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Generation and Trapping of a Cage Annulated Vinylidenecarbene and Approaches to Its Cycloalkyne Isomer

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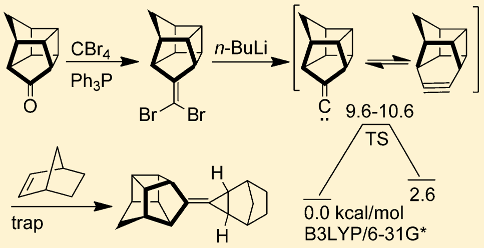
S *Supporting Information*

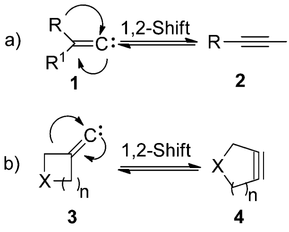
ABSTRACT: A novel cage-annulated (bis-homocubyl) vinylidenecarbene has been generated and successfully trapped without any intermediacy of its cycloalkyne isomer. The greater kinetic and thermodynamic stability of the vinylidenecarbene vis-à-vis its cycloalkyne isomer has been predicted by DFT B3LYP/6-31G* calculations. The calculated results suggest the prospects of the cycloalkyne becoming amenable for trapping, if generated under suitable experimental conditions, owing to the substantial kinetic energy barrier associated with its possible ring contraction via 1,2-shift to the vinylidenecarbene isomer and marginal ground state energy difference. However, all of our attempts to directly generate and trap the cycloalkyne yielded unsatisfactory results. Attempted generation and trapping of a C2-symmetric bis-vinylidenecarbene from a bis-vinylidenedibromide met with unexpected failure.



■ INTRODUCTION

The rearrangement involving a 1,2-shift of vinylidenecarbenes or carbenoids **1**, commonly known as the Fritsch−Buttenberg−Wiechell (FBW) rearrangement,[1,2] is a well-established method for the synthesis of acetylenes **2** (Scheme 1a).[3] Mechanistic investigations of this transformation as well as its applications to numerous systems in which the migrating group is an alkyl, aryl or heteroaryl group have been reported.[4] Thermal rearrangement of acetylenes **2** to vinylidenecarbenes **1** under FVP conditions has also been described.[5]

Scheme 1



The rearrangement of a cyclic vinylidenecarbene **3** to its corresponding cycloalkyne[6−13] is an important variant of the FBW rearrangement in that it is extremely effective in the generation of cyclic acetylenic systems **4** that are otherwise difficult to synthesize (Scheme 1b).[14] This is by taking advantage of the fact that although cyclobutyne has been reported to have rearranged to cyclopropylidenecarbene,[9] cyclopentyne and its higher homologues, in general, with a notable exception,[8] are thermodynamically more stable than their corresponding cycloalkylidenecarbenes. These alkynes are still transient species and only cyclooctyne and its higher homologues are isolable.[15]

Despite the detailed experimental[6−13] and theoretical[11−13] investigations on the generation, trapping, and the mechanistic implications associated with the transient existence of cycloalkynes, studies on cycloalkynes that are part of a complex framework, *viz* highly strained polycycles, are relatively scarce.[16−18] Owing to the high degree of strain associated with polycyclic cage hydrocarbons, cage annulated reactive intermediates often exhibit interesting and unexpected properties. For instance, in contrast to the behavior of the parent or relatively unstrained systems,[10−12] certain cage-annulated cyclopentylidenecarbenes **5**, **7** and **9** have been found to be kinetically and thermodynamically more stable than their corresponding cyclohexynes **6**, **8** and **10**, respectively (Scheme 2).[16−18] While all the carbenes **5**, **7** and **9** have been generated and trapped,[16−18] their corresponding alkynes **6**, **8** and **10**, respectively, remained elusive. For instance, attempts to trap the cyclohexyne isomer **10** of carbene **9** failed as it underwent spontaneous ring contraction to **9** via 1,2-shift.[18]

In this scenario, we report on the generation and trapping of a novel cage-annulated cyclopentylidenecarbene without any intermediacy of its corresponding cycloalkyne. Our attempts to directly generate and trap the alkyne as well as a symmetrical bis-vinylidenecarbene are also reported here.

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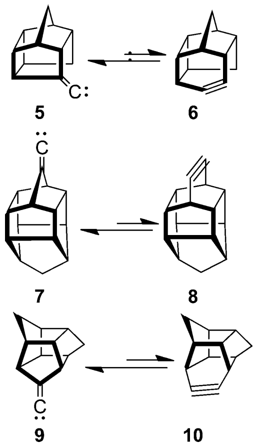
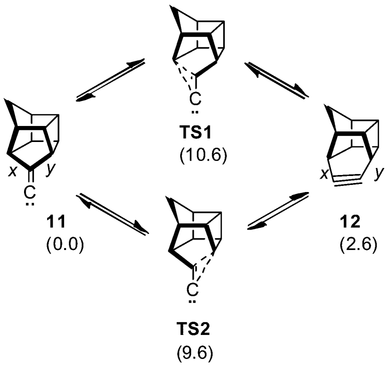
Scheme 2



RESULTS AND DISCUSSION

Calculations were performed for the rearrangement of cage-annulated cyclopentylidenecarbene **11** to its corresponding cycloalkyne **12** using hybrid *ab initio*/DFT B3LYP/6-31G* level of theory (Scheme 3).[19] The influence of electron correlation on the energies of cycloalkylidenecarbene-cycloalkyne rearrangements has been reported previously,[12] and the studies have shown that DFT satisfactorily describes the energies and reactions of carbenes.[20] To incorporate the solvation effect, single point calculations were performed with integral equation formalism polarizable continuum model (IEFPCM) in THF.[21] Since carbene **11** and its corresponding alkyne **12** are devoid of any symmetry, the rearrangement could, in principle, take place via two different transition states, that is, **TS1** and **TS2** involving the migration of bond *x* and the migration of bond *y*, respectively.

Scheme 3. B3LYP/6-31G* Calculated Relative Energies (kcal mol^{-1}) for the Interconversion Between Vinylidenecarbene 11 and Cycloalkyne 12 in THF

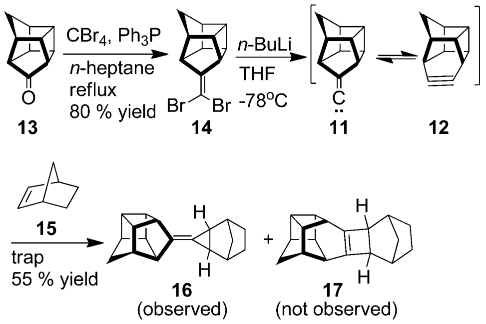


The calculated results predicted that the activation barriers for transition states **TS1** and **TS2** in THF were 10.6 and 9.6 kcal mol^{-1}, respectively (Scheme 3). Furthermore, the ground state energy for alkyne **12**, predicted to be higher by 2.6 kcal mol^{-1} than that of carbene **11**, indicated the thermodynamic preference for the vinylidenecarbene **11** as compared to cycloalkyne **12** (Scheme 3).

The above results suggested that the interconversion between the two reactive species, **11** and **12**, via the 1,2-shift, though mechanistically possible, would be less likely due to high energy barriers. Instead, carbene **11**, if generated, was likely to get trapped in situ without any intermediacy of its alkyne isomer **12**. Similarly, trapping of alkyne **12** also seemed plausible under suitable experimental conditions.

Armed with this valuable theoretical appraisal, we initiated our experimental studies, at first, toward the generation of cyclopentylidenecarbene **11** and to see whether it rearranges to cycloalkyne **12** under our experimental conditions. To this end, dibromomethylenation[22] of pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one(1,3-bishomocubanone) **13**[23,24] was carried out using CBr_4 and Ph_3P which provided dibromide **14** in 80% yield (Scheme 4) whose structure was confirmed by ^{13}C NMR (δ 70.9, CBr_2 and 158.2, $C{=}CBr_2$). The dibromide **14** was then treated with *n*-BuLi in THF at −78 °C in the presence of norbornene **15** as the trap. Analysis of ^{1}H and ^{13}C NMR spectra of the trapped product which was formed in 55% yield indicated that it was indeed **16**, the product arising from trapping of vinylidenecarbene **11**. There was no evidence for the formation of the trapped product **17** arising from cycloalkyne **12**. This suggested that the rearrangement via 1,2-shift of carbene **11** to alkyne **12** did not take place under the experimental conditions employed which was consistent with our theoretical predictions (*vide supra*). However, the trapped product **16** was found to be an inseparable mixture of isomers in ~1:1 ratio. The presence of the cyclopropylidene moiety in **16** was confirmed by the fact that the two hydrogens of both the isomers are highly shielded (δ 0.63 and 0.84 for one isomer and δ 0.69 and 0.99 for the other) in ^{1}H NMR and the two olefinic carbons of both the isomers are separated by >30 ppm in ^{13}C NMR (i.e., 109.9 and 141.4 for one isomer and 110.0 and 141.5 for the other). These data for **16** correlated well with those reported for other cage vinylidenecarbene trapped products (Table 1).[17,18]

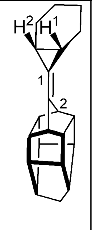
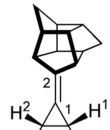
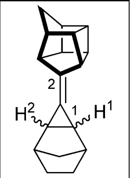
Scheme 4

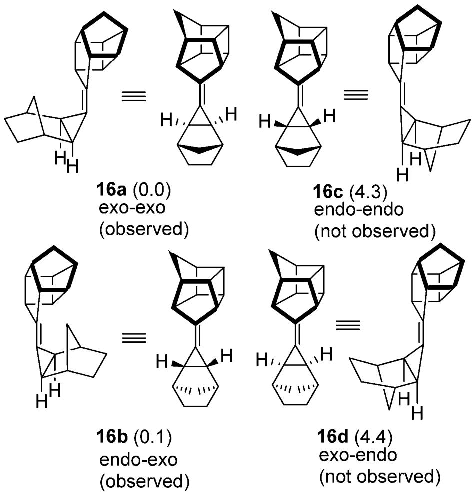


The two isomers formed in ca. 1:1 ratio arise from approach of carbene **11** only from the exo face of the norbornene framework despite the fact that, in principle, the addition of carbene **11** to norbornene **15** could provide as many as four stereoisomeric products **16a−d** (Figure 1). This is confirmed by the fact that the two shielded hydrogens (δ 0.63 and 0.84 or δ 0.69 and 0.99) are coupled only to each other (d, J = 9.4 Hz) indicating their endo orientation. This observation suggested that, although four isomers **16a−d** are possible, the two stereoisomers formed arise from approach of norbornene **15** toward carbene **11** from the exo and endo side, respectively, of the cage framework leading to the formation of **16a** and **16b**, respectively, as shown in Figure 1.

The experimental results described above were further supported by hybrid *ab initio*/DFT calculations in THF. Transition states located for all four possible products **16a−d** at

Table 1. Correlation of the ^{1}H and ^{13}C NMR Spectral Data of Product 16 with Analogous Compounds in Literature[17,18]

carbene trapped product			
	18[17]	**19**[18]	**16**
^{13}C NMR (C1, C2, ppm)	C1 125.2 C2 147.1	C1 114.3 C2 136.0	C1 109.9, 110.0 C2 141.4, 141.5
^{1}H NMR (H1, H2, ppm)	0.99-1.06	0.75-0.95	0.61-1.00



16a (0.0)
exo-exo
(observed)

16c (4.3)
endo-endo
(not observed)

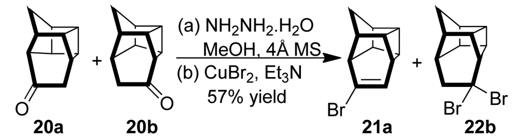
16b (0.1)
endo-exo
(observed)

16d (4.4)
exo-endo
(not observed)

Figure 1. B3LYP/6-31G* relative transition state energies (kcal mol^{-1}) for the trapping of vinylidenecarbene **11** with norbornene **15** in THF.

B3LYP/6-31G* suggest that the approach of carbene **11** from the *exo* face of norbornene **15** is energetically favored over the corresponding approach from the *endo* face (Figure 1). However, the two possible approaches of carbene **11** toward the *exo* face of norbornene **15** were almost of equal energy (Figure 1), thus supporting the experimental observation (*vide supra*).

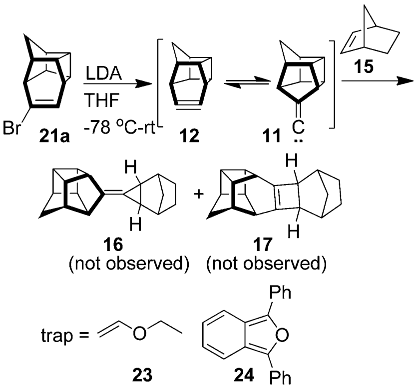
Scheme 5



The theoretical calculations predict that carbene **11** and alkyne **12** would be amenable for trapping under appropriate experimental conditions as both the species are separated by a substantial kinetic barrier (Scheme 3). Therefore, having succeeded in the generation and trapping of carbene **11**, we turned our attention to possible direct generation and trapping of alkyne **12**. To this end, ketone **20** was prepared as a mixture of isomers in 62% yield via diazomethane mediated one carbon ring expansion of bis-homocubanone **13**.[25] Since experimental details are sketchy[25] and all our attempts to fully separate the two regioisomers **20a** and **20b** failed, the mixture as such was subjected to gem-dibromination via hydrazones (Scheme 5).[26] The product was a mixture of two components which were separated by preparative TLC. Analysis of the ^{1}H NMR spectra of the two components indicated that one is a bromoalkene (δ 6.28, dd, J = 6.9, 1.6 Hz, 1H, olefinic) and the other a gem-dibromide (δ 4.52, dd, J = 4.0, 1.8 Hz, 2H, CBr_2-CH_2). This was further confirmed by ^{13}C NMR (δ 66.0, s, CBr_2, gem-dibromide and δ 122.9, s, C-Br and 129.3, d, C=CBr bromoalkene). The regiochemistry was assigned (**21a** for bromoalkene and **22b** for gem-dibromide) based on extensive NMR experiment on the triflate of ketone **20** (*vide infra*).

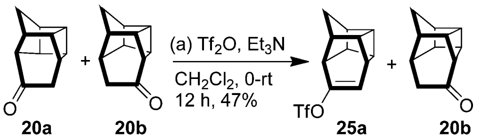
The above results suggested that the gem-dibromide derived from ketone **20a** underwent spontaneous dehydrobromination to bromoalkene **21a** while gem-dibromide **22b** remained stable. Marchand et al had reported generation of a cage cycloalkyne from bromoalkene and isomerization of cycloalkyne to alkylidenecarbene.[18] We felt that bromoalkene **21a** on further elimination of HBr would afford alkyne **12** which could be trapped using a suitable reactant. To test whether there was any possibility of isomerization of alkyne **12** to carbene **11**, our carbene trap norbornene **15** was initially employed as the trapping agent (Scheme 6). Furthermore, literature reports reveal that strained cycloalkynes could react with alkenes in a [2 + 2] fashion under thermal conditions.[27] Unfortunately, attempted generation of alkyne **12** from bromide **21a** and trapping the former with alkenes such as norbornene **15** and vinyl ether **23**,[7] and a diene such as DPIBF **24**[10] afforded unsatisfactory results. This result, though negative, confirmed that the rearrangement of alkyne **12**, presumably generated from bromoalkene **21a**, to carbene **11** was not feasible under these experimental conditions. This corroborated well with our theoretical calculation results which predicted a high kinetic barrier for the rearrangement of alkyne **12** to carbene **11** (Scheme 3).

Scheme 6



Since bromoalkene **21a** did not turn out to be a good precursor for alkyne **12**, we proceeded to prepare the enol triflate of ketones **20** in anticipation that it would be a superior substrate for the generation of alkyne **12**. Much to our amusement, treatment of the isomeric mixture of cage ketones **20** with triflic anhydride and Et_3N resulted in isomerically pure enol triflate **25a** (^{1}H NMR δ 5.90, dd, J = 7.5, 2.3 Hz, 1H, olefinic; ^{13}C NMR δ 116.0, d, C=COTf; 118.7, q, J = 318.8 Hz, CF_3; 151.4, s, C-OTf) in 47% yield along with unreacted ketone (Scheme 7). The structure of triflate **25a** was assigned

Scheme 7

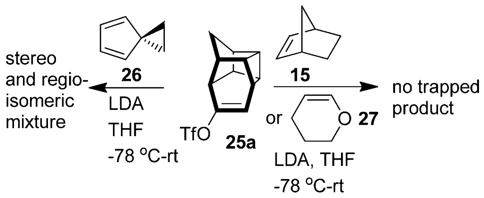


based on extensive NMR experiments such as ^{1}H−^{1}H COSY, HSQC and HMBC (Table S1, Supporting Information). The olefinic proton H3 in **25a** has a vicinal coupling of *J* = 7.5 Hz with H2 and an allylic coupling of *J* = 2.3 Hz with H5.

The confirmed regiochemistry of **25a** and the isolation of unreacted ketone **22b** suggested that triflate formation from ketone **20b** is not feasible or extremely slow due to relatively higher strain in the corresponding triflate as opposed **25a**. Therefore, it appeared reasonable to attribute the same reason for the elimination of HBr to form bromoalkene from one of the two isomeric gem-dibromides (Scheme 5). By analogy, structure **21a** was assigned to the bromoalkene and **22b** to the gem-dibromide.

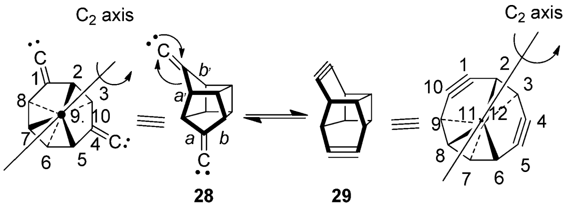
While treatment of triflate **25a** with LDA in the presence of excess (20 equiv) spirodiene **26**[28] provided a complex mixture of regio- and stereoisomers, similar reaction with norbornene **15** or dihydrofuran **27** as the trap did not provide the alkyne trapped product (Scheme 8). But nevertheless, there was no evidence for the formation of the already characterized carbene trapped product **16** either when norbornene **15** was used as the trap. Thus, cycloalkyne **12**, though predicted to be amenable for trapping, remained elusive.

Scheme 8



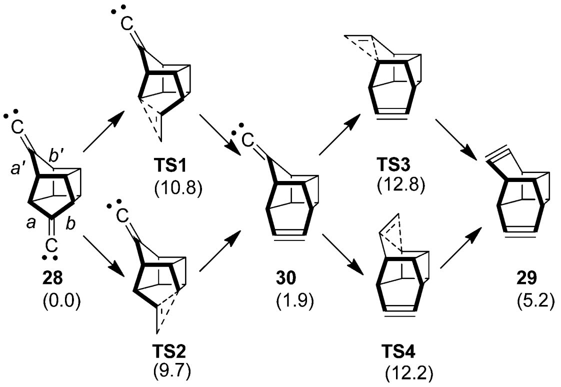
Having successfully generated and trapped carbene **11**, we embarked on the idea of generating a unique bis-alkylidenecarbene **28** and investigate its mechanistically possible rearrangement to the bis-alkyne **29** (Scheme 9). To our knowledge, although a bis-carbene has been generated,[29] there is no report in the literature so far of the generation and trapping of a bis-vinylidenecarbene. Furthermore, it was felt that since the bis-alkylidenecarbene **28** possesses C_2 symmetry, the problem associated with the possible formation of regioisomers of the trapped product would not arise.

Scheme 9



Initially, calculations analogous to the ones carried out for the interconversion between carbene **11** and alkyne **12**, that is, DFT were carried out in the case of the interconversion between bis-carbene **28** and bis-alkyne **29** as well (Scheme 10). Careful examination of Scheme 10 suggests that since bis-carbene **28** and bis-alkyne **29** are C_2 symmetric, only one transition state is expected for the interconversion (bonds *a*, *a′* and *b*, *b′* are identical). However, the computational parameters permit one to consider the interconversion only in a stepwise fashion as shown in Scheme 10. But, nevertheless, this limitation was not expected to influence the final outcome of the calculations.

Scheme 10. B3LYP/6-31G* Level Calculated Relative TS Energy Differences (kcal mol^{-1}) for the Rearrangement of Carbene 28 to Alkyne 29 and vice versa in THF

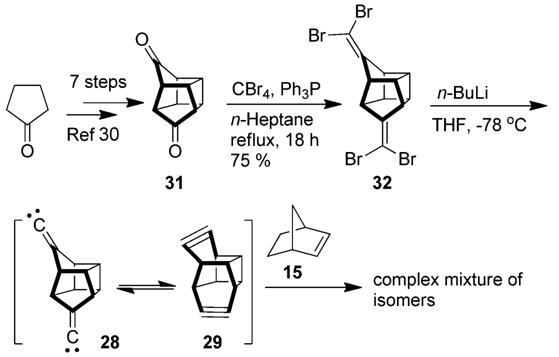


First of all, the rearrangement of bis-alkylidenecarbene **28** to monocycloalkyne **30** was considered (Scheme 10). This rearrangement could take place, in principle, *via* migration of bond *a* (**TS1**) or via migration of bond *b* (**TS2**). The calculated results suggest that the relative thermodynamic stability of bis-carbene **28** is more compared to monoalkyne **30** (Scheme 10). However, substantial kinetic barriers of 10.8 and 9.7 kcal mol^{-1}, respectively, for **TS1** and **TS2**, have been observed for the rearrangement.

Subsequently, the transition state energy calculations for the rearrangement of monoalkyne **30** to bis-alkyne **29** were performed. It is obvious from Scheme 10 that although bis-alkyne **29** is thermodynamically less stable than monoalkyne **30** by 3.3 kcal mol^{-1}, there is substantial kinetic barrier for the interconversion between the two.

To verify the above theoretical predictions, pentacyclo-[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6,10-dione **31** was identified as the key precursor for the generation of carbene **28**. Thus **31** was synthesized from cyclopentanone in 7 steps as reported earlier (Scheme 11).[30] As in the case of bis-homocubanone **13**,

Scheme 11



diketone **31** was converted to the tetrabromide **32** in good yield using triphenylphosphine and carbon tetrabromide (Scheme 11). The structure of tetrabromide **32** was unambiguously established by single crystal X-ray analysis (Table S3, Supporting Information). However, treatment of tetrabromide **32** with *n*-BuLi (4 equiv) in the presence of excess trap (norbornene **15**) provided a complex mixture which was quite unexpected due to its symmetrical nature. Even the major fraction isolated did not provide any satisfactory evidence for the formation of the bis-vinylidenecarbene trapped product.

We have examined the apparent failure to achieve the cycloalkyne trapped products from their respective starting materials by computing the relative strains caused during the process. We have setup the isodesmic reactions to examine the strain caused in the formation of cycloalkyne **12** from **20a** or **20b** (Scheme S1, Supporting Information). The calculated results indicate that cycloalkyne **12** is 54.8 kcal/mol more strained than its corresponding carbonyl product **20a**. The formation of cycloalkyne **12** from **20b** is even more strained (58.0 kcal/mol). Further the same exercise performed for the generation of carbene **11** from the corresponding carbonyl compound **13** suggests that carbene **11** is 2.5 kcal/mol less strained than carbonyl compound **13** (Scheme S2, Supporting Information). These results show that the formation of carbene **11** is much easier compared to alkyne **12**. The formation of bromoalkene from gem-dibromide **20a** is more facile compared to the gem-dibromide **20b** (Scheme S3, Supporting Information). The isodesmic reactions constructed to calculate the strain involved in such processes suggest that the formation of bromoalkene **21a** is more facile by 1.6 kcal/mol compared to the corresponding bromoalkene **20b** qualitatively support the observed results. The apparent failure for the formation of triflate from **20b** is also revealed from isodesmic reactions. The triflate formed from **20b** is 4.4 kcal/mol more strained than **20b**, whereas, the triflate formed from **20a** is much less strained (1.30 kcal/mol).

■ CONCLUSIONS

In conclusion, the intercoversion between a vinylidenecarbene and its cycloalkyne isomer that are part of a 1,3-bishomocubyl system has been investigated by theoretical calculations and experimental studies. Our calculation results at hybrid *ab initio*/DFT levels suggested that both species would be amenable for trapping, if generated under different experimental conditions. Since the two are separated by substantial kinetic energy barrier, but at the same time, have comparable ground state energy differences, one could be trapped upon generation without any intermediacy of the other.

Subsequent experimental studies have led to successful trapping of the carbene using norbornene without any rearrangement of carbene to its cycloalkyne isomer. Attempted direct generation and trapping of the alkyne as well as a symmetrical bis-vinylidenecarbene provided unsatisfactory results. The isodesmic reactions calculated for the formation of carbenes and alkynes suggested that the latter are difficult to obtain due to the strain caused from their corresponding starting compounds though having thermodynamic stability comparable to carbenes.

■ EXPERIMENTAL SECTION

General. The melting points recorded are uncorrected. NMR spectra (^{1}H, ^{1}H decoupled ^{13}C, APT, ^{1}H−^{1}H COSY, HSQC and HMBC) were recorded with TMS as the internal standard. The coupling constants (*J* values) are given in Hz. High resolution mass spectra were recorded under DCI or ESI Q-TOF conditions. X-ray data were collected on a diffractometer equipped with graphite monochromated Mo Kα radiation. The structure was solved by direct methods shelxs97 and refined by full-matrix least-squares against F^2 using shelxl97 software.

Computational. All geometries were fully optimized with B3LYP/6-31G* level of theory.[31] The ground state and transition state geometries were characterized by vibrational frequency analysis. Single point calculations were performed with integral equation formalism polarizable continuum model (IEFPCM) employing B3LYP/6-31G* optimized geometries.[21]

6-(Dibromomethylene)pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane (14). To a stirred solution of ketone **13** (0.296 g, 2 mmol) in dry *n*-heptane (40 mL) was added CBr$_4$ (0.995 g, 3 mmol) followed by PPh$_3$ (1.57 g, 6 mmol) under N$_2$ and the resulting mixture was refluxed for 53 h. The reaction mixture was cooled to ambient temperature, the brown precipitate was filtered and the residue was washed with ether (2 × 20 mL). The resulting filtrate was concentrated *in vacuo* and the crude residue was flushed through a short pad of neutral alumina using *n*-hexane as eluent to afford pure dibromide **14** as a colorless liquid, which solidified upon storage in the refrigerator. Yield 722 mg, 80%; mp 54−55 °C; IR (film) cm^{-1} 2981 (s), 2925 (m), 2853 (m), 1663 (w), 1276 (m), 1184 (m), 785 (s), 746 (m), 658 (m); ^{1}H NMR (CDCl$_3$) δ 1.40 (d, *J* = 12.0 Hz, 1H), 1.66 (d, *J* = 12.0 Hz, 1H), 2.60−3.40 (m, 8H); ^{13}C NMR (CDCl$_3$) δ 39.4 (d), 40.1 (t), 40.6 (d), 41.5 (d), 43.4 (d), 44.4 (d), 45.6 (d), 47.6 (d), 53.5 (d), 70.9 (s), 158.2 (s); MS (DCI, CH$_4$) *m/z* (rel intensity) 303 ([(M − 1) + 4]$^+$, 5), 301 ([(M − 1) + 2]$^+$, 10), 299 ([M − 1]$^+$, 10), 238 (54), 236 (100), 234 (54), 221 (39), 142 (55), 141 (31); HRMS (DCI, CH$_4$) calcd for $C_{11}H_9Br_2{}^{79}$ 298.9071, found 298.9081.

6-(Tricyclo-[3.2.1.0^{2,4}]oct-7′-ylidene)pentacyclo-[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane (16). To a solution of dibromide **14** (1.0 g, 3.3 mmol) and norbornene (3.1 g, 33 mmol, 10 equiv) in dry THF (50 mL) under nitrogen at −78 ^{o}C was added dropwise *n*-BuLi (3.3 mL, 8.25 mmol, 2.5 M solution in hexanes) over 15 min. The stirring was continued at this temperature for another 2.5 h and then the reaction mixture was brought to 0 ^{o}C over a period of 1 h. Subsequently, the reaction mixture was quenched by dropwise addition of saturated aqueous NH$_4$Cl (20 mL). The aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were washed with water (3 × 50 mL), brine (30 mL), dried over anhyd Na$_2$SO$_4$ and concentrated *in vacuo*. The light yellow crude residue was subjected to column chromatography on silica gel using *n*-hexane as eluent to afford pure 6-(tricyclo[3.2.1.0^{2,4}]oct-7′-ylidene) pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane **16** as an inseparable mixture (∼1:1) of isomers. Colorless solid; Yield 428 mg, 55%; mp 151−154 °C; IR (CHCl$_3$) cm^{-1} 2959 (s), 2856 (m), 1454 (w), 1270 (w), 1229 (s), 762 (s); ^{1}H NMR (CDCl$_3$) δ 0.62 (d, *J* = 9.5 Hz, 1H), 0.69 (d, *J* = 9.5 Hz, 1H), 0.84 (d, *J* = 9.5 Hz, 1H), 0.99 (d, *J* = 9.5 Hz, 1H), 1.16−1.64 (m, 19H), 2.26 (dd, *J* = 8.0, 1.4 Hz, 2H), 2.33 (dd, *J* = 6.0, 1.6 Hz, 2H), 2.57−2.91 (m, 13H); ^{13}C NMR (CDCl$_3$) δ 20.65 (2 × d), 20.67 (d), 21.1 (d), 29.0 (2 × t), 29.1 (2 × t), 30.5 (t), 30.6 (t), 37.6 (2 × d), 37.7 (d), 37.8 (d), 39.7 (t), 39.8 (t), 39.9 (d), 40.1 (d), 40.6 (d), 40.7 (d), 41.7 (d), 41.8 (d), 42.5 (d), 42.6 (d), 43.4 (2 × d), 44.1 (d), 44.2 (d), 48.0 (d), 48.2 (d), 50.3 (d), 50.4 (d), 109.9 (s), 110.0 (s), 141.3 (s), 141.4 (s); MS (DCI, CH$_4$) *m/z* (rel intensity) 236 (M$^+$, 22), 207 (37), 167 (37), 142 (98), 83 (100); HRMS (DCI, CH$_4$) calcd for $C_{18}H_{20}$ 236.1565, found 236.1583.

Pentacyclo[6.3.0.0^{2,7}.0^{5,11}.0^{6,9}]undecanone (20).[25] To a solution of diazomethane (14 mmol) in ether (60 mL) was added methanol (4 mL). The resulting yellow cold solution was poured into another flask containing cage annulated ketone **13** (0.292 g, 2 mmol). The flask was kept in refrigerator for 48 h. Glacial acetic acid (∼1 mL) was added to the ethereal solution dropwise until the yellow color disappeared. The organic layer was washed with a saturated solution of sodium bicarbonate (2 × 20 mL) followed by water (3 × 10 mL), dried over anhyd Na$_2$SO$_4$ and the solvent was evaporated *in vacuo* to afford a yellow viscous oil. This was subjected to silica gel column chromatography (gradient elution in 0−5% ethylacetate/*n*-hexane as eluent) to afford pure ketone **20a−b** as an inseparable mixture in ∼1:1 ratio GC-MS analysis). Light yellow viscous oil; Yield 198 mg, 62%; IR (neat, cm^{-1}) 2963 (s), 2862 (w), 1707 (s), 1450 (w), 1397 (w), 1346 (m), 507 (w); 1.42 (d, J = 10.7 Hz, 2H), 1.65 (d, J = 10.7 Hz, 2H), 1.87−2.21 (m, 2H), 2.24−2.64 (m, 10H), 2.72−2.86 (m, 6H), 3.01−3.13 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 33.2 (d), 35.7 (d), 36.4 (d), 36.9 (t), 37.2 (t), 37.7 (d), 39.5 (t), 39.6 (d), 40.5 (t), 40.8 (d), 41.4 (d), 41.6 (d), 41.7 (d), 42.1 (d), 42.4 (d), 43.0 (d), 43.5 (d), 44.9 (d), 55.8 (d), 213.7 (s), 217.3 (s); MS (DCI, CH$_4$) m/z (rel intensity) 160 (M$^+$, 31), 117 (100), 95 (44), 66 (67).

Gem-dibromination of Ketone 20a−b. To a stirred suspension of powdered molecular sieves (4 Å, activated, 1 g) in dry methanol (5 mL) under N$_2$ was added hydrazine hydrate (0.93 g, 18.6 mmol) over a period of 20 min. To this stirred mixture was added a solution of ketone **20** (0.136 g, 0.93 mmol) in methanol (5 mL) at ambient temperature and stirring was continued for another 3 h. The reaction mixture was then filtered and the residue was washed with ether (3 × 5 mL). The combined filtrate was concentrated *in vacuo* without heating to get crude hydrazone. In another dry two-necked flask was taken copper(II) bromide (1.24 g, 5.58 mmol) to which dry methanol (5 mL) was added followed by triethylamine (0.282 g, 2.79 mmol) in dry methanol (5 mL). The reaction mixture was placed in an ice−water bath and the crude hydrazone (0.187 g, 0.93 mmol) in methanol (10 mL) was added to it very slowly over a period of 20 min. The stirring was continued at the same temperature for 4 h, after which the reaction mixture was quenched by aqueous ammonia solution (25%, 10 mL) during which the dark brown solution turned blue. The reaction mixture was extracted with ether (3 × 20 mL) and the combined organic layers were washed with brine (10 mL), dried over anhyd Na$_2$SO$_4$ and concentrated *in vacuo*. The crude residue was subjected to silica gel column chromatography using n-hexane as eluent to afford a mixture of bromoalkene **21a** and gem-dibromide **22b** in ∼1:1 ratio. Total yield 111 mg, 57%. The two components were carefully separated by preparative thin layer chromatography.

4-Bromopentacyclo[6.3.0.0^{2,7}.0^{5,11}.0^{6,9}]undec-3-ene (21a). Colorless liquid; IR (Neat, cm^{-1}) 2965 (s), 2863 (m), 1609 (w), 1439 (w), 1342 (m), 1287 (s), 1041 (m), 879 (m), 644 (m); ^{1}H NMR (CDCl$_3$) δ 1.43 (ABq, J = 10.6 Hz, 2H), 2.20−3.40 (m, 8H), 6.28 (dd, J = 6.9, 1.6 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 36.4 (d), 37.2 (d), 37.5 (d), 39.8 (d), 40.4 (d), 41.7 (d), 43.4 (d), 44.2 (d), 54.0 (d), 122.9 (s), 129.3 (d); MS (DCI, CH$_4$) m/z (rel intensity) 223 ([M − H + 2]$^+$, 30), 221 ([M − H]$^+$, 21), 157 (39), 155 (20), 143 (21), 142 (41), 141 (34), 125 (43), 113 (40), 111 (62), 109 (35), 99 (56), 97 (82), 95 (43), 91 (62); HRMS calcd for C$_{11}$H$_{10}$Br^{79} ([M − H]$^+$) 220.9965, found 220.9994.

3,3′-Dibromopentacyclo[6.3.0.0^{2,7}.0^{5,11}.0^{6,9}]undecane (22b). Colorless solid; mp 59−60 °C; IR (CHCl$_3$, cm^{-1}) 2963 (m), 1451 (m), 1266 (s), 740 (s); ^{1}H NMR (CDCl$_3$) δ 1.47 (ABqd, J = 11.0, 1.5 Hz, 2H), 2.08 (ddd, J = 12.4, 4.0, 1.8 Hz, 1H), 2.32−2.40 (m, 1H), 2.48−2.54 (m, 1H), 2.54−2.62 (m, 1H), 2.64−2.70 (m, 1H), 2.78−2.86 (m, 1H), 2.89−2.97 (m, 1H), 2.99−3.06 (m, 2H), 4.52 (dd, J = 4.0, 1.8 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 35.8 (d), 38.8 (d), 41.3 (t), 43.3 (d), 43.6 (t), 47.4 (d), 47.9 (d), 51.8 (d), 53.0 (d), 64.2 (d), 66.0 (s); MS (DCI, CH$_4$) m/z (rel intensity) 225 ([M-Br+2]$^+$, 50), 223 ([M − Br]$^+$, 42), 197 (17), 183 (13), 169 (15), 147 (14), 143 (17), 127 (26), 113 (28), 97 (43), 85 (65), 71 (85), 57 (100); HRMS calcd for C$_{11}$H$_{12}$Br^{79} ([M − Br]$^+$ 223.0122, found 223.0161.

4-(Trifluoromethanesulfonyl)pentacyclo[6.3.0.0^{2,7}.0^{5,11}.0^{6,9}]-undec-3-ene (25a). In a dry two-necked flask under nitrogen, dry DCM (10 mL) was added followed by ketone **20a−b** (160 mg, 1 mmol) dropwise at 0 °C. Triflic anhydride (338 mg, 1.2 mmol, 0.22 mL) followed by Et$_3$N (0.32 mL, 1.5 mmol) was added to it at the same temperature. After maintaining low temperature for 1 h, the reaction mixture was gradually brought to room temperature overnight. It was then quenched with saturated aqueous NH$_4$Cl (5 mL) and extracted with DCM (2 × 10 mL). The combined organic layer was washed thoroughly with brine (50 mL), dried over anhyd Na$_2$SO$_4$ and evaporated *in vacuo* to afford crude enol-triflate as a yellow liquid, which was subjected to chromatography on silica gel column using n-hexane as eluent to afford single pure triflate **25a** as a colorless liquid. Yield 129 mg, 47%; IR (Neat, cm^{-1}) 2977 (s), 2868 (m), 1655 (m), 1420 (s), 1212 (s), 1089 (m), 913 (s), 760 (s), 742 (s), 614 (s), 512 (m); ^{1}H NMR (CDCl$_3$) δ 1.38 (d, J = 10.7 Hz, 1H), 1.57 (d, J = 10.7 Hz, 1H), 2.31−2.42 (m, 2H), 2.46−2.54 (m, 2H), 2.64−2.74 (m, 1H), 2.80−2.86 (m, 1H), 3.04−3.09 (m, 1H), 3.35−3.40 (m, 1H), 5.90 (dd, J = 7.5, 2.3 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ 35.1 (d), 36.3 (t), 37.8 (d), 40.0 (d), 40.3 (d), 41.9 (d), 42.6 (d), 44.6 (d), 46.8 (d), 116.0 (d), 118.7 (q, J = 318.8 Hz), 151.4 (s); MS (ES+) m/z (rel intensity) 293 (MH$^+$, 18), 279 (88), 168 (37), 102 (100); HRMS calcd for C$_{12}$H$_{12}$O$_3$F$_3$S (MH$^+$) 293.0459, found 293.0452; Confirmed by ^{1}H−^{1}H COSY, HSQC and HMBC experiments.

Attempted trapping of cycloalkyne **12** using norbornene **15**. To a stirred solution of norbornene **15** (1.12 g, 12 mmol) and enol-triflate **25a** (350 mg, 1.2 mmol) in THF (6 mL) was added LDA, freshly generated from n-BuLi (4.5 mL, 7.2 mmol, 1.6 M solution in hexanes) and diisopropylamine (0.7 mL, 7.9 mmol) at −78 °C. The low temperature was maintained for another 3 h and the reaction mixture was brought to room temperature gradually. The resulting dark brown mixture was stirred at room temperature overnight and the reaction mixture was quenched with saturated solution of NH$_4$Cl (5 mL), and extracted with ether (3 × 10 mL). The combined organic layer was dried over anhyd Na$_2$SO$_4$ and evaporated in vacuo to afford the crude product **27** as a dark-brown liquid which was purified by passing through a small plug of silica gel using n-hexane as eluent. Colorless oil. Yield 73 mg. TLC and NMR (^{1}H and ^{13}C) analysis of this oil suggested it to be a complex mixture of isomers.

6,10-bis-(Dibromomethylene)pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]-decane (32). To a dry two-necked flask, equipped with a reflux condenser under N$_2$, was taken diketone **31** (23 mg, 0.0142 mmol) in n-heptane (15 mL). To this solution under stirring was added CBr$_4$ (0.141 g, 0.426 mmol) and Ph$_3$P (0.223 g, 0.852 mmol). The resulting mixture was refluxed for 15 h, cooled to room temperature and filtered. The residue was washed with ether (3 × 10 mL) and the combined filtrate was evaporated to get a solid which was flushed through a short pad of neutral alumina using n-hexane to afford a colorless solid of **32**. Yield 50 mg, 75%; mp 218−220 °C; IR (CH$_2$Cl$_2$, cm^{-1}) 3011 (w), 2977 (w), 1666 (w), 1258 (m), 1099 (m), 1029 (m), 760 (s), 670 (w); ^{1}H NMR (CDCl$_3$) δ 2.95−3.05 (m, 2H), 3.25−3.35 (m, 2H), 3.35−3.40 (m, 4H); ^{13}C NMR (CDCl$_3$) δ 156.6 (s), 73.5 (s), 52.2 (d), 45.2 (d), 44.3 (d), 39.8 (d); MS (DCI, CH$_4$) m/z (rel intensity) 476 ([M + 8]$^+$, 2), 474 ([M + 6]$^+$, 8), 472 ([M + 4]$^+$, 12), 470 ([M + 2]$^+$, 8), 468 (M$^+$, 2), 397 (5), 395 (15), 393 (15), 391 (5), 314 (7), 312 (15), 310 (7); 238 (50), 236 (100), 234 (50); HRMS calcd for C$_{12}$H$_8$Br$_2$^{79}Br$_2$^{81} 471.7319, found 471.7301; Selected crystallographic parameters for **32**: C$_{12}$H$_8$Br$_4$, M = 471.82, monoclinic, space group C 2/c, a = 15.8820(16) Å, b = 9.5654(7) Å, c = 11.5424 (12) Å, β = 1132.725(10)°,V = 1288.1(2) Å^3, D_c = 2.433 Mg/m^3, Z = 4, F(000) = 880, λ = 0.70930 Å, μ = 12.465 mm^{-1}, Total unique reflections =1169/1127 [R(int) = 0.0713], T = 293(2) K, θ range =2.75 to 24.97 °, Final R indices [$I > 2\sigma(I)$]: R1 = 0.0775, wR2 = 0.1861, R(all data): R1 = 0.1077, wR2 = 0.2030.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR correlation tables, X-ray data table, DFT B3LYP/6-31G* calculated coordinates of products and transition states and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. A. P. Marchand in honor of his pioneering contributions to cage chemistry.

■ REFERENCES

(1) (a) Fritsch, P. *Liebigs Ann. Chem.* **1894**, *272*, 319–324. (b) Buttenberg, W. P. *Liebigs Ann. Chem.* **1894**, *272*, 324–327. (c) Wiechell, H. *Liebigs Ann. Chem.* **1894**, *272*, 337–344.

(2) Selected reviews: (a) Knorr, R. *Chem. Rev.* **2004**, *104*, 3795–3849. (b) Feldman, K. S. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Elsevier: London, 2004; Vol. *4*, pp 133–170. (c) Eymery, F.; Iorga, B.; Savignac, P. *Synthesis* **2000**, 185–213. (d) Braun, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 430–451. (e) Kirmse, W. *Angew. Chem., Int. Ed.* **1997**, *36*, 1164–1170. (f) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383–405. (g) Hartzler, H. D. In *Carbenes*; Moss, R. A., Jones, M., Jr., Eds.; Wiley and Sons: New York, 1983; Vol. *2*, pp 43–100.

(3) Selected reviews: (a) Gleiter, R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 27–44. (b) Bennett, M. A.; Schwemlein, H. P. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1296–1320. (c) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081–1119. (d) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539–556. (e) Ye, F.; Orita, A.; Doumoto, A.; Otera, J. *Tetrahedron* **2003**, *59*, 5635–5643. For a recent article: (f) Ye, F.; Orita, A.; Doumoto, A.; Otera, J. *Tetrahedron* **2003**, *59*, 5635–5643.

(4) Selected recent articles: (a) Tsuboya, N.; Hamasaki, R.; Ito, M.; Mitsuishi, M.; Miyashita, T.; Yamamoto, Y. *J. Mater. Chem.* **2003**, *13*, 511–513. (b) Feldman, K. S.; Perkins, A. L.; Masters, K. M. *J. Org. Chem.* **2004**, *69*, 7928–7932. (c) Sahu, B.; Namboothiri, I. N. N.; Persky, R. *Tetrahedron Lett.* **2005**, *46*, 2593–2597. (d) Luu, T.; Morisaki, Y.; Cunningham, N.; Tykwinski, R. R. *J. Org. Chem.* **2007**, *72*, 9622–9629. (e) Rezaei, H.; Yamanoi, S.; Chemla, F.; Normant, J. F. *Org. Lett.* **2000**, *2*, 419–421. (f) Gibtner, T.; Hampel, F.; Gisselbrecht, J.-P.; Hirsch, A. *Chem.—Eur. J.* **2002**, *8*, 408–432. (g) Shun, A. L. K. S.; Tykwinski, R. R. *J. Org. Chem.* **2003**, *68*, 6810–6813. (h) Tobe, Y.; Iwasa, N.; Umeda, R.; Sonoda, M. *Tetrahedron Lett.* **2001**, *42*, 5485–5488. (i) Eisler, S.; Chahal, N.; McDonald, R.; Tykwinski, R. R. *Chem.—Eur. J.* **2003**, *9*, 2542–2550. (j) Shun, A. L. K. S.; Chernick, E. T.; Eisler, S.; Tykwinski, R. R. *J. Org. Chem.* **2003**, *68*, 1339–1347. (k) Yanagisawa, H.; Miura, K.; Kitamura, M.; Narasaka, K.; Kaori, A. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2009–2026. (l) Kaafarani, B. R.; Wex, B.; Wang, F.; Catanescu, O.; Chien, L. C.; Neckers, D. C. *J. Org. Chem.* **2003**, *68*, 5377–5380. (m) Gais, H.-J.; Reddy, L. R.; Babu, G. S.; Raabe, G. *J. Am. Chem. Soc.* **2004**, *126*, 4859–4864.

(5) (a) Brown, R. F. C. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 655–666. and the references cited therein. (b) Mabry, J.; Johnson, R. P. *J. Am. Chem. Soc.* **2002**, *124*, 6497–6501.

(6) (a) Fitjer, L.; Modaressi, S. *Tetrahedron Lett.* **1983**, *24*, 5495–5498. (b) Gilbert, J. C.; Baze, M. E. *J. Am. Chem. Soc.* **1984**, *106*, 1885–1886. (c) Harada, T.; Iwazaki, K.; Otani, T.; Oku, A. *J. Org. Chem.* **1998**, *63*, 9007–9112. (d) Baxter, G. J.; Brown, R. F. *Aust. J. Chem.* **1978**, *31*, 327–339.

(7) Laird, D. W.; Gilbert, J. C. *J. Am. Chem. Soc.* **2001**, *123*, 6704–6705.

(8) Xu, L.; Lin, G.; Tao, F.; Brinker, U. H. *Acta Chem. Scand.* **1992**, *46*, 650–653.

(9) Baumgart, K.-D.; Szeimies, G. *Tetrahedron Lett.* **1984**, *25*, 737–740.

(10) Erickson, K. L.; Wolinsky, J. *J. Am. Chem. Soc.* **1965**, *87*, 1142–1143.

(11) Tseng, J.; McKee, M. L.; Shevlin, P. B. *J. Am. Chem. Soc.* **1987**, *109*, 5474–5477.

(12) Johnson, R. P.; Daoust, K. J. *J. Am. Chem. Soc.* **1995**, *117*, 362–367.

(13) (a) Gilbert, J. C.; Kirschner, S. *Tetrahedron* **1996**, *52*, 2279–2290. (b) Bachrach, S. M.; Gilbert, J. C.; Laird, D. W. *J. Am. Chem. Soc.* **2001**, *123*, 6706–6707. (c) Hayes, R. L.; Fattal, E.; Govind, N.; Carter, E. A. *J. Am. Chem. Soc.* **2001**, *123*, 641–657.

(14) (a) Kawase, T.; Darabi, H. R.; Uchimiya, R.; Oda, M. *Chem. Lett.* **1995**, 499–500. (b) Kataoka, M.; Ando, T. M.; Nakagawa, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 177–184.

(15) Selected reviews: (a) Hopf, H.; Grunenberg, J. *Strained Hydrocarbons* **2009**, 375–397. (b) Krebs, A.; Wilke, J. *Top. Curr. Chem.* **1983**, *109*, 189–233.

(16) Marchand, A. P.; Kumar, K. A.; Rajagopal, D.; Eckrich, R.; Bott, S. G. *Tetrahedron Lett.* **1996**, *37*, 467–470.

(17) Marchand, A. P.; Alihodzic, S.; Bott, S. G.; Watson, W. H.; Bodige, S. G.; Gilardi, R. *Tetrahedron* **1998**, *54*, 13427–13434.

(18) Marchand, A. P.; Namboothiri, I. N. N.; Ganguly, B.; Bott, S. G. *J. Am. Chem. Soc.* **1998**, *120*, 6871–6876.

(19) (a) Spartan'06 Wavefunction, Inc.: Irvine, CA. (b) Frisch, M. J. et al. *Gaussian 03*, Revision E.01; Gaussian, Inc.: Wallingford, CT, 2004.

(20) (a) Shustov, G. V.; Liu, M. T. H.; Rauk, A. *J. Phys. Chem. A* **1997**, *101*, 2509–2513. (b) Zhu, Z.; Bally, T.; Stracener, L. L.; McMahon, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 2863–2874. (c) Pliego, J. R.; De Almeida, W. B., Jr.; Celebi, S.; Zhu, Z.; Platz, M. S. *J. Phys. Chem. A* **1999**, *103*, 7481–7486.

(21) (a) Canćes, M. T.; Mennucci, B.; Tomasi, J. *Chem. Phys. Lett.* **1997**, *107*, 3032. (b) Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *106*, 5151.

(22) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769–3772.

(23) Cookson, R. C.; Hudec, J.; Williams, R. O. *J. Chem. Soc. (C)* **1967**, 1382–1385.

(24) (a) Dilling, W. L. *Chem. Rev.* **1966**, 373–393. (b) Mehta, G.; Pandey, P. N.; Ho, T.-L. *J. Org. Chem.* **1976**, *41*, 953–956. (c) Ogino, T.; Awano, K. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2811–2818.

(25) Hirao, K.; Abe, E.; Yonemitzu, O. *Tetrahedron Lett.* **1975**, *47*, 4131–4134.

(26) For procedure: Takeda, T.; Sasaki, R.; Yamauchi, S.; Fujiwara, T. *Tetrahedron* **1997**, *53*, 557–566.

(27) Gilbert, J. C.; McKinley, E. G.; Hou, D.-R. *Tetrahedron* **1997**, *53*, 9891–9902 and the references therein. See also refs 6–13.

(28) Singh, V. *Indian J. Chem.* **1996**, *35B*, 303–311.

(29) Klaic, L.; Aleskovic, M.; Veljkovic, J.; Mlinaric-Majerski, K. *J. Phy. Org. Chem.* **2008**, *21*, 299.

(30) (a) Chapman, N. B.; Key, J. M.; Toyne, K. J. *J. Org. Chem.* **1970**, *35*, 3860–3868. (b) Paquette, L. A.; James, D. R.; Klein, G. *J. Org. Chem.* **1978**, *43*, 1287–1292. (c) Bird, C. W.; Coffee, E. C. J.; Schmidt, B. W. C. *Synth. Commun.* **1993**, *23*, 613–620.

(31) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.