Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 6335

www.rsc.org/obc

PAPER

Substituent effects on the rate of formation of azomethine ylides. A computational investigation†

Harold D. Banks*

Received 12th April 2011, Accepted 15th June 2011
DOI: 10.1039/c1ob05588g

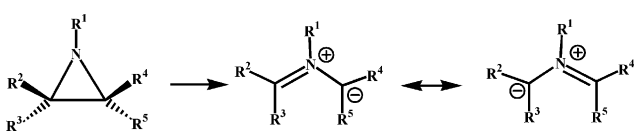
The effect of substituents on the rate of conrotatory thermal cleavage of aziridine has been studied at the MP2(Full)/6-311++G(d,p)//MP2(Full)/6-31+G(d) level and also using SCS-MP2 methodology. While the parent compound has a high free energy of activation (194.6 kJ mol^{-1}), this value could be drastically lowered by substituent effects. Anionic species were found to be particularly effective in increasing the calculated reaction rate. The potential utility of this approach in 1,3-dipolar cycloaddition is discussed.

Introduction

The click chemistry concept introduced by the Sharpless group[1] and its implementations within the strict requirements for such reactions resulted in a substantial body of productive research. With the discovery of the Cu(I)-catalyzed 1,3-dipolar cycloaddition of alkynes or alkenes with azides under mild conditions,[2] the vast majority of these studies utilized this reaction. For biological systems for which the presence of Cu(I) would present a potential toxicity liability, Bertozzi[3] developed an innovative approach that was free of metal ions by taking advantage of relief of strain energy in the transition state when the dipolarophile is a cyclooctyne.

Azomethine ylides occupy an important place in synthetic organic chemistry.[4] In addition to their extensive use in 1,3-dipolar cycloaddition,[5] they have very recently been employed as intermediates in isomerization,[6] dimerization,[7] and three-component coupling.[8] As synthetic challenges become greater due to molecular complexity or sensitivity to elevated temperature, it is useful to have approaches available that increase reaction rate. For reactions in which azomethine formation is the rate-determining step this amounts to lowering the free energy of activation to an acceptable level. This project consisted of an investigation of the effect of substituents on the free energy of activation of a particularly useful source of azomethine ylides, the thermal, conrotatory cleavage of aziridines. It was spurred by previous studies of the effect of substituents on the rate of nucleophilic attack on 3- and 4-membered rings, reactions that also involve the generation of a dipolar transition state.[9]

We were intrigued by the possibility that 1,3-dipolar cycloaddition chemistry could be conducted under mild conditions where the 1,3-dipole would be an azomethine ylide produced from substituted aziridines as the dipolarophiles. (Scheme 1.) The literature indicated that such reactions require elevated temperatures and extended reaction times.[10] Assuming that formation of the azomethine ylide is the rate-determining step (*vide infra*), our approach to achieving a reasonable reaction rate was to computationally examine substituent effects on C–C bond cleavage of the aziridine. This thermal reaction 4-electron electrocyclic reaction occurs with conrotation.[11] Before this chemistry can be effectively studied, those substituted aziridines that lack a C_2 axis have two unique modes of conrotation that will differ in energy. Preference for one of these modes, outward or inward, by a substituent, is termed torquoselectivity.[12] The overall rate constant for a given aziridine is a function of the rate constants for the outward and inward conrotatory modes. Accordingly, the first step in this investigation was determination of the rates of these distinctive modes; we recently reported[13] the results a study of a large number of substituted aziridines that found that outward rotation was mostly favored by substituents that were electronegative or anionic, while electropositive or cationic groups favored inward rotation. If the free energies of activation of one of the two conrotatory modes is less than 17.1 kJ mol^{-1} that of the other at 298 K, more than 99.9% of the reaction proceeds through this pathway as demonstrated by transition state theory.[14]



Scheme 1 Thermolysis of a substituted aziridine.

With a view to discovering reactions that embrace even biological systems, the maximum free energy of activation tolerated was 95.2 kJ mol^{-1}. This corresponds to a unimolecular reaction that is

U.S. Army Edgewood Chemical Biological Center, APG, Maryland 21010-2454, USA. E-mail: harold.banks@us.army.mil

† Electronic supplementary information (ESI) available: Energies of the reactants, transition states, their Cartesian coordinates, the transition state unique imaginary frequencies, Wiberg Bond Indices for haloaziridines **2–13**, and their transition state atomic distances. See DOI: 10.1039/c1ob05588g

complete (10 half-lives) in a 14 h period (overnight) at 298 K. While previous reports have found the formation of the azomethine ylide to be the slow step in 1,3-dipolar cycloaddition chemistry, it is conceivable that substituent effects would change the relative rates of these mechanistic steps; thus, the rates of azomethine ylides with dipolarophiles ethyne and ethene (if proton abstraction from ethyne were possible) were studied. When an aziridine that lacks a plane of symmetry undergoes thermal C–C bond cleavage, there are two conceivable symmetry-allowed conrotatory modes; torquoselectivity[8] is a measure of preference for the clockwise or counterclockwise mode of rotation (alternatively designated outward or inward with respect to the cleaving heterocyclic ring) as the C–C bond is thermally ruptured. For such an aziridine, these rotational modes have potentially different energy requirements that must be evaluated to determine their contributions to the overall rate of the reaction. We recently reported[8] the results of a study of the torquoselectivity[9] of a large number of substituted aziridines. Outward rotation of the substituent was largely favored for these aziridines. Substituents that followed an outward rotational modality tended to be electronegative or anionic, while electropositive or cationic groups favored inward rotation.

In the present investigation the rates of reaction of sixty one new substituted aziridines, chosen on the basis of the previous results[13] were computed. Gratifyingly, this extensive research led to the discovery of an aziridine (**106**) that meets our reactivity criterion. It is not unreasonable to speculate that future substituent modifications will also result in acceptable reactivity.

Methods and computational details

Ab initio calculations were performed at the MP2(Full)/6-311++G(d,p)//MP2(Full)/6-31+G(d) level by means of the Gaussian 03 suite of programs[15] for determination of energies and the NBO charges[16,17] (keyword, pop = SaveNBOs). For comparison, the recently introduced SCS-MP2 method[18] was employed. Using this spin component scaled approach, $E_{\text{SCS-MP2}} = E_{\text{HF}} + 1.20E_{\alpha\beta} + 0.333(E_{\alpha\alpha} + E_{\beta\beta})$. These energies have been found to be more accurate than those calculated by MP2.[18h] For the rate with **106** that proved computationally excessively expensive using the MP2(Full) calculations, an acceptably accurate result at considerably lower expense was obtained using the G3(MP2) method.[19] A few calculations were performed (with similar compounds, *i.e.*, **18**, **84**, and **89**, to confirm the acceptable agreement of the results of this method with MP2(Full) and SCS-MP2. Gas phase calculations were deemed to be sufficient for calculation of relative energies since using a water solvent model (SCI-PCM[20,21]) aziridine and 2-fluoroaziridine produced only modest changes in relative rates (<25 kJ mol^{-1}). The minor effect of solvent on the rate azomethine ylide formation has also been observed experimentally.[5f] A scaling factor of 0.9646 was used[22] for the thermal correction to the computed energies at a reaction temperature of 298.15 K. Criteria for finding the transition states and ground states were calculation of one and zero imaginary frequencies, respectively. GaussView 3.09[23] was used for animation of the sole imaginary frequency and IRC calculations were used to confirm identification of the transition states. Rate differences between invertomers were found to be insignificant. Using 2-substituents such as CH_3CO and $OCOCH_3$ for which conformational isomerism[24] could affect the calculations, it was possible to determine that the energy differences were <4 kJ mol^{-1}. These differences were judged too small to justify the expense of an exhaustive study of each ground and corresponding transition state for all pertinent compounds. Relative reaction rates were obtained from transition state theory.[14] Strain energies were estimated using the method of Dudev and Lim.[25]

Results and discussion

A question arises in virtually all computational investigations. If one is to use these findings as guidance in the laboratory, how accurate are the results? Fortunately, experimental data are available.[26] Given our computational resources we were able to investigate one of these large aziridines ($R^1 = C_6H_{11}$, $R^2 = CN$) for which kinetic data has been published.[26a] The experimental study was conducted at 120° C in toluene. Using the IEFPCM solvent model,[20] $T = 393$ K and no PV correction for the change of standard state from the gas to liquid phase since the number of reactant and product species in the rate-determining step was invariant, the ΔG_{act} from the MP2 calculation was 127.6 kJ mol^{-1}; however, SCS-MP2 gave 133.0 kJ mol^{-1} in stunning agreement with the reported value of 133.9 kJ mol^{-1}. Since this expensive calculation is only one verification of the methodology, additional calculations are planned to further substantiate these findings.

For this discussion the ΔG_{act} values calculated by MP2 instead of SCS-MP2 methodology will be used; similar qualitative conclusions can be reached using the alternative method. We began with an analysis of the behavior of the relatively simple, monatomic halogen substituents with a view to gain insights into the results for thermolysis of the more complex mono- and polysubstitued aziridines. Due to space limitations, only the conclusions of these computations will be presented; however the interested reader is referred to the ESI† to obtain the pertinent data. It was found that the reaction rate is decreased by the *gem*-difluoro effect,[27,28] and the accumulation of positive charge on the ring carbons. Geminal substitution requires one of the substituents to rotate with unfavorable torquoselectivity, while *trans* stereochemistry is desirable so that both substituents may rotate in the most energetically favorable manner. Increased rates relative to **1** are associated with polarizable substituents. Relief of ring strain and electrostatic effects do not contribute to stabilization of the transition state.

(a) Monosubstitution

Having obtained some mechanistic insights as the result of determining the substituent effects of haloaziridines **2–13**, the ΔG_{act} values of a series of monosubstituted aziridines were calculated. The present study adds a significant number of compounds to the original work.[13] These are found presented in Table 1 in order of increasing ΔG_{act}. Whenever the torquoselective modes differed by less than 17.1 kJ mol^{-1} resulting in more than 0.1% of the reaction calculated to proceed by means of the less favorable conrotatory path, this ΔG_{act} is given in parentheses. All of these compounds were calculated to thermally cleave faster than **1**. While it is readily apparent that none of these substituents is capable of lowering the free energy of activation barrier below the sought-after 95.2 kJ mol^{-1}, organoborane **14** calculated previously[13] was found to be the most reactive of the compounds examined. This

Table 1 Free energies of activation in kJ mol^{-1} for thermal cleavage of C_2-monosubstitued aziridines. See text for details

Aziridine	R^2	ΔG_{act}MP2	ΔG_{act}SCS-MP2
14	BH_2	97.3	100.3
15	Li-	133.3 (134.8)	130.4
16	AcO-	137.5	143.7
17	$F_2C{=}CF$-	150.6	134.5
18	Ph	151.0	165.8
19	*o*-FC_6H_4	151.5	158.5
20	(*E*)-(CHO)CH=CH-	156.0	164.3
21	*p*-$NO_2C_6H_4$-	157.4	165.3
22	NH_2	157.7	165.0
23	CH_3CO	159.5 (161.7)	161.8
24	OCH_3	160.8	169.4
25	SCH_3	161.6	170.1
26	$N(CH_3)_2$	161.9	170.9
27	HC≡C-	162.5	170.9
28	$H_2C{=}CH$-	163.4	172.5
29	$NHCOCH_3$	163.8	171.0
30	SO_3^-	163.9	175.9
31	FC≡C-	164.2	172.6
32	SH	164.2	173.2
33	COOH	165.3	170.9
34	CN	167.2	185.5
35	CHO	167.4 (169.2)	162.9
36	OH	167.7 (179.3)	170.4
37	tBu	180.0 (199.0)	187.1
38	SO_3H	181.0 (182.9)	188.1
39	SiH_3	182.3 (182.3)	188.6
39	SiH_3	182.3 (182.3)	188.6
40	$COOCH_3$	182.7 (186.4)	191.7
41	Na	183.8 (196.6)	180.9
42	$Si(CH_3)_3$	184.1 (184.3)	190.5
43	CH_3	184.7 (202.2)	192.2
44	COO^-	186.5	191.8
45	CF_3	187.0 (193.9)	193.3
46	CH_2F	188.4 (189.6)	191.3

result may be rationalized by the fact that the electropositive boron atom experiences favorable electrostatic interactions with the dipole created by the ring atoms in the transition state. The polarizability[29] of the SH group (7.73) is considerably higher than that of OH (1.52), yet the ΔG_{act} values for the 2-thiol **32** and 2-alcohol **36** are similar: 164.2 and 167.7 kJ mol^{-1}, respectively. A possible explanation for these chalcogen substituents that favor outward rotation is that the stabilization due to the electron-releasing resonance effect of oxygen compensates for its electron-withdrawing inductive effect offsets its low polarizability. Comparison of **43**, **28** and **27** demonstrates that the free energy barrier decreases as unsaturation increases, although an ethynyl substituent is only marginally more effective than an ethenyl group. Electron-withdrawing groups attached to ethylenic positions (**20** and **17**) further increase reaction rate, while substitution of a fluoro group in **31** or replacement of the terminal carbon by nitrogen (**34**) slightly retards the rate relative to **27**. Attachment of a phenyl ring in **18** effectively lowers ΔG_{act}. An *ortho*-fluoro (**19**) or a *para*-nitro group (**21**) do not lead to large perturbations. Replacement of hydrogen by methyl as in primary amine **22** *vs*. tertiary amine **26** or with chalcogen substituents, alcohol **35** *vs*. ether **24** or thiol **32** *vs*. thioether **25**, produces only a minor change in ΔG_{act}. The outcome produced by these four substituents is rather constant. Fluorine substitution at a saturated position produces a slight transition state destabilization (compare **45** and **46** to **43**) while methyl substitution (**37** and **43**) also results in trivial stabilization. Substitution of silicon for carbon (**37** and **42**) is similarly uneventful. Acetate **16**, however, is considerably more reactive than the isomeric methoxycarbonyl derivative **40**. Since both groups are electron-withdrawing by means of inductive effects,[30] it is not unreasonable to assume that an electron-releasing resonance effect by the acetate oxygen is responsible. Ketone **23** is more reactive than aldehyde **35** perhaps due to the increased polarizability of the methyl group. The most sluggish organosulfur compound is sulfonic acid **38** whose ΔG_{act} is lowered considerably when converted to its conjugate base **30** increasing electron-withdrawing ability. Contrarily, abstraction of a proton from amino acid **33** gives rise to a considerable rate reduction in **44**. The ground state **44** would tend to be more stable relative to its transition state than **33**; a smaller difference is to be expected for interaction of the ground state N–H group with the larger sulfonate group of **30** relative to its transition state.

(b) Polysubstitution

The most reactive polysubstituted compound of Table 2, **47**, has a free energy of activation that is *ca*. 30 kJ mol^{-1} too high to reach the stated goal of this research project. Clearly the outward rotating phenyl groups of this *trans* diastereomer are capable of providing transition state stabilization by means of conjugation as was the case for monosubstituted **18** (see Fig. 1.) As has been observed for the haloaziridines, the *trans* diastereomer is invariably more reactive than the *cis* (**47** > **54**; **50** > **56**; **67** > **68**) since unfavorable inward rotation is required by one group by one group of the *cis* isomer; however, the reactivity of *bis*-trifluoromethyl compounds **62** and **63** are virtually identical due to the observation that inward and outward rotational modes for this substituent differ by only 7 kJ mol^{-1}. The role of electron-withdrawing group acceleration may be further appreciated by the result with *trans*-dialdehyde **48**. Replacement of one phenyl group of **47** by a vinyl (**49**) or chloro (**50**) group led to lower reactivity; it is noteworthy that a chloro group is about as effective as a double bond. Addition of a second *trans* substituent other than Ph can result in marked decreases in ΔG_{act}, as, for example, by addition of CHO, AcO and CF_3 (Tables 4 and 5, see Fig. 2). Geminal diphenyl substitution in **65** led to rate inhibition. This is due to the inability of both phenyl groups to achieve conjugation to the developing azomethine ylide, coupled with the necessity that one of the substituents move in the unfavorable inward direction.

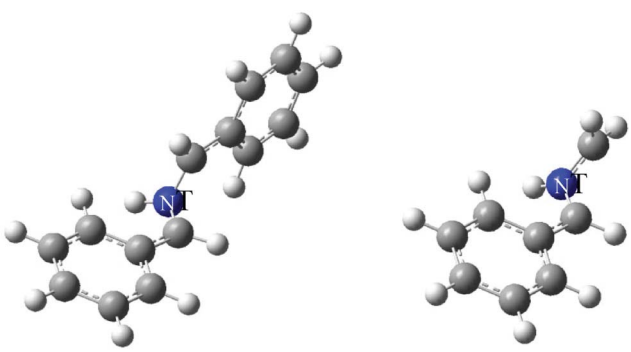


Fig. 1 Transition states for **47** and **18**.

The ΔG_{act} lowering effect of vinylic conjugation (55.2 kJ mol^{-1}) may be appreciated by comparing trifluoro compound **6** to **57**.

Table 2 Free energies of activation of polysubstitued aziridines. See the text for details

Aziridine	R^1	R^2	R^3	R^4	R^5	ΔG_{act}MP2	ΔG_{act}SCS-MP2
47	H	Ph	H	H	Ph	113.4	126.4
48	H	CHO	H	H	CHO	123.7	130.8
49	H	Ph	H	H	H_2C═CH-	126.2	134.0
50	H	Ph	H	H	Cl	128.8	147.3
51	H	AcO	H	H	AcO	131.7	140.9
52	H	*p*-$NO_2C_6H_4$	H	H	Cl	138.4	144.7
53	H	Ph	H	H	F	141.1	149.7
54	H	Ph	H	Ph	H	142.3	151.1
55	H	Ph	H	Cl	Cl	144.3	152.9
56	H	Ph	H	Cl	H	146.9 (161.0)	157.0
57	H	H_2C═CH-	F	F	F	150.6	173.5
58	H	$MeSO_2$-	H	H	H_2C═CH-	155.1	163.2
59	H	F	H	H	OMe	159.3	168.7
60	H	F	H	H	OH	160.7 (167.8)	168.7
61	H	H_2C═CH-	H_2C═CH-	H	H	162.2	157.4
62	H	CF_3	H	CF_3	H	165.0	174.0
63	H	CF_3	H	H	CF_3	165.3 (178.5)	173.8
64	H	FCH_2	H	FCH_2	H	166.8	174.5
65	H	Ph	Ph	H	H	169.0	178.7
66	H	Ph	H	F	F	176.4	182.5
67	H	Me	H	H	Me	181.2	191.1
68	H	Me	H	Me	H	191.0	210.0

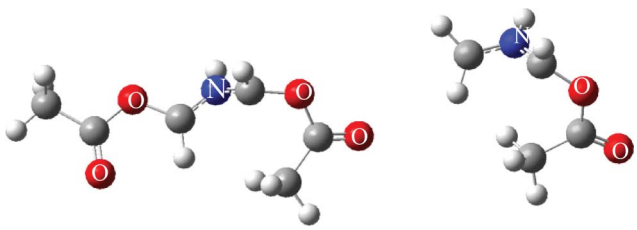


Fig. 2 Transition states for *trans*-diacetate **51** and monoacetate **16**.

Similarly, aromatic conjugation in difluorophenyl derivative in **66** produces a compound that is more reactive than **3**, and replacement of one of the Ph groups of **47** with vinyl (**49**) increase ΔG_{act} by a mere 12.8 kJ mol^{-1}.

(c) Substitution at nitrogen

The consequences of nitrogen substitution were studied next (Table 3.) With the exception of the N–CN derivative, all compounds were more reactive than **1**, but too unreactive to satisfy our requirements. Electron-releasing effects of substituents attached to nitrogen are able to contribute to the dispersal of the partial positive charge on nitrogen in the transition state. Generally the energy of the transition state tended to be less sensitive to substitution at nitrogen than at the carbon positions. The benzyl protecting group found in **75** that is often employed synthetically as a protecting group produced virtually the same calculated reactivity as the computationally friendly methyl group (**74**.)

(d) Anionic substituents

Since the uncharged substituted aziridines investigated to this point did not fall below the target ΔG_{act}, anionic species were studied. The approximation given above that gas phase computations are acceptable in solution is no longer valid since anions are likely to be intimately associated with cations except in polar aprotic solvents such as DMSO. It is also possible that 2-azaallylic anions are formed more rapidly than the isomeric azomethine ylides for N-deprotonated species. At the level of calculation employed in this research effort, we have been unable to find evidence for formation of 2-azaallylic anions in the gas phase or in DMSO. In spite of the realization that computational results with anions in the gas phase would not be directly transferable to solution work in the laboratory, they were deemed theoretically useful to provide information as the sensitivity of the thermolysis reaction to electronic effects. The results are presented in

Table 3 Free energies of activation of N-substituted aziridines. See text for details

Aziridine	R^1	R^2	R^3	R^4	R^5	ΔG_{act}MP2	ΔG_{act}SCS-MP2
69	Me	H_2C═CH	H	H	H	151.7(165.7)	172.8
70	Me	F	H	H	H	163.2	170.7
71	Ph	H	H	H	H	167.1	174.0
72	F	H	H	H	H	174.7	184.9
73	$COOCH_3$	H	H	H	H	178.2	191.6
74	Me	H	H	H	H	182.9	191.1
75	Bn	H	H	H	H	184.6	192.0
76	OH	H	H	H	H	193.1	197.1
77	Cl	H	H	H	H	179.8	204.5
78	CN	H	H	H	H	204.9	209.9

Table 4 Free energies of activation of substituted aziridines monoanions. See text for details

Aziridine	R^1	R^2	R^3	R^4	R^5	ΔG_{act}MP2	ΔG_{act}SCS-MP2
79	H	NH^-	H	H	H	43.5	75.7
80	H	O^-	H	H	H	47.5	46.7
81	–	Ph	H	H	Ph	52.4	36.6
82	–	Ph	H	H	H	73.2	109.9
83	–	*p*-FC_6H_4	H	H	H	75.0	81.1
84	–	CN	H	H	H	87.2	91.8
85	–	CF_3	H	H	H	101.7	107.2
86	–	H	H	H	H	103.6	107.9
87	H	S^-	H	H	H	115.7	123.1
88	O^-	F	H	H	H	117.2	128.7
89	COO^-	Ph	H	H	H	120.2	126.5
90	COO^-	*p*-$OMeC_6H_4$	H	H	H	120.2	127.0
91	COO^-	*o*-FC_6H_4	H	H	H	121.9	149.2
92	COO^-	H	H	H	H	147.8	152.4
93	O^-	$H_2C{=}CH$	H	H	H	148.0	148.6
94	O^-	Ph	H	H	H	150.2	152.0
95	O^-	H	H	H	H	150.7	156.0
96	COO^-	F	H	H	H	152.7	123.3
97	*p*-$C_6H_4O^-$	H	H	H	H	153.3	159.4
98	H	*o*-PhO^-	H	H	Cl	159.1	168.5
99	–	F	F	H	H	161.9	161.0
100	H	SO_3^-	H	H	H	163.9	172.4
101	$CH(COCH_3)COO^-$	H	H	H	H	176.3	182.5
102	SO_3^-	H	H	H	H	180.1	187.1
103	COOMe	–	H	H	H	184.4	183.6
104	H	COO^-	H	H	H	186.5	192.3
105	–	F	F	F	F	207.8	203.9

Table 4. Noteworthy are the effects of heteroatomic anions at C_2 in **79** and **80**, as well as the rather low ΔG_{act} results for carbamates **89–92**.

Very recently it was decided to determine whether the ΔG_{act} values for carbamates could be augmented by taking advantage of lessons learned from *trans*-2,3-diphenyl derivative **47**, giving rise to *trans*-2,3-diphenylaziridine-1-carboxylate, **106**. G3(MP2) calculations were performed on this structure. The G3(MP2) method has the advantage of being reasonably accurate and less computationally expensive. As noted above in the section on computational methods, this result was grounded with the MP2(Full) and SCS-MP2 calculations, by comparisons with the results for **18**, **84** and **89**, compounds that are structurally similar to **106**. The ΔG_{act} values obtained were 140.0, 90.3 and 107.0 kJ mol^{-1} in acceptable agreement with the results listed in Tables 1 and 4. When this computational approach was applied to **106**, a ΔG_{act} of 73.5 kJ mol^{-1} was obtained. Not only is this ΔG_{act} below our established threshold, but in both aqueous solution [31] and in the gas phase [32] carbamic acid has been found to be stronger than formic acid, signifying that its conjugate base is less basic than formate. This should place the newly computationally discovered compound but presently unknown compound within the range of the temperature and pH required for bioorthogonality.[3] Carbamates are susceptible to decarboxylation[32] under certain conditions, however, the product of this reaction, **81**, should be quite reactive, and could have useful applications. It should be emphasized that this discovery is strictly applicable only in the gas phase. The computational work has successfully identified a reasonable candidate compound that satisfies the ΔG_{act} requirements; however, given the number of remaining variables, transition to the laboratory is the next logical step. A potential synthetic strategy may be envisioned.[33] Computations to identify additional substituted aziridine synthetic targets that meet the stated requirements are underway.

(e) Effect of the heteroatom

It is useful at this juncture to examine the effect of the heteroatom on thermal C–C ring cleavage. Some years ago, Houk and co-workers[34] calculated the activation energies for a large number of 3-substituted cyclobutenes at the HF/6-31G*//3-21G level. The free energies of activation of representative 3-substituted cyclobutenes were computed at the level of theory employed in this investigation for direct comparison to those of the corresponding aziridines (see Table 5.) The aziridines are substituted at C_2 with the exception of the N-deprotonated anion.

With the exception of the anion, the cyclobutenes studied are considerably more reactive than the aziridines. This is not unreasonable since the transition state in azomethine ylide formation should require a larger energy input to effect charge separation. With the exception of the OH group, aziridine is more responsive to substituent effects than cyclobutene. This observation is doubtless due to the higher polarity of the heterocyclic transition state with accompanying greater sensitivity to substituent properties.

(f) 1,3-Dipolar cycloaddition

One potential application of this method of using substituents to increase the rate of ring cleavage is in the area of click chemistry. In introducing this research effort, it was noted that the click chemistry approach has had a significant impact on the practice of synthetic organic chemistry. Click chemistry is limited to reactions that are modular, broad in scope, high-yielding, and stereospecific. Only reactions that feature innocuous, readily removed byproducts, and nonchromatographic product isolation

Table 5 Comparison of substituent effects for 3-cyclobutenes and aziridines. See text for details

	3-Substituted cyclobutenes		Substituted aziridines		
Substituent	ΔG_{act}/kJ mol^{-1}	Relative rate	ΔG_{act}/kJ mol^{-1}	Relative rate	k_{Cybut}/k_{Azir}
H	139.1	1.00E+00	194.6	1.00E+00	5.20E+09
F, F	172.7	1.33E-06	222.7	1.19E-05	5.81E+11
F	144.0	1.41E-01	176.7	1.37E+03	5.38E+05
CH_3CO	121.2	1.40E+03	159.5	1.41E+06	5.17E+06
Ph	111.2	7.85E+04	151.0	4.37E+07	9.39E+06
OH	100.6	5.76E+06	167.7	5.16E+04	5.81E+11
BH_2	42.5	8.40E+16	97.2	4.43E+26	3.83E+09
Anion	114.1	2.42E+04	151.0	8.75E+15	1.44E-02

that can be preformed neat or with harmless or easily removed solvent are acceptable. If a sensitive functionality is present in a synthetic route, or if a biological process is being studied, these stringent conditions must be supplemented by the requirement that the reaction occur under exceedingly mild reaction conditions (< 37° C and a pH between 7.0 and 8.0). Click chemistry embraces cycloadditions, nucleophilic substitution, non-aldol carbonyl chemistry and addition to unsaturated C–C bonds. In lieu of azides, one can conceive of many other dipoles that would be effective dipoles. As noted above, azomethine ylides are effective participants in 1,3-dipolar cycloaddition chemistry.[35] Of particular interest is our calculated finding of relatively rapid C–C ring cleavage of anionic species, a class of compound that in the form of metal salts have been demonstrated to be useful in 1,3-dipolar cycloaddition chemistry experimentally.[36,37] The NBO charges of transition state formed from **1** are provided in Fig. 3. If the charges on hydrogen are summed into the carbons, it is apparent that the negative charge is distributed over the heavy atoms, with each carbon having a significant negative charge (–0.309, hydrogens summed.)

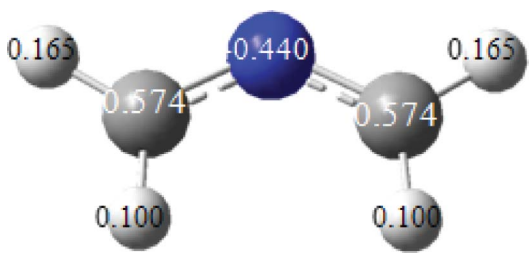


Fig. 3 NBO Charges for the product of C–C cleavage of N-deprotonated aziridine.

(g) Rate-determining step in 1,3-dipolar cycloaddition of substituted aziridines

While the literature indicates that formation of an azomethine ylide from an aziridine is the slow, rate-limiting step in 1,3-dipolar cycloaddition chemistry,[2f,10c] it is essential to determine if this finding is valid for the compounds studied herein. For an acceptable reaction, neither 1,3-dipole formation or cycloaddition[38] may exceed 95.2 kJ mol^{-1}. To determine if this chemistry might have click chemistry applications, preliminary studies were conducted for representative compounds (parent compound, **1**; two compounds, **16** and **18**, that form their azomethine ylides considerably more rapidly than **1**, a compound of intermediate reactivity **34** anion **86** and stabilized anion **84**.) The results are provided in Table 6. In these cases, cycloaddition is the considerably more facile reaction; however, it may not be assumed from this sampling of substrates that the relative reactivities of the mechanistic steps of every reaction will obtain.

Table 6 Free energies of activation for C–C bond cleavage and cycloaddition of the resulting azomethine ylide. See text for details

Aziridine	ΔG_{act} (kJ mol^{-1}) C–C bond cleavage	ΔG_{act} (kJ mol^{-1}) cycloaddition
1	194.6	40.8[a]
16	137.5	22.7[a]
18	151.0	43.6[a]
86	103.6	23.5[b]
84	87.2	53.2

[a] Reaction with ethyne. [b] Reaction with ethene.

Conclusions

The effects of a diverse group of substituents on the rate of conrotatory thermal cleavage of aziridines has been studied computationally. In order for the reaction to occur under conditions that are compatible with sensitive functionalities in a chemical synthesis and the study of biological systems, it was decided to search for substrates that cleave completely at room temperature in reasonable timeframe. Subsequent reactions with the generated azomethine ylide would have to occur at least as fast, in order for this chemistry to be useful. No neutral compounds examined in this study satisfied these criteria. In general, the free energy of activation was found to decrease as the electron-withdrawing ability or conjugation of a substituent attached to carbon increased. Anionic species were identified that had suitable ΔG_{act} values, however, their basicity with the exception of the recently discovered *trans*-2,3-diphenylaziridine-1-carboxylate was too high. The additional electron pair of anionic species did not enter into the electrocyclic chemistry, and the remaining 4-electron system follows a conrotatory thermal process as demanded by the rules of conservation of orbital symmetry.[11] The use of G3MP2 methodology that has been found to produce reasonably accurate results with significantly lowered computation cost resulted in a reaction rate for *trans*-2,3-diphenyl-*N*-carbamate that is fast enough to be acceptable by the criterion set forth in this investigation.

Computations are continuing to find substituted aziridine anions that cleave with acceptable rates yet have low basicity. The

ultimate test of our results is the successful deployment of this compound and those suggested by its structure in the laboratory.

References

1 (*a*) M. G. Finn and V. Fokin, ed., *Chem. Soc. Rev.*, 2010, **39**, 1231–1405; (*b*) H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2031; (*c*) K. B. Sharpless, *Drug Discovery Today*, 2003, **8**, 1128; (*d*) F. Himo, T. Lovell, R. Higraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless and V. V. Folkin, *J. Am. Chem. Soc.*, 2005, **127**, 210; (*e*) A. Krasinski, Z. Radic, R. Manetsch, J. Raushel, P. Taylor, K. B. Sharpless and H. C. Kolb, *J. Am. Chem. Soc.*, 2005, **127**, 6686; (*f*) F. Shi, J. P. Waldo, Y. Chen and R. C. Larock, *Org. Lett.*, 2008, **10**, 2409; (*g*) L. Campbell-Verduyn, P. H. Elsinga, L. Mirfeizi, R. A. Dierckx and B. L. Feringa, *Org. Biomol. Chem.*, 2008, **6**, 3461; (*h*) G. Kumararswamy, K. Ankamma and A. Pitchaiah, *J. Org. Chem.*, 2007, **72**, 9822; (*i*) N. J. Agard, J. A. Prescher and C. R. Bertozzi, *J. Am. Chem. Soc.*, 2004, **126**, 15046; (*j*) J. E. Moses and A. D. Moorhouse, *Chem. Soc. Rev.*, 2007, **36**, 1249; (*k*) M. V. Gil, M. J. Arefalo and O. Lopez, *Synthesis*, 2007, 1589.

2 (*a*) M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952; (*b*) C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057; (*c*) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596.

3 (*a*) P. V. Chang, E. M. Sletten, J. M. Baskin, I. A. Miller, N. J. Agard, A. Lo and C. R. Bertozzi, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 1821; (*b*) J. M. Baskin and C. R. Bertozzi, *Aldrichchimica Acta*, 2010, **43**, 15; (*c*) J. C. Jewett and C. R. Bertozzi, *Chem. Soc. Rev.*, 2010, **39**, 1272; (*d*) K. A. Kalesh, H. Shi, J. Ge and S. Q. Yao, *Org. Biomol. Chem.*, 2010, **8**, 1749; (*e*) E. M. Sletten and C. R. Bertozzi, *Angew. Chem., Int. Ed.*, 2009, **48**, 6974; (*f*) J. C. Jewett, E. M. Sletten and C. R. Bertozzi, *J. Am. Chem. Soc.*, 2010, **132**, 3688.

4 (*a*) S. Catak, M. D. D'hooghe, T. Verstraelen, D. Hemelsoet, A. Van Nieuwenhove, H-H. Ha, M. Waroquier, N. De Kimpe and V. Van Speyboeck, *J. Org. Chem.*, 2010, **75**, 4530; (*b*) M. K. Ghorai and D. P. Tiwari, *J. Org. Chem.*, 2010, **75**, 6173; (*c*) A. Koonhang, J. L. Gailey, R. M. Coates, H. K. Erickson, D. Owen and C. D. Poulter, *J. Org. Chem.*, 2010, **75**, 4769; (*d*) B. M. Trost, S. Malhotra, D. E. Olson, A. Maruniak and J. Du Bois, *J. Am. Chem. Soc.*, 2009, **131**, 4190; (*e*) A. Okano, S. Oishi, T. Tanaka, N Fujii and H. Ohno, *J. Org. Chem.*, 2010, **75**, 3396; (*f*) A. Armstrong, R. D. C. Pullin, C. R. Jenner and J. N. Scutt, *J. Org. Chem.*, 2010, **75**, 3499; (*g*) M. Dammacco, L. Degennara, S. Florio, R. Luisi, B. Musio and A. Altomare, *J. Org. Chem.*, 2009, **74**, 6319; (*h*) R. Hili and A. K. Yudin, *J. Am. Chem. Soc.*, 2006, **128**, 14772; (*i*) P. D. Pohlhaus, R,K. Bowman and J. S. Johnson, *J. Am. Chem. Soc.*, 2004, **126**, 2294; (*j*) A. Ciogli, A. Fioravanti, F. Gasparrini, L. Pellacani, E. Rizzatos, D. Sinelli and P. A. Tardella, *J. Org. Chem.*, 2009, **74**, 9314; (*k*) S. C. Valdez and J. L. Leighton, *J. Am. Chem. Soc.*, 2009, **131**, 14638; (*l*) J. Collins, U. Rinner, M. Moser and T. Hudlicky, *J. Org. Chem.*, 2010, **75**, 3069; (*m*) N. Assem, A. Natarajan and A. K. Yudin, *J. Am. Chem. Soc.*, 2010, **132**, 10986; (*n*) R. Huang, M. A. Holbert, M. K. Tarrant, S. Curtet, D. R. Colquhoun, B. M. Dancy, B. C. Dancy, Y. Hwang, Y. Tang, K. Meeth, R. Marmorstein, R. N. Cole, S. Khochbin and P. A. Cole, *J. Am. Chem. Soc.*, 2010, **132**, 9986; (*o*) M. R. Fructos, E. Álvarez, M. M. Diaz-Requejo and P. J. Pérez, *J. Am. Chem. Soc.*, 2010, **132**, 4600; (*p*) R. Hili and A. K. Yudin, *J. Am. Chem. Soc.*, 2009, **131**, 16404; (*q*) L. K. Otttesen, J. Jaroszewski and H. Franzyk, *J. Org. Chem.*, 2010, **75**, 4983; (*r*) H. Hu, J. A. Faraldos and R. M. Coates, *J. Am. Chem. Soc.*, 2009, **131**, 11998.

5 For reviews, see: (*a*) A. Padwa and S. S. Murphree, *Arkivoc*, 2006, **6**; (*b*) M. Pinho and M. V. D. Teresa, *Eur. J. Org. Chem.*, 2006, **13**, 2873; (*c*) N. Tagmatarchis and M. Prato, *Synlett*, 2003, 768; (*d*) Y Terao, M. Aono and K. Achiwa, *Heterocycles*, 1988, **27**, 981; (*e*) A. Padwa, in *Comprehensive Organic Synthesis*, B. M Trost and I. Fleming, ed., New York, 1991, 1085; (*f*) J. W. Lown in *1,3-Dipolar Cycloaddition Chemisty*, Vol. 1, A. Padwa, Ed., New York, 1984, 653; (*g*) I. Coldham and R. Hufton, *Chem. Rev.*, 2005, **105**, 2765; For a discussion of the effect of substituents on C–C as opposed to C–N, see; (*h*) S. Paasche, M. Arnone, R. F. Fink, T. Schirmeister and B. Engels, *J. Org. Chem.*, 2009, **74**, 5244; (*i*) C. Najera and J. M. Sansano, *Curr. Org. Chem.*, 2003, **7**, 1105; (*j*) G Pandey, P. Banerjee and S. R. Gadre, *Chem. Rev.*, 2006, **106**, 4484; (*k*) L. M. Stanley and M. P. Sibi, *Chem. Rev.*, 2008, **108**, 2887.

6 I. Deb, D. Das and D. Seidel, *Org. Lett.*, 2011, **13**, 812.

7 P. V. Guerra and V. A. Yaylayan, *J. Agric. Food Chem.*, 2010, **58**, 12523.

8 M. R. Chaulagain and Z. D. Aron, *J. Org. Chem.*, 2010, **75**, 8271.

9 (*a*) H. D. Banks, *J. Org. Chem.*, 2008, **73**, 2510; (*b*) H. D. Banks, *Org. Biomol. Chem.*, 2009, **7**, 4496; (*c*) H. D. Banks, *J. Org. Chem.*, 2003, **68**, 2639.

10 (*a*) A. Padwa and L. Hamilton, *Tetrahedron Lett.*, 1965, 4363; (*b*) Y. Hayashi, T. Kumamoto, M. Kawahata, K. Yamaguchi and T. Ishikawa, *Tetrahedron*, 2010, **66**, 3836; (*c*) R Huisgen, W. Scheer and H. Mader, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 602; (*d*) R. Huisgen and W. Scheer, *Tetrahedron Lett.*, 1971, 481; (*e*) G. Mloston, A. Linden and H. Heimgartner, *Helv. Chim. Acta*, 1998, **81**, 558.

11 R. B. Woodward, R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag, Weinheim, Germany, 1970.

12 For an excellent review of this phenomenon, see (*a*) S. M. Bachrach, *Computational Organic Chemistry*, Wiley, Hoboken, NJ, 2007; (*b*) I. Coldham and R. Hufton, *Chem. Rev.*, 2005, **105**, 2765.

13 H. D. Banks, *J. Org. Chem.*, 2010, **75**, 2510.

14 See, for example: T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, 2nd ed.; New York, 1981, p 194.

15 *Gaussian 03*, Revision C.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.

16 (*a*) A. E. Reed, R. B. Weinstock and F. Weinhold, *J. Chem. Phys.*, 1985, **83**, 735–746; (*b*) A. E. Reed and F. Weinhold, *J. Chem. Phys.*, 1985, **83**, 1736; (*c*) A. E. Reed, F. Weinhold, L. A. Curtiss and D. J. Pochatko, *J. Chem. Phys.*, 1986, **84**, 5687; (*d*) A. E. Reed, L. A. Curtiss and F. Weinhold, *Chem. Rev.*, 1988, **88**, 899; (*e*) J. E. Carpenter and F. Weinhold, *J. Am. Chem. Soc.*, 1988, **110**, 368; (*f*) L. Goodman, V. Pophristic and F. Weinhold, *Acc. Chem. Res.*, 1999, **32**, 983; (*g*) E. D. Glendening, R. Faust, A. Streitwieser, K. P. C. Vollhardt and F. Weinhold, *J. Am. Chem. Soc.*, 1993, **115**, 10952.

17 NBO charges proved to be useful in our earlier studies of nucleophilic substitution reactions (Ref. 6a). Electrostatic energies derived from this method depend critically on the population analysis used by Gaussian 03. Atomic charges are not physical observables, are not necessarily centered at the nuclei. An excellent discussion of atomic charge is available: K. B. Wiberg and P. R. Rablen, *J. Comput. Chem.*, 1993, **14**, 1504.

18 (*a*) S. Grimme, *J. Chem. Phys.*, 2003, **118**, 9095; (*b*) S. Grimme, *J. Comput. Chem.*, 2003, **24**, 1529; (*c*) I. Hala-Kryspin and S. Grimme, *Organometallics*, 2004, **23**, 5581; (*d*) S. Grimme, C. Mück-Lichtenfeld, E-U. Würthwein, A. W. Ehlers, T. P. M. Goumans and K. Lammertsma, *J. Phys. Chem. A*, 2006, **119**, 2583; (*e*) S. Grimme, M. Steinmetz and M. Korth, *J. Org. Chem.*, 2006, **72**, 2118; (*f*) T. Schwabe and S. Grimme, *Acc. Chem. Res.*, 2008, **41**, 569; (*g*) F. Neese, A. Hansen, F. Wennmohs and S. Grimme, *Acc. Chem. Res.*, 2009, **42**, 641; (*h*) S. E. Wheeler, A. Moran, S. N. Pieniazek and K. N. Houk, *J. Phys. Chem. A*, 2009, **113**, 10376.

19 L. A. Curtiss, P. C. Redfern, V. Rassolov and J. A. Pople, *J. Chem. Phys.*, 1999, **110**, 4703 The author is grateful to a referee for this suggestion.

20 (*a*) K. B. Wiberg, T. A. Keith, M. J. Frisch and M. J. Murcko, *J. Phys. Chem.*, 1995, **99**, 9072; (*b*) E. Cancès, B. Mennucci and J. Tomasi, *J. Chem. Phys.*, 1997, **107**, 3032.

21 For reviews of solvent effects see: (*a*) C. J. Cramer and D. G. Truhlar, *Acc. Chem. Res.*, 2008, **41**, 760; (*b*) J. Tomasi, B. Mennuci and R. Cammi, *Chem. Rev.*, 2005, **105**, 2999; (*c*) M. Ororozo and F. J. Luque, *Chem. Rev.*, 2000, **100**, 4187; (*d*) C. J. Cramer and D. G. Truhlar, *Chem. Rev.*, 1999, **99**, 2161.

22 J. B. Foresman and Æ. Frisch, *Exploring Chemistry with Electronic Structure Methods*, 2nd ed., Gaussian Inc., Pittsburgh, PA, 1996.

23 *GaussView 3.0*, Gaussian Inc., Carnegie Office Park, Blg. 6, Pittsburgh, PA 15106.

24 For a discussion of conformational isomerism of ketones and esters, see E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, New York, 1994, pp 617–619.
25 (*a*) T. Dudev and C. Lim, *J. Am. Chem. Soc.*, 1998, **120**, 4450; (*b*) Details of our application of this method are provided in Ref. 9a.
26 (*a*) A. Derdour and F. Texier, *Can. J. Chem.*, 1984, **63**, 3605; (*b*) A. C. Oehlschlager, A. S. Yim and M. H. Adhtar, *Can. J. Chem.*, 1978, **56**, 273; (*c*) R. Huisgen and H. Mader, *J. Am. Chem. Soc.*, 1971, **93**, 1777.
27 For discussions of the chemistry of organofluorine compounds see (*a*) R. D. Chambers, *Fluorine in Organic Chemistry*, Oxford, 2004; (*b*) D. M. Lemal, *J. Org. Chem.*, 2004, **69**, 1; (*c*) T. Kitazume and T. Yamazaki, *Experimental Methods in Organic Fluorine Chemistry*, Tokyo, 1998; (*d*) W. R. Dolbier Jr., *J. Fluorine Chem.*, 2005, **126**, 157; (*e*) L. Hunter, *Beilstein J. Org. Chem.*, 2010, **6**, DOI: 10.3762/bjoc.6.38; (*f*) B. E. Smart, in *Chemistry of Organic Fluorine Compounds II: A Critical Review*M. Hudlicky and A. E. Pavlath, ed.; ACS Monograph 187; American Chemical Society, Washington, DC, 1995; pp 979–1010.
28 D. M. Lemal, *J. Org. Chem.*, 2004, **69**, 1.
29 W. J. le Noble, *Highlights of Organic Chemistry*, New York, 1974, p 83.
30 (*a*) X. Creary and M. A. Butchko, *J. Am. Chem. Soc.*, 2001, **123**, 1569; (*b*) N. D. Scheep and J. Wirz, *J. Am. Chem. Soc.*, 1994, **116**, 11749; (*c*) R. Damico, *J. Org. Chem.*, 1968, **33**, 1550; (*d*) E. P. Painter and N. H. Kurihara, *Can. J. Chem.*, 1967, **45**, 1475; (*e*) S. J. Cristol and B. Franzus, *J. Am. Chem. Soc.*, 1957, **79**, 2488.
31 (*a*) X. Creary and M. A. Butchko, *J. Am. Chem. Soc.*, 2001, **123**, 1569; (*b*) N. D. Scheep and J. Wirz, *J. Am. Chem. Soc.*, 1994, **116**, 11749; (*c*) R. Damico, *J. Org. Chem.*, 1968, **33**, 1550; (*d*) E. P. Painter and N. H. Kurihara, *Can. J. Chem.*, 1967, **45**, 1475; (*e*) S. J. Cristol and B. Franzus, *J. Am. Chem. Soc.*, 1957, **79**, 2488.
32 M. Caplow, *J. Am. Chem. Soc.*, 1968, **90**, 6795.
33 Syntheses of *trans*-2,3-diphenylaziridine: *S* (*a*) Y. Arroyo, A. Meana, M. Sanz-Tejedor, M. Ascension, I Alonso and J. L. Farcia Rucano, *Chem.–Eur. J.*, 2010, **16**, 9874; (*b*) Arroyo, A. Meana, M. Sanz-Tejedor, M. Ascension, I Alonso and J. L. Farcia Rucano, *J. Org. Chem.*, 2009, **74**, 4217; (*c*) J-L. Hsu and J-M. Fang., *J. Org. Chem.*, 2001, **66**, 8573 *R*; (*d*) X. Li, N. Chen and J. Xu, *Synthesis*, 2010, 3423; (*e*) B. Ritzen, M. C. M. van Oers, F. L. van Delft, L. Floris and F. P. T. Rutjes, *J. Org. Chem.*, 2009, **74**, 7548; (*f*) A. Reyes and E. Juaristi, *Chirality*, 1998, **10**, 95; (*g*) N-trialkylamine preparation: T. W. Greene, *Protective Groups in Organic Synthesis*, New York, 1991, pp. 389Formation of *O*-silylcarbamates with supercritical CO_2; (*h*) M. J. Fuchter, C. J. Smith, M. W. S. Tsang, A. Boyer, S. Saubern, J. H. Ryan and A. B. Holmes, *Chem. Commun.*, 2008, 2152 The carbamate anion may be formed by deprotection using a suitable reagent (see Greene above, p. 262.).
34 S. Niwayama, E. A. Kallel, D. C. Spellmeyer, C. Sheu and K. N. Houk, *J. Org. Chem.*, 1996, **61**, 2813.
35 For reviews, see: (*a*) A. Padwa and S. S. Murphree, *Arkivoc*, 2006, 6; (*b*) M. Pinho and M. V. D. Teresa, *Eur. J. Org. Chem.*, 2006, **13**, 2873; (*c*) N. Tagmatarchis and M. Prato, *Synlett.*, 2003, 768; (*d*) Y. Terao, M. Aono and K. Achiwa, *Heterocycles*, 1988, **27**, 981; (*e*) A. Padwa, in *Comprehensive Organic Synthesis*, B. M. Trost and I. Fleming, ed., New York, NY, 1991; p 1085; For a discussion of the effect of substituents on C–C as opposed to C–N, see; (*f*) S. Paasche, M. Arnone, R. F. Fink, T. Schirmeister and B. Engels, *J. Org. Chem.*, 2009, **74**, 5244; (*g*) C. Najera and J. M. Sansano, *Curr. Org. Chem.*, 2003, **7**, 1105; (*h*) G. Pandey, P. Banerjee and S. R. Gadre, *Chem. Rev.*, 2006, **106**, 4484; (*i*) L. M. Stanley and M. P. Sibi, *Chem. Rev.*, 2008, **108**, 2887.
36 *N*-Lithioaziridines have been used for intra- and intermolecular cycloadditions: See W. H. Pearson, M. A. Walters, M. K. Rosen and W. G. Harter, *Arkivoc*, 2002, **(viii)**, 91 and references cited therein.
37 Azomethine ylide metal salts have been extensively studied in the Grigg laboratory: See R. Grigg, S. Husinic and V. Savić, *J. Serb. Chem. Soc*, 2010, **75**, 1 and references cited therein.
38 Theoretical treatments of 1,3-cycloaddition are available. Distortion/interaction energy: (*a*) L. Xu, C. E. Doubleday and K. N. Houk, *J. Am. Chem. Soc.*, 2010, **132**, 3029 and references cited therein. Activation strain model: W. J. van Zeist and F. M. Bickelhaupt, *Org. Biomol. Chem.*, 2010, **8**, 3118 and references cited therein; (*b*) B. Engels and M. Christl, *Angew. Chem., Int. Ed.*, 2009, **48**, 7968.

