The Bicyclo[2.2.2]octyl Carbene System as a Probe for Migratory Aptitudes of Hydrogen to Carbenic Centers

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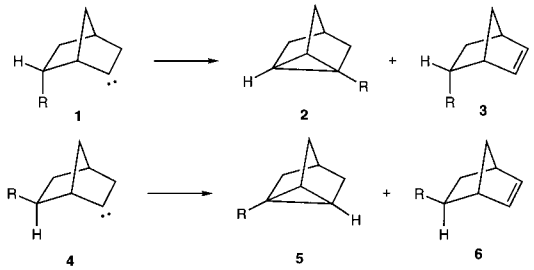
Received July 3, 2000. Revised Manuscript Received October 19, 2000

Abstract: A series of tosylhydrazone derivatives of *exo*-6-substituted bicylo[2.2.2]octan-2-ones have been prepared. Thermal decomposition of the sodium salts of these tosylhydrazones gives carbene-derived products from 1,3-migration of either the C6 hydrogen (perturbed) or the C7 hydrogen (unperturbed), along with smaller amounts of alkenes derived from 1,2-hydrogen migration. The *exo*-6-substituent strongly activates 1,3-hydrogen migration in the case of $SiMe_3$ and weakly activates it in the case of CH_3 substitution. Thiomethoxy and carbomethoxy are weakly deactivating, while cyano and methoxy groups are strongly deactivating. B3LYP/6-31G* calculations on these substituted carbenes and transition states are in qualitative agreement with the ease of 1,3-hydrogen migration of perturbed vs unperturbed hydrogen. These experimental results and computational studies suggest carbene stabilization due to the *exo*-6-silyl group. They also suggest a reactant-like transition state for 1,3-hydrogen migration in which the inductive effect influences ease of migration. In the case of the exo-6-methoxy group, the inductive effect overwhelms any potential resonance-stabilizing effects.

Introduction

One of the fundamental processes that singlet carbenes undergo is 1,2-migration of adjacent hydrogen to the carbenic center to form olefinic products.[1] The optimal stereochemical alignment for this migration is one in which the C−H bond is aligned with the vacant p-orbital of the carbene.[2] The effect of substituents on this 1,2-migration, which has been termed "bystander assistance" by Nickon, has also been examined.[3] In addition to the 1,2-migration process, more remote hydrogen can also migrate to the carbenic center.[4] The intramolecular 1,3-hydrogen migration process, often termed "1,3-insertion", results in cyclopropane formation and will be a focus of this study.

We[5] and others[6,7] have been interested in the chemistry of carbenes that contain silicon in the proximity of the carbenic center. This interest grows out of our finding that silicon has a high propensity to migrate to carbenic centers. During the course of these studies, we have used 6-substituted 2-norbornyl carbenes **1** as a probe for 1,3-migratory aptitudes of various groups R.[8] Groups such as CH_3, CH_2SiMe_3, Ph, and OCH_3 are loath to migrate to the carbenic center in **1**, and the alkenes **3** are the major products generated. However, $SiMe_3$ is an efficient migrator, and the tricyclic **2** (R = $SiMe_3$) is formed exclusively.



We have now turned our attention to the influence of substituents on the 1,3-migratory aptitude of hydrogen to proximate carbenic centers. The bicyclo[2.2.1]hept-2-yl system **4** is of limited value as a probe since the parent carbene **4** (R = H) gives almost exclusive 1,3-migration, forming 99.5% of nortricyclane, **5** (R = H).[9] Increases in migratory aptitude due to *exo*-6-substitution are therefore difficult to detect. The bicyclo[2.2.2]oct-2-yl carbene system has therefore been used as a probe for relative migratory aptitudes of hydrogen. The behavior of the parent carbene **7** has been described, and intramolecular rearrangement of **7** leads to 70% of the tricyclic alkane **8** along with 30% of the alkene **9**.[10] We report here our experimental findings on the rearrangement pathways for substituted carbenes of type **10**, where migration of H_a competes with migration of H_b. The chemistry of the related 5-methoxy derivative **11** was also investigated. Also reported are computational studies on carbene **7**, as well as substituted variations **10** and **11**.

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(2) (a) Press, L. S.; Shechter, H. *J. Am. Chem. Soc.* **1979**, *101*, 509. (b) Nickon, A.; Bronfenbrenner, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 2022.

(3) Nickon, A. *Acc. Chem. Res.* **1993**, *26*, 84.

(4) Friedman, L.; Shechter, H. *J. Am. Chem. Soc.* **1961**, *83*, 3159.

(5) (a) Creary, X.; Wang, Y.-X. *Tetrahedron Lett*. **1989**, *19*, 2493. (b) Creary, X.; Wang, Y.-X. *J. Org. Chem.* **1994**, *59*, 1604. (c) Creary, X.; Jiang, Z.; Butchko, M.; McLean, K. *Tetrahedron Lett.* **1995**, *37*, 579.

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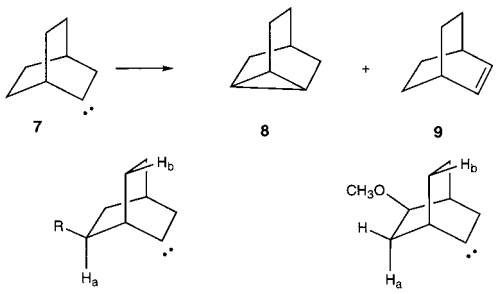
(7) Kirmse, W.; Konrad, W.; Schnitzler, D. *J. Org. Chem.* **1994**, *59*, 3821.

(8) Creary, X.; Wang, Y.-X. *Res. Chem. Intermed.* **1994**, *20*, 201.

(9) (a) Friedman, L.; Shechter, H. *J. Am. Chem. Soc.* **1961**, *83*, 3159. (b) Freeman, P. K.; George, D. E.; Rao, V. N. M. *J. Org. Chem.* **1964**, *29*, 1682.

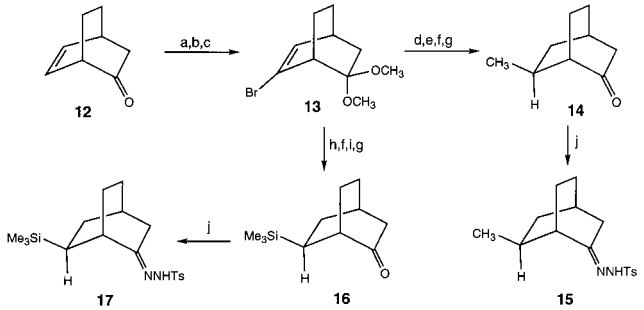
(10) Grob, C. A.; Hostynek, J. *Helv. Chim. Acta* **1963**, *46*, 1676.

10.1021/ja002407+ CCC: $20.00 © 2001 American Chemical Society
Published on Web 02/02/2001

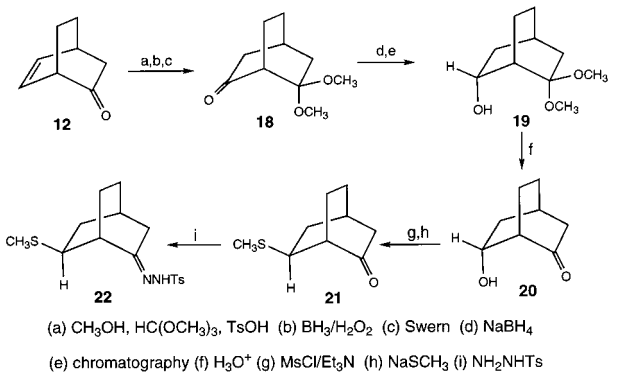


Results

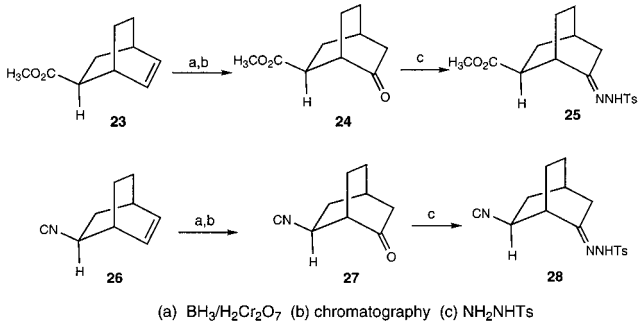
Synthetic Aspects. The precursors to the desired carbenes **10** and **11** were tosylhydrazones derived from the corresponding ketones. The preparation of ketone **14** used methodology similar to that developed by the groups of Vogel and Salomon.[11] Bicyclo[2.2.2]oct-5-en-2-one, **12**, was reacted with PhSeBr followed by oxidation, selenoxide elimination, and ketalization to give the vinyl bromide **13**. Lithium−halogen exchange followed by methylation, diimide reduction, and hydrolysis gave a mixture of the known ketone **14** and the *endo*-methyl stereoisomer. Separation of the desired ketone **14** was accomplished by chromatography, and this ketone was converted by the standard method to the tosylhydrazone **15**. In similar fashion, lithium−halogen exchange on **13** followed by silylation, hydrolysis, and catalytic hydrogenation produced ketone **16**, which was separated by silica gel chromatography from the epimeric ketone.[12] The stereochemistry of **16** was confirmed by the observation of W-coupling (1.8 Hz) of the *endo*-6-hydrogen at δ 1.09 with the appropriately situated hydrogen atom on C7. Conversion of **16** to the tosylhydrazone **17** was straightforward.



The precursor to the *exo*-6-thiomethoxy carbene was also prepared starting with bicyclo[2.2.2]oct-5-en-2-one, **12**. Ketalization followed by hydroboration/oxidation gave a mixture of alcohols which was further oxidized (Swern) to a mixture of ketone **18** and the 5-keto regioisomer. Reduction with $NaBH_4$ gave a mixture of three alcohols from which the desired *endo*-alcohol **19** was readily separated. This alcohol is strongly intramolecularly hydrogen bonded, as indicated by the sharp O−H stretch at 3522 cm^{-1} and the lack of a free O−H stretch, even in dilute CCl_4 solution. This intramolecular hydrogen bonding results in facile chromatographic separation of **19**, which elutes more readily than the isomeric alcohol products. Hydrolysis of **19** gave the known β-hydroxyketone **20**,[13] which was converted in a straightforward manner to the mesylate. Reaction of the mesylate with $NaSCH_3$ in methanol gave the *exo*-6-thiomethoxy ketone **21**, which was readily converted to the carbene precursor, tosylhydrazone **22**. The *exo*-stereochemistry of the thiomethoxy group in **21** was confirmed by the observation of W-coupling (1.8 Hz) of the *endo*-6-hydrogen atom at δ 2.90 with the appropriate hydrogen atom on C7.



The precursor tosylhydrazones to the *exo*-6-carbomethoxy and the *exo*-6-cyano carbenes were prepared by analogous procedures. The *exo*-ester **23** was formed as the minor product in the Diels−Alder reaction of methylacrylate with cyclohexadiene.[14] This was separated from the major *endo*-isomer by a saponification−iodolactonization−re-esterification procedure.[15] The pure *exo*-ester **29** was then subjected to hydroboration followed by chromic acid oxidation. The 2- and 3-keto regioisomers were then separated by chromatography, and the desired isomer **24** was converted by standard methods to the corresponding tosylhydrazone **25**. The *exo*-nitrile **26** was also available from a Diels−Alder reaction (acrylonitrile and cyclohexadiene), which gave a 50:50 mixture of *exo*- and *endo*-isomers.[16] These isomers were readily separated by chromatography on silica gel, and the pure *exo*-isomer **26** was subjected to the same protocol, which gave the tosylhydrazone **28**.



This hydroboration/chromic acid oxidation sequence was also used to form a mixture of the ketoethers **31** and **32**, which were separated by column chromatography. The starting methyl ether **30** used in this sequence was prepared by a standard methylation procedure on the pure *exo*-alcohol **29**,[17] which was available as the minor product formed in the hydride reduction of the ketone **12**.

(11) (a) Carrupt, P.-A.; Vogel, P. *Tetrahedron Lett.* **1982**, *23*, 2563. (b) Lal, K.; Salomon, R. G. *J. Org. Chem.* **1989**, *54*, 2628.

(12) The stereochemistry of this epimeric ketone was verified by conversion to the tosylhydrazone and an X-ray analysis.

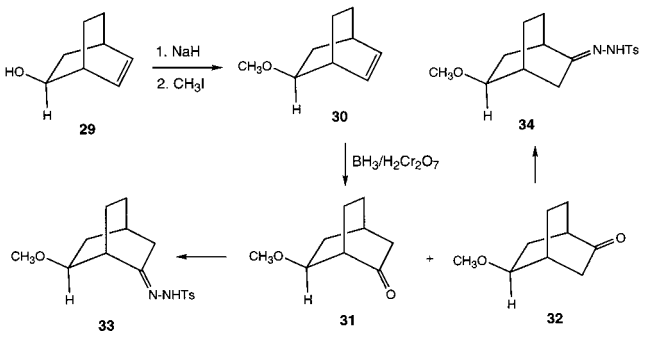
(13) Almqvist, F.; Eklund, L.; Frejd, T. *Synth. Commun.* **1993**, 1499.

(14) Brecknell, D. J.; Carman, R. M.; Day, P. J. *Aust. J. Chem.* **1984**, *37*, 2323.

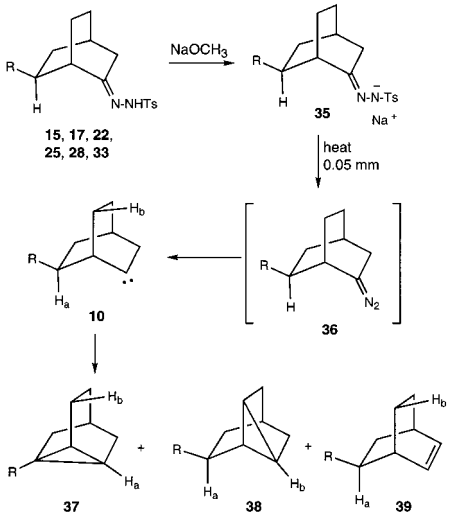
(15) Ohwada, T.; Uchiyama, M.; Tsuji, M.; Okamoto, I.; Shudo, K. *Chem. Pharm. Bull.* **1996**, *44*, 296.

(16) Alder, K.; Krieger, H.; Weiss, H. *Chem. Ber.* **1955**, *88*, 144.

(17) (a) Brown, H. C.; Muzzio, J. *J. Am. Chem. Soc.* **1966**, *88*, 2811. (b) Brown, R. S.; Marcinko, R. W. *J. Am. Chem. Soc.* **1977**, *99*, 6500. (c) Fraser, R. R.; O'Farrell, S. *Tetrahedron Lett.* **1962**, *24*, 1143.

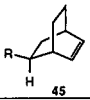
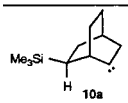
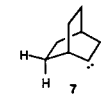
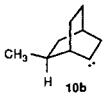
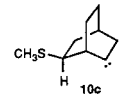
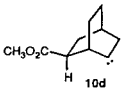
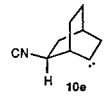
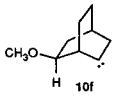
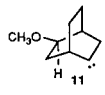


Tosylhydrazone Salt Pyrolyses. The tosylhydrazones **15**, **17**, **22**, **25**, **28**, **33**, and **34** served as sources of the desired carbenes **10** and **11**. Thus, treatment of these tosylhydrazones with sodium methoxide led to the corresponding salts **35**, and pyrolysis under vacuum generated the carbenes **10**, presumably via the in situ-generated diazo compounds **36**.[18] The working assumption is that these reactions all involve the carbenes **10** as discrete intermediates and that loss of nitrogen and carbene rearrangement are not concerted processes. Indeed, studies[19,20] have suggested that free carbenes can sometimes be bypassed in reactions involving nitrogenous precursors. These concerns have been summarized in a caveat presented by Nickon.[3] However, since our reactions are not excited-state photochemical reactions, and the migrating hydrogens are not anti to the departing nitrogen in the diazo compound, it is a reasonable assumption that loss of nitrogen is not concerted with hydrogen migration.



These tosylhydrazone salt pyrolyses gave the two possible 1,3-hydrogen migration products, **37** and **38**, as major products, along with minor amounts of alkene **39** formed from 1,2-hydrogen migration. In the case of tosylhydrazones **25** and **28**, small amounts of the isomeric alkenes *endo*-6-carbomethoxybicyclo[2.2.2]oct-2-ene and *endo*-6-cyanobicyclo[2.2.2]oct-2-ene were also formed. These minor *endo*-alkene products presumably arise from epimerization of the *exo*-alkenes **39** under the reaction conditions, where there is a slight excess of sodium methoxide. Product mixtures were separated by preparative gas chromatography, and structures were determined by NMR spectroscopic methods and/or independent syntheses. Table 1 summarizes the products formed under these pyrolytic conditions.

Table 1. Products from Rearrangement of Carbenes **7**, **10**, and **11**

Carbene	 43	 44	 45
 10a	100	0	0
 7	70[a]	-	30[a]
 10b	54	27	19
 10c	20	51	29
 10d	9	61	30[b]
 10e	0	62	38[c]
 10f	0	70	30
 11	0	81	19

[a] Data from ref 6. [b] Combined yield of *exo* (15%)- and *endo* (15%)-isomers. See text. [c] Combined yield of *exo* (29%)- and *endo* (9%)-isomers. See text.

Immediately apparent is the contrasting behavior of the silyl-substituted tosylhydrazone **17** (R = $SiMe_3$) relative to those of the other substrates. This system gives exclusive migration of the trimethylsilyl-activated hydrogen H_a, forming **37** (R = $SiMe_3$). Neither the potential tricyclic product **38** (R = $SiMe_3$) from 1,3-migration of H_b, nor the alkene **38** (R = $SiMe_3$) from 1,2-hydrogen migration, is observed. Silicon appears to exert an unusually strong activating effect such that H_a migration is exclusive.

The tosylhydrazone **15** (R = CH_3) gives preferential 1,3-insertion into the tertiary CH bond (H_a) relative to the secondary CH bond (H_b). Hence, methyl activation of H_a migration appears to be a small but measurable effect. By way of contrast, the thiomethoxy group slightly *deactivates* H_a migration, as indicated by the formation of the tricyclic thioether **38** (R = SCH_3) as the major product from **22** (R = SCH_3). In view of this unexpected deactivation by SCH_3, the OCH_3 derivative **33** was examined. In this case, H_a is *completely deactivated*, and the exclusive tricyclic ether formed is **38** (R = OCH_3). As in all cases except **17**, there is also some alkene **39** produced.

In a further search for deactivating substituents, the ester derivative **25** (R = CO_2CH_3) was examined. Indeed, H_a is

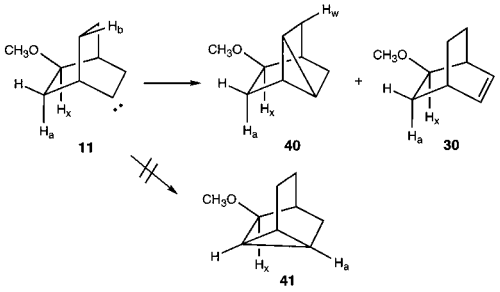
(18) For a discussion of the tosylhydrazone salt pyrolysis method of diazo compound and carbene generation, see: (a) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735. (b) Kaufman, G. M.; Smith, J. A.; Vander Stouw, G. G.; Shechter, H. *J. Am. Chem. Soc.* **1965**, *87*, 935. (c) Creary, X. *Org. Synth.* **1986**, 64, 207.

(19) For a recent study and leading references, see: Thamattoor, D. M.; Jones, M., Jr.; Pan, W.; Shevlin, P. B. *Tetrahedron Lett.* **1996**, *37*, 8333. For a computational study related to concerted nitrogen loss/hydrogen migration, see also: Keating, A. E.; Garcia-Garibay, M. A.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 10805.

(20) (a) Huang, H.; Platz, M. S. *Tetrahedron Lett.* **1996**, *37*, 8337. (b) Jackson, J. E.; Platz, M. S. In *Advances in Carbene Chemistry*; Brinker, U. H., Ed.; JAI Press Inc.: Greenwich, CT, 1994; Volume 1, p. 89−160.

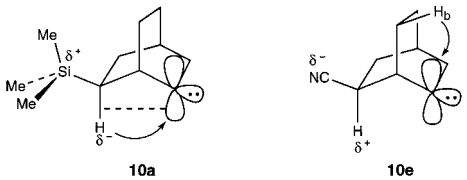
deactivated by this electron-withdrawing ester substituent, but a small amount (9%) of H_a still migrates. However, CO_2CH_3 appears to be somewhat more deactivating than SCH_3. The potent electron-withdrawing cyano group in **28** (R = CN) gives complete deactivation of H_a such that the only tricyclic product formed is **38** (R = CN).

In view of the unexpected behavior of carbene **10f** (R = OCH_3), the 5-methoxy isomer **11** was examined. Interestingly, only one tricyclic product, **40**, was observed in the product mixture. It was important to distinguish between **40** and the other potential product, the isomer **41**, for which spectroscopic differences should be quite subtle. The structure of **40** was based on NMR spectroscopic evidence, which showed the hydrogen labeled H_x as a multiplet at δ 3.206 (J = 9.5, 3.7, 3.7, 1.3 Hz) coupled to four different hydrogens. The 1.3-Hz W-coupling of H_x with H_w is clearly visible, as are the 9.5 Hz cis coupling with H_a, the 3.7-Hz trans coupling, and the 3.7-Hz coupling with the adjacent bridgehead H. These couplings rule out the potential isomer **41**, in which H_x should have only three coupling interactions and no large (≈10 Hz) coupling interaction.

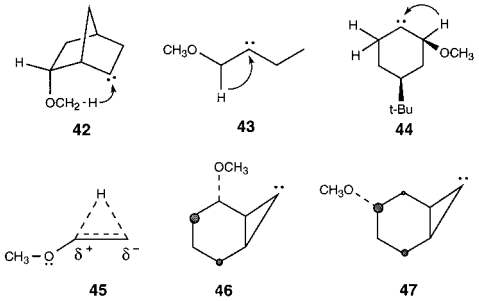


Discussion

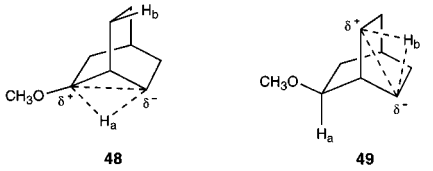
What is the origin of the activating effect of the trimethylsilyl group on H_a in carbene **10a**? Qualitatively, it is suggested that the effect of the electropositive silicon atom is to increase the hydridic nature of H_a. Since migrations to electrophilic carbene centers presumably begin with an interaction with the vacant carbene orbital, increasing the hydridic character of H_a should increase the ease of hydrogen migration. The electron-donor properties of the methyl group in carbene **10b** (R = CH_3) also account for the increased propensity for H_a migration relative to H_b migration. By way of contrast, the electron-withdrawing carbomethoxy and cyano groups exert the opposite effect; i.e., they increase the *acidic* character of H_a. Hence, the carbenes **10d** and **10e** show decreased propensity for H_a migration, with H_a being completely deactivated by the strongly electron-withdrawing cyano group. This deactivation of 1,3-hydrogen migration by electron-withdrawing groups is analogous to the deactivation of 1,2-hydrogen migration recently reported for the CF_3 group.[21]



The effect of the methoxy group on carbene **10f** is of much interest. The complete deactivation of H_a contrasts with previous results, which indicate that oxygen can increase migratory aptitudes of adjacent hydrogen. The bystander assistance factor of Nickon[3] for OCH_3 suggests that oxygen is quite activating. The carbenic center in **42** inserts readily into the "oxygen-activated" C−H bond of the methyl group.[8] Carbenes **43**[22] and **44**[23] show increased propensity for migration of the "oxygen-activated" hydrogens to the carbenic center. Certain carbenes are also known to insert preferentially into the " oxygen-activated" α-C−H bond of ethers.[24−26] This activation has been rationalized in terms of a transition state **45** involving hydridic character in the hydrogen that begins to migrate to the vacant orbital of the carbene.[22] The nonbonding electrons on oxygen stabilize this transition state. Despite these observations and rationalization, the effect of the methoxy group remains complex. Carbenoid **46** (generated from the dibromocyclopropane and methyllithium) inserts into the CH bonds remote from the methoxy group, while **47** inserts preferentially into the CH bond α to the methoxy group.[27] Conformational and electronic effects appear to be important in these insertions.



The lack of migration of H_a in carbene **10f** suggests that the transition state for H_a migration is *not* stabilized. The effect of the methoxy group in carbene **10f** is quite subtle. Conjugative stabilization of a transition state such as **48** cannot be a major factor. Therefore, the extent of charge development in transition state **48** is suggested to be smaller than that in transition state **45**. Hence, the conjugative electron-donating influence of the methoxy group is overwhelmed by the inductive effect of the methoxy group. The transition state for H_b migration, **49**, is not destabilized by the inductive effect of the methoxy group, and hence H_b migrates. These results suggest that the methoxy group can be either an activator or a deactivator of hydrogen migration to carbenic centers. The amount of charge development in the transition state will be critical in determining the methoxy effect in carbenes.



In the regioisomeric carbene **11**, H_a remains deactivated relative to H_b migration. Although further removed from the carbenic center, the inductive effect of the remotely oriented methoxy group apparently remains strong enough to completely deactivate H_a toward 1,3-migration. The deactivating effect of

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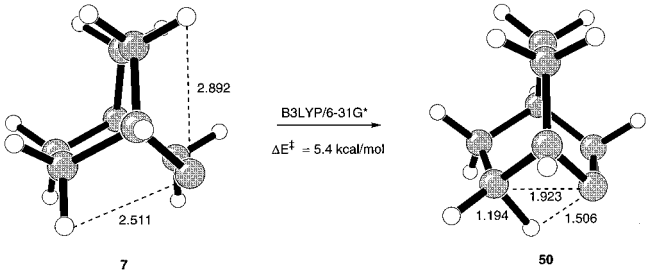
Table 2. Barriers for 1,3-Hydrogen Migration in Carbene **7** at Various Computational Levels

method	$\Delta E^{\ddagger}$ (kcal/mol)
HF/STO-3G	31.7
HF/3-21G*	23.6
HF/6-31G*	17.5
B3LYP/6-31G*	5.4
B3LYP/6-31G**	4.2
MP2/6-31G*	1.6
MP3/6-31G*//B3LYP/6-31G*	5.9

sulfur on H_a in carbene **10c** ($R = SCH_3$) can also be rationalized in terms of inductive effects. Conjugative stabilization of the transition state for H_a migration is minimal. However, because of the smaller inductive effect of sulfur relative to oxygen, a small amount of H_a (20%) still migrates.

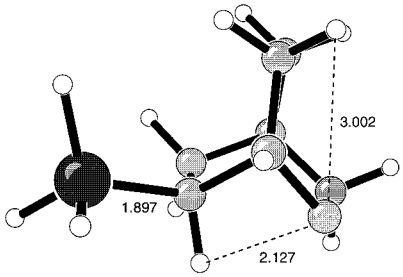
Computational Studies. Ab initio molecular orbital calculations have now been used to shed further light on bicyclo[2.2.2]-octy-2-yl carbenes and migration processes. Over the years, numerous calculations on carbenes have been carried out. We desired a reasonably fast, yet reliable method for evaluating carbene and transition state energies and geometries. Recently, high-level MP2 calculations[28] as well as density functional methods[29] have been used in carbene studies. A previous computational study has been carried out on bicyclic carbenes at the BHandHLYP/DZP level.[30] Some recent carbene computational studies have been carried out at the B3LYP/6-31G* level.[31] A B3LYP/6-31G* evaluation of substituent effects on 1,2-hydrogen and 1,2-phenyl migration to carbene centers has also recently appeared.[32] To evaluate the various computational levels, preliminary studies were therefore carried out on the parent bicyclo[2.2.2]octy-2-yl carbene **7** and the transition state for 1,3-hydrogen migration at a variety of computational levels. The carbene **7** is calculated to be an unsymmetrical species, with the *endo*-hydrogen on C6 tilted slightly toward the carbenic center. The degree of tilt depends on the computational level, with Hartree−Fock methods showing only minimal deformation from the symmetrical species. The B3LYP/6-31G* optimized geometry of **7** is shown here.



7 **50**

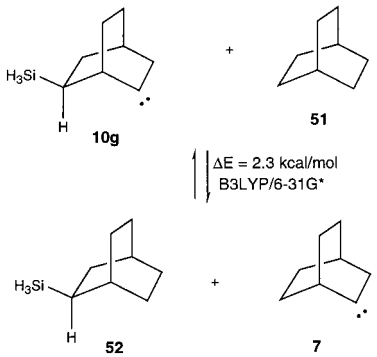
Shown also is the geometry of the transition state **50** for 1,3-hydrogen migration of the C6 hydrogen. Table 2 gives values of $\Delta E^{\ddagger}$ ($E_{50} - E_7$) for this migration at various computational levels. Immediately apparent from Table 2 is the fact that Hartree−Fock methods give unrealistically large values (31.7 to 17.5 kcal/mol) of $\Delta E^{\ddagger}$. The B3LYP method, which includes electron correlation, gives a more "reasonable" value of 5.4 kcal/mol for $\Delta E^{\ddagger}$, while the MP2 value of 1.6 kcal/mol probably underestimates the barrier to 1,3-hydrogen migration. The MP3 value (calculated using the B3LYP/6-31G* optimized geometry) is comparable to the B3LYP value, but this calculation is more time-consuming. Therefore, the B3LYP/6-31G* calculation was the method of choice as a rapid, yet reasonable method for the carbenes and transition states studied.[33]

The calculated geometry of carbene **10g** ($R = SiH_3$) is of interest. For computational ease, this analogue was evaluated instead of the more time-consuming carbene **10a** ($R = SiMe_3$).



10g

The B3YLP/6-31G* optimized structure of **10g** is twisted such that the *endo*-6-hydrogen is significantly closer (2.127 Å) to the carbenic center than the analogous 7-hydrogen (3.002 Å). This distortion is not believed to be steric in origin, since calculations on **10b**, **10c**, **10e**, and **10f** do not show such twisting. The distortion in **10g** suggests a stabilizing interaction of the carbene vacant orbital with the *endo*-C6−H orbital. In order to evaluate this interaction energetically, the stability of **10g** was compared to that of the unsubstituted carbene **7** using the isodesmic reaction of carbene **10g** with bicyclo[2.2.2]octane, **51**. On the basis of this reaction, carbene **10g** is stabilized by 2.3 kcal/mol relative to the unsubstituted carbene **7**.



B3LYP/6-31G* optimized transition states were calculated for H_a migration (**53**) and for H_b migration (**54**) for a number of carbenes. This allows calculation of $\Delta E^{\ddagger}$ for these 1,3-hydrogen migrations. Results are summarized in Table 3. In the case of carbene **10g** ($R = SiH_3$), H_a (which is already tilted

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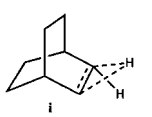
(33) The B3LYP/6-31G* value of $\Delta E^{\ddagger}$ for 1,2-hydrogen migration in carbene **7**, via transition state **i**, is 7.5 kcal/mol and is consistent with the experimental observation that this process is less facile than 1,3-hydrogen migration.

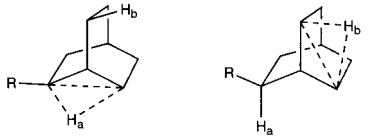


i

Table 3. C2−H_a Distances and B3LYP/6-31G* Barriers for 1,3-Hydrogen Migration in Carbenes **7**, **10**, and **11**

carbene	$\Delta E_a^{\ddagger}$ (kcal/mol), H_a migration	$\Delta E_b^{\ddagger}$ (kcal/mol), H_b migration	C2−H_a distance (Å)
7	5.4		2.511
10g (R = SiH_3)	2.6	7.3	2.127
10b (R = CH_3)	3.6	5.3	2.281
10c (R = SCH_3)	3.9	4.7	2.871
10e (R = CN)	6.8	5.4	2.869
10f (R = OCH_3)	7.4	5.0	2.956
11 (5-OCH_3)	7.8	4.9	2.978

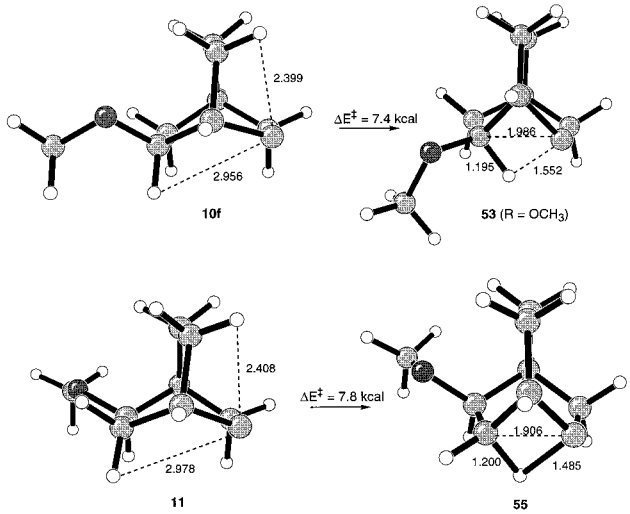
toward the carbenic center) migrates with the extremely low activation energy of 2.6 kcal/mol. On the other hand, migration of the further removed H_b is significantly more difficult (7.3 kcal/mol). This study supports the notion that a stabilizing interaction between the carbene vacant orbital and the silicon-induced hydridic C−H bond results in a facile 1,3-migration process of H_a. These computational results are in line with the experimental observation that carbene **10a** (R = $SiMe_3$) rearranges exclusively by migration of H_a.



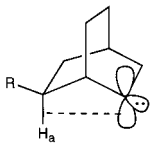
Experimentally, the methyl group in carbene **10b** (R = CH_3) activates H_a slightly, and this is in qualitative agreement with the calculated barriers in Table 3. Of note is the fact that the calculated barrier to H_a migration in **10b** (3.6 kcal/mol) is not as low as in the case of SiH_3 substitution. Also in qualitative agreement with the experimental data are the computational results for carbene **10f** (R = CN). The cyano group is calculated to be deactivating ($\Delta E^{\ddagger}$ = 6.8 kcal/mol), and this is indeed what is observed experimentally. These results parallel those recently calculated for the effect of methyl and cyano groups on 1,2-hydrogen shifts in carbenes of type CH_3-C-CH_2R.[28]

The calculated effects of OCH_3 substitution on carbenes **10e** (R = OCH_3) and **11** shed further light on the methoxy effect. Computationally, the methoxy group in carbene **10e** significantly deactivates H_a migration ($\Delta E^{\ddagger}$ = 7.4 kcal/mol). As previously suggested on the basis of the experimental behavior of **10e**, this is a manifestation of the large inductive effect of the methoxy group in transition state **53** (R = OCH_3), where the resonance effect of methoxy is small. Interestingly, the deactivation of H_a in carbene **11** by the more remote β-OCH_3 group is even larger than the deactivation by the α-OCH_3 in carbene **10e**. Methoxy deactivation of H_a in carbene **11** ($\Delta E^{\ddagger}$ = 7.8 kcal/mol) represents an inductive effect which remains large in transition state **55**. The fact that the barrier to H_a migration in carbene **10e** (R = OCH_3) is *only* 7.4 kcal/mol suggests that there is some offsetting resonance stabilization of transition state **53** (R = OCH_3). Hence, these calculations support the suggestion that the inductive effect of methoxy can be the dominant feature controlling 1,3-hydrogen migrations in carbenes, but there can also be a variable offsetting resonance effect.

More careful examination of the calculated structure of carbenes **10g** (R = SiH_3) and **10f** (R = OCH_3) reveals distortions which depend on the substituent. In the case of **10f** (R = OCH_3), H_a (which does not migrate) is significantly more removed (2.956 Å) from the carbene center than in **10g** (R = $SiHe_3$) (2.127 Å), where migration of H_a is facile. This trend is



seen in other calculated structures of the carbenes in Table 3. The distance between the carbene center C2 in **10** and H_a mirrors the ease of migration of H_a. Indeed, there is a good correlation (r = 0.99; omit **10c** (SCH_3)) in a plot of $\Delta E^{\ddagger}$ vs the C2−H_a distance. This phenomenon is interpreted as a stabilizing interaction between the carbene center and H_a which decreases as H_a becomes less hydridic with respect to the carbenic center. In other words, a tilt of H_a toward the carbene center is indicative of a stabilizing interaction which makes H_a more prone to migrate.



The agreement between the B3LYP/6-31G* calculated barriers to hydrogen migration and the products formed from carbenes **10** and **11** is quite good in all cases except for carbene **10c** (R = SCH_3). In this case, the computational study predicts that H_a migration ($\Delta E^{\ddagger}$ = 3.9 kcal/mol) should be slightly more facile than H_b migration ($\Delta E^{\ddagger}$ = 4.7 kcal/mol). This is not the case; i.e., experimentally SCH_3 slightly *deactivates* H_a migration. Thus, while the B3LYP/6-31G* computational method appears to be quite good at predicting large activating and deactivating trends, this method may not be as useful in sorting out inductive and resonance effects in certain transition states, where there is a delicate balance between the two.

Conclusions

exo-6-Substituted bicyclo[2.2.2]oct-2-yl carbenes, **10**, are a useful probe for the effect of substituents on the migratory aptitude of hydrogen to the carbene center. Electron-donating substituents activate the perturbed hydrogen (H_a) toward 1,3-migration, whereas electron-withdrawing substituents decrease migratory aptitudes of H_a. Of the substituents studied, $SiMe_3$ was highly activating, CH_3 was slightly activating, SCH_3 was slightly deactivating, CO_2CH_3 was strongly deactivating, and OCH_3 and CN were completely deactivating. A β-OCH_3 substituent also completely deactivated H_a in carbene **11**. These observations are consistent with a reactant-like transition state in which the inductive effect of both α- and β-OCH_3 groups overwhelms any potential resonance-stabilizing effects. The effect of the methoxy group on H_a is therefore quite different from the methoxy effect in 1,2-hydrogen migrations.

Molecular orbital calculations at the B3LYP/6-31G* level give insight into the geometry of *exo*-6-substituted bicyclo[2.2.2]-oct-2-yl carbenes, as well as barriers to 1,3-hydrogen migration. The SiH_3-substituted carbene **10g** is stabilized by a favorable interaction of the carbene vacant orbital with the *endo*-6-C−H bond, resulting in a very small barrier to migration (2.6 kcal/mol). With the exception of the SCH_3 system, B3LYP/6-31G* calculations are in qualitative agreement with experimentally determined migratory aptitudes of perturbed hydrogens (H_a). The 5-OCH_3 substituent in carbene **11** is calculated to be even more deactivating toward H_a migration than the 6-OCH_3 substituent in carbene **10e**. This is consistent with minor conjugative stabilization in the transition state for H_a migration to the carbene center in **10e**.

Experimental Section

Preparation of Ketal 13. A solution of 5.837 g of PhSeBr (24.7 mmol) in 15 mL of THF was added dropwise to a solution of 2.967 g of bicyclo[2.2.2]oct-5-ene-2-one **12**[34] (24.3 mmol) in 15 mL of tetrahydrofuran (THF) at 0 °C. The reaction mixture was stirred at room temperature for 6 h and then cooled to −30 °C. An additional 15 mL of THF was added followed by 1.798 g of acetic acid (29.9 mmol). Aqueous hydrogen peroxide (5.701 g of 30%; 50.3 mmol) was then added dropwise at −30 °C. The mixture was then stirred at room temperature for 6 h. The mixture was then taken up into 200 mL of ether, and the ether extract was washed with Na_2CO_3 solution and saturated NaCl solution and dried over a mixture of Na_2SO_4 and $MgSO_4$. After filtration, the solvent was removed using a rotary evaporator. The crude product was then chromatographed on 25 g of silica gel and eluted with increasing amounts of ether in hexanes. The chromatographed product was then fractionally distilled to give 3.479 g (58% yield) of 6-bromobicyclo[2.2.2]oct-5-en-2-one, bp 56−60 °C (0.05 mmHg). ^{1}H NMR of **13** ($CDCl_3$): δ 6.63 (d of d, J = 2.1, 6.9 Hz, 1 H), 3.35 (d of t, J = 2.7, 4.8 Hz, 1 H), 3.08 (m, 1 H), 2.12−1.54 (m, 6 H). ^{13}C NMR of **13** ($CDCl_3$): δ 209.3, 136.0, 117.6, 58.0, 39.8, 34.4, 24.3, 23.2.

A mixture of 3.475 g of 6-bromobicyclo[2.2.2]oct-5-ene-2-one (17.3 mmol), 2.254 g of trimethylorthoformate (21.2 mmol), and 65 mg of *p*-toluenesulfonic acid (0.37 mmol) in 25 mL of methanol was stirred at room temperature for 19 h, and 0.4 mL of 1.0 M $NaOCH_3$ in methanol was then added to neutralize the acid catalyst. The solvent was removed using a rotary evaporator, and the crude product was distilled to give 4.150 g of ketal **13** (97% yield), bp 58−62 °C (0.05 mmHg). ^{1}H NMR of **13** ($CDCl_3$): δ 6.40 (d of d, J = 2.1, 7.2 Hz, 1 H), 3.21 (s, 3 H), 3.20 (s, 3 H), 3.04 (d of t, J = 3.0, 5.1 Hz, 1 H), 2.72 (m, 1 H), 1.84 (m, 1 H), 1.60−1.30 (m., 5 H). ^{13}C NMR of **13** ($CDCl_3$): δ 133.4, 121.3, 105.8, 49.0, 48.5, 47.6, 38.1, 33.9, 24.2, 20.6. HRMS (EI): calcd for $C_{10}H_{15}BrO_2$ 246.0255, found 246.0251.

Preparation of *exo*-6-Trimethylsilylbicyclo[2.2.2]octan-2-one, 16. A solution of 1.590 g (6.44 mmol) of bromoketal **13** in 22 mL of THF was cooled to −78 °C, and 8.9 mL of 1.7 M *tert*-butyllithium in pentane (15.1 mmol) was added dropwise. After 45 min at −78 °C, 1.72 g of $ClSiMe_3$ was added. The mixture was slowly warmed to room temperature, and after 2.5 h, the mixture was quenched with water and vigorously stirred for 5 min. The mixture was taken up into ether, and the ether extract was washed with water and saturated NaCl solution and dried over a mixture of Na_2SO_4 and $MgSO_4$. After filtration, the solvents were removed using a rotary evaporator. The residue was distilled, and, after a small forerun, 1.076 g (86% yield) of 6-trimethylsilylbicyclo[2.2.2]oct-5-en-2-one was collected, bp 85−87 °C (1.5 mmHg). ^{1}H NMR of 6-trimethylsilylbicyclo[2.2.2]oct-5-en-2-one ($CDCl_3$): δ 6.71 (d of d, J = 6.0, 0.8 Hz, 1 H), 3.196 (m, 1 H), 2.97 (heptet, J = 2.9 Hz, 1 H), 1.98 (m, 2 H), 1.87 (m, 1 H), 1.77 (m, 1 H), 1.53−1.32 (m, 2 H), 0.056 (s, 9 H). ^{13}C NMR of 6-trimethylsilylbicyclo[2.2.2]oct-5-en-2-one ($CDCl_3$): δ 213.6, 145.3, 142.8, 50.9, 40.5, 33.3, 24.3, 22.3, −2.3. HRMS (EI): calcd for $C_{11}H_{18}OSi$ 194.1128, found 194.1123.

A solution of 291 mg of 6-trimethylsilylbicyclo[2.2.2]oct-5-en-2-one in 12 mL of ether containing 33 mg of 10% Pd-on-carbon was hydrogenated at 50 psi for 2.5 h using a Parr hydrogenation apparatus. The solution was filtered to remove the catalyst, and the ether was removed using a rotary evaporator. Gas chromatographic analysis showed a mixture of *endo*-6-trimethylsilylbicyclo[2.2.2]octan-2-one and *exo*-6-trimethylsilylbicyclo[2.2.2]octan-2-one, **16**, in a 1:1 ratio. This product mixture was chromatographed on 20 g of silica gel and eluted with increasing amounts of ether (2−5%) in hexanes. The *endo*-6-trimethylsilylbicyclo[2.2.2]octan-2-one eluted first, followed by the *exo*-6-trimethylsilylbicyclo[2.2.2]octan-2-one, **16**. ^{1}H NMR of *endo*-6-trimethylsilylbicyclo[2.2.2]octan-2-one ($CDCl_3$): δ 2.31−2.04 (m, 4 H), 1.93−1.56 (m, 5 H), 1.45 (m, 1 H), 1.14 (d of d of d, J = 11.6, 8.2, 1.6 Hz, 1 H), −0.053 (s, 9 H). ^{13}C NMR of *endo*-6-trimethylsilylbicyclo-[2.2.2]octan-2-one ($CDCl_3$): δ 217.8, 44.9, 43.5, 27.9, 27.4, 26.6, 23.8, 23.7, −3.4. ^{1}H NMR of **16** ($CDCl_3$): δ 2.38 (m, 1 H), 2.70−2.16 (m, 3 H), 1.96−1.45 (m, 6 H), 1.090 (d of d of t, J = 11.6, 8.0, 1.8 Hz, 1 H), 0.064 (s, 9 H). ^{13}C NMR of **16** ($CDCl_3$): δ 216.8, 43.5, 42.7, 28.5, 26.2, 25.4, 21.0 (d), 21.0 (t), −2.3. HRMS (EI): calcd for $C_{11}H_{20}OSi$ 196.1283, found 196.1279.

Preparation of Methyl Ketone 14. A solution of 1.557 g (6.3 mmol) of bromoketal **13** in 20 mL of THF was cooled to −78 °C, and 8.6 mL of 1.7 M *t*-BuLi in pentane (14.6 mmol) was added dropwise. After the mixture was stirred at −78 °C for 45 min, a solution of 2.61 g of methyl iodide (18.4 mmol) in 2 mL of THF was added. The reaction mixture was then warmed to room temperature and stirred for 2.5 h. The mixture was then quenched with water and extracted with ether. The ether extract was washed with water and saturated NaCl solution and dried over a mixture of Na_2SO_4 and $MgSO_4$. After filtration, the ether was removed using a rotary evaporator, and the crude product was distilled to give 1.040 g (91% yield) of 2,2-dimethoxy-6-methylbicyclo[2.2.2]oct-5-ene, bp 68−70 °C (2.0 mmHg). ^{1}H NMR ($CDCl_3$): δ 5.85 (d of m, J = 1.6 Hz, 1 H), 3.20 (s, 3 H), 3.14 (s, 3 H), 2.61 (m, 1 H), 2.53 (m, 1 H), 1.83 (d, J = 1.6 Hz, 3 H), 1.75 (m, 1 H), 1.56−1.42 (m, 3 H), 1.26 (m, 1 H), 1.10 (m, 1 H).

A solution of 2.829 g of glacial acetic acid (47.1 mmol) in 10 mL of methanol was added dropwise over 1 h to a suspension of 4.540 g of freshly prepared[35] potassium azodicarboxylate (23.2 mmol) and 509 mg of 2,2-dimethoxy-6-methylbicyclo[2.2.2]oct-5-ene (2.79 mmol) in 10 mL of methanol at room temperature under nitrogen. The reaction mixture was stirred at room temperature for 6 h. At this point, the yellow color of the azodicarboxylate was no longer present. An additional 4.511 g of potassium azodicarboxylate (23.2 mmol) was added to the reaction mixture, followed by the dropwise addition of 2.922 g of glacial acetic acid in 5 mL of methanol. The mixture was then stirred at room temperature for an additional 17 h, and 10 mL of water was then added. Most of the methanol solvent was then removed using a rotary evaporator, and the remaining residue was extracted into ether. The ether extract was washed with 1 M Na_2CO_3 solution and saturated NaCl solution and dried over a mixture of Na_2SO_4 and $MgSO_4$. After filtration, the ether was removed using a rotary evaporator to give 311 mg of crude products.

The crude products obtained above were dissolved in 3 mL of THF, and 3 mL of 1% aqueous H_2SO_4 was added. After being stirred at room temperature for 5 h, the mixture was neutralized with Na_2CO_3 and extracted with ether. The ether extract was dried in the usual manner, and solvent was removed using a rotary evaporator to give 224 mg of a mixture containing approximately 36% 6-methylbicyclo[2.2.2]oct-5-en-2-one, 23% *endo*-6-methylbicyclo[2.2.2]octan-2-one,[36] and 41% *exo*-6-methylbicyclo[2.2.2]octan-2-one, **14**.[36a] A pure sample of **14** was isolated by preparative gas chromatography using an 8-ft 5% SE30 on Chromosorb G column at 120 °C. ^{1}H NMR of **14** ($CDCl_3$): δ 2.24−1.50 (m, 10 H), 1.15 (m, 1 H), 1.08 (d, J = 6.6 Hz, 3 H). ^{13}C NMR of **14** ($CDCl_3$): δ 218.0 (quat), 48.6 (CH), 43.4 (CH_2), 34.0 (CH_2), 28.4 (CH), 27.1 (CH), 25.4 (CH_2), 19.4 (CH_3), 17.2 (CH_2).

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Preparation of 2,2-Dimethoxy-*endo*-6-hydroxybicyclo[2.2.2]-octane, 19. A mixture of 4.66 g of bicyclo[2.2.2]oct-5-en-2-one, **12**, 6.10 g of trimethylorthoformate, and 39 mg of *p*-toluenesulfonic acid in 30 mL of methanol was stirred at room temperature for 21 h, and 0.38 mL of 1.0 M $NaOCH_3$ in methanol was then added. The solvent was removed using a rotary evaporator, and the crude product was distilled to give 6.20 g (97% yield) of 2,2-dimethoxybicyclo[2.2.2]oct-5-ene, bp 60−61 °C (2 mmHg). ^{1}H NMR of 2,2-dimethoxybicyclo-[2.2.2]oct-5-ene ($CDCl_3$): δ 6.28 (m, 1 H), 6.21 (m, 1 H), 3.20 (s, 3 H), 3.13 (s, 3 H), 2.82 (m, 1 H), 2.64 (m, 1 H), 1.80 (m, 1 H), 1.62−1.47 (m, 3 H), 1.26 (m, 1 H), 1.12 (m, 1 H). ^{13}C NMR of 2,2-dimethoxybicyclo[2.2.2]oct-5-ene ($CDCl_3$): δ 134.4, 131.3, 105.9, 48.8, 47.7, 38.8, 36.6, 30.8, 24.0, 20.2.

A solution of 5.53 g of 2,2-dimethoxybicyclo[2.2.2]oct-5-ene, prepared above, in 60 mL of THF was cooled to 0 °C, and 16.5 mL of 1.0 M BH_3 in THF was added. The mixture was then stirred for 7 h at room temperature, and a solution of 4.8 g of NaOH in 35 mL of water was carefully added dropwise. Aqueous 30% H_2O_2 (11.7 g) was then added dropwise, and the mixture was stirred for 10 h at room temperature. Solid NaCl was then added to saturate the aqueous phase, and the organic phase was separated and dried over a mixture of Na_2SO_4 and $MgSO_4$. The solvent was removed using a rotary evaporator, and the residue was distilled to give 5.33 g (87%) of a mixture of of 2,2-dimethoxy-*exo*-5-hydroxybicyclo[2.2.2]octane and 2,2-dimethoxy-*exo*-6-hydroxybicyclo[2.2.2]octane, bp 85−90 °C (0.1 mmHg), in a 57:43 ratio as determined by NMR.

A solution of 6.45 g of dimethyl sulfoxide in 65 mL of CH_2Cl_2 was cooled to −78 °C, and 8.88 g of trifluoroacetic anhydride in 8 mL of CH_2Cl_2 was added dropwise. The mixture was stirred for 10 min at −78 °C, and a solution of 5.50 g of the alcohol mixture prepared above in 5 mL of CH_2Cl_2 and 1 mL of DMSO was added slowly dropwise with stirring. After the addition was complete, 11.6 g of triethylamine was added dropwise at −78 °C, and the mixture was allowed to warm to room temperature. Water was added, and the CH_2Cl_2 phase was separated, washed with another portion of water, and dried over a mixture of Na_2SO_4 and $MgSO_4$. The solvent was removed using a rotary evaporator, and the residue was distilled to give 5.37 g (97%) of a mixture of 2,2-dimethoxybicyclo[2.2.2]octan-5-one and 2,2-dimethoxybicyclo[2.2.2]octan-6-one, bp 70−75 °C (0.05 mmHg).

The mixture of ketones prepared above (5.365 g) was dissolved in 50 mL of methanol containing 1.0 g of NaOH, and 2.33 g of $NaBH_4$ was added to the solution at 10 °C. The mixture was slowly warmed to 50 °C and kept at that temperature for 1.5 h. The mixture was cooled to room temperature, and a solution of 3.0 g of NaOH in 3 mL of water was added. Most of the methanol was then removed using a rotary evaporator, and 15 mL of water was added. The residue was extracted with about 200 mL of ether, and the ether was dried over a mixture of Na_2SO_4 and $MgSO_4$. The solvent was removed using a rotary evaporator, and the entire residue was chromatographed on 75 g of silica gel. The column was eluted with increasing amounts of ether in hexanes. The pure alcohol **19**, bp 58−59 °C (0.1 mmHg) (1.586 g; 30%), eluted with 25% ether in hexanes. The other two alcohol products, 2,2-dimethoxy-*exo*-5-hydroxybicyclo[2.2.2]octane and 2,2-dimethoxy-*endo*-5-hydroxybicyclo[2.2.2]octane, eluted with 35−60% ether in hexanes. ^{1}H NMR of **19** ($CDCl_3$): δ 3.35 (br s, 1 H), 3.236 (s, 3 H), 3.196 (s, 3 H), 2.16−1.24 (m, 10 H). ^{13}C NMR of **19** ($CDCl_3$): δ 103.3, 68.3, 48.6, 47.0, 38.5, 38.4, 36.2, 25.9, 22.9, 19.4. HRMS (EI): calcd for $C_{10}H_{18}O_3$ 186.1257, found 186.1260.

Preparation of *exo*-6-Thiomethoxybicyclo[2.2.2]octan-2-one, 21. A solution of 495 mg of 2,2-dimethoxy-*endo*-6-hydroxybicyclo[2.2.2]-octane, **19**, in 8 mL of CH_2Cl_2 was stirred as 226 mg of 5% aqueous HCl was added. After 45 min, 25 mg of $NaHCO_3$ was added, and the CH_2Cl_2 solution of *endo*-6-hydroxybicyclo[2.2.2]octan-2-one, **20**,[13] was dried over a mixture of Na_2SO_4 and $MgSO_4$. After filtration, 510 mg of CH_3SO_2Cl was added to the solution, and the mixture was cooled to −10 °C. A solution of 595 mg of Et_3N in 3 mL of CH_2Cl_2 was added to the stirred solution, which was then warmed to 0 °C. An aqueous workup followed with ether extraction. The ether extract was washed with dilute HCl solution and dried over a mixture of Na_2SO_4 and $MgSO_4$. The solvent was removed using a rotary evaporator, and the crude mesylate derivative of *endo*-6-hydroxybicyclo[2.2.2]octan-2-one was washed with a small amount of hexanes and dried under vacuum at 15 mm. The yield of mesylate was 443 mg (69% based on **19**). ^{1}H NMR ($CDCl_3$): δ 5.171 (m, 1 H), 3.015 (s, 3 H), 2.72 (m, 1 H), 2.40−2.24 (m, 3 H), 2.00−1.51 (m, 6 H). ^{13}C NMR ($CDCl_3$): δ 211.6, 78.3, 47.7, 44.3, 39.4, 34.2, 27.6, 23.3, 20.0. HRMS (EI): calcd for $C_9H_{14}O_4S$ 218.0613, found 218.0604.

A solution of 160 mg of $NaSCH_3$ and 141 mg of the mesylate prepared above in 3.5 mL of methanol under nitrogen was refluxed for 2.5 h. The mixture was then transferred to a separatory funnel with water and ether, and a standard aqueous workup followed. The ether extract was washed with water and saturated NaCl solution and dried over a mixture of Na_2SO_4 and $MgSO_4$. The ether solvent was removed using a rotary evaporator, and the residue was chromatographed on 2 g of silica gel. The thioether **21** (78 mg; 71% yield) eluted with 10% ether in hexanes. ^{1}H NMR of **21** ($CDCl_3$): δ 3.10 (m, 1 H), 2.44−2.31 (m, 2 H), 2.29−2.24 (m, 2 H), 2.23−2.10 (m, 2 H), 2.051 (m, 3 H), 1.80−1.50 (m, 3 H), 1.38 (m, 1 H). ^{13}C NMR of **21** ($CDCl_3$): δ 215.7, 45.9, 43.7, 40.6, 33.3, 28.1, 24.8, 17.5, 14.8. HRMS (EI): calcd for $C_9H_{14}OS$ 170.0765, found 170.0761.

Preparation of *exo*-6-Carbomethoxybicyclo[2.2.2]octan-2-one, 24. A solution of 741 mg of *exo*-ester **23**[15] (4.46 mmol) in 5 mL of THF was cooled to 0 °C, and 3.6 mL of 1.0 M BH_3 in THF (3.6 mmol) was added dropwise. The mixture was stirred at 0 °C for 30 min and then at room temperature for an additional 30 min. The reaction mixture was then recooled to 0 °C, and 5 mL of water was added. A solution of chromic acid, prepared by dissolving 1.59 g of $Na_2Cr_2O_7$ dihydrate (5.34 mmol) in 10 mL of 15% aqueous H_2SO_4, was then added dropwise to the reaction mixture at 0 °C. After being stirred for 4 h at room temperature, the mixture was diluted with 10 mL of water and extracted with ether. The ether extract was washed with water and saturated NaCl solution and dried over a mixture of Na_2SO_4 and $MgSO_4$. The ether was removed using a rotary evaporator to give a mixture containing 59% of *exo*-6-carbomethoxybicyclo[2.2.2]octan-2-one, **24**,[37] and 41% of *exo*-5-carbomethoxybicyclo[2.2.2]octan-2-one.[37] Chromatography (30% ether in hexanes) on 50 g of silica gel gave 387 mg of **24** (48% yield) as the first eluent, mp 38−39 °C, and 264 mg of *exo*-5-carbomethoxybicyclo[2.2.2]octan-2-one (33% yield) as the second eluent, mp 58−62 °C. ^{1}H NMR of **24** ($CDCl_3$): δ 3.73 (s, 3 H), 2.88 (m, 1 H), 2.61 (q, J = 3.0 Hz, 1 H), 2.28−2.24 (m, 3 H), 2.19 (m, 1 H), 1.95−1.70 (m, 4 H), 1.58 (m, 1 H). ^{13}C NMR of **24** ($CDCl_3$): δ 214.74 (quat), 174.09 (quat), 52.11 (q, J = 146 Hz), 44.43 (d, J = 144 Hz), 43.72 (t, J = 128 Hz), 38.15 (d, J = 132 Hz), 27.55 (d, J = 138 Hz), 27.33 (t, J = 133 Hz), 24.17 (t, J = 127 Hz), 19.14 (t, J = 128 Hz).

Preparation of *exo*-6-Cyanobicyclo[2.2.2]octan-2-one, 27. A solution of 1.141 g of *exo*-nitrile **26**[38] in 10 mL of THF was cooled to 0 °C, and 5.0 mL of 1.0 M BH_3 in THF was added dropwise. The mixture was then stirred at room temperature for 1.5 h and recooled to 0 °C, and 1 mL of water was added. A solution of chromic acid, prepared by dissolving 3.4 g of $Na_2Cr_2O_7$ dihydrate in 20 mL of water and adding 3.6 mL of H_2SO_4, was then added dropwise to the reaction mixture at 0 °C. After being stirred for 12 h at room temperature, the mixture was diluted with water and extracted with ether. The ether extract was washed with water and saturated NaCl solution and dried over a mixture of Na_2SO_4 and $MgSO_4$. Solvent was removed using a rotary evaporator, and the residue was chromatographed on 20 g of silica gel. A small amount of unreacted nitrile **26** eluted with 10% ether in hexanes. Pure cyanoketone **27** (346 mg; 27%) eluted with 40−45% ether in hexanes, and this was followed by fractions containing mixtures of **27** and the isomeric product *exo*-5-cyanobicyclo[2.2.2]octan-2-one. ^{1}H NMR of **27** ($CDCl_3$): δ 3.054 (m, 1 H), 2.517 (q, J = 2.8 Hz, 1 H), 2.40−2.20 (m, 3 H), 2.17−1.81 (m, 5 H), 1.71 (m, 1 H). ^{13}C NMR of **27** ($CDCl_3$): δ 212.0, 120.8, 43.8, 43.6, 29.9, 27.2, 24.7, 23.8, 19.4. HRMS (EI): calcd for $C_9H_{11}NO$ 149.0841, found 149.0844.

Preparation of *exo*-6-Methoxybicyclo[2.2.2]oct-2-ene, 30. Sodium hydride (720 mg of a 60% dispersion in mineral oil) was freed from

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(38) The pure *exo*-nitrile **32** was isolated by silica gel chromatography (2.5% ether in hexanes) of the Diels−Alder adducts from acrylonitrile and cyclohexadiene.[16]

oil by rinsing with hexanes (2 × 5 mL), and 5 mL of THF was then added under nitrogen. A solution of 587 mg of *exo*-alcohol **29**[39] in 10 mL of THF was then added dropwise to the suspension. The mixture was heated at reflux under nitrogen for 23 h, and 5.4 g of methyl iodide was then added to the mixture. Reflux was continued for an additional 24 h. After being cooled, the mixture was quenched with water and extracted with ether. The ether extract was washed with water, saturated NaCl solution, and dried over a mixture of Na_2SO_4 and $MgSO_4$. After filtration, the ether was removed using a rotary evaporator, and the crude product was distilled to give 598 mg of *exo*-ether **30**,[40] bp 71−73 °C (20 mmHg). ^{1}H NMR of **30** ($CDCl_3$): δ 6.29 (t, J = 7.1 Hz, 1 H), 6.15 (t, J = 7.5 Hz, 1 H), 3.34−3.27 (m, 1 H), 3.30 (s, 3 H), 2.76 (m, 1 H), 2.49 (m, 1 H), 1.92 (m, 1 H), 1.75 (m, 1 H), 1.61 (m, 1 H), 1.30−1.00 (m, 3 H). ^{13}C NMR of **30** ($CDCl_3$): δ 36.21 (d, J = 163 Hz), 131.62 (d, J = 165 Hz), 78.56 (d, J = 145 Hz), 56.17 (q, J = 140 Hz), 33.50 (t, J = 131 Hz), 33.19 (d, J = 137 Hz), 29.79 (d, J = 137 Hz), 25.82 (t, J = 130 Hz), 17.55 (t, J = 132 Hz).

Hydroboration−Oxidation of *exo*-6-Methoxybicyclo[2.2.2]oct-2-ene. Preparation of Ketones 31 and 32. A solution containing 536 mg of *exo*-6-methoxybicyclo[2.2.2]oct-2-ene, **30**, in 6 mL of THF was cooled to 0 °C, and then 3.4 mL of 1.0 M of BH_3 in THF was added dropwise. The mixture was stirred at 0 °C for 30 min and then at room temperature for an additional 30 min. The reaction mixture was then recooled to 0 °C and quenched by slow addition of 5 mL of water. A solution of chromic acid was prepared by dissolving 1.38 g of sodium dichromate dihydrate in 10 mL of 15% aqueous H_2SO_4. This chromic acid solution was then added dropwise to the reaction mixture at 0 °C. After being warmed to room temperature and stirred for 4 h, the mixture was diluted with 10 mL of water and extracted with ether. The ether extract was washed with water and saturated NaCl solution and dried over a mixture of Na_2SO_4 and $MgSO_4$. After filtration, the ether was removed using a rotary evaporator to give a mixture containing 61% ketone **31** and 39% ketone **32**. This mixture was chromatographed on 73 g of silica gel. Ketone **31** (279 mg; 47% yield) eluted first with 30% ether in hexanes, and ketone **32** (168 mg; 28% yield) eluted second. ^{1}H NMR of **31** (major product) ($CDCl_3$): δ 3.64 (d of d of d of d, J = 1.3, 3.3, 3.3, 9.7 Hz, 1 H), 3.28 (s, 3 H), 2.65 (q, J = 3.1 Hz, 1 H), 2.26−1.52 (m, 10 H). ^{13}C NMR of **31** ($CDCl_3$): δ 215.89 (quat), 74.60 (d, J = 145 Hz), 56.25 (q, J = 141 Hz), 46.92 (d, J = 141 Hz), 43.91 (t, J = 130 Hz), 34.66 (t, J = 132 Hz), 27.43 (d, J = 139 Hz), 24.30 (t, J = 130 Hz), 15.86 (t, J = 132 Hz). HRMS (EI): calcd for $C_9H_{14}O_2$ 154.0994, found 154.0966. ^{1}H NMR of **32** (minor product) ($CDCl_3$): δ 3.55 (d of d of d of d, J = 1.3, 3.7, 3.7, 8.5 Hz, 1 H), 3.33 (s, 3 H), 2.37 (sextet, J = 3.0 Hz, 1 H), 2.25 (m, 1 H), 2.20−1.60 (m, 7 H), 1.44 (m, 1 H). ^{13}C NMR of **32** ($CDCl_3$): δ 216.38 (quat), 76.75 (d, J = 140 Hz), 56.30 (q, J = 140 Hz), 42.35 (d, J = 140 Hz), 41.37 (t, J = 132 Hz), 31.47 (t, J = 131 Hz), 31.21 (d, J = 133 Hz), 23.01 (t, J = 130 Hz), 17.65 (t, J = 128 Hz). HRMS (EI): calcd for $C_9H_{14}O_2$ 154.0994, found 154.0996.

Preparation of Tosylhydrazones. General Procedure. Tosylhydrazine (1.03 equiv) was suspended in a small amount of absolute methanol, and the appropriate ketone (1.00 equiv) in a small amount of methanol was added in one portion with stirring until the mixture became homogeneous. After a period of time, the tosylhydrazones crystallized. The mixture was then cooled in a freezer, and the methanol was decanted using a pipet. The last traces of solvent were removed under vacuum. The following procedure is representative.

A suspension of 151 mg of tosylhydrazine (0.809 mmol) in 0.5 mL of methanol was stirred as 133 mg of ketone **21** (*exo*-6-SCH_3) (0.781 mmol) in 1.5 mL of methanol was added. Upon addition of the ketone, the mixture became homogeneous. A precipitate formed after 5 min, and the mixture was kept at room temperature for 1 h. The mixture was placed in a freezer for 12 h, and the methanol was then decanted from the cold mixture. The remaining solid was dried using a rotary evaporator for several hours to give 254 mg of tosylhydrazone **22** (96% yield), mp 186−190 °C. ^{1}H NMR of **22** ($CDCl_3$): δ 7.84 (d, J = 8.2, 2 H), 7.56 (bs, 1 H), 7.32 (d, J = 8.2 Hz, 2 H), 2.90 (d of d of d of d, J = 1.0, 5.7, 5.7, 10.4 Hz, 1 H), 2.46 (q, J = 2.9 Hz, 1 H), 2.44 (s, 3 H), 2.25 (m, 1 H), 2.12−2.10 (br, 2 H), 2.07−1.94 (m, 2 H), 2.02 (s, 3 H), 1.61 (t, J = 11.0 Hz, 1 H), 1.44−1.33 (m, 2 H), 1.26 (d of m, J = 14.1 Hz, 1 H). ^{13}C NMR of **22** ($CDCl_3$): δ 163.81 (quat), 144.06 (quat), 135.51 (quat), 129.60 (d, J = 161 Hz), 127.93 (d, J = 166 Hz), 41.95 (d, J = 142 Hz), 37.60 (d, J = 140 Hz), 33.53 (t, J = 131 Hz), 31.82 (t, J = 128 Hz), 26.51 (d, J = 136 Hz), 24.75 (t, J = 129 Hz), 21.66 (q, J = 127 Hz), 18.42 (t, J = 133 Hz), 14.79 (q, J = 138 Hz). Anal. Calcd for $C_{16}H_{22}N_2O_2S_2$: C, 56.77; H, 6.55. Found: C, 56.80; H, 6.50.

Pyrolysis of Tosylhydrazone Salts. General Procedure.[18] The solid tosylhydrazone (1.00 equiv) was placed in a flask, and 1.06 equiv of $NaOCH_3$ (1.0 M in methanol) was added with stirring. After the tosylhydrazone disssolved, the methanol solvent was removed using a rotary evaporator. The solid salt was further dried by evacuation at 15 mmHg and at 0.05 mmHg. The flask containing the dry salt was then fitted with a short path distillation head and a receiver flask and placed in an oil bath. The temperature of the oil bath was gradually raised to 80 °C, and then the receiver flask was cooled in a dry ice−acetone bath. The temperature of the oil was then raised gradually to 180 °C while the system was maintained under vacuum. During this time, the pressure rose to approximately 2 mmHg and then decreased back to 0.05 mmHg. The products of these pyrolyses collected in the cold receiver flask. Product ratios were determined by ^{1}H NMR spectroscopy. Pure samples of products were isolated by preparative gas chromatography. Results of these pyrolyses are given in Table 1. The alkenes **39** were identified by NMR spectral comparison with authentic samples. NMR spectral data for tricyclic products **37** and **38** are given in the Supporting Information. The following procedure is representative.

Tosylhydrazone **34** (*exo*-5-OCH_3) (288 mg; 0.890 mmol) was dissolved in 0.95 mL of 1.0 M $NaOCH_3$ (0.95 mmol) in methanol. The mixture was stirred at room temperature for 10 min, and the methanol was then removed using a rotary evaporator. The salt was dried on a rotary evaporator for 1 h and further dried using a vacuum pump (0.05 mmHg) for 3 h. Vacuum pyrolysis, as described above, of the dry sodium salt gave 71.2 mg of a mixture containing 81% of tricyclic compound **40** and 19% of olefin **30**. The olefin **30** was identified by NMR spectral comparison with an authentic sample prepared as described above. ^{1}H NMR of **40** ($CDCl_3$): δ 3.23 (s, 3 H), 3.19 (d of d of d of d of d, J = 1.3, 3.7, 3.7, 9.5 Hz, 1 H), 2.17 (d of d of d, J = 3.1, 9.5, 14.8 Hz, 1 H), 2.09 (d of d of d, J = 3.3, 5.8, 5.8 Hz, 1 H), 1.91 (d, J = 12 Hz, 1 H), 1.72 (d of d of d, J = 2.2, 6.4, 12.3 Hz, 1 H), 1.67 (d of d of d, J = 2.6, 4.0, 14.8 Hz, 1 H), 1.44 (d, 12 Hz, 2 H), 1.21 (d of d, J = 1.3, 7.7 Hz, 2 H), 0.68 (d of d of d of d of d, J = 2.6, 2.6, 7.7, 7.7, 1 H). ^{13}C NMR of **40** ($CDCl_3$): δ 78.35 (d, J = 131 Hz), 55.40 (q, J = 140 Hz), 33.74 (d, J = 138 Hz), 29.63 (t, J = 132 Hz), 25.67 (t, J = 127 Hz), 23.44 (t, J = 129 Hz), 15.67 (d, J = 170 Hz), 15.20 (d, J = 169 Hz), 10.96 (d, J = 161 Hz). HRMS (EI): calcd for $C_9H_{14}0$ 138.1045, found 138.1043.

Computational Studies. Ab initio molecular orbital calculations were performed using the Gaussian 94 and Gaussian 98 series of programs.[41] Structures of carbenes were characterized as minima via frequency calculations which showed no negative frequencies.

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Acknowledgment is made to the National Science Foundation for support of this research.

Supporting Information Available: Structures and energies of carbenes **7**, **10b**, **10c**, **10e**, **10f**, **10g**, and **11**, transition states for carbene rearrangements, and NMR spectral data for compounds **37**, **38**, and **39c** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA002407+