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Factors Controlling the Alkyne Prins Cyclization: The Stability of Dihydropyranyl Cations

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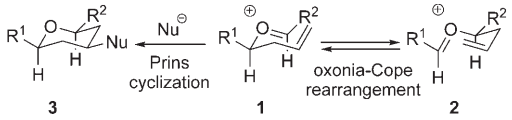
Abstract: The relative stability of the intermediates involved in the alkyne Prins cyclization and the competitive 2-oxonia-[3,3]-sigmatropic rearrangement was studied. This rearrangement was shown to occur slowly under typical alkyne Prins cyclization conditions when the allenyl oxocarbenium ion that results from the rearrangement is similar to or higher in energy than the starting alkynyl oxocarbenium ion. The formal 2-oxonia-[3,3]-sigmatropic rearrangement may be disfavored by destabilizing the resultant allenyl oxocarbenium ion or by stabilizing an intermediate dihydropyranyl cation. The trimethylsilyl group as a substituent at the alkyne and electron-withdrawing groups (CH_2Cl and CH_2CN) located at the α-position to the carbinol center are shown to be effective. DFT calculations suggest that these substituents stabilize the dihydropyranyl cations, thus leading to a more uniform reorganization of the electronic density in the ring, and do not have a direct effect on the formally positively charged carbon atom.

Keywords: alcohols · cations · cyclization · rearrangement · silanes

Introduction

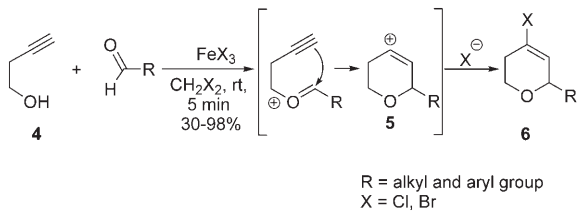
During the past two decades the Prins cyclization has emerged as a powerful tool in the synthesis of tetrahydropyran rings.[1] This methodology uses homoallylic alcohol[2] or homoallylic acetals[3] to generate an oxocarbenium ion as an intermediate to give the corresponding tetrahydropyran ring and has been applied to the synthesis of natural products.[4] While this reaction shows great potential in organic synthesis, two deleterious problems have been reported: a mixture of products and racemization.[5]

Several authors have reported mechanistic studies that show that the oxonia-Cope rearrangement is the main competitive process in the Prins cyclization (Scheme 1).[6] A detailed study, including factors that modulate these competitive processes, was recently reported by Rychnovsky and coworkers.[6b–d] The Prins cyclization of alkynes with homopropargyl acetals has also been reported, but this methodology has attracted much less attention.[7]



Scheme 1. Prins cyclization and oxonia-Cope rearrangement.

We recently described the alkyne Prins cyclization between homopropargyl alcohols and aldehydes in the presence of inexpensive, environmentally friendly, stable iron(III) halides to obtain 2-alkyl-4-halo-5,6-dihydro-2*H*-pyrans **6** (Scheme 2).[8] Trying to extend this study, we explored this methodology for the synthesis of 2,6-disubtituted dihydropyrans with secondary homopropargyl alcohols. However, the treatment of pent-4-yn-2-ol and 3-methylbutanal in the presence of iron(III) chloride led to unsaturated (*E*)-β-hy-



Scheme 2. Synthesis of 2-alkyl-4-halo-5,6-dihydro-2*H*-pyrans.

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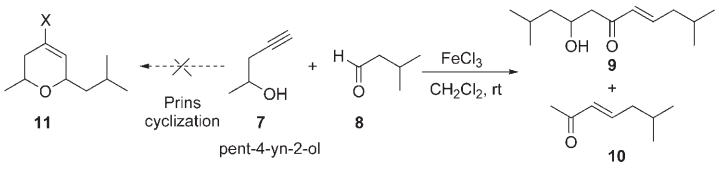
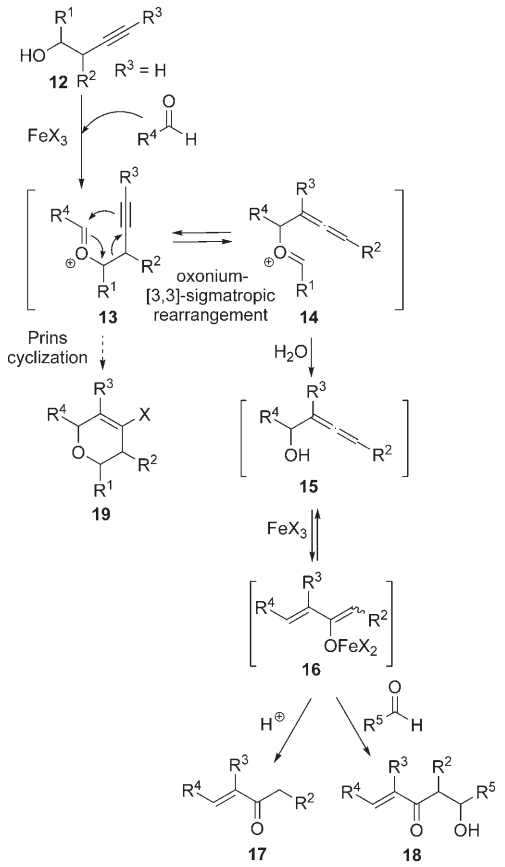
droxyketone **9** and (*E*)-α,β-unsaturated ketone **10** in a 2.5:1 ratio and 65% yield, without any trace of the expected Prins-type cyclic product **11** (Scheme 3).[9]



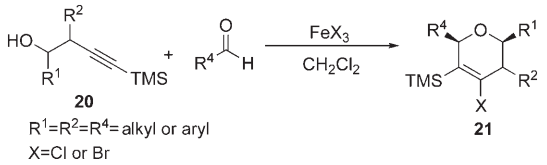
Scheme 3. Coupling of secondary homopropargyl alcohols and aldehydes catalyzed by iron(III) halides.

The addition of secondary homopropargyl alcohols to aldehydes promoted by ferric halide generates the oxocarbenium ion **13**, which undergoes a 2-oxonia-[3,3]-sigmatropic rearrangement to give allenolate **15**. Further intramolecular 1,3-oxygen transposition generates the unsaturated enolate **16**. Protonation or a subsequent coupling reaction with a suitable aldehyde leads to compounds **17** or **18**, respectively (Scheme 4). Thus, the course of the reaction (rearrangement or Prins cyclization) depends directly on the stability of the species involved, namely, **13** versus **14**.



Scheme 4. Proposed mechanism for the addition of secondary homopropargyl alcohols to aldehydes.

One of the factors that affects the relative stability of the sigmatropic isomers of this rearrangement is the nature of the R^4 group. Thus, when the bulkiness of R^4 is increased from methyl to cyclohexyl, the Prins dihydropyran was obtained as the major product. However, this is a particular case that does not permit full control over the sigmatropic rearrangement versus alkyne Prins cyclization. Recently, we reported that the presence of the trimethylsilyl (TMS) group at the triple bond ($R^3 = SiMe_3$) of secondary homopropargyl alcohols favors the alkyne Prins cyclization and minimizes the 2-oxonia-[3,3]-sigmatropic rearrangement as a competitive alternative pathway (Scheme 5).[10] This cyclization is highly stereoselective and affords *cis*-dihydropyran as the only isomer. The presence of the silyl group at the alkyne moiety is essential to achieve the reaction because when the acetylene unit is substituted with a methyl group the process is inhibited. In addition, the size of the substituent at the silicon atom is also a critical factor. For example, when the triple bond bears a triisopropylsilyl group instead of TMS, the reaction does not take place.



Scheme 5. Silyl alkyne Prins cyclization with silylated secondary homopropargyl alcohols and aldehydes.

Herein, we describe the different factors that control the alkyne Prins cyclization. We provide evidence that the relative rate of the formal 2-oxonia-[3,3]-sigmatropic rearrangement versus alkyne Prins cyclization depends on the type of substituents at the homopropargyl alcohol. The difference in energy between the initial cations and the product of the oxonia Cope rearrangement increases upon incorporating electron-withdrawing groups. In addition, we show that TMS and electron-withdrawing groups stabilize the dihydropyranyl cation intermediate by reorganizing the electronic density of the six-membered ring and not by its direct effect on the positively charged carbon atom.

Results and Discussion

Control of the alkyne Prins cyclization versus the sigmatropic rearrangement: The relative stability of intermediates **13** and **14** (Scheme 4) is the key factor to consider, inasmuch as it can favor the Prins reaction or the corresponding domino process. Therefore, we decided to perform theoretical calculations at the B3LYP/6–31G(d) level for simplified structures[11] with a trimethylsilyl group at the triple bond (**25** to **27**) and compared the results of these studies with our previous results from compounds **22**–**24**, **28**, and **29**.[10] The relative energies obtained from these calculations are summar-

ized in Figure 1. As reported before, the silyl dihydropyranyl cation **23** is 7.7 kcal mol^{-1} less stable than its open form and is protected from ring-opening by an activation energy of

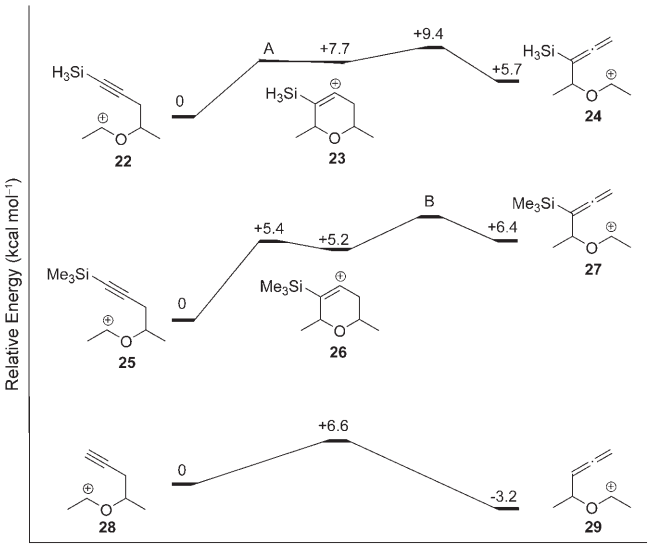
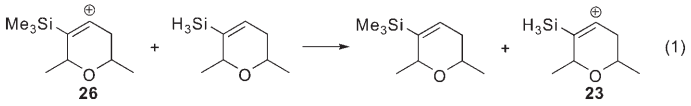


Figure 1. Silyl substituent effects on the relative-energy profile of formal 2-oxonia-[3,3]-sigmatropic rearrangements.

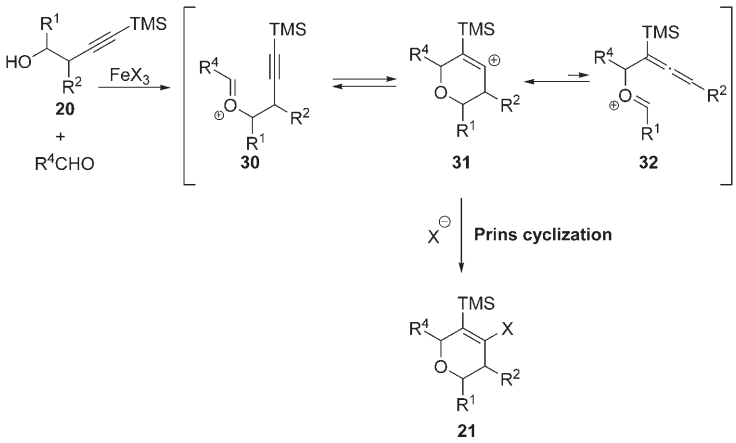
1.7 kcal mol^{-1}. This rearrangement is an endothermic process, thus being less favored than without silicon. Furthermore, the replacement of a silane group with a TMS group as a substituent results in a less-favored rearrangement. Thus, the α-trimethylsilyl allenyl cation **27** is 6.4 kcal mol^{-1} less stable than **25**, and the trimethylsilyl dihydropyranyl cation **26** is 1.2 kcal mol^{-1} more stable than **27**.[12]

In addition, the stabilities of the β-silyl cyclic vinyl cations were evaluated in the isodesmic hydride transfer equation.[13] The isodesmic reaction [Eq. (1)] shows that the silyl-substituted dihydropyranyl cation **23** is 32.7 kcal mol^{-1} higher in energy than cation **26**.



(1)

This stabilization is consistent with our proposed mechanism (Scheme 6), in which the dihydropyranyl cation **31** serves as a branch point in a 2-oxonia-[3,3]-sigmatropic rearrangement (**30**→**32**) and Prins cyclization (**31**→**21**). On the basis of calculations described above, we surmised that the generation of a trimethylsilyl dihydropyranyl cation, such as **31**, should lead to the alkyne silyl Prins product **21** more rapidly than the α-trimethylsilyl allenyl cation **32,**[14] formed by the Grob-type ring-opening reaction.[15] Cation **31** could then be trapped by attack of the corresponding halide, subsequently leading to the alkyne silyl Prins product **21**.

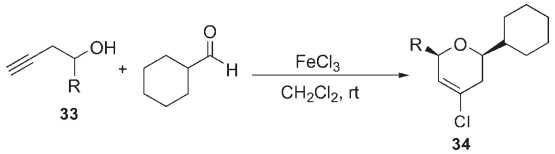


Scheme 6. Proposed mechanism for the silyl alkyne Prins cyclization.

Since the incorporation of a trimethylsilyl group as a substituent (**25**–**27**) favors the Prins cyclization by destabilization of the allenic cation **27**, we reasoned that similar results may be obtained by introducing other types of substituent that destabilize the corresponding allenic cation and consequently accelerate the Prins cyclization.

Based on the excellent work of Rychnovsky and co-workers,[6a] which showed that stabilizing and destabilizing groups near the carbinol center also affected the diastereoselectivity of the Prins cyclization, we decided to study the influence of electron-withdrawing groups located at the α-position of the hydroxy group, such as chloride or nitrile, on the relative rate of the ring-opening process versus alkyne Prins cyclization (Table 1). The corresponding secondary homopropargyl alcohols used for this study were prepared according to a reported procedure[16] and are further documented in the Supporting Information. Table 1 shows that in secondary homopropargyl alcohols with electron-withdrawing groups the alkyne Prins cyclization is a rapid process relative to the formal 2-oxonia-[3,3]-sigmatropic rearrangement. The *cis*-2,6-disubstituted dihydropyran was the main product with chloromethyl and cyanomethyl substituents, as electron-withdrawing groups favor the alkyne Prins cyclization (Table 1, entries 1 and 2, respectively), although the yield was lower with the cyanomethyl group.

Table 1. Substituent effects on the rate of the Prins Cyclization versus the formal 2-oxonia-[3,3]-rearrangement.



Entry	Substrate	R	Product	Yield [%][a]
1	**33a**	CH_2Cl	**34a**	68
2	**33b**	CH_2CN	**34b**	35

[a] Traces of noncyclic products through the formal 2-oxonia-[3,3]-sigmatropic rearrangement were not detected; the starting materials **33a** and **33b** were totally consumed.

DFT calculations: To provide further insight into the observed electronic effects, DFT theoretical calculations at the B3LYP/6–31G(d) level were performed on simplified structures. The results of these calculations are summarized in the energy diagram shown in Figure 2.

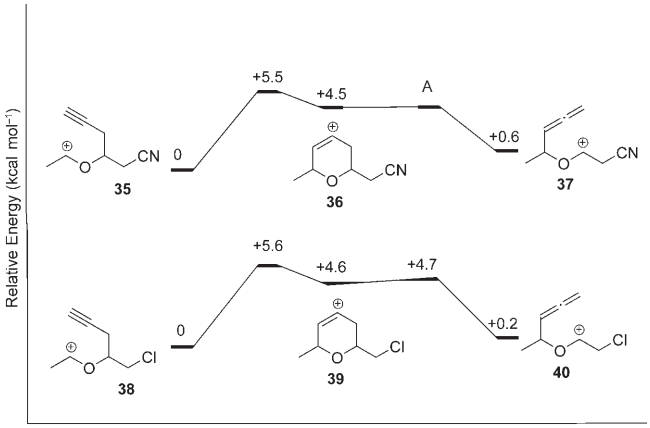
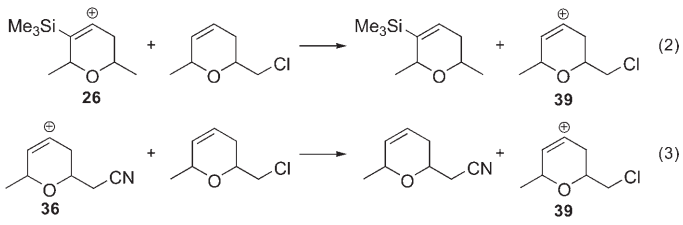


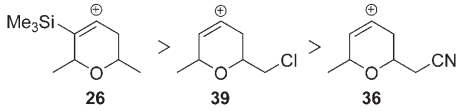
Figure 2. Substituent effects on the relative-energy profile of a formal 2-oxonia-[3,3]-rearrangement.

It should be noted that we were unable to locate a dihydropyranyl cation intermediate for the alkynyl carbocation **28**, thus presumably indicating a concerted pathway to **29** in an exothermic process (3.2 kcal mol^{-1}; Figure 1). The incorporation of cyanomethyl and chloromethyl substituents shows that both processes are slightly endothermic, thus permitting the dihydropyranyl cations **36** and **39**, respectively, to be detected as intermediate species. A ring-opening process from the dihydropyranyl cation **39** to the allenyl cation **40** requires a small activation energy of 0.1 kcal mol^{-1}, whereas ring-opening from **39** to **38** requires 1.0 kcal mol^{-1}. With the cyanomethyl substituent, the process is slightly more endothermic, but has a very similar energy diagram to the chloromethyl substituent. This increased energy of allenyl cations **37** and **40** (versus **35** and **38** respectively), which favors the alkyne Prins cyclization, is consistent with our hypothesis and the experimental data of Table 1. However, dihydropyranyl cation intermediates **36** and **39** are less protected from ring-opening (very small activation energy) to form allenyl cations **37** and **40** than the trimethylsilyl cation **26**. These data suggest that the dihydropyranyl cations **36** and **39** are more prone to ring-opening than **26**.



In addition, the isodesmic reaction in Equation (2) shows that TMS dihydropyranyl cation **26** is 25.7 kcal mol^{-1} lower in energy than cation **39**. Also, the isodesmic reaction in Equation (3) shows that the chloride-substituted dihydropyranyl cation **39** is 4.0 kcal mol^{-1} lower in energy than cation **36**.

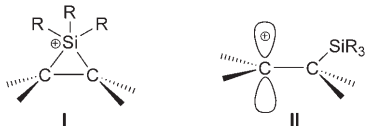
These two isodesmic reactions permit us to order the different dihydropyranyl cations **26**, **39**, and **36** in decreasing stability (Scheme 7). Interestingly, such an order is consistent with the obtained yields in the alkyne Prins cyclization, as **26** was obtained in the highest yield and **36** the lowest.



Scheme 7. Decreasing stability of the substituted dihydropyranyl cations.

Thus, we demonstrated that certain substituents (Me_3Si, CH_2Cl, and CH_2CN) stabilize the dihydropyranyl cations, with Me_3Si being the most effective. We then turned our attention to the reasons why these substituents stabilize dihydropyranyl cations.

Stability of dihydropyranyl cations: It is now well known that the silyl group hyperconjugatively stabilizes the intermediate β-carbenium ion. This process is called the β-effect,[17] as discovered by Ushakov and Itenberg in 1937.[18] The origin of this effect is more commonly attributed to the strongly stabilizing interaction between the C–Si bond orbital and a developing or fully formed empty p orbital of the carbenium ion at the β-position to the silicon atom.[19] The structure of the postulated intermediate species could be described as either a bridged structure **I**, in which the silicon atom exploits the ability to expand its coordination, or a β-silylated carbenium ion **II** (Scheme 8).[20]

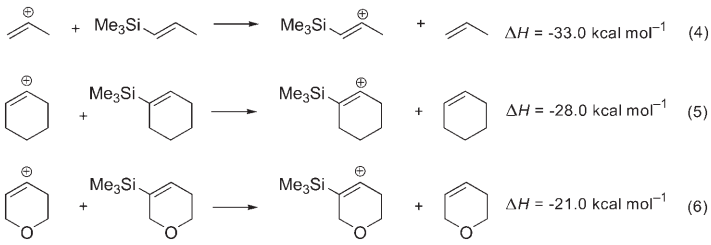


Scheme 8. Structure of the postulated species in the β-effect of a silicon atom in carbocations.

Vinyl cations are especially well suited for the study of β-hyperconjugation. The $C^+=C_\beta$ bond is shorter than a single bond and the σ bond of a β-substituent to the C_β atom is in the plane of the vacant 2p orbital on the C^+ atom, thus allowing maximum overlap for hyperconjugation. An NMR study of several β-silyl vinyl cations, developed by Siehl,[21] shows hyperconjugative stabilization of the positive charge by β-silyl substituents (Scheme 9). There are several studies on cyclic vinyl cations,[22] but to the best of our knowledge

Scheme 9. Si–C_β hyperconjugative stabilization in α-aryl-β-silyl vinyl cations.

none in which the β-silyl effect is considered.[23] For this reason, we decided to perform DFT calculations at the B3LYP/6–31G(d) level on different vinyl cations to observe the stabilization of the β-trimethylsilyl group with respect to the positive charge [see the isodesmic reactions in Eqs (4)–(6)].



Equation (4) shows the stabilizing effect of the β-silyl group in acyclic vinyl cations. Although it is evident that cyclic vinyl cations are less stable than acyclic analogues,[22a] the stabilizing effect of the β-trimethylsilyl group in cyclic vinyl cations can be seen from Equations (5) and (6).

Two methods were applied to confirm and analyze the structures of these cyclic vinyl cations.

1) Atoms-in-molecules (AIM) method: The method[24] of using the topology of the electronic charge density $\rho(r)$ provides accurate mapping of the chemical concept of atom, bond, and structure. The nuclear positions behave topologically as local maxima in $\rho(r)$. A bond critical point is found between each pair of nuclei, which are considered to be linked by a chemical bond. Furthermore, a ring critical point appears as a consequence of any ring of bonded atoms. A single-point energy calculation was performed on the previously optimized geometries by using B3LYPT/6–311+G-(d,p)//B3LYP/6–31G(d) for all the atoms involved to obtain the necessary electronic density for AIM analysis. This procedure showed that the dihydropyranyl and TMS dihydropyranyl cations are stable structures, as shown in molecular graphs (Figure 3).

Table 2 shows the numerical parameters at the different bond critical points that correspond to significant bonds in the cyclic vinyl cation structures.[25] The six bond critical points guarantee a ring system with prevailing covalent bonds, since the covalent interactions are defined by large electron-charge density values $\rho(r)$ in the bond region and negative values of its laplacian of charge density $\nabla^2\rho(r)$. However, the C2–C3 and C5–C6 bonds have lower $\rho(r)$ values and lesser covalent character (Table 2, entries 3, 4, 9, and 10, respectively). The bond ellipticity ε, a measure of the shape of the electron-density distribution in a plane

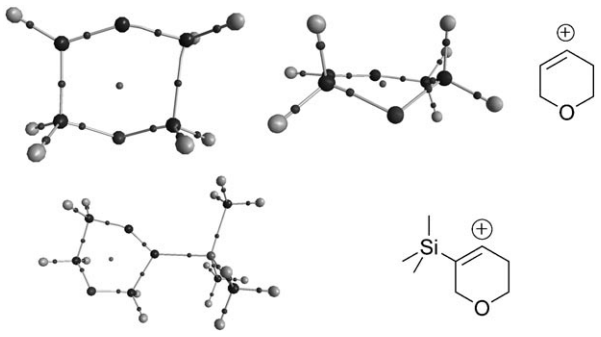


Figure 3. Molecular graphs that correspond to dihydropyranyl and trimethylsilyl dihydropyranyl cations. Small dots in bond paths are the bond critical points; small dots in the ring are ring critical points.

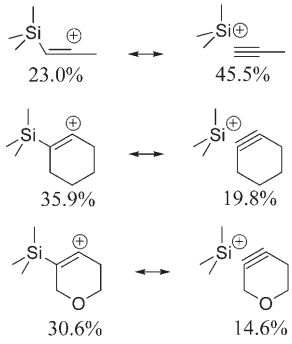
Table 2. AIM study of dihydropyranyl and TMS dihydropyranyl cations.

Entry	Bond	R	$\rho(r)$ [e a_0^{-3}]	$\nabla^2\rho(r)$ [e a_0^{-5}]	ε	λ_1/λ_3
1	C1–C2	H	0.368	−1.104	0.336	3.629
2	C1–C2	TMS	0.380	−1.153	0.220	3.601
3	C2–C3	H	0.201	−0.356	0.056	1.048
4	C2–C3	TMS	0.173	−0.232	0.041	0.882
5	C3–O4	H	0.264	−0.386	0.086	0.866
6	C3–O4	TMS	0.276	−0.443	0.096	0.901
7	O4–C5	H	0.293	−0.386	0.092	0.778
8	O4–C5	TMS	0.273	−0.405	0.067	0.855
9	C5–C6	H	0.131	−0.105	0.097	0.721
10	C5–C6	TMS	0.177	−0.262	0.048	0.922
11	C6–C1	H	0.307	−0.867	0.096	2.148
12	C6–C1	TMS	0.289	−0.783	0.050	1.879

through the bond critical point and perpendicular to the bond, has a range of around $\rho(r)=0.04$–0.09 according to the expected σ character (circular electronic distribution) of these bonds. In the case of bond C1–C2 (Table 2, entries 1 and 2, respectively) these values are greater, therefore showing one π orbital and a double-bond character for this interaction.[26]

The strength of a covalent bond depends on the electron density shared between the two bonded atoms and is also associated with the value of $\rho(r)$. A comparative analysis of the electron-charge density and the absolute value of selected bond critical points λ_1/λ_3 of C2–C3 and C5–C6 shows us the strength of these bonds between the unsubstituted structure and the TMS derivative. When R = H, C2–C3 is stronger than C5–C6 ($\rho(r)=0.201$ vs 0.131; Table 2, entries 3 and 9, respectively), but the replacement of the hydrogen atom by the TMS group produces a density reorganization that leads to similar $\rho(r)$ values ($\rho(r)=0.173$ and 0.177; Table 2, entries 4 and 10, respectively). Bond C2–C3 becomes stronger and C5–C6 weaker, but both become structurally more similar, thus reinforcing the ring character of the structure.

2) Natural bond orbital (NBO) analysis: In acyclic vinyl cations with β-silyl groups, Siehl reported the hyperconjugative stabilization of a positive charge.[21] We performed a NBO analysis[27] to provide evidence that this stabilization can occur in cyclic vinyl cations. In this analysis, the electronic wave function is interpreted in terms of a set of occupied Lewis orbitals and a set of unoccupied non-Lewis orbitals. Natural-resonance-theory analysis performed by the NBO 5.0 program shows that the contribution of the alkyne resonance structure (45.5%) is greater than the vinyl cation contribution (23.0%) in the case of the acyclic vinyl cation. In the cyclic vinyl cation, the alkyne resonance structure contribution decreases from the TMS cyclohexenyl (19.8%) to the TMS dihydropyranyl cation (14.6%), probably as a result of the angle and torsional strains (ring strains) of the alkyne function in a six-membered ring (Scheme 10). Therefore, there is less hyperconjugative stabilization of β-silyl groups in cyclic than acyclic vinyl cations.[28] However, we did not observe direct stabilization of the cyclic vinyl cation charge by the TMS group (Table 3; compare entries 1 and 2 with 3 and 4, respectively, in terms of the charge distribution).



Scheme 10. Si–C_β hyperconjugative stabilization in α-aryl-β-silyl vinyl cations.

Delocalization effects can be identified from the presence of off-diagonal elements of the Fock matrix on basis of the NBO and the strength of these delocalization interactions can be estimated by the second-order perturbation energies (donor–acceptor). This analysis is carried out by examining all the possible interactions between "filled" (donor) Lewis-type NBOs and "empty" (acceptor) non-Lewis NBOs and estimating their energy by using the second-order perturbation theory. These interactions lead to donation of occupancy from the localized NBOs of the idealized Lewis structure into the empty non-Lewis orbitals. Table 3 shows the main second-order perturbative energy interaction and the bond order of some selected bonds of the cyclic vinyl cations.

In the first case with the cyclohexenyl cation (Table 3, entry 1), there is an electron-donating contribution from the σ_{C2-C3} and σ_{C5-C6} orbitals towards the p orbital of the vinyl cation at C1 (p_1). The major contribution comes from the σ_{C5-C6} orbital (51.0 kcal mol^{-1}), thus causing a weakening of this bond, as can be seen in the bond order (C5–C6: 0.634 versus C2–C3: 0.958). The same behavior was observed for the dihydropyranyl cation (Table 3, entry 2), both σ orbitals contribute to the vinyl cation stabilization, but in this case the contribution of the σ_{C5-C6} orbital is even greater than for cyclohexenyl (59.5%), in which there is an additional interaction between the unshared electron pair on the endocyclic oxygen atom and the σ_{C5-C6} orbital, which is similar to the well-known anomeric effect.[29] This electronic donation from the endocyclic oxygen atom contributes to raising the electron density of the σ_{C5-C6} orbital, thus leading to a more weakened C5–C6 bond. The total and covalent bond order of C5–C6 decreases from the cyclohexenyl cation to the dihydropyranyl cation, as seen by comparing the total and covalent bond orders (Table 3, entries 1 and 2). The C2–C3 bond has a more covalent character than C5–C6 (0.848 versus 0.361, respectively; Table 3, entry 2). For this reason, the cyclic structure of the dihydropyranyl cation is strongly allenic in character.

Table 3. NBO analysis of cyclic vinyl cations.

Entry	Energy interaction[a] [kcal mol^{-1}]	Bond order[b]	Charges[c]
1	25.1 $\sigma_{2,3}\rightarrow p_1$; 51.0 $\sigma_{5,6}\rightarrow p_1$	0.958 **0.858**; 0.634 **0.565**	+0.40; -0.25; -0.53
2	26.6 $\sigma_{2,3}\rightarrow p_1$; 59.5 $\sigma_{5,6}\rightarrow p_1$; 18.7 lp→$\sigma^*_{5,6}$	0.922 **0.848**; 0.416 **0.361**	+0.34; -0.29; -0.54
3	20.8 $\sigma_{Si,2}\rightarrow p_1$; 26.0 $\sigma_{2,3}\rightarrow p_1$; 34.7 $\sigma_{5,6}\rightarrow p_1$	0.928 **0.817**; 0.931 **0.847**	+0.38; -0.45; -0.54
4	17.2 $\sigma_{Si,2}\rightarrow p_1$; 31.5 $\sigma_{2,3}\rightarrow p_1$; 34.5 $\sigma_{5,6}\rightarrow p_1$; 13.2 lp→$\sigma^*_{2,3}$; 12.5 lp→$\sigma^*_{5,6}$	0.883 **0.768**; 0.775 **0.639**	+0.34; -0.48; -0.56
5	43.2 $\sigma_{2,3}\rightarrow p_1$; 29.3 $\sigma_{5,6}\rightarrow p_1$; 12.7 lp→$\sigma^*_{2,3}$; 11.0 lp→$\sigma^*_{5,6}$	0.722 **0.569**; 0.785 **0.656**	–

[a] Main second-order perturbative energy interaction. [b] Total (normal) and covalent bond orders (bold). [c] Main charge distributions.

Different behavior was observed in the trimethylsilyl cyclic vinyl cations as a result of the presence of the substituent silyl groups. In the TMS cyclohexenyl cation (Table 3, entry 3), both the σ orbitals contribute electrons towards p_1 in almost the same order of magnitude as the σ_{C2-Si} orbital does towards p_1 (20.8 kcal mol^{-1}). The presence of the TMS group reinforces the ring character of this cation, thus leading to an almost equal contribution from the C2–C3 and C5–C6 bonds, of which the latter is stronger with greater covalency relative to the cyclohexenyl cation (Table 3, entry 1). In the TMS dihydropyranyl cation (Table 3, entry 4), there is stabilization of the σ_{C2-C3}, σ_{C5-C6}

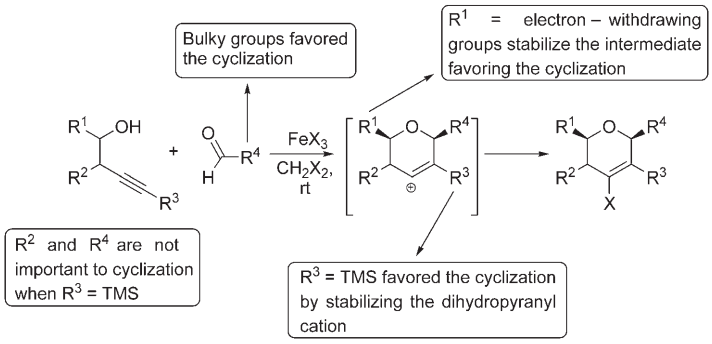
(31.5 and 34.5 kcal mol^{-1}, respectively), and σ_{C2-Si} (17.2 kcal mol^{-1}) orbitals and an equal destabilizing interaction between the unshared electron pairs on the oxygen atom and the σ_{C2-C3} and σ_{C5-C6} orbitals (13.2 and 12.5 kcal mol^{-1}, respectively). The TMS group produces a slight weakening of the C2−C3 bond, thus reinforcing the C5−C6 bond with respect to the dihydropyranyl cation (Table 3, entry 2). The bond order values of C2−C3 and C5−C6 are almost equal. Therefore, the cyclic structure is reinforced, thus decreasing the possibility of the allenic form.

The β-silyl substituents increase the bond order C5−C6 to make it almost equal to C2−C3 (Table 3, entries 3 and 4). Furthermore, the presence of the β-TMS group stabilizes the cyclic vinyl cation by inducing a more uniform reorganization of the electron density in the ring and not by a direct effect on the positively charged carbon atom at C1$^+$.

NBO analysis of dihydropyranyl cations with electron-withdrawing groups at C5, such as dihydropyranyl **39**, showed similar behavior to those cations described above (Table 3, entry 5). This analysis shows that σ_{C2-C3} and σ_{C5-C6} stabilize the p_1 orbital, an equal interaction between the unshared electron pairs on the oxygen atom and the σ_{C2-C3} and σ^*_{C5-C6} orbitals, with the same electron-density reorganization as above. In this case, the chloromethyl substituent at C5 produces a similar ring stabilization to the β-silyl groups. The bond orders of C2−C3 and C5−C6 are almost equal, which is in agreement with the experimental data of Table 1.

Conclusion

In summary, to control the alkyne Prins cyclization versus the 2-oxonia-[3,3]-rearrangement the nature of the substituents in both the homopropargyl alcohol and aldehyde is important (Scheme 11). In secondary homopropargyl alcohols, one of the factors that affects the relative stability of the sigmatropic isomers of this rearrangement is the bulkiness of the R^4 group. However, the most important factor is the presence of groups able to destabilize the resultant allenyl oxocarbenium ion. Thus, TMS groups at R^3 or electron-withdrawing groups at R^1 disfavored the allenyl oxocarbenium ion of the 2-oxonia-[3,3]-sigmatropic rearrangement, thus favoring the alkyne Prins cyclization. However, the substituents at R^2 and R^4 have no influence over the control of the cyclization when R^3 = TMS. In addition, stabilizing the dihydropyranyl cation intermediate raises the energy of the transition state for ring-opening and effectively eliminates the 2-oxonia-[3,3]-rearrangement. Ab initio theoretical calculations show that the TMS group stabilizes the six-membered ring structure of the dihydropyranyl cation by reorganizing the electronic density and not by a direct β-silyl effect over the positively charged carbon atom.



Scheme 11. Factors controlling the alkyne Prins cyclization.

Experimental Section

General methods and computational data are given in the Supporting Information.

General procedure for a ferric chloride-promoted alkyne Prins cyclization (Table 1): Anhydrous $FeCl_3$ (1 equiv) was added in one portion to a solution of secondary homopropargyl alcohol (1 equiv) and aldehyde (1 equiv) in dry CH_2Cl_2 (0.1 M). The reaction was concluded after approximately 1 min, quenched by the addition of water with stirring for 10 min, and the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried over magnesium sulfate, and the solvent was removed under reduced pressure. This crude reaction mixture was purified by flash column chromatography on silica gel (eluent: *n*-hexane/EtOAc).

Preparation of the starting materials and products in Table 1:

1-Chloropent-4-yn-2-ol and 1-cyanopent-5-yn-3-ol: Prepared in a racemic form following the previously reported procedure.[30,31]

***cis*-4-Chloro-2-chloromethyl-6-cyclohexyl-3,6-dihydro-2*H*-pyran (33a; Table 1, entry 1)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.78 (s, 1H), 3.93 (s, 1H), 3.76 (m, 1H), 3.54 (dd, J = 11.2, 5.7 Hz, 1H), 3.44 (dd, J = 11.2, 5.6 Hz, 1H), 2.30 (m, 2H), 1.64 (m, 5H), 1.46 (m, 1H), 1.07 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 128.5 (C), 125.3 (CH), 79.5 (CH), 73.6 (CH), 45.9 (CH_2), 42.3 (CH), 36.1 (CH_2), 28.1 (CH_2), 27.6 (CH_2), 26.2 (CH_2), 25.9 ppm (2 CH_2); IR (film): $\tilde{\nu}$ = 2931.4, 1730.9, 1670.4, 1589.5 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{18}Cl_2O$ (249.07): C 57.84 H 7.28; found: C 57.85 H 7.64.

***cis*-2-(4-Chloro-6-cyclohexyl-3,6-dihydro-2*H*-pyran-2-yl)acetonitrile (34a; Table 1, entry 2)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.78 (s, 1H), 3.96 (s, 1H), 3.85 (m, 2H), 2.55 (d, J = 5.9 Hz, 2H), 2.29 (m, 2H), 1.65 (m, 5H), 1.43 (m, 1H), 1.07 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 127,7 (C), 125.4 (CH), 116.4 (C), 79.5 (CH), 69.3 (CH), 42.2 (CH), 37.4 (CH_2), 28.1 (CH2), 27.4 (CH_2), 26.1 (CH_2), 25.9 (2 CH_2), 23.8 ppm (CH_2); IR (film): $\tilde{\nu}$ = 2931.6, 1731.3, 1673.7, 1599.2 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{18}ClNO$ (239.11): C 65.13 H 7.57; found: C 65.13 H 7.87.

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[1] a) R. C. Winstead, T. H. Simpson, G. A. Lock, M. D. Schiavelli, D. W. Thompson, *J. Org. Chem.* **1986**, *51*, 277–279; b) T. A. Blumenkopf, G. C. Look, L. Overman, *J. Am. Chem. Soc.* **1990**, *112*, 4399–4403.

[2] Direct Prins cyclization: a) M. J. Cloninger, L. E. Overman, *J. Am. Chem. Soc.* **1999**, *121*, 1092–1093; b) L. Coppi, A. Ricci, M. Tadei, *J. Org. Chem.* **1988**, *53*, 913–915; c) W.-C. Zhang, G. S. Viswana-

than, C.-J. Li, *Chem. Commun.* **1999**, 291–292; d) X.-F. Yang, J. T. Mague, C.-J. Li, *J. Org. Chem.* **2001**, *66*, 739–741; e) J. S. Yadav, B. V. S. Reddy, G. M. Kumar, Ch. V. S. R. Murthy, *Tetrahedron Lett.* **2001**, *42*, 89–91; f) S. R. Crosby, J. R. Harding, C. D. King, G. D. Parker, C. L. Willis, *Org. Lett.* **2002**, *4*, 3407–3410; g) A. P. Dobbs, S. Martinovic, *Tetrahedron Lett.* **2002**, *43*, 7055–7057; h) A. P. Dobbs, S. J. J. Guené, S. Martinovic, S. J. Coles, M. B. Hursthouse, *J. Org. Chem.* **2003**, *68*, 7880–7883; i) J. S. Yadav, B. V. S. Reddy, M. S. Reddy, N. Hiranjan, A. Prasad, *Eur. J. Org. Chem.* **2003**, 1779–1783; j) D. L. Aubele, C. A. Lee, P. E. Floreancig, *Org. Lett.* **2003**, *5*, 4521–4523; k) K.-P. Chan, T.-P. Loh, *Org. Lett.* **2005**, *7*, 4491–4494; l) K. Kataoka, Y. Ode, M. Matsumoto, J. Nokami, *Tetrahedron* **2006**, *62*, 2471–2483; m) G. Sabitha, B. Reddy, M. Bhikshapathi, J. S. Yadav, *Tetrahedron Lett.* **2006**, *47*, 2807–2810.

[3] a) L. E. Overman, A. Castañeda, T. A. Blumenkopf, *J. Am. Chem. Soc.* **1986**, *108*, 1303–1304; b) C. Semeyn, R. Blaauw, H. Hiemstra, W. N. Speckmap, *J. Org. Chem.* **1997**, *62*, 3426–3427; c) J. J. Jaber, K. Mitsui, S. D. Rychnovsky, *J. Org. Chem.* **2001**, *66*, 4679–4686; d) E. H. Al-Matairi, S. R. Crosby, J. Darzi, J. R. Harding, R. A. Hughes, C. D. King, T. J. Simpson, R. W. Smith, C. L. Willis, *PhysChemComm* **2001**, 836–836; e) R. Jaste, J. Vitale, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2004**, *126*, 9904–9905; f) J. E. Dalgard, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2004**, *126*, 15662–15663.

[4] a) M. Bratz, W. H. Bullock, L. E. Overman, T. J. Takemoto, *J. Am. Chem. Soc.* **1995**, *117*, 5958–5966; b) J. A. Charonat, N. Nishimura, B. W. Travers, J. R. Waas, *Synlett* **1996**, 1162–1164; c) S. V. Pansare, R. P. Jain. *Org. Lett.* **2000**, *2*, 175–177; d) S. Marumoto, J. J. Jaber, J. P. Vitale, S. D. Rychnovsky, *Org. Lett.* **2002**, *4*, 3919–3922; e) K. N. Cossey, R. L. Funk, *J. Am. Chem. Soc.* **2004**, *126*, 12216–12217; f) J. E. Dalgard, S. D. Rychnovsky, *Org. Lett.* **2005**, *7*, 1589–1591; g) J. P. Vitale, S. A. Wolckenhauer, N. A. Do, S. D. Rychnovsky, *Org. Lett.* **2005**, *7*, 3255–3258; h) K. Meilert, M. A. Brimble, *Org. Lett.* **2005**, *7*, 3497–3500; i) L. S. M. Miranda, B. A. Meireles, J. S. Costa, V. L. P. Pereira, *Synlett* **2005**, 869–871; j) C. S. Barry, N. Busby, J. R. Harding, C. L. Willis, *Org. Lett.* **2005**, *7*, 2683–2686; k) D. L. Aubele, S. Wan, P. E. Floreancig, *Angew. Chem.* **2005**, *117*, 3551–3554; *Angew. Chem. Int. Ed.* **2005**, *44*, 3485–3488; l) X.-F. Yang, M. W. Wang, Y. Zhang, C.-J. Li, *Synlett* **2005**, 1912–1916; m) G. Sabitha, K. B. Reddy, G. S. K. K. Reddy, N. Fatima, J. S. Yadav, Synlett **2005**, 2347–2351; n) X. Tian, J. J. Jaber, S. D. Rychnovsky, *J. Org. Chem.* **2006**, *71*, 3176–3183; o) K.-P. Chan, Y. H. Ling, T.-P. Loh, *Chem. Commun.* **2007**, 939–941; p) H. Y. Ko, D. G. Lee, M. A. Kim, H. J. Kim, J. Park, M. S. Lah, E. Lee, *Org. Lett.* **2007**, *9*, 141–144; q) J. S. Yadav, N. N. Kumar, M. S. Reddy, A. R. Prasad, *Tetrahedron* **2007**, *63*, 2689–2694; r) J. S. Yadav, P. P. Rao, M. S. Reddy, N. V. Rao, Prasad, A. R. *Tetrahedron Lett.* **2007**, *48*, 1469–1471.

[5] a) L. D. M. Lolkema, H. Hiemstra, C. Semeyn, W. N. Speckamp, *Tetrahedron* **1994**, *50*, 7115–7128; b) L. D. M. Lolkema, H. Hiemstra, C. Semeyn, L. Ashek, W. N. Speckamp, *Tetrahedron* **1994**, *50*, 7129–7140; c) S. D. Rychnovsky, S. Marumoto, J. J. Jaber, *Org. Lett.* **2001**, *3*, 3815–3818; d) W. R. Roush, G. J. Dilley, *Synlett* **2001**, 955–959; e) S. R. Crosby, J. R. Harding, C. D. King, G. D. Parker, C. L. Willis, *Org. Lett.* **2002**, *4*, 577–580; f) C. J. Barry, S. R. Crosby, J. R. Harding, R. A. Hughes, C. D. King, G. D. Parker, C. L. Willis, *Org. Lett.* **2003**, *5*, 2429–2432.

[6] a) C. S. Barry, N. Bushby, J. R. Harding, R. A. Hughes, G. D. Parker, R. Roe, C. L. Willis, *Chem. Commun.* **2005**, 3727–3729; b) R. Jasti, C. D. Anderson, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2005**, *127*, 9939–9945; c) R. Jasti, S. D. Rychnovsky, *Org. Lett.* **2006**, *8*, 2175–2178; d) R. Jasti, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2006**, *128*, 13640–13648.

[7] a) W. H. Bunelle, D. W. Seamon, D. L. Mohler, T. F. Ball, D. W. Thompson, *Tetrahedron Lett.* **1984**, *25*, 2653–2654; b) M. L. Melany, G. A. Lock, D. W. Thompson, *J. Org. Chem.* **1985**, *50*, 3925–3927; c) N. A. Nikolic, E. Gonda, C. P. D. Longford, N. T. Lane, D. W. Thompson, *J. Org. Chem.* **1989**, *54*, 2748–2751.

[8] a) P. O. Miranda, D. D. Diaz, J. I. Padrón, J. Bermejo, V. S. Martín, *Org. Lett.* **2003**, *5*, 1979–1982; b) P. O. Miranda, D. D. Diaz, J. I. Padrón, M. A. Ramírez, V. S. Martín, *J. Org. Chem.* **2005**, *70*, 57–62; c) P. O. Miranda, R. M. Carballo, M. A. Ramirez, V. S. Martín, J. I. Padron, *Arkivoc*, **2007**, *iv*, 331–343.

[9] P. O. Miranda, M. A. Ramírez, J. I. Padrón, V. S. Martín, *Tetrahedron Lett.* **2006**, *47*, 283–286.

[10] P. O. Miranda, M. A. Ramírez, V. S. Martín, J. I. Padrón, *Org. Lett.* **2006**, *8*, 1633–1636.

[11] The "metallic" participation of the Fe^{III} center was not included in the ab initio theoretical calculation; $FeCl_3$ was considered as just a Lewis acid.

[12] A high-energy transition state B of the α-TMS allenyl cation **29** should exist; in this case, the ring-opening activation energy of the conversion of the trimethylsilyl dihydropyranyl cation **28** into **29** is greater than from the conversion of **28** into cation **27**, which requires only 0.2 kcal mol^{-1}.

[13] The energy comparison of several intermediates with a different number of atoms (e.g., **25** and **28**) is not possible by ab initio theoretical calculations; to allow this comparison we used the concept of an isodesmic reaction, a reaction (actual or hypothetical) in which the types of bonds made in forming the products are the same as those which are broken in the reactants (IUPAC definition, **1997**).

[14] For the reverse pathways from allenic alcohols to homopropargyl alcohols, see: K.-C. Lee, M.-J. Lin, T.-P. Loh, *Chem. Commun.* **2004**, 2456–2457.

[15] Prins cyclization can be considered to be the reverse of a Grob fragmentation; see R. W. Alder, J. N. Harvey, M. T. Oakley, *J. Am. Chem. Soc.* **2002**, *124*, 4960–4961.

[16] K. Subburaj, S. Okamoto, F. Sato, *J. Org. Chem.* **2002**, *67*, 1024–1026, and references therein.

[17] a) L. H. Sommer, F. C. Whitemore, *J. Am. Chem. Soc.* **1946**, *68*, 485–487; b) L. H. Sommer, E. Dofjman, G. M. Golberg, F. C. Whitmore, *J. Am. Chem. Soc.* **1946**, *68*, 488–489; c) I. Fleming, *Chem. Soc. Rev.* **1981**, *10*, 83–111; d) for a comprehensive review, see: J. B. Lambert, *Tetrahedron* **1990**, *46*, 2677–2689; e) K. A. Nguyen, M. S. Gordon, G. Wang, J. B. Lambert, *Organometallics* **1991**, *10*, 2798–2803.

[18] S. N. Ushakov, A. M. Itenberg, *Zh. Obshch. Khim.* **1937**, *7*, 2495–2498.

[19] E. W. Colvin, *Silicon in Organic Synthesis*, Butterworths, London, **1981**.

[20] B. Chiavarino, M. E. Crestoni, S. Fornarini, *J. Am. Chem. Soc.* **1998**, *120*, 1523–1527, and references therein.

[21] H.-U. Siehl, *Pure Appl. Chem.* **1995**, *67*, 769–775.

[22] a) H. Mayr, R. Schneider, D. Wilhelm, P. v. R. Schleyer, *J. Org. Chem.* **1981**, *46*, 5336–5340; b) M. Slegt, R. Gronheid, D. van der Vlugt, M. Ochiai, T. Okuyama, H. Zuilhof, H. S. Overkleeft, G. Lodder, *J. Org. Chem.* **2006**, *71*, 2227–2235.

[23] NMR characterization and X-ray structure of a β-disilacyclohenelidene-substituted vinyl cation has been reported; see: a) T. Müller, R. Meyer, D. Lennartz, H.-U. Siehl, *Angew. Chem.* **2000**, *112*, 3203–3206; *Angew. Chem. Int. Ed.* **2000**, *39*, 3074–3077; b) T. Müller, M. Juhasz, C. A. Reed, *Angew. Chem.* **2004**, *116*, 1569–1572; c) T. Müller, D. Margraf, Y. Syha, *J. Am. Chem. Soc.* **2005**, *127*, 10852–10860.

[24] a) R. F. W. Bader in *Atoms in Molecules: A Quantum Theory, The International Series of Monographs of Chemistry* (Eds: J. Halpen, M. L. H. Green), Clarendon Press, Oxford, **1990**, pp. 1–438; b) R. F. W. Bader, *Chem. Rev.* **1991**, *91*, 893; c) P. Popelier in *Atoms in Molecules: An Introduction*, Prentice Hall, Harlow, New York, **2000**, pp. 1–164; d) R. J. Gilespie, P. L. A. Popelier in *Chemical Bonding and Molecular Geometry: From Lewis to Electron Densities*, Oxford University Press, Oxford, UK, **2001**, pp. 134–268.

[25] The numbering system is centered on the positively charged carbon atom.

[26] The triple bond has a symmetrical circular distribution of electronic density, and the ellipticity value is also zero as in the single bond case.

[27] *NBO 5.0*, E. D. Glendenning, J. K. Badenhoop, A. E. Reed, J. E. Carpenter, J. A. Bohmann, C. M. Morales, F. Weinhold, Theoretical Chemistry Institute, University of Wisconsin, Madison, **2001**; in the

NBO analysis, the full-density matrix is partitioned into localized one- (core and lone pair) and two-center orbitals (the NBOs) that describe a Lewis-type structure.

[28] In this hyperconjugative study, we have considered only the resonance structures with a contribution equal or greater than 10%.

[29] This interaction is similar to an alternative and widely accepted explanation of the anomeric effect, which is a stabilizing interaction between the unshared electron pair on the one heteroatom (the endocyclic one in a sugar ring) and the σ* orbital for the axial (exocyclic) C–X bond; obviously, in our case there is no anomeric carbon atom.

[30] K. Subburaj, S. Okamoto, F. Sato, *J. Org. Chem.* **2002**, *67*, 1024–1026.

[31] N. V. Groza, I. V. Ivanov, G. R. Stepan, G. I. Myagkova, S. Nigam, *Tetrahedron* **2002**, *58*, 9859–9863.

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