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Experimental and quantum-mechanical investigation of the vinylsilane-iminium ion cyclization †

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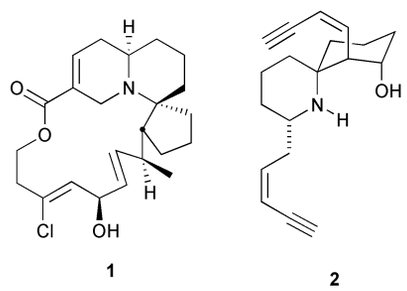
A vinylsilane-ketiminium ion cyclization involving iminium species derived from amines **6** and **7** was investigated experimentally as a possible approach to some biologically interesting 1-azaspirocycles. However, even under conditions of microwave irradiation at high temperatures no such cyclization was observed whereas (in line with previous results) the corresponding vinylsilane-aldiminium ion cyclizations were more successful. Aldiminium species substituted α to nitrogen displayed no diastereoselectivity in the cyclization of precursors derived from **6** while high *trans* diastereoselectivity could be obtained for iminium species derived from **7**. Quantum-mechanical investigations of the general reaction mechanism underlined the lack of reactivity of ketiminium species and also convincingly explained the observed diastereoselectivities of aldiminium species. The calculations further revealed that (*Z*)-vinylsilanes cyclize *via* a silicon-stabilized β-carbocation, and that any formal aza-Cope rearrangement of the starting material to an allylsilane-iminium species does *not* take place in a concerted fashion. However, the calculations show that the aza-Cope rearrangement precedes cyclization for the corresponding (*E*)-vinylsilanes, the overall reaction being energetically slightly less favoured than cyclization of the (*Z*)-isomers.

Introduction

The 1-azaspirocyclic system[1] is characteristic of several biologically significant natural products, exemplified in Fig. 1 by halichlorine **1**[2,3] and histrionicotoxin **2**.[4–6] Our group has a long-standing interest in developing synthetic routes to such compounds,[7,8] a major part of the challenge being presented by the nitrogen-bearing stereogenic center in the target molecules.



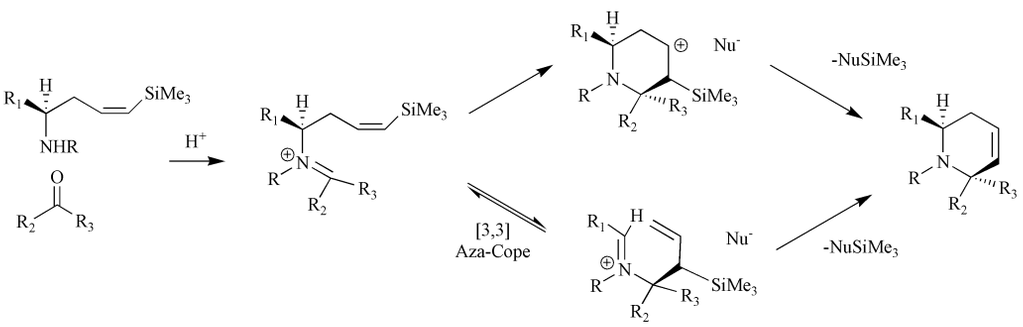
1 **2**

Fig. 1

† Electronic supplementary information (ESI) available: experimental procedures, spectroscopic data and copies of ^{13}C NMR spectra for compounds **4**–**16**. Selected bond lengths in geometry optimized structures of α-substituted (*Z*)-vinylsilanes. Cartesian coordinates, raw energies and lower frequencies of computationally characterized species **17A**–**32H**. See http://www.rsc.org/suppdata/ob/b2/b212333a/

In contemplating possible routes to the 1-azaspirocyclic portion of halichlorine, we considered the option of extending the vinylsilane-iminium ion cyclization introduced by Overman and coworkers (Scheme 1).[9–15] For a synthesis of halichlorine, this would obviously involve reaction of a ketiminium species and, in view of the complete lack of literature precedent, such a stratagem must be considered as bold since the vast majority of known vinylsilane-iminium ion cyclizations utilize precursors based on formaldehyde,[10–12,16–18] with a few examples being reported for iminium ions formed from higher aldehydes,[11,13–15,19] but none from ketones. We were also unable to find examples of azaspirocyclization *via* reaction of vinyl silanes with the more reactive *N*-acyliminium[20,21] species. As far as we are aware, the only reports[22–24] which describe azaspirocyclization *via* organosilicon chemistry all involve the more reactive[25] allylsilane species, the most recent example[22,23] having an *N*-*o*-nitrobenzoyl-activated ketiminium precursor. Our first task was therefore to construct a model system and to search for reaction conditions which would allow spirocyclization *via* a vinylsilane-ketiminium ion reaction (*vide infra*).

Notwithstanding the specific goal outlined above, our interest in the vinylsilane-iminium ion reaction was of a more general nature since cyclizations based on this process are mechanistically intriguing. Two different reaction pathways have been suggested,[9–15] with the first, more direct, mechanism (Scheme 1, upper half) involving iminium ion formation



Scheme 1

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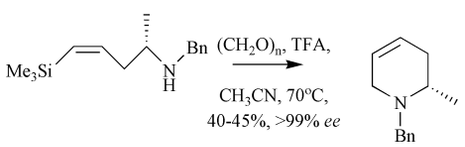
followed by cyclization to give the β-carbocation which is stabilized by overlap between the vacant p-orbital and the correctly aligned C–Si bond. This is followed by facile loss of the silyl group promoted by an external nucleophile. Alternatively, the iminium ion has been suggested to participate in a [3,3]-sigmatropic aza-Cope rearrangement (Scheme 1, lower half) to give the more reactive allylsilane followed by cyclization and concomitant loss of the silyl group. The latter mechanism becomes of particular interest when the iminium species shown in Scheme 1 has $R_1 \neq H$, since the aza-Cope process coupled with iminium ion equilibration could lead to complete racemization of enantiomerically pure starting materials. Overman has presented convincing evidence for the intervention of the aza-Cope rearrangement: isolation of some Eschweiler–Clarke methylated starting material, as an isomeric mixture of (*E*)- and (*Z*)-vinylsilanes, from the endocyclic reaction of iminium ions derived from secondary amines and formaldehyde, while no olefin isomerization was observed in the absence of formaldehyde.[9–12] The result shown in Scheme 2 is also interesting in this respect since in contrast to earlier reports[13] such substrates could be transformed into iminium ions with formaldehyde and directly cyclized with only minor amounts of racemization.[14]

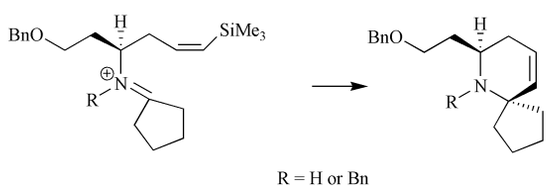


Scheme 2

These results indicate that even if the aza-Cope rearrangement occurs, the successive cyclization process must be faster than the iminium ion equilibration. In accordance with these results, analogous cyclizations involving vinylsilanes and some chiral *N*-acyliminium ions have also been reported to take place with only partial loss of enantiopurity.[26]

Generally, the stereochemistry of the vinylsilane moiety is not critical since both *cis*- and *trans*-vinylsilanes have been reported to cyclize.[10] However, in the case of cyclization of a substrate unable to participate in the aza-Cope rearrangement, *only* the (*Z*)-vinylsilane led to product.[15,19] This result emphasizes the importance of stabilization of the developing β-carbocation; easy access to correct alignment of the C–Si bond with the vacant p-orbital is possible only for the (*Z*)-vinylsilane.[9,15,19] Thus, when the aza-Cope rearrangement is precluded, the cyclization still takes place and it is quite possible that both suggested mechanisms coexist even when the iminium ion precursor can rearrange.

Returning to the projected halichlorine synthesis, we decided to start by examining the model spirocyclization shown in Scheme 3. For this purpose, the vinyl silanes **6** and **7** were prepared in racemic form as shown in Scheme 4, the (*Z*)-vinylsilanes being chosen in order to favour cyclization *via* the β-carbocation intermediate if this were the dominant mechanistic pathway.

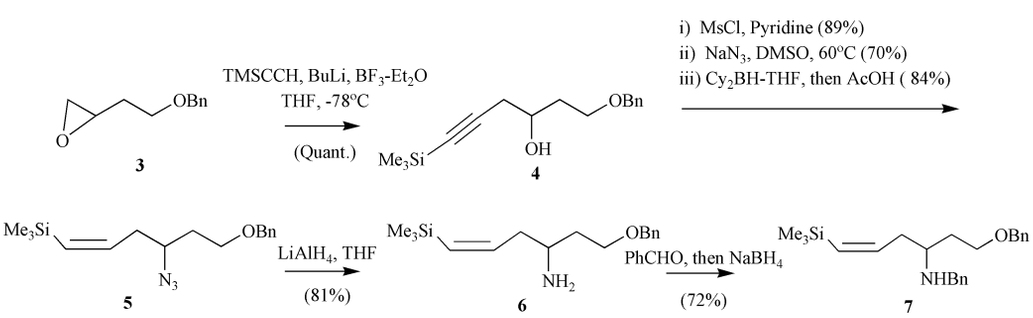


Scheme 3

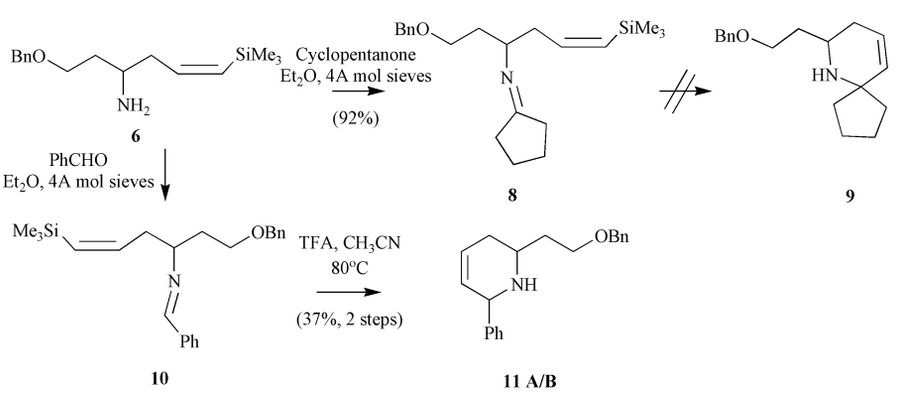
Results and discussion

1. Cyclization studies: aldimines *vs.* ketimines

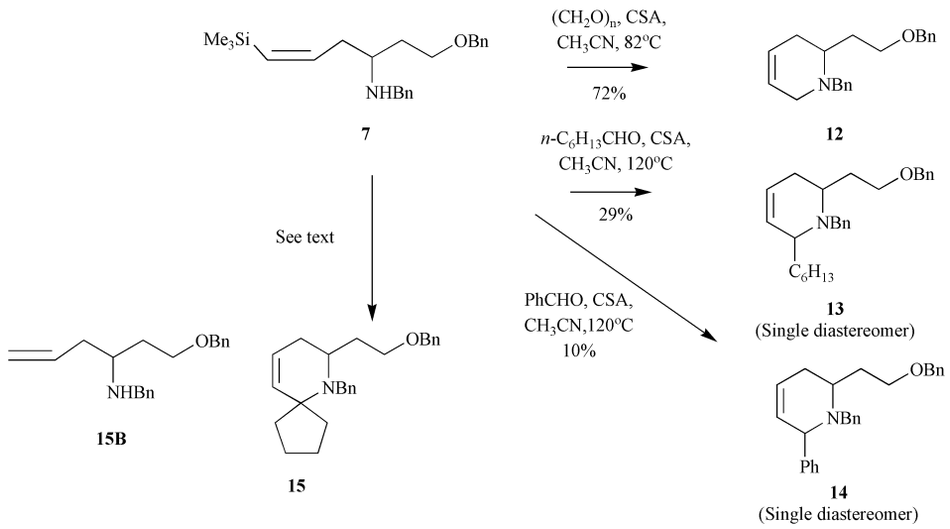
Vinylsilane-iminium ion cyclizations of *preformed* imines have so far only been reported to take place in moderate yields with acyclic imines derived from non-enolizable aldehydes[11,13,14] in the presence of Brønsted acids. To investigate the corresponding ketimine cyclization, amine **6** was treated with cyclopentanone to afford **8** in 92% yield (Scheme 5). Unfortunately, no cyclization to spirocycle **9** occurred, either by treatment of **8** with TFA in refluxing CH_3CN or by *in situ* imine formation and subsequent treatment with TFA at reflux. Attempts to promote the cyclization of **8** with the Lewis acids TMSOTf, $BF_3{\cdot}OEt_2$, $TiCl_4$ or $Ti(^iPrO)_4$ at either −78 °C or room temperature or alternatively activation of **8** by *in situ* acylation with



Scheme 4



Scheme 5



Scheme 6

p-$NO_2C_6H_4COCl$ were also unsuccessful. In a control experiment, amine **6** was transformed into imine **10** and subjected to TFA in CH_3CN at 80 °C. This gave cyclized products **11A** and **11B** as a 1 : 1 diastereomeric mixture in a moderate 37% combined yield. Lack of diastereoselectivity in such cyclizations has been noted earlier for analogous imines.[13,14]

Most vinylsilane-iminium ion cyclizations in the literature have been reported to take place by *in situ* treatment of a secondary amine with excess paraformaldehyde in CH_3CN or another polar solvent at reflux in the presence of a strong Brønsted acid,[10–12] while cyclization with heptanal as the aldehyde required reaction temperatures of 120 °C.[11] Accordingly, application of standard cyclization conditions (paraformaldehyde, CSA, refluxing CH_3CN) to amine **7** also promoted a smooth cyclization to give **12** in 72% yield (Scheme 6). The analogous reaction with heptanal at 120 °C gave the cyclized product **13** as a single diastereomer although in only 29% yield, while the less reactive benzaldehyde afforded diastereomerically pure **14** in 10% yield. Compound **14** was shown by NOE difference experiments to be the *trans*-2,6-isomer with the phenyl group pseudoequatorial (Fig. 2). Attempted cyclization by treatment of **7** with cyclopentanone and CSA at 140 °C led only to a slow protodesilylation while use of the stronger acid TfOH led to complete and rapid protodesilylation to give **15B** in 75% isolated yield.

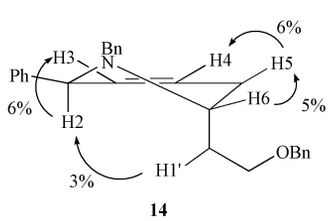
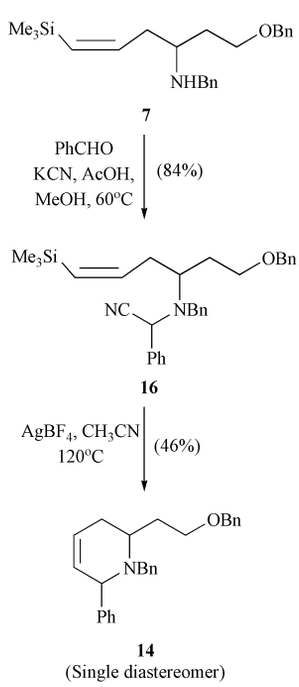


Fig. 2 Relevant NOEs for **14**.

In an attempt to raise the yields of these cyclizations and to promote the desired ketiminium reaction, experiments were carried out with microwave irradiation as the source of heat.[27] Unfortunately, microwave irradiation reactions of **7** with heptanal, benzaldehyde and cyclopentanone, respectively, with CSA in acetonitrile at 160 °C gave results similar to those obtained under thermal conditions, while reaction temperatures of 200 °C effected only decomposition of both starting material and products. The microwave irradiation experiments were also performed with the milder acid pyridinium p-toluenesulfonate (PPTS) or totally without addition of acid in either acetonitrile, methanol or water, as the solvents, but no cyclization was detectable. The same lack of reactivity was observed when equimolar amounts of **7** and benzaldehyde were adsorbed on solid supports (zeolites, neutral Al_2O_3, silica gel or montmorillonite K10) followed by heating in a commercial microwave oven.

The yield of **14** could be enhanced somewhat by conversion[28] of **7** into the α-aminonitrile **16** in 84% yield (Scheme 7) followed by $AgBF_4$-promoted cyanide abstraction and cyclization.[11,13,14] This gave **14** in 46% yield, exclusively as the *trans*-diastereomer, as noted for the previous cyclization (Scheme 6). The stereoselective formation of the *trans*-isomer is also in accordance with previously reported results for silver-promoted cyclization of some other α-aminonitriles.[13,14] Disappointingly, the analogous conversion of **7** into the α-aminonitrile by treatment with cyclopentanone did not proceed even at 120 °C (for comparison, quantitative conversion of cyclopentanone with benzylamine took place at 60 °C). At this point we abandoned our attempts to find reaction conditions conducive to cyclization of ketiminium ions with vinyl silanes.



Scheme 7

2. Quantum mechanical investigations of reaction mechanism

Having established that ketiminium species are too unreactive toward vinylsilanes, we now return to the general question of

Table 1 (*Z*)-Vinylsilanes. Calculated free energies relative to starting iminium ions **17**, in kJ mol^{-1}

	R = H				R = Me			
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**
18	27.4	78.9	72.8	121.8	38.2	94.9	81.4	125.0
19	2.5	56.7[b]	51.7	97.2[b]	18.0	87.2	62.6	116.0
20	33.4	91.8	83.0	136.2	38.4	103.2	83.1	133.4
21	−5.8	75.2	48.8	99.0	−15.9	49.6	42.2	91.5
22	[a]	[a]	[a]	[a]	23.6	92.7	66.9	120.3
23	54.2	105.6	100.8	146.1	60.8	113.7	108.6	142.3

[a] Not determined. [b] The trimethylsilyl group had migrated to C4 in the geometry optimization.

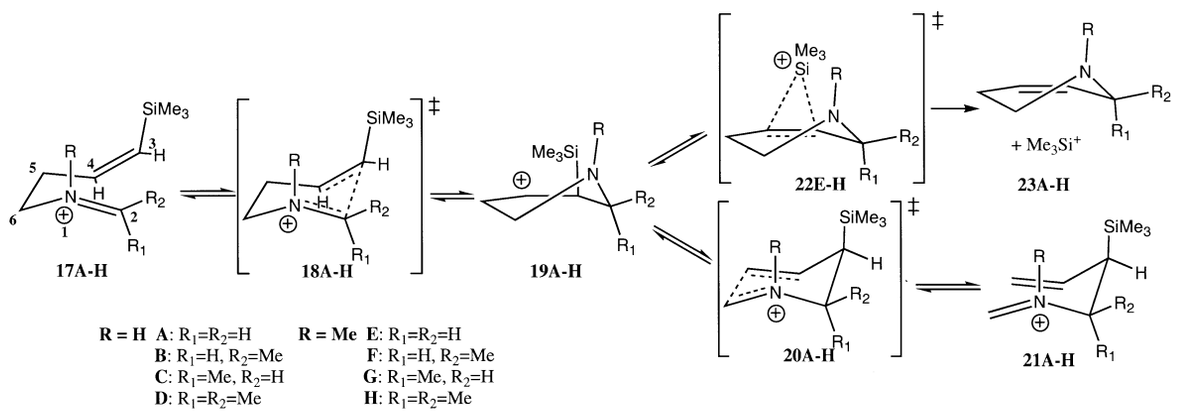


Fig. 3 Calculated mechanism for cyclization of (*Z*)-vinylsilanes.

reaction mechanism (Scheme 1) and the diastereoselectivity observed in the present investigation (Schemes 6 and 7) and in others.[13,14] For mechanistic insight we decided to investigate the vinylsilane-iminium ion cyclization by quantum-mechanical methods at the B3LYP level,[29–36] which to the best of our knowledge has not been reported previously. Both reactions of iminium species derived from primary (Fig. 3, **A**–**D**) and secondary (Fig. 3, **E**–**H**) amines with formaldehyde, acetaldehyde and acetone, respectively, were studied (Fig. 3, **17**). Since both the (*E*)- and the (*Z*)-iminium ions in principle can cyclize, two sets of calculations were carried out for aldiminium ions with the methyl substituent either pseudoequatorial (Fig. 3, **B** and **F**) or -axial (Fig. 3, **C** and **G**), respectively, in chair-like transition states and intermediates. All calculations were conducted *in vacuo* since solvation effects are believed to be largely independent of the methyl substitution pattern and thus to be of equal size for similar structures, regardless of the number of methyl groups.

2.1 (*Z*)-Vinylsilanes. For all (*Z*)-vinylsilanes, both with protonated imines (**17A**–**D**) and *in situ* formed iminium ions (**17E**–**H**), the first steps of the reaction mechanism can be described as depicted in Fig. 3. The well-known hyperconjugative stabilization of the β-carbocation by the silyl substituent is great enough to allow for short-lived intermediates **19** and thus any aza-Cope rearrangement to form **21** (*via* transition states **20**) does *not* take place concertedly for (*Z*)-vinylsilanes.

Since all calculations were carried out in the absence of external nucleophiles, the transition states **22** for direct loss of the silyl substituent[37] actually proved to be transition states for facile migration of the trimethylsilyl substituent from C3 to C4 (only calculated for **E**–**H**). From **19A** as the simplest example, an intermediary π-silyl complex similar in structure to transition states **22** was localized and proved to be only 0.6 kJ mol^{-1} higher in energy than **19A** which clearly demonstrates the softness of the energy curve. No further calculations were carried out *in vacuo* for the unaided elimination of the silyl substituent since the irreversible loss of the silyl substituent is presumed to be energetically much more favourable in the presence of external nucleophiles. The relative energies of product amines together with the free trimethylsilyl cation (**23**) were also calculated but due to the high energy of the unstabilized silyl cation in the gas phase, these energies do not reflect the presumed stability of the product amines.

Surprisingly, the β-carbocations **19** are stable only with a pseudoaxial *N*-substituent. The result of forcing R into pseudoequatorial positions followed by energy minimizations was also partial loss of the silyl substituent to give intermediary π-silyl complexes similar in structure to transition states **22** but with R pseudoequatorial.

As can be seen from the calculated free energies relative to reactant iminium ions **17** for all transition states and intermediates (Table 1, depicted in Fig. 4), the two largest energy barriers of similar heights in the reaction profile are for the initial formation of the β-carbocations **19** *via* transition states **18** and the rearrangement to allylsilanes **21** *via* transition states **20**. The three possible pathways available to **19** [reversal to **17**, rearrangement to **21** and the facile irreversible loss of the silyl substituent to give **23** (*vide supra*)] are all energetically so feasible that they presumably coexist. In the following discussion formation of the initial cyclization transition states **18** has been emphasized.

The calculations also show that the energies to form transition states **18** are very dependent on the degree of substitution of the iminium carbon, with the iminium ions **17A** and **17E** from formaldehyde being the most reactive and the ketiminium ions **17D** and **17H** being the least reactive. A combination of steric bulk and alkyl group stabilization of the positive charge would account for this. This is in line with the experimental results, where even microwave irradiation did not provide sufficient energy for the cyclization of ketiminium ions, and it does not seem likely that suitable reaction conditions for this type of cyclization can be found.

The reaction profiles for cyclization of the (*E*)- and (*Z*)-aldiminium ions (**17B/F** and **17C/G**, respectively) are generally very similar with the latter being slightly favoured, so there can only be smaller steric clashes between a pseudoequatorial methyl group (**B/F**) and the pseudoaxial trimethylsilyl substituent in the various chair-like transition states and intermediates. When *N*-alkyl substituents are present, this

Table 2 (*Z*)-Vinylsilanes. Selected bond lengths in geometry optimized structures, in Å

	R = H				R = Me			
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**
17 C2–C3	4.539	4.650	4.540	4.646	3.518	3.668	4.652	4.744
18 C2–C3	2.007	1.791	1.918	1.779	1.944	1.852	1.906	1.849
19 C2–C3	1.548	1.498[a]	1.554	1.501[a]	1.568	1.589	1.572	1.586
20 C2–C3	1.627	1.652	1.640	1.671	1.612	1.647	1.605	1.664
17 C5–C6	1.543	1.540	1.543	1.541	1.551	1.545	1.544	1.544
18 C5–C6	1.617	1.638	1.621	1.631	1.627	1.638	1.628	1.639
19 C5–C6	1.560	1.547[a]	1.557	1.545[a]	1.589	1.586	1.587	1.575
20 C5–C6	2.108	2.072	2.102	2.070	2.067	2.020	2.042	2.007
17 C3–Si	1.915	1.912	1.914	1.912	1.914	1.909	1.902	1.905
18 C3–Si	1.955	1.989	1.965	1.998	1.965	1.986	1.970	1.989
19 C3–Si	2.175	2.193[a]	2.174	2.184[a]	2.104	2.134	2.103	2.170
20 C3–Si	1.955	1.969	1.963	1.970	1.981	1.984	1.988	1.984

[a] The trimethylsilyl group had migrated to C4 in the geometry optimization, **19** C4–Si is given.

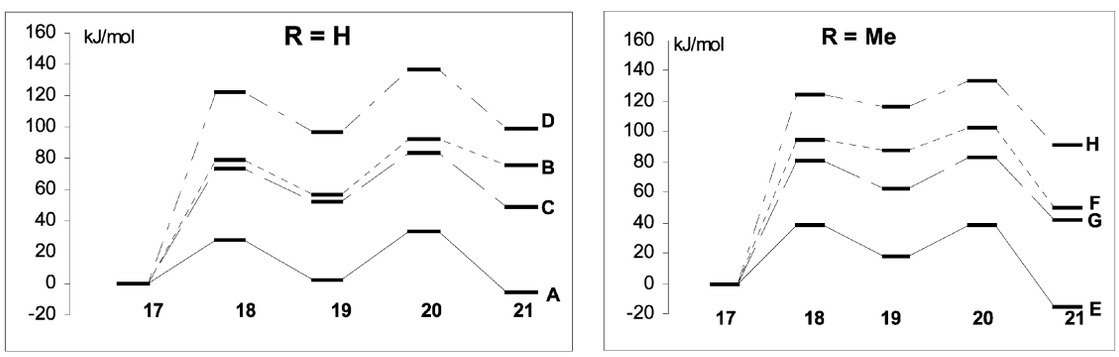
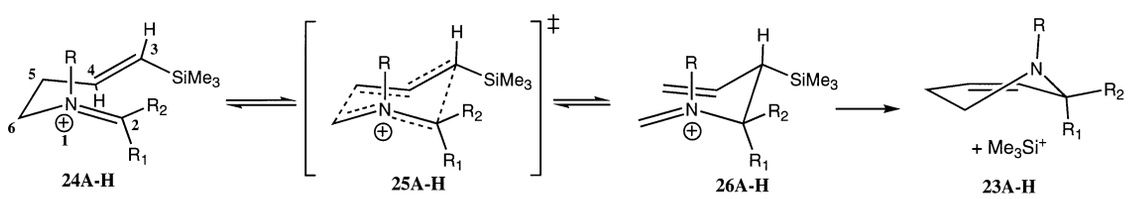


Fig. 4 Free energy reaction profiles for (*Z*)-vinylsilanes.



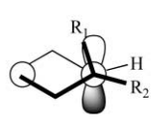
R = H **A**: R_1=R_2=H **R = Me** **E**: R_1=R_2=H
B: R_1=H, R_2=Me **F**: R_1=H, R_2=Me
C: R_1=Me, R_2=H **G**: R_1=Me, R_2=H
D: R_1=R_2=Me **H**: R_1=R_2=Me

Fig. 5 Calculated mechanism for cyclization of (*E*)-vinylsilanes.

reactivity difference (**G** compared to **F**) is somewhat more pronounced, however (see Fig. 4, R = Me).

The stabilizing hyperconjugation when the C–Si bond and the vacant p-orbital of the β-carbocations **19** are coplanar is demonstrated in particular by the elongated C–Si bonds (Table 2, **19** C3–Si) where this bond length is in the range of 2.103–2.193 Å compared to C–Si bond lengths of 1.902–1.915 Å observed for **17** and 1.880–1.890 Å observed for the three methyl groups on silicon. This is in accordance with the work of White *et. al.*[38] who have shown by X-ray crystallography that the Si–C bond lengthens with increasing electron demand. Another interesting feature is that the C2–C3 distance in transition states **18** is generally shorter when pseudoequatorial methyl groups are present (**B**,**D**,**F**,**H**). This could be interpreted as a later transition state in accordance with Hammond's postulate and the Marcus equation,[39,40] since unfavourable sterical clashes of the pseudoequatorial methyl groups (R_2=Me) and the pseudoaxial trimethylsilyl substituent in the carbocations **19B**,**D**,**F** and **H** raise their energies and therefore delay the transition states for their formation.

2.2 (*E*)-Vinylsilanes. In contrast to the (*Z*)-vinylsilanes, all the analogous (*E*)-vinylsilanes **24A**–**H** have only a poor overlap between the C–Si σ-orbital and the empty p-orbital since these cannot be coplanar (Fig. 6). In accordance with this, our calculations revealed no β-carbocations analogous to **19** as intermediates in the reactions of (*E*)-vinylsilanes[41] and these substrates thus participate in the aza-Cope rearrangement in a concerted fashion prior to cyclization (Fig. 5). As can be seen from the calculated free energies (Table 3, depicted in Fig. 7), the energy barriers for the rearrangement follow the same pattern as for the (*Z*)-vinylsilanes, *i.e.* they are very dependent on the degree of substitution of the iminium carbon. Thus, the iminium ions **24A/E** from formaldehyde are the least hindered and most reactive while rearrangement of the ketiminium ions **24D/H** is much higher in energy.



(*Z*)-vinylsilanes : R_1=Me_3Si, R_2=H
(*E*)-vinylsilanes : R_1=H, R_2=Me_3Si

Fig. 6 Orientation of C–Si bond and empty p-orbital in (*Z*)- and (*E*)-vinylsilane carbocations.

Table 3 (*E*)-Vinylsilanes. Calculated free energies relative to starting iminium ions **24**, in kJ mol^{-1}

	R = H				R = Me			
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**
25	35.1	82.9	92.5	140.6	48.4	91.4	89.1	133.1
26	9.0	60.4	60.5	115.4	9.3	57.5	49.3	108.2
23	68.8	112.4	115.3	160.7	86.2	123.3	122.2	157.7

Table 4 (*E*)-Vinylsilanes. Selected bond lengths in geometry optimized structures, in Å

	R = H				R = Me			
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**
24 C2–C3	4.408	4.491	4.430	4.479	3.223	4.608	4.358	3.791
25 C2–C3	1.634	1.650	1.656	1.676	1.654	1.674	1.673	1.697
24 C5–C6	1.544	1.542	1.545	1.544	1.557	1.543	1.544	1.547
25 C5–C6	1.959	1.958	1.963	1.964	1.913	1.915	1.922	1.930
24 C3–Si	1.906	1.904	1.904	1.902	1.905	1.900	1.899	1.898
25 C3–Si	1.966	1.974	1.967	1.979	1.960	1.967	1.961	1.973

Table 5 α-Substituted (*Z*)-vinylsilanes. Calculated free energies relative to starting iminium ions **27C** (R = H) and **27G** (R = Me), respectively, in kJ mol^{-1}

	R = H				R = Me			
	A	**B**	**C**	**D**	**E**	**F**	**G**	**H**
27	−6.3	−6.5	0	0.1	−18.3	−14.6	0	−7.7
28	66.4	76.1	65.2	84.8	76.7	78.3	68.6	81.9
29	49.3[a]	60.0[a]	45.8	59.1	70.5	69.9	51.5	53.9
30	69.1	82.0	64.4	83.5	76.1	81.7	60.3	70.5
31	−3.3	4.1	1.7	11.7	−6.5	−2.3	−8.3	−2.7
32	98.2	102.5	102.4	98.3	140.4	143.3	143.3	140.5

[a] The trimethylsilyl group had partly migrated to give a π-silyl complex in the geometry optimization.

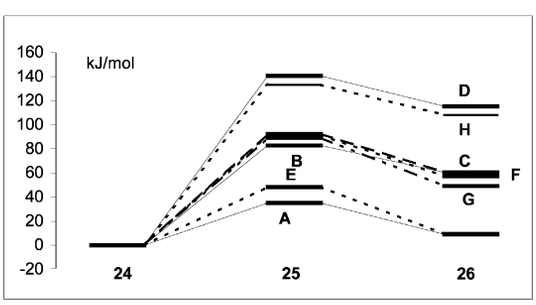


Fig. 7 Free energy reaction profiles for (*E*)-vinylsilanes.

The lack of effective hyperconjugation of the C–Si bond for (*E*)-vinylsilanes is also demonstrated by C–Si bonds in the range of 1.960–1.979 Å (Table 4) in the transition states **25** compared to the elongated C–Si bonds in the range of 2.103–2.193 Å observed for the β-carbocations **19** from the (*Z*)-vinylsilanes. The bond lengths in the transition states **25** are generally slightly longer for the ketiminium ions (**25D/H**) which might be interpreted as a "looser" transition state caused by unfavourable steric interactions of the additional methyl groups.

The activation energies are generally slightly higher than for the corresponding (*Z*)-vinylsilanes but probably not enough to preclude the reaction to occur with iminium ions derived from formaldehyde[42] or higher aldehydes. For the (*E*)-vinylsilanes, the small reactivity difference between (*E*)- and (*Z*)-iminium ions (**24B/F** and **24C/G**, respectively) is in favour of the former, presumably due to smaller steric clashes between a pseudoequatorial methyl group (**B/F**) and the pseudoequatorial trimethylsilyl substituent.

2.3 α-Substituted (*Z*)-vinylsilanes. In an attempt to explain the observed diastereoselectivity in the vinylsilane-iminium ion cyclization when substituents α to nitrogen of a secondary amine were present (**13** and **14**, Schemes 6 and 7) together with the complete lack of diastereoselectivity for preformed imines from primary amines (**11A/B**, Scheme 5), the calculations were repeated for aldiminium ions with a methyl group either pseudoequatorial (R_4 = Me, **A**,**B**,**E** and **F**) or -axial (R_3 = Me, **C**,**D**,**G** and **H**) at C6 as a model study of the experimentally investigated benzyloxyethyl substituent (Fig. 8). Once more, silicon's hyperconjugative stabilization of the β-carbocation allowed for a short-lived intermediate **29**, implying that any aza-Cope rearrangement of **27** to **31** takes place in a stepwise fashion (*cf.* Section 2.1).

As can be seen (Table 5, depicted in Fig. 9), the energy barriers for formation of the initial transition states **28A**–**H** and for the aza-Cope rearrangements **30A**–**H** are of similar heights in the reaction sequence. For protonated imines (R=H, **A**–**D**) two favoured initial transition states of comparable energies, **28A** (66.4 kJ mol^{-1}) and **28C** (65.2 kJ mol^{-1}), both with a pseudoequatorial α-substituent (R_4 = Me) are found. Since **28A** and **28C** lead to diasteomerically different products, *i.e.* **32A** and **32C** which are *cis* and *trans* with respect to the ring substituents, respectively, this lack of energy difference also corresponds well with the observed lack of diastereoselectivity in the cyclization of preformed imines (*e.g.* **11A/B**, Scheme 5). In contrast to these results, one transition state **28G** (68.6 kJ mol^{-1}) is formed more readily than the remaining three for *in situ* formed iminium ions (R = Me, **E**–**H**). This corresponds well with the observed diastereoselectivity for iminium ions from secondary amines (*e.g.* **13** and **14**, Schemes 6 and 7). In analogy with the unsubstituted (*Z*)-vinylsilanes from secondary amines (Table 1,

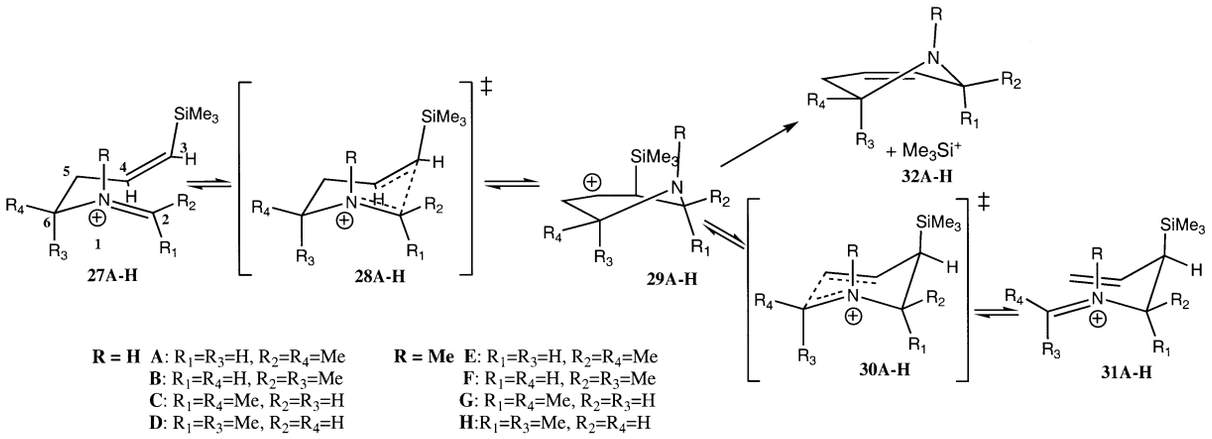


Fig. 8 Calculated mechanism for cyclization of α-substituted (*Z*)-vinylsilanes.

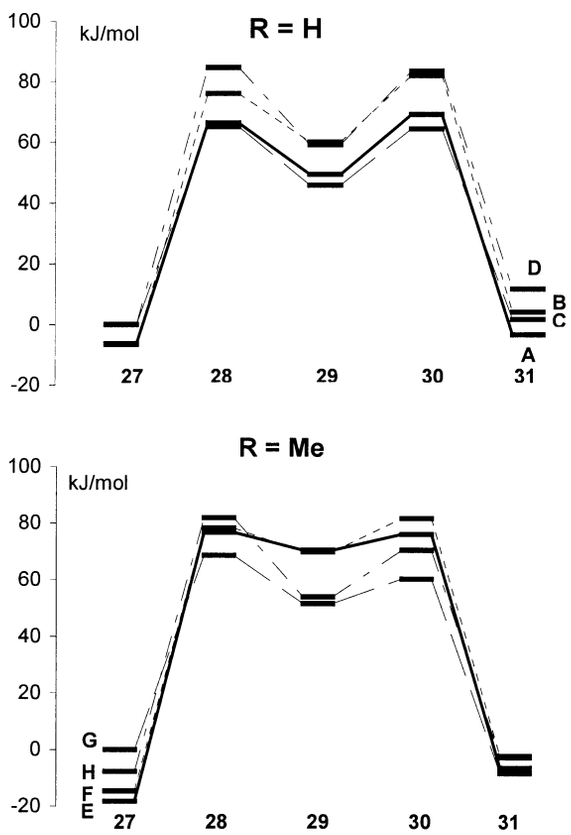


Fig. 9 Free energy reaction profiles for α-substituted (*Z*)-vinylsilanes.

18G compared to **18F**), the (*Z*)-iminium ion with its pseudo-axial methyl group (R_1 = Me) suffers from the least steric hindrance in the transition state **28G** while in all cases (**28A**, **28C** and **28G**), a pseudoequatorial α-substituent (R_4 = Me) is favoured. Quite interestingly, when the energies of the rearranged intermediates **31** relative to reacting iminium ions **27** are compared with the results for the rearranged aldiminium ions in Table 1 (**21B/C/F/G**, E = 42.2 − 75.2 kJ mol^{-1}), it can be seen that when alkyl substituents are present at C6, the energy difference between **31** and **27** is much smaller (Table 4, E = −6.5 − 11.7 kJ mol^{-1}). Altogether, the results of the quantum-mechanical calculations are in excellent agreement with the observed reactivity/diastereoselectivity trends in the vinylsilane-iminium ion cyclization.

Conclusions

In summary, a vinylsilane-ketiminium ion cyclization was investigated experimentally as a possible approach to 1-aza-spirocycles but even under conditions of microwave irradiation at high temperatures, no cyclization was observed. In line with previous results[11,13–15,19] vinylsilane-iminium ion cyclizations employing electrophilic species derived from aldehydes were more successful. High *trans* diastereoselectivity could be obtained for the cyclization of iminium species from secondary amines substituted α to nitrogen while no diastereoselectivity was observed for analogous cyclizations of iminium species from primary amines. Quantum-mechanical investigations of the reaction mechanism further underlined the difficulties of finding reaction conditions appropriate for cyclization of ketiminium species. The calculations also revealed that (*Z*)-vinylsilanes cyclize *via* a silicon-stabilized β-carbocation, and that any rearrangement of the starting material to an allylsilane-iminium species does *not* take place *via* a concerted aza-Cope rearrangement. For (*E*)-vinylsilanes, however, the aza-Cope rearrangement precedes cyclization and the overall reaction is energetically slightly less favoured than cyclization of the (*Z*)-isomers. Our calculations also provide the first cogent explanation for the observed *trans* diastereoselectivity for (*Z*)-vinylsilane iminium ions from secondary amines with substituents α to nitrogen and the lack of diastereoselectivity for (*Z*)-vinylsilane iminium ions from the corresponding primary amines.

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