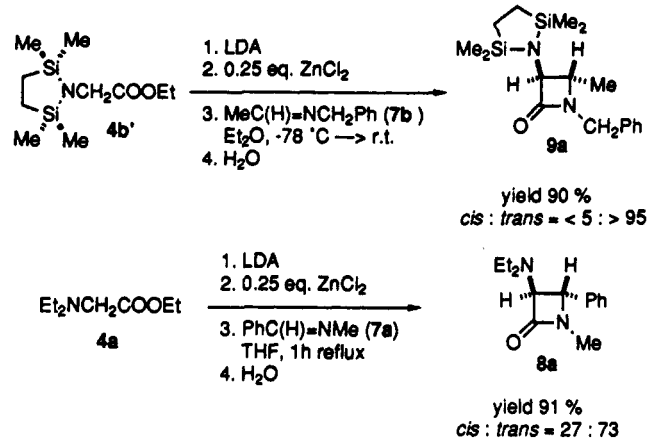


Table III. "One-Pot" Preparation of 3-(Diethylamino)-2-azetidinones (8)

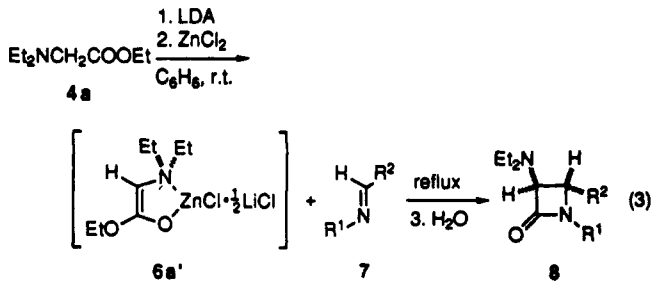
entry	compd	R^1	R^2	yield[a] (%)	cis/trans ratio[b]
1	**8a**	Me	Ph	98	23:77
2	**8b**	CH_2Ph	Ph	98	6:94
3	**8c**	*t*-Bu	Ph	0	-
4	**8d**	$SiMe_3$/H[c]	Ph	93	<1:>99[d]
5	**8e**	$SiMe_3$/H[c]	C≡CPh	98	<1:>99[d]
6	**8f**	$SiMe_3$/H[c]	C≡C$SiMe_3$	97	<1:>99[d]

[a] Yields of the isolated crude products. [b] Determined by ^1H NMR integration of the characteristic proton signals of the crude products. [c] Replaced by a proton upon hydrolysis. [d] Cis isomer not detected with ^1H NMR spectroscopy.

Synthesis of 1-Unsubstituted-3-(disubstituted amino)-4-substituted-2-azetidinones. Solvent and Substituent Effects. In order to determine the factors that influence the stereochemical course of the reactions of zinc enolates **6** with imines **7** a detailed study of these reactions under thermodynamically controlled conditions was undertaken. These experiments require α-amino zinc ester enolates that are stable at elevated temperatures; this is the case for zinc enolates of *N,N*-dialkyl-substituted glycine esters, most of which are stable up to 80 °C.[9b,c]

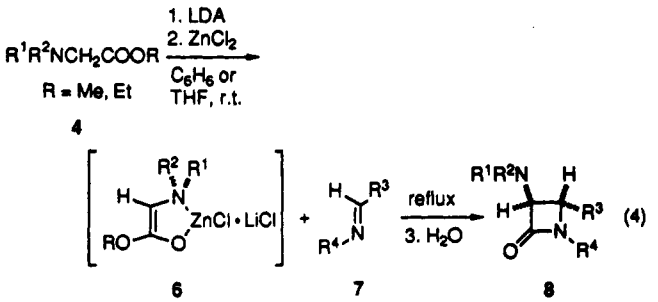
We determined the influence of the imine substituents by reacting the in situ prepared zinc enolate **6a'** with different imines (eq 3; see Table III). Except for **7c**, reactions of **6a'** with imines **7** afforded 2-azetidinones **8** in

(17) Shibasaki, M.; Ishida, Y.; Iwasaki, G.; Iimori, T. *J. Org. Chem.* **1987**, *52*, 3488.
(18) Chiba, T.; Nagatsuma, M.; Nakai, T. *Chem. Lett.* **1984**, 1927.



excellent yields with a moderate to excellent trans stereoselectivity (de 56–99%). When the amino nitrogen of the imine is protected with a trimethylsilyl group, excellent diastereoselectivities are found (entries 4–6). This protecting group is easily removed by aqueous (or slightly acidic) workup, resulting in 2-azetidinone product with a secondary amido function that is suitable for further derivatization. Removal of the trimethylsilyl substituent of the ethynyl group in **8f** is accomplished in high yield (91%) by reaction with KOH in methanol. The resulting 2-azetidinone **8f'** is a useful starting material for construction of bicyclic 2-azetidinone systems via cyclization reactions.

The influence of the substituents on the nitrogen atom of the α-amino zinc ester enolates **6** on the stereochemistry of their reactions with imines was subsequently studied (eq 4; see Table IV). The yields of 2-azetidinones **8** are

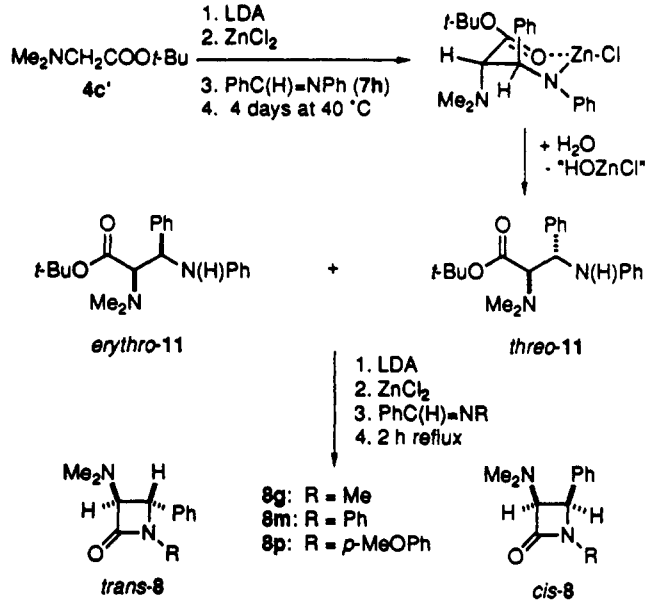


good to excellent and generally somewhat lower in THF than in benzene. The diastereoselectivity of the reactions varies from none to excellent and is dependent on both the starting esters **4** and the solvent. With increasing bulk of the amino substituents (R^1 and R^2) more of the trans isomer of **8** is produced and the electronic effects of these substituents also influence the reaction stereoselectivity. With *N*-methyl-*N*-phenylglycine ethyl ester **4g**, the only ester containing an electron-withdrawing substituent, the highest de's are obtained. Furthermore, the solvent plays an important role, and a change from apolar benzene to (weakly) polar THF[19] results in an increased yield of *cis*-2-azetidinones **8**.

The stereoselectivity of the reactions of zinc enolates with imines is also influenced by the imine N-substituent. With activated imines, i.e. imines substituted with a group capable of stabilizing a negative charge on the imino nitrogen (e.g. aryl, silyl), there is a remarkable increase in trans stereoselectivity (see Table V, eq 4, and entries 2–5 in Table III). In contrast to the nonstereoselective reaction of zinc enolate **6c** with imine **7a**, the reactions of **6c** with imines **7f** and **7h** proceed with an excellent trans stereoselectivity (entries 1 and 2). Even in THF, exclusively *trans*-2-azetidinone **8l** is formed.

The Possible Occurrence of Retro-Aldolization during the Synthesis of 3-Amino-2-azetidinones.

Scheme VI



Kagan et al. and Gaudemar et al. have shown that for Reformatsky reactions with imines, the initial stereoselectivity of the C–C bond formation may be lost during the ring closure to a 2-azetidinone as a result of retro-aldolization.[5,20] We have conducted several experiments to find out if this reaction also occurs in our synthesis of 3-amino-2-azetidinones. The general idea is outlined in Scheme VI. When the reaction of an ester enolate with an imine is stopped prior to ring closure to a 2-azetidinone, aldolates **11** are isolated. If retro-aldolization occurs, different 2-azetidinone products should be isolated when these aldolates are subjected to ring-closure conditions in the presence of another imine.[5]

Reaction of the in situ prepared zinc enolate of *N,N*-dimethylglycine *tert*-butyl ester (**4c'**) with *N*-benzylidene-*N*-phenylamine (**7h**) at 40 °C in a mixture of benzene and Et_2O (4:1 v/v) afforded aldolate **11** in 89% yield (erythro:threo = 90:10)[21a] along with 11% of *trans*-1-phenyl-3-(dimethylamino)-4-phenyl-2-azetidinone, **8m**.[21b] Pure *erythro*-aldolate **11** was obtained in 80% yield after recrystallization from hot hexane. This aldolate was subjected to ring-closure conditions in the presence of imines **7a** and **7i**. The results of these reactions are given in Table VI. In the presence of imines **7a** and **7i** no traces of 2-azetidinones **8g** and **8p** were found. The reactions are not clean, since 2-azetidinone **8m** is formed in moderate yields and considerable amounts of starting imine **7h** were isolated. This may be the consequence of the use of strong bases for deprotonation[22] that can induce side reactions.

(19) For a classification of solvents on basis of polarity, see: (a) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737. (b) *Solvents and Solvent Effects in Organic Chemistry*; Reichardt, C., Ed.; Weinheim: Basel, 1988.

(20) (a) Kagan, H. B.; Basselier, J. J.; Luche, J. L. *Tetrahedron Lett.* **1964**, *16*, 941. (b) Luche, J. L.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1969**, 3500. (c) Luche, J. L.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1971**, 1971.

(21) (a) The terms erythro and threo are in this case equivalent with syn and anti, respectively. (b) The reaction starting from *N,N*-dimethylglycine methyl ester (**4c**) afforded *trans*-**8m** in 75% yield along with 20% of the noncyclized aldolate **11'**.

(22) The synthesis of 2-azetidinones by cyclization of β-amino esters is well-known, and mild bases like Grignards, trialkylaluminum, or triflates in combination with $CaCO_3$ are commonly used. See for example: (a) Mukerjee, A. K.; Srivastava, R. C. *Synthesis* **1973**, 327. (b) Moreau, J. L.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1975**, 1211. (c) Shono, T.; Tsubata, K.; Okmaya, N. *J. Org. Chem.* **1984**, *49*, 1056. (d) Woodward, R. B.; Heusker, K.; Gasteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbrüggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852. (e) Cainelli, G.; Contento, M.; Drusiani, A.; Panunzio, M. *J. Chem. Soc., Chem. Commun.* **1985**, 240. (f) Masamune, S.; Kamata, S.; Schilling, W. *J. Am. Chem. Soc.* **1975**, *97*, 3515. (g) Miyachi, N.; Kanda, F.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 3511.

Table IV. Reactions of in Situ Prepared Zinc Enolates (6) of N,N-disubstituted Glycine Esters (4) with Imine 7a (R^3 = Ph, R^4 = Me)

entry	enolate	R^1	R^2	reaction time[a] (h) C_6H_6 (THF)	product, yield[b] (%) C_6H_6 (THF)	cis/trans ratio[c] C_6H_6 (THF)
1	6c	Me	Me	6 (8)	8g, 91 (80)	47 (70):53 (30)
2	6d	-(CH_2)$_4$-		3.5 (8)	8h, 87 (77)	57 (73):43 (27)
3	6e	CH_2Ph	CH_2Ph	8 (8)	8i, 80 (75)	33 (50):67 (50)
4	6a	Et	Et	0.5 (1.5)	8a, 98 (88)	23 (58):77 (42)
5	6f	t-Bu	Me	20 (40)	8j, 90 (72)	16 (25):84 (75)
6	6g	Ph	Me	4 (4)	8k, 94 (80)	2 (18):98 (82)

[a] Reflux time, not optimized. [b] Yields of the isolated crude products. [c] Determined by ^{1}H NMR integration of the characteristic proton signals of the crude products.

Table V. Reactions of in Situ Prepared Zinc Enolates (6) of N,N-Disubstituted Glycine Alkyl Esters with Activated Imines (7) (in C_6H_6)

entry	enolate	imine	R^3	R^4	product, yield[a] (%)	cis/trans ratio[b]
1[c]	6c	7f	C≡CSiMe_3	SiMe_3/H[d]	8l, 90	<1:>99[e]
2	6c	7h	Ph	Ph	8m, 81	9:91
3	6g	7f	C≡CSiMe_3	SiMe_3/H[d]	8n, 99	<1:>99[e]
4	6e	7d	Ph	SiMe_3/H[d]	8o, 94	<1:>99[e]

[a] Yields of the isolated crude products. [b] Determined by ^{1}H NMR integration of the characteristic proton signals of the crude products. [c] In THF, exclusively *trans*-8l is formed in 60% yield. [d] Replaced by a proton upon hydrolysis. [e] Cis isomer not detected with ^{1}H NMR spectroscopy.

Furthermore, the prolonged heating required for the ring-closure reaction may cause partial decomposition of the organic products.

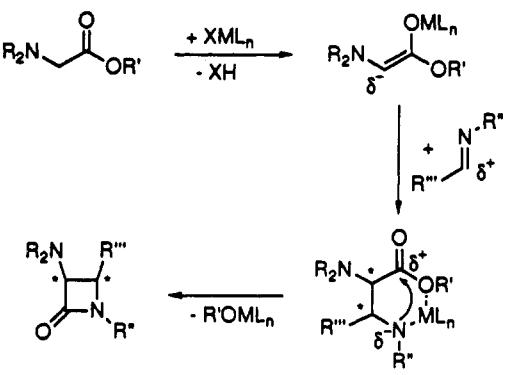
Despite the use of pure *erythro*-11 as starting material, mixtures of *cis*- and *trans*-2-azetidinone 8m were formed (entries 1 and 2). However, this loss of stereochemistry is probably caused by the deprotonation conditions; when deprotonation was carried out at low temperatures (entry 3) no loss of stereochemistry was found. When pure *erythro*-aldolate 11 was dissolved in methanol-d_4, containing 10% of NaOMe-d_3, at room temperature all N-H protons were instantaneously exchanged by deuterium. After 2 days at room temperature, 15% of the C^α-protons were exchanged by deuterium. After 4 h at 60 °C, 80% of the C^α-protons were exchanged. Furthermore, pure *erythro*-11 was converted to a *erythro*/*threo* mixture (80:20). Hence, under thermodynamically controlled conditions, and in the presence of a (strong) base and a proton donor, loss of stereochemistry can occur. However, this is not the result of retro-aldolization but of deprotonation/protonation of the acidic C^α-protons.

We believe that the formation of mixtures of *cis*- and *trans*-2-azetidinones described in this paper is not caused by loss of stereochemistry via retro-aldolization, but is the result of other factors (vide infra).

Discussion

The Mechanism of the 2-Azetidinone Formation. The mechanism of the 2-azetidinone formation from enolates and imines is outlined in Scheme VII. It is analogous to the well-known aldol condensation, but includes an additional ring-closure step. We have evidence that the first step of the reaction is activation of the incoming imine by coordination of the imino nitrogen to the metal atom of the enolate.[23] This coordination makes the C=N bond more polarized and the carbon becomes a better electrophilic center. A second function of the metal cation is to bring the reactants in close proximity to each other and thus enhance the rate of the reaction. The next step is a nucleophilic attack of the enolate anion on the electrophilic carbon of the imine. During this C–C bond formation two new chiral centers are formed and the stereochemistry of the final 2-azetidinone product is determined. Several authors have shown that this step may be an equilibrium, since loss of stereoselectivity via retro-aldolization has been observed.[5,20] However, our results with pure *erythro*-aldolate 11 show that retro-aldolization during our synthesis of 3-amino-2-azetidinones is unlikely. The aldolates react further by an intramolecular nucleophilic attack of the amide nitrogen on the ester function and subsequent elimination of metal alkoxide leads to the 2-azetidinone product. The driving force for this ring closure is the elimination of metal alkoxide, which releases enough energy to compensate for that required to make the 2-azetidinone ring.

Scheme VII



Aspects of the Stereoselectivity of the Ester Enolate–Imine Condensation. I. General. In the literature several transition states for aldol-type reactions have been proposed, including both closed, rigid cyclic transition states and open, noncyclic transition states.[24] Because we feel that the first step in our reactions is coordination of the imine by its nitrogen atom to the metal cation, then in our case the reactions are likely to proceed through rigid cyclic chair- or boat-type transition states, as first proposed by Zimmerman and Traxler.[24d] The structures of these transition states are dependent on the configuration (*E* or *Z*) of both the enolate and the imine.

Our recent studies on the properties and structures of pure α-amino (organo)zinc ester enolates have shown that,

(23) ^{1}H NMR studies on pure zinc and aluminum enolates of N,N-disubstituted glycine alkyl esters showed initial complexation of the imine to the metal. Detailed studies on the preparation and reactions of these pure enolates will be presented in forthcoming papers.[9c,d]

(24) (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Wiley-Interscience: New York, 1982; Vol. 13, p 1. (b) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 3, pp 154–161. (c) Li, Y.; Paddow-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481. (d) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

Table VI. Product Distributions (%) for the Ring-Closure Reactions of Aldolate 11 in the Presence of Different Imines 7[a]

entry	8m	cis:trans	7h	11	erythro:threo	4c′	other products
1[b]	42	7:93	40	20	>98:<2[c]	<2[c]	unidentified, ≈5[d]
2[e]	52	27:73	8	23	95:5	<2[c]	7a, 15
3[f]	53	<2:>98[c]	40	5	>98:<2[c]	<2[c]	7i, 95: unidentified, ≈10[d]

[a] Determined by ^{1}H NMR integration of the characteristic proton signals of the isolated crude products. [b] *n*-BuLi/$ZnCl_2$ at room temperature; 20 h of reflux. [c] Not detected with ^{1}H NMR spectroscopy. [d] The proton signals indicate that this or these products contain a *n*-butyl group that most likely has been transferred from lithium to an organic fragment. [e] LDA/$ZnCl_2$/PhC(H)=NMe (7a) at room temperature; 20 h of reflux. [f] *n*-BuLi/$ZnCl_2$ at −50 °C; PhC(H)=N-*p*-C_6H_4OMe (7i) at room temperature; 20 h of reflux.

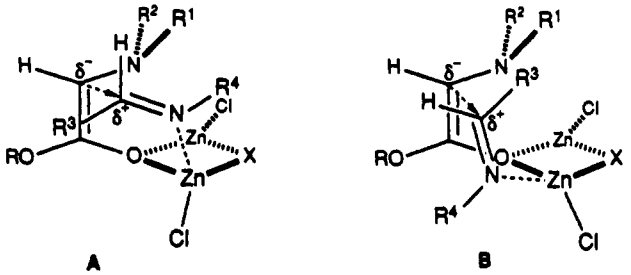


Figure 1. Proposed transition states for the reaction of zinc enolates (6) with imines (7). (A) Erythro C–C bond formation; ring closure leads to *trans*-3-amino-2-azetidinones. (B) Threo C–C bond formation; ring closure leads to *cis*-3-amino-2-azetidinones.

with the exception of **6b** and **6b′**, these enolates have exclusively the *Z* configuration both in solution and in the solid state.[9b,c] Furthermore, the configuration of the in situ prepared zinc enolates was also determined to be *Z*; this configuration is imposed by intramolecular Zn–N coordination, which is also responsible for the stability of these compounds. The absence of such intramolecular Zn–N coordination in **6b** and **6b′** has two effects: (i) in solution only a small fraction of the molecules has a *Z* configuration, and (ii) these enolates have poor stability; even at −30 °C there is decomposition to self-condensation products.[9c] Because the configuration of the zinc enolates **6b** and **6b′** is predominantly *E*, the trans stereoselectivity observed for their reactions with imines 7 cannot, therefore, be the result of thermodynamic control, as for the reactions of the other zinc enolates (vide infra), but must result from kinetic control. This is consistent with our expectations since there is evidence that the *Z* isomers of enolates **6b** and **6b′** are more reactive than the *E* isomers,[25] and that there is a rapid equilibrium between the *E* and *Z* isomers of enolate **6b′**.[9c] Therefore, we conclude that in all zinc-mediated reactions shown in this paper, the configuration of the reactive intermediate zinc enolates is *Z*. This enolate configuration, combined with the *E* configuration of most imines,[26a] enables construction of two different transition states, A and B, which we can use to explain the formation of *trans*- and *cis*-2-azetidinones, respectively (see Figure 1). The energy difference between A and B will be influenced by steric and electronic effects of both the reactant substituents and the solvent; a large energy difference will result in a high stereoselectivity for the C–C bond formation.

Lithium enolates **5b′** and **5e** have almost exclusively the *E* configuration,[9c] and therefore, their reactions with imines 7 proceed mainly via a chairlike transition state that leads to the formation of *cis*-2-azetidinones.[27]

II. Substituent Effects. The results given in Table IV indicate that the energy difference between A and B is mainly determined by steric factors. Going from two small methyl groups (entry 1) to a large tertiary butyl group on the amino nitrogen (entry 5), the diastereoselectivity of the reaction with imine **7a** increases from zero to fairly good. Surprisingly, with imine **7a** the reaction of zinc enolate **6g** (R^1 = Ph) shows an even higher stereoselectivity (entry 6) than that of zinc enolate **6f** (R^1 = *t*-Bu; entry 5), even though a phenyl group is sterically less demanding than a tertiary butyl group. The explanation for this is that, through delocalization of electron density by the phenyl group in **6g**, the amino nitrogen becomes less basic, resulting in a longer Zn–N coordination bond. This longer bond results in a destabilization of transition state B (the R^1 and R^2 substituents come closer to R^3), while transition state A is more stabilized (the R^1 and R^2 substituents move further away from R^4). As a consequence, the formation of *trans*-2-azetidinone **8k** via A is more favored than *cis*-**8k** via B.

The large enhancement of the trans stereoselectivity found for reactions of zinc enolates 6 with activated imines cannot be explained by steric factors alone. Compare, for example, entry 1 of Table IV with entries 1 and 2 of Table V; the change from a methyl group to a trimethylsilyl or phenyl group (R^4 in Figure 1) should not result in better stabilization of transition state A over B. A likely explanation is that the electron-withdrawing effect of the groups attached to the imino nitrogen (e.g., silyl, phenyl) results in more polarization of the C=N bond (i.e. the carbon becomes more electrophilic) and thus less activation through Zn–(imine)N interaction is required. On this basis it is to be expected that the Zn–N coordination bond is longer for activated imines, and as a result, the repulsions between R^4 and R^1/R^2 in transition state A are decreased. Therefore, transition state A is the more stabilized and consequently more *trans*-2-azetidinone is formed. This explanation concerning the imine effect also rationalizes why the lithium enolates are unreactive toward unactivated *N*-alkylimines. For sufficient activation of the imine strong Li–(imine)N interaction is necessary, i.e. a short Li–N distance, and this would cause severe steric strain between the substituents on the imines and enolates. This reasoning is supported by the fact that the transition state in the reaction between zinc enolates **6a′** and **6b′** and unactivated imine **7c**, which is N-substituted with a bulky tertiary butyl group, is also sterically strained and poor yields of the 2-azetidinone products are obtained.

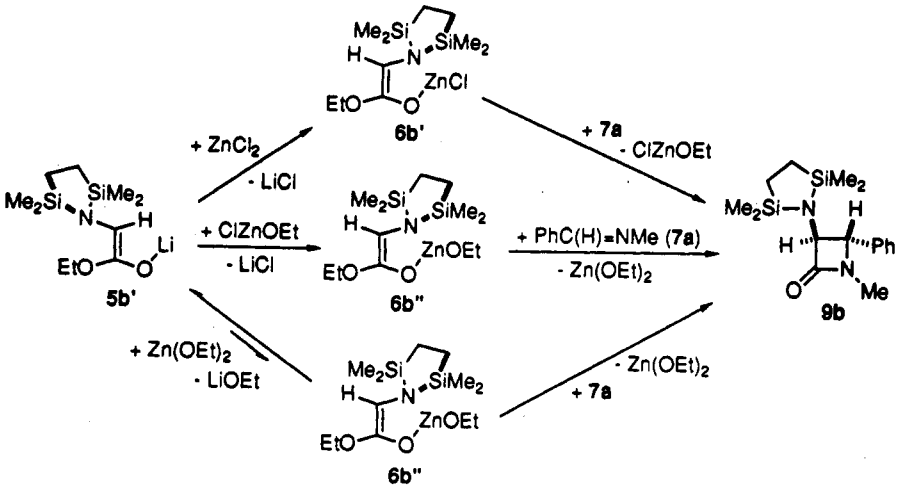
III. Solvent Effects. Because of its strong donor properties, THF will compete with an imine for a coordination site at the zinc center and, therefore, rates of reaction are lower in THF than in benzene. The lower yields of 2-azetidinones 8 obtained in these reactions are due to partial decomposition of the enolates at higher temperatures.[28] Furthermore, on going from benzene to

(25) Examination of the ^{13}C chemical shifts of the trimethylsilyl enol ethers of **6b′** showed that the electron density and hence the nucleophilicity of the α-carbon atoms of the *Z* isomer is higher (causing an upfield shift) than that of the *E* isomer.[9c]

(26) (a) Patai, S. In *The Chemistry of the Carbon–Nitrogen Double Bond*; Patai, S., Ed.; Interscience: London, 1970; pp 363–407. (b) Burnett, D. A.; Hart, D.; Liu, J. *J. Org. Chem.* **1986**, *51*, 1930.

(27) The formation of *trans*-2-azetidinones starting from *E*-enolates is sterically almost impossible.

Scheme VIII



THF one observes an increase in the amount of *cis*-2-azetidinone formed; thus the relative energies of transition states A and B are slightly different in these two solvents. From our studies on the properties of α-amino (organo)zinc ester enolates we know that their configuration is not solvent-dependent and that their reactions are chelation-controlled.[9c] Therefore, changes in the stereoselectivity of the reactions in different solvents must be caused by slight alterations of the conformations of the transition states A and B as a result of the presence or absence of coordinated THF molecules.

Mechanism of the Reactions with Catalytic Amounts of Zinc Dichloride. In order to explain the results for the reactions of lithium enolates **5** with imines **7** in the presence of catalytic amounts of $ZnCl_2$, we propose the mechanism in Scheme VIII. Reaction of the chlorozinc enolate **6b'** (formed in the initial step from $ZnCl_2$ and lithium enolate) with imine **7a** results in the fast formation of 2-azetidinone **9b** and ClZnOEt. The latter can then react with a second equivalent of lithium enolate **5b'** to give LiCl and ethoxyzinc enolate **6b"**, which immediately reacts with imine **7a** to afford 2-azetidinone **9b** and $Zn(OEt)_2$. At low temperatures the rate of transmetalation of lithium enolate **5b'** with $Zn(OEt)_2$ to generate LiOEt and ethoxyzinc enolate **6b"** is assumed to be slow. Transmetalation occurs at room temperature to generate a small concentration of ethoxyzinc enolate **6b"** and this reacts, as outlined above, with imine **7a** to afford **9b** and $Zn(OEt)_2$, which is available for a subsequent cycle. The enhancement of the stereoselectivity when using a catalytic amount of $ZnCl_2$ is most likely the result of a better kinetic control, because of the low concentration of zinc enolate **6b"** that is available for reaction with imine **7a**.

Additional experiments which help confirm the correctness of this proposed mechanism include the following: (i) When the reaction of lithium enolate **5b'** with imine **7a** is performed in the presence of $Zn(OEt)_2$, there is no observable reaction at −78 °C (1 h). However, when the reaction mixture is gradually warmed up to room temperature a conversion of ca. 50% to *trans*-2-azetidinone **9b** is found after 4 h, and the conversion rises to 80% after 24 h. (ii) In the presence of Et_2Zn a slow reaction to *trans*-2-azetidinone **9b** is observed; after 2 days at room temperature **9b** is isolated in 40% yield. From these two experiments it is obvious that with decreasing electronegativity of groups **X** initially attached to the zinc atom, i.e. Cl > OEt > Et, the transmetalation reaction of the lithium enolate **5b'** with ZnX_2 becomes slower because the driving force, formation of LiX, diminishes.

Our proposed mechanism provides a simple explanation for the fact that the reactions are not catalytic in apolar, noncoordinating solvents. Whereas in THF a homogeneous solution is obtained and the transmetalation between lithium enolate **5a** and ClZnOEt or $Zn(OEt)_2$ is rather easy, in benzene the insolubility of the inorganic salts (e.g. LiCl, $Zn(OEt)_2$) causes the equilibria shown in Scheme VIII to lie completely to the side of the lithium enolate **5a**.

Concluding Remarks

The condensation of in situ prepared α-amino metal ester enolates with imines is a very useful route for the synthesis of 3-amino-2-azetidinones, since it combines high yields with high diastereoselectivities. Lithium enolates react only with activated imines, affording selectively *cis*-3-amino-2-azetidinones in excellent yields. Zinc enolates react with both activated and unactivated imines, affording (selectively) *trans*-3-amino-2-azetidinones in good to excellent yields. The diastereoselectivity of the zinc-mediated reactions can be tuned by changing the substituents of the reagents as well as the polarity of the solvent in which the reactions are performed.

Bulky and electron-withdrawing groups attached to the α-amino nitrogen of the enolate generally induce a high trans stereoselectivity in these reactions, whereas small and electron-donating groups provide almost no stereoselectivity. Electron-withdrawing groups attached to the imino nitrogen are generally attended with an increased trans stereoselectivity. When the reactions are carried out in polar solvents (e.g. THF), more of the *cis*-2-azetidinones are formed than in apolar solvents (e.g. benzene).

Furthermore, for unactivated imines, the zinc-mediated ester enolate–imine condensation is applicable using catalytic amounts of $ZnCl_2$, provided that the reaction is carried out in coordinating solvents (e.g. Et_2O, THF). The use of catalytic amounts of $ZnCl_2$ also enhances the diastereoselectivity of the reactions.

Previous studies on the structures of the intermediate enolates have shown that α-amino zinc ester enolates have a *Z* configuration, whereas the lithium enolates generally have an *E* configuration.[9b,c] Thus, the zinc-mediated re-

(28) At higher temperatures the amino nitrogen metal coordination is very weak or even absent and the stabilizing effect of the intramolecular coordination is lost. Therefore the enolates are prone to self-condensation reactions, as observed for ester enolates that do not contain an intramolecularly coordinating α-substituent (see ref 14).

(29) Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787.
(30) Rühlmann, K.; Kuhrt, G. *Angew. Chem.* **1968**, *80*, 797.

actions are chelation-controlled, whereas the lithium-mediated reactions are (in most cases) not. On the basis of this knowledge, we propose two highly ordered transition states that can be used to explain the stereoselectivities observed thusfar in the zinc-mediated reactions.

On the basis of the results and proposed mechanistic scheme reported herein we have recently developed a highly enantioselective synthesis of 3-amino-2-azetidinones, which are key intermediates for the synthesis of monocylic as well as bicyclic β-lactam antibiotics.[7d,31]

Experimental Section

General Data. All manipulations with air-sensitive reagents were carried out in a dry, oxygen-free, nitrogen atmosphere using standard Schlenk techniques. Solvents were dried and distilled from sodium/benzophenone prior to use. All standard chemicals were purchased from Aldrich Chemical Co. or Janssen Chimica. The N,N-disubstituted glycine esters **4** were prepared via a simple condensation of a secondary amine with an appropriate alkyl bromoacetate.[9c] 2,2,5,5-Tetramethyl-1-aza-2,5-disilacyclopentane-1-acetic acid ethyl ester (**4b'**) and *N,N*-bis(trimethylsilyl)-glycine ethyl ester (**4b**) were prepared according to literature procedures.[29,30] Imines **7** were prepared by standard methods.[26] ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 or a Varian EM-360 NMR spectrometer in chloroform-*d* or benzene-d_6, using TMS as an external standard (0.0 ppm). All coupling constants are presented in hertz (Hz). Boiling and melting points are uncorrected. Preparative HPLC was performed on a Philips-4100 system using a Supelcosil PLC-18 column. Elemental analyses were performed by the Institute of Applied Chemistry (TNO), Zeist, The Netherlands.

Synthesis of Dry Zinc Dichloride. As described above, it is very important to use extremely dry $ZnCl_2$ for the reactions. Since commercially available $ZnCl_2$ always contains a significant amount of H_2O,[16a] we here present a detailed experimental procedure, based on a modified literature procedure.[16b]

Two moles (130.76 g) of pure zinc metal pieces (purchased from BDH Chemicals Ltd, Poole, England) were placed in a 2-L three-necked flask equipped with a reflux condensor, a large magnetic stirring bar, a gas-inlet tube connected to an HCl gas cylinder and a nitrogen system, and a stopper. On the zinc pieces was placed 1 L of Et_2O, and then dry HCl was passed through the solution until it was saturated. The HCl flow was stopped, while a small nitrogen pressure was maintained. When the dihydrogen evolution had stopped, the etheral layer was again saturated with hydrogen chloride. This procedure was repeated until all zinc metal had disappeared. This usually took 2–3 days.

A two-layer system was formed, the lower containing $ZnCl_2 \cdot x Et_2O \cdot y HCl$. The solvent was removed in vacuo (0.1 mmHg; 50 °C), resulting in a white solid. This solid was powdered and heated in vacuo (0.01 mmHg; 150 °C) for several hours to remove complexed Et_2O and HCl. Finally a fine, white powder of pure $ZnCl_2$ was obtained that could be redissolved in Et_2O to obtain stock solutions of up to 3.0 M concentrations.

Synthesis of EtZnO(EtO)C=C(H)NEt$_2$·LiCl (6a). To a stirred solution containing 2.02 g (20 mmol) of *i*-Pr_2NH in 30 mL of Et_2O was added 20 mmol of *n*-BuLi (13.33 mL of a 1.5 M solution in hexanes). The resulting solution was stirred for 10 min, and then 3.18 g (20 mmol) of *N,N*-diethylglycine ethyl ester (**4a**) was added at room temperature to form a white suspension of the lithium enolate (**5a**). This suspension was stirred for 30 min and then cooled to −35 °C. At this temperature, a solution containing 2.60 g (20 mmol) of EtZnCl[32] in 15 mL of Et_2O was added with stirring, resulting in the formation of a heavy precipitate in a colorless solution. This suspension was stirred for 30 min at −35 °C and then allowed to warm to room temperature and stirred for another 30 min. The clear solution was then decanted from the precipitate, which was washed three times with 15-mL portions of *n*-pentane. Finally the product was dried in vacuo at ambient temperature, yielding 4.50 g (76%) of **6a** as an air-sensitive white solid. ^1H NMR (C_6D_6): δ 3.70 (s, 1 H, *HC*=C), 3.60 (m, 2 H, OCH_2CH_3), 2.65 (m, 4 H, NCH_2CH_3), 1.55 (t, 3 H, $ZnCH_2CH_3$), 1.15 (m, 9 H, NCH_2CH_3 and OCH_2CH_3), 0.50 (m, 2 H, $ZnCH_2CH_3$). Anal. Calcd for $C_{10}H_{21}NO_2ZnLiCl$: C, 40.70; H, 7.17; N, 4.74; Zn, 22.16. Found: C, 40.56; H, 7.58; N, 4.65; Zn, 22.09.

Synthesis of ClZnO(EtO)C=C(H)NEt$_2$·$^1/_2$LiCl (6a'). To a stirred suspension of 1.65 g (10 mmol) of LiO(EtO)C=C(H)NEt_2 (**5a**) in 25 mL of Et_2O was added 10 mmol (10.0 mL of a 1.0 M solution in Et_2O) of $ZnCl_2$ at room temperature. A slightly exothermic reaction occurred. The reaction mixture was stirred for 1 h at room temperature, resulting in a pale yellow solution containing some white precipitated material (LiCl). The solid was removed by filtration and extracted with two 20-mL portions of diethyl ether. The combined etheral extracts were concentrated in vacuo affording a pale yellow foamy solid. This was washed with two 30-mL portions of *n*-pentane. Finally the product was dried in vacuo, yielding 2.25 g (75%) of **6a'** as an air-sensitive pale yellow solid. The ^1H NMR spectrum unfortunately showed only broad signals (from −80 to 80 °C) but showed the presence of complexed Et_2O. Hydrolysis of the compound affords only the starting glycine ester **4a**, indicating that no side products are formed. The ^{13}C NMR spectrum showed broad resonances, but the enolate structure is clear: ^{13}C NMR (C_6D_6): δ 162.99 (HC=*C*(O)OEt), 85.21 (*HC*=C(O)OEt), 63.19 (OCH_2CH_3), 52.17 (NCH_2CH_3), 14.68 (OCH_2CH_3), 10.50 (NCH_2CH_3). Anal. Calcd for $C_8H_{16}NO_2ZnCL \cdot {}^1/_2LiCl \cdot {}^1/_4Et_2O$: C, 36.17; H, 6.24; N, 4.69; Cl, 17.80; Li, 1.16; Zn, 21.88. Found: C, 35.19; H, 6.28; N, 4.49; Cl, 17.72; Li, 1.20; Zn, 21.47.

General Procedure for the (One-Pot) Synthesis of 3-(Disubstituted amino)-2-azetidinones (8). To a stirred solution containing 1.01 g (10 mmol) of *i*-Pr_2NH in 30 mL of solvent (benzene, toluene, or THF) was added 10 mmol of *n*-BuLi (6.67 mL of a 1.5 M solution in hexanes). The resulting solution was stirred for 10 min, and then 10 mmol of a N,N-disubstituted glycine ester was added at room temperature. The reaction mixture was stirred for an additional 15 min, and then 10 mmol of $ZnCl_2$ (10.0 mL of a 1.0 M solution in Et_2O) was added. After the mixture was stirred for 30 min, 10 mmol of an appropriate imine was added. Then the reaction mixture was refluxed until no further formation of 2-azetidinone **8** could be detected by ^1H NMR. The reaction mixture was allowed to cool to room temperature and then quenched with 20 mL of a saturated aqueous NH_4Cl solution. The precipitated salts were filtered off through a sintered-glass fritt. The aqueous layer was separated and extracted with two 30-mL portions of Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to afford the crude 2-azetidinone products. The composition of these crude products was examined with ^1H NMR, before performing any purification step. The crude products were purified by recrystallization, flash chromatography, or preparative HPLC techniques.

***trans*-1-Methyl-3-(*N,N*-diethylamino)-4-phenyl-2-azetidinone (8a).** Pale yellow solid, 2.27 g (98%). The ^1H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 23:77). ^1H NMR (C_6D_6): trans, δ 7.15–6.88 (m, 5 H, ArH), 4.10 (d, 1 H, *J* = 1.7, NCHC*H*Ph), 3.86 (br s, 1 H, NC*H*CHPh), 2.59 (m, 4 H, NCH_2CH_3), 2.34 (s, 3 H, NCH_3), 0.89 (t, 6 H, NCH_2CH_3); cis, δ 4.11 (d, 1 H, *J* = 4.6, NCHC*H*Ph), 4.02 (d, 1 H, *J* = 4.6, NC*H*CHPh), 2.43 (s, 3 H, NCH_3), 2.43 (m, 4 H, NCH_2CH_3), 0.64 (t, 6 H, NCH_2CH_3). ^{13}C NMR ($CDCl_3$): trans, δ 168.12 (C=O), 136.66, 128.28, 127.47, 125.47 (ArC), 80.69 (NCHCHPh), 60.36 (NCHCHPh), 43.31 (NCH_2CH_3), 25.73 (NCH_3), 11.69 (NCH_2CH_3); cis, δ 168.40 (C=O), 135.08, 127.56, 127.35, 125.65 (ArC), 74.09 (NCHCHPh), 62.97 (NCHCHPh), 44.11 (NCH_2CH_3), 26.32 (NCH_3), 11.81 (NCH_2CH_3). The pure trans isomer was obtained as colorless crystals after one crystallization from hot hexane, mp 70–71 °C. Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.13; H, 8.80; N, 11.73.

***trans*-1-Benzyl-3-(*N,N*-diethylamino)-4-phenyl-2-azetidinone (8b).** Pale yellow oil, 3.02 g (98%). The ^1H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 6:94). ^1H NMR ($CDCl_3$): trans, δ 7.40 (m, 10 H, ArH), 5.10 (d, 1 H, *J* = 15.0, NCH_2Ph), 4.60 (d, 1 H, *J* = 1.5, NCHC*H*Ph), 4.20 (d, 1 H, *J* = 1.5, NC*H*CHPh), 3.90 (d,

(31) Van der Steen, F. H.; Kleijn, H.; Britovsek, G. J. P.; Jastrzebski, J. T. B. H.; van Koten, G. *J. Org. Chem.*, in press.
(32) Boersma, J.; Noltes, J. G. *Tetrahedron Lett.* **1966**, *18*, 1521.

1 H, J = 15.0, NCH_2Ph), 2.90 (m, 4 H, NCH_2CH$_3$), 1.20 (t, 6 H, NCH$_2$CH_3); cis, δ 7.45 (m, 10 H, ArH), 5.09 (d, 1 H, J = 14.8, NCH_2Ph), 4.62 (d, 1 H, J = 4.7, NCHCHPh), 4.46 (d, 1 H, J = 4.7, NCHCHPh), 3.89 (d, 1 H, J = 14.8, NCH_2Ph), 2.62 (m, 4 H, NCH_2CH$_3$), 0.88 (t, 6 H, NCH$_2$CH_3). ^{13}C NMR (CDCl$_3$): trans, δ 168.57 (C=O), 136.83, 135.23, 128.62, 128.33, 128.16, 127.85, 127.32, 126.08 (ArC), 80.53 (NCHCHPh), 58.25 (NCHCHPh), 43.74 (NCH$_2$Ph), 43.50 (NCH$_2$CH$_3$), 12.08 (NCH$_2$CH$_3$). The pure trans isomer was obtained as a colorless oil after separation using preparative HPLC techniques (eluent MeOH/H$_2$O (80:20 v/v)).

***trans*-3-(*N*,*N*-Diethylamino)-4-phenyl-2-azetidinone (8d).** Pale yellow solid, 2.03 g (93%). The cis isomer was not detected by ^{1}H NMR spectroscopy. ^{1}H NMR (CDCl$_3$): trans, δ 7.33–7.24 (m, 5 H, ArH), 6.76 (br s, 1 H, NH), 4.63 (d, 1 H, J = 2.0, NCHCHPh), 3.95 (d, 1 H, J = 2.0, NCHCHPh), 2.72 (dq, 4 H, NCH_2CH$_3$), 0.98 (t, 6 H, NCH$_2$CH_3). ^{13}C NMR (CDCl$_3$): δ 170.50 (C=O), 139.65, 128.83, 127.96, 125.68 (ArC), 81.76 (NCHCHPh), 55.92 (NCHCHPh), 44.10 (NCH$_2$CH$_3$), 12.61 (NCH$_2$CH$_3$). The product was purified by crystallization from hot hexane to afford colorless crystals, mp 128–130 °C. Anal. Calcd for C$_{13}$H$_{18}$N$_2$O: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.29; H, 8.39; N, 12.79.

***trans*-3-(*N*,*N*-Diethylamino)-4-(phenylethynyl)-2-azetidinone (8e).** Pale brown solid, 2.49 g (98%). The cis isomer was not detected by ^{1}H NMR spectroscopy. ^{1}H NMR (CDCl$_3$): trans, δ 7.42–7.24 (m, 5 H, ArH), 6.48 (br s, 1 H, NH), 4.42 (m, 2 H, NCHCHC≡C), 2.74 (dq, 4 H, NCH_2CH$_3$), 1.09 (t, 6 H, NCH$_2$CH_3). ^{13}C NMR (CDCl$_3$): δ 169.10 (C=O), 131.69, 128.67, 128.38 (ArC), 122.21 (C≡CPh), 86.43 (C≡CPh), 81.39 (NCHCHC≡C), 43.83 (NCH$_2$CH$_3$), 42.79 (NCHCHC≡C), 12.39 (NCH$_2$CH$_3$). The product was purified by crystallization from hot hexane to afford pale yellow crystals, mp 116–117 °C. Anal. Calcd for C$_{15}$H$_{18}$N$_2$O: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.29; H, 7.56; N, 11.57.

***trans*-3-(*N*,*N*-Diethylamino)-4-[(trimethylsilyl)ethynyl]-2-azetidinone (8f).** Pale brown solid, 2.31 g (97%). The cis isomer was not detected by ^{1}H NMR spectroscopy. ^{1}H NMR (C$_6$D$_6$): trans, δ 6.34 (br s, 1 H, NH), 4.30 (d, 1 H, J = 2.2, NCHCHC≡C), 3.86 (d, 1 H, J = 2.2, NCHCHC≡C), 2.49 (m, 4 H, NCH_2CH$_3$), 0.89 (t, 6 H, NCH$_2$CH_3), 0.15 (s, 9 H, Si(CH$_3$)$_3$). ^{13}C NMR (CDCl$_3$): δ 169.19 (C=O), 102.95 (C≡CSiMe$_3$), 91.00 (C≡CSiMe$_3$), 81.26 (NCHCHC≡C), 43.77 (NCH$_2$CH$_3$), 42.60 (NCHCHC≡C), 12.28 (NCH$_2$CH$_3$), –0.23 (Si(CH$_3$)$_3$). The product was purified by crystallization from hot hexane to afford colorless crystals, mp 108–109 °C. Anal. Calcd for C$_{12}$H$_{22}$N$_2$OSi: C, 60.46; H, 9.30; N, 11.75. Found: C, 60.07; H, 9.16; N, 11.67.

***trans*-3-(*N*,*N*-Diethylamino)-4-ethynyl-2-azetidinone (8f').** To a stirred solution of 5.40 g (22.6 mmol) of **8f** in 100 mL of MeOH was added 1.3 g (23 mmol) of KOH in 8 mL of H$_2$O. The reaction mixture was stirred for 1 h at room temperature, after which all volatile material was removed in vacuo. The white residue was dissolved in 50 mL of Et$_2$O and washed with two small portions of H$_2$O. The Et$_2$O was dried over Na$_2$SO$_4$ and concentrated in vacuo to afford 3.40 g (91%) of pure **8f'** as an off-white solid, mp 92–93 °C. ^{1}H NMR (CDCl$_3$): δ 6.84 (br s, 1 H, NH), 4.30 (d, 1 H, J = 2.1, NCHCHC≡C), 4.15 (dd, 1 H, J = 2.1 and 2.0, NCHCHC≡C), 2.66 (m, 4 H, NCH_2CH$_3$), 2.45 (d, 1 H, J = 2.0, C≡CH), 1.02 (t, 6 H, NCH$_2$CH_3). ^{13}C NMR (CDCl$_3$): δ 169.21 (C=O), 81.40 (C≡CH), 80.98 (NCHCHC≡C), 74.06 (C≡CH), 44.71 (NCH$_2$CH$_3$), 41.85 (NCHCHC≡C), 12.29 (NCH$_2$CH$_3$). Anal. Calcd for C$_9$H$_{14}$N$_2$O: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.37; H, 8.48; N, 16.68.

1-Methyl-3-(*N*,*N*-dimethylamino)-4-phenyl-2-azetidinone (8g). Pale yellow oil, 1.85 g (91%). The ^{1}H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 47:53). ^{1}H NMR (C$_6$D$_6$): trans, δ 7.15–6.94 (m, 5 H, ArH), 4.19 (d, J = 2.1, 1 H, NCHCHPh), 3.43 (br s, 1 H, NCHCHPh), 2.34 (s, 3 H, NCH$_3$), 2.20 (s, 6 H, N(CH$_3$)$_2$); cis, δ 7.15–7.07 (m, 5 H, ArH), 3.90 (d, J = 4.6, 1 H, NCHCHPh), 3.37 (d, J = 4.6, 1 H, NCHCHPh), 2.27 (s, 3 H, NCH$_3$), 1.97 (s, 6 H, N(CH$_3$)$_2$). ^{13}C NMR (CDCl$_3$): trans δ 166.97 (C=O), 138.45, 129.21, 127.58, 126.55 (ArC), 84.15 (NCHCHPh), 60.36 (NCHCHPh), 42.69 (N(CH$_3$)$_2$), 26.14 (NCH$_3$); cis, δ 167.66 (C=O), 134.71, 128.49, 128.32, 128.21 (ArC), 77.19 (NCHCHPh), 62.40 (NCHCHPh), 43.60 (N(CH$_3$)$_2$), 26.51 (NCH$_3$). The isomers were separated by flash chromatography (Al$_2$O$_3$/5% H$_2$O; eluent CHCl$_3$). The pure cis isomer was obtained as pale yellow crystals after crystallization from Et$_2$O, mp 82–83 °C. Anal. Calcd for C$_{12}$H$_{16}$N$_2$O: C, 70.56; H, 7.90; N, 13.71. Found: C, 69.79; H, 7.86; N, 13.54.

1-Methyl-3-(1-pyrrolidyl)-4-phenyl-2-azetidinone (8h). Pale yellow oil, 1.99 g (87%). The ^{1}H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 57:43). ^{1}H NMR (C$_6$D$_6$): trans, δ 7.14–6.93 (m, 5 H, ArH), 4.15 (d, 1 H, J = 2.1, NCHCHPh), 3.62 (d, 1 H, J = 2.1, NCHCHPh), 2.35 (s, 3 H, NCH$_3$), 2.63–2.21 (m, 4 H, NCH_2CH$_2$CH$_2$CH_2), 1.53–1.27 (m, 4 H, NCH$_2$CH_2CH_2CH$_2$); cis, δ 3.98 (d, 1 H, J = 4.6, NCHCHPh), 3.61 (d, 1 H, J = 4.6, NCHCHPh), 2.32 (s, 3 H, NCH$_3$). ^{13}C NMR (CDCl$_3$): trans, δ 161.98 (C=O), 134.01, 128.58, 127.72, 127.45 (ArC), 79.74 (NCHCHPh), 60.76 (NCHCHPh), 50.66 (NCH$_2$CH$_2$CH$_2$CH$_2$), 26.28 (NCH$_3$), 23.08 (NCH$_2$CH$_2$CH$_2$CH$_2$); cis, δ 167.40 (C=O), 134.61, 127.89, 127.57, 125.76 (ArC), 75.07 (NCHCHPh), 61.73 (NCHCHPh), 51.62 (NCH$_2$CH$_2$CH$_2$CH$_2$), 26.10 (NCH$_3$), 22.96 (NCH$_2$CH$_2$CH$_2$CH$_2$). The diastereomers could not be separated by crystallization or chromatography.

***trans*-1-Methyl-3-(*N*,*N*-dibenzylamino)-4-phenyl-2-azetidinone (8i).** Pale yellow oil, 2.85 g (80%). The ^{1}H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 33:67). ^{1}H NMR (C$_6$D$_6$): trans, δ 7.31–6.74 (m, 15 H, ArH), 4.11 (d, 1 H, J = 1.9 Hz, NCHCHPh), 4.03 (br s, 1 H, NCHCHPh), 3.90 (d, 2 H, J = 13.6, NCH_2Ph), 3.57 (d, 2 H, J = 13.6, NCH_2Ph), 2.29 (s, 3 H, NCH$_3$); cis, δ 4.19 (d, 1 H, J = 5.0, NCHCHPh), 3.76 (d, 1 H, J = 5.0, NCHCHPh), 3.75 (d, 2 H, J = 13.6, NCH_2Ph), 3.51 (d, 2 H, J = 13.6, NCH_2Ph), 2.37 (s, 3 H, NCH$_3$). ^{13}C NMR (C$_6$D$_6$): trans, δ 168.02 (C=O), 138.68, 138.16, 129.44, 129.05, 128.56, 128.16, 127.50, 126.58 (ArC), 80.61 (NCHCHPh), 60.87 (NCHCHPh), 55.45 (CH$_2$Ph), 26.14 (NCH$_3$). The pure trans isomer was obtained as white crystals after two recrystallizations from Et$_2$O/pentane (1:1 v/v), mp 108 °C. Anal. Calcd for C$_{24}$H$_{24}$N$_2$O: C, 80.87; H, 6.79; N, 7.86. Found: C, 80.84; H, 6.82; N, 7.99.

***trans*-1-Methyl-3-(*N*-*tert*-butyl-*N*-methylamino)-4-phenyl-2-azetidinone (8j).** Pale yellow oil, 2.22 g (90%). The ^{1}H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 16:84). ^{1}H NMR (C$_6$D$_6$): trans, δ 7.19–6.91 (m, 5 H, ArH), 4.23 (br s, 1 H, NCHCHPh), 4.16 (d, 1 H, J = 1.8, NCHCHPh), 2.37 (s, 3 H, N(t-Bu)CH_3), 2.35 (s, 3 H, NCH$_3$), 0.85 (s, 9 H, N(C(CH_3)$_3$)CH$_3$); cis, δ 4.31 (d, 1 H, J = 5.2, NCHCHPh), 3.94 (d, 1 H, J = 5.2, NCHCHPh), 2.51 (s, 3 H, N(t-Bu)CH_3), 2.10 (s, 3 H, NCH$_3$), 0.86 (s, 9 H, N(C-(CH_3)$_3$)CH$_3$). ^{13}C NMR (CDCl$_3$): trans, δ 170.27 (C=O), 137.01, 128.97, 128.21, 126.55 (ArC), 78.70 (NCHCHPh), 60.00 (NCHCHPh), 53.96 (C(CH$_3$)$_3$), 30.39 (N(t-Bu)CH$_3$), 27.27 (C(CH$_3$)$_3$), 26.55 (NCH$_3$); cis, δ 169.03 (C=O), 136.36, 128.57, 127.97, 126.68 (ArC), 72.35 (NCHCHPh), 65.42 (NCHCHPh), 51.29 (C-(CH$_3$)$_3$), 33.04 (N(t-Bu)CH$_3$), 26.89 (C(CH$_3$)$_3$). The diastereomers were separated using HPLC techniques (eluent: MeOH/H$_2$O (75:25 v/v)). Anal. Calcd for C$_{15}$H$_{22}$N$_2$O: C, 73.13; H, 9.00; N, 11.37. Found: C, 71.73; H, 9.26; N, 11.07.

***trans*-1-Methyl-3-(*N*-methyl-*N*-phenylamino)-4-phenyl-2-azetidinone (8k).** Pale brown solid, 2.50 g (94%). The ^{1}H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 2:98). ^{1}H NMR (C$_6$D$_6$): trans, δ 7.12–6.36 (m, 10 H, ArH), 4.66 (br s, 1 H, NCHCHPh), 4.00 (d, 1 H, J = 1.8, NCHCHPh), 2.91 (s, 3 H, N(Ph)CH_3), 2.31 (s, 3 H, NCH$_3$); cis, δ 4.87 (d, 1 H, J = 4.6, NCHCHPh), 4.02 (d, 1 H, J = 4.6, NCHCHPh), 2.64 (s, 3 H, N(Ph)CH_3), 2.46 (s, 3 H, NCH$_3$). ^{13}C NMR (CDCl$_3$): trans, δ 167.76 (C=O), 149.26, 137.12, 129.75, 129.64, 129.20, 126.86, 119.22, 114.91 (ArC), 78.35 (NCHCHPh), 63.51 (NCHCHPh), 35.42 (N(Ph)CH$_3$), 27.35 (NCH$_3$). The pure trans isomer was obtained as colorless crystals after one recrystallization from Et$_2$O, mp 84 °C. Anal. Calcd for C$_{17}$H$_{18}$N$_2$O: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.33; H, 6.91; N, 10.35. The pure cis isomer crystallized from the mother liquor as brown crystals, mp 137 °C.

***trans*-3-(*N*,*N*-Dimethylamino)-4-[(trimethylsilyl)ethynyl]-2-azetidinone (8l).** Pale brown oil, 1.89 g (90%). The cis isomer was not detected by ^{1}H NMR spectroscopy. ^{1}H NMR (C$_6$D$_6$): trans, δ 6.30 (br s, 1 H, NH), 3.97 (br s, 1 H, NCHCHC≡C), 3.89 (d, 1 H, J = 2.1, NCHCHC≡C), 2.09 (s, 6 H, N(CH$_3$)$_2$), 0.14 (s, 9 H, Si(CH$_3$)$_3$). ^{13}C NMR (CDCl$_3$): δ 167.66 (C=O), 102.64 (C≡CSiMe$_3$), 90.89 (C≡CSiMe$_3$), 82.86 (NCHC-HC≡C), 41.77 (N(CH$_3$)$_2$), 40.77 (NCHCHC≡C), –0.24 (Si(CH$_3$)$_3$).

The product was purified by crystallization from Et_2O/hexane (1:1 v/v) to afford colorless crystals, mp 115 °C. Anal. Calcd for $C_{10}H_{18}N_2OSi$: C, 57.10; H, 8.63; N, 13.32. Found: C, 56.64; H, 8.46; N, 13.50.

***trans*-1-Phenyl-3-(*N*,*N*-dimethylamino)-4-phenyl-2-azetidinone (8m).** Pale yellow solid, 2.15 g (81%). The ^1H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 9:91). ^1H NMR ($CDCl_3$): trans, δ 7.41–7.01 (m, 10 H, ArH), 5.03 (d, 1 H, J = 2.1, NCHC*H*Ph), 3.84 (d, 1 H, J = 2.1, NC*H*CHPh), 2.49 (s, 6 H, N(CH_3)$_2$); cis, δ 5.13 (d, 1 H, J = 5.2, NCHC*H*Ph), 4.01 (d, 1 H, J = 5.2, NC*H*CHPh). ^{13}C NMR ($CDCl_3$): trans, δ 165.25 (C=O), 137.49, 137.26, 129.25, 129.08, 128.32, 128.22, 125.68, 124.12, 117.38 (ArC), 82.54 (N*C*HCHPh), 58.05 (NCH*C*HPh), 42.39 (N(CH_3)$_2$); cis, δ 75.93 (N*C*HCHPh), 60.89 (NCH*C*HPh), 43.45 (N(CH_3)$_2$). The pure trans isomer was obtained as off-white crystals after one recrystallization from hot hexane, mp 107 °C. Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.53; H, 6.75; N, 10.58.

***trans*-3-(*N*-Methyl-*N*-phenylamino)-4-[(trimethylsilyl)-ethynyl]-2-azetidinone (8n).** Brown solid, 2.70 g (99%). The cis isomer was not detected by ^1H NMR spectroscopy. ^1H NMR (C_6D_6): trans, δ 7.15 (m, 2 H, ArH), 6.80 (m, 3 H, ArH), 5.98 (br s, 1 H, NH), 4.96 (br s, 1 H, NC*H*CHC≡C), 3.62 (d, 1 H, J = 2.2, NCHC*H*C≡C), 2.61 (s, 3 H, NCH_3), 0.16 (s, 9 H, Si(CH_3)$_3$). ^{13}C NMR (C_6D_6): δ 166.45 (C=O), 148.99, 129.44, 119.54, 115.26 (ArC), 103.72 (C≡CSiMe$_3$), 91.54 (C≡CSiMe$_3$), 78.04 (NCHCH-C≡C), 44.51 (N(CH_3)$_2$), 34.59 (NCH*C*HC≡C), −0.20 (Si(CH_3)$_3$). The product was purified by crystallization from Et_2O/pentane (1:1 v/v) to afford colorless crystals, mp 136 °C. Anal. Calcd for $C_{15}H_{20}N_2OSi$: C, 66.13; H, 7.40; N, 10.28. Found: C, 65.59; H, 7.66; N, 10.21.

***trans*-3-(*N*,*N*-Dibenzylamino)-4-phenyl-2-azetidinone (8o).** Pale yellow solid, 3.22 g (94%). The cis isomer was not detected by ^1H NMR spectroscopy. ^1H NMR ($CDCl_3$): trans, δ 7.40–7.23 (m, 15 H, ArH), 6.20 (br s, 1 H, NH), 4.75 (d, 1 H, J = 2.1, NC*H*CHPh), 4.08 (d, 1 H, J = 2.1, NCHC*H*Ph), 3.96 (d, 2 H, J = 13.6, NC*H*$_2$Ph), 3.73 (d, 2 H, J = 13.6, NC*H*$_2$Ph). ^{13}C NMR ($CDCl_3$): trans, δ 169.91 (C=O), 139.36, 138.03, 128.93, 128.82, 128.30, 128.06, 127.27, 125.62 (ArC), 80.21 (N*C*HCHPh), 55.35 (NCH*C*HPh), 55.06 (N*C*H$_2$Ph). The pure trans isomer was obtained as colorless crystals after one crystallization from Et_2O/THF (1:1 v/v), mp 150 °C. Anal. Calcd for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18. Found: C, 80.00; H, 6.37; N, 8.18.

***cis*-3-(*N*,*N*-Dibenzylamino)-4-phenyl-2-azetidinone (8o).** The reaction was carried out in THF as described in the general procedure, but without addition of $ZnCl_2$. Pale yellow solid, 3.11 g (91%). The ^1H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 84:16). ^1H NMR ($CDCl_3$): cis, δ 7.43–7.00 (m, 15 H, ArH), 6.52 (br s, 1 H, NH), 4.78 (d, 1 H, J = 5.3, NC*H*CHPh), 4.54 (dd, 1 H, J = 5.3 and J = 1.8, NCHC*H*Ph), 3.67 (d, 2 H, J = 13.6, NC*H*$_2$Ph), 3.51 (d, 2 H, J = 13.6, NC*H*$_2$Ph). ^{13}C NMR ($CDCl_3$): cis, δ 170.42 (C=O), 138.56, 137.40, 128.91, 128.52, 128.12, 127.79, 127.13, 127.07 (ArC), 73.69 (N*C*HCHPh), 58.31 (NCH*C*HPh), 55.53 (N*C*H$_2$Ph). The pure cis isomer was obtained as colorless crystals, containing enclosed diethyl ether, after one recrystallization from Et_2O, mp 80 °C. Anal. Calcd for $C_{23}H_{22}N_2O \cdot {}^1/_2Et_2O$: C, 79.12; H, 7.17; N, 7.38. Found: C, 79.14; H, 7.15; N, 7.43.

General Procedure for the (One-Pot) Synthesis of 3-(Silyl-protected amino)-2-azetidinones (9). To a stirred solution containing 1.01 g (10 mmol) of i-Pr$_2$NH in 30 mL of solvent (Et_2O or THF) at −78 °C was added 10 mmol of n-BuLi (6.67 mL of a 1.5 M solution in hexanes). The solution was stirred for 10 min at −78 °C and then 10 mmol of **4b** or **4b'** was added. The reaction mixture was stirred for an additional 15 min at −78 °C, and then 10 mmol of $ZnCl_2$ (10.0 mL of a 1.0 M solution in Et_2O) was added and after stirring for 30 min 10 mmol of an appropriate imine was added at −78 °C. Then the reaction mixture was stirred for 1 h at −78 °C, after which the reaction mixture was allowed to warm to room temperature and quenched with 20 mL of a saturated aqueous NH_4Cl solution. The precipitated salts were filtered off through a sintered-glass fritt. The aqueous layer was separated and extracted with two portions of Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to afford the crude 2-azetidinone products 9. The composition of these crude products were examined with ^1H NMR before performing any purification step. Whenever possible, the crude products were purified by recrystallization or flash chromatography.[33]

***trans*-1-Benzyl-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-methyl-2-azetidinone (9a).** Pale yellow oil, 3.25 g (98%). The ^1H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 9:91). ^1H NMR ($CDCl_3$): trans, δ 7.28 (m, 5 H, ArH), 4.62 (d, 1 H, J = 14.9, NCH_2Ph), 4.01 (d, 1 H, J = 14.9, NCH_2Ph), 3.79 (d, 1 H, J = 1.9, NC*H*CHMe), 3.21 (dq, 1 H, J = 1.9 and 6.1, NCHC*H*Me), 1.19 (d, 3 H, J = 6.1, CH_3), 0.68 (m, 4 H, SiCH_2CH_2Si), 0.07, 0.02 (s, 6 H, Si(CH_3)$_2$); cis, δ 4.57 (d, 1 H, J = 14.9, NCH_2Ph), 4.42 (d, 1 H, J = 4.6, NC*H*CHMe), 4.07 (d, 1 H, J = 14.9, NCH_2Ph), 3.64 (dq, 1 H, J = 4.6 and 6.2, NCHC*H*Me), 0.99 (d, 3 H, J = 6.2, CH_3). ^{13}C NMR ($CDCl_3$): trans, δ 168.79, (C=O), 138.87, 128.40, 128.01, 127.38 (ArC), 68.46 (N*C*HCHMe), 58.67 (NCH*C*HMe), 43.73 (N*C*H$_2$Ph), 16.40 (CH_3), 7.80 (Si*C*H$_2$*C*H$_2$Si), 0.32, 0.05 (Si(CH_3)$_2$). The diastereomers could not be separated by crystallization or flash chromatography. Attempts to obtain analytically pure material failed because of partial hydrolysis of the protecting disilyl moiety during the process of purification.[33]

***trans*-1-Methyl-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-phenyl-2-azetidinone (9b).** Pale yellow solid, 3.09 g (97%). The ^1H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 8:92). ^1H NMR ($CDCl_3$): trans, δ 7.44–7.17 (m, 5 H, ArH), 4.10 (d, 1 H, J = 1.8, NCHC*H*Ph), 4.05 (m, 1 H, N*C*HCHPh), 2.75 (br s, 3 H, NCH_3), 0.85–0.63 (m, 4 H, SiCH_2CH_2Si), 0.12 (s, 6 H, Si(CH_3)$_2$), 0.04 (s, 6 H, Si(CH_3)$_2$); cis, δ 4.74 (d, 1 H, J = 5.6, NC*H*CHPh), 4.50 (d, 1 H, J = 5.6, NCHC*H*Ph). ^{13}C NMR ($CDCl_3$): trans, δ 170.23 (C=O), 137.03, 128.83, 128.25, 126.18 (ArC), 72.92 (N*C*HCHPh), 68.63 (NCH*C*HPh), 26.58 (NCH_3), 7.94 (Si*C*H$_2$*C*H$_2$Si), 0.59, 0.10 (Si(CH_3)$_2$). The pure trans isomer was obtained as colorless crystals after one crystallization from Et_2O/pentane (1:1 v/v), mp 91 °C. Anal. Calcd for $C_{16}H_{28}N_2OSi_2$: C, 60.33; H, 8.23; N, 8.79; Si, 17.63. Found: C, 60.33; H, 8.46; N, 8.54; Si, 17.45.

***trans*-1-Methyl-3-[*N*,*N*-bis(trimethylsilyl)amino]-4-phenyl-2-azetidinone (9c).** Pale yellow oil, 2.41 g (75%). The cis isomer was not detected by ^1H NMR spectroscopy. ^1H NMR ($CDCl_3$): trans, δ 7.37–7.14 (m, 5 H, ArH), 4.08 (d, 1 H, J = 1.9, NCHC*H*Ph), 3.99 (m, 1 H, N*C*HCHPh), 2.68 (br s, 3 H, NCH_3), 0.04 (s, 18 H, Si(CH_3)$_3$. ^{13}C NMR ($CDCl_3$): trans, δ 171.73 (C=O), 136.92, 128.86, 128.17, 125.80 (ArC), 75.29 (N*C*HCHPh), 68.63 (NCH*C*HPh), 26.68 (NCH_3), 2.43 (Si(CH_3)$_3$). Recrystallization from Et_2O afforded the pure trans isomer as off-white crystals, mp 103 °C. Anal. Calcd for $C_{16}H_{28}N_2OSi_2$: C, 59.95; H, 8.80; N, 8.74; Si, 17.52. Found: C, 57.61; H, 8.12; N, 9.10; Si, 15.57.[33]

***trans*-3-(2,2,5,5-Tetramethyl-1-aza-2,5-disilacyclopentyl)-4-phenyl-2-azetidinone (9e).** Pale yellow oil that crystallizes upon standing, 2.91 g (96%). The ^1H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 14:86). ^1H NMR ($CDCl_3$): trans, δ 7.12 (m, 5 H, ArH), 6.29 (br s, 1 H, NH), 4.23 (d, 1 H, J = 2.1, N*C*HCHPh), 3.92 (d, 1 H, J = 2.1, NCHC*H*Ph), 0.70 (s, 4 H, Si*C*H$_2$*C*H$_2$Si), 0.13, 0.05 (Si(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): trans, δ 171.65 (C=O), 139.34, 128.76, 128.13, 125.51 (ArC), 73.61 (N*C*HCHPh), 62.76 (NCH*C*HPh), 7.97 (Si*C*H$_2$*C*H$_2$Si), 0.45 (Si(CH_3)$_2$). Recrystallization from hot hexane afforded the pure trans isomer as off-white crystals, mp 101 °C.

***cis*-3-(2,2,5,5-Tetramethyl-1-aza-2,5-disilacyclopentyl)-4-phenyl-2-azetidinone (9e).** The reaction was carried out in THF as described in the general procedure, but without addition of $ZnCl_2$. Pale yellow oil that crystallizes upon standing, 3.00 g (99%). The ^1H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 96:4). ^1H NMR ($CDCl_3$): cis, δ 7.41–7.22 (m, 5 H, ArH), 6.67 (br s, 1 H, NH), 4.81 (dd, 1 H, J = 5.0 and J = 1.6, NCHC*H*Ph), 4.77 (d, 1 H, J = 5.0, N*C*HCHPh), 0.62–0.50 (m, 4 H, SiCH_2CH_2Si), −0.02, −0.15 (Si-

(33) Because the protecting disilyl moiety is very susceptible to hydrolysis, the separation by chromatographic techniques was usually accompanied by partial deprotection of the amine function. Therefore, it was not always possible to obtain analytically pure samples. Furthermore, elemental analyses of azetidinones 9 proved difficult because of partial hydrolysis during sampling.

(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): cis, δ 171.58 (C=O), 137.08, 128.19, 127.90 (ArC), 68.34 (N*C*HCHPh), 59.62 (NCH*C*HPh), 8.09 (Si-*C*H$_2$*C*H$_2$Si), 0.50, −0.18 (Si(CH_3)$_2$). Recrystallization from Et_2O afforded the pure cis isomer as off-white crystals, mp 136.5 °C. Anal. Calcd for $C_{15}H_{24}N_2OSi_2$: C, 59.16; H, 7.94; N, 9.20. Found: C, 57.47; H, 7.99; N, 9.37.

***trans*-3-[*N*,*N*-Bis(trimethylsilyl)amino]-4-phenyl-2-azetidinone (9f).** Pale yellow oil, 2.32 g (70%). The cis isomer was not detected by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$): trans, δ 7.10 (m, 5 H, ArH), 6.25 (br s, 1 H, NH), 4.25 (d, 1 H, *J* = 2.0, NC*H*CHPh), 3.98 (d, 1 H, *J* = 2.0, NCHC*H*Ph), 0.19 (s, 18 H, Si(CH_3)$_3$); authentic cis, δ 4.64 (d, 1 H, 5.2, NC*H*CHPh), 4.46 (d, 1 H, *J* = 5.2, NCHC*H*Ph). ^{13} NMR ($CDCl_3$): trans, δ 173.51 (C=O), 138.97, 128.58, 127.89, 125.19 (ArC), 75.67 (N*C*HCHPh), 63.11 (NCH*C*HPh), 2.48 (Si(CH_3)$_3$). Recrystallization from hot hexane afforded the pure trans isomer as off-white crystals, mp 111 °C. Anal. Calcd for $C_{15}H_{28}N_2OSi_2$: C, 58.77; H, 8.55; N, 9.14. Found: C, 58.34; H, 8.51; N, 9.08.

***trans*-3-(2,2,5,5-Tetramethyl-1-aza-2,5-disilacyclopentyl)-4-[(trimethylsilyl)ethynyl]-2-azetidinone (9g).** Pale yellow oil, 3.03 g (93%). The ^{1}H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 3:97). ^{1}H NMR ($CDCl_3$): trans, δ 6.47 (br s, 1 H, NH), 4.35 (d, 1 H, *J* = 2.2, NC*H*CHC≡C), 3.77 (d, 1 H, *J* = 2.2, NCHC*H*C≡C), 0.73–0.68 (m, 4 H, Si*C*H$_2$*C*H$_2$Si), 0.09 (br s, 12 H, Si(CH_3)$_2$), 0.05 (s, 9 H, Si(CH_3)$_3$). ^{13}C NMR ($CDCl_3$): trans, δ 170.08 (C=O), 102.74 *C*≡CSiMe$_3$), 91.40 (C≡*C*SiMe$_3$), 72.53 (N*C*HCHC≡C), 50.07 (NCH*C*HC≡C), 5.42 (Si*C*H$_2$*C*H$_2$Si), 0.50, −0.10 (Si(CH_3)$_2$), −0.29 (Si(CH_3)$_3$). Attempts to obtain solid material by recrystallization invariably resulted in partial hydrolysis of the protecting disilyl moiety. Complete deprotection of **9g** gave pure **10g** as an off-white solid (vide infra).

General Procedure for the Deprotection of 3-(2,2,5,5-Tetramethyl-1-aza-2,5-disilacyclopentyl)-2-azetidinones. The 2-azetidinones **9** can be easily deprotected by acid-catalyzed hydrolysis in MeOH. However, in order to isolate the pure 2-azetidinones **10**, a rather tedious chromatographically separation is necessary to remove the 1,2-bis(methoxydimethylsilyl)ethane that is formed. A more convenient procedure is as follows: 10 mmol of a protected 2-azetidinone **9** is dissolved in 50 mL of Et_2O. To this solution is added 20 mL of a 1.0 M solution of HCl in water. This two-layer system is well-stirred for 1 h, and then the etheral layer is separated and the water layer is extracted with another 10 mL of Et_2O. The water layer is then brought to pH ≈ 8 with a 1.0 M solution of KOH in water and extracted with three portions of CH_2Cl_2. After drying with Na_2SO_4 the CH_2Cl_2 layer is concentrated in vacuo to afford the pure 2-azetidinone **10**.

***trans*-1-Benzyl-3-amino-4-methyl-2-azetidinone (10a).** Pale yellow oil, 1.79 g (94%). The ^{1}H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 9:91). ^{1}H NMR ($CDCl_3$): trans, δ 7.26 (m, 5 H, ArH), 4.54 (d, 1 H, *J* = 15.2, C*H*$_a$H$_b$Ph), 4.05 (d, 1 H, *J* = 15.2, CH$_a$*H*$_b$Ph), 3.63 (d, 1 H, *J* = 1.9, NC*H*CHCH$_3$), 3.23 (dq, 1 H, *J* = 1.9 and 6.2, NCHC*H*CH$_3$), 1.59 (br s, 2 H, NH$_2$), 1.18 (d, 3 H, NCHCHC*H*$_3$).

***trans*-1-Methyl-3-amino-4-phenyl-2-azetidinone (10b).** Colorless oil, 1.60 g (91%). The ^{1}H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 8:92). ^{1}H NMR ($CDCl_3$): trans, δ 7.31 (m, 5 H, ArH), 4.19 (d, 1 H, *J* = 1.8, NC*H*CHPh), 3.91 (m, 1 H, NCHC*H*Ph), 2.76 (br s, 3 H, NCH$_3$), 1.91 (br s, 2 H, NH$_2$); cis, δ 4.75 (d, 1 H, *J* = 4.9, NC*H*CHPh), 4.47 (d, 1 H, *J* = 5.2, NCHC*H*Ph), 2.83 (s, 3 H, NCH$_3$). ^{13}C NMR ($CDCl_3$): trans, δ 170.33 (C=O), 136.59, 128.67, 128.16, 125.89 (ArC), 70.23 (NCHCHPh), 67.28 (NCH*C*HPh), 26.53 (NCH$_3$); cis, δ 64.60 (N*C*HCHPh), 63.60 (NCH*C*HPh). The pure trans isomer was obtained in 91% yield as a colorless solid when started from pure *trans*-**9b**, mp 51.5 °C. Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 66.66; H, 7.04; N, 15.47.[34]

***trans*-3-Amino-4-phenyl-2-azetidinone (10e).** Pale yellow solid, 1.20 g (75%). The ^{1}H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 14:86). ^{1}H NMR ($CDCl_3$): trans, δ 7.36 (m, 5 H, ArH), 6.51 (br s, 1 H, NH), 4.37 (d, 1 H, *J* = 2.1, NC*H*CHPh), 3.94 (d, 1 H, *J* = 2.1, NCHC*H*Ph), 1.25 (br s, 2 H, NH$_2$); cis, δ 4.89 (d, 1 H, *J* = 5.2, NC*H*CHPh), 4.50 (d, 1 H, *J* = 5.2, NCHC*H*Ph). ^{13}C NMR ($CDCl_3$): trans, δ 171.69 (C=O), 138.97, 128.84, 128.27, 125.54 (ArC), 71.12 (N*C*HCHPh), 62.76 (NCH*C*HPh). The diastereomers could not be separated by crystallization or chromatography.

***trans*-3-Amino-4-[(trimethylsilyl)ethynyl]-2-azetidinone (10g).** Because of the suspected sensitivity of the acetylenic group toward strong acidic media, deprotection of **9g** was accomplished by stirring overnight in THF/H_2O (2:1 v/v). The water layer was extracted with two portions of CH_2Cl_2, and the combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo to afford crude **10g** as a pale brown solid. The product was purified by washing with two small portions of cold (−30 °C) Et_2O and after drying in vacuo 1.37 g (75%) of pure **10g** was obtained as an off-white solid, mp 122 °C. ^{1}H NMR ($CDCl_3$): trans, δ 6.62 (br s, 1 H, NH), 4.23 (d, 1 H, *J* = 2.2, NC*H*CHC≡C), 3.92 (d, 1 H, *J* = 2.2, NCHC*H*C≡C), 1.97 (br s, 2 H, NH$_2$), 0.15 (s, 9 H, Si(CH_3)$_3$). ^{13}C NMR ($CDCl_3$): 170.33 (C=O), 102.04 (*C*≡CSiMe$_3$), 91.47 (C≡*C*SiMe$_3$), 70.25 (N*C*HCHC≡C), 49.74 (NCH*C*HC≡C), −0.27 (Si(CH_3)$_3$). Anal. Calcd for $C_8H_{14}N_2OSi$: C, 52.71; H, 7.74; N, 15.37. Found: C, 50.91; H, 7.84; N, 14.36.[34]

Synthesis of *erythro*-*N*,*N*-Dimethyl-3-(phenylamino)-phenylalanine *tert*-Butyl Ester (11). To a stirred solution containing 20 mmol of LDA in 50 mL of a 4:1 mixture of benzene and Et_2O was added 20 mmol (3.18 g) of *N*,*N*-dimethylglycine *tert*-butyl ester at 0 °C. The resulting white suspension was stirred for 30 min at room temperature. Then 20 mmol of $ZnCl_2$ (20.0 mL of a 1.0 M solution in Et_2O) was added, and after the mixture was stirred for 30 min 20 mmol (3.62 g) of *N*-benzylidene-*N*-phenylamine was added. The resulting pale yellow suspension was stirred for 4 days at 40 °C and then quenched with 25 mL of a saturated aqueous NH_4Cl solution. The precipitated salts were filtered off through a sintered-glass fritt. The aqueous layer was separated and extracted twice with 50 mL of Et_2O. The combined extracts were dried over Na_2SO_4 and concentrated in vacuo, affording 6.81 g of a pale yellow oil, which solidified upon standing. The ^{1}H NMR spectrum revealed that the product was a mixture of imine **7h**, 2-azetidinone **8m**, and **11** (erythro:threo = 90:10) in a ratio of 10:10:90. Recrystallization from hot hexane afforded 5.44 g (80%) of the pure erythro isomer as an off-white solid. ^{1}H NMR ($CDCl_3$): erythro, δ 7.39–7.05 (m, 7 H, ArH), 6.67–6.51 (m, 3 H, ArH), 5.28 (br s, 1 H, NH), 4.67 (br d, 1 H, *J* = 5.7, NC*H*(COO*t*-Bu)CHPh), 3.11 (d, 1 H, *J* = 5.7, NCH-(COO*t*-Bu)C*H*Ph), 2.35 (s, 6 H, N(CH_3)$_2$), 1.23 (s, 9 H, C(CH_3)$_3$); threo, δ 7.39–7.05 (m, 7 H, ArH), 6.67–6.51 (m, 3 H, ArH), 5.28 (br s, 1 H, NH), 4.47 (d, 1 H, *J* = 11.7, NC*H*(COO*t*-Bu)CHPh), 3.24 (d, 1 H, *J* = 11.7, NCH(COO*t*-Bu)C*H*Ph), 2.42 (s, 6 H, N(CH_3)$_2$), 1.29 (s, 9 H, C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$): erythro, δ 170.21 (C=O), 147.20, 139.56, 128.96, 128.32, 127.25, 127.03, 116.98, 113.04 (ArC), 82.47 (*C*(CH_3)$_3$), 74.91 (N*C*H(COO*t*-Bu)-CHPh), 57.10 (NCH(COO*t*-Bu)*C*HPh), 43.11 (N(CH_3)$_2$), 27.69 (C(*C*H$_3$)$_3$); threo, δ 168.13 (C=O), 150.67, 145.16, 128.91, 128.54, 127.93, 127.35, 117.64, 114.05 (ArC), 83.21 (*C*(CH_3)$_3$), 75.65 (N*C*H(COO*t*-Bu)CHPh), 58.34 (NCH(COO*t*-Bu)*C*HPh), 41.04 (N(CH_3)$_2$), 28.16 (C(*C*H$_3$)$_3$).

Acknowledgment. The research presented in this paper has been financially supported by Gist-brocades nv., The Netherlands. Dr J. Verwey of Gist-brocades n.v. is kindly acknowledged for his suggestions and stimulating discussions.

Supplementary Material Available: ^{1}H NMR spectra of the compounds **8b,h,j,n**, **9a–c,e**, **10a,b,e,g**, and **11** (13 pages). Ordering information is given on any current masthead page.

(34) (a) The values of the elemental analyses indicate that the 3-amino-2-azetidinones **10** most likely contain complexed water. An X-ray structure determination of pure crystalline 3-amino-2-azetidinone **10b** revealed that both the 3-amino hydrogens and the amido oxygen are involved in a strong three-dimensional network of hydrogen bonds.[34b] Therefore it is plausible that the compound is rather hygroscopic and incorporation of water is likely to occur upon standing in air. (b) van der Steen, F. H.; Spek, A. L.; van Koten, G. *Acta Crystallogr. C*, in press.