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Generation and Interception of Bicyclo[3.2.1]oct-2-yne: An Experimental and Theoretical Mechanistic Study

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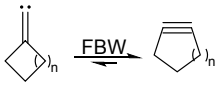
T. E. Anderson,[a] Beauty K. Chabuka,[b] Igor V. Alabugin,*[b] Dasan M. Thamattoor,*[a] and David Lee Phillips*[c]

Bicyclo[3.2.1]oct-2-yne was generated from the Fritsch–Buttenberg–Wiechell rearrangement of 2-norbornylidene carbene. The rearrangement preferentially involves migration of a tertiary carbon over a secondary carbon, a trend that contrasts with rearrangements of acyclic carbenes and which may be attributable to hyperconjugative effects promoted by the bridged structure of the carbene.

Exocyclic alkylidene carbenes **1** provide appealing precursors to strained cycloalkynes **2** due to their tendency to undergo 1,2-migratory shifts known as Fritsch–Buttenberg–Wiechell (FBW) rearrangements (Scheme 1).[1] A number of cyclopentyne,[2-3] cylcohexyne,[4-6] and polycyclic alkyne[7-9] derivatives have been generated through FBW rearrangements of alkylidene carbenes. Strained carbocyclic and heterocyclic alkynes are of growing interest in organic synthesis due to their potential for providing access to complex molecular scaffolds.[10]

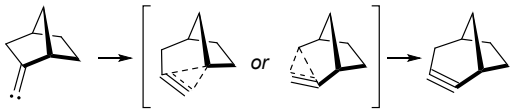


1 2

Scheme 1. Fritsch–Buttenberg–Wiechell (FBW) rearrangement of exocyclic alkylidene carbenes **1** cycloalkynes **2**

Generation of cyclic alkynes via FBW rearrangements have primarily involved deprotonation of bromoethylene-cycloalkanes[7-9] or the lithiation of dibromomethylene-cycloalkanes.[11-15] These preparations require harsh reaction conditions that include high temperatures in the case of deprotonation, and low temperatures in the case of lithiation, that can influence the pathways of reactivity. There is moreover some ambiguity as to whether these reactions involve real carbenes, or metal-coordinated carbenoid intermediates.[7,16-17] These uncertainties make such approaches unsuitable for mechanistic investigations into FBW rearrangements.

Our laboratory has developed a photochemical approach to the generation of alkylidene carbenes that proceeds under mild conditions and ambient temperatures.[5-6,18-20] Herein, we demonstrate the utility of this method for the generation of bicyclo[3.2.1]oct-2-yne (**4**) via the FBW rearrangement of 2-norbornylidene carbene (**3**, Scheme 2). To our knowledge, the two previously reported preparations of **4** have involved the use of halogenated precursors, high temperatures, and strongly basic conditions.[21-22] Furthermore, FBW rearrangement in **3** can proceed by two possible pathways, involving migration of the tertiary γ-carbon (via **TSa**) or the secondary γ-carbon (via **TSb**), both of which yield the same product **4**. Thus, these two pathways cannot be distinguished under ordinary conditions. In this work, we demonstrate the use ^{13}C-labelling experiments which permitted elucidation of the rearrangement mechanism, and revealed a preference for migration of the tertiary rather than secondary carbon.



3 (photochemically generated) TSa TSb 4

Scheme 2 Photochemical generation of bicyclo[3.2.1]oct-2-yne (**4**) via the FBW rearrangement of 2-norbornylidene carbene (**3**)

Precursor **7** was synthesized, as shown in Scheme 3A, with the aim of photolytically generating 2-norbonylidene carbene (**3**), which would provide access to bicyclo[3.2.1]oct-2-yne (**4**) via FBW rearrangement. The presence of the methylene bridge in bicyclo[3.2.1]oct-2-yne (**4**) is predicted to inflict 23.8 kcal/mol

[a] *Department of Chemistry, Colby College, Waterville, Maine 04901, USA*
[b] *Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306, United States*
[c] *Department of Chemistry, The University of Hong Kong, Pok Fu Lam 999077, Hong Kong, S.A.R., P. R. China*
† Footnotes relating to the title and/or authors should appear here.
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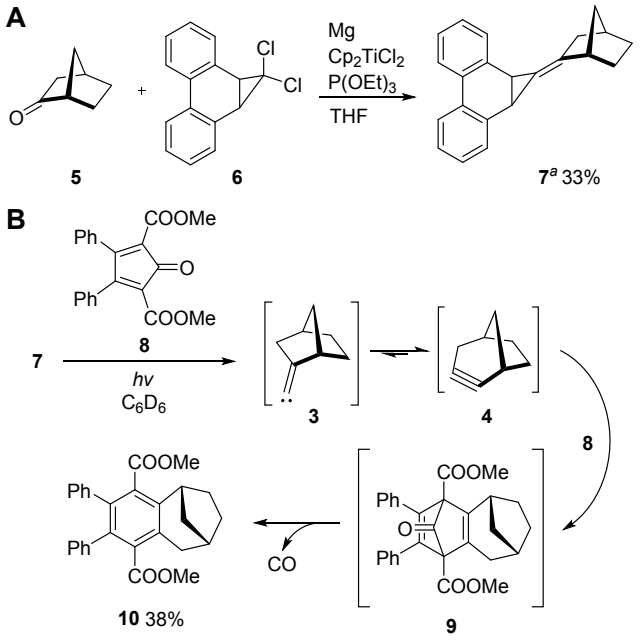
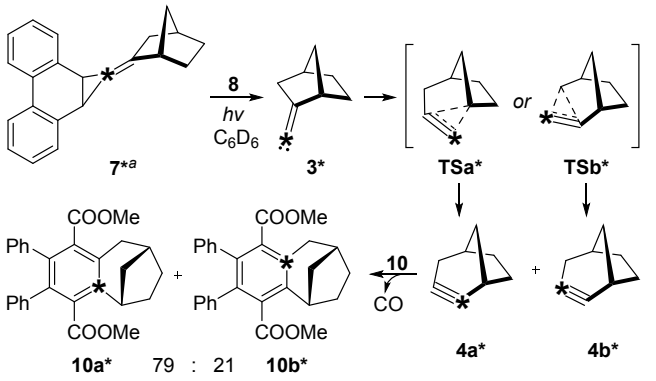
of strain energy relative to monocyclic cyclooctyne (Figure S1). The known dichlorocyclopropyl phenanthrene derivative **6** was first prepared by the cyclopropanation of phenanthrene with chloroform under basic conditions.[23] Precursor **7** was then synthesized from norcamphor (**5**) and **6** by adapting a procedure previously reported by Takeda *et* al.[24] Photolysis of **7** in the presence of diene **8** resulted in the formation of adduct **10**, likely via decarbonylation of the initially formed Diels–Alder product **9**,[4-6] implicating the intermediacy of bicyclo[3.2.1]oct-2-yne (**4**, Scheme 3B).



[a]Mixture of *endo* and *exo* diastereomers (See Supporting Information)

Scheme 3. (**A**) Synthesis of precursor **7**. (**B**) Trapping of bicyclo[3.2.1]oct-2-yne (**4**), generated by photolysis of **7** and FBW rearrangement of 2-norbonylidene carbene (**3**)

The pathway of FBW rearrangement in norbornylidene carbene **3** was investigated with the use of the ^{13}C-labelled precursor **7*** (Scheme 4). Precursor **7*** was prepared similarly to its non-enriched analogue **7**, but with a ^{13}C-labelled dichlorocyclopropyl phenanthrene derivative **6*** synthesized from 25% ^{13}C-enriched chloroform (See Synthetic Procedures in Supporting Information). Photolytic generation of the ^{13}C-labelled alkylidene carbene **3*** in the presence of diene **8** yielded isotopomers **10a*** and **10b*** in a ratio of 79:21,[25] revealing a preference for migration of the tertiary γ-carbon (via **TSa**). The ratio of isotopomer products indicates a 0.72 kcal/mol difference in free energy between the transition state barriers of the two rearrangement pathways ($\Delta G^{\ddagger}_{TSb} - \Delta G^{\ddagger}_{TSa}$).[26] The preference for migration of the tertiary carbon over the secondary carbon is the opposite of that previously reported for acyclic alkylidene carbenes,[27-29] indicating that the geometric constraints imposed by the bicyclic structure of **3** likely play a significant role in influencing the pathway of FBW rearrangement.



[a]Mixture of *endo* and *exo* diastereomers (See Supporting Information)

Scheme 4. FBW rearrangement of ^{13}C-labelled 2-norbonylidene carbene (**3***). An asterisk (*) denotes a ^{13}C-enriched carbon

Calculations performed at the CCSD(T)/def2-TZVPP//M06-2X/def2-TZVP[30-33] level of theory are in close agreement with the experimental data.[34] Bicyclo[3.2.1]oct-2-yne (**4**) is predicted to be more thermodynamically stable than the corresponding alkylidene carbene **3** by 10.57 kcal/mol (Figure 1). FBW rearrangement involving the migration of the tertiary carbon is likewise favored, with a transition state **TSa** that is predicted to be 0.72 kcal/mol lower in energy than that of the competing migratory pathway, **TSb**, in which a secondary carbon undergoes migration.

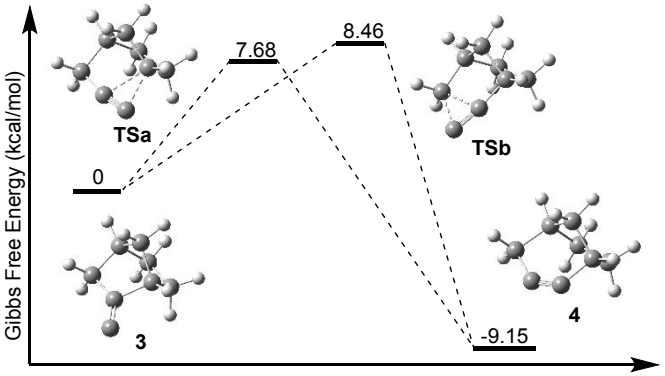
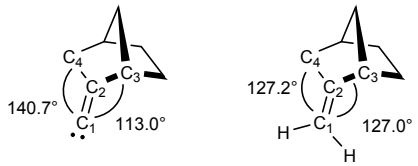


Figure 1. Potential energy surface for the FBW rearrangement of 2-norbonylidene carbene (**3**) to bicyclo[3.2.1]oct-2-yne (**4**), computed at CCSD(T)/CPCM$_{(benzene)}$/def2-TZVPP//M06-2X/CPCM$_{(benzene)}$def2-TZVP

Preference for the migratory pathway involving **TSa** appears to result from the geometric constraints within the cyclic structure of 2-norbonylidene carbene (**3**). The endocyclic sp^2 carbon within carbene **3** exhibits bond angles that are distorted compared to those of the analogous alkene **11** (Figure 2), with a C_1–C_2–C_3 bond angle, which includes the migrating bond of the major pathway, contracted by almost 13° and a C_1–C_2–C_4 bond angle, which includes the migrating bond in the minor rearrangement pathway, enlarged by 12°. This distortion results in a structure that more closely resembles the major transition state **TSa**, situating the tertiary carbon C_3 closer to the migratory terminus at carbon C_1, while distancing C_4 from C_1.



3 11

Figure 2. Distortion of the alkylidenecarbene bond angle in 2-norbonylidene carbene (**3**) compared to the alkene bond angle in 2-methylenebicyclo[2.2.1]heptane (**11**)

The bond angle distortion around the endocyclic sp^2 carbon in carbene **3** likely arises from hyperconjugative interactions involving the divalent exocyclic sp carbon. Similar distortions in alkylidene carbenes with aryl substituents are believed to arise from donation of electron density into the empty p orbital at the divalent carbon site (π → p and σ → p).[35] NBO calculations for 2-norbonylidene carbene (**3**), show a strong stabilizing hyperconjugative interaction (24.7 kcal/mol) between the C_2–C_3 bond and the vacant p orbital on the alkylidene carbene center C_1 (σ_{C-C} → p, Figure 3A). By contrast, the stabilizing interaction between the C_2–C_4 bond and empty p orbital is much weaker (4.4 kcal/mol). The contribution of homohyperconjugation involving the C_3–hydrogen bond and the p orbital on C_1 (σ_{C-H} → p, Figure 3B),[36] analogous to agostic interactions in organometallic Schrock carbenoids,[37] is weak (< 0.5 kcal/mol) in the carbene but become significant in TSa (16.8 kcal/mol) and the product alkyne (6.5 kcal/mol) (see Supporting Information). This interaction is stronger with the C_3–hydrogen bond of the bridgehead carbon, which is constricted to be roughly in plane with the vinylidene group ($\theta C_1C_2C_3H_3$, 17°, Figure 3C), compared to the C_4–hydrogen bonds ($\theta C_1C_2C_4H_1$, 58° and $\theta C_1C_2C_4H_2$, 62°, Figure 3C). The favorable interaction may explain why the vinylidene group is distorted towards the tertiary carbon C_3 rather than the secondary carbon C_4, and why the migratory trend differs from that observed in acyclic alkylidene carbenes.[27-29]

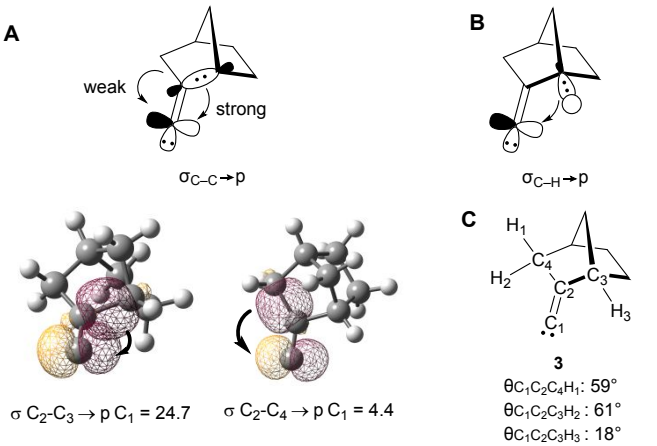


Figure 3. Possible (**A**) hyperconjugative and (**B**) homohyperconjugative interactions in 2-norbornyl-idene carbene (**3**). (**C**) The ground-state geometry of **3**, calculated at CCSD(T)/def2-TZVPP//M06-2X/def2-TZVP

In summary, we have provided a new and mild route to bicyclo[3.2.1]oct-2-yne (**4**) through the FBW rearrangement of photochemically generated 2-norbornylidene carbene (**3**). Previous efforts to access this strained polycyclic alkyne have required halogenated precursors in conjunction with high-temperatures and high basicity,[21-22] conditions which can complicate mechanistic interpretation of reactivity,[7,16-17,21-22] and which limit the range of reagents that can be used to trap the unstable, transient alkyne. The approach employed herein unambiguously generates the free alkylidenecarbene **3**, allowing for elucidation of the specific pathways of FBW rearrangement with the use of the ^{13}C-labelled precursor **7***. The experimental and computational data both indicate that migration of the tertiary γ-carbon is favored over that of the secondary γ-carbon, with a difference in transition state energies for the two rearrangement pathways of 0.72 kcal/mol. This preference for migration of the tertiary carbon contrasts with previously reported trends in acyclic alkylidene carbenes,[27-29] potentially due to specific hyperconjugative and homohyperconjugative interactions that become favorable within the rigid caged structure of 2-norbornylidene carbene (**3**). The bridgehead carbon–hydrogen bond proximal to the vinylidene group is constrained in an orientation that is nearly in-plane with the vinylidene group, allowing for donation of electron density into the empty p orbital of the carbene (σ_{C-H} → p). The consistency between the experimental and computational data suggests that the photochemical approach to alkylidenecarbene generation used herein is a reliable method for mechanistic investigations of FBW rearrangements.

Author contributions

The manuscript was written through the contributions of all authors, who have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare

Data availability

Data for this article, including experimental procedures, NMR data, and computational details have been included as part of the Supplementary Information

Acknowledgements

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Data Availability Statement
The data underlying this study are available in the published article and its Supporting Information.

Supporting Information Statement
Experimental procedures, spectral data, and Cartesian coordinates of the relevant optimized structures.