Bull Soc Chim Fr (1995) 132, 86-94

Diastereocontrol *via* cosolvents in the zinc ester enolate-imine condensation route to β-lactams

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(received 7 July 1994, accepted 21 November 1994)

Summary – Strongly coordinating polar cosolvents influence the diastereoselectivity of the C–C coupling reaction of the chlorozinc enolate **1b** of ethyl 2,2,5,5-tetramethyl-1-aza-2,5-disila-cyclopentane-1-acetate with *N*-alkyl and *N*-silyl imines in THF at −78°C. The corresponding lithium enolate **1a** does not react with *N*-alkyl imines. Whereas DMSO and sulfolane did not change the *cis/trans* ratio, the use of three equivalents NMP, TMU and DMPU led to a significant increase in the amount of *cis*-β-lactams formed. HMPA was found to be the best cosolvent in promoting the formation of the *cis*-diastereoisomer. Other reaction parameters were also shown to have small influences on the *cis/trans* ratio. When instead of LDA (2,4,6-triisopropylphenyl)lithium (TIP-Li) was used to deprotonate the ester, the formation of *cis*-β-lactams was slightly enhanced; the enantioselectivity of the C–C coupling reaction was not influenced by the base. An extra equivalent of $ZnCl_2$ in the reaction mixture also favored the formation of *cis*-β-lactams. The change from *trans*- to *cis*-β-lactams is discussed in terms of enolate aggregation equilibria and competing transition states. Moreover, the (*E*)-(*Z*)-equilibrium of zinc enolate **1b** is operative in the absence of a coordinating amine, suggesting the intermediacy of an isomeric C-metallated species.

zinc ester enolate-imine condensation / β-lactams / solvent effects / stereoselectivity

Introduction

The azetidin-2-one ring is the common structural feature of the β-lactam antibiotics, to which they attribute their antibacterial activity. Usually, this activity is associated with a *cis* substitution pattern at the 3- and the 4-position of the ring [1], although there are also some biologically active *trans*-β-lactams, *eg*, carbapenems [2], thienamycin [3] and aztreonam [4]. Therefore, the development of synthetic methods that allow control of the diastereoselectivity and enantioselectivity is an important topic in the synthesis of β-lactams. In the ester enolate-imine condensation route to β-lactams, the diastereoselectivity of the products is controlled by the metal counterion [5]. The reaction of zinc ester enolates with imines affords *trans*-azetidin-2-ones in a one-pot reaction, combining high yields with excellent stereoselectivity. Zinc enolates produce *trans*-azetidin-2-ones almost exclusively [6], whereas lithium [5] or tin [7] enolates afford predominantly the *cis*-diastereoisomers. The zinc enolates display a superior reactivity, both in the C–C coupling reaction and the subsequent ring-closure reaction [6]. Therefore, tuning of the diastereoselectivity of the zinc-mediated reaction, allowing access to either *trans*- or *cis*-azetidin-2-ones, would constitute a major improvement of this route to synthetic β-lactams.

In the related aldol condensation of lithium enolates much effort has been spent on elucidating the mechanistic aspects of the reaction [8]. The reactivity and regioselectivity was found to be affected by the reaction conditions, *eg*, solvent, base and temperature effects. Until recently, zinc enolates had not been subjected to such detailed investigations. We have already reported [6a] that the diastereoselectivity of the zinc-mediated ester enolate-imine condensation reaction is affected by changing the solvent from benzene (apolar, class A) [9], giving exclusively *trans*-β-lactams, to THF (weakly polar, class B) [9], in some cases giving significant amounts of *cis*-β-lactams. Moreover, in these cases a complete inversion of the diastereoselectivity towards the exclusive formation of *cis*-β-lactams from zinc enolates can be accomplished [10], by changing the solvent from Et_2O to THF containing 20 vol % hexamethylphosphoramide (HMPA). Unfortunately, the use of HMPA in commercial processes is severely restricted due to its high toxicity, which prompted us to look for substitutes [11]. We therefore investigated the influence of several polar (class C) [9] solvents on the zinc-mediated ester enolate-imine condensation reaction. We have previously employed ethyl 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane-1-acetate **1** as the ester in the ester enolate-imine condensation. We have used this ester extensively, because the facile removal of the Stabase protecting group [12] allows an easy access to valuable 3-amino substituted β-lactams. Furthermore, the C–C coupling reaction of the chlorozinc enolate of **1** with imines is essentially complete at −30°C. We

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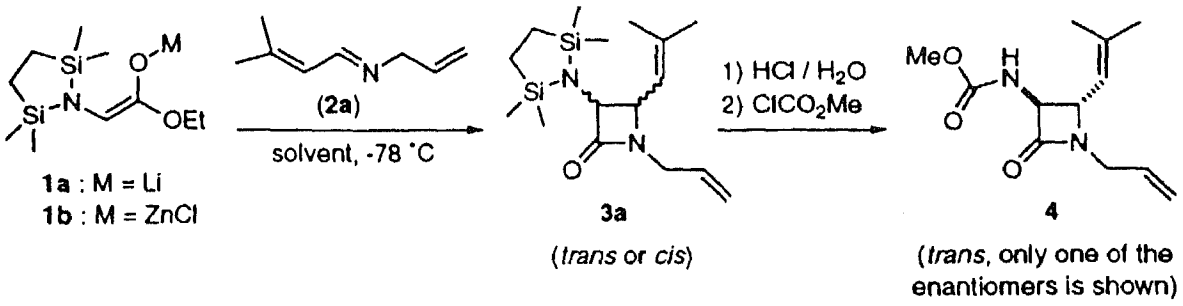
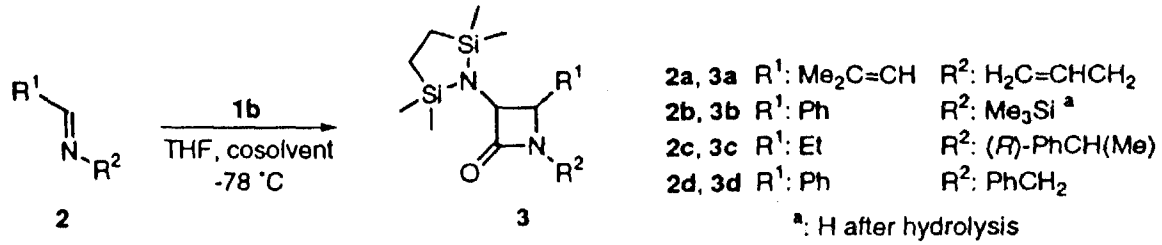


Fig 1



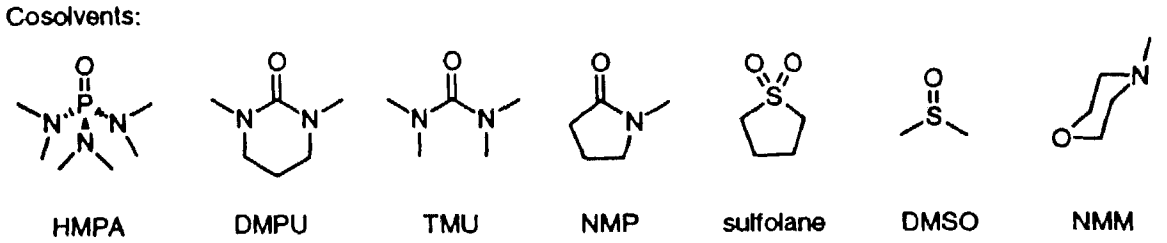


Fig 2

have never observed "retro-aldolization", and the kinetic products are obtained. Further, we investigated the effect of substituting diisopropylamine by other bases in the deprotonation step, and the influence of excess $ZnCl_2$ on the stereochemistry of the reaction.

Results

The C–C coupling reaction of the chlorozinc enolate **1b** of ethyl 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane-1-acetate [12] and *N*-(3-methylbut-2-enylidene) prop-2-enylamine **2a** in THF afforded a 36:64 *cis/trans* mixture of the novel β-lactam **3a** in 72% isolated yield (figure 1).

When the reaction was performed in Et_2O, only *trans*-**3a** was obtained (de > 98%), which was isolated as the white crystalline methylcarbamate **4** after removal of the Stabase [12] moiety (H_2O/THF) and protection (MeOCOCl/NEt_3, benzene). The *cis*-diastereoisomer of **3a** was obtained from the reaction in THF/HMPA by recrystallization from pentane. Thus, both diastereoisomers of the product β-lactam could be synthesized from zinc enolate **1b**, controlled by the solvent. The lithium enolate **1a** did not afford β-lactams upon reaction with imine **2a**.

Based upon this observation, we undertook the study of the effects of several polar additives (see figure 2) on the diastereoselectivity of the C–C coupling reaction of zinc enolate **1b** with various imines. We have previously reported the results of reactions (in THF) of **1b** with *N*-benzylidene-trimethylsilylamine **2b**, *N*-propylidene-(*R*)-1-phenylethylamine **2c** and *N*-benzylidene-benzylamine **2d**, which all gave *cis/trans* mixtures [6a, b]. To study the effects of polar cosolvents, all reactions were performed under the same standard conditions (for details see the *Experimental section*). The cosolvents were dried according to literature procedures [13]. The products were characterized by ^1H and ^{13}C NMR spectroscopy, and product ratios and conversions were determined by integration of characteristic peaks in the ^1H NMR spectra. At −78°C, ester **1** was deprotonated with LDA, transmetallated with $ZnCl_2$ and reacted with the appropriate imine **2a-c**. The results of these reactions in the presence of several polar cosolvents are presented in table I.

The addition of three equivalents of *N*-methyl-pyrrolidinone (NMP), tetramethylurea (TMU), *N*,*N*-dimethyl-propylideneurea (DMPU) or HMPA resulted in the formation of more *cis*-β-lactam, although the observed des were moderate. DMSO and sulfolane have no significant influence on the outcome of the reaction, whereas *N*-methylmorpholine (NMM) slightly enhanced the formation of the *trans*-β-lactam. Furthermore, a very efficient chirality transfer is operative in the reactions of the chiral imine **2c** in the presence of DMPU and HMPA, since only one *cis*-diastereoisomer

Table I. Influence of cosolvents on *cis/trans* ratio for β-lactams **3a-c**[a].

cosolvent[b]	3a conversion[c]	3a *cis/trans*	3b conversion[c]	3b *cis/trans*	3c conversion[c]	3c *cis/trans*	de
none	72	36:64	96 (93)	14:86	92 (87)	18:82	78[d]
NMM	74	25:75	–	–	–	–	
DMSO	78 (72)	32:68	–	–	–	–	
sulfolane	82	40:60	–	–	–	–	
NMP	88 (80)	68:32	52	42:58	–	–	
TMU	73	69:31	75 (64)	43:57[e]	84	75:25	
DMPU	58	84:16	44	50:50	77	84:16	[f]
HMPA	78 (68)	92:8	36	57:43	96 (89)	> 98:< 2	[f]

[a] Reactions were performed in THF; *cis/trans* ratios and conversions (%) were determined by integration of characteristic ^{1}H NMR signals. [b] Cosolvent/enolate/imine molar ratio is 3:1:1. [c] Values in brackets are isolated yields (%). [d] de of *trans*-diastereoisomer. [e] in Et_2O : conversion 49%, *cis/trans* = 25:75. [f] only one *cis*-diastereoisomer was observed.

was observed by ^{1}H NMR. It is noteworthy that the chemical yield of the β-lactam **3b** decreases sharply in the presence of polar cosolvents. This is not due to the limited stability of imine **2b**, as its known decomposition product [14] was not observed by ^{1}H NMR.

Table II. Influence of base on diastereoselectivity.

imine	LDA conv[a]	LDA *cis/trans*	LHMDS conv[a]	LHMDS *cis/trans*	TIP-Li conv[a]	TIP-Li *cis/trans*
2a	82	36:64	78	32:68	26	> 90:< 10
2b	92	14:86	81	17:83	76	33:67
2c	90	18:82[b]	–	–	79	28:72[b]
2d	95	< 2:> 98	94	< 2:> 98	83	6:94

[a] Reactions were performed in THF; *cis/trans* ratios and conversions (%) were determined by integration of characteristic ^{1}H NMR signals. [b] de *trans*-**2c** : 78%.

In the above reactions, LDA was used to deprotonate the ester, which resulted in the presence of one equivalent of diisopropylamine in the reaction mixture. Because earlier studies indicated that the enolate (*E*)-(*Z*) equilibration requires free diisopropylamine, the effect of using LiHMDS and 2,4,6-triisopropyl-phenyllithium (TIP-Li) [15, 16] was investigated, since it produces non-coordinating conjugate acids, ie hexamethyldisilazane and 1,3,5-triisopropyl-benzene. Because the deprotonation of ester **1** with the sterically hindered TIP-Li is slow, this step was performed by stirring the reaction mixture for 30 min at −30°C. The zinc enolate **1b** generated with this base tends to give more *cis*-β-lactams (table II), although the effect is small. LiHMDS gives essentially the same results as LDA.

We have observed earlier that the amount of $ZnCl_2$ used to generate the zinc enolate **1b** affects the diastereoselectivity of the subsequent C–C coupling reaction [6c]. Furthermore, in some cases, complexation of the imine to $ZnCl_2$ influences both the rate and the diastereoselectivity of the reaction [6c, f]. Therefore, we have also investigated the effect of excess zinc chloride in the reaction of imine **2a**. Complexation of the imine to $ZnCl_2$, prior to the addition to the solution containing the enolate, resulted in a significantly enhanced formation of *cis*-β-lactam, from a 36:64 *cis/trans*-ratio to 61:39. Exactly the same result was obtained when two equivalents of $ZnCl_2$ were used in the transmetallation of the intermediate lithium enolate. However, the cosolvent effects and Lewis acid effects are not cumulative and in the presence of three equivalents of TMU, no effect of excess $ZnCl_2$ was observed. The observed *cis/trans* ratio of 69:31 is in fact exactly identical to the outcome of the reaction of the zinc enolate with three equivalents of TMU without excess $ZnCl_2$ (see table I).

Discussion

General

The synthesis of *cis*-β-lactams from *N*-alkyl and *N*-allyl-substituted imines is hampered by the unreactivity of lithium enolates towards these imines. Zinc enolates afford *trans*-β-lactams (eg, the novel *trans*-β-lactam **4**) when the reaction with these imines is performed in apolar or weakly polar solvents. The application of zinc enolates in the synthesis of *cis*-β-lactams (eg, *cis*-**3a**, in THF/HMPA) by increasing the solvent polarity is a major improvement of this methodology.

In the organic chemistry of metals with high Lewis acidity, large solvent effects are often observed. The reaction rates of a wide variety of organolithium reactions are dramatically enhanced by HMPA [17], via dissociation of aggregates into highly reactive monomers, ion pairs or triplets, or free ions [18]. Complexes of $Li(HMPA)_n^+$ (n = 1 to 4) have been observed by [7] Li and ^{31}P NMR below −100°C [19]. Cationic zinc (as $Zn(ClO_4)_2$) forms tetracoordinated $Zn(HMPA)_4^{2+}$ complexes in equilibrium with free HMPA [20]. However, the mechanism by which HMPA modifies the reactivity and selectivity of lithium enolates [21] and dienolates [22] is still not well established. The effects of HMPA on zinc enolates have not been mentioned at all.

Because of the high toxicity of HMPA, substitutes have been used in lithium-mediated reactions [10]. The best results were obtained with the cyclic ureas DMPU and DMEU (*N*,*N*-dimethyl-ethyleneurea). DMEU is not compatible with our reaction conditions, because it crystallizes from THF below −30°C. Acyclic ureas have

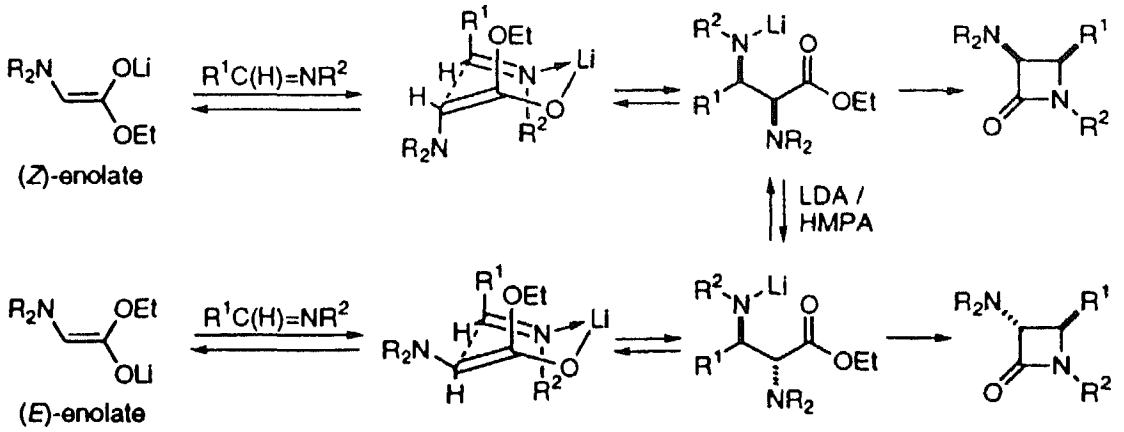


Fig 3

also been suggested [23] but their influence on organolithium reactions was much less pronounced [11b]. To our knowledge, no studies on the influence of ureas on the reactivity of organozinc species have been reported. It must be noted that in connection with the biological importance of Zn, the kinetics of the complexation of Zn^{2+} by dimethylthiourea as ZnL_4^{2+} has already been studied by ^1H NMR [24].

Solvent effects on transition-state structures

The diastereoselectivity of the reactions of lithium enolates with activated imines changed from almost exclusively *cis* to predominantly *trans* upon addition of HMPA [21]. This influence was rationalized by a rapid *syn-anti* equilibrium of the intermediate β-amino esters, and a rate-determining ring-closure step (fig 3). Due to the lower steric hindrance in the ring-closure transition state, formation of the *trans*-β-lactam will be faster than the corresponding reaction to the *cis*-diastereoisomer.

In the present zinc-mediated reaction, the inverse change of diastereoselectivity from *trans* to *cis*-β-lactams obviously cannot be attributed to a similar equilibrium. Rather, the simultaneous formation of both *trans*- and *cis*-β-lactams, and the continuous change of the *cis/trans* ratio for all three imines studied upon changing the cosolvent from DMSO *via* NMP, TMU and DMPU to HMPA, suggest the occurrence of two competing transition states. Evidently, the relative stability of the transition states is influenced by the good coordinating properties of class C solvents [9].

Zinc enolates are not present in solution as well-defined species, but as a mixture of aggregates, *eg*, tetramers and dimers have been identified and characterized for ethylzinc enolates [6e]. The excellent diastereoselectivity of reactions of zinc enolates in apolar solvents implies that out of the possible interaggregate equilibria, only one (probably dimeric) [6e] species is the kinetically active one. Strongly coordinating solvents, like HMPA, are likely to interfere with the aggregation equilibria, creating less aggregated (monomeric?) and thus more reactive enolates [25], reacting *via* a more reactant-like transition state.

Transition states

The highly diastereoselective formation of *trans*-β-lactams [6] in the reaction of zinc ester enolates with imines in apolar or weakly polar solvents (class A or B) [9] is the result of a highly ordered transition-state complex [6d]. Activation of the imine by coordination to the metal [6c] is an essential step in this reaction. The stereochemistry of the ester enolate-imine condensation reaction has been rationalized *via* a chelated six-membered chair transition state **A** [6d, 26] (fig 4), involving a (*Z*)-enolate and an (*E*)-imine [27], analogous to the transition state of the related aldol reaction [8, 28]. The steric hindrance between the bulky enolate substituent and R^1 is minimized in this transition state. In theory, the boat transition state **D** of an (*E*)-enolate and an (*E*)-imine would also result in a *trans*-β-lactam.

Quenching experiments have clearly demonstrated that zinc enolate **1b** is present in THF solution as a 93:7 equilibrium mixture of the (*E*)- and (*Z*)-isomers [6b]. To account for the excellent diastereo- and enantioselectivity observed for the C–C coupling reaction of **1b** with imines in apolar and weakly polar solvents, the two isomers must be in fast equilibrium. Furthermore, the reaction of the (*Z*)-enolate (7 %), resulting in the *trans*-β-lactam, should be at least 100 times faster than the reaction of the (*E*)-enolate (93%), affording the *cis*-β-lactam.

The formation of *cis*-β-lactams (in more polar solvents) involves transition states **B** or **C** [26]. The boat transition state **B** of a (*Z*)-enolate with an (*E*)-imine is strongly disfavored due to steric repulsion of the bulky Stabase protected amino group in an axial position on the one hand and the metal center and R^1 on the other hand. The *cis*-β-lactams are more likely to be formed by the reaction of the (*E*)-imine with an (*E*)-enolate *via* the chair transition state **C**, which is destabilized relative to **A** by a gauche interaction between R^1 and the bulky (1-aza-2,5-disila)cyclopentyl group. Theoretically, a non-chelating transition state **E** or the ionic analogue **F** might be favored in the presence of HMPA, because this solvent is known to coordinate to cations very effectively [18-20]. However, the formation of separated ion pairs from organozinc species has no precedent. The high diastereo- and enantioselectivity

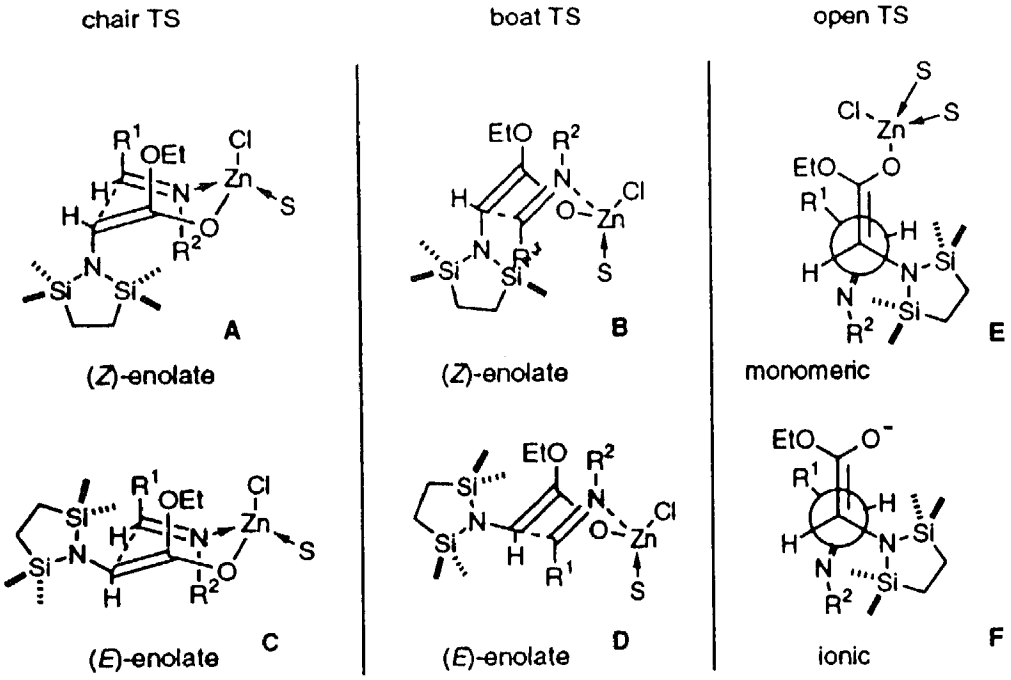


Fig 4

of the reaction of enolate **1b** with chiral imine **2c** in the presence of HMPA strongly suggests that a highly ordered transition state is operative. The efficient chirality transfer (ee > 98%) from the α-methylbenzylgroup at the imine nitrogen atom to the newly formed stereogenic centers of the *cis*-β-lactams is not in accord with the open transition states **E** and **F**.

Transition states **A** and **C**, together with the presence of the fast (*E*)-(*Z*) enolate equilibrium, account for the cosolvent effects in the ester enolate-imine condensation reactions. In THF containing three equivalents of HMPA, the relative stability of the transition states is altered by the formation of more reactive enolates. The more reactant-like transition state allows a longer imine N-Zn coordination bond [29] which relieves the steric strain of transition state **C** to a greater extent than that of transition state **A**. Therefore, the energy difference between the two transition states determining the formation of *cis*- and *trans*-**3a** is decreased.

Base influence

It has been shown by us [6b, d] and other research groups [30] that diisopropylamine can coordinate to the metal enolate after deprotonation of the ester with LDA, thus influencing the interaggregate equilibria and the reactivity. Moreover, diisopropylamine (pKa = 35.7) [31] or hexamethyldisilazane (pKa = 29.8) [31] are thought to be involved in the (*E*)-(*Z*) equilibrium of the zinc enolates of ester **1** *via* intermediate formation of the free ester and the zinc amide [6f] (fig 5). The use of TIP-Li as a base, generating a non-coordinating, non-acidic (pKa > 40) conjugate acid, was therefore expected to influence the outcome of the reaction by blocking the (*E*)-(*Z*) equilibrium.

In the C–C coupling reactions with imines **2b-d**, the observed change in diastereoselectivity is small. The chemical yields are lower when TIP-Li is used as a base, indicating that the reactivity of the enolate has decreased. In the C–C coupling reaction with imine **2a**, the *trans*-β-lactam is not observed. However, in view of the low conversion (26%), and the observation of non-cyclized products and unknown decomposition products, no conclusions about the influence of TIP-Li can be drawn for this particular reaction. Notably, there is no influence of the base on the enantioselectivity of the C–C coupling reaction with imine **2c**, affording the *trans*-β-lactam. Thus, whether LDA or TIP-Li is used to deprotonate the ester, the same transition state **A** (fig 4) is operative. This means that even in the absence of a weak acid, the (*E*)-(*Z*) equilibrium is still possible, which points to the intermediacy of a C-metallated enolate (fig 5). For zinc enolates C-metallation is not without precedent : the Reformatsky reagent $BrZnCH_2CO_2R$ is an intermediate between O- and C-metallation, as has been shown by X-ray structure determination [32]. This equilibrium between C- and O-metallated species might also account for the enolate (*E*)-(*Z*) isomerization in the presence of diisopropylamine.

Stoichiometry

It has been shown by us and other workers that the presence of Lewis acids in the reaction mixture might change the diastereoselectivity of the C–C coupling reaction with imines [6c, e, f] and aldehydes [33]. In the C–C coupling reaction of imine **2a** with ester enolate **1b**, the presence of an excess of $ZnCl_2$ increased the formation of *cis*-β-lactam. Because it made no difference whether the excess $ZnCl_2$ was added to the enolate or the imine, complexation of the imine to the Lewis acid

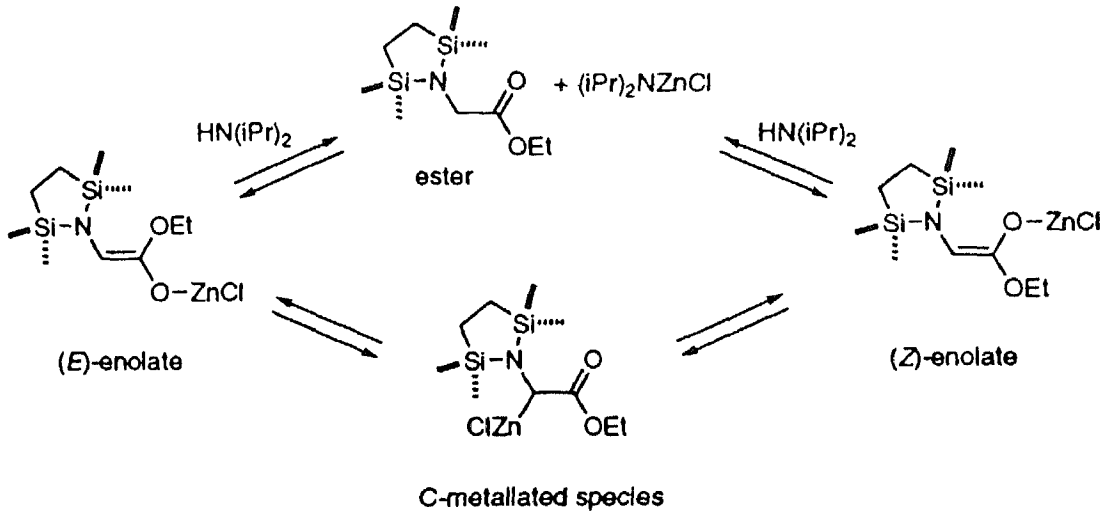


Fig 5

is not essential. The observed diastereoselectivity indicates that in the presence of excess $ZnCl_2$ the relative reactivities of the kinetically active enolate species in solution have changed. We have reported earlier [6a] that the addition of Lewis acids shifts the tetramer-dimer equilibrium of similar zinc enolates to the side of the dimer, but the influence of $ZnCl_2$ on the relative reactivities of the (*E*) and (*Z*)-enolates is still unclear. A quantitative study of the interaggregate and conformational equilibria of **1b** is not possible, because the ^1H NMR spectra of zinc enolates generally show multiple and mostly broad signals, due to the presence of several aggregates in solution.

Concluding remarks

The zinc-mediated ester enolate-imine condensation reaction offers an entry to both *cis-* and *trans-β*-lactams by varying the solvent polarity. This approach has been used in the synthesis of the novel *N*-allyl-*β*-lactams *cis-***3a** and *trans-***4**. The *cis-β*-lactam could not be obtained *via* the lithium enolate **1a**, because it does not react with *N*-allyl imine **2a**.

In the reaction of the chlorozinc enolate **1b** with imines, the *cis/trans* ratio is susceptible to solvent effects. In general, when the reaction is performed in THF containing three equivalents of a strongly coordinating cosolvent, *eg*, HMPA, DMPU, TMU or NMP, the amount of *cis-β*-lactam increases. Unfortunately, none of the investigated cosolvents was as efficient as HMPA in promoting the formation of *cis-β*-lactams. In the presence of these strongly coordinating cosolvents, competing reaction pathways involving both (*E*)- and (*Z*)-enolates become accessible, leading to *cis-* and *trans-β*-lactams, respectively. The high asymmetric induction, observed in the formation of *cis-β*-lactams from enolate **1b** with chiral imine **2c** indicates that in these reactions a highly ordered transition state, consisting of an (*E*)-enolate and an (*E*)-imine, is operative.

The influence of the base used in the deprotonation step (LDA, LHMDS or TIP-Li) is marginal at best. The fast (*E*)-(*Z*) equilibrium of enolate **1b** is still operative in the absence of a weakly acidic amine in solution, which implies the intermediacy of a C-metallated enolate rather than the free starting ester and a zinc amide.

Experimental section

General data

All synthetic manipulations involving air-sensitive compounds were performed under a dry, inert N_2 atmosphere using standard Schlenk techniques. THF and Et_2O were dried and distilled from sodium/benzophenone prior to use. The cosolvents were dried according to literature methods [13], distilled and stored over molsieves (3 Å). Diisopropylamine and hexamethyldisilazane were distilled at atmospheric pressure and stored over molsieves (3 Å). Ethyl 2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane-1-acetate **1** [8], imines [34] and dry zinc chloride [35] were prepared according to literature procedures. The analytical data of 3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-phenylazetidin-2-one [6b] and 1-((*R*)-1-phenylethyl)-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)-4-ethylazetidin-2-one [6d] have been reported. ^1H and ^{13}C NMR spectra were recorded on a Bruker WP 200 and a Bruker WP 300 spectrometer in chloroform-*d* or benzene-d_6. All coupling constants are presented in hertz (Hz). IR spectra were recorded on a Mattson Galaxy FTIR 5000 spectrometer. Melting points and boiling points are uncorrected. Analyses were performed by Dornis und Kolbe Mikroanalytisches Laboratorium, Mühlheim a/d Ruhr, Germany.

• N-*(3-methylbut-1-enylidene)prop-2-enylamine* **2a**
The imine was obtained as a brownish yellow oil and was stored at −30°C.
Yield : 98%.
^1H NMR ($CDCl_3$) : δ 1.76, 1.80 (s, 6H), 3.96 (d, J = 5.5 Hz, 2H), 5.0 (m, 2H), 5.9-6.0 (m, 2H), 8.07 (d, J = 9.3 Hz, 1H).
^{13}C NMR ($CDCl_3$) : δ 18.3, 26.2, 63.2, 115.3, 125.0, 135.9, 146.6, 160.0.

General procedure for the C–C coupling reaction, deprotonation with LDA

To a well-stirred, cooled (−78°C) solution of diisopropylamine (0.42 g, 4.1 mmol) in THF (20.0 mL), *n*-butyllithium

(4.0 mmol, 2.5 mL of a 1.6 M solution in hexanes) was added. After 10 min ester **1** (0.98 g, 4.0 mmol) was added and the solution was stirred for 15 min. Next $ZnCl_2$ (4.0 mmol, 3.7 mL of a 1.09 M solution in THF) was added, followed by the cosolvent (12.0 mmol). After stirring for 20 min at −78°C the imine (4.0 mmol) was added. The homogeneous reaction mixture was stirred at −78°C for 1 h. The temperature was then allowed to rise to −30°C in 1 h and kept at that temperature for 20 h, until finally the temperature was raised to room temperature. After concentration to 10 mL and addition of Et_2O (20 mL), the reaction mixture was quenched with a saturated ammonium chloride solution and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried on magnesium sulfate, filtrated and concentrated *in vacuo*.

Deprotonation with TIP-Li

To a cooled (−30°C) solution of TIP-Li/Et_2O (1.13 g, 4.0 mmol) in THF (20.0 mL) was added ester **1** (0.98 g, 4.0 mmol). To accomplish complete deprotonation, stirring was continued for 30 min at this temperature before the reaction mixture was cooled to −78°C. After addition of $ZnCl_2$ (4 mmol, 3.7 mL of a 1.09 M solution in THF), the reaction and work-up were performed as described for LDA. The hydrolysis product of TIP-Li, 1,3,5-triisopropylbenzene, appeared to be a good internal standard.

• Cis *4-(2-methylprop-1-enyl)-1-(prop-2-enyl)-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl) azetidin-2-one* cis-**3a**

Isolated from the reaction mixture of the C–C coupling in THF/HMPA by crystallization from pentane.

Yield : 1.55 g (3.8 mmol, 76%).

Mp : 52.5°C.

IR (KBr) : 1 747, 1 670, 1 645 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.02, 0.10 (s, 12H), 0.55-0.81 (m, 4H), 1.62, 1.72 (s, 6H), 3.40 (dd, J = 6.9 Hz and 15.4 Hz, 1H), 3.91 (dd, J = 5.0 Hz and 15.4 Hz, 1H), 4.16 (dd, J = 4.4 Hz and 9.9 Hz, 1H), 4.50 (d, J = 4.4 Hz, 1H), 5.1 (m, 3H), 5.7 (m, 1H).

^{13}C NMR ($CDCl_3$) δ 0.2, 0.8, 8.1, 18.3, 26.2, 42.6, 56.3, 64.5, 117.6, 120.1, 132.3, 139.2, 169.1.

Anal calc for $C_{16}H_{30}N_2OSi_2$: C, 59.57; H, 9.37; N, 8.68; Si, 17.41. Found : C, 58.91; H, 9.27; N, 8.58; Si, 17.18.

• Trans *4-(2-methylprop-1-enyl)-1-(prop-2-enyl)-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl) azetidin-2-one* trans-**3a**

^1H NMR ($CDCl_3$) : Characteristic signals : δ 0.04, 0.10 (s, 12H), 1.65, 1.74 (s, 6H), 5.01 (d, J = 10.2 Hz, 1H).

^{13}C NMR ($CDCl_3$) : δ 0.3, 0.4, 8.0, 18.5, 25.9, 42.4, 61.1, 68.5, 118.4, 121.5, 132.4, 139.2.

• *4-Phenyl-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)azetidin-2-one* **3b**

^1H NMR ($CDCl_3$) : Characteristic signals of the *cis*-diastereoisomer : δ : −0.17, −0.01 (s, 12H), 4.78 (d, J = 4.8 Hz, 1H), 4.83 (dd, J = 4.8 Hz and 1.8 Hz, 1H), 6.36 (br s, 1H).

Characteristic signals of the *trans*-diastereoisomer : δ 0.08, 0.18 (s, 12H), 4.09 (d, J = 2.0 Hz, 1H), 4.40 (dd, J = 2.0 Hz, 1H), 6.33 (br s, 1H).

• *4-Ethyl-1-((R)-1-phenylethyl)-3-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentyl)azetidin-2-one* **3c**

Characteristic signals of the major *trans*-diastereoisomer : δ 0.84 (t, J = 7.4 Hz, 3H), 1.63 (d, J = 7.2 Hz, 2H), 3.78 (d, J = 2.3 Hz, 1H), 4.79 (q, J = 7.2 Hz, 2H).

Characteristic signals of the minor *trans*-diastereoisomer : δ 1.72 (d, J = 7.2 Hz, 2H), 3.81 (d, J = 2.4 Hz, 1H).

Characteristic signals of the major *cis*-diastereoisomer : δ 0.76 (t, J = 7.4 Hz, 3H), 1.74 (d, J = 7.2 Hz, 2H), 4.33 (d, J = 4.9 Hz, 1H), 4.69 (q, J = 7.2 Hz, 2H).

The other *cis*-diastereoisomer was not observed in the NMR spectra.

• Trans *3-(methoxycarbonylamino)-4-(2-methylprop-1-enyl)-1-(prop-2-enyl)azetidin-2-one* **4**

The C–C coupling reaction was performed on a 20 mmol scale in Et_2O, *via* procedure A. The crude product (brown oil, conversion 82%, de > 95%) was stirred in THF/H_2O (90:10 v/v, 10 mL) for 16 h. After addition of H_2O (10 mL), the deprotected product was isolated by extraction with CH_2Cl_2 (3×10 mL). The organic layer was dried on Na_2SO_4, filtrated, and evaporated to dryness. The resulting brown oil was redissolved in benzene (30 mL), to which $ClCO_2Me$ (1.79 g, 19 mmol) was added. A solution of NEt_3 (4.0 g, 40 mmol) in benzene (10 mL) was added slowly *via* a dropping funnel. After stirring the reaction mixture for 1 h at rt, it was poured into saturated aqueous NH_4Cl (50 mL). Extraction with Et_2O/pentane (1:1 v/v), concentration and cooling yielded a sticky solid. After washing rapidly with cold Et_2O, the product was recrystallized from Et_2O/pentane affording **4** as a white crystalline compound.

Yield : 1.48 g (62%).

Mp 102°C.

IR (KBr) : 3 283, 1 747, 1 722, 1 672, 1 643 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.62, 1.70 (s, 6H), 3.40 (dd, J = 7.8 Hz and 15.7 Hz, 1H), 3.62 (s, 3H), 3.97 (dd, J = 4.8 Hz and 15.7 Hz, 1H), 4.23-4.32 (m, 2H), 5.0-5.4 (m, 3H), 5.69 (m, 1H), 6.04 (d, J = 7.5 Hz, 1H).

^{13}C NMR ($CDCl_3$) : δ 18.4, 25.9, 42.7, 52.4, 58.1, 64.3, 118.2, 120.3, 131.9, 140.4, 156.2, 166.8.

Anal calc for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found : C, 60.54; H, 7.74; N, 11.74.

Acknowledgment

The authors wish to thank Gist-brocades, Delft, The Netherlands for financially supporting this research. Dr J Verweij and Dr APG Kieboom are kindly acknowledged for their stimulating discussions.

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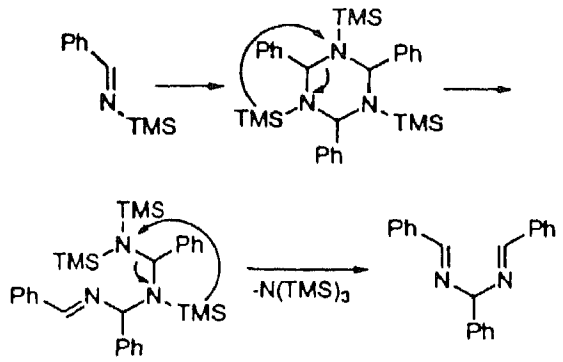

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