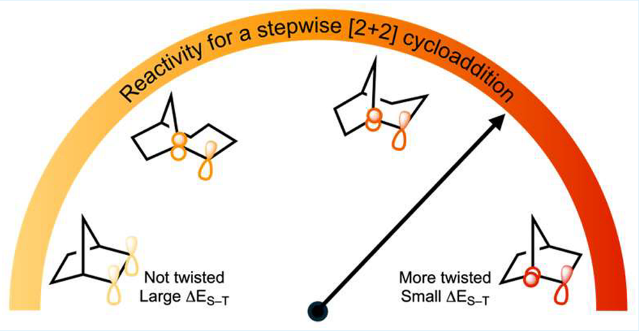
OL Organic Letters

Can Twisted Double Bonds Facilitate Stepwise [2 + 2] Cycloadditions?

Renan V. Viesser, Clayton P. Donald, Jeremy A. May, and Judy I. Wu*

Cite This: https://doi.org/10.1021/acs.orglett.4c00879

ABSTRACT: Computational studies for a series of low to high strain anti-Bredt alkenes suggest that those with highly twisted bridgehead double bonds and a small singlet−triplet energy gap may undergo facile stepwise [2 + 2] cycloadditions to furnish four membered rings. A selection of reaction substrates, including ethylene, acetylene, perfluoroethylene, and cyclooctyne are considered.



[2 + 2] cycloadditions are the most efficient way to make four membered rings—two π-bonds break and two σ-bonds form. Under thermal conditions, concerted [2 + 2] cycloadditions are symmetry forbidden.[1] But stepwise [2 + 2] cycloadditions can be achieved by stabilizing the formation of a diradical,[2,3] a zwitterionic[4,5] intermediate, or by metal complexation.[6,7] Ketenes and allenes have an additional orthogonal π-bond[8−10] and can form four membered rings via a diradical mechanism. Stepwise [2 + 2] cycloadditions involving halogenated alkenes,[11] polarized double bonds,[12,13] and allyl carbocations[14] also are known. Recently, Houk et al. reported an example of an enzyme catalyzed thermal [2 + 2] cycloaddition reaction.[15] In this computational study, we explore whether twisting a double bond[16,17]—such as those in an anti-Bredt alkene—might facilitate stepwise [2 + 2] cycloaddition reactions.

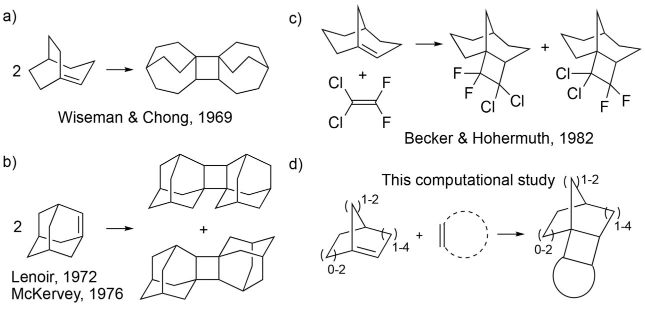


Figure 1. Known examples of stepwise [2 + 2] cycloadditions involving anti-Bredt alkenes.

Anti-Bredt alkenes are bicyclic compounds with a double bond at the bridgehead position, and some examples of stepwise [2 + 2] cycloaddition reactions with anti-Bredt alkenes are known (Figure 1). A trapped bicyclo[3.2.2]non-1-ene dimer, formed by facile stepwise [2 + 2] cycloaddition of the bridgehead double bonds, was first reported by Wiseman et al.[18] Dimers of adamantene form readily upon dehalogenation of 1,2-diiododamantane.[19,20] By comparing the reaction of 2-norbornene (**16**) to that of bicyclo[4.2.1]non-1-ene (**12**) and bicyclo[3.3.1]non-1-ene (**14**), Becker and Hohermuth showed that the strained double bonds of **12** and **14** yielded faster stepwise [2 + 2] cycloadditions with 1,1-dichloro-2,2-difluoroethene and at milder conditions.[21] **12** and **14** also gave facile concerted [2 + 2] cycloaddition reactions with a ketene.[22] The twisted double bonds of *trans*-cycloalkenes (n = 7−10, n is the number of ring atoms) exhibit higher reactivity compared to their unstrained *cis*-analogues.[21] In these examples, the reactivity of the twisted double bond mimics that of a twisted alkene (cf. the D_{2d} geometry of the lowest singlet and triplet excited state of ethylene).[23] Note that a concerted photochemical [2 + 2] cycloaddition only occurs if the reacting double bonds do not twist upon photoexcitation (e.g., in the photodimerization of thymine).[24]

We hypothesized that anti-Bredt alkenes with more twisted bridgehead double bonds might give lower reaction barriers to a stepwise [2 + 2] cycloaddition. Here, we investigated the reaction profiles for stepwise [2 + 2] cycloaddition reactions

Received: March 9, 2024
Revised: April 24, 2024
Accepted: April 26, 2024

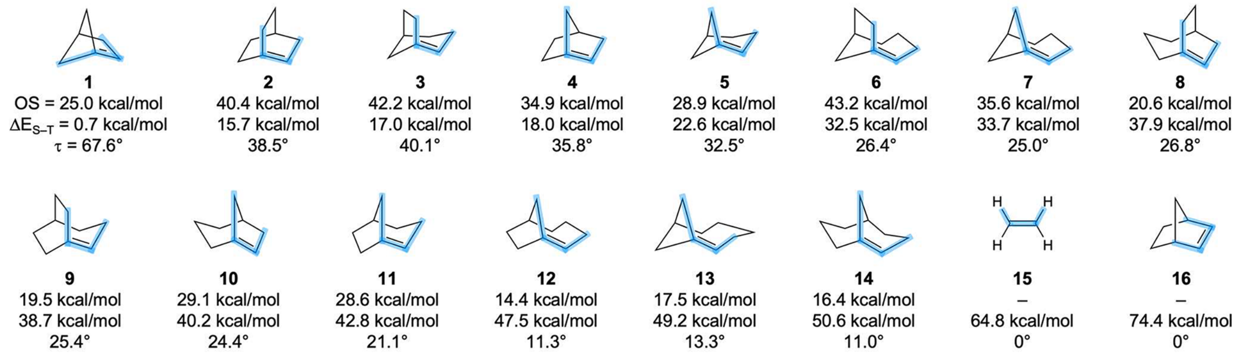


Figure 2. Anti-Bredt alkenes studied (**1**−**14**), ethylene (**15**), and 2-norbornene (**16**). Olefin strain (OS) values are taken from ref 26. Singlet−triplet energy gaps (ΔE_{S-T}) and the averaged values of the torsional angle across the bridgehead double bond were computed at (U)ωB97X-D/6-311+G(d,p). Averaged torsional angles (τ) were taken between the CCCC angle highlighted in blue and the CCCH dihedral indicated in Figure S1.

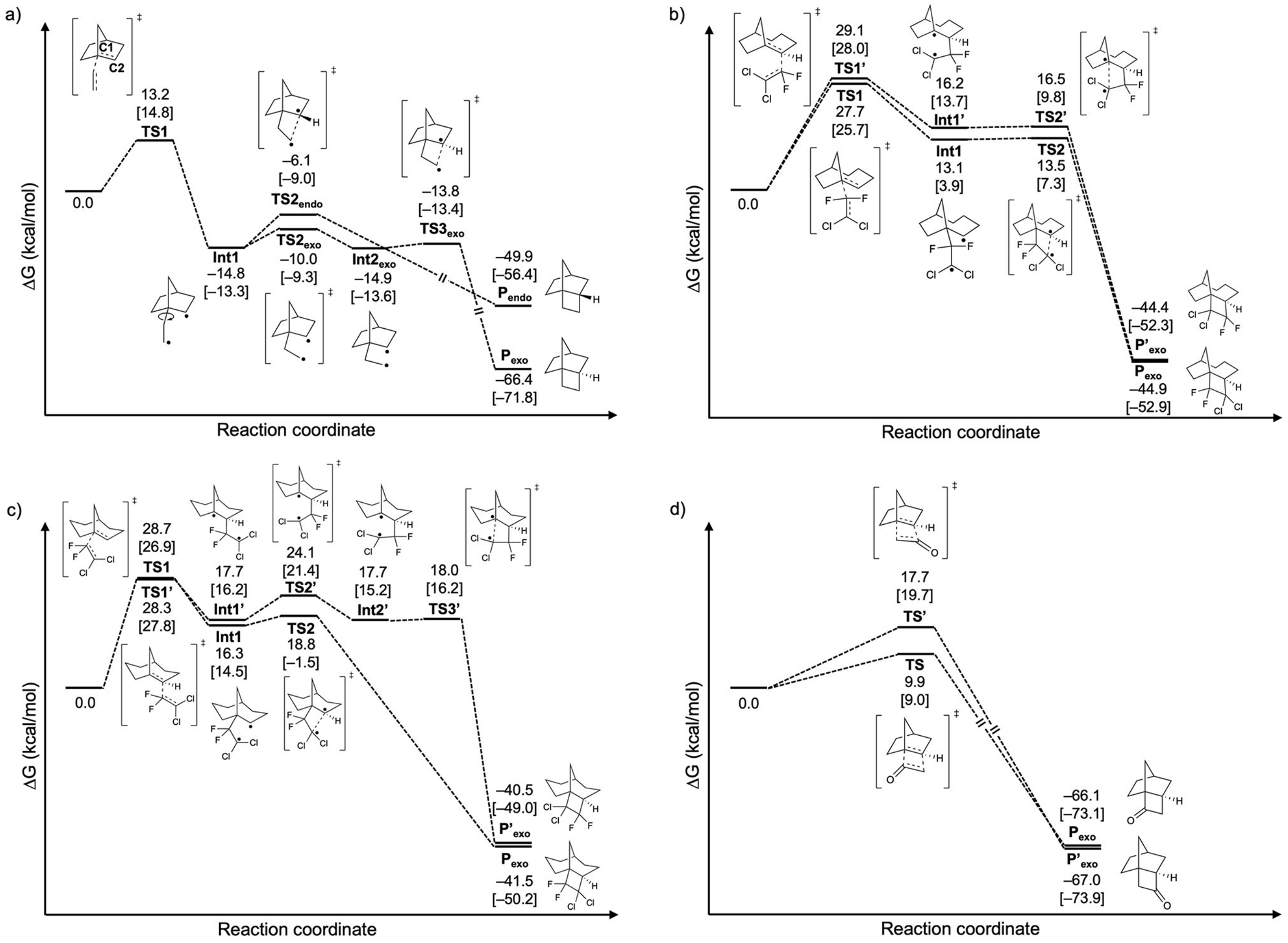


Figure 3. Computed reaction profiles for the [2 + 2] cycloadditions of (a) **4** and ethylene, (b) **12** and 1,1-dichloro-2,2-difluoroethylene (in **TS1**, a σ-bond first forms at C1; in **TS1′**, a σ-bond first forms at C2), (c) **14** and 1,1-dichloro-2,2-difluoroethylene, and (d) **4** and ethenone at (U)ωB97X-D/6-311+G(d,p). Single-point energies at (U)CCSD(T)/6-311+G(d,p) are shown in brackets. Note that in (c), single-point (U)CCSD(T) results indicate a barrierless radical recombination upon forming **Int1**.

for a series of anti-Bredt alkenes (**1**−**14**) with low to high olefin strain (OS) (Figure 2). Ethylene (**15**) and 2-norbornene (**16**) are included for comparison. OS values, evaluated via empirical force-field calculations by comparing the strain energy of an alkene to that of the corresponding alkane, were first proposed by Schleyer and Maier as an index to predict the stabilities of bridgehead alkenes.[25,26] Based on the proposed Schleyer−Maier OS index, OS values equal or lower than 17 kcal/mol are defined as “isolable”, those with 17 < OS < 21 are called “observable”, and those with OS values above 21 kcal/mol are deemed “unstable.” Based on previously reported OS values,[25,26] compounds **12**−**14** fall into the “isolable” category and compounds **1−11** are classified as "observable" or "unstable." Indeed, both **12**[27] and **14**[28,29] have been isolated, while **4** and **8** have been observed only through trapping experiments.[18,30] Note, in Figure 2, that the computed singlet−triplet energy gaps (ΔE_{S-T}) for compounds **1−16** correlate inversely (R^2 = 0.923) the torsional angles across the bridgehead double bond (τ).

We first investigated the reaction between **4** and ethylene to test whether a twisted double bond might yield a feasibly low activation barrier for a stepwise [2 + 2] cycloaddition. Compound **4** has only been observed by trapping experiments[30] due to a largely twisted bridgehead double bond (OS = 34.9 kcal/mol, τ = 35.8°) and therefore is a good candidate to test our hypothesis. A reaction profile for the stepwise [2 + 2] cycloaddition of **4** and ethylene is shown in Figure 3a. All structures were optimized in the gas phase, at the (U)ωB97X-D[31]/6-311+G(d,p)[32,33] level, and a broken symmetry approach[34] applying the (guess = mix) keyword was used for the diradical species. $\langle S^2 \rangle$ values for all compounds shown in Figure 2 are included to Table S1. Prior benchmarking studies of Ess and Cook showed that ωB97X-D provided reasonably accurate singlet−triplet energy gaps for open-shell singlet diradicals.[35] Single-point energies calculated at (U)CCSD-(T)[36]/6-311+G(d,p) for all stationary points for the reaction profiles shown in Figure 3 are in good agreement with DFT values.

In the first step, ethylene adds to C1 (bridgehead carbon) of **4** and forms a σ-bond, leading to a 1,4-diradical intermediate (**Int1**) (Figure 3a). The computed activation free energy barrier for this step only is $\Delta G^\ddagger$ = 13.2 kcal/mol and contrasts with that of **16** (an isomer of **4**) with ethylene ($\Delta G^\ddagger$ = 43.6 kcal/mol). Although a σ-bond also can form first at C2 and then at C1, generating a radical at C2 is preferred over C1 due to the local planar geometry at C2. Thus, the computed barrier for first forming a σ-bond at C2 is higher ($\Delta G^\ddagger$ = 17.7 kcal/mol) (see details in the Supporting Information).

In the second step, a second σ-bond forms at C2. From **Int1**, the ethylene fragment can either approach from the *endo* face and form $\mathbf{P_{endo}}$, or attack from the *exo* face ($\Delta G^\ddagger$ = 4.8 kcal/mol) and upon rotation of the first σ-bond to align the interacting orbitals, form $\mathbf{P_{exo}}$ (Figure 3a). In this reaction, the *exo* product is both kinetically and thermodynamically favored. Intrinsic reaction coordinate (IRC) calculations of **TS3** lead directly to $\mathbf{P_{exo}}$ suggesting a barrierless radical combination step. Given the very low rotational and radical combination barriers, the diradical intermediates reside on a relatively flat energy surface and are susceptible to nonstatistical dynamic effects.[37−41]

We further examined the reactions of **12** and **14** with 1,1-dichloro-2,2-difluoroethene, previously reported by Becker and Hohermuth[21] (Figure 3b,c). As expected by an increased p character at the F-substituted carbon of 1,1-dichloro-2,2-difluoroethene, a σ-bond first forms between the CF_2 fragment and either C1 (via **TS1**) or C2 (via **TS1′**) of the bicyclic compound. Computed barriers for the reaction with **12** (C1:27.7 kcal/mol, C2:29.1 kcal/mol) and with **14** (C1:28.7 kcal/mol, C2:28.3 kcal/mol) are consistent with reported experimental conditions (i.e., the need for heating at 80 °C). From **Int1** and **Int1′**, forming the second σ-bond is near barrierless for both **12** and **14**. IRC calculations for the radical recombination step (i.e., **TS2** and **TS2′** for **12** and **TS2** and **TS3′** for **14**) suggests a post-transition state bifurcation,[42] leading to either a high-energy zwitterionic structure or the observed $\mathbf{P_{exo}}$ and $\mathbf{P'_{exo}}$ products.

Notably, a twisted double bond can also facilitate a concerted [2 + 2] cycloaddition reaction. The reaction between **4** and ethenone, forming adducts $\mathbf{P'_{exo}}$ and $\mathbf{P_{exo}}$, proceeds through a low barrier (<20 kcal/mol, Figure 3d), and contrasts with that of **16** and ethenone ($\Delta G^\ddagger$ = 37.4 kcal/mol) (see details in the Supporting Information).

Since formation of the first σ C−C bond is the rate-determining step, we proceeded with computing and comparing the gas-phase activation free energies ($\Delta G^\ddagger$) of that step for compounds **1−16** with four different substrates: ethylene, perfluoroethylene, acetylene, and cyclooctyne. Figure 4 shows excellent agreement between the computed $\Delta G^\ddagger$ barriers and the singlet−triplet energy gaps (ΔE_{S-T}) of the anti-Bredt alkene considered, confirming our hypothesis that strain at the bridgehead double bond position lowers the reaction barrier for a stepwise [2 + 2] cycloaddition. According to the extent of bridgehead double bond twisting, we cluster the results into three groups: **1−5** (torsional angles, τ > 30°) **6−14** (30° > τ > 10°), and **15−16** (no torsional strain) (Results for a first σ-bond formed at C2 show the same trend. Relevant data are included in Figure S4.)

We note that the bridgehead reactivities of compounds **1−14** may be anticipated by relating these bicyclic structures to their corresponding *trans*-cycloalkene structures. Considering the smaller of the rings containing the bridgehead double bond for each structure, compound **1** contains a *trans*-cyclopentene, compounds **2−5** contain a *trans*-cyclohexene, compounds **6−11** contain a *trans*-cycloheptene, and compounds **12−14** contain a *trans*-cyclooctene. Like the anti-Bredt alkenes, *trans*-cycloalkenes can display twisted double bonds as a result of ring strain. Small *trans*-cycloalkenes with up to five ring atoms will impose tremendous torsional strain, and thus only the *cis*-isomers have been isolated.[43] *Trans*-cyclohexenes were observed as transient photochemical species.[44] Recently, Weaver et al.[45,46] demonstrated the use of visible light to activate the *cis-/trans*-photoisomerization of a cyclohexene and showed that the resulting *trans*-cycloalkene could then readily undergo addition reactions with alcohols and urethanes. *Trans*-cycloheptenes and *trans*-cyclooctenes can be prepared and can drive strain-promoted reactions,[43,47−51] and even larger cycloalkenes rings have less twisted double bonds.[52]

We began our analyses by examining the reaction barriers of compounds **1−16** with two unactivated substrates: ethylene (Figure 4a) and acetylene (Figure 4b). Computed activation free energy barriers ($\Delta G^\ddagger$) for compounds **1−5** all fall below 20 kcal/mol. These results suggest that, at room temperature, even unactivated alkenes and alkynes can be used as trapping agents to capture compounds **1−5** via a stepwise [2 + 2] cycloaddition reaction. Analogous reactions with imines or carbonyls can thus form four membered ring heterocycles. The computed free energy barriers increase as the bridgehead double bonds twist less. Computed $\Delta G^\ddagger$ values for **6−14** are above 25 kcal/mol when reacting with ethylene (26−38 kcal/mol, Figure 4a) and acetylene (26−35 kcal/mol, Figure 4b), and those for systems with an untwisted double bond, **15** and **16**, are above 40 kcal/mol.

We then considered the reaction barriers of compounds **1−16** with two activated substrates: perfluoroethylene (i.e., a double bond activated by rehybridization,Figure 4c) and cyclooctyne (i.e., a spring-loaded triple bond, Figure 4d). Bartlett and others found that halogenated alkenes could form

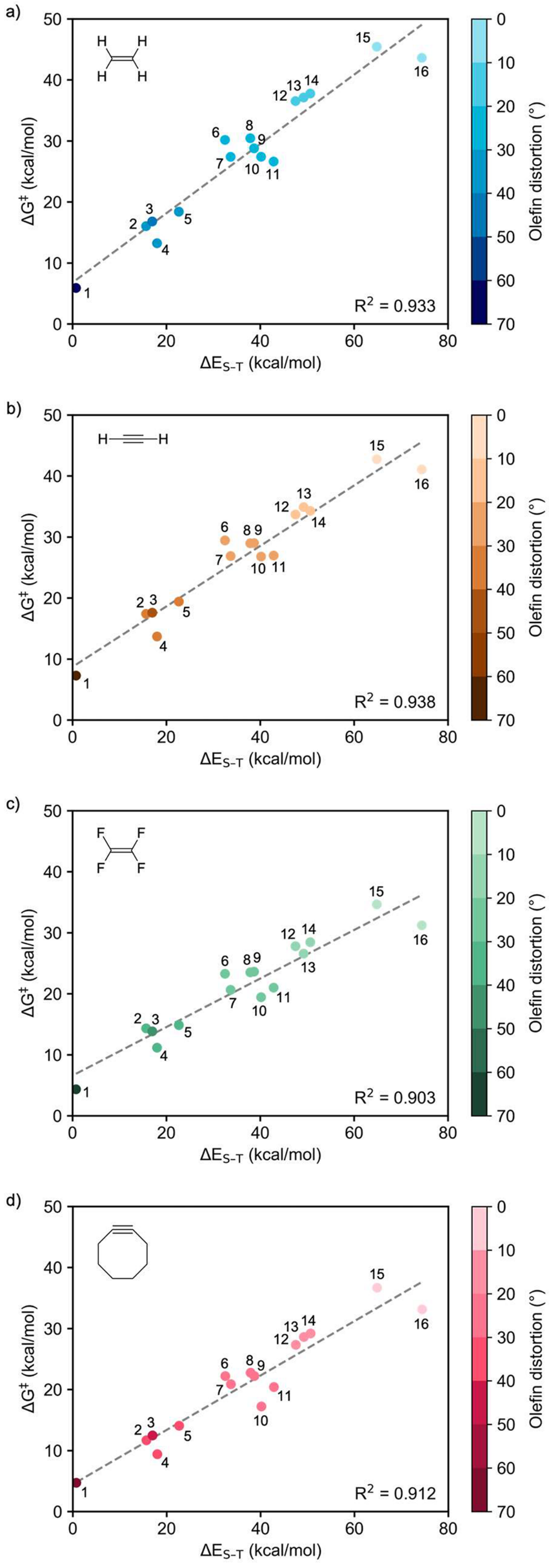


Figure 4. Correlation between computed activation free energy barriers ($\Delta G^{\ddagger}$) for the formation of a first σ-bond at the bridgehead position vs computed singlet−triplet energy gaps (ΔE_{S-T}) for compounds **1**−**16**, reacting with (a) ethylene, (b) acetylene, (c) tetrafluoroethylene, and (d) cyclooctyne. Activation free energy barriers were computed at (U)ωB97X-D/6-311+G(d,p).

[2 + 2] adducts with dienes through a stepwise cycloaddition mechanism.[11] Later, Weigert and Davis[53] showed that the reaction between tetrafluoroethylene and butadiene gave a [4 + 2] adduct under thermodynamic control, but a [2 + 2] adduct appears under kinetic control. Preference for a [2 + 2] adduct under kinetic control was attributed to increased p character of the two CF bonds, which weakens the π-bond and stabilizes a pyramidalized diradical intermediate (i.e., Bent's rule).[2,54]

As shown in Figure 4c, the computed free energy barriers for compounds **1**−**5** all fall below 15 kcal/mol, and even those of **6**−**14** (19−28 kcal/mol) are lowered, with **6**−**11** giving $\Delta G^{\ddagger}$ values lower than 25 kcal/mol. Computed $\Delta G^{\ddagger}$ values for **15** (34.7 kcal/mol) and **16** (31.2 kcal/mol) are also lower compared with that of the same reaction with ethylene. Activated alkynes show the same trend. As shown in Figure 4d, the computed free energy barriers for compounds **1**−**5** all fall below 15 kcal/mol, and those for **6**−**14** (17−30 kcal/mol) are lowered, with **6**−**11** giving $\Delta G^{\ddagger}$ values lower than 25 kcal/mol. Computed $\Delta G^{\ddagger}$ values for **15** (36.7 kcal/mol) and **16** (33.1 kcal/mol) also are lower compared to that of the same reaction with acetylene. These results suggest that, at room temperature, several of these bicyclic compounds (**1**−**11**) may undergo stepwise [2 + 2] cycloadditions with activated alkenes and alkynes. At higher temperature, even anti-Bredt alkenes with moderately twisted bridgehead double bonds can be trapped by a stepwise [2 + 2] cycloaddition reaction (cf. Becker and Hohermuth's work showing [2 + 2] adducts of **12** and **14** with 1,1-dichloro-2,2-difluoroethene at 80 °C).

Cyclobutane and cyclobutene motifs are frequently found in bioactive natural products, as templates for drug discovery, and as intermediates in organic synthetic pathways.[5,55−58] Driven by the significance of these motifs in biological and synthetic contexts, developing approaches to access four membered rings remains a desired goal,[59,60] and we hope that the model study reported here will encourage developments of synthetic strategies for accessing four membered rings by use of twisted double bonds. In addition to stepwise thermally allowed [2 + 2] cycloadditions, these strained alkenes also may facilitate concerted thermally allowed [2 + 2] cycloadditions with ketenes.

■ ASSOCIATED CONTENT

Data Availability Statement

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

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c00879.

Details for computational methods, structures of studied compounds, correlation between singlet-triplet energy gap and olefin distortion, $\langle S^2 \rangle$ values, σ bond data, reaction profile, computed free energy barriers with a first σ C−C bond formed at C2, and optimized Cartesian coordinates for all structures (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Judy I. Wu − *Department of Chemistry, University of Houston, Houston, Texas 77204, United States;* orcid.org/0000-0003-0590-5290; Email: jiwu@central.uh.edu

Authors

Renan V. Viesser − *Department of Chemistry, University of Houston, Houston, Texas 77204, United States;* orcid.org/0000-0002-4176-6067

Clayton P. Donald − *Department of Chemistry, University of Houston, Houston, Texas 77204, United States;* orcid.org/0000-0002-5379-273X

Jeremy A. May − *Department of Chemistry, University of Houston, Houston, Texas 77204, United States;* orcid.org/0000-0003-3319-0077

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.orglett.4c00879

Author Contributions

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

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

J.I.W. thanks the National Institute of General Medicine Sciences (NIGMS) of the National Institutes of Health (NIH) (R35GM133548) and the Alfred P. Sloan Research Foundation (FG-2020-12811) for financial support. J.A.M. thanks the National Science Foundation (NSF) (CHE-2102282) for financial support. We thank the Research Computing Data Core at the University of Houston for computational resources.

■ REFERENCES

(1) Woodward, R. B.; Hoffmann, R. The Conservation of Orbital Symmetry. *Angew. Chem., Int. Ed.* **1969**, *8*, 781−932.

(2) Svatunek, D.; Pemberton, R. P.; Mackey, J. L.; Liu, P.; Houk, K. N. Concerted [4 + 2] and Stepwise (2 + 2) Cycloadditions of Tetrafluoroethylene with Butadiene: DFT and DLPNO-UCCSD(T) Explorations. *J. Org. Chem.* **2020**, *85*, 3858−3864.

(3) Hashimoto, Y.; Tantillo, D. J. Mechanism and the Origins of Periselectivity in Cycloaddition Reactions of Benzyne with Dienes. *J. Org. Chem.* **2022**, *87*, 12954−12962.

(4) Panova, M. V.; Medvedev, M. G.; Mar'yasov, M. A.; Lyssenko, K. A.; Nasakin, O. E. Redirecting a Diels−Alder Reaction toward (2 + 2)-Cycloaddition. *J. Org. Chem.* **2021**, *86*, 4398−4404.

(5) Xu, Y.; Conner, M. L.; Brown, M. K. Cyclobutane and Cyclobutene Synthesis: Catalytic Enantioselective [2 + 2] Cycloadditions. *Angew. Chem., Int. Ed.* **2015**, *54*, 11918−11928.

(6) Hoyt, J. M.; Schmidt, V. A.; Tondreau, A. M.; Chirik, P. J. Iron-catalyzed Intermolecular [2 + 2] cycloadditions of unactivated alkenes. *Science* **2015**, *349*, 960−963.

(7) Pagar, V. V.; RajanBabu, T. V. Tandem catalysis for asymmetric coupling of ethylene and enynes to functionalized cyclobutanes. *Science* **2018**, *361*, 68−72.

(8) Alcaide, B.; Almendros, P.; Aragoncillo, C. Exploiting [2 + 2] cycloaddition chemistry: achievements with allenes. *Chem. Soc. Rev.* **2010**, *39*, 783−816.

(9) Wahl, J. M.; Conner, M. L.; Brown, M. K. Allenoates in Enantioselective [2 + 2] Cycloadditions: From a Mechanistic Curiosity to a Stereospecific Transformation. *J. Am. Chem. Soc.* **2018**, *140*, 15943−15949.

(10) Xu, W.; Cong, X.; An, K.; Lou, S.-J.; Li, Z.; Nishiura, M.; Murahashi, T.; Hou, Z. Regio- and Diastereoselective Formal [2 + 2] Cycloaddition of Allenes with Amino-Functionalized Alkenes by Rare-Earth-Catalyzed $C(sp^2)$−H Activation. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202210624.

(11) Bartlett, P. D. 1,2- and 1,4-Cycloaddition to Conjugated Dienes. *Science* **1968**, *159*, 833−838.

(12) Huisgen, R. Tetracyanoethylene and Enol Ethers. A Model for 2 + 2 Cycloadditions via Zwitterionic Intermediates. *Acc. Chem. Res.* **1977**, *10*, 117−124.

(13) Zeng, L.; Xu, J.; Zhang, D.; Yan, Z.; Cheng, G.; Rao, W.; Gao, L. Catalytic Enantioselective [2 + 2] Cycloaddition of α-Halo Acroleins: Construction of Cyclobutanes Containing Two Tetrasubstituted Stereocenters. *Angew. Chem., Int. Ed.* **2020**, *59*, 21890−21894.

(14) Hong, Y. J.; Tantillo, D. J. How cyclobutanes are assembled in nature − insights from quantum chemistry. *Chem. Soc. Rev.* **2014**, *43*, 5042−5050.

(15) Wang, H.; Zou, Y.; Li, M.; Tang, Z.; Wang, J.; Tian, Z.; Strassner, N.; Yang, Q.; Zheng, Q.; Guo, Y.; Liu, W.; Pan, L.; Houk, K. N. A cyclase that catalyses competing 2 + 2 and 4 + 2 cycloadditions. *Nat. Chem.* **2023**, *15*, 177−184.

(16) Wu, J. I.; van Eikema Hommes, N. J. R.; Lenoir, D.; Bachrach, S. M. The quest for a triplet ground-state alkene: Highly twisted C = C double bonds. *J. Phys. Org. Chem.* **2019**, *32*, No. e3965.

(17) Lenoir, D.; Smith, P. J.; Liebman, J. F. Distorted Alkenes. In *Strained Hydrocarbons: Beyond the van't Hoff and Le Bel Hypothesis*; Dodziuk, H., Ed.; Wiley, 2009; pp 103−146.

(18) Wiseman, J. R.; Chong, J. A. Bredt's Rule. IV. Bicyclo[3.2.2]non-1-ene and Bicyclo[3.2.2]non-1(7)-ene, Examples of Bridged *trans*-Cycloheptenes. *J. Am. Chem. Soc.* **1969**, *91*, 7775−7777.

(19) Lenoir, D. Versuche Zum Nachweis von Tricyclo[3,3,1,13,7]-dek-1-en (Adamanten) Als Zwischenstube Bei Der Bisdehalogenierung von 1-brom-2-jod-adamantan mit Lithium-butylen. *Tetrahedron Lett.* **1972**, *13*, 4049−4052.

(20) Burns, W.; Grant, D.; McKervey, M. A.; Step, G. Non-coplanar Double Bonds; The Existence of Adamantene. *J. Chem. Soc. Perkin Trans 1* **1976**, 234−238.

(21) Becker, K. B.; Hohermuth, M. K. [2 + 2]-Cycloadditions to Strained Bridgehead Olefins. I. 1,1-Dichloro-2,2-difluoroethene. *Helv. Chim. Acta* **1982**, *65*, 229−234.

(22) Becker, K. B.; Hohermuth, M. K.; Rihs, G. [2 + 2]-Cycloadditions to Strained Bridgehead Olefins. II. Diphenylketene. *Helv. Chim. Acta* **1982**, *65*, 235−242.

(23) Weeraratna, C.; Amarasinghe, C.; Joalland, B.; Suits, A. G. Ethylene Intersystem Crossing Caught in the Act by Photofragment Sulfur Atoms. *J. Phys. Chem. A* **2020**, *124*, 1712−1719.

(24) Rauer, C.; Nogueira, J. J.; Marquetand, P.; González, L. Cyclobutane Thymine Photodimerization Mechanism Revealed by Nonadiabatic Molecular Dynamics. *J. Am. Chem. Soc.* **2016**, *138*, 15911−15916.

(25) Martella, D. J.; Jones, M.; Schleyer, P. v. R.; Maier, W. F. Tricyclo[4.3.1.13,8]undec-3-ene (Homoadamant-3-ene). Stability of Bridgehead Olefins. *J. Am. Chem. Soc.* **1979**, *101*, 7634−7637.

(26) Maier, W. F.; Schleyer, P. V. R. Evaluation and Prediction of the Stability of Bridgehead Olefins. *J. Am. Chem. Soc.* **1981**, *103*, 1891−1900.

(27) Wiseman, J. R.; Chan, H.-F.; Ahola, C. J. Bredt's Rule. II. Synthesis of Bicyclo[4.2.1]non-1(2)-ene and Bicyclo[4.2.1]non-1(8)-ene. *J. Am. Chem. Soc.* **1969**, *91*, 2812−2813.

(28) Wiseman, J. R. Bredt's Rule. Bicyclo[3.3.1]non-1-ene. *J. Am. Chem. Soc.* **1967**, *89*, 5966−5968.

(29) Marshall, J. A.; Faubl, H. Bicyclo[3.3.1]non-1−1ne. *J. Am. Chem. Soc.* **1967**, *89*, 5965−5966.

(30) Keese, R.; Krebs, E.-P. Concerning the Existence of 1-Norbornene. *Angew. Chem., Int. Ed.* **1971**, *10*, 262−263.

(31) Chai, J.-Da; Head-Gordon, M. Long-range corrected hybrid density functionals with damped atom-atom dispersion corrections. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615−6620.

(32) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. Self-consistent molecular orbital methods. XX. A basis set for correlated wave functions. *J. Chem. Phys.* **1980**, *72*, 650−654.

(33) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. V. R. Efficient Diffuse Function-augmented Basis Sets for Anion

Calculations. III. The 3-21+G Basis Set for First-row Elements, Li−F. *J. Comput. Chem.* **1983**, *4*, 294−301.

(34) Gräfenstein, J.; Cremer, D. Can density functional theory describe multi-reference systems? Investigation of carbenes and organic biradicals. *Phys. Chem. Chem. Phys.* **2000**, *2*, 2091−2103.

(35) Ess, D. H.; Cook, T. C. Unrestricted Prescriptions for Open-Shell Singlet Diradicals: Using Economical Ab Initio and Density Functional Theory to Calculate Singlet-Triplet Gaps and Bond Dissociation Curves. *J. Phys. Chem. A* **2012**, *116*, 4922−4929.

(36) Raghavachari, K.; Trucks, G. W.; Pople, J. A.; Head-Gordon, M. A. Fifth-Order Perturbation Comparison of Electron Correlation Theories. *Chem. Phys. Lett.* **1989**, *157*, 479−483.

(37) Hoffmann, R.; Swaminathan, S.; Odell, B. G.; Gleiter, R. A Potential Surface for a Nonconcerted Reaction. Tetramethylene. *J. Am. Chem. Soc.* **1970**, *92*, 7091−7309.

(38) Carpenter, B. K. Dynamic Matching: The Cause of Inversion of Configuration in the [1,3] Sigmatropic Migration? *J. Am. Chem. Soc.* **1995**, *117*, 6336−6344.

(39) Carpenter, B. K. Dynamic Behavior of Organic Reactive Intermediates. *Angew. Chem., Int. Ed.* **1998**, *37*, 3340−3350.

(40) Carpenter, B. K. Energy Disposition in Reactive Intermediates. *Chem. Rev.* **2013**, *113*, 7265−7286.

(41) Tantillo, D. J. Beyond transition state theory−Non-statistical dynamic effects for organic reactions. *Adv. Phys. Org. Chem.* **2021**, *55*, 1−16.

(42) Nguyen, Q. N. N.; Tantillo, D. J. When to Let Go − Diradical Intermediates from Zwitterionic Transition State Structures? *J. Org. Chem.* **2016**, *81*, 5295−5302.

(43) Bucci, R.; Sloan, N. L.; Topping, L.; Zanda, M. Highly Strained Unsaturated Carbocycles. *Eur. J. Org. Chem.* **2020**, *2020*, 5278−5291.

(44) Jin, S.; Nguyen, V. T.; Dang, H. T.; Nguyen, D. P.; Arman, H. D.; Larionov, O. V. Photoinduced Carboborative Ring Contraction Enables Regio- and Stereoselective Synthesis of Multiply Substituted Five-Membered Carbocycles and Heterocycles. *J. Am. Chem. Soc.* **2017**, *139*, 11365−11368.

(45) Schoch, T. D.; Weaver, J. D. Efforts toward Synthetic Photosynthesis: Visible Light-Driven CO_2 Valorization. *J. Am. Chem. Soc.* **2023**, *145*, 14945−14951.

(46) Das, P.; DeSpain, M.; Ethridge, A.; Weaver, J. D. Exploiting Visible Light Triggered Formation of *trans*-Cyclohexene for the Contra-thermodynamic Protection of Alcohols. *Org. Lett.* **2023**, *25*, 7316−7321.

(47) Thalhammer, F.; Wallfahrer, U.; Sauer, J. Reaktivität Einfacher Offenkettiger Und Cyclischer Dienophile Bei Diels-Alder-Reaktionen Mit Inversem Elektronenbedarf. *Tetrahedron Lett.* **1990**, *31*, 6851−6854.

(48) Sanzone, J. R.; Woerpel, K. A. High Reactivity of Strained Seven-Membered-Ring *trans*-Alkenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 790−793.

(49) Singh, K.; Fennell, C. J.; Coutsias, E. A.; Latifi, R.; Hartson, S.; Weaver, J. D. Light Harvesting for Rapid and Selective Reactions: Click Chemistry with Strain-Loadable Alkenes. *Chem.* **2018**, *4*, 124−137.

(50) Fang, Y.; Zhang, H.; Huang, Z.; Scinto, S. L.; Yang, J. C.; am Ende, C. W.; Dmitrenko, O.; Johnson, D. S.; Fox, J. M. Photochemical syntheses, transformations, and bioorthogonal chemistry of *trans*-cycloheptene and sila *trans*-cycloheptene Ag(I) complexes. *Chem. Sci.* **2018**, *9*, 1953−1963.

(51) Xie, F.; Jia, X.; Zhu, Z.; Wu, Y.; Jiang, H.; Yang, H.; Cao, Y.; Zhu, R.; Zhou, B.; Du, J.; Tang, Y. Chemical trigger-enabled bioconjugation reaction. *Org. Biomol. Chem.* **2021**, *19*, 8343−8351.

(52) Barrows, S. E.; Eberlein, T. H. Cis and Trans Isomers of Cycloalkenes. *J. Chem. Educ.* **2005**, *82*, 1334−1339.

(53) Weigert, F. J.; Davis, R. F. Synthesis and aromatization of 2 + 2 cycloadducts of butadienes and tetrafluoroethylene. *J. Fluor. Chem.* **1993**, *63*, 69−84.

(54) Wang, S. Y.; Borden, W. T. Why Is the π Bond in Tetrafluoroethylene Weaker Than That in Ethylene? An Ab Initio Investigation. *J. Am. Chem. Soc.* **1989**, *111*, 7282−7283.

(55) Namyslo, J. C.; Kaufmann, D. E. The Application of Cyclobutane Derivatives in Organic Synthesis. *Chem. Rev.* **2003**, *103*, 1485−1537.

(56) Piao, S.-J.; Song, Y.-L.; Jiao, W.-H.; Yang, F.; Liu, X.-F.; Chen, W.-S.; Han, B.-N.; Lin, H.-W. Hippolachnin A, a New Antifungal Polyketide from the South China Sea Sponge *Hippospongia lachne*. *Org. Lett.* **2013**, *15*, 3526−3529.

(57) Dembitsky, V. M. Bioactive cyclobutane-containing alkaloids. *J. Nat. Med.* **2007**, *62*, 1−33.

(58) Vilaine, J. P.; Thollon, C.; Villeneuve, N.; Peglion, J. L. Procoralan, a new selective I_f current inhibitor. *European Heart Journal Supplement* **2003**, *5*, G26−G35.

(59) Li, J.; Gao, K.; Bian, M.; Ding, H. Recent advances in the total synthesis of cyclobutane-containing natural products. *Org. Chem. Front.* **2020**, *7*, 136−154.

(60) Wen, K.-G.; Peng, Y.-Y.; Zeng, X.-P. Advances in the catalytic asymmetric synthesis of quaternary carbon containing cyclobutanes. *Org. Chem. Front.* **2020**, *7*, 2576−2597.