

The Nucleophilic Reactivity of
Fluoromethoxycarbene

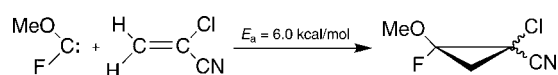
Robert A. Moss,* Min Zhang, and Karsten Krogh-Jespersen*

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

moss@rutchem.rutgers.edu; krogh@rutchem.rutgers.edu

Received June 7, 2010

ABSTRACT

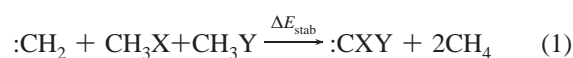


Activation parameters are reported for the additions of fluoromethoxycarbene (FCOMe) to α -chloroacrylonitrile, methyl acrylate, and acrylonitrile. The reactivity of FCOMe is compared to that of dichlorocarbene and chloromethoxycarbene.

We are presently engaged in a comprehensive and quantitative study of reactivity across the gamut of carbenic philicity, from electrophiles, through ambiphiles, to nucleophiles.¹ Among typical electrophilic carbenes, we have reported absolute rate constants of alkene additions and the associated activation parameters for dichlorocarbene (CCl_2),² chloro-fluorocarbene (ClCF),³ and difluorocarbene (CF_2).^{4,5} Representing ambiphilic carbenes, we described the reactivity of chloromethoxycarbene (ClCOMe),⁶ and uncovered latent nucleophilic properties of CCl_2 .⁷

Now we consider the reactivity of fluoromethoxycarbene (FCOMe), which resides in the border area between the ambiphilic ClCOMe and the nucleophilic dimethoxycarbene ($\text{MeO})_2\text{C}$. In terms of its calculated carbenic selectivity index (m_{CXY}),⁸ FCOMe ($m_{\text{CXY}} = 1.85$) lies between ClCOMe ($m_{\text{CXY}} = 1.59$) and ($\text{MeO})_2\text{C}$ ($m_{\text{CXY}} = 2.22$). Not only is FCOMe likely to be more nucleophilic than ClCOMe ,⁸ but

it should also be more stable and less reactive. Thus, Rondan et al. provide a quantitative measure of carbenic stability relative to methylene, ΔE_{stab} , defined as the negative of the computed HF/4-31G//STO-3G energies of the isodesmic reactions defined by eq 1.⁹ ΔE_{stab} values (kcal/mol) of the carbenes of current interest are CCl_2 , 26.5; ClCF , 42.8; CF_2 , 62.8; ClCOMe , 60.3; and FCOMe, 74.2,⁹ with FCOMe predicted to be the most stabilized of these species.



Fluoromethoxydiazirine (**1**) was first made by Mitsch et al., who found that its thermal decomposition gave FCOMe, which added to tetrafluoroethylene in 61.5% yield.¹⁰ We prepared **1** by a diazirine exchange reaction¹¹ of bromomethoxydiazirine with fluoride ion.¹² Thermal decomposition of **1** in methyl acrylate or acrylonitrile at 80 °C led to the corresponding cyclopropanes, **2** and **3**.¹²

Here, we also describe the addition of FCOMe to α -chloroacrylonitrile to form cyclopropanes **4**,¹³ and we report

(1) For a review, see: Moss, R. A. Carbenic Philicity. In *Carbene Chemistry from Fleeting Intermediates to Powerful Reagents*; Bertrand, G., Ed.; Dekker: New York, 2002; p 57f.

(2) Moss, R. A.; Tian, J.; Sauers, R. R.; Ess, D. H.; Houk, K. N.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **2007**, *129*, 5167.

(3) Moss, R. A.; Tian, J.; Sauers, R. R.; Skalit, C.; Krogh-Jespersen, K. *Org. Lett.* **2007**, *9*, 4053.

(4) Moss, R. A.; Wang, L.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **2009**, *131*, 2128.

(5) For summaries, see: (a) Moss, R. A.; Wang, L.; Zhang, M.; Skalit, C.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **2008**, *130*, 5634. (b) Moss, R. A. *J. Phys. Org. Chem.* **2010**, *23*, 293.

(6) Moss, R. A.; Zhang, M. *Org. Lett.* **2008**, *10*, 4045.

(7) Moss, R. A.; Zhang, M.; Krogh-Jespersen, K. *Org. Lett.* **2009**, *11*, 1947.

(8) Moss, R. A. *Acc. Chem. Res.* **1980**, *13*, 58.

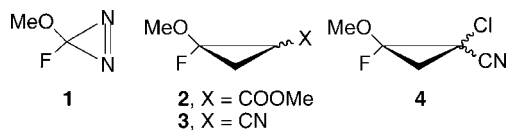
(9) Rondan, N. G.; Houk, K. N.; Moss, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 1770.

(10) Mitsch, R. A.; Neubar, E. W.; Koshar, R. J.; Dybvig, D. H. *J. Heterocycl. Chem.* **1965**, *2*, 371.

(11) Moss, R. A. *Acc. Chem. Res.* **2006**, *39*, 267.

(12) Moss, R. A.; Fedorynski, M.; Terpinski, J.; Denney, D. Z. *Tetrahedron Lett.* **1986**, *27*, 419.

(13) Complete NMR and mass spectroscopic data for cyclopropanes **2–4** appear in the Supporting Information. For known¹² cyclopropanes **2** and **3**, ¹H and ¹⁹F NMR data are included, along with mass spectra.



absolute rate constants and activation parameters for the additions of FCOME to all three electron deficient olefins. A very poor yield and a complicated product mixture precluded extension of our study to the electron rich olefin, tetramethylethylene.

We first determined k_{abs} for the addition of FCOME to chloroacrylonitrile (CIACN) by laser flash photolysis (LFP). LFP of diazirine **1** in 1,2-dichloroethane (DCE) afforded FCOME, which absorbed at 256 nm; cf. Figure S-1 in the Supporting Information. We calculate the $\sigma \rightarrow p$ carbenic absorption of FCOME at 259 nm with an oscillator strength of 0.04 (see the Supporting Information for computational details).

LFP at 24 °C gives $k_{\text{abs}} = 1.15 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ for the FCOME addition to CIACN, where k_{abs} is derived from a correlation of the observed rate constants for disappearance of the FCOME absorption at 256 nm vs the concentration of CIACN in DCE at six concentrations between 0.0 and 0.9 M; cf. Figure S-3 in the Supporting Information. Next, k_{abs} was similarly determined at an additional four temperatures; cf. Figures S-2 and S-4 to S-6 in the Supporting Information. Precise temperatures (± 0.1 °C) were measured at the instant of LFP via a thermocouple immersed in the reaction solution.

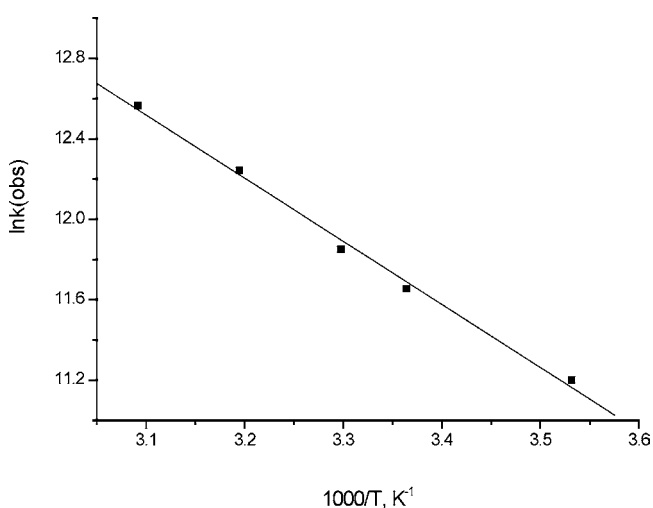


Figure 1. Determination of activation parameters for addition of FCOME to α -chloroacrylonitrile: $E_a = 6.24 \text{ kcal/mol}$; $A = 4.60 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$; $\Delta S^\ddagger = -16.3 \text{ eu}$; $r = -0.997$.

An Arrhenius plot of $\ln k_{\text{abs}}$ vs $1/T$ appears in Figure 1, where k_{abs} varies from 7.32×10^4 to $2.87 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ across a temperature range of 283 to 323 K. The slope and intercept of the least-squares correlation line afford $E_a = 6.24 \text{ kcal/mol}$, $\log A = 9.66 \text{ M}^{-1} \text{ s}^{-1}$, and $\Delta S^\ddagger = -16.3 \text{ eu}$. A second, independent determination of these parameters is

illustrated by Figures S-7 to S-11 in the Supporting Information, leading to the Arrhenius correlation plot of Figure S-12 from which $E_a = 5.80 \text{ kcal/mol}$, $\log A = 9.35 \text{ M}^{-1} \text{ s}^{-1}$, and $\Delta S^\ddagger = -17.7 \text{ eu}$. Average values of the activation parameters from the two determinations are $E_a = 6.0 \pm 0.2 \text{ kcal/mol}$, $\log A = 9.5 \pm 0.15 \text{ M}^{-1} \text{ s}^{-1}$, and $\Delta S^\ddagger = -17.0 \pm 0.7 \text{ eu}$.

Next, we determined the kinetics and activation parameters for the additions of FCOME to acrylonitrile (ACN) and methyl acrylate (MeAc), relative to CIACN. The photolysis of diazirine **1** in ACN or MeAc led to numerous byproducts, as well as to cyclopropanes **2** or **3**. Therefore, additions to these olefins were carried out with FCOME generated by the thermolysis of **1** in DCE/olefin solutions (80 °C, 48 h, sealed tube). Clean product mixtures of cyclopropanes **2** or **3** (as well as **4** from CIACN) were obtained under these conditions. Pure cyclopropanes were isolated by preparative GC and spectroscopically characterized.¹³

For ACN vs CIACN, $k_{\text{rel}} = k_{\text{ACN}}/k_{\text{CIACN}}$ was determined at four temperatures (ca. 50, 60, 70, and 77 °C), with the exact temperature controlled by a circulating hot ethylene glycol bath. Depending on temperature, the reactions required 8–48 h for completion, as signaled by the absence of diazirine absorption at 348 nm. Capillary GC analysis of the product cyclopropanes, coupled with standard competition reaction analysis,¹⁴ then gave k_{rel} for the addition of FCOME to ACN vs CIACN at the separate temperatures; cf. Table S-1 in the Supporting Information.¹⁵ Note that the GC's flame ionization detector was calibrated with known mixtures of the purified product cyclopropanes.

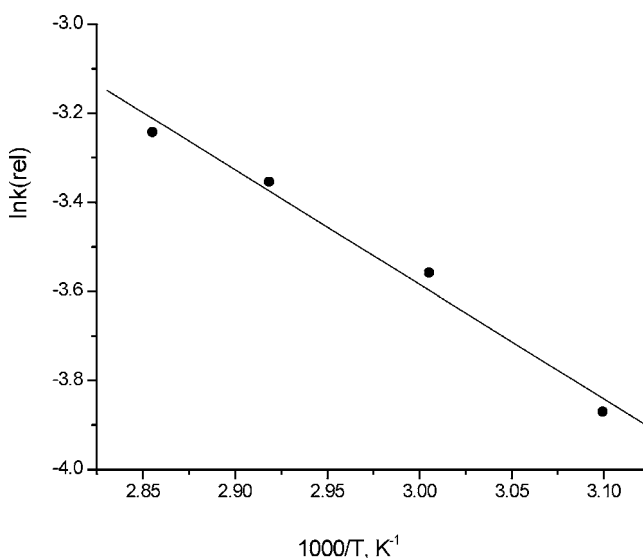


Figure 2. Differential activation energy for the competitive addition of FCOME to acrylonitrile vs α -chloroacrylonitrile in DCE solution: $\Delta E_a = 5.11 \text{ kcal/mol}$; $\Delta \log A = 1.80 \text{ M}^{-1} \text{ s}^{-1}$; $\Delta \Delta S^\ddagger = 8.22 \text{ eu}$; $r = -0.991$.

An Arrhenius plot of $\ln(k_{\text{ACN}}/k_{\text{CIACN}})$ vs $1/T$ is shown in Figure 2, where k_{rel} varies from 0.021 to 0.039 over the 323–350 K temperature range. Values of $\Delta E_a = 5.11 \text{ kcal/}$

mol, $\Delta \log A = 1.80 \text{ M}^{-1} \text{ s}^{-1}$, and $\Delta \Delta S^\ddagger = 8.22 \text{ eu}$ are obtained from the slope and intercept of the correlation line. Combined with the absolute activation parameters measured for the addition of FCOME to CIACN (see above), we obtain the following (absolute) activation parameters for FCOME adding to ACN: $E_a = 11.1 \text{ kcal/mol}$, $\log A = 11.3 \text{ M}^{-1} \text{ s}^{-1}$, and $\Delta S^\ddagger = -8.8 \text{ eu}$

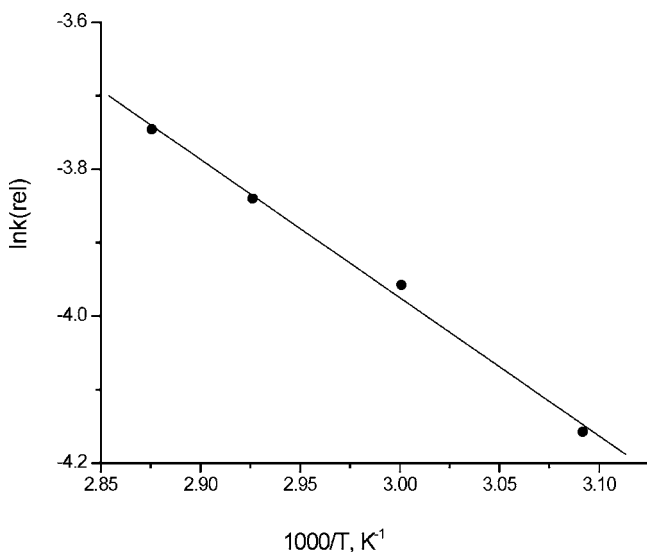


Figure 3. Differential activation energy for the competitive addition of FCOME to methyl acrylate vs chloroacrylonitrile in DCE solution: $\Delta E_a = 3.74 \text{ kcal/mol}$; $\Delta \log A = 0.726 \text{ M}^{-1} \text{ s}^{-1}$; $\Delta \Delta S^\ddagger = 3.32 \text{ eu}$; $r = -0.997$.

Similarly, we determined rate constants and activation parameters for the addition of FCOME to MeAcr, relative to CIACN. Details and data appear in Table S-2 in the Supporting Information;¹⁵ an Arrhenius plot of $\ln(k_{\text{MeAcr}}/k_{\text{CIACN}})$ is shown in Figure 3. A good correlation line, obtained from four values of k_{rel} (0.0157–0.0236) determined at temperatures ranging from 50.3 to 74.6 °C, afforded $\Delta E_a = 3.74 \text{ kcal/mol}$, $\Delta \log A = 0.726 \text{ M}^{-1} \text{ s}^{-1}$, and $\Delta \Delta S^\ddagger = 3.32 \text{ eu}$. Combined with the absolute activation parameters measured for the addition of FCOME to CIACN, we obtain the following activation parameters for FCOME adding to MeAcr: $E_a = 9.7 \text{ kcal/mol}$, $\log A = 10.2 \text{ M}^{-1} \text{ s}^{-1}$, and $\Delta S^\ddagger = -13.7 \text{ eu}$

A satisfactory cross-check experiment¹⁴ links the k_{rel} values of the MeAcr, ACN, and CIACN triad. A calculated value for $k_{\text{ACN}}/k_{\text{MeAcr}}$ at $69 \pm 0.5 \text{ }^\circ\text{C}$ can be obtained from the data presented in Tables S-1 and S-2: $(k_{\text{ACN}}/k_{\text{CIACN}}) \times (k_{\text{CIACN}}/k_{\text{MeAcr}}) = 0.0349 \times 46.5 = 1.62$. The corresponding measured value (average of two runs) is 1.83 ± 0.01 .

Values of E_a , $\log A$, and ΔS^\ddagger , together with derived values of ΔH^\ddagger and ΔG^\ddagger , for the additions of FCOME to CIACN,

Table 1. Activation Parameters for Halocarbene–Alkene Additions^a

carbene	alkene ^b	E_a	$\log A$	ΔH^\ddagger	ΔS^\ddagger	$-T\Delta S^\ddagger$	ΔG^\ddagger
CCl_2^c	CIACN	5.4	11.2	4.8	-9.1	2.7	7.5
CCl_2^c	MeAcr	6.7	11.0	6.1	-9.9	2.9	9.1
CCl_2^c	ACN	6.9	11.1	6.3	-9.8	2.9	9.2
CICOMe ^d	CIACN	3.9	8.8	3.4	-20	5.7	9.1
CICOMe ^d	MeAcr	7.0	9.0	6.4	-19	5.4	11.9
CICOMe ^d	ACN	6.4	9.1	5.8	-19	5.4	11.1
FCOMe ^e	CIACN	6.0	9.5	5.4	-17	5.1	10.5
FCOMe ^e	MeAcr	9.7	10.2	9.2	-14	4.1	13.2
FCOMe ^e	ACN	11.1	11.3	10.5	-8.8	2.6	13.2

^a Units are kcal/mol for E_a , ΔH^\ddagger , $-T\Delta S^\ddagger$, and ΔG^\ddagger ; $\text{M}^{-1} \text{ s}^{-1}$ for $\log A$; cal/(deg·mol) for ΔS^\ddagger . ΔH^\ddagger is calculated at 283 K (CCl_2 and CICOMe) or 303 K (FCOMe); ΔG^\ddagger is calculated at 298 K. Errors are $\pm 0.2 \text{ kcal/mol}$ for E_a and ΔH^\ddagger , $\pm 0.7 \text{ eu}$ for ΔS^\ddagger , and $\pm 0.3 \text{ kcal/mol}$ for ΔG^\ddagger . ^b CIACN = α -chloroacrylonitrile; MeAcr = methyl acrylate, ACN = acrylonitrile. ^c In pentane; from ref 7. ^d In DCE; from ref 6. ^e In DCE; this work.

ACN, and MeAcr appear in Table 1. Also collected there are analogous activation parameters for the additions of CCl_2 and CICOMe to the same olefins.^{6,7}

The experimental values of the activation parameters in Table 1 are qualitatively consistent with the computed values of the carbene stabilization energies, ΔE_{stab} .⁹ The latter increase in the order $\text{CCl}_2 < \text{CICOMe} < \text{FCOMe}$, while the experimental values of E_a , ΔH^\ddagger , and ΔG^\ddagger increase in precisely the same order. The more stabilized the carbene, the greater the activation barrier, to alkene addition.

We carried out DFT electronic structure calculations at the B3LYP/6-311+G(d) level for the nine carbene additions of Table 1. Calculations were carried out simulating both idealized gas phase and continuum solvent conditions; some computed data pertaining to the transition states (TS) for these reactions are collected in Tables S-3 to S-8 of the Supporting Information. Overall, the two approaches result in very similar values for the tabulated properties and identical conclusions may be drawn from either data set (gas phase or solution). The TS for the addition of FCOME to CIACN is pictured as a representative example in Figure 4.

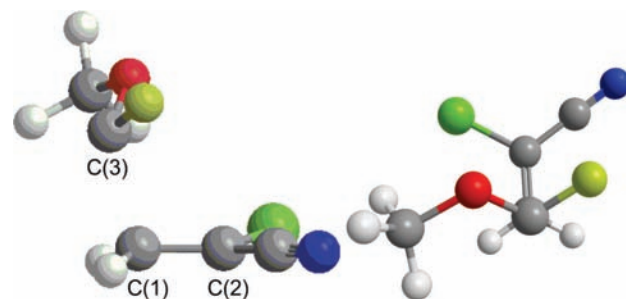


Figure 4. Transition state for the *syn*-F/*syn*-CN addition of FCOME to CIACN: side view (left) and top view (right). Note the numbering: C(1) = CH_2 terminus of the alkene; C(2) = substituted terminus of the alkene; C(3) = carbene carbon.

(14) Moss, R. A. In *Carbenes*; Jones, M., Jr., Moss, R. A., Eds.; Wiley: New York, 1973; Vol. 1, p 153f.

(15) Analytical details appear in Table S-1. The Supporting Information also includes GC traces of cyclopropanes 2–4.

In keeping with the Hammond principle that a more stable and less reactive intermediate traverses a later and more product-like TS, the computational results in Tables S-3 and S-4 show that the FCOMe TSs are later than those of the ClCOMe additions which, in turn, are later than the TSs for the CCl₂ additions. Thus, both the C(1)–C(3) and C(2)–C(3) separations (cf. Figure 4 for numbering), which represent the forming C–C bonds, are shortest (most product-like) in the FCOMe TSs, and longest in the CCl₂ TSs. At the same time, the C(1)–C(2) alkene double bond exhibits the largest TS elongation toward the product C(1)–C(2) cyclopropane single bond in the FCOMe additions, and the smallest elongation in the CCl₂ additions.

The relative lateness of the TSs is also reflected in the puckering angles, β and γ , at the CH₂ and substituted ends of the C(1)–C(2) alkene bond, respectively. As shown in Tables S-3 and S-4, the hydrogens at this bond's CH₂ terminus bend away from the approaching carbene, while the substituents at the other end bend toward the carbene. In general, these TS puckering angles, especially β , increase in the order CCl₂ < ClCOMe < FCOMe; also $\beta > \gamma$.

The computed TSs also suggest significant nucleophilic character for all nine examined addition reactions. In each case, C(3) of the approaching carbene is positioned "outside" of C(1), the CH₂ terminus of the alkene substrate: in the continuum solvent calculations (Table S-4), the C(3)–C(1)–C(2) angles range from 100.0° for the CCl₂–ACN TS to 106.7° for the FCOMe–MeAcr TS, with the angles generally increasing in the order FCOMe > ClCOMe > CCl₂. Bond formation is accordingly far more advanced for CXY addition at the unsubstituted C(1), in keeping with a nucleophilic Michael addition character.

The carbene tilt angle (α), defined as the (smaller) angle between the bisector of the X–C–Y carbene angle and the alkene C=C, is a qualitative indicator of the philicity of the carbene–alkene addition. For a purely electrophilic carbene attack, α would be 0°, whereas tilt angles >45° indicate significant nucleophilic character.⁹ The tables show that all three carbenes add to these electron-deficient alkenes in a nucleophilic fashion ($\alpha > 45^\circ$), but that ClCOMe and

FCOMe ($63^\circ < \alpha < 70^\circ$) express significantly greater nucleophilicity than CCl₂ ($50^\circ < \alpha < 53^\circ$); cf. Table S-4.

Charge analysis (Tables S-5 and S-6, Supporting Information) supports the nucleophilic character of these carbene addition reactions. From Mulliken population analyses,¹⁶ all three carbenes are seen to be net donors of electron density (i.e., nucleophiles) toward the electron-poor alkenes in the TS. The extent of electron donation is in the order FCOMe > ClCOMe > CCl₂, as anticipated based on the carbene m_{CXY} values (see above). Considering natural charges,¹⁷ however, CCl₂ appears to be a weak electrophile (accepting charge from the alkenes in the TS), while ClCOMe and FCOMe remain nucleophiles. The ordering of carbene electron donation is unchanged.

As we observed previously,^{5a,7} the computed DFT activation parameters diverge from the measured values; compare Table 1 with Tables S-7 and S-8 (Supporting Information). Although the ordering of activation enthalpies (ΔH^\ddagger) is generally reproduced (FCOMe > ClCOMe > CCl₂), the computed values are too low for CCl₂ by ~3 kcal/mol, whereas with ClCOMe and FCOMe they are too large by ~2–4 kcal/mol even though B3LYP generally underestimates reaction barrier heights.¹⁸ More striking is the discrepancy between the computed and experimental values of ΔS^\ddagger . The computed (isolated molecule) values are much more negative (–31 to –36 eu) than the measured (condensed phase) values (–9 to –20 eu). As a result, the computed values of ΔG^\ddagger are strongly dominated by their $-T\Delta S^\ddagger$ components, and are considerably larger than the experimental values of ΔG^\ddagger . We continue to ponder the fundamental reasons for these systematic discrepancies.¹⁹

In conclusion, the measured rate constants and activation parameters for FCOMe additions to electron-deficient alkenes reveal a more pronounced nucleophilic character in comparison to analogous reactions of ClCOMe and CCl₂. Computed transition state structural and charge parameters support this picture.

Acknowledgment. We are grateful to the National Science Foundation and the Petroleum Research Fund for financial support.

Supporting Information Available: Figures S-1 to S-35 and Tables S-1 to S-8 as described in the text, NMR and mass spectra, GC traces, computational details, and optimized geometries, absolute energies, electronic excitation energies, and oscillator strengths of relevant species. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL1013119

(16) Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1833.

(17) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

(18) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2005**, *109*, 5656.

(19) These discrepancies are unlikely to be due to the solvent (CH₂Cl₂) employed here; large differences in computed and observed entropies of activation have been found in carbene additions conducted in pentane as well.^{5a}