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Cascade reactions of HDDA-benzynes with tethered cyclohexadienones: strain-driven events originating from *ortho*-annulated benzocyclobutenes†

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Intramolecular net [2 + 2] cycloadditions between benzyne intermediates and an electron-deficient alkene to give benzocyclobutene intermediates are relatively rare. Benzynes are electrophilic and generally engage nucleophiles or electron-rich π -systems. We describe here reactions in which an alkene of a tethered enone traps thermally generated benzynes in a variety of interesting ways. The number of atoms that link the benzyne to C4 of a cyclohexa-2,5-dienone induces varying amounts of strain in the intermediates and products. This leads to a variety of different reaction outcomes by way of various strain-releasing events that are mechanistically intriguing. This work demonstrates an underappreciated class of strain that originates from the adjacent fusion of two rings to both C1–C2 and C2–C3 of a benzenoid ring – *i.e.* '*ortho*-annulation strain'. DFT computations shed considerable light on the mechanistic diversions among various reaction pathways as well as allow more fundamental evaluation of the strain in a homologous series of *ortho*-annulated carbocycles.

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Introduction

Reactive intermediates possess, inherently, a relatively high amount of potential energy. Arynes, one of the most versatile of all such intermediates, are well known to engage alkenes in net [2 + 2] cycloaddition reactions to produce benzocyclobutenes.^{1,2} Simple alkenes and their more electron rich analogs such as enol ethers and enamines comprise the vast majority of such transformations. In contrast, there are very few reports of the reaction of an aryne with an electron-deficient alkene in an analogous fashion, a reflection no doubt of the electrophilic nature of an aryne.³

A significant feature of the work reported here is the way in which an atypical and underappreciated type of strain can lead to unusual modes of reactivity. In particular, we describe species in which the strain and novel reactivity originate from the simultaneous fusion of two adjacent rings to the C1–C2 and C2–C3 bonds of an aromatic ring. This contrasts with the more classical and well-studied classes of strained ring systems (*e.g.*, propellanes, bicyclobutanes, cyclophanes, cyclic alkynes, *etc.*).^{4,5}

Results and discussion

We set out to explore reactions of benzynes with a conjugated enone that was tethered to the benzyne in such a fashion as to allow for benzocyclobutene formation. We envisioned using a triyne-containing cyclohexadienone substrate such as **1** to thermally produce the benzyne **2**, which would allow us to assess its ability to generate the benzocyclobutene derivative **3** (Fig. 1a). We carried out an initial set of DFT computations using the simplified tethered benzyne **4** to learn about the energetics of such a process (Fig. 1b). The intermediate diradical **5** can exist as either a *cis*- or *trans*-fused diastereomer. The calculations show a large difference in the barriers leading to each ($\Delta\Delta G^\ddagger = 17.9 \text{ kcal mol}^{-1}$). The kinetically less favorable formation of the *trans*-isomer is reflective of the higher torsional strain necessary for proper orbital overlap in the TS. Closure of the *cis*-isomer of diradical **5** to the all-*cis* isomer of the benzocyclobutene derivative **6** occurs *via* a very low-barrier collapse of the diradical. This simple study suggested that there should be a substantial preference for formation of only one of the diastereomeric, *cis*-fused products (*i.e.*, structure **6** with both Hs up rather than with both Hs down).

Encouraged, we synthesized the triyne **7a**⁸ and observed its efficient conversion to the isomeric, hexacyclic benzocyclobutene product **8a** when heated at 85 °C in 1,2-dichloroethane (1,2-DCE) (Fig. 1c). The structure of this product was initially deduced from NMR analyses and later corroborated by an X-ray

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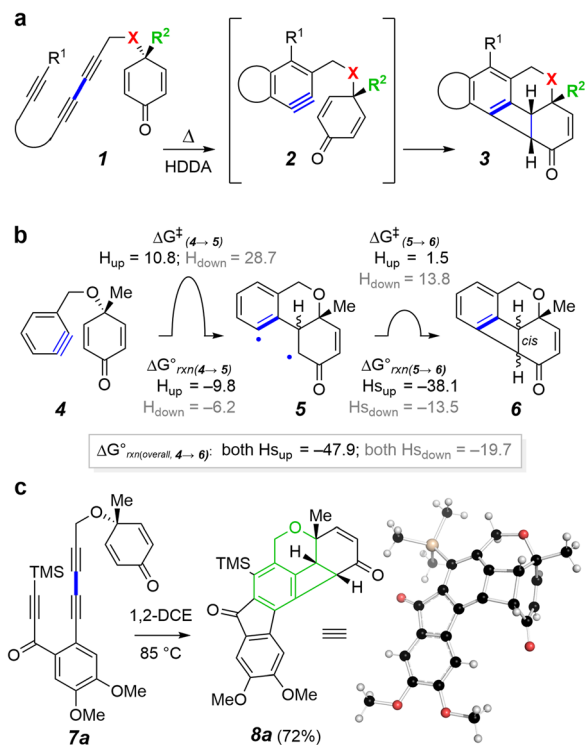


Fig. 1 (a) Concept of trapping a HDDA benzyne by the electron-poor alkene in a tethered cyclohexadienone. (b) DFT^a relative energies of the stationary points converting model benzyne **4** to the benzocyclobutene **6** (via the diradical **5**). (c) First example of a benzocyclobutene-forming reaction from a cyclohexadienone. ^a[(U)B3LYP-GD3BJ/6-311++G(d,p), SMD: dichloroethane]; we have previously used unrestricted B3LYP with the D3BJ dispersion correction in the optimization of other singlet diradical structures in the context of aryne chemistry.^{6,7}

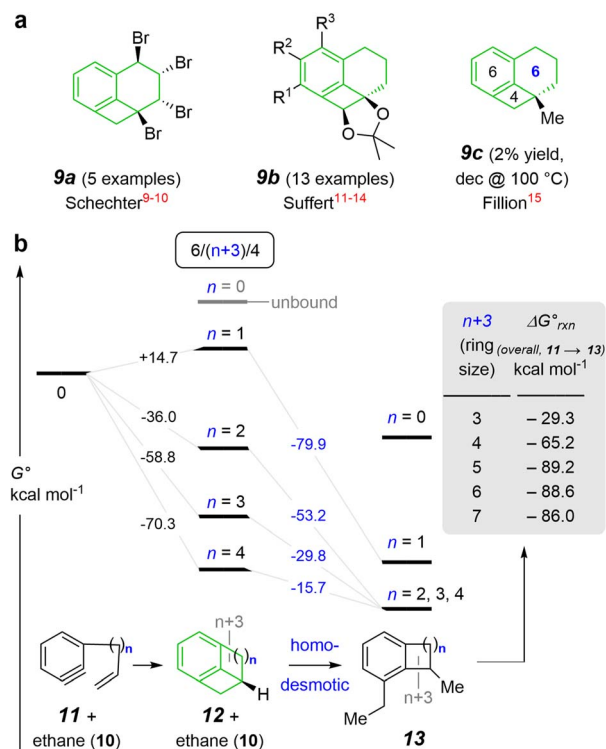


Fig. 2 (a) The three known classes of compounds containing a [6/6/4] tricyclic substructure. (b) Differences in DFT^a free energies of all three sets of minima for the conversion of **11** + ethane (**10**) to **13** via **12** + ethane (all energies within each series of homologs have been referenced to the energy of the tethered alkene **11** + ethane). ^a[MN15/6-311+G(d,p)].

diffraction study. The presence of the tricyclo[5.3.1.0 (ref. 3 and 8)]oxadodecatriene subunit in **8a** (green bonds), comprises three contiguously fused (*ortho*-annulated) rings and includes three adjacent sp^2 -hybridized benzenoid carbons.

We wondered how common this type of substructural motif might be. Structure searching the literature identified only three types of such skeletons (**9a–b**, Fig. 2a), all fully carbocyclic (our search allowed for O- and N-heterocyclic variants as well, but none were found).^{9–16} Moreover, we could locate no examples of a skeleton in which the saturated 6-membered ring in **9** is, instead, a contracted 5-membered cycle. This implies that these sorts of fused polycycles house a relatively rare type of strain. One indication of the severity of the ring strain in **8a** was observed by the rapid onset of dark color of the crystalline sample almost immediately after it was melted (218–220 °C). Thermal lability of **8a** was also suggested by its partial injector temperature-dependent conversion to a new product (see below, Fig. 5a) during GC analysis.

To probe how much strain might reside within tricyclic skeletons related to the one present in **8a** and **9**, we performed a set of DFT computations of the energetic minima for ethane (**10**) and the five sets of model compounds **11–13** (Fig. 2b).¹⁷

Here, we will call the skeletons present in **12** as $[6/(n+3)/4]$ tricycles; we varied n (the number of intervening methylene units) from 0 to 4. The energy of the starting benzyne **11** for each of the five sets of homologs was set to be 0 (all energies in kcal mol⁻¹). A minimum could not be located for the most highly strained $[6/3/4]$ tricycle **12** ($n = 0$). The calculation instead optimized to a ring-cleaved species. The ΔG° between the starting benzyne and the tricycle **12** for each of the successively larger rings (4- to 7-membered) progressively became more exergonic – an indication of the relative strain in the homologous series of $[6/(n+3)/4]$ tricycles. To evaluate the strain in each of **12** more directly, we calculated the homodesmotic reaction in which the C(sp^3)–C(sp^3) bond in ethane was exchanged for the C(sp^3)–C(sp^3) bond in the four-membered ring in each of **12**.^{18,19} The energetic changes (ΔG° values in blue) for these ethanolyse reflect the amount of strain released by cleavage of the smallest ring in each *ortho*-annulated tricycle.²⁰

In view of the substantial strain in these $[6/(n+3)/4]$ tricycles, it occurred to us that it might be possible to “store” the inherent strain energy of a benzyne within such a tricyclic subunit and subsequently utilize it to drive additional interesting transformations. If so, these benzocyclobutenes could be viewed as primed for further dissipation of the potential energy brought



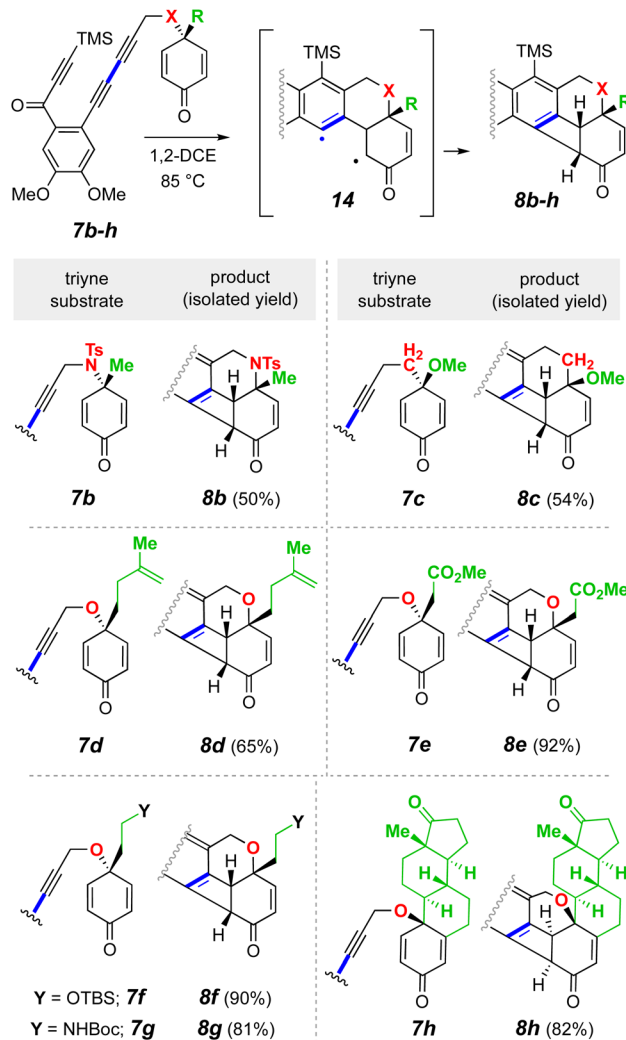


Fig. 3 [6/6/4]-Benzocyclobutenes **8b–h** produced from triynone precursors **7b–h**.

to the reaction *via* the three alkynes in the benzyne precursors. It is relevant that the triyne to benzyne conversion *via* a hexadehydro-Diels–Alder (HDDA) cyclization is computed to be, typically, 40–50 kcal mol⁻¹ exergonic.²¹ This overall idea seemed most promising to pursue for the case where $n = 3$, especially in light of the fact that we already had in hand the knowledge of the existence of the readily handleable [6/6/4] tricyclic derivative **8a**.

We present here an array of benzocyclobutene derivatives prepared by intramolecular reaction between an HDDA benzyne and a tethered cyclohexadienone (Fig. 3 and 4). We then show a variety of strain-driven transformations, some quite unexpected, that these strained species were observed to undergo (Fig. 5–8). At the end of the manuscript (Fig. 9), we will return to the case of a potential (and more highly strained) [6/5/4] tricyclic intermediate.

A number of additional types of substrates will participate in this enone cycloaddition chemistry to produce isolable benzocyclobutene derivatives. Those based on the

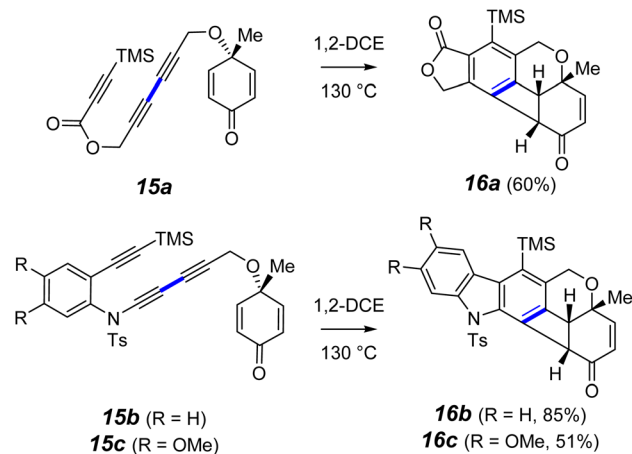


Fig. 4 Triyne substrates **15a–c** containing different triyne tethers also cyclize to [6/6/4]-benzocyclobutenes.

dimethoxyphenyl ketone linker are shown in Fig. 3. In substrates **7b** and **7c**, the oxygen atom in the oxymethylene tether present in **7a** has been replaced by an NTs or a CH₂ group, respectively. Substrates **7d–h**, in which the quaternary methyl group in **7a** is replaced with a variety of different substituents, demonstrate the compatibility of an array of common functional groups with the transformation. The structures of **8b–h** were assigned based on their analogous proton NMR characteristics *vis-à-vis* **8a** for key portions of the spectra. Additionally, the structure of the estrone-derived product **8h** was subjected to DP4+²² probability analysis,¹⁷ which showed definitive agreement with the assigned structure. In no instance did we detect the presence of an alternative diastereomeric benzocyclobutene (*cf.* **6-Hs_{up}** *vs.* **6-Hs_{down}**) when analyzing the crude product mixtures.

We also examined three additional benzyne substrates that had different linkers between the diyne and dienophile (Fig. 4). Each proceeded smoothly to provide the lactone- and carbazole-containing products **16a**, and **16b**, respectively.

We next investigated whether some of these strained intermediates would undergo further transformation by thermal processes. The first hint of that possibility came in the form of the decomposition upon melting **8a**, as mentioned earlier. This observation prompted us to explore the fate of **8a** upon being heated to a temperature higher than that used to create it (*i.e.*, >85 °C). When a solution of **8a** was heated at 130 °C in 1,2-dichloroethane (1,2-DCE), it gave rise to an isomeric product, the structure of which was not immediately apparent. More than one candidate structure was under consideration even after fairly detailed analysis of the 1D and 2D NMR data, although it was clear that an isolated alkene was present in the molecule. Therefore, we sought to make a crystalline derivative and turned to the very useful Rychnovsky OsO₄·TMEDA method, which involves *in situ* derivatization of alkenes and crystallization of their osmate esters.²³ The newly formed isomer of **8a** was treated with 1.0 equivalent of a 1 : 1.1 mixture of OsO₄ and TMEDA in dichloromethane resulting in efficient formation of a 1 : 1 adduct. Vapor diffusion (DCM *vs.*



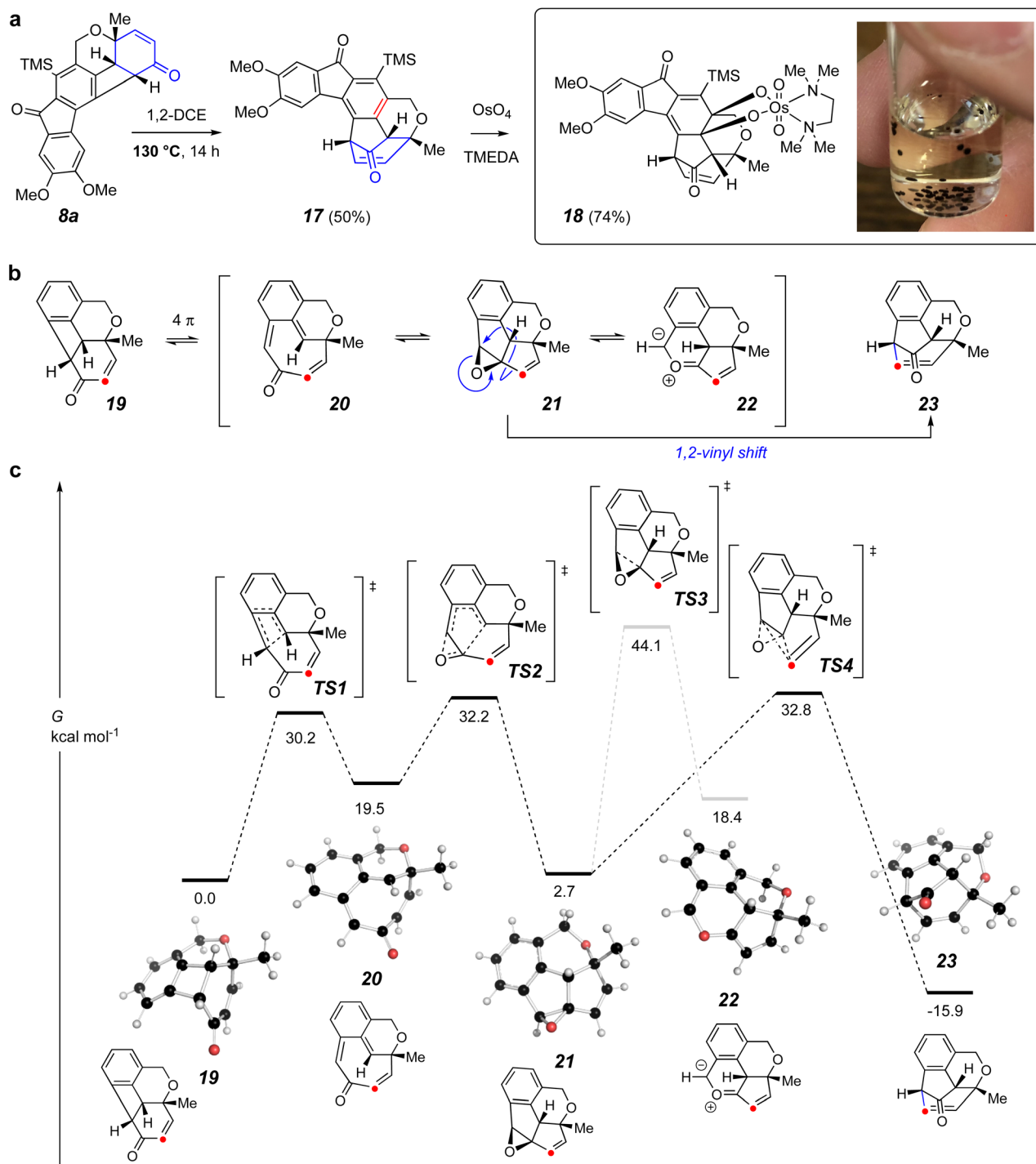


Fig. 5 (a) First indication of a strain-driven rearrangement of a [6/4/6] benzocyclobutene (**8a**) and confirmation of its structure by an unusual osmylation of the arene ring in **17** (see page S305 in the ESI† for a 3D rendering of the X-ray diffraction structure). (b) Proposed reaction pathway using the truncated model compound **19** and passing through *o*-xylene and epoxide intermediates **20** and **21**, respectively. (c) A DFT^a potential energy surface (PES) suggesting that the observed pathway is viable. ^a[MN15/6-311++G(d,p), SMD: dichloroethane]²⁴.

pentane) gave black crystals characteristic of an osmate ester (see photo in Fig. 5a). An X-ray diffraction analysis was performed, and we were amazed to see that the osmate had been formed by addition to a pair of adjacent carbons on the aromatic ring to give the product **18**, leaving the alkene intact!

Accordingly, we could then definitively assign the structure of the rearranged [6/6/4]-benzocyclobutenes **8a** as **17**.

How did **17** arise? The essential aspects of the proposed mechanism are shown using the truncated structures **19**–**23** (Fig. 5b). We envisioned a pathway in which **19** proceeds to the *o*-



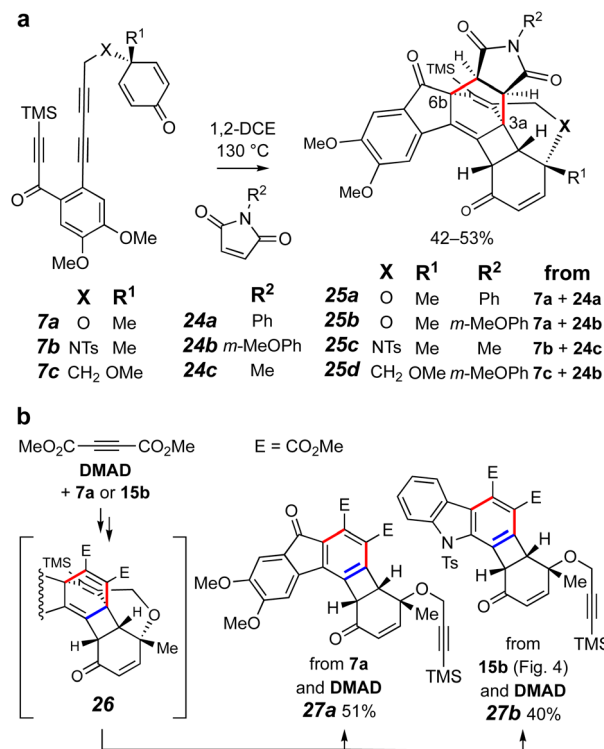


Fig. 6 Unexpected Diels–Alder adduct formation between the benzocyclobutenes derived from 7a–c and 15b and (a) dienophilic malimides and (b) dimethyl acetylenedicarboxylate (DMAD).

xylylene **20** and epoxide **21** enroute to **23**. We again turned to DFT computations to further evaluate this thinking (Fig. 5c). Our goal here was to demonstrate the viability of various stationary states required for this overall PES. Because of the absence of structural features (especially the conjugated polyyne tether) that would be expected to alter the energies of these states, perhaps dramatically, the various ΔG and ΔG^\ddagger specific values should be taken as qualitative. Nonetheless, this did demonstrate the mechanistic viability of (i) a conrotatory electrocyclic ring-opening of **19** to **20**, (ii) an unorthodox, aromatization-driven, concerted cyclization in which the carbonyl oxygen atom captures benzylic cation character in the forming epoxide ring in **21** and (iii) an unusual 1,2-vinyl migration with concomitant epoxide ring-opening leading to **23**.

With this mechanistic thinking in mind, we explored the thermal chemistry of the benzocyclobutenes derived from **7a** (and some of its analogs) in the presence of several types of trapping agents that might engage one of the reactive species on this manifold (Fig. 6a). Initially, a mixture of **7a** and *N*-phenylmaleimide (**24a**) was heated at 130 °C in 1,2-DCE. Again, to our surprise, the principal product, **25a**, was one in which the malimide had engaged the arene ring as a dienophile in a [4 + 2] cycloaddition reaction. This mode of reaction was then observed in reactions of additional maleimide derivatives with the triyne substrates **7a**, **7b** and **7c**, leading to **25b**, **25c** and **25d**, respectively.

We then used dimethyl acetylenedicarboxylate (DMAD) as a trapping agent with the triyne substrates **7a** and **15b** (Fig. 6b).

Again, each underwent preferential [4 + 2] cycloaddition across the aromatic ring in the intermediate benzocyclobutenes (*cf.* **26**). However, this was now followed by a rapid retro-Diels–Alder event under the reaction conditions to rearomatize the benzenoid ring in each of the final products **27a** and **27b**. All of the reactions in Fig. 6 reflect a degree of distortion of the arene ring that renders it susceptible to [4 + 2] cycloaddition events. Indeed, the crystal structure of **8a** shows that the *ortho*-annulated benzenoid ring has three internal dihedral angles (among the six) within the arene ring distorted to the extent of 13–19° and that the internuclear distance of the *para* carbons that engage in the DA reactions²⁵ (and give rise to C3a and C6b in **25** and **26**) is 2.65 Å while the other two pairs of *para* carbon internuclear distances are both 2.85 Å.

We have found several additional reactions in which cleavage of the cyclobutene was the dominant strain-relieving driving force (Fig. 7), as first seen in the conversion of **8a** to **17** (Fig. 5a). First, when **7b** was heated in 1,2-DCE containing 10 equivalents of acetic acid, the rearranged acetate ester **28** was

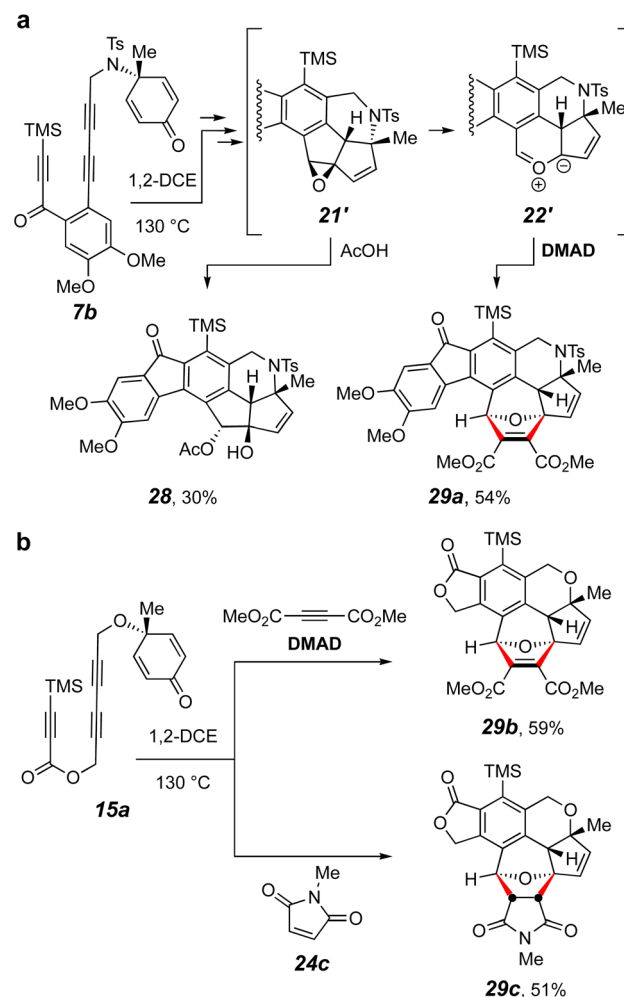


Fig. 7 (a) Trapping reactions in which either the intermediate epoxide **21'** or carbonyl ylide **22'** was intercepted, providing experimental support of the computed PES shown in Fig. 5b and c. (b) Analogous trapping reactions of a related 1,3-dipolar intermediate.



the only isolated product (Fig. 7a). We infer that this arises by an acid-catalyzed opening of the epoxide intermediate **21'**. Second, when triyne **7b** was heated in 1,2-DCE containing **DMAD**, the 1,3-dipolar cycloaddition product **29a** was the only isolated product. This provides clear evidence for the carbonyl ylide **22'** as a species on the reaction pathway. Similar 1,3-dipolar cycloaddition products were obtained starting from the triyne **15a** using **DMAD** or *N*-methylmaleimide (**24c**), leading to the formation of **29b** or **29c**, respectively (Fig. 7b). These experimental outcomes support the key aspects of the model computations described in Fig. 5c: namely, the intermediacy of epoxide analogs of both **21** and 1,3-dipole analogs of **22**.

We also explored the behavior of substrates **30a** and **30b**, each containing a spirocyclic ketal moiety within the linker (Fig. 8). If these were to have followed the 2 + 2 reaction pathway, the *ortho*-annulated intermediate benzocyclobutene would have contained an 8-membered ring (*i.e.*, a [6/8/4] substructure). Instead, and perhaps not surprisingly, the reactions took a different, although still interesting, course. Namely, **30a** gave rise to **34a** and **35**, two unusual polycycloisomerization products. The structure of each was assigned by extensive 1D and 2D NMR spectroscopic studies, and that of the cyclopropane-containing compound **35** was further verified by an X-ray diffraction study. Likewise, the ester-linked triyne **30b**

gave the phenol derivative **34b**, an analog of **34a**, as the sole isolated product (Fig. 8b).

The formation of these polycyclic products can be rationalized by attack of the distal ketal oxygen to the electrophilic benzyne carbon atom in, *e.g.*, **31**. Cyclization of the 1,3-zwitterion **32** by conjugate addition to an enone would produce the new zwitterion **33**, which simultaneously houses both an enolate anion and oxonium cation. This could bifurcate *via* eliminative opening shown with red arrows to give, ultimately, the phenol derivative **34a** or through the cyclopropane-forming event indicated with the blue arrows. Since there are a number of diastereomeric possibilities for structure **33**, it is certainly possible that certain one(s) are preferentially leading to **34a** *vs.* **35**. A control experiment demonstrated that isolated **35** is very stable when heated independently at 85 °C for 20 h in CDCl₃, ruling it out as a precursor to **34a**. Finally, it is also notable that in these reactions the alkynes in **30a** fueled not only the formation of the benzyne but, in turn, the production of a compound containing the most classic of all strained cyclic hydrocarbons – a cyclopropane.

We were, of course, interested in learning what would happen using a substrate with a shorter, single-atom tether between the triyne and cyclohexadienone. Would that be capable of giving rise to a yet more highly strained [6/5/4] *ortho*-annulated benzocyclobutene skeleton? Thus, we prepared the substrate **36** and heated it to induce benzyne-formation (Fig. 9a). A very clean conversion to the unexpected pentacyclic product **39**, which contains a newly formed benzochromene subunit was observed. It was difficult to envision a mechanistic pathway that involved initial addition of the proximal benzyne carbon to C_β of the enone to account for this outcome. We then considered the alternative addition of the proximal benzyne carbon to C_α of the enone to form **37** (in truncated form) this mechanism would proceed from **40**, *via* **41** and **42**, to **43** (Fig. 9b). The final step involves a pseudo-6π-electrocyclic ring closure of **42** to **43** (*cf.*, **38** to **39**) in which there is a concomitant hydrogen atom migration. Notable features of this overall mechanism are (i) the β-cleavage within diradical **37** (or **41**), which gives rise to the α,3-dehydrotoluene species **38** (or **42**) and (ii) the unusual, concerted migration of a hydrogen atom that accompanies the electrocyclization of **38** to **39** (or **42** to **43**), which is further seen in **TS7**. These unorthodox events are indicated to be energetically feasible by the DFT PES shown in Fig. 9c (*cf.* *E*_{acts} *via* **TS5–TS7**).

Conclusions

Because alkynes are of relatively high potential energy, their transformation into products often occurs with a high degree of exothermicity. In this work we have shown reaction sequences that not only use three alkynes to fuel the formation and trapping of benzyne intermediates²¹ to produce *ortho*-annulated benzocyclobutenes, but that these polycycles temporarily house strain that can then be released to give rise to a variety of additional unorthodox transformations. These include osmylation of an arene π-bond, Diels–Alder additions

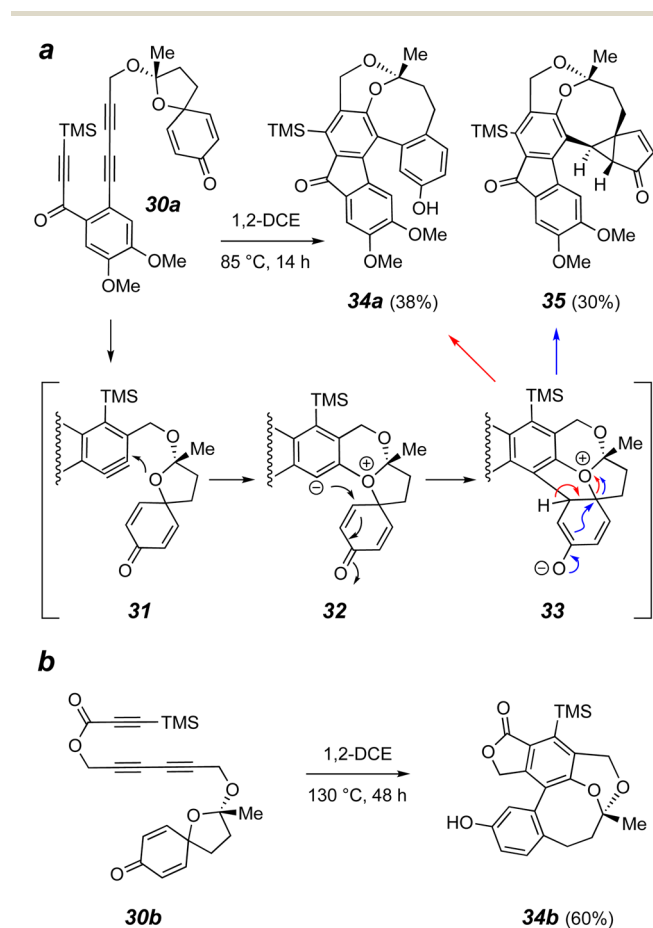


Fig. 8 Novel polycycloisomerization products arising from substrates containing a ketal within the cyclohexadienone-to-triyne linker.



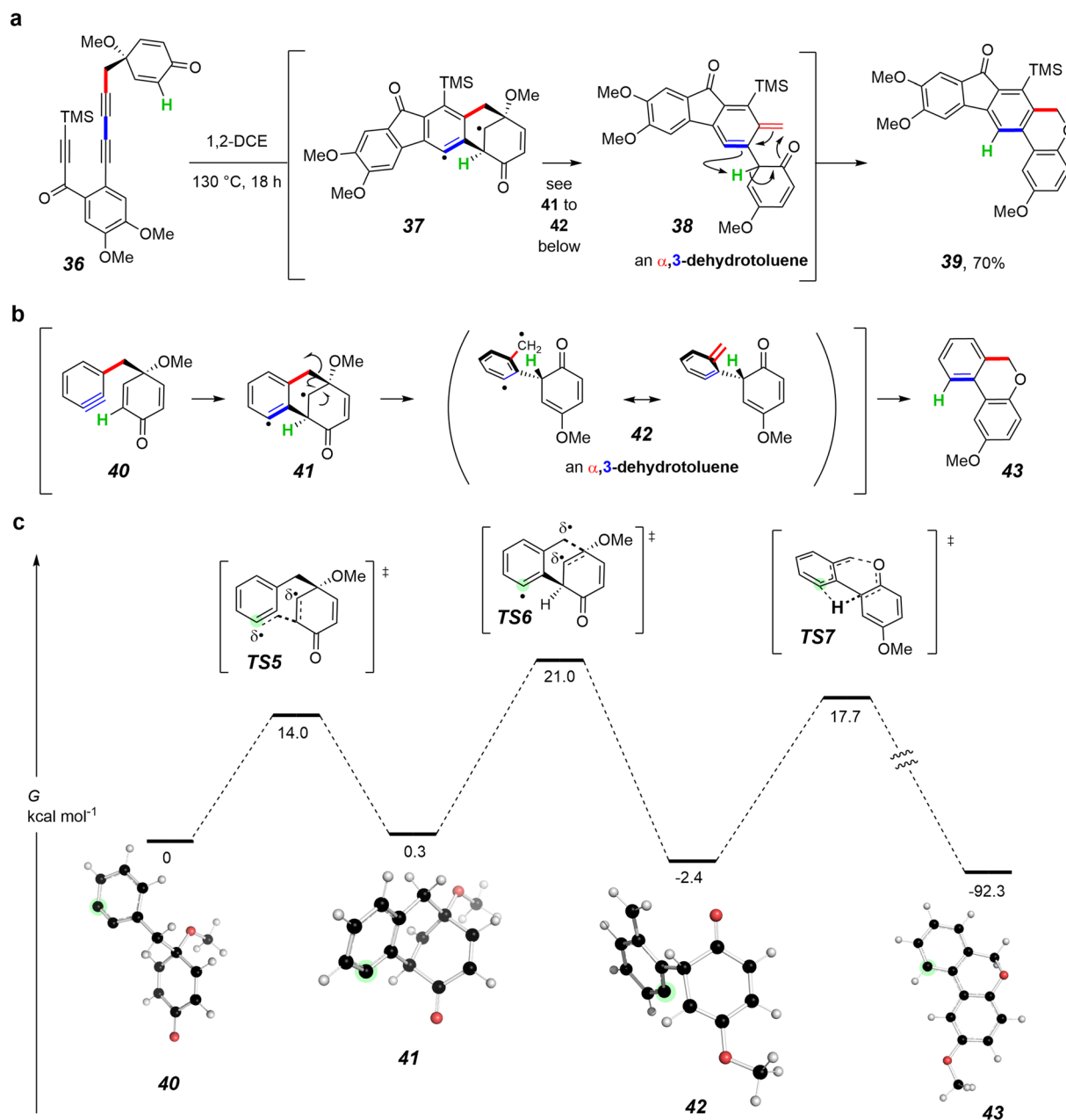


Fig. 9 (a) An unexpected reaction outcome starting from triyne **36** having a one-atom tether. (b) A mechanistic rationale involving initial C–C bond formation to C_α of the enone (**40** to **41**), β-cleavage to an α,3-dehydrotoluene derivative (**41** to **42**), and an unusual electrocyclic ring closure with concomitant hydrogen atom migration (**42** to **43**). (c) DFT^a results showing the energetic feasibility of this pathway. ^a[(U)B3LYP-GD3BJ/6-311++G(d,p), SMD: dichloroethane].

to a distorted arene, rearrangements to epoxide and 1,3-dipolar intermediates, and uncatalyzed 1,2-alkene migration of an epoxide.

The work highlights the importance of an underappreciated type of strain: namely, one arising from the presence of two rings fused, adjacently, to C1–C2 and C2–C3 of a parent benzenoid ring. We refer to that here as *ortho*-annulation strain. The amount of strain energy embedded within this type of substructure is demonstrated by DFT computations of homodesmotic reactions between ethane and a series of tricyclic hydrocarbons (**12**, Fig. 2b).

Finally, the studies also demonstrate that the electron-deficient alkene of an enone can undergo initial bond formation at either its β- or α-carbons, depending on the length of the tether between the benzyne and enone. The former proceeds to net 2 + 2 cycloadducts, a rare process for electron-poor alkenes with arynes, whereas the latter undergoes an unusual process involving β-scission of a diradical leading to yet another strained reactive intermediate, an α,3-dehydrotoluene derivative. Energy release from thermal reactions of alkynes can be captured and then progressively liberated to drive atypical sequences of reactions.



Experimental

General procedure for HDDA cyclization reactions

The triyne substrate (1 equiv.) was dissolved in 1,2-dichloroethane and placed in a screw-capped culture tube. The capped tube was heated at 85 °C for 14 hours. The solvent was removed under reduced pressure, and the residue was purified by MPLC (hexanes:EtOAc, 4:1) to provide the benzocyclobutene product.

Data availability

The data upon which the conclusions in this manuscript are based are provided in the ESI† document and in a .zip file of a master Mestrenova file of all NMR spectra.

Author contributions

B. S. C. performed the majority of the experimental work. D. S. S. performed some of the experimental work and all of the computational studies; all authors interpreted the data and D. S. S. and T. R. H. co-wrote the manuscript.

Conflicts of interest

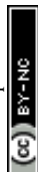
There are no conflicts to declare.

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