Macromol. Symp. ***134**, 95–104 (1998)*

New Adventures with Divalent Carbon Intermediates

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Abstract. *Part I:* Reactions of 3-substituted 1-azabicyclo[1.1.0]butanes (**1a** and **1b**) with dichlorocarbene proceed in each case via nitrogen ylide intermediates with concomitant ring opening to afford the corresponding dihaloimines (**2a** and **2b**, respectively). *Part II:* Vinylidenecarbene-cycloalkyne equilibria have been studied in three polycarbocyclic systems, i.e., **10a**-**10b**, **20a**-**20b**, and **27a**-**27b**. In all three systems, only the vinylidenecarbene intermediate can be trapped *in situ* by cyclohexene. The results of site-specific ^{13}C labeling studies that employ **9**-C(8)-$^{13}CBr_2$ (enriched with 4 atom-% ^{13}C), **19**-C(4)-$^{13}CBr_2$ (enriched with 5 atom-% ^{13}C), and **23**-C(4)-$^{13}CBr_2$ (enriched with 10 atom-% ^{13}C) also support this conclusion and suggest that cycloalkyne intermediates, if formed in these systems, must rearrange very rapidly to the corresponding (thermodynamically favored) vinylidenecarbenes. *Part III:* Base-promoted reactions of *N*-tosyl- and *N*-benzhydrylazetidin-3-ones (i.e., **30a** and **30b**, respectively) with diethyl diazomethylphosphonate (DAMP), when performed in the presence of cyclohexene, in each case afford exclusively the product that results via *in situ* trapping of the corresponding vinylidenecarbene.

INTRODUCTION

For the past several years, our respective research groups at the University of North Texas and at the University of Łódź have pursued common interests in the synthesis and chemistry of novel polycarbocyclic compounds (Ref. 1) and of 3-substituted 1-azabicyclo[1.1.0]-butanes (Ref. 2). The results of three recently completed studies that combine these topics with a shared interest in reactive intermediates (divalent carbon species) are reported herein.

RESULTS AND DISCUSSION

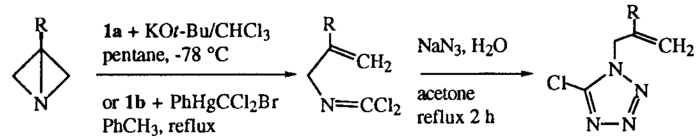
I. Reactions of 3-substituted 1-azabicyclobutanes with Dichlorocarbene

Reaction of 3-ethyl-1-azabicyclo[1.1.0]butane (**1a**) with $CHCl_3$-KO*t*-Bu afforded a ring-opened product, 1,1-dichloro-2-aza-4-ethylpenta-1,4-diene (**2a**, Scheme 1), which was characterized via conversion to the corresponding *N*-substituted 5-chloro-1,2,3,4-tetrazole, **3a** (Ref. 3). Reaction of 3-phenyl-1-azabicyclo[1.1.0]butane (**1b**) with "Seyferth's reagent"

CCC 1022-1360/98/$ 17.50

($PhHgCCl_2Br$) afforded 1,1-dichloro-2-aza-4-phenylpenta-1,4-diene (**2b**, Scheme 1), which also was characterized via conversion to a tetrazole derivative (i.e., **3b**) (Ref. 3). Subsequently, the corresponding reaction of phenylchlorocarbene with **1a** in pentane at 25 °C was shown to proceed with a rate constant $k = 3.2 \times 10^8\ M^{-1}s^{-1}$, a result that was considered to provide evidence for the incursion of a nitrogen ylide-mediated reaction (Ref. 4).

Scheme 1



1a: R = Et
1b: R = Ph

2a (R = Et)
2b (R = Ph)

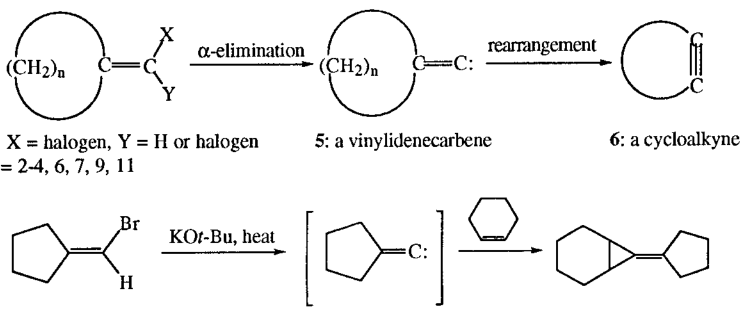
3a (R = Et)
3b (R = Ph)

II. Vinylidenecarbene-Cycloalkyne Equilibria in Polycarbocyclic Systems

A. The Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-ylidenecarbene System. Vinylidenecarbene-cycloalkyne equilibria have been studied in several monocyclic systems (Ref. 5). As an example, α–elimination of Br_2 from dibromomethylenecyclobutane (**4**, X = Y = Br, n = 3) results exclusively in formation of cyclopentyne, which can be trapped *in situ* by an alkene to form a substituted cyclobutene (see Scheme 2) (Ref. 5). By way of contrast, base promoted elimination of HBr from bromomethylenecyclopentane (**7**) generates the corres-ponding vinylidenecarbene (**5**, n = 4). When this reaction is performed in the presence of cyclohexene, the corresponding norcarane, **8**, is isolated in low yield (Scheme 2) (Ref. 6).

Recently, we reported two methods for generating reactive intermediates in the pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (PCU) ring system (Ref. 7). First, the low-temperature re-action of 8-(dibromomethylene)-PCU (**9**, Scheme 3) with *n*-BuLi-THF, when performed in the presence of cyclohexene, afforded a cycloadduct, **11**. Subsequent reaction of **11** with di-

Scheme 2



4: X = halogen, Y = H or halogen
n = 2-4, 6, 7, 9, 11

5: a vinylidenecarbene

6: a cycloalkyne

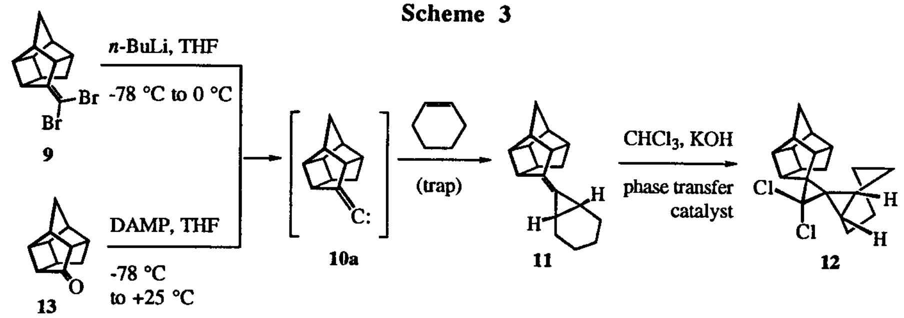
7

5 (n = 4)

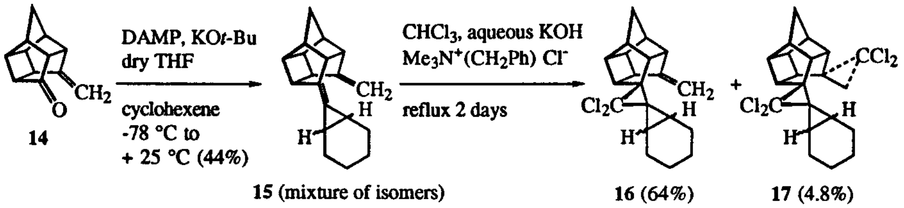
8 (11%, Ref. 6)

chlorocarbene (Ref. 8) afforded **12**, whose structure was established unequivocally via application of X-ray crystallographic methods. Similarly, the corresponding base promoted reaction of PCU-8-one (**13**) (Ref. 9) with diethyl diazomethylphosphonate (DAMP, Ref. 5c), when performed in the presence of cyclohexene (trap), afforded **11** (30% yield). These results suggest that the same reactive intermediate, i.e., vinylidenecarbene **10a**, was produced in both reactions. Closely analogous results were also obtained via base promoted reaction of 8-methylene-PCU-11-one (**14**) with DAMP (see Scheme 4).

Scheme 3



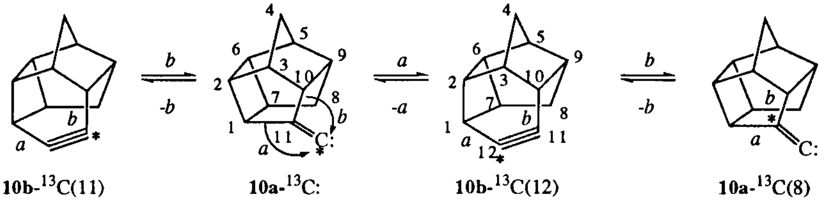
Scheme 4



For the reaction of **9** with *n*-BuLi, further evidence regarding the potential intermediacy of cage-annulated cyclohexyne **10b** was sought via a site-specific ^{13}C labeling study. Thus, reaction of PCU-8-^{13}CBr$_2$ [i.e., **9**-C(8)-^{13}CBr$_2$ enriched with 4 atom-% ^{13}C] with *n*-BuLi at low temperature in the presence of cyclohexene (trap) afforded the corresponding ^{13}C labeled cycloadduct **11**. This material was isolated and purified, and its gated-decoupled ^{13}C NMR spectrum was integrated carefully. Analysis of the integrated ^{13}C NMR spectrum established that no scrambling of the ^{13}C label had occurred. This result can be interpreted in either of two ways: (i) Perhaps **10b** is not energetically accessible from **10a** and that there is no incursion of **10b** on the reaction profile by which **10a** is formed via *n*-BuLi promoted α-elimination of bromine from **9**. (ii) Alternatively, a substantial difference might exist between the relative migratory aptitudes of bonds *a* and *b* in **10a**-^{13}C: (Scheme 5). In this event, a single equilibrium might be established between **10a**-^{13}C: and either **10b**-^{13}C(11) or **10b**-^{13}C(11) (Scheme 5), neither of which alone is capable of scrambling the ^{13}C label. Then, if **10a** happens to be significantly more reactive than **10b** toward cyclohexene (trapping agent), only the vinylidenecarbene-cyclohexene trapping product would be formed in which no scrambling of the ^{13}C label had occurred.

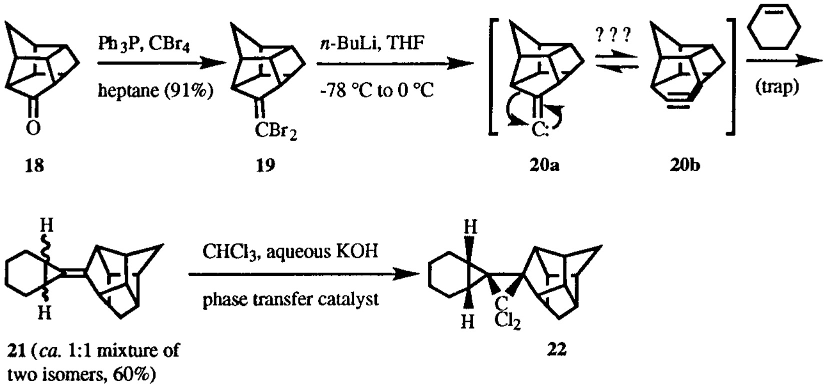
B. The Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-4-ylidenecarbene System. Reaction of **19** (Scheme 6) with *n*-BuLi in THF at low temperature resulted in the generation of a reactive intermediate that could be trapped *in situ* by cyclohexene. The resulting pro-

Scheme 5



duct, i.e., **21** (Scheme 6), consisted of an inseparable mixture of two isomeric cycloadducts, (determined via analysis of the ^{13}C NMR spectrum of **21**). The mixture of isomeric cycloadducts thereby obtained was allowed to react with dichlorocarbene (Ref. 8). Fractional recrystallization of the resulting product resulted in the isolation of an isomerically pure compound, **22**, whose structure was established unequivocally via application of X-ray crystallographic methods. Based upon these observations, we conclude that the low temperature reaction of **19** with *n*-BuLi produced the corresponding vinylidenecarbene, **20a**. This carbene, like **10a** (Scheme 3), displays no tendency to rearrange to the corresponding cycloalkyne.

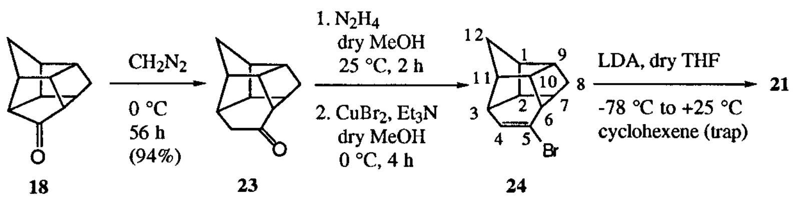
Scheme 6



Subsequently, a method was devised whereby the **20a** and/or **20b** might be accessed from the "cycloalkyne side" of the equilibrium. The synthetic methodology that was employed for this purpose is shown in Scheme 7. Thus, diazomethane promoted ring expansion of **18** (Ref. 10) afforded **23** (94% yield). Attempted conversion of **23** into the corresponding geminal dibromide (Ref. 11) under the conditions shown in Scheme 7 proceeded with concomitant elimination of HBr, thereby affording a cage-annulated bromoalkene, **24**.

An attempt was made to generate cycloalkyne **20b** directly via low temperature reaction of **24** with lithium diisopropylamide (LDA) in dry THF. However, when this reaction was performed in the presence of added cyclohexene, only **21** was isolated (mixture of isomeric cycloadducts). We conclude that if **20b** is formed at all via this reaction, it rearranges spontaneously and very rapidly to the corresponding vinylidenecarbene (**20a**), the only reactive intermediate that is capable of being trapped *in situ* by cyclohexene.

Scheme 7

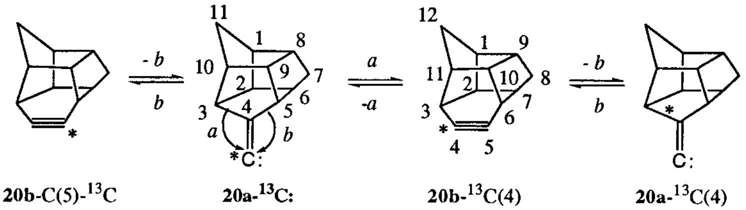


In order to address the issue of the putative intermediacy of **20b** in the low temperature reaction of **24** with LDA-THF, two separate site-specific ^{13}C labeling studies were performed. In the first study, reaction of **19**-C(4)-$^{13}CBr_2$ (enriched with 5 atom-% ^{13}C) with *n*-BuLi at low temperature in the presence of cyclohexene (trap) afforded the corresponding ^{13}C labeled cycloadduct **21** as an inseparable mixture of diastereoisomers (*vide supra*). This material was isolated and purified, and its gated-decoupled ^{13}C NMR spectrum was integrated carefully. Analysis of the integrated ^{13}C NMR spectrum established that no scrambling of the ^{13}C label had occurred, as would be required by the incursion of of cycloalkyne **20b** (see Scheme 8). We conclude from this result that **20b** is not energetically accessible via the corresponding vinylidenecarbene (**20a**) and that there is no incursion of the former species on the reaction profile by which **20a** is formed via *n*-BuLi promoted α-elimination of bromine from **19**.

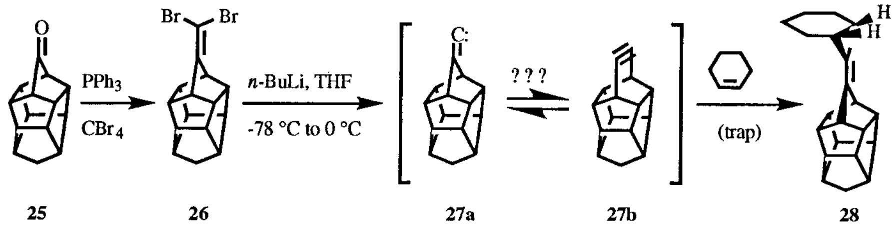
In the second site-specific ^{13}C labeling study, ring expansion of **18** (Ref. 10), when performed via the method shown in Scheme 7 by using $^{13}CH_2N_2$, afforded **23**-C(4)-$^{13}CBr_2$ (enriched with 10 atom-% ^{13}C). Subsequently, this material was converted into **24**-C(4)-^{13}C, again by using the procedure shown in Scheme 7. Then, **24**-$^{13}C(4)$ was reacted with LDA-THF at low temperature in the presence of cyclohexene (trap), thereby affording the corresponding ^{13}C labeled cycloadduct **21**. This material was isolated and purified, and its gated-decoupled ^{13}C NMR spectrum was integrated carefully. Analysis of the integrated ^{13}C NMR spectrum established that the ^{13}C label had become scrambled over *both* vinyl carbon positions in **21**, as would be required by the incursion of cycloalkyne **10b** (see Scheme 8). This result confirms the fact that **20b**-$^{13}C(4)$ is formed directly in this reaction [via base promoted elimination of HBr from **24**-$^{13}C(4)$] and that prior to being trapped *in situ* by cyclohexene, this cycloalkyne intermediate rearranges very rapidly to the corresponding vinylidenecarbene. This cycloalkyne-vinylidenecarbene rearrangement occurs via two equally probable competing pathways, thereby resulting in scrambling of the ^{13}C label between the two vinyl carbon atoms in the trapping product, **21**.

C. The Heptacyclo[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}.0^{10,14}]tetradecan-7-ylidene-carbene System. Compound **26** (Ref. 12, Scheme 9) was prepared via reaction of cage ketone **25** (Ref. 13) with Ph_3P-CBr_4. Subsequent low temperature reaction of **26** with *n*-BuLi-THF in the presence of cyclohexene led to the formation of a single cycloadduct, **28**. The structure of **28** was established unequivocally via application of X-ray crystallographic methods.

Scheme 8



Scheme 9

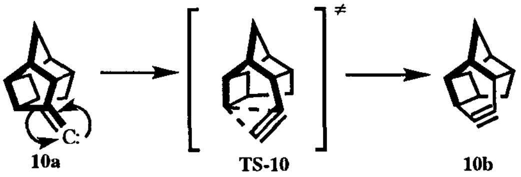


D. Computational Results. Semiempirical and ab initio molecular orbital calculations have been performed in an effort to gain further insight into the relative stabilities of the various vinylidenecarbene-cycloalkyne equilibria that have been considered in the present study (Refs. 14 and 15). The results thereby obtained in the pentacyclo[$5.4.0.0^{2,6}.0^{3,10}.0^{5,9}$]undecan-8-ylidenecarbene system for rearrangement of vinylidenecarbene **10a** to cycloalkyne **10b** via transition state **TS-10** are shown in Table 1 (Ref. 7). These computational results indicate that vinylidenecarbene **10a** is thermodynamically more stable than cycloalkyne **10b** and that a substantial energy barrier must be surmounted in order for **10a** to rearrange to **10b**. Similar results are predicted for the analogous vinylidenecarbene-cycloalkyne rearrangements (i) of the species **29a-29b**, generated via base promoted reaction of **14** with DAMP (see Scheme 4; computational results are given in Table 2), (ii) of the species, **20a-20b**, produced via low tem-perature reaction of **19** with *n*-BuLi-THF (see Scheme 6; computational results appear in Table 3), and (iii) of the species, **27a-27b**, produced via low temperature reaction of **26** with *n*-BuLi-THF (see Scheme 8; computational results appear in Table 4).

III. Generation and Trapping of *N*-Substituted-3-azetidinylidenecarbenes. (Ref. 16)

A. Experimental Results. Reactive intermediates were generated via base-promoted reactions of *N*-tosyl- and *N*-benzhydrylazetidin-3-one [**30a** (Ref. 17) and **30b** (Refs. 18 and 19), respectively] with diethyl diazomethylphosphonate (DAMP, Ref. 5c) in the presence of cyclohexene (trap). In each case, a single cycloadduct was obtained that subsequently was shown to result via *in situ* trapping of a vinylidenecarbene intermediate (i.e., **31a** and **31b**, respectively, Scheme 10) (Ref. 16). Importantly, this result stands in contrast with the behavior of the corresponding carbocyclic system, cyclobutanylidenecarbene, which has been shown to rearrange spontaneously to cyclopentyne (Ref. 5). Thus, we find that the dominant reaction pathway for the aza-system involves carbene chemistry, whereas that for the all-carbon system reflects cycloalkyne chemistry.

Table 1. Absolute and relative energies from semiempirical and ab initio calculations (Ref. 7)



Computational Method	Vinylidenecarbene **10a** (singlet)	Transition State **TS-10**	Cycloalkyne **10b**
AM1 (kcal-mol^{-1})	147.39 (0)	184.84 (37.4)	153.95 (6.6)
HF/3-21G(*) (total energies, in hartrees)	–458.71852 (0)	–458.67003 (30.4)	–458.68723 (19.6)
HF/6-31G(*) (total energies, in hartrees)[b]	–461.03539 (0)	–460.99899 (22.8)	–461.00537 (18.8)

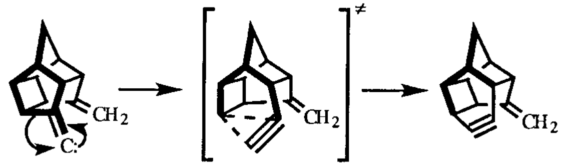
[a] Relative energies (kcal-mol^{-1}) for each series are in parentheses.
[b] The zero-point energy contribution has been applied to these values.

B. Computational Results. (Refs. 14,15) The results of semiempirical molecular orbital calculations (AM1 Hamiltonian, Refs. 19,20) indicate that ring expansions of *N*-substituted azetidin-3-ylidenecarbenes to the corresponding 1-azacyclopent-3-ynes (where the *N*-substituents are varied along the series R = H, Ts, and CHPh$_2$) are consistently *endo*thermic by 5.4-10.6 kcal-mol^{-1} (Ref. 16). These results contrast dramatically with the corresponding computational results for ring expansion of cyclobutylidenecarbene to cyclopentyne, which is predicted to be *exo*thermic by *ca.* 1 kcal-mol^{-1} (Refs. 5d, 21). Reasonable explanations have been forwarded (Ref. 16) to account for the differing chemical behavior displayed by the aza-cyclic carbene *vis-à-vis* that of the corresponding carbocyclic carbene.

ACKNOWLEDGMENT

We thank the Office of Naval Research (Grant N00014-94-1-1039 to A. P. M.), the United States Air Force (Contract F29601-92-K-0018 to A. P. M.), the Robert A. Welch Foundation (Grants B-963 to A. P. M., B-1202 to S. G. B.), the Polish Academy of Sciences (Grant CPBP-01.13.1.12 to R. B.), and the University of North Texas Faculty Research Committee (to S. G. B.) for financial support of this study. A. G. thanks the Rector, University of Łódź, for a predoctoral fellowship (1984-1990).

Table 2. Absolute and relative energies from semiempirical and ab initio calculations

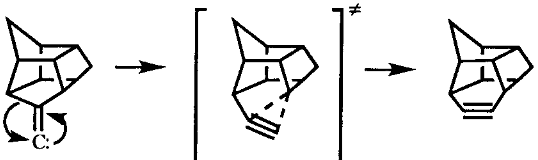


29a **TS-29** **29b**

Computational Method	Vinylidenecarbene **29a** (singlet)	Transition State **TS-29**	Cycloalkyne **29b**
AM1 (kcal-mol^{-1})	173.24 (0)	210.74 (37.5)	179.26 (6.0)
HF/3-21G(*) (total energies, in hartrees)^{b}	–496.34962 (0)	–496.30123 (30.4)	–496.31943 (19.6)
HF/6-31G(*) (total energies, in hartrees)^{b}	–498.87259 (0)	–498.83812 (22.8)	–498.84518 (18.8)

^{a}Relative energies (kcal-mol^{-1}) for each series are in parentheses.
^{b}The zero-point energy contribution has been applied to these values.

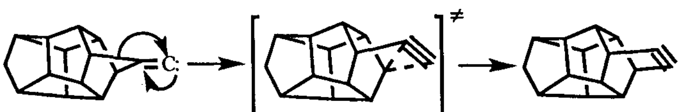
Table 3. Absolute and relative energies from semiempirical and ab initio calculations



20a **TS-20** **20b**

Computational Method	Vinylidenecarbene **20a** (singlet)	Transition State **TS-20**	Cycloalkyne **20b**
AM1 (kcal-mol^{-1})^{b}	153.83 (0)	193.09 (39.3)	174.89 (21.1)
HF/3-21G(*) (total energies, in hartrees)^{b}	–458.73222 (0)	–458.67110 (38.3)	–458.68458 (29.8)
HF/6-31G(*) (total energies, in hartrees)^{b}	–461.26697 (0)	–461.21884 (30.1)	–461.22266 (27.6)

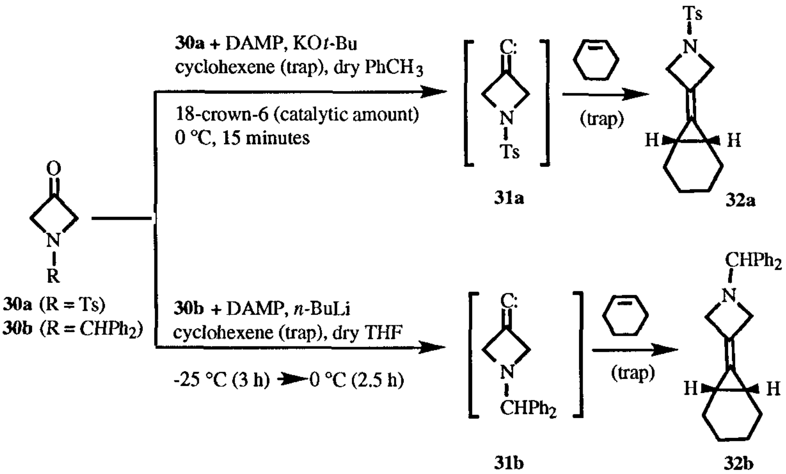
^{a}Relative energies (kcal-mol^{-1}) for each series are in parentheses.
^{b}The zero-point energy contribution has been applied to these values.



27a **TS-27** **27b**

Computational Method	Vinylidenecarbene **27a** (singlet)	Transition State **TS-27**	Cycloalkyne **27b**
AM1 (kcal-mol^{-1})	140.27 (0)	177.96 (37.7)	158.74 (18.5)
HF/3-21G(*) (total energies, in hartrees)^{b}	−572.63417 (0)	−572.58672 (29.8)	−572.59224 (26.3)
HF/6-31G(*) (total energies, in hartrees)^{b}	−575.79568 (0)	−575.73865 (35.8)	−575.75147 (27.7)

[a]Relative energies (kcal-mol^{-1}) for each series are in parentheses.
[b]The zero-point energy contribution has been applied to these values.



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(14) All calculations were performed by using SPARTAN software on an SGI INDIGO2 platform (UNIX operating system). Full geometry optimizations were performed at semiempirical (AM1, Ref. 15) and ab initio [HF/3-21G(*) and HF/6-31G(*)] levels. Vibrational frequency calculations were used to characterize the first-order transition state (single imaginary frequency). SPARTAN computer software (version 4.0.3) was purchased from Wavefunction, Inc., 18401 von Karman, Suite 370, Irvine, CA 92715.

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