1,3- vs. 1,5-Cyclization of azomethine ylides derived from 1-azabuta-1,3-dienes and difluoro- and dichlorocarbenes. Experimental and quantum-chemical study

Alexander F. Khlebnikov,*a Mikhail S. Novikov,*a Stanislav A. Dolgikh,*a and Joerg Magullb

aDepartment of Chemistry, St. Petersburg State University, Universitetskiy pr. 26, 199504 St. Petersburg, Russia
bInstitut für Anorganische Chemie, Georg-August-Universität, Tammannstrasse 4, D-37077 Göttingen, Germany
E-mail: Alexander.Khlebnikov@pobox.spbu.ru

Dedicated to Prof. Oleg Kulinkovich on the occasion of his 60th birthday

Abstract
1,3- vs. 1,5-Cyclization of azomethine ylides derived from 1-azabuta-1,3-dienes and difluoro- and dichlorocarbenes, leading to halogenosubstituted aziridine or pyrrole derivatives, was investigated. Calculations of the reaction profiles were carried out at the B3LYP/6-31G* level to evaluate factors responsible for the predominant transformation pathways of the ylides.

Keywords: 1-Azabuta-1,3-dienes, difluorocarbene, dichlorocarbene, azomethine ylides, cyclizations, pyrroles, quantum-chemical calculations

Introduction

Azomethine ylides formed by carbene reactions with 1-azabuta-1,3-dienes can potentially undergo 1,3-cyclization to aziridines or 1,5-cyclization to form pyrrolines (Scheme 1).¹

Scheme 1
Reactions of carbenes and carbenoids with 1-azabuta-1,3-dienes have been studied poorly and only on an example of halosubstituted carbenes.\textsuperscript{1,2} The reaction of \(N\)-phenylimine of cinnamic aldehyde with dichlorocarbene resulted in the preparation of 2,2-dichloro-1-phenyl-3-styrylaziridine (yield 64\%) formed by 1,3-cyclization of the corresponding azomethine ylide.\textsuperscript{3} By contrast, azomethine ylides generated from \(N\)-alkyl-1-azabuta-1,3-dienes and aryl(chloro)carbenes undergo 1,5-cyclization to give 1,2,3-trisubstituted pyrroles in 15-65\% yields.\textsuperscript{4} gem-Difluoroaziridines which might be expected to arise from 1,3-cyclization of difluoroazomethine ylides formed by the reaction of difluorocarbene with imines have never been detected in such reactions.\textsuperscript{2,5-7} At the same time, the products of the 1,5-cyclization of difluoroazomethine ylides, involving the C=C bond of the furan ring, have been obtained in good yields in the reaction of difluorocarbene with \(N\)-(5-R-furan-2-ylmethylidene)anilines.\textsuperscript{6} Since the formation of difluoroazomethine ylides in the reaction of difluorocarbene with imines have also been evidenced by the 1,3-dipolar cycloaddition to activated acetylenes and ethylenes,\textsuperscript{2,5-7} difluoroaziridines can be obtained by intramolecular nucleophilic substitution and are fairly stable,\textsuperscript{8} the reason why these compounds do not form in the reaction of difluorocarbene with the C=N bond is unclear. The aim of the present experimental and theoretical research was to find out factors responsible for the nature of products of the reactions of difluoro- and dichlorocarbenes with 1-azabuta-1,3-dienes and for the direction of cyclization of halosubstituted azomethine ylide intermediates.

**Results and Discussion**

We studied the reactions of difluoro- and dichlorocarbenes with 1-azabuta-1,3-dienes 1\textsuperscript{a-d} (Scheme 2).

![Scheme 2](image)

Difluorocarbene was generated by reduction of dibromodifluoromethane with active lead (obtained by reduction of aqueous lead acetate with sodium borohydride) in dichloromethane in the presence of tetrabutylammonium bromide under ultrasound irradiation. Dichlorocarbene was generated by thermal decomposition of sodium trichloroacetate in chloroform in the presence of benzyltriethylammonium chloride (TEBA).

It was found that the result of the reaction of azadiene 1\textsuperscript{a} with difluorocarbene depends on the quantity of the source of difluorocarbene introduced in reaction. With 1.2 eq of the source of difluorocarbene, we isolated as the major product fluoropyrrole 2 (yield 23\%). This product
probably arises via intermediate formation of difluoroazomethine ylide 3, 1,5-cyclization of the latter into difluoropyrroline 4, and subsequent HF elimination (Scheme 3).

Scheme 3

The reaction with a double excess of the source of difluorocarbene gave, along with fluoropyrrole 2 (17%), trifluoromethylpyrrole 5 (13%) whose structure was proved by X-ray diffraction (Figure 1). With a triple excess of the source of difluorocarbene, trifluoromethylpyrrole 5 formed as a single product and was isolated in 34% yield (Scheme 4).

Scheme 4

Figure 1. Perspective view of the X-ray crystal structure of 5.
The formation of trifluoromethylpyrrole 5 can be explained either by difluorocarbene insertion into the C-F bond of fluoropyrrole 4 or by cyclopropanation of pyrrole 2 to form cyclopropapyrrole 6 with subsequent heterolytic cleavage of the C-C-bond in the three membered ring under action of fluoride ion (Scheme 5).

Scheme 5

The reactions of difluorocarbene with 1-azabuta-1,3-dienes 1b-d yielded no identifiable products.

The reaction of azadiene 1a with dichlorocarbene resulted in preparation of compound 7 in 35% yield (Scheme 6). The structure of the product 7 was proved by $^1$H, $^{13}$C NMR spectroscopy and elemental analysis.

Scheme 6

The probable route to compound 7 involves formation of ylide 8, subsequent 1,3-cyclization of the latter into aziridine 9, and, finally, conversion of this unstable product into imidoyl chloride 10 (cf. $^9$).
The latter takes up trichloroacetyl chloride formed by thermolysis of the source of dichlorocarbene (sodium trichloroacetate) to give adduct 11. The adduct undergoes halophilic attack with trichloromethide to form anion 12 which cyclizes into pyrrolidone 13 whose subsequent hydrolysis gives rise to final reaction product 7 (Scheme 7). Similar processes were earlier observed in the hydrodechlorination of trichloroacetamides under the conditions of thermocatalytic decomposition of sodium trichloroacetate in chloroform.\(^\text{10}\)

The reactions of azadienes 1b,c with dichlorocarbene afforded both 1:1 adducts, chloropyrroles 14a,b, and pyridine derivatives 15a and 16a,b formed from one molecule of azadiene and two molecules of dichlorocarbene (Scheme 8). The structures of all compounds were proved by \(^1\)H, \(^{13}\)C NMR spectroscopy and elemental analysis. The structure of compound 16a was further elucidated by X-ray diffraction (Figure 2).

![Figure 2](image-url)
Scheme 8

Chloropyrroles 14a,b are formed via 1,5-cyclization of dichloroazomethine ylides 17a,b, arising by the reaction of the starting azadienes with dichlorocarbene, into dichloropyrrolines 18a,b, followed by dehydrochlorination. Pyridone 15a is likely to be formed by the following mechanism. An electrophilic dichlorocarbene readily adds to a nucleophilic enamine C=C bond of pyrroline 18a to give cyclopropapyrrole 19a. Further, which is characteristic of aminosubstituted dichlorocyclopropanes, the three-membered ring undergoes cleavage by a bond opposite to the dichloromethylene group, yielding tetrahydropyridine derivative 20a (Scheme 9). Hydrolysis of the latter on silica during chromatographic treatment of the reaction mixture gives rise to pyridone 15a. Alternatively, the latter can arise via hydrolysis of salt 22a formed by dehydrochlorination of compound 20a.
Scheme 9

The formation of dihydropyridines 16a,b may occur by two routes. The reaction of pyridinium salts 22a,b with trichloromethide gives compounds 23 a,b which hydrolyze on silica into compounds 16a,b. Pyridinium salts 22a,b may also be formed via a route involving cyclopropanation of the major reaction products pyrroles 14a,b, leading to cyclopropapyrroles 21a,b, and cleavage of the three-membered ring by a bond opposite to the dichloromethylene group. Evidence for the possible formation of intermediates 21a,b was obtained in a separate experiment on the thermocatalytic decomposition of sodium trichloroacetate in the presence of pyrrole 14a, which resulted in the isolation of compound 16a in a low yield (cf.1). (Scheme 10).

Scheme 10
Thus, dichloroylides 17a,b formed by the reaction of azadienes 1b,c with dichlorocarbene, unlike dichloroylide 8 from azadiene 1a and dichloroylide from azadiene 1d, undergo 1,5-rather than 1,3-cyclization.

To find out reasons for the different behavior of difluoro- and dichlorosubstituted azomethine ylides and reveal factors responsible for the preferential cyclization pathway, we performed computations of reaction profiles using the Gaussian suite of quantum-chemical programs. Geometry optimizations of intermediates, transition states, reactants, and products in the gas phase were performed at the B3LYP/6-31G* level. For the sake of simplicity, as models for approximation of the chemical behavior of ylides from azadienes 1a-d we took azadienes 23a-c, 24a-c, in view of the expectation that the phenyl groups eliminated on passing from 1a-d to 23a-c,24a-c would not strongly affect both 1,3- and 1,5-cyclization of the corresponding ylides. Energy parameters of the reactions shown in Scheme 11 were obtained.

According to the computation results, the most populated are ylides s-trans-23a-c (Figures 3, 8, 13). These results are consistent with the NMR spectra of 1-azabuta-1,3-dienes 1a-d. Compounds 1a-d were prepared by condensation of the corresponding aldehyde and amine. Therewith, a single (E)-isomer of azadienes 1b-d and a mixture of the (E) - and (Z)-isomers of azadiene 1a are formed. In the latter case, the major (Z)-isomer 1a was the only isolated in the crystalline state, and it was reacted with carbenes.
The computation results are presented in Figures 3-15. The resulting data show that the barriers to the formation of difluorosubstituted azomethine ylides in the reactions of difluorocarbene with azadienes 23-24a-c are 6.4-12.4 kcal mol\(^{-1}\), whereas the formation of dichlorosubstituted azomethine ylides in the reactions of dichlorocarbene with azadienes is barrierless. The lack of barriers to ylide formation in the case of dichlorocarbene is associated with the much higher energy of the latter, and is consistent with available reactivity data for these two species. Even if we assume that more advanced quantum-chemical approaches or an augmented basis set will reveal a low barrier (the fact that DFT B3LYP/6-31G(d) does not reveal this barrier suggests that it is very low), this by no means will affect conclusions given below. As follows from Figures 4-7, 9-12, 14, 15, there is a radical difference in the reactions of difluoro- and dichlorocarbenes, leading to difluoro- and dichlorosubstituted azomethine ylides. This difference consists in that the barriers to 1,3-cyclizations leading to aziridines or 1,5-cyclizations leading to pyrrolines are always lower than the barriers to dissociation of these intermediates to the starting dichlorocarbene and azadiene, whereas the barriers to the corresponding cyclization reactions of difluorosubstituted azomethine ylides are mostly higher than the barriers to dissociation of these intermediates to the starting difluorocarbene and azadiene. In other words, dichlorocarbene reactions with azadienes are irreversible, whereas difluorocarbene reactions with azadienes are reversible.

Analysis of the computation results for the reaction of difluorocarbene with azadienes 23a, 24a shows that the barriers to the 1,3-cyclization of ylides 25\(^{F}\)a, 27\(^{F}\)a, 28\(^{F}\)a, 30\(^{F}\)a into the corresponding aziridines are higher than the barriers to dissociation of these intermediates into the starting materials. Pyrrole 31\(^{F}\)a can be formed only by 1,5-cyclization of ylide 28\(^{F}\)a which can result from either the reaction of difluorocarbene with azadiene s-cis-23a or s-trans→s-cis-isomerization of ylide 25\(^{F}\)a. Since azadiene s-trans-23a the most populated (Figure 3) and more reactive than azadiene s-cis-23a (Figure 4), ylide 25\(^{F}\)a is preferentially formed. However, the latter prefers to dissociate rather than to isomerize into ylide 28\(^{F}\)a. As a result, difluorocarbene is consumed in reactions whose barriers are lower than the barrier to the isomerization 25\(^{F}\)a → 28\(^{F}\)a, equal to 10.5 kcal mol\(^{-1}\), for example, in dimerization leading to tetrafluoroethene.\(^{13}\) These computational results explain the absence of both 1,3- and 1,5-cyclization products in difluorocarbene reactions of azadienes 1b,c.

A different picture is observed in dichlorocarbene reactions. The reaction of dichlorocarbene with the most populated azadiene s-trans-23a (Figure 6) gives rise to ylide 25\(^{Cl}\)a whose barrier to cyclization into aziridine 26\(^{Cl}\)a (10.2 kcal mol\(^{-1}\)) is higher than the barrier to conversion into ylide 28\(^{Cl}\)a (9.4 kcal mol\(^{-1}\)). The latter may also be formed by the reaction of dichlorocarbene with the second most populated azadiene s-cis-23a (Figure 6). Ylide 28\(^{Cl}\)a has a much lower barrier to 1,5-cyclization into pyrrole 31\(^{Cl}\)a (2.8 kcal mol\(^{-1}\)) than that to 1,3-cyclization into aziridine 29\(^{Cl}\)a (14.2 kcal mol\(^{-1}\)). These data fit experimental results, namely, the formation of pyrrole derivatives 14a,b and their subsequent reaction products, compounds 15a and 16a,b, in the reactions of dichlorocarbene with azadienes 1b,c.
Figure 3. Free energy diagram for interconversion of \( N \)-methyl-1-azabuta-1,3-diene stereoisomers 23a, 24a. Free energies [kcal mol\(^{-1}\)] computed at the B3LYP/6-31G* level. Energies are reported with respect to imine s-trans-23a.

Figure 4. Reaction profiles for formation of difluoroazomethine ylides from s-cis- and s-trans-\( N \)-methyl-1-azabuta-1,3-dienes 23a and interconversion of ylides 25\(^F\)a, 28\(^F\)a and their 1,3-cyclization into aziridine 26\(^F\)a and 1,5-cyclization into pyrroline 31\(^F\)a. Free energies [kcal mol\(^{-1}\)] computed at the B3LYP/6-31G* level. Energies are reported with respect to ylide 27\(^F\)a.
Figure 5. Reaction profiles for formation of difluoroazomethine ylides from s-cis- and s-trans-N-methyl-1-azabuta-1,3-dienes 24a and interconversion of the ylides 27F\textsubscript{a}, 30F\textsubscript{a} and their 1,3-cyclization into aziridines 26F\textsubscript{a}, 29\textsubscript{F}. Free energies [kcal mol\textsuperscript{-1}] computed at the B3LYP/6-31G* level. Energies are reported with respect to ylide 27F\textsubscript{a}.

Figure 6. Reaction profiles for formation of dichloroazomethine ylides from s-cis- and s-trans-N-methyl-1-azabuta-1,3-dienes 23a and interconversion of the ylides 25Cl\textsubscript{a}, 28Cl\textsubscript{a} and their 1,3-cyclization into aziridine 26Cl\textsubscript{a} and 1,5-cyclization into pyrroline 31Cl\textsubscript{a}. Free energies [kcal mol\textsuperscript{-1}] computed at the B3LYP/6-31G* level. Energies are reported with respect to ylide 27Cl\textsubscript{a}.
Figure 7. Reaction profiles for formation of dichloroazomethine ylides from s-cis- and s-trans-N-methyl-1-azabuta-1,3-diienes 24a and interconversion of the ylides 27\textsuperscript{Cl}\textsubscript{a}, 30\textsuperscript{Cl}\textsubscript{a} and their 1,3-cyclization into aziridines 26\textsuperscript{Cl}\textsubscript{a}, 29\textsuperscript{Cl}\textsubscript{a}. Free energies [kcal mol\textsuperscript{-1}] computed at the B3LYP/6-31G* level. Energies are reported with respect to ylide 27\textsuperscript{Cl}\textsubscript{a}.

2-Phenyl substitution in azadienes 23, 24 produces considerable changes in the energy characteristics of both their reactions with carbenes and reactions of the corresponding ylides. Moreover, an appreciable change in the relative population of azadienes themselves is observed (Figure 8). The reaction of difluorocarbene with the most populated azadiene s-trans-23b results in formation of ylide 25\textsuperscript{F}\textsubscript{b} whose barrier to isomerization into ylide 28\textsuperscript{F}\textsubscript{b} (6.6 kcal mol\textsuperscript{-1}) lower than the barrier to dissociation into the starting molecules (7.1 kcal mol\textsuperscript{-1}) and 1,3-cyclization into aziridine 26\textsuperscript{F}\textsubscript{b} (7.8 kcal mol\textsuperscript{-1}) (Figure 9). Ylide 28\textsuperscript{F}\textsubscript{b} has a low barrier to 1,5-cyclization into pyrroline 31\textsuperscript{F}\textsubscript{b} (4.3 kcal mol\textsuperscript{-1}), which is much lower than the barrier to its dissociation into the starting azadiene and difluorocarbene (10.5 kcal mol\textsuperscript{-1}) (Figure 9). By contrast, the barriers to dissociation of ylide 27\textsuperscript{F}\textsubscript{b}, 30\textsuperscript{F}\textsubscript{b} is lower than the barriers to their 1,3-cyclization into aziridines 26\textsuperscript{F}\textsubscript{b}, 29\textsuperscript{F}\textsubscript{b} (Figure 10). Thus, the fact that we obtained pyrrole 2 in the reaction of azadiene 1a with difluorocarbene completely agrees with computation results, and the formation of this product is most likely to occur via addition of difluorocarbene to s-trans-azadiene 1a, isomerization of s-trans-isomer ylide 2a to s-cis-isomer, and cyclization of the latter.
Figure 8. Free energy diagram for interconversion of stereoisomers of \( N \)-methyl-1-azabuta-1,3-diene 23b, 24b. Free energies [kcal mol\(^{-1}\)] computed at the B3LYP/6-31G\(^{*}\) level. Energies are reported with respect to imine \( s\)-trans-23b.

Figure 9. Reaction profiles for formation of difluoroazomethine ylides from \( s\)-cis- and \( s\)-trans-\( N \)-methyl-1-azabuta-1,3-dienes 23b and interconversion of the ylides 25\(^{\text{Fb}}\), 28\(^{\text{Fb}}\) and their 1,3-cyclization into aziridine 26\(^{\text{Fb}}\), 29\(^{\text{Fb}}\) and 1,5-cyclization into pyrrolidine 31\(^{\text{Fb}}\). Free energies [kcal mol\(^{-1}\)] computed at the B3LYP/6-31G\(^{*}\) level. Energies are reported with respect to ylide 28\(^{\text{Fb}}\).
**Figure 10.** Reaction profiles for formation of difluoroazomethine ylides from *s-cis*- and *s-trans*-N-methyl-1-azabuta-1,3-dienes 24b and interconversion of the ylides 27Fb, 30Fb and their 1,3-cyclization into aziridine 26Fb, 29Fb. Free energies [kcal mol⁻¹] computed at the B3LYP/6-31G* level. Energies are reported with respect to ylide 28Fb.

**Figure 11.** Reaction profiles for formation of dichloroazomethine ylides from *s-cis*- and *s-trans*-N-methyl-1-azabuta-1,3-dienes 23b and interconversion of the ylides 25Clb, 28Clb and their 1,3-cyclization into aziridine 26Clb, 29Clb and 1,5-cyclization into pyrroline 31Clb. Free energies [kcal mol⁻¹] computed at the B3LYP/6-31G* level. Energies are reported with respect to ylide 25Clb.
The computation results for model reactions of dichlorosubstituted azomethine ylides $^{25\text{Cl}}b$, $^{27\text{Cl}}b$ $^{28\text{Cl}}b$, $^{30\text{Cl}}b$ (Figures 11, 12) fit the experiment in which compound 7 was obtained, via intermediate formation of aziridine 9, in the reaction of dichlorocarbene with azadiene 1a. Thus, 2-phenyl substitution in azadienes 23, 24 makes the barriers to 1,3-cyclization of ylides $^{25\text{Cl}}b$, $^{27\text{Cl}}b$ $^{28\text{Cl}}b$, $^{30\text{Cl}}b$ into aziridines (Figures 11, 12) lower compared to ylides $^{25\text{Cl}}a$, $^{27\text{Cl}}a$ $^{28\text{Cl}}a$, $^{30\text{Cl}}a$ (Figures 6, 7) containing no phenyl substituent. The most favorable way of stabilization of dichloroylides $^{25\text{Cl}}b$, $^{27\text{Cl}}b$, $^{30\text{Cl}}b$ formed by dichlorocarbene reactions with the most populated azadienes $s$-$trans$-$^{23b}$, $s$-$trans$-$^{24b}$, $s$-$cis$-$^{24b}$ is cyclization into aziridine (Figures 11, 12). Therewith, the ylide formed from dichlorocarbene and the most populated azadiene $s$-$trans$-$^{23b}$ (Figure 8) has a lowered barrier to 1,3-cyclization into aziridine $^{26\text{Cl}}b$ than the barrier to isomerization into ylide $^{28\text{Cl}}b$ which can undergo 1,5-cyclization into pyrroline $^{31\text{Cl}}b$ (Figure 11).

![Figure 12](image_url)

**Figure 12.** Reaction profiles for formation of difluoroazomethine ylides from $s$-$cis$- and $s$-$trans$-$N$-methyl-1-azabuta-1,3-dienes $^{24b}$ and interconversion of the ylides ylides $^{27\text{Cl}}b$, $^{30\text{Cl}}b$ and their 1,3-cyclization into aziridine $^{26\text{Cl}}b$, $^{29\text{Cl}}b$. Free energies [kcal mol$^{-1}$] computed at the B3LYP/6-31G* level. Energies are reported with respect to ylide $^{25\text{Cl}}b$.

In going from $N$-methylazadienes $^{23a}$, $^{24a}$ to $N$-phenylazadienes $^{23c}$, $^{24c}$, the relative stability of azadiene isomers changes only slightly, but the energy profiles for formation and reactions of the corresponding difluoro- and dichloroylides are affected considerably (Figures 3, 13-15). The reaction of difluorocarbene with the most populated azadiene $s$-$trans$-$^{23c}$ (Figure...
13) gives rise to ylide $^{25F}_c$. Compared to ylide $^{25F}_b$, ylide $^{25F}_c$ has a lower barrier to 1,3-cyclization into aziridine and higher barrier to transformation into ylide $^{28F}_c$ which might further transform into pyrroline $^{31F}_c$ (Figure 14). Therewith, the barrier to dissociation into the starting molecules decreases and becomes lower by 5.2 kcal mol$^{-1}$ lower than the barrier to 1,3-cyclization into aziridine. As a result, difluorocarbene is consumed in side reactions with barriers lower than 11.9 kcal mol$^{-1}$. These results explain the absence of both 1,3- and 1,5-cyclization products in the reaction of difluorocarbene with azadiene $^{1d}$.

In the reaction of this azadiene with dichlorocarbene, replacement of the $N$-methyl substituents by $N$-phenyl, too, decreases the barrier to 1,3-cyclization into aziridine and increases the barrier of the isomerization $^{27Cl}_c \rightarrow ^{28Cl}_c$ (Figure 15). Therewith, the barrier to 1,3-cyclization of ylide $^{27Cl}_c$ turns to be 4.9 kcal mol$^{-1}$ lower than the barrier to isomerization into ylide $^{28Cl}_c$ which might further transform into pyrrolidine $^{30Cl}_c$. There results are consistent with experimental data,$^3$ namely, the formation of dichloroaziridine from azadiene $^{1d}$ in the reaction with dichlorocarbene and the absence of the corresponding pyrrole derivatives from the reaction products.

Figure 13. Free energy diagram for interconversion of stereoisomers of $N$-phenyl-1-azabuta-1,3-diene $^{23c}$, $^{24c}$. Free energies [kcal mol$^{-1}$] computed at the B3LYP/6-31G* level. Energies are reported with respect to imine $s$-trans-$^{23c}$. 

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Figure 14. Reaction profiles for formation of difluoroazomethine ylides from s-trans- and s-cis-N-phenyl-1-azabuta-1,3-dienes 23c and interconversion of the ylides 25F<sub>c</sub>, 28F<sub>c</sub> and their 1,3-cyclization into aziridine 26F<sub>c</sub>, 29F<sub>c</sub> and 1,5-cyclization into pyrroline 31F<sub>c</sub>. Free energies [kcal mol<sup>-1</sup>] computed at the B3LYP/6-31G* level. Energies are reported with respect to ylides 25F<sub>c</sub>.

Figure 15. Reaction profiles for formation of difluoroazomethine ylides from s-trans- and s-cis-N-phenyl-1-azabuta-1,3-dienes 23c and interconversion of the ylides 25Cl<sub>c</sub>, 28Cl<sub>c</sub> and their 1,3-cyclization into aziridine 26Cl<sub>c</sub>, 29Cl<sub>c</sub> and 1,5-cyclization into pyrroline 31Cl<sub>c</sub>. Free energies [kcal mol<sup>-1</sup>] computed at the B3LYP/6-31G* level. Energies are reported with respect to ylides 25Cl<sub>c</sub>. 
Thus, our experiments gave evidence to show that the reactions of 1-azabuta-1,3-dienes with difluoro- and dichlorocarbenes are quite sensitive to substituents in the azadiene and to the nature of the halogen. As follows from computations, the reactions of dichlorocarbene with azadienes are generally irreversible, whereas the reactions of difluorocarbene with azadienes are reversible. Reaction result is also strongly dependent on the geometry of the azadiene, since it predetermines the geometry of the primary azomethine ylide intermediate. Kinetic ylides formed from the most stable $s$-trans-azadienes are incapable to 1,5-cyclization into pyrrolines, and the latter can arise exclusively via $s$-trans $\rightarrow$ $s$-cis-isomerization of the primary ylide. As shown by computations and experiments, this process is made possible by a certain structural modification of the ylide, i.e. introduction of substituents. With difluoroylides whose 1,3-cyclization is unfavored by energy and does not compete with other processes, the $s$-trans-ylide $\rightarrow$ $s$-cis-ylide isomerization is facilitated by introduction of a bulky (Ph) substituent in the 2-position of the parent azadiene. By contrast, with dichloroylides the $s$-trans $\rightarrow$ $s$-cis isomerization leading eventually to pyrroline formation is realized only in the absence of Ph substituents in the 1 and 2 positions. Phenyl substitution in one of these positions produces such a strong decrease in the 1,3-cyclization barrier that aziridine formation becomes the major reaction. The observed difference in the effects of substituents in the azadiene on the structure and behavior of difluoro- and dichloroylides is associated not only with the difference in the van der Waals radii of chlorine and fluorine, but also with the pyramidalization of the NCHlg$_2$ fragment on replacement of chlorine by the more electronegative fluorine.

Comparison of the experimental and computational results for dihalocarbene reactions with azadienes leads us to conclude that DFT methods at the simple B3LYP/6-31G* level of theory which allows profound computations without severe simplification of real structures can be used for selecting substrates for purposeful synthesis of 1,3- or 1,5-cyclization products.

**Experimental Section**

**General Procedures.** The melting points were determined on a Boetius melting point apparatus (uncorrected values are given). $^1$H (300 MHz) and $^{13}$C (75 MHz) NMR spectra were measured with a Bruker DPX 300 spectrometer and $^{19}$F NMR (235 MHz) with Brucker Avance 250 spectrometer. 13C NMR assignments were made using DEPT spectra. Microanalyses were performed on a EuroEA3000 (Eurovector). The mass spectra were run on MAT-731 and MAT CH-7 instruments. X-Ray crystallography data were collected with a STOE IPDS II instrument, using graphite monochromatized MoKα radiation ($\lambda = 0.71073$ Å). Complete crystallographic data, as a CIF file, have been deposited with the Cambridge Crystallographic Data Centre (CCDC Nos 670514 & 670515). Copies can be obtained free of charge from: CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. (e-mail: deposit@ccdc.cam.ac.uk, http://www.ccdc.cam.ac.uk/deposit).

The reaction mixtures were separated by column chromatography on Merck-60 silica gel. Methylene chloride and chloroform were dried by distillation over P$_2$O$_5$. Commercial
tetrabutylammonium bromide was dried in a dessicator over P_2O_5. Compounds 1a-d were prepared by condensation of the corresponding aldehyde and amine. Active lead was prepared as described earlier.\(^7\)\(^a\)

**Computational details**

All calculations were performed with the B3LYP density functional method\(^1\)\(^4\) by using the Gaussian suite of quantum chemical programs.\(^1\)\(^1\) Geometry optimizations of intermediates, transition states, reactants, and products in the gas phase were performed at the B3LYP/6-31G* level using Gaussian 03. Stationary points on the respective potential-energy surfaces were characterized at the same level of theory by evaluating the corresponding Hessian indices. Careful verification of the unique imaginary frequencies for transition states was carried out to check whether the frequency indeed pertains to the desired reaction coordinate. Intrinsic reaction coordinates (IRC) were calculated to authenticate all transition states.\(^1\)\(^5\)

**A typical experimental procedure (A) for the reaction of difluorocarbene with azadienes**

Azadiene 1a (1.00 g, 3.36 mmol), Bu_4NBr (1.30 g, 4.04 mmol), and CF_2Br_2 (1.06 g, 5.04 mmol) were added to a flask charged with freshly prepared active lead (0.836 g, 4.04 mmol) under a layer of CH_2Cl_2 (10 mL). The flask was closed with a stopper which was fixed so as to keep a slight excess pressure, immersed in a sonic cleaner (37 kHz, 160 W) and irradiated with ultrasound until the lead was consumed completely (5 h). The solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel (eluent: hexane-ether) to afford after recrystallization 0.250 g (23%) of 1-benzyl-2-fluoro-3,5-diphenyl-1H-pyrrole 2 as a colorless solid: mp 74-75 °C (hexane-ether). \(^1\)H NMR (300 MHz, CDCl_3): \(\delta\) 5.14 (2H, s, CH_2), 6.44 (1H, d, ^4J_{HF} = 6.5 Hz, C^4-H), 7.04-7.62 (15H, m, CH_arom). \(^1\)C NMR (75 MHz, CDCl_3): \(\delta\) 46.5 (d, ^3J_{CF} = 1.8 Hz, CH_2), 101.3 (d, ^3J_{CF} = 4 Hz, C^5), 104.2 (d, ^3J_{CF} = 3 Hz, C^4), 125.3, 125.5, 125.5, 126.1, 126.4, 127.3, 127.4, 128.6, 128.7, 132.3, 137.5 (C_arom), 133.0 (d, ^2J_{CF} = 5 Hz, C^3), 145.1 (d, ^1J_{CF} = 267 Hz, C^2). \(^1\)F NMR (235 MHz, CDCl_3): \(\delta\) 24.2. HRMS: m/z calcld for C_{23}H_{18}FN: 327.1423; found 327.1428.

Pyrrole 2. 0.055 g (17%) and 1-benzyl-2-(trifluoromethyl)-3,5-diphenyl-1H-pyrrole (3). 0.050 g (13%) were prepared by the typical procedure (A) from azadiene 1a (0.297 g, 1 mmol), Bu_4NBr (0.645 g, 2 mmol), and CF_2Br_2 (0.525 g, 2.5 mmol) and active lead (0.414 g, 2 mmol) for 60 h. A mixture of hexane and benzene was used for column chromatography. Pyrrole 3: colorless solid: mp 84-85 °C (ether). \(^1\)H NMR (300 MHz, CDCl_3): \(\delta\) 5.36 (2H, s, CH_2), 6.36 (1H, s, C^4-H), 6.93-7.51 (15H, m, CH_arom). \(^1\)C NMR (75 MHz, CDCl_3): \(\delta\) 49.9 (q, ^4J_{CF} = 2.7 Hz, CH_2), 111.6 (C^4), 117.4 (q, ^2J_{CF} = 36 Hz, C^2), 122.4 (q, ^1J_{CF} = 269 Hz, CF_3), 125.5, 127.0, 127.1, 127.9, 128.3, 128.4, 128.5, 129.4, 129.5, 131.7, 135.1, 138.4 (C_arom), 129.7 (q, ^3J = 2.9 Hz, C^3), 139.2 (q, ^4J_{CF} = 2 Hz, C^5). \(^1\)F NMR (235 MHz, CDCl_3): 108.9. Anal. Calcd for C_{24}H_{18}F_3N: C 76.4, H 4.8, N 3.7. Found: C 75.6, H 5.2, N 3.5. Crystal data for 3. C_{24}H_{18}F_3N, MW 377.39, orthorhombic, P2(1)2(1)2(1) (N 19), \(a\) = 6.0064(4), \(b\) = 12.7219(9), \(c\) = 24.3210(17) Å, \(V\) =
A typical experimental procedure (B) for the reaction of difluorocarbene with azadienes.

A solution of azadiene 1a (0.446 g, 1.5 mmol), and benzyltriethylammonium chloride (0.102 g, 0.45 mmol) in 20 ml of chloroform was heated to the boiling point, and sodium trichloroacetate (3.5 g, 18.9 mmol) was added in small portions over a period of 1 h under vigorous stirring, maintaining the mixture slightly boiling. The solvent was removed under reduced pressure on a rotary evaporator, 50 ml of dichloromethane was added to the residue, the mixture was filtered through a 1-cm layer of celite, the filtrate was evaporated, and the residue was subjected to column chromatography on silica gel (eluent: hexane-ether) to afford after recrystallization 0.230 g (35%) of 1-benzyl-3,3-dichloro-4-phenyl-4-(E)-styryl-pyrrolidine-2,5-dione (7) as a colorless solid: mp 122-123 °C (hexane-ether). 1H NMR (300 MHz, CDCl3): δ 4.90 (2H, s, CH2), 6.37 (1H, d, J = 16.0 Hz, CH), 6.49 (1H, d, J = 16.0 Hz, CH), 7.20-7.66 (15H, m, CH arom). 13C NMR (75 MHz, CDCl3): δ 43.7 (CH2), 66.1 (C4), 86.1 (C3), 126.4, 126.8, 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 132.4, 134.6, 135.2 (C arom), 128.8 (CH/C=C), 136.0 (CH/C=C), 167.7 (C=O), 171.4 (C=O). Anal. Calcd for C22H19Cl2NO2: C 68.8, H 4.4, N 3.2. Found: C 68.9, H 4.5, N 3.1.

1-Benzyl-2-chloro-3-methyl-1H-pyrrole (14a) 0.173 g (28%), 1-benzyl-5-chloro-3-methyl-1H-pyridin-2-one (15a) 0.027 g (4%), and 1-benzyl-3,6-dichloro-5-methyl-2-trichloromethyl-1,2-dihydropyrididine (16a) 0.025 g (2%) were prepared by the typical procedure (B) from azadiene 1b (0.477 g, 3 mmol) for 0.5 h.

Pyrrole 14a. Colorless oil: 1H NMR (300 MHz, CDCl3): δ 2.13 (3H, s, CH3), 5.10 (2H, s, CH2), 6.10 (1H, d, J = 2.9 Hz, C′-H), 6.63 (1H, d, J = 2.9 Hz, C′′-H), 7.14-7.40 (5H, m, CH arom). 13C NMR (75 MHz, CDCl3): δ 11.1 (CH3), 50.4 (CH2), 109.3 (C′), 113.7 (C3), 115.1 (C2), 119.5 (C5), 126.8, 127.5, 128.6, 137.6 (C arom). MS (70 eV) m/z (%): 207 ([M+2]+, 7), 205 ([M]+, 22), 92 (10), 91 (100), 89 (4), 65 (17), 51 (7). Anal. Calcd for C12H12ClN: C 70.1, H 5.9, N 6.8. Found: C 70.4, H 5.5, N 6.7.

Pyridone 15a. Colorless solid, mp 158-158.5 °C (hexane-ether). 1H NMR (300 MHz, CDCl3): δ 2.41 (3H, s, CH3), 5.54 (2H, s, CH2), 6.08 (1H, s, C′-H), 6.82 (1H, s, C′′-H), 7.10-7.32 (5H, CH arom). 13C NMR (75 MHz, CDCl3): δ 14.6 (CH3), 52.7 (CH2), 111.4 (C′), 118.5 (C5), 126.9, 127.3, 128.5, 138.4 (C arom), 129.1 (C4), 133.3 (C3), 166.8 (C=O). Anal. Calcd for C13H12ClNO: C 66.8, H 5.2, N 6.0. Found: 66.8, H 5.2, N 5.9.

Pyridine 16a. Colorless solid, mp 70.5-71 °C (MeOH). 1H NMR (300 MHz, CDCl3): δ 1.84 (3H, s, CH3), 4.26 (1H, d, J = 16.0 Hz, CH2), 5.20 (1H, d, J = 16.0 Hz, CH2), 4.69 (1H, s, C2-H), 6.34 (1H, s, C′-H), 7.17-7.39 (5H, m, CH arom). 13C NMR (75 MHz, CDCl3): δ 16.5 (CH3), 58.7 (CH2), 78.2 (C3), 101.5 (CCl3), 111.3 (C5), 112.1 (C2), 127.3, 127.9, 128.7, 132.2 (C arom),
130.8 (C⁴), 136.9 (C⁶). Anal. Calcd for C₁₄H₁₂Cl₅N: C 45.3, H 3.3, N 3.8. Found: C 45.3, H 3.6, N 3.7. Crystal data for 16a. C₁₄H₁₂Cl₅N, MW 371.50, monoclinic, P 2(1)/n (no. 14), a = 9.7510(7), b = 13.9648(9), c = 11.9486(8), β = 104.990(0) °, Å, V = 1571.68(18) Å³, Z = 4, T = 293(2) K, F(000) = 752, D_caled = 1.570 g·cm⁻³, R_all = 0.0435, wR₂ = 0.1030, 15638 reflections (2644 independent reflections with R_int = 0.0753).

**Pyridine 16a.** 0.025 g (3%) were obtained also from pyrrole 14a (0.500 g, 2.44 mmol) by the typical procedure (B) for 0.8 h.

1-Benzyl-2-chloro-3-phenyl-1H-pyrrole (14b) 0.153 g (25%), and 1-benzyl-3,6-dichloro-5-phenyl-2-trichloromethyl-1,2-dihydropyridine (16b) 0.050 g (5%) were prepared by the typical procedure (B) from azadiene 1b (0.509 g, 2.3 mmol) for 0.5 h.

**Pyrrole 14b.** Colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 5.20 (2H, s, CH₂), 6.50 (1H, d, ³J = 3.1 Hz, C⁴-H), 6.77 (1H, d, ³J = 3.1 Hz, C⁵-H), 7.20-7.77 (10H, CH_arom). ¹³C NMR (75 MHz, CDCl₃): δ 50.5 (CH₂), 108.2 (C⁴), 113.1 (C³), 120.5 (C²), 120.7 (C⁵), 126.0, 126.9, 127.1, 127.7, 128.3, 128.7, 134.6, 137.1 (C_arom). Anal. Calcd for C₁₇H₁₄ClN: C 76.3, H 5.3, N 5.2. Found: C 76.4, H 5.6, N 5.5.

**Pyridine 16b.** Colorless solid, mp 77-78 °С (MeOH). ¹H NMR (300 MHz, CDCl₃): δ 4.41  (1H, d, ²J = 16.0 Hz, CH₂), 4.82 (1H, s, C²-H), 5.39 (1H, d, ²J = 16.0 Hz, CH₂), 6.62 (1H, s, C⁴-H), 7.24-7.41 (10H, CH_arom). ¹³C NMR (75 MHz, CDCl₃): δ 59.1 (CH₂), 78.0 (C²), 101.4 (CCl₃), 112.4 (C⁵), 116.8 (C³), 127.2, 127.2, 128.1, 128.2, 128.8, 128.9, 132.7, 136.7 (C_arom), 130.4 (C⁴), 136.7 (C⁶). Anal. Calcd for C₁₉H₁₄Cl₅N: C 52.6, H 3.3, N 3.2. Found: 52.8, H 3.4, N 3.2.

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**References and Notes**