Diazirines: Carbene Precursors Par Excellence

ROBERT A. MOSS*

*Department of Chemistry and Chemical Biology,
Rutgers, The State University of New Jersey,
New Brunswick, New Jersey, 08903*

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ABSTRACT

Diazirines are prime precursors for carbenes. In this Account, we discuss the synthetic and mechanistic dimensions that govern the range, availability, and utility of diazirines. We focus on the Graham reaction, which affords halodiazirines from amidines in a one-pot procedure, and the diazirine exchange reaction, which allows easy replacement of an initial diazirine's halo substituent by a variety of other nucleophiles. Together, the Graham reaction and the diazirine exchange reaction provide an extraordinarily wide range of diazirine precursors for electrophilic, ambiphilic, and nucleophilic carbenes.

Introduction

A major channel of carbene chemistry involves the use of laser flash photolysis (LFP), which permits the spectroscopic visualization of carbenes on the nanosecond or picosecond time scales and the measurement of rate constants and activation parameters.[1] However, to deploy laser-based spectroscopic methods, we require appropriate carbene precursors. In view of their accessibility and user-friendly nitrogen leaving group, diazirines are an appropriate choice.[2,3] We have discussed the centrality of diazirine precursors to the understanding of carbenic reactivity,[4,5] but here we focus on the diazirines themselves, particularly the synthetic and mechanistic dimensions that govern their variety, availability, and utility in carbene chemistry.

The Graham Reaction

Graham discovered the remarkable one-pot hypohalite oxidation of amides to halodiazirines (eq 1), where R =

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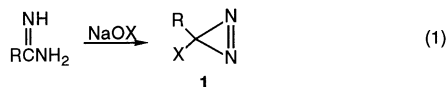
alkyl, alkoxy, phenyl, or vinyl, and X = Cl or Br.[6] In one case (R = Me), inclusion of acetate ion also gave some acetoxydiazirine. Diazirines from the Graham reaction afford access to a host of halocarbenes, RCX, with a wide variety of substituents,[6] and many studies of Graham-derived carbenes soon followed.[5] Further broadening of

Robert A. Moss is the Louis P. Hammet Professor of Chemistry at Rutgers University, where he has been on the faculty since 1964. He received his doctoral and postdoctoral training at the University of Chicago (Prof. G. L. Closs) and at Columbia University (Prof. R. Breslow). He has also been a Visiting Scientist or Professor at MIT, Oxford, The Weizmann Institute, the Politechnika (Warsaw), and the Hebrew University of Jerusalem.

Scheme 1
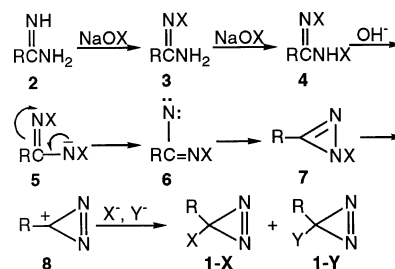
diazirine availability required attention to the mechanism of Graham's reaction.

Graham offered the mechanism shown in Scheme 1.[6] We verified the halogenation steps by isolation of intermediates **3** and **4** (R = *i*-Pr or MeO).[7] As required by Scheme 1, treatment of **4** with aqueous NaOH saturated with NaCl afforded the diazirines **1-X** (R = *i*-Pr or MeO, X = Cl).[7] However, none of the other intermediates of the scheme have been directly observed. Base-catalyzed conversion of **4** to *N*-haloisodiazirine **7** could occur via α-elimination to iminonitrene **6**, followed by cyclization, or directly from *N*-anion **5** by halide displacement,[6] but how is **7** converted to **1**? Graham suggested ionization of **7** to diazirinium ion **8** because of his observation of ions with *m/e* corresponding to **8** in the mass spectra of the halodiazirines **1**.[6] Additionally, **8** is attractive because of its resemblance to the isoelectronic cyclopropenium cation.[6] Conversion of **8** to **1** would then follow by reaction with halide. However, Graham also recognized that **7** could give **1** by a S$_N$2′ reaction (eq 2), bypassing cation

(2)
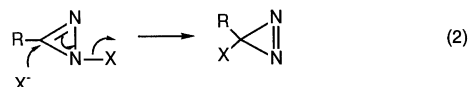
8.[6]

Even without choosing between the diazirinium or S$_N$2′ mechanistic options, it is clear that inclusion of a "foreign" nucleophile in a Graham oxidation should afford a new diazirine, **1-Y**, as well as the expected **1-X** (Scheme 1). We reasoned that it might be possible to *exchange* the halide of diazirines **1** for other nucleophiles, perhaps via diazirinium ion **8** formed by ionization of **1**. Although this mechanism is incorrect (see below), the synthetic plan worked splendidly.

The Diazirine Exchange Reaction

Phenylbromodiazirine (R = Ph, X = Br) reacted with NaOMe in polar solvents to give phenylmethoxydiazirine (R = Ph, X = OMe, eq 3); cf. Table 1, entry 1.[8] In this initial

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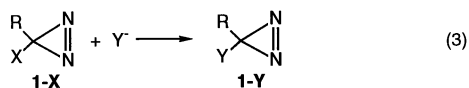
example of the diazirine exchange reaction, we suggested

* E-mail: moss@rutchem.rutgers.edu.

Table 1. Examples of the Diazirine Exchange Reaction[a]

| entry	R	X	Y	ref
1	Ph	Br	MeO	8
2	Ph	Br	F	10
3	Ph	Cl	F	10
4	PhO	Cl	F	10
5	Ph	Br	CN	10,14
6	CF_3	Br	F	18
7	Ph	Br	R_2NH[b]	26
8	Me	Br	F	27
9	Me	Br	MeO	27
10	Me	Br	CN	27
11	MeO	Br	F	29
12	PhO	Cl	F	31
13	PhO	Cl	MeO	32
14	MeO	Cl	MeO	33
15	c-C_3H_5[c]	Br	MeO	34
16	Me_3CCH_2	Br	MeO	35
17	$PhOCH_2$	Br	F	36
18	Me_3CCH_2	Br	F	36
19	c-C_3H_5[c]	Br	F	36
20	c-C_4H_7[d]	Br	F	36
21	CF_3CH_2O	Br	F	37
22	CF_3CH_2O	Br	CF_3CH_2O	37
23	CH_3O	Cl	CF_3CH_2O	37
24	Me	Br	CF_3CH_2O	38
25	c-C_3H_5[c]	Br	CF_3CH_2O	38
26	$C_7F_{15}CH_2O$	Br	$C_7F_{15}CH_2O$	39a
27	CF_3	Br	MeO	40
28	$PhCH_2O$	Cl	CN	41
29	Ph	Br	AcO	43
30	Ph	Br	ArCOO	44
31	ArO	Cl	ArO	49
32	ArO[e]	Cl	F	50
33	Cl	ArO[e]	F	50
34[f]	Cl	ArO[e]	Cl	51

[a] Refer to eq 3 for R, X, and Y. Examples are tabulated in order of presentation. [b] *N,N'*-Dimethylethylenediamine. [c] Cyclopropyl. [d] Cyclobutyl. [e] Ar = *p*-nitrophenyl. [f] See also ref 52.

the intermediacy of an "intimate diazirinium cation–bromide ion pair".[8] Phenylmethoxycarbene (PhCOMe), generated from the diazirine, proved to be an ambiphilic carbene with pronounced nucleophilic character.[9]

Phenylbromodiazirine or phenylchlorodiazirine were converted to phenylfluorodiazirine simply by stirring with "molten" tetrabutylammonium (TBA) fluoride at 25 °C,[10] Table 1, entries 2 and 3. The new diazirine was a convenient photochemical source of phenylfluorocarbene (PhCF).[12] Similarly, phenoxychlorodiazirine was converted to phenoxyfluorodiazirine (Table 1, entry 4), progenitor of phenoxyfluorocarbene (PhOCF).[10] These were the first preparations of fluorodiazirines not involving dangerous or inconvenient manipulations of explosive perfluoroformamidine,[11] fluoroamine,[12] or difluorocyanamide[13] precursors.

Cyanide was also an effective nucleophile, converting phenylbromodiazirine to phenylcyanodiazirine (Table 1, entry 5), a precursor of phenylcyanocarbene (PhCCN).[10] Although the diazirine was unstable, it was useful for the preparation of phenylcyanocyclopropanes via PhCCN.[14]

Remarkably, reaction of phenylbromodiazirine with azide cleanly gave benzonitrile (eq 4).[10] The reaction was

$$\text{Ph}\diagup\!\!\!\diagdown\text{Br} \quad N_2 \quad \xrightarrow{\text{TBA}^+ N_3^-} \quad \text{PhCN} \tag{4}$$
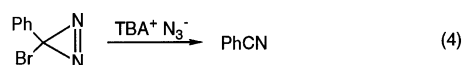
first order in diazirine and azide, showed a significant leaving group effect (Br > Cl), and was accelerated by electron-releasing substituents on the phenyl group (i.e., the Hammett ρ was -1.03).[15] We suggested the mechanism of eq 5, in which the formation of intimate ion pair

$$\tag{5}$$
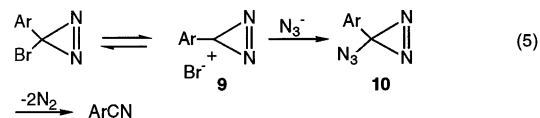
9 was rate-limiting; capture of **9** by azide would produce the azidodiazirine **10**, from which loss of nitrogen would furnish PhCN.[15] Molecular orbital calculations suggested that the azidodiazirine would be very unstable, leading to PhCN by several ill-defined pathways.[15]

Mechanistic Considerations

Graham suggested that *N*-haloisodiazirine **7** could ionize to diazirinium ion **8** (Scheme 1).[6] The isodiazirine is a high-energy isomer of *C*-diazirine **1**; restricted HF/3-21G calculations place **7** (R = Me, X = Cl) ~18 kcal/mol above **1-Cl** (R = Me).[16] The parent diazirinium ion, despite its superficial resemblance to the aromatic cyclopropenium ion, is calculated to have a negative delocalization energy,[17] and the ionization of **7** to **8** (R = Me) is estimated to require ~23 kcal/mol.[16] Clearly, ionization of **1** to **8** must be substantially more endothermic, even in polar solvents. Therefore the ionization of **1** to **8** (eq 5) seems problematical.

Further experiments suggest that the ionization mechanism is indeed unlikely. Dailey found that 3-trifluoromethyl-3-bromodiazirine (**11**) was readily converted to the corresponding fluorodiazirine (**12**) by treatment with TBAF (eq 6), Table 1, entry 6.[18] Noting the powerful

$$\tag{6}$$
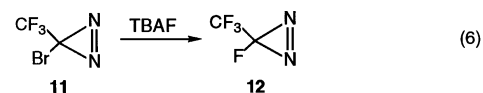
destabilizing effect of a CF_3 group on a potential diazirinium cation (**8**, R = CF_3), Dailey suggested that the exchange reaction occurred by a double S_N2' pathway (eq 7),[18] where the second step is Graham's alternative for the

$$\tag{7}$$
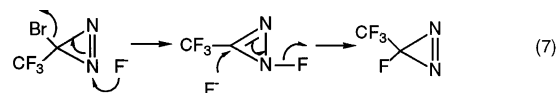
7 → 1 conversion in Scheme 1.[6]

Shortly thereafter, Creary reported that the phenyldiazirinium cation could not be readily generated under solvolytic conditions.[19] We too observed that methoxybromodiazirine gave no evidence for the methoxydiazirinium cation (**8**, R = MeO) upon treatment with $AgNO_3$, $AlBr_3$, SbF_5/SO_2, H_2SO_4, $AlCl_3$, AgF, or FSO_3H.[7] Lewis acids did not convert halodiazirines to diazirinium ions. Indeed, more recently, we found that Lewis acids attack halodiazirines at *nitrogen*, initiating their conversion into halocarbenes.[20] For example, phenylchlorodiazirine gave PhCCl upon reaction with $AlCl_3$,[20] and benzoyl-

Scheme 2
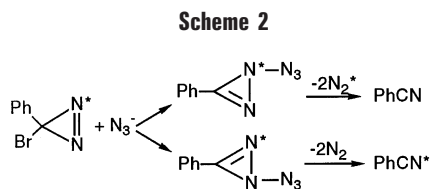
oxyfluorodiazirine afforded PhCH$_2$OCF on treatment with SbF$_5$.[21] The carbenes then underwent further Lewis acid-mediated reactions.

What is the mechanism of the halodiazirine−azide reaction (eq 4)? Excluding the ionization mechanism (eq 5), Dailey[22] and Creary[23] simultaneously reported labeling experiments that supported a S$_N$2′ alternative. Dailey observed that reaction of ^{15}N-labeled phenylbromodiazirine gave PhCN containing 50% of ^{15}N, cf., Scheme 2.[22] This result excludes *C*-azidodiazirine **13**, the expected
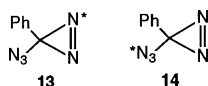
intermediate in the ionization mechanism (eq 5), which would afford only unlabeled PhCN. Creary and Sky independently performed the same experiment, obtained similar results, and also proposed the S$_N$2′ scenario of Scheme 2.[23] Additionally, they carried out the complementary labeling experiment (eq 8), in which unlabeled
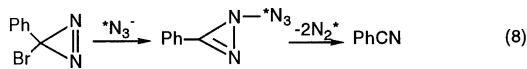
phenylbromodiazirine reacted with terminally labeled ^{15}N-azide ion. The unlabeled PhCN product is consistent with the S$_N$2′ mechanism; if a labeled *C*-azidodiazirine (**14**) had intervened, the PhCN would have contained ∼50% ^{15}N.[23]

As Creary notes,[23] *N*-azidodiazirines are short-lived, rapidly extruding nitrogen.[24] They do not survive long enough to undergo a second S$_N$2′ reaction and give a *C*-azidodiazirine. However, when a *C*-halodiazirine enters a S$_N$2′ reaction with nucleophiles such as F$^-$, OMe$^-$, or CN$^-$, the resulting N-substituted isodiazirine is more persistent and can undergo a second S$_N$2′ reaction yielding the C-substituted diazirine exchange product, cf. eq 7.

Further Extensions of Diazirine Exchange

Combination of the Graham synthesis of halodiazirines with subsequent diazirine exchange has provided precursors for a wide-ranging exploration of carbenic reactivity and philicity.[4,5,9,25] Some examples are presented in this section.

Phenylbromodiazirine reacts with a variety of primary and secondary amines to give aminophenyldiazirines, which decompose to aminophenylcarbenes, Table 1, entry 7. The latter can be trapped intramolecularly to yield N-heterocycles.[26]

Alkylhalodiazirines are also competent substrates: methylbromodiazirine readily reacts with fluoride, methoxide, or cyanide to give the appropriate exchange products (eq 9), Table 1, entries 8−10.[27] In further analogy to the
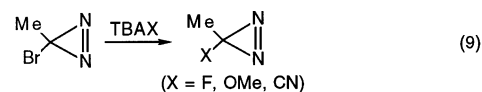
reactions of phenylbromodiazirine, treatment of methylbromodiazirine with azide ion gives acetonitrile in 95% yield.[27] Importantly, these new diazirines afford the corresponding carbenes (MeCF, MeCOMe, and MeCCN) upon photolysis or thermolysis. MeCOMe was studied spectroscopically and found to be a remarkably selective nucleophilic carbene.[28] Diazirine exchange converts methoxybromodiazirine, a Graham product, to methoxyfluorodiazirine, Table 1, entry 11.[29] The latter provides methoxyfluorocarbene (MeOCF), anticipated to be ambiphilic like its better-characterized MeOCCl analogue.[4,5,30] Similarly, phenoxyfluorodiazirine is obtained by the reaction of phenoxychlorodiazirine and fluoride, Table 1, entry 12.[31] Thermolysis of the new diazirine gives phenoxyfluorocarbene (PhOCF), which is ambiphilic in its selectivity toward alkenes.[31]

Next, we considered dioxacarbenes, potential precursors for strongly nucleophilic carbenes. Phenoxychlorodiazirine (**15a**) was converted to phenoxymethoxydiazirine (**16a**) by exchange with NaOMe (eq 10), Table 1, entry 13.[32]
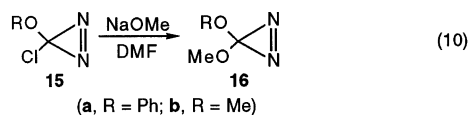
Diazirine **16a** gave phenyoxymethoxycarbene (PhOCOMe), which was clearly nucleophilic in its addition to olefins, in accord with computational prediction.[32]

Similarly, we prepared dimethoxydiazirine, precursor to the archetypal nucleophilic carbene, dimethoxycarbene (MeOCOMe). Reaction of methoxychlorodiazirine[6] **15b** with NaOMe in DMF gave the desired dioxadiazirine **16b** (eq 10), Table 1, entry 14.[33] Dimethoxycarbene, photochemically generated from **16b**, was characterized spectroscopically and exhibited marked nucleophilic selectivity toward alkenes.[33]

Diazirine exchange reactions also afforded precursors for "tuned" oxacarbenes with modulated electronic properties. Thus, cyclopropylmethoxydiazirine **17** (Table 1,
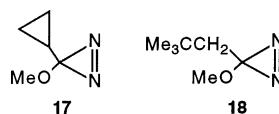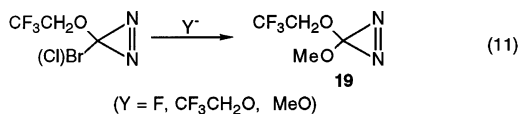

entry 15) gave cyclopropylmethoxycarbene (*c*-C$_3$H$_5$COMe) in which the usual cyclopropylcarbene ring expansion was suppressed by electron donation from the methoxy substituent.[34] Instead, the carbene displayed ambiphilic−nucleophilic reactivity toward alkenes and methanol.[34]

Similarly, neopentylmethoxydiazirine **18** (Table 1, entry 16) gave neopentylmethoxycarbene (Me$_3$CCH$_2$COMe) in which the usual 1,2-H migration of alkylcarbenes was inhibited.[35] Indeed, the series of neopentylcarbenes, Me$_3$CCH$_2$CX with X = Cl, F,[36] and OMe, exhibited a regular diminution in the rate of 1,2-H migration.[35] Related alkylfluorodiazirines (Table 1, entries 17−20) gave alkyl-

fluorocarbenes, which helped define the modulation of intramolecular carbenic rearrangements by the fluorine substituent.[36]

The trifluoroethoxy substituent is a "modified" methoxy substituent that permits the fine-tuning of carbenic reactivity.[35] We elaborated a series of trifluoroethoxycarbenes generated from trifluoroethoxydiazirines **19**. The latter were prepared from trifluoroethoxybromo(or chloro)diazirine by exchange reactions (eq 11), Table 1, entries

$$CF_3CH_2O \underset{(Cl)Br}{\overset{}{\diagup}} \diazirine \xrightarrow{Y^-} CF_3CH_2O \underset{MeO}{\overset{}{\diagup}} \diazirine \quad \mathbf{19} \tag{11}$$

(Y = F, CF$_3$CH$_2$O, MeO)

21–24.[37] Trifluoroethoxy (TFE)-substituted carbenes generated from diazirines **19** displayed a gradation of ambiphilic to nucleophilic selectivities toward alkenes.[37] Diazirine precursors for trifluoroethoxymethylcarbene and trifluoroethoxycyclopropylcarbene were also prepared by exchange reactions (Table 1, entries 24 and 25).[38] These carbenes reacted 1–2 orders of magnitude more rapidly than their methoxy analogues.[38] The electron-withdrawing inductive effect of the CF$_3$ portion of the TFE substituent diminished the electron-donating potency of the oxygen, so TFE was less stabilizing than MeO as a carbenic substituent.[38]

We also prepared long chain fluoroalkyloxydiazirines as precursors to (polyfluoroalkyl)oxacarbenes **20** and **21**,

$$C_7F_{15}CH_2O\ddot{O}CCl \qquad (C_7F_{15}CH_2O)_2C\colon$$
$$\mathbf{20} \qquad\qquad \mathbf{21}$$
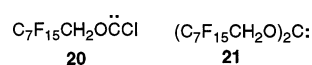
which were of interest as affinity probes and hydrophobic membrane reagents.[39a] Diazirines are generally useful in these biological applications.[39b–d] The precursor of **21** was prepared by exchange chemistry (Table 1, entry 26), whereas that of **20** was a Graham product.[39]

Finally, we note two "push–pull" carbenes, methoxytrifluoromethylcarbene (MeOCCF$_3$)[40] and benzyloxycyanocarbene (PhCH$_2$OCCN).[41] Despite the possibility of special stabilization of these carbenes by substituents of opposed electronic properties, both appeared to be electrophiles of undiminished reactivity toward alkenes.[40,41] Precursors for these carbenes were prepared by diazirine exchange (Table 1, entries 27 and 28).

Radical Initiated Exchange

Creary discovered that the arylhalodiazirine–azide exchange could also follow a S$_{RN}$1 radical chain mechanism (eq 12), traversing a diazirinyl radical, ultimately giving a

(12)
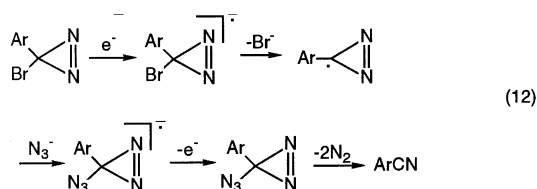
C-azidodiazirine, which rapidly decomposed to ArCN.[24,42] This alternative was favored over the S$_N$2′ mechanism

(Scheme 2) when Ar carried electron-withdrawing substituents, which stabilized the initially formed anion radical. The reaction could be photoinitiated or initiated by electron-transfer reagents. In some cases, the unstable *C*-azidodiazirine could be observed spectroscopically.[42]

We found related exchange processes that afforded acetoxydiazirines. Thus, phenylbromodiazirine reacted with TBA acetate in DMF to give phenylacetoxydiazirine (Table 1, entry 29).[43] The reaction exhibited an oxygen-dependent induction period, was accelerated by electron-withdrawing para substituents, could be initiated by superoxide ion, and also gave small quantities of phenyldiazirine by a reductive pathway. An electron-transfer initiated S$_{RN}$1 mechanism appeared likely, as elaborated in Scheme 3.[43]
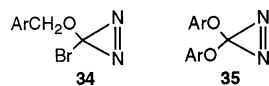
Scheme 3
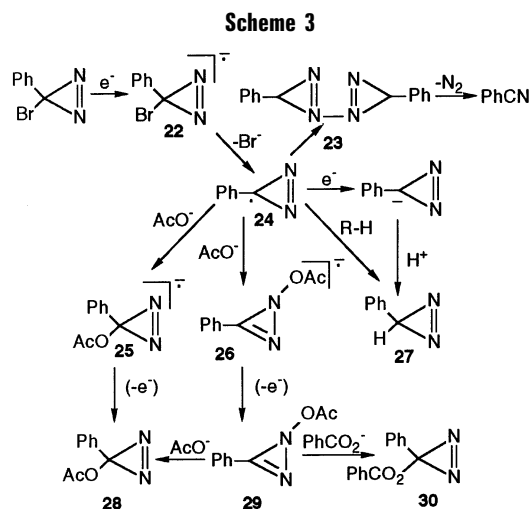
The most direct pathway from phenylbromodiazirine to phenylacetoxydiazirine involves anion radical **22**, phenyldiazirinyl radical **24**, *C*-acetoxydiazirinyl radical anion **25**, and product **28**. However, initiation of the reaction with TBA *benzoate* instead of TBA acetate yields no phenylbenzoyloxydiazirine (**30**); only PhCN appears, presumably via dimerization of diazirinyl radical **24**, followed by decomposition of dimer **23**.[43] Benzoate anion may simply be too unreactive to capture **24**. Remarkably, with *both* TBA acetate and TBA benzoate present, both acetoxydiazirine **28** (32%) and benzoyloxydiazirine **30** (28%) form (accompanied by ~5% of phenyldiazirine **27**).[43] To account for this "synergistic" formation of **30**, we suggested the involvement of *N*-acetoxyisodiazirine **29**. Capture of diazirinyl radical **24** at nitrogen rather than carbon would yield *N*-acetoxydiazirinyl radical anion **26**, from which loss of an electron (to phenylbromodiazirine) would give **29**. S$_N$2′ reaction of **29** with acetate or benzoate would then give **28** or **30**.

The synergistic acetate/benzoate exchange reactions of arylbromodiazirines make available a number of arylacetoxydiazirines **31** and phenylaroyloxydiazirines **32**
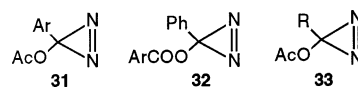
(Table 1, entry 30).[44] The acyloxycarbenes (ArCOAc, Ph-COOCAr) generated from these diazirines undergo 1,2-acyl migrations affording diketones. Detailed mechanistic studies of these rearrangements have appeared.[44,45] Alkyl-acetoxydiazirines **33** cannot be made by the $S_{RN}1$ exchange process, presumably because alkyldiazirinyl radicals are not as readily formed as the phenyldiazirinyl radical. However, diazirines **33** (R = Et, *i*-Pr, PhCH$_2$) are available by "modified" Graham reactions in which the appropriate amidine is oxidized with aqueous NaOCl saturated with NaOAc. Here the *N*-chloroisodiazirine Graham intermediate gives competing S_N2' reactions with chloride and acetate affording mixtures of **33** and the analogous chlorodiazirine.[46]

Radicals can also be generated by diazirine fragmentation. Arylmethoxybromodiazirines **34**, prepared by Gra-


ham oxidation of arylmethylisouronium salts, fragment homolytically to arylmethyl radicals directly from the diazirines' excited state.[47] The thermally generated aryl-methoxybromocarbenes (ArCH$_2$OCBr) gave the expected[48] ionic fragmentations to ArCH$_2$Br but did not afford ArCH$_2$ radicals. The latter, which could be visualized by LFP and intercepted by H-donors, arose only from the excited diazirines.[47]

Similarly, diaryloxydiazirines **35** fragment thermally to diaryloxycarbenes (ArOCOAr), whereas photolysis of **35** gives both the carbenes and aryloxyradicals (ArO•). The latter, which can be observed by LFP and quenched with α-tocopherol, arise via the diazirines' excited state.[49] Diazirines **35** were prepared by diazirine exchange reactions (Table 1, entry 31).[49]

Dihalodiazirines

Difluorodiazirine and chlorofluorodiazirine have been prepared from explosive or inconvenient precursors,[11–13] but can the diazirine exchange reaction be extended to the preparation of *dihalodiazirines*? Monohalodiazirines are readily available from the Graham procedure (eq 1), so dihalodiazirines could be made by exchange if "R" were converted into a leaving group. This has now been accomplished.

Phenoxychlorodiazirine **36a**, available by Graham oxi-

(**a**, X=H; **b**, X=NO$_2$)
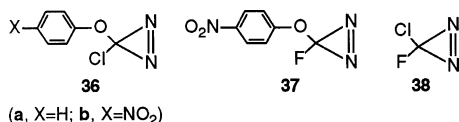
dation,[49] was nitrated with NO$_2^+$BF$_4^-$ to form the *p*-nitro derivative **36b**. Here, the *p*-nitrophenoxy unit is a potential leaving group with a fugacity comparable to that of chloride. Diazirine **36b** reacted with TBAF to produce both diazirine **37** by F/Cl exchange and chlorofluorodiazirine **38** by F/ArO exchange (Table 1, entries 32 and 33).[50] Formation of **37** and **38** is readily explained by double

S_N2' reactions in which N-attack by F$^-$ on **36** displaces either Cl$^-$ or ArO$^-$. The resulting *N*-fluorodiazirines, **39** or **40**, are then converted to **37** or **38** by a second S_N2'
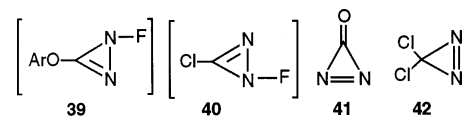
reaction with F$^-$.[50]

A remarkable feature of this reaction is the simultaneous *ipso* attack of F$^-$ on the *p*-nitrophenyl group of **36b**, which produces *p*-nitrofluorobenzene and diazirinone **41**, the diaza analogue of cyclopropenone.[50] Diazirinone has a lifetime of ≤5 min at 25 °C, fragmenting to CO and N$_2$ with an exothermicity >90 kcal/mol.[50]

Finally, reaction of diazirine **36b** with a nucleophilic chloride mixture (TBACl, CsCl, and the ionic liquid 1-butyl-3-methylimidazolium chloride) at 40–50 °C generates dichlorodiazirine (**42**) by an analogous mechanism (Table 1, entry 34).[51,52] Diazirine **42**, removed under vacuum from the reaction mixture and trapped in pentane at −70 °C, is a spectroscopically useful precursor to dichlorocarbene. We imagine that reaction of **37** with F$^-$ might give difluorodiazirine by exchange, as well as diazirinone by ipso attack.

Conclusion

Together, the hypohalite oxidation of amidines to halodiazirines (Graham reaction) and the halide/nucleophile exchange reactions of halodiazirines provide an extraordinarily wide range of diazirine precursors for electrophilic, ambiphilic, and nucleophilic carbenes. The diazirines are ideal precursors for spectroscopic studies of carbenes, either by matrix isolation or in solution by LFP. The variety of available diazirine substituents enables both broad and detailed surveys of carbenic reactivity and selectivity.

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