Stereoselective Synthesis of *cis*- and *trans*-β-Lactams via α-Amino Ester Enolates and 1-Aza-4-hetero-1,3-butadiene Systems. Molecular Structure of $EtOC(O)C(H)(NEt_2)C(H)(\overline{N(H)\text{-}t\text{-}Bu)C(H)=N(t\text{-}Bu)}ZnCl_2$: An Unexpectedly Isolated Aldolate

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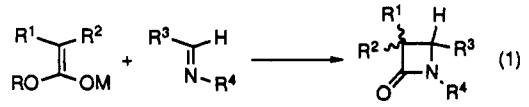
Lithium and zinc enolates of N,N-diprotected glycine esters 1 react with 1-aza-4-hetero-1,3-butadiene systems 4 selectively affording *cis*- and *trans*-3-amino-4-functionalized-2-azetidinones in excellent yields, respectively. The reactions with 1,4-diaza-1,3-butadiene systems are far more selective (de ≥90%) than those with 1-aza-4-oxo- and 1-aza-4-thio-1,3-butadiene systems (de 0–85%). In apolar solvents some of the reactions between the zinc enolates 2 and functionalized imines 4 partly stop at the stage of the C–C coupled product, probably because the metal center migrates to a chelating position between the nitrogen and the hetero atom of the imine. Consequently, elimination of the metal alkoxide and ring closure to a 2-azetidinone product is not likely to occur anymore. This view is supported by the isolation and structural characterization of a $ZnCl_2$ complex of a C–C coupled product, erythro-$EtOC(O)C(H)(NEt_2)C(H)(\overline{N(H)\text{-}t\text{-}Bu)C(H)=N(t\text{-}Bu)}ZnCl_2$ (8), which furthermore demonstrates that erythro C–C bond formation leads to a *trans*-2-azetidinone product. In polar solvents the migration of the metal center is prevented and exclusively 2-azetidinone products are isolated.

Introduction

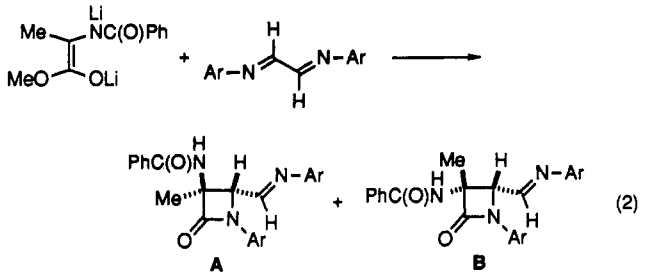
Functionalized monocyclic 2-azetidinones are an important class of compounds because of their use in the synthesis of β-lactam antibiotics.[1] During the last decade, the condensation of ester enolates with imines has become one of the major routes to mono- and bicyclic β-lactam systems (eq 1).[2]



(1)

In previous papers, we have reported about the diastereoselective synthesis of *trans*-3-amino-2-azetidinones by condensation of in situ prepared zinc enolates of N,N-disubstituted glycine esters with simple imine systems.[3] Furthermore, we and others have shown that lithium enolates of N,N-disubstituted glycine esters react with activated imines, i.e., N-substituted with an electron-withdrawing group, to selectively afford *cis*-3-amino-2-azetidinones.[3e,4] We next shifted our attention to functionalized imine systems like, for instance, N,N′-disubstituted α-diimines, which would give access to 3-amino-4-imino-2-azetidinones. By hydrolysis of the 4-imino group, an aldehyde function may be obtained. The synthesis of substituted 4-imino-2-azetidinones is of particular interest, since substituted 3-amino-4-formyl-2-azetidinones have proven to be versatile synthons for the synthesis of both monobactam and isocepham antibiotics.[5]

Alcaide et al. have described the condensation of some lithium ester enolates with *N,N′*-diaryl-α-diimines.[6] Only a few combinations of lithium ester enolates and *N,N′*-diaryl-α-diimines gave the desired 4-imino-2-azetidinones in good yields. The reaction of the dilithium enediolate of methyl 2-(benzoylamino)propionate with *N,N′*-di(*p*-methoxyphenyl)-1,4-diaza-1,3-butadiene appeared to be nonstereoselective, affording a 55:45 mixture of 3-amino-2-azetidinones A and B, respectively (eq 2).



(2)

In this paper, we report the full details of our findings concerning the highly stereoselective reactions of zinc and lithium α-amino ester enolates with 1-aza-4-hetero-1,3-butadiene systems that afford functionalized *trans*- and *cis*-2-azetidinones, respectively, in high yields. A few of the results presented in this paper have been published in a preliminary paper.[3d]

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Table I. Synthesis of *trans*-3-((Protected)amino)-2-azetidinones 5[a]

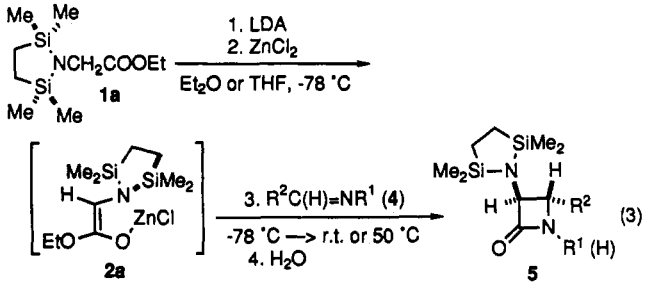
entry	imine	R^1	R^2	product, yield[b] (%)	cis:trans ratio[c]
1	**4a**	*t*-Bu	C(H)=N-*t*-Bu	**5a**, 94 (92)	⟨1:⟩99[d]
2	**4b**	*t*-Bu	2-pyridyl	**5b**, 88 (99)	⟨1:⟩99[d]
3	**4c**	$SiMe_3$/H[e]	2-pyridyl	**5c**, 82 (96)	⟨1:⟩99[d]
4	**4d**	*t*-Bu	2-thienyl	**5d**, 0	
5[f]	**4e**	$SiMe_3$/H[e]	2-thienyl	**5e**, 87 (97)	15 (50):85 (50)
6	**4f**	$SiMe_3$	2-furyl	**5f**, 92 (93)	8 (35):92 (65)
7	**4g**	*t*-Bu	C(Me)=O	**5g**, 0	
8	**4h**	*t*-Bu	C(OMe)=O	**5h**, 0	

[a] Reactions performed in Et_2O; yields and product ratios given in parentheses are for reactions performed in THF. [b] Yields of the isolated crude products. [c] Determined by ^1H NMR integration of the characteristic proton signals of the crude products. [d] Cis isomer not detected with ^1H NMR spectroscopy. [e] Upon hydrolysis replaced by a proton. [f] Reaction performed with the $ZnCl_2$ complex of 4e; uncomplexed 4e resulted in a lower stereoselectivity (cis:trans = 30:70).

Results

Synthesis of *trans*-1-(Un)substituted-3-amino-4-functionalized-2-azetidinones. In order to obtain 3-amino-4-functionalized-2-azetidinones of pharmaceutical interest, the primarily objectives should be focused on products containing an easily accessible free amino function (NH_2) at the 3-position. In previous papers, we have reported the successful application of 1,2-bis(dimethylsilyl)ethane as a protective group of the amino function.[3b,d,e]

Reactions of the in situ prepared zinc enolate **2a** of 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane-1-acetic acid ethyl ester (**1a**) with several functionalized imines **4** (eq 3) afforded *trans*-2-azetidinones **5** in excellent yields as shown in Table I. When the reactions are carried out



(3)

in THF the yields are generally higher than in Et_2O because in THF the reaction mixture remains homogeneous, whereas in Et_2O solid material, presumably consisting of insoluble complexes of the imine substrates with the inorganic salts present in solution,[7] is deposited during the reaction. The reactions of zinc enolate **2a** with imines **4a–c** containing a nitrogen donor functionality afford exclusively *trans*-2-azetidinones **5a–c**, irrespective of the solvent in which the reactions are performed. The reactions with imines **4e** and **4f** containing either an oxygen or a sulfur donor functionality display a better stereoselectivity in Et_2O than in THF, as has previously been observed for reactions of α-amino zinc ester enolates with simple imines.[3c,e] The remarkable difference between imines **4a–c** containing a nitrogen donor functionality and imines **4d–f** containing an oxygen or sulfur donor functionality is also clear from the fact that imine **4d**, containing a tertiary butyl group on the imino nitrogen, does not react with zinc enolate **2a** (entry 4), whereas imines **4a** and **4b** afford

Table II. Synthesis of *cis*-3-((Protected)amino)-2-azetidinones 5

entry	imine	R^1	R^2	product, yield[a] (%)	cis:trans ratio[b]
1	**4a**	*t*-Bu	C(H)=N-*t*-Bu	**5a**, <10	⟨5:⟩95[c]
2	**4b**	*t*-Bu	2-pyridyl	**5b**, 0	
3	**4c**	$SiMe_3$/H[d]	2-pyridyl	**5c**, 92	91:9
4	**4e**	$SiMe_3$/H[d]	2-thienyl	**5e**, 99	94:6
5	**4f**	$SiMe_3$/H[d]	2-furyl	**5f**, 95	97:3

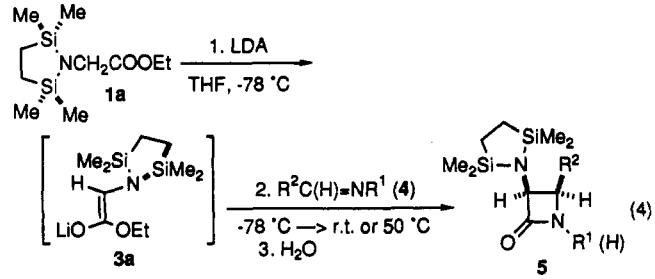
[a] Yields of the isolated crude products. [b] Determined by ^1H NMR integration of the characteristic proton signals of the crude products. [c] Cis isomer not detected with ^1H NMR spectroscopy. [d] Upon hydrolysis replaced by a proton.

trans-2-azetidinones **5a** and **5b**, respectively, in high yields. The synthesis of **5a** is of particular interest, since deprotection of the 3-amino group and transformation of the 4-imino group into an aldehyde function by acid-catalyzed hydrolysis affords 1-*tert*-butyl-3-amino-4-formyl-2-azetidinone (**5a′**), a versatile synthon for several monobactam and penem antibiotics.

Unfortunately, attempts to get direct access to a carbonyl function at the 4-position of the 2-azetidinone ring failed. The reaction of zinc enolate **2a** with α-imino ketone **4g** afforded only polymerization products of **4g**, and with α-imino ester **4h** only starting materials were recovered. Especially the lack of reactivity of the α-imino ester **4h** is quite surprising, since the reaction of Et_2Zn with **4h**, proceeding via an intermediate zinc enolate, affords *trans*-1-*tert*-butyl-3-(*N*-*tert*-butyl-*N*-ethylamino)-4-(methoxycarbonyl)-2-azetidinone in quantitative yields.[8]

Synthesis of *cis*-1-(Un)substituted-3-amino-4-functionalized-2-azetidinones. As we have reported in the preceding paper,[3e] and has also previously been reported by Overman et al.,[4a] Hart et al.,[4b] and Cainelli et al.,[4c,d] the lithium enolate **3a** of 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane-1-acetic acid ethyl ester reacts with activated imines, e.g., N-substituted with an aryl or silyl group, to afford predominantly *cis*-2-azetidinones in reasonable to good yields.

Reactions of the lithium enolate **3a** with 1-trimethylsilyl-substituted 1-aza-4-hetero-1,3-butadienes in THF (eq 4) afforded *cis*-2-azetidinones **5** in high yields as shown Table II. As expected, the lithium enolate **3a** did show



(4)

a poor reactivity toward the unactivated, *N*-alkyl-substituted imines **4a** and **4b** (entries 1 and 2); only with **4a** a small amount of *trans*-2-azetidinone **5a** was observed in the ^1H NMR spectrum of the crude isolated material. However, with activated imines **4c–f** a smooth and highly selective reaction to *cis*-2-azetidinones **5c–f** was observed. Cianelli et al. also have described the synthesis of the 2-thienyl (**5e**) and 2-furyl (**5f**) substituted cis compounds via the reaction of the lithium enolate **3a**; however, in their case the 2-azetidinones were isolated in low yields (35–40%).[9]

(7) After workup no imines or aldehydes are found in the isolated material, and we know that, for example, the $ZnCl_2$ complexes of *N,N′*-di-*tert*-butyl-1,4-diaza-1,3-butadiene and 2,2′-dipyridyl are insoluble in diethyl ether.

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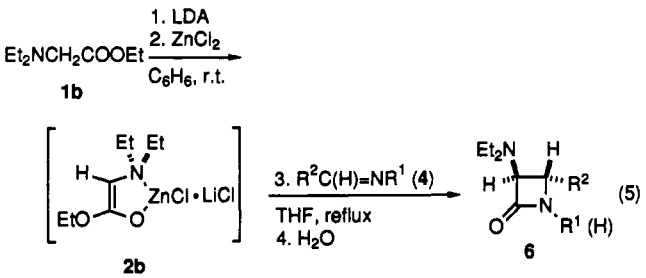
Table III. Synthesis of *trans*-3-(Diethylamino)-2-azetidinones 6[a]

entry	imine	R^1	R^2	product, yield[b] (%)	cis:trans ratio[c]
1	**4a**	*t*-Bu	C(H)=N-*t*-Bu	**6a**, 93 (92)	15 (8):85 (92)
2	**4b**	*t*-Bu	2-pyridyl	**6b**, 84	(1:)99[d]
3	**4d**	*t*-Bu	2-thienyl	**6d**, 0	
4[f]	**4e**	$SiMe_3/H^e$	2-thienyl	**6e**, 92 (87)	11 (6):89 (94)
5	**4f**	$SiMe_3/H^e$	2-furyl	**6f**, 98 (96)	27 (23):73 (77)
6	**4g**	*t*-Bu	C(Me)=O	**6g**, 0	
7	**4h**	*t*-Bu	C(OMe)=O	**6h**, 0	

[a] Reactions performed in THF; yields and product ratios given in parentheses are for reactions partially performed in benzene (see text and Scheme I). [b] Yields of the isolated crude products. [c] Determined by ^1H NMR integration of the characteristic proton signals of the crude products. [d] Cis isomer not detected with ^1H NMR spectroscopy. [e] Upon hydrolysis replaced by a proton. [f] Reaction performed with the $ZnCl_2$ complex of 4e.

Synthesis of *trans*-1-(Un)substituted-3-(diethylamino)-4-functionalized-2-azetidinones. Because we wanted to compare the stereoselectivity of the reactions of α-amino zinc ester enolates with 1-aza-4-hetero-1,3-butadienes performed under kinetic (as in the previous sections with zinc enolate **2a**) and under thermodynamic control, we have examined the reactions of the zinc enolate (**2b**) of *N,N*-diethylglycine ethyl ester (**1b**) with several functionalized imines **4**. These reactions are far slower and have to be carried out at 60–80 °C, i.e., under thermodynamic control (eq 5).[3e] The results are summarized in Table III.



The reactions of zinc enolate **2b** with the functionalized imines **4** in benzene did not afford the desired 2-azetidinones **6** alone, but also (minor) amounts of noncyclized aldolates **7** (vide infra). However, when the reactions were either carried out directly in THF or when benzene was replaced by THF after the C–C bond formation was completed exclusive formation of 2-azetidinones **6** in excellent yields was observed.

At first glance there are some similarities between the reactions which are carried out under kinetic (i.e., with zinc enolate **2a**) and thermodynamic control (i.e., with zinc enolate **2b**). For both **2a** and **2b** reactions with imines **4d**, **4g**, and **4h** resulted either in polymerization, as in the case of imine **4g**, or recovery of starting materials. However, there are also some marked differences. While the reactions of zinc enolate **2a** with imines **4** did show a strong influence of the donor atoms present in the functional groups of the imines on the diastereoselectivity of these reactions (vide supra), such effects are smaller in the reactions of zinc enolate **2b** with imines **4**; diastereomeric excesses ranging from 46% for 2-furyl- (entry 5) to 98% for 2-pyridyl-substituted imine (entry 2). Furthermore, only a minor solvent effect was observed for the reaction of zinc enolate **2b** with imines **4a**, **4e**, and **4f** (entries 1, 4, and 5). When these reactions are initially carried out in benzene, which is then replaced by THF, a slightly better trans stereoselectivity is observed than when these reactions are carried out in THF alone. The reactions of imines **4e** and **4f** with zinc enolate **2b** are more stereoselective than the same reactions with zinc enolate **2a** in THF, indicating that the reaction conditions, i.e., kinetic vs thermodynamic control, indeed do have a strong influence on the stereochemical course of the reactions (see Discussion).

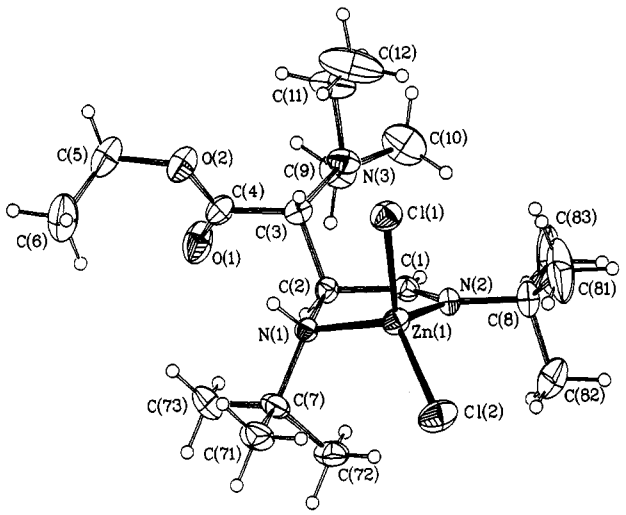


Figure 1. An ORTEP drawing (30% probability level), together with the adopted numbering scheme, of the molecular structure of $EtOC(O)C(H)(NEt_2)C(H)(\overline{N(H)\text{-}t\text{-}Bu})C(H)=N(t\text{-}Bu)ZnCl_2$ (**8**).

Synthesis and X-ray Structure of the Zinc Dichloride Complex of (μ,μ″)*N*-*tert*-Butyl-2-(*N*′,*N*′-diethylamino)-3-(*N*″-*tert*-butylimino)-α-alanine Ethyl Ester (8). As noted in the preceding section, the reaction of zinc enolate **2b** with imine **4a** in benzene, followed by aqueous workup, afforded minor amounts of side products. Apart from the expected *cis*- and *trans*-2-azetidinones **6a** (70% yield), two more products were isolated (30% yield), which we assumed to be the noncyclized erythro and threo aldolates (erythro:threo ratio = 92:8) on basis of NMR data. Interestingly, elemental analysis showed that the latter aldolates contain $ZnCl_2$, which apparently is very strongly coordinated, since it remains attached to the product even in the presence of large amounts of water. Upon addition of Et_2O the aldolate complexes crystallized out. Recrystallization from benzene afforded the pure erythro isomer as colorless crystals. Because we were interested in the mode of complexation of $ZnCl_2$ to the aldolate and, furthermore, wanted to confirm the assignment of the erythro configuration we carried out an X-ray structure determination. An ORTEP drawing showing the molecular structure of the zinc dichloride complex of erythro-(μ,μ″)*N*-*tert*-butyl-2-(*N*′,*N*′-diethylamino)-3-(*N*″-*tert*-butylimino)-α-alanine ethyl ester (**8**) is given in Figure 1.

Crystals of **8** are monoclinic. The unit cell contains four monomeric molecules, which form dimers through hydrogen bridges (Cl(1)···H(1) = 2.60 (3) Å) over an inversion center. The zinc dichloride molecule is N,N′-chelate bound to the organic molecule through two (strong) dative bonds with the nitrogen atoms of the former α-diimine molecule. A rationale for the formation of the complex **8** is given in the discussion. The zinc atom is four-coordinated, with

(9) Most likely, these low yields are caused by the fact that they used in situ prepared imines **4e** and **4f**, prepared from the nitrile compounds by reduction with $Li(i\text{-}Bu)_2BuAlH$ or $Na(MeOCH_2CH_2)_2AlH_2$ and subsequent transmetalation with 2 equiv of Me_3SiCl.[4d] We have obtained far better yields of 2-azetidinones **5e** and **5f** because we used the pure imines **4e** and **4f**, prepared according to a literature procedure by Hart et al.[4b]

Table IV. Geometrical Data of the Zinc Atoms in Several $ZnCl_2$ Complexes with Organic Fragments Containing Two Nitrogen Donor Atoms

compd	Zn–Cl (Å)	Zn–N (Å)	Cl–Zn–Cl (deg)	N–Zn–N (deg)	ref
8	2.226 (1)	2.119 (3)	117.00 (4)	82.6 (1)	
	2.216 (1)	2.052 (3)			
$Me_2NCH_2CH_2$-NMe_2·$ZnCl_2$	2.213 (4)	2.107 (8)	119.4 (2)	87.9 (4)	10a
	2.204 (4)	2.057 (9)			
$Et_2NCH_2C(H)$-$(CH_2PPh_3)NEt_2$·$ZnCl_2$	2.2354 (5)	2.143 (1)	117.08 (2)	88.01 (5)	10b
	2.2090 (5)	2.111 (1)			
2,2′-Bipyridyl·$ZnCl_2$	2.210 (1)	2.064 (2)	117.1 (1)	80.3 (1)	10c
	2.198 (1)	2.053 (2)			
Bispyridine·$ZnCl_2$	2.228 (2)	2.052 (6)	120.9 (1)	106.3 (2)	10d
	2.215 (2)	2.046 (5)			

a distorted tetrahedral geometry as observed in other $ZnCl_2$ complexes with two nitrogen donors (see Table IV). The Zn–Cl and Zn–N bond lengths are within the normal range; the zinc–amino nitrogen distance of 2.119 (3) Å being significantly longer than the zinc–imino nitrogen distance of 2.052 (3) Å. The large Cl–Zn–Cl angle found in the $ZnCl_2$ complexes is the result of minimization of the electrostatic repulsions between the two chlorine atoms.[10]

The bond lengths and angles of the organic fragment are all within the normal range, except for those of the imino-*tert*-butyl group (C(8), C(81), C(82), and C(83)). These atoms have large thermal parameters indicative of a slight disorder as is often observed in other structures containing an imino-*tert*-butyl group.[11]

The structure determination confirms the expected erythro configuration around the C(2)–C(3) bond. Ring closure between N(1) and C(4) in **8** would produce *trans*-2-azetidinone **6a**, showing that erythro C–C bond formation eventually leads to *trans*-2-azetidinones. As can been seen in the structure, the ethoxy group is well-positioned for elimination of EtOZnCl provided that the chlorozinc fragment is located in the position of H(11), which is the case in the precursor complex **7** (see Discussion). However, the strong chelating coordination between N(1) and N(2) in **8** prevents the elimination of EtOZnCl.

The yield of **8** can be improved to 70% when zinc enolate **2b** is reacted with the preformed $ZnCl_2$ complex of *t*-Bu-DAB **4a**. Precomplexation of **4a** to $ZnCl_2$ has only a minor effect on the stereoselectivity of the reaction; the ratio of erythro/threo changes from 92:8 for the reaction with uncomplexed **4a** to 83:17 with precomplexed **4a**.

Discussion

Stereochemical Aspects. Recently, we have proposed two transition states that explain the observed trans stereoselectivity for the reactions of α-amino zinc ester enolates with simple imines.[3e] Because the imines used in the present study contain a second donor atom (i.e., N, O, or S) these imines may be either monodentate (as in C) or bidentate (as in D) bound to the metal center in the transition state (see Figure 2).

We have shown that zinc enolates are associated through strong Zn–O coordination bonds (as in C).[12] For bidentate

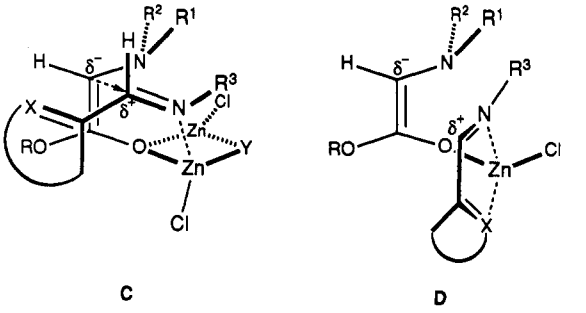


Figure 2. Schematic representations of two possible coordination modes of 1-aza-4-hetero-1,3-butadiene systems to α-amino zinc ester enolates (C, monodentate; D, bidentate).

bonding of the imine substrate to zinc, these Zn–O bonds must be cleaved to give monomeric species (as in D), and in our opinion this is not very probable. Furthermore, if the imine is bidentate bound to the zinc center, it is not in a good position for intramolecular C–C bond formation with the enolate anion (see D in Figure 2). Therefore, we assume that the transition states proposed for reactions with simple imines in previous papers are also valid for the reactions given in this paper,[3c,e] i.e., the introduction of a second donor atom in the imines does not result in a marked change of the geometries of the transition states.

The difference in reactivity and stereoselectivity between imines **4a–c** (containing a N-donor atom) and **4d–f** (containing an O- or S-donor atom) may well be the result of the fact that 1,4-diaza-1,3-butadiene systems possess a nearly planar ligand skeleton, both in the free ligand and in its metal complexes,[13] where it can be bound in either the *E-cis-E* bidentate or in the *E-trans-E* monodentate (as in C) or bridging bonding mode. This planarity of 1,4-diaza-1,3-butadiene systems has two effects: (i) a steric effect that causes an extra restriction of the conformation of the transition state(s), which results in a very high trans stereoselectivity of the 2-azetidinone formation, and (ii) an electronic effect; the planarity of the skeleton allows maximal resonance stabilization, which results in a higher electron density on the nitrogen atoms of the 1,4-diaza-1,3-butadiene systems and hence a better coordination to the zinc atom of the enolate and a lower energy of activation for the C–C bond formation. 1-Aza-4-oxo-1,3-butadiene systems exist in the nonplanar gauche conformation,[14] and although MNDO and AM1 calculations show that *C*-(2-thienyl)imines prefer planar arrangements as a result of π-conjugation (as is observed in the solid-state structures),[15] the energy barrier for rotation around the central C–C bond is lower than in the 1,4-diaza-1,3-butadiene systems.[16] Therefore, the *C*-(2-furyl)- and *C*-(2-

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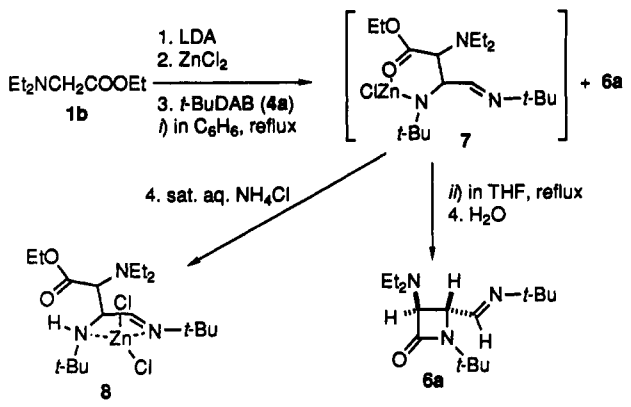
Scheme I



thienyl)imines show a similar behavior as the *C*-phenylimines, i.e., the presence of a hetero functionality in imines **4e–f** does not result in a more restricted conformation of the transition states and likewise, a comparable stereoselectivity as for reactions of zinc enolate **2a** with *N*-benzylidene-*N*-(trimethylsilyl)amine is observed.[3e] This is supported by the fact that the reaction of zinc enolate **2a** with the $ZnCl_2$ complex of **4e**, resulting in a more restricted conformation of the transition state,[17] displays a better stereoselectivity than the reaction with the free imine **4e** (entry 5, Table I).

The reason for the poor reactivity of imines **4d**, **4g**, and **4h** with respect to C–C bond formation may well be that the combination of a nonplanar gauche conformation of these 1-aza-4-hetero-1,3-butadiene systems and the large tertiary butyl group on the imino nitrogen prevents coordination to the zinc atoms and consequently no reaction with zinc enolates **2** is observed (note: PhC(H)=N-*t*-Bu does not react with zinc enolates **2** either[3e]). The use of a more activating substituent on the imino nitrogen, e.g., aryl or silyl, should result in a higher reactivity of these systems and would give direct access to 3-amino-4-carbonyl-substituted-2-azetidinones.[18]

The fact that reactions of lithium enolate **3a** with functionalized *N*-(trimethylsilyl)imines **4** result in the almost exclusive formation of *cis*-2-azetidinones **5** (de 82–94%) is the result of a different configuration of the active enolate species; i.e., for zinc enolate **2a** the *Z* isomer is the reactive species,[3e,12b] whereas the lithium enolate **3a** has exclusively the *E* configuration and thus the *E* isomer is the reactive species.[3e,12b] Consequently, the transition states for the reactions involving the lithium enolate **3a** are constructed of an *E* enolate and an *E* imine. The energy difference between these two possible transition states (one with a chair-like and one with a boat-like conformation) is higher for *E* enolates,[19] and therefore a high cis stereoselectivity is observed.

Formation of the Coordination Complex 8. A rationale for the formation of the $ZnCl_2$ complex of (μ,μ'')-*N*-*tert*-butyl-2-(*N'*,*N'*-diethylamino)-3-(*N''*-*tert*-butylimino)-α-alanine ethyl ester (**8**) is outlined in Scheme I. The first step of the proposed mechanism is the usual C–C bond formation between zinc enolate **2b** and α-diimine **4a**, giving an aldolate **7** that may react in two possible ways. The first is the usually observed elimination of EtOZnCl, accompanied by a ring closure of the organic fragment to give 2-azetidinone **6a**. The second is the migration of the zinc atom in the aldolate **7** to form a strong chelating coordination between the amido nitrogen and imino nitrogen of the former α-diimine molecule. After aqueous workup with saturated NH_4Cl the $ZnCl_2$ complex **8** is formed.

The organic part of the aldolate **7** contains two oxygen and three nitrogen donor atoms that are all suitable for coordination to the zinc atom. Since in **7** the zinc atom is attached to the amido-nitrogen atom (N(1) in the crystal structure of **8**, see Figure 1), the formation of four different chelate rings can be anticipated; two six-membered rings with either the carbonyl- or the ethoxy-oxygen atom,[20] and two five-membered rings with either the amino- (N(3)) or the imino-nitrogen atom (N(2)). Of these coordination modes the two latter ones are more likely, since formation of five-membered rings are energetically more favorable than of six-membered rings. Finally, the formation of a five-membered chelate ring with the imino-nitrogen atom (N(2)) is preferred for two reasons: (i) coordination to the amino-nitrogen (N(3)) would result in an unfavorable eclipsed conformation of the C(2)–C(3) bond and (ii) coordination to a sp^3-hybridized nitrogen atom (N(3)) is weaker than to a sp^2-hybridized nitrogen atom (N(2)), because of the greater s-character in the latter.

The migration of the zinc atom to the imino nitrogen in the aldolate **7** can be prevented by carrying out the reaction in a (strong) donating solvent like for instance THF or pyridine. When the reaction is performed in THF, 2-azetidinone **6a** is formed in 93% yield (cis:trans ratio = 15:85) as a single product. When the first step of the reaction, i.e., C–C bond formation, is performed in benzene and the subsequent ring-closure reaction in THF, a similar result is obtained (92% yield; cis:trans ratio = 8:92).

Concluding Remarks

With our method both *cis*- and *trans*-3-amino-4-functionalized-2-azetidinones **5** are selectively accessible via the reactions of respectively lithium and zinc enolates of 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane-1-acetic acid ethyl ester **1a** with 1-aza-4-hetero-1,3-butadienes **4**.

When the functional group of imines **4** contains a nitrogen donor atom, usually a better stereoselectivity (de >95%) is obtained than when it contains an oxygen or sulfur donor atom (de 0–85%). This is most likely the result of a more restricted conformation of the transition states in the case of 1,4-diaza-1,3-butadiene systems, whereas in the case of the 1-aza-4-oxo- and 1-aza-4-thio-1,3-butadiene systems no further restrictions are imposed, in comparison with the previously postulated transition states in the case of simple imines.[3e]

Reactions of the zinc enolate of *N*,*N*-diethylglycine ethyl ester **1b** with 1-aza-4-hetero-1,3-butadiene systems selectively afford *trans*-2-azetidinones **6** (de 46–98%) in excellent yields. These reactions proceed via a two-step mechanism involving C–C bond formation and ring-closure. The isolation of erythro-**8** supports this mechanism, and furthermore the molecular structure of **8** establishes that erythro C–C bond formation results in the formation of *trans*-2-azetidinones.

(17) Because the imine bond is sufficiently activated in the $ZnCl_2$ complex, it may be that in this case the reaction does not proceed via a cyclic rigid transition state ("intramolecular" C–C bond formation) but proceeds via an intermolecular reaction between the zinc enolate and $ZnCl_2$ complex.

(18) Preliminary experiments have shown that zinc enolate **2a** indeed reacts with *N*-aryl-substituted α-imino esters.

(19) (a) *E* Enolates are known to react far more selective than *Z* enolates in aldol-type condensations;[19b] the formation of *trans*-3-amino-2-azetidinones via the *E* enolate is highly unlikely since in the transition-state a large amount of steric-strain would result. (b) See, for example (and references cited therein): 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.

(20) When the zinc atom is coordinated to the ethoxy oxygen, a rapid elimination of EtOZnCl and ring closure to a 2-azetidinone will occur.

Experimental Section

General Data. All manipulations with air-sensitive reagents were carried out under 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. *N,N*-Diethylglycine ethyl ester was prepared via a simple condensation of diethylamine with ethyl bromoacetate. 2,2,5,5-Tetramethyl-1-aza-2,5-disilacyclopentane-1-acetic ethyl ester was prepared according to a literature procedure.[21] Imines 4 were prepared by standard methods.[4b,14c,22] ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 or a Varian EM-360 NMR spectrometer in chloroform-d_1 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.

General Procedure for the (One-Pot) Synthesis of 3-(2,2,5,5-Tetramethyl-1-aza-2,5-disilacyclopentyl)-2-azetidinones (5). To a stirred, cooled (−78 °C) solution containing *i*-Pr_2NH (1.01 g, 10 mmol) in 30 mL of solvent (Et_2O or THF) 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 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane-1-acetic ethyl ester (2.45 g, 10 mmol) 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 the mixture was stirred for 0.5 h 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 up to room temperature or, when neccesary to complete ring closure, boiled under reflux for 1 h 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 50-mL portions of Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to afford the crude 2-azetidinones 5. The contents of these crude products were examined with ^1H NMR before performing any purification step. Whenever possible,[23] the crude products were purified by recrystallization, flash chromatography, or preparative HPLC techniques.

***trans*-1-*tert*-Butyl-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-(*N*-*tert*-butylimino)-2-azetidinone (5a).** Pale yellow solid, isolated yield 3.45 g (94%). The cis isomer was not detected by ^1H NMR spectroscopy. ^1H NMR ($CDCl_3$): trans, δ 7.46 (d, 1 H, *J* = 7.8, *HC*=N-*t*-Bu), 4.00 (d, 1 H, *J* = 1.8, NC*H*CHCH=N), 3.82 (dd, 1 H, *J* = 7.8 and *J* = 1.8, NCH*CH*CH=N), 1.31 (s, 9 H, C=N-*t*-Bu), 1.21 (s, 9 H, N-*t*-Bu), 0.78–0.61 (m, 4 H, SiCH_2CH_2Si), 0.12, 0.09 (s, 6 H, Si(CH_3)$_2$. ^{13}C NMR ($CDCl_3$): trans, δ 168.57 (*C*=O), 158.12 (*C*=N), 66.62 (NCHCHCH=N), 64.44 (NCHCHCH=N), 57.35 (C=N*C*(CH_3)$_3$), 54.13 (N*C*(CH_3)$_3$), 29.34 (C=NC(CH_3)$_3$), 28.62 (NC(CH_3)$_3$, 7.98 SiCH_2CH_2Si), 0.81, 0.15 (Si(CH_3)$_2$). The product was purified by crystallization from Et_2O to afford colorless crystals, mp 99 °C. Anal. Calcd for $C_{18}H_{37}N_3OSi_2$: C, 58.80; H, 10.14; N, 11.43; Si, 15.28. Found: C, 57.43; H, 10.29; N, 11.47; Si, 15.32.

***trans*-1-*tert*-Butyl-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-(2-pyridyl)-2-azetidinone (5b).** Pale yellow solid, isolated yield 3.57 g (99%). The cis isomer was not detected by ^1H NMR spectroscopy. ^1H NMR ($CDCl_3$): trans, δ 8.58 (m, 1 H, pyr-*H*), 7.68 (m, 1 H, pyr-*H*), 7.25 (m, 2 H, pyr-*H*), 4.30 (d, 1 H, *J* = 1.9, NC*H*CH-pyr), 4.13 (m, 1 H, NCHC*H*-pyr), 1.21 (s, 9 H, N-*t*-Bu), 0.78–0.61 (m, 4 H, SiCH_2CH_2Si), 0.09, 0.03 (s, 6 H, Si(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): 169.94 (*C*=O), 159.68, 149.56, 136.57, 122.80, 121.25 (pyr-*C*), 69.91 (NCHCH-pyr), 67.18 (NCH*C*H-pyr), 54.24 (*C*(CH_3)$_3$), 28.27 (C(*C*H_3)$_3$), 8.02 (SiCH_2C-H_2Si), 0.60, 0.29 (Si(*C*H_3)$_2$). Purification by recrystallization from Et_2O afforded colorless crystals, mp 109 °C.[24]

***trans*-3-(2,2,5,5-Tetramethyl-1-aza-2,5-disilacyclopentyl)-4-(2-pyridyl)-2-azetidinone (5c).** Pale yellow solid, isolated yield 2.93 g (96%). The cis isomer was not detected by ^1H NMR spectroscopy. ^1H NMR ($CDCl_3$): trans, δ 8.58 (m, 1 H, pyr-*H*), 7.67 (m, 1 H, pyr-*H*), 7.25 (m, 2 H, pyr-*H*), 6.81 (br s, 1 H, N*H*), 4.46 (d, 1 H, *J* = 2.0, NC*H*CH-pyr), 4.24 (m, 1 H, NCHC*H*-pyr), 0.78–0.68 (m, 4 H, SiCH_2CH_2Si), 0.09, 0.03 (s, 6 H, Si(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): 171.62 (*C*=O), 158.56, 149.60, 136.84, 122.96, 120.44 (pyr-*C*), 72.37 (NCHCH-pyr), 63.58 (NCH*C*H-pyr), 7.95 (SiCH_2CH_2Si), 0.43, 0.32 (Si(*C*H_3)$_2$). The product was purified by crystallization from hexane to afford colorless crystals, mp 102 °C. Anal. Calcd for $C_{14}H_{23}N_3OSi_2$: C, 55.04; H, 7.59; N, 13.75; Si, 18.39. Found: C, 54.80; H, 7.47; N, 14.67; Si, 16.56.

***cis*-3-(2,2,5,5-Tetramethyl-1-aza-2,5-disilacyclopentyl)-4-(2-pyridyl)-2-azetidinone (5c).** The reaction was carried out in THF as described in the general procedure, but without addition of $ZnCl_2$; pale yellow solid, isolated yield 2.81 g (92%). The ^1H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 91:9). ^1H NMR ($CDCl_3$): cis, δ 8.56 (m, 1 H, pyr-*H*), 7.67 (m, 1 H, pyr-*H*), 7.36 (m, 1 H, pyr-*H*), 7.20 (m, 1 H, pyr-*H*), 6.56 (br s, 1 H, N*H*), 4.90 (dd, 1 H, *J* = 5.0 and 1.5, NCHC*H*-pyr), 4.84 (d, 1 H, *J* = 5.0, NC*H*CH-pyr), 0.63–0.44 (m, 4 H, SiCH_2CH_2Si), −0.04, −0.07 (s, 6 H, Si(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): 170.88 (*C*=O), 157.04, 149.08, 135.75, 122.84, 122.78 (pyr-*C*), 68.36 (NCHCH-pyr), 60.62 (NCH*C*H-pyr), 7.97 (SiCH_2CH_2Si), 0.59, −0.06 (Si(*C*H_3)$_2$). The pure cis isomer was obtained as colorless crystals after one crystallization from hexane, mp 98 °C. Anal. Calcd for $C_{14}H_{23}N_3OSi_2$: C, 55.04; H, 7.59; N, 13.75. Found: C, 54.41; H, 7.48; N, 13.91.

***trans*-3-(2,2,5,5-Tetramethyl-1-aza-2,5-disilacyclopentyl)-4-(2-thienyl)-2-azetidinone (5e).** Pale yellow oil, isolated yield 2.70 g (87%). The ^1H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 15:85). ^1H NMR ($CDCl_3$): trans, δ 7.27 (m, 1 H, thienyl-*H*), 7.06–6.94 (m, 2 H, thienyl-*H*), 6.29 (br s, 1 H, N*H*), 4.67 (d, 1 H, *J* = 1.9, NC*H*CH-thienyl), 4.24 (d, 1 H, *J* = 1.9, NCHC*H*-thienyl), 0.78–0.68 (m, 4 H, SiCH_2CH_2Si), 0.09 (s, 6 H, Si(CH_3)$_2$), 0.04 (s, 6 H, Si(CH_3)$_2$). The diastereoisomers could not be separated by crystallization or chromatography.[23]

***cis*-3-(2,2,5,5-Tetramethyl-1-aza-2,5-disilacyclopentyl)-4-(2-thienyl)-2-azetidinone (5e).** Pale yellow solid, isolated yield 2.84 g (99%). The ^1H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 94:6). ^1H NMR ($CDCl_3$): cis, δ 7.30–7.24 (m, 1 H, thienyl-*H*), 7.01–6.95 (m, 2 H, thienyl-*H*), 6.74 (br s, 1 H, N*H*), 4.95 (d, 1 H, *J* = 4.7, NC*H*CH-thienyl), 4.75 (dd, 1 H, *J* = 4.7 and 1.9, NCHC*H*-thienyl), 0.66–0.64 (m, 4 H, SiCH_2CH_2Si), −0.02, −0.03 (s, 6 H, Si(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): cis, δ 170.71 (*C*=O), 140.93, 126.76, 126.54, 126.09 (thienyl-*C*), 68.18 (NCHCH-thienyl), 55.93 (NCH*C*H-thienyl), 8.02 (SiCH_2CH_2Si), 0.48, −0.23 (Si(*C*H_3)$_2$). The pure cis isomer was obtained as colorless crystals after one crystallization from benzene/Et_2O (1:3 v/v), mp 117 °C.[24]

***trans*-1-(Trimethylsilyl)-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-(2-furyl)-2-azetidinone (5f).** Even after aqueous workup, the protecting silyl group at the 1-position is not removed. Purification of this compound did not succeed because always mixtures of 1- and 3-amino-protected and -deprotected compounds were isolated; pale yellow oil, isolated yield 3.37 g (92%). 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 7.69 (m, 1 H, furyl-*H*), 6.34 (m, 1 H, furyl-*H*), 6.27 (m, 1 H, furyl-*H*), 4.46 (d, 1 H, *J* = 2.1, NC*H*CH-furyl), 4.11 (d, 1 H, *J* = 2.1, NCHC*H*-furyl), 0.72–0.66 (m, 4 H, SiCH_2CH_2Si), 0.12 (s, 9 H, Si(CH_3)$_3$), 0.10, 0.04 (s, 6 H, Si(CH_3)$_2$).

***cis*-3-(2,2,5,5-Tetramethyl-1-aza-2,5-disilacyclopentyl)-4-(2-furyl)-2-azetidinone (5f).** The reaction was carried out in THF as described in the general procedure, but without addition of $ZnCl_2$; pale yellow solid, isolated yield 2.72 g (95%). The

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(23) Because the protecting disilyl moiety is very susceptible toward 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 of 2-azetidinones 5.
(24) The data of the elemental analyses of the 2-azetidinone were not satifactory because of partial hydrolysis during sampling.

^{1}H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 97:3). ^{1}H NMR ($CDCl_3$): cis, δ 7.38 (m, 1 H, furyl-H), 6.33 (m, 1 H, furyl-*H*), 6.58 (br s, 1 H, N*H*), 6.29 (m, 1 H, furyl-*H*), 4.76 (dd, 1 H, J = 4.6 and 1.3, NCHC*H*-furyl), 4.69 (d, 1 H, J = 4.6, NC*H*CH-furyl), 0.69–0.50 (m, 4 H, SiCH_2CH_2Si), 0.06, 0.02 (s, 6 H, Si(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): cis, δ 170.88 (*C*=O), 151.14, 142.36, 110.52, 109.34 (furyl-*C*), 67.64 (NCH*C*H-furyl), 53.68 (N*C*HCH-furyl), 7.97 (SiCH_2CH_2Si), 0.58, –0.11 (Si(CH_3)$_2$). The pure cis isomer was obtained as colorless crystals after one crystallization from Et_2O/THF (1:1 v/v), mp 126.5 °C. Anal. Calcd for $C_{13}H_{22}N_2O_2Si_2$: C, 53.02; H, 7.53; N, 9.51; Si, 19.08. Found: C, 52.07; H, 7.31; N, 9.45; Si, 18.80.

General Procedure for the (One-Pot) Synthesis of 1-(Un)substituted-3-(*N*,*N*-diethylamino)-4-substituted-2-azetidinones (6). To a stirred solution containing 1.01 g (10 mmol) of *i*-Pr_2NH in 30 mL of solvent (benzene 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 1.59 g (10 mmol) of *N*,*N*-diethylglycine ethyl 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, and after stirring for 0.5 h at room temperature 10 mmol of an appropriate imine was added. Then the reaction mixture was refluxed until no further formation of 2-azetidinone could be detected by ^{1}H NMR. When the reaction was carried out in benzene, most of the solvent was removed in vacuo. To the resulting suspension was added 30 mL of THF, giving a clear yellow solution, which was refluxed for 30 min. 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 50-mL portions of Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to afford the crude 2-azetidinones 6. The contents of these crude products were examined with ^{1}H NMR, before performing any purification step. The crude products were purified by recrystallization or flash chromatography.

***trans*-1-*tert*-Butyl-3-(*N*,*N*-diethylamino)-4-(*N*-*tert*-butylimino)-2-azetidinone (6a).** Pale yellow oil, isolated yield 2.60 g (92%). 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 7.47 (d, 1 H, J = 7.6, *H*C=N-*t*-Bu), 4.19 (dd, 1 H, J = 7.6 and 1.8, NCHC*H*CH=N), 3.86 (d, J = 1.8, NC*H*CHCH=N), 2.65 (q, 4 H, NCH_2CH_3), 1.51 (s, 9 H, C=N-*t*-Bu), 1.26 (s, 9 H, N-*t*-Bu), 0.97 (t, 6 H, NCH$_2CH_3$). ^{13}C NMR ($CDCl_3$): trans, δ 167.74 (*C*=O), 158.31 (*C*=N), 73.09 (NCH*C*-HCH=N), 58.14 (N*C*HCHCH=N), 57.04 (C=N*C*(CH_3)$_3$), 54.27 (N*C*(CH_3)$_3$), 43.46 (NCH_2CH_3), 29.12 (C=NC(CH_3)$_3$), 28.38 (NC(CH_3)$_3$), 12.13 (NCH$_2CH_3$). The pure trans isomer was obtained as a colorless oil after flash chromatography (Al_2O_3(neutral), Et_2O).

***trans*-1-*tert*-Butyl-3-(*N*,*N*-diethylamino)-4-(2-pyridyl)-2-azetidinone (6b).** Pale yellow solid, isolated yield 2.32 g (84%). The cis isomer was not detected by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$): trans, δ 8.54 (d, 1 H, pyr-*H*), 7.73–7.64 (m, 1 H, pyr-*H*), 7.34–7.16 (m, 2 H, pyr-*H*), 4.71 (d, 1 H, J = 1.6, NCHC*H*-pyr), 3.97 (d, 1 H, J = 1.6, NC*H*CH-pyr), 2.79–2.64 (dq, 4 H, NCH_2CH_3), 1.22 (s, 9 H, N-*t*-Bu), 0.96 (t, 6 H, NCH$_2CH_3$). ^{13}C NMR ($CDCl_3$): trans, δ 169.24 (*C*=O), 160.34, 149.52, 136.79, 122.66, 120.84 (pyr-*C*), 78.21 NCH*C*H-pyr), 59.18 (N*C*HCH-pyr), 54.60 (*C*(CH_3)$_3$), 43.74 (NCH_2CH_3), 28.20 (C(CH_3)$_3$), 12.30 (NC-H_2CH_3). The product was purified by crystallization from pentane to afford colorless crystals, mp 51 °C.

***trans*-3-(*N*,*N*-Diethylamino)-4-(2-thienyl)-2-azetidinone (6e).** The reaction was carried out according to the general procedure, however, with the preformed complex of $ZnCl_2$ with *N*-(trimethylsilyl)thiophene-2-carbaldimine in THF, which resulted in better yields; yellow oil, isolated yield 2.06 g (92%). The ^{1}H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 11:89). ^{1}H NMR ($CDCl_3$): trans, δ 7.26–7.22 (m, 1 H, thienyl-*H*), 7.01–6.98 (m, 2 H, thienyl-*H*), 6.77 (br s, 1 H, N*H*), 4.91 (d, 1 H, J = 1.9, NCHC*H*-thienyl), 4.13 (d, 1 H, J = 1.9, NC*H*CH-thienyl), 2.75 (q, 4 H, NCH_2CH_3), 1.03 (t, 6 H, NCH$_2CH_3$); cis, δ 7.28–7.16 (m, 2 H, thienyl-*H* and N*H*), 6.98–6.89 (m, 2 H, thienyl-*H*), 4.89 (d, 1 H, J = 4.7, NCHC*H*-thienyl), 4.32 (d, 1 H, J = 4.7, NC*H*CH-thienyl), 2.56 (dq, 4 H, NCH_2CH_3), 0.78 (t, 6 H, NCH$_2CH_3$). ^{13}C NMR ($CDCl_3$): trans, δ 169.81 (*C*=O), 143.89, 127.19, 124.86, 124.54 (thienyl-*C*), 82.49 (NCH*C*H-thienyl), 52.02 (N*C*HCH-thienyl), 43.94 (NCH_2CH_3), 12.55 (NCH$_2CH_3$). The pure trans isomer was obtained as pale yellow crystals after one crystallization from Et_2O/hexane (2:1 v/v), mp 101 °C. Anal. Calcd for $C_{11}H_{16}N_2OS$: C, 59.90; H, 7.19; N, 12.49; S, 14.29. Found: C, 58.58; H, 7.24; N, 12.40; S, 13.97.

***trans*-3-(*N*,*N*-Diethylamino)-4-(2-furyl)-2-azetidinone (6f).** Yellow solid, isolated yield 1.99 g (96%). The ^{1}H NMR spectrum revealed that the product was a mixture of cis and trans isomers (cis/trans ratio 23:77). ^{1}H NMR ($CDCl_3$): trans, δ 7.39–7.37 (m, 1 H, furyl-*H*), 6.50 (br s, 1 H, N*H*), 6.35–6.28 (m, 2 H, furyl-*H*), 4.66 (d, 1 H, J = 2.0, NC*H*CH-furyl), 4.32 (d, 1 H, J = 2.0, NCHC*H*-furyl), 2.74 (dq, 4 H, NCH_2CH_3), 1.03 (t, 6 H, NCH$_2CH_3$); cis, δ 7.40 (d, 1 H, J = 0.9, furyl-*H*), 6.60 (br s, 1 H, N*H*), 6.35–6.28 (m, 2 H, furyl-*H*), 4.70 (d, 1 H, J = 4.6, NC*H*CH-furyl), 4.47 (dd, 1 H, J = 4.6 and 0.9, NCHC*H*-furyl), 2.65–2.34 (m, 4 H, NCH_2CH_3), 0.89 (t, 6 H, NCH$_2CH_3$); ^{13}C NMR ($CDCl_3$): trans, δ 169.80 (*C*=O), 152.25, 142.67, 110.55, 107.44 (furyl-*C*), 78.92 (NCH*C*H-furyl), 49.29 (N*C*HCH-furyl), 43.63 (NCH_2CH_3), 12.35 (NCH$_2CH_3$); cis, δ 170.34 (*C*=O), 151.86, 141.91, 110.63, 107.88 (furyl-*C*), 75.76 (NCH*C*H-furyl), 54.06 (N*C*HCH-furyl), 44.45 (NCH_2CH_3), 12.86 (NCH$_2CH_3$). The pure trans isomer was obtained as colorless crystals after one crystallization from Et_2O, mp 123 °C. Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.41; H, 7.82; N, 13.38.

Synthesis of the Zinc Dichloride Complex of (μ,μ'')*N*-*tert*-Butyl-2-(*N'*,*N'*-diethylamino)-3-(*N''*-*tert*-butylimino)-α-alanine Ethyl Ester (8). To a stirred solution containing *i*-Pr_2NH (2.02 g; 20 mmol) in 50 mL of benzene 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 was added at room temperature. The reaction mixture was stirred for 15 min, and then 20 mmol of $ZnCl_2$ (20.0 mL of a 1.0 M solution in Et_2O) was added, upon which a white solid (LiCl) began to precipitate. The suspension was stirred for another 30 min, and then 6.08 g (20 mmol) of the $ZnCl_2$ complex of *N*,*N'*-di-*tert*-butyl-1,4-diaza-1,3-butadiene was introduced. The reaction mixture was stirred for 5 h at 70 °C. The reaction mixture was allowed to cool to room temperature and then quenched with 40 mL of a saturated aqueous NH_4Cl solution. The aqueous layer was separated and extracted with two 30-mL portions of benzene. The combined extracts were dried on Na_2SO_4 and concentrated in vacuo to afford a pale yellow oil. Upon addition of Et_2O white crystals began to precipitate. The crystals were isolated on a glass fritt, rinsed with Et_2O, and dried in vacuo, yield 6.65 g (70%). The ^{1}H NMR spectrum revealed that the product was a mixture of erythro and threo isomers (erythro:threo = 83:17). ^{1}H NMR (C_6D_6): erythro, δ 7.78 (d, 1 H, J = 2.3, *H*C=N), 4.64 (d, 1 H, J = 9.6, EtOOCC*H*), 4.14 (br d, 1 H, J = 9.6, NC*H*C(H)=N), 4.06–3.86 (m, 2 H, OCH_2CH_3), 3.03 (br s, 1 H, N*H*), 2.52 (q, 4 H, NCH_2CH_3), 1.30 (s, 9 H, C=N-*t*-Bu), 1.15 (s, 9 H, N-*t*-Bu), 1.08–0.91 (m, 9 H, OCH$_2CH_3$ and NCH$_2CH_3$); threo, δ 7.88 (d, 1 H, J = 2.3, *H*C=N), 4.30 (d, 1 H, J = 10.0, EtOOCC*H*), 4.09–3.72 (m, 3 H, N(C*H*)C(H)=N and OCH_2CH_3), 3.44 (br s, 1 H, N*H*), 2.68 (q, 4 H, NCH_2CH_3), 1.21 (s, 9 H, C=N-*t*-Bu), 1.08–0.82 (m, 18 H, N-*t*-Bu and OC-H_2CH_3 and NCH$_2CH_3$). ^{13}C NMR ($CDCl_3$): δ 170.75 (*C*=O), 168.72 (*C*=N), 65.96 (EtOOC*C*H), 61.55 (OCH_2CH_3), 60.64 (C=N*C*(CH_3)$_3$), 56.12 (C=N*C*(CH_3)$_3$), 55.46 (N*C*HC(H)=N), 45.77 (NCH_2CH_3), 29.27 (C=NC(CH_3)$_3$), 28.12 (CNC(CH_3)$_3$), 14.40 (OCH$_2CH_3$), 14.03 (NCH$_2CH_3$). Recrystallization from hot benzene afforded the pure erythro isomer as colorless crystals, mp 142 °C. Anal. Calcd for $C_{18}H_{37}N_3O_2Cl_2Zn$: C, 46.62; H, 7.82; N, 9.12; Cl, 15.14, Zn, 14.16. Found: C, 46.63; H, 7.82; N, 9.13; Cl, 15.14; Zn, 14.16.

Structure Determination of the Zinc Dichloride Complex of (μ,μ'')*N*-*tert*-Butyl-2-(*N'*,*N'*-diethylamino)-3-(*N''*-*tert*-butylimino)-α-alanine Ethyl Ester (8). Crystal data, collection, and refinement for 8: $C_{18}H_{37}N_3O_2Cl_2Zn$, M = 463.80, monoclinic, space group $P2_1/n$, a = 11.192 (1) Å, b = 13.413 (1) Å, c = 16.073 (1) Å, β = 91.04 (1)°, U = 2412.5 (3) Å^3, Z = 4, F(000) = 984, D_c = 1.28 g cm^{-3}, T = 295 K, Mo Kα (Zr-filtered) radiation (λ =

0.71073 Å), μ(Mo Kα) = 12.8 cm^{-1}.

Crystals of **8** were grown from benzene. A colorless block-shaped crystal (0.14 × 0.26 × 0.53 mm), mounted in a Lindemann glass capillary, was used for data collection on an Enraf-Nonius CAD-4F diffractometer. Unit cell dimensions were calculated from the SET4 setting angles of 25 carefully centered reflections in the range 25° < 2θ < 38°.[25] The intensity data of 4604 reflections were collected within one quadrant of the reflection sphere (−13 ≤ h ≤ 13, −15 ≤ k ≤ 0, 0 ≤ l ≤ 19; 1.27 ≤ θ ≤ 25.0°). Scan mode $\omega/2\theta$ with $\Delta\omega$ = (0.60 + 0.35 tan θ)°. The reflections were corrected for Lorentz and polarization effects. Averaging of equivalent reflections resulted in 2905 independent reflections (R_{int} = 0.017) with $I \geq 2.5\sigma(I)$. Three reference reflections (−1 −8 0, 4 3 7, and −3 0 9) were measured every hour and showed a small linear decay of 2% during 67 h of X-ray exposure time.

The structure was solved by Patterson (SHELXS-86)[26b] and Fourier methods and refined on F by full-matrix least-squares techniques (SHELX-76).[26a] All hydrogen atoms were located in a difference Fourier map and except for H(1), H(11), H(21), and H(31) refined riding on their carrier atoms with C–H = 0.98 Å. In the final cycles of the refinement 254 parameters (including an extinction parameter) were varied, which resulted in the R value of 0.038, wR = 0.042, $w^{-1} = (\sigma^2(F) + 0.00028F^2)$ and S = 1.09. Six common isotropic thermal parameters for the hydrogen atoms were used because of the large difference in the anisotropic parameters of the non-hydrogen atoms in different parts of the molecule. Especially atoms C(81), C(82), and C(83) have a large thermal motion, indicating a slightly disordered *tert*-butyl group. The average and maximum shift error ratios were 0.045 and 0.047 (for H(11) y/b), respectively. Final residual electron density: −0.25 ≤ $\Delta\rho$ ≤ 0.55 eÅ^{-3}, the highest densities lying near C(81), C(82), and C(83). Scattering factors were taken from Cromer and Mann and corrected for anomalous dispersion.[27] The structure determination and refinement were carried out on an in-house microvax-II cluster. All derived geometry calculations were performed with the programs of the EUCLID package.[26c]

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Registry No. **1a**, 78605-23-9; **1b**, 2644-21-5; **4a**, 30834-74-3; **4b**, 21478-42-2; **4c**, 135639-14-4; **4d**, 63503-18-4; **4e**, 107768-97-8; **4f**, 83948-29-2; **4g**, 67122-50-3; **4h**, 111601-45-7; *trans*-**5a**, 135682-67-6; *cis*-**5a**, 135682-68-7; *trans*-**5b**, 129276-50-2; *trans*-**5c**, 133693-68-2; *cis*-**5c**, 135613-77-3; *trans*-**5e**, 135613-78-4; *cis*-**5e**, 135613-79-5; *trans*-**5f**, 135613-80-8; *cis*-**5f**, 135613-81-9; *trans*-**6a**, 135613-82-0; *cis*-**6a**, 135613-83-1; *trans*-**6b**, 133693-65-9; *trans*-**6e**, 133693-66-0; *cis*-**6e**, 135613-84-2; *trans*-**6f**, 133693-67-1; *cis*-**6f**, 135613-85-3; *erythro*-**8**, 135613-86-4; *threo*-**8**, 135682-69-8; *N*-(trimethylsilyl)thiophene-2-carbaldimine–zinc chloride complex, 135639-15-5; *N,N'*-di-*tert*-butyl-1,4-diaza-1,3-butadiene–zinc chloride complex, 79949-45-4.

Supplementary Material Available: Tables of final coordinates, bond distances, angles, anisotropic thermal parameters for non-hydrogen atoms, and fractional coordinates and isotropic thermal parameters for hydrogen atoms and ^{1}H NMR spectra of some of the new compounds (16 pages); tables with observed and calculated structure factors (26 pages). Ordering information is given on any current masthead page.

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Novel Synthesis of *N,N*-Diarylarylmethanamines from *N*-(Arylmethylene)arenamines and (Arylmethoxy)arenes

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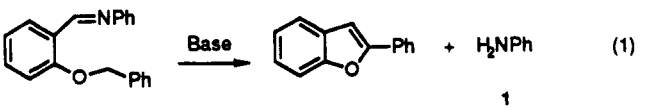
Various *N,N*-diarylarylmethanamines were synthesized by the reaction of *N*-(arylmethylene)arenamines with (arylmethoxy)arenes in dimethylformamide solution in the presence of a strong base as a catalyst which is obtained *in situ* by reacting metallic sodium with this solvent. In general, the reaction may be depicted as the reduction of the imine and addition, on the original imino nitrogen atom, of the aryl group (of the aryloxy moiety) of the ether and presumably oxidation of the arylmethoxy group of the ether to its corresponding aldehyde. Side reactions and a proposed reaction mechanism are discussed.

Introduction

The anil reaction discovered by Siegrist[1,2] has been used to synthesize a large number of substituted stilbenes by the reaction of Schiff's bases with methyl-substituted aromatic compounds. The preparation of 2-phenylbenzofuran[3] (eq 1) by a base-catalyzed intramolecular



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condensation reaction of 2-(phenylmethoxy)-*N*-phenylbenzenemethylenamine has been described. It was expected that the acyclic analogue of this reaction might result in a new preparation of aromatic enol ethers that could then be hydrolyzed readily to the corresponding deoxybenzoins and thus provide the intermediates for the

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