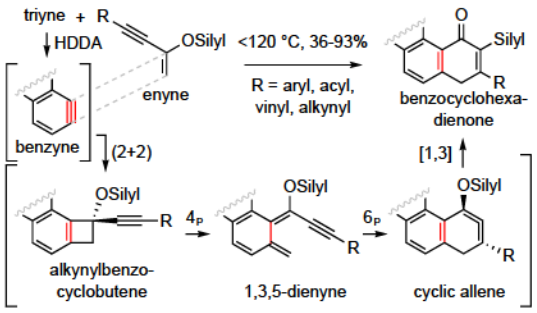
A cascade of strain-driven events converting benzynes to alkynylbenzocyclobutenes to 1,3-dien-5-ynes to cyclic allenes to benzocyclohexadienones

Qian Xu and Thomas R. Hoye*

Department of Chemistry, University of Minnesota, 207 Pleasant St. SE, Minneapolis, MN 55455 USA

Supporting Information Placeholder

ABSTRACT: Here, we report a strain-promoted cascade reaction that proceeds via multiple strained intermediates, ultimately all driven by the high potential energy inherent in alkyne triple bonds (C≡C). More specifically, four alkynes (three from an HDDA benzyne precursor and the fourth from a conjugated enyne reaction partner) are transformed into eight of the skeletal carbons in the benzocyclohexadienone products. The reaction pathway proceeds, sequentially, via strained benzyne, benzocyclobutene, and cyclic allene intermediates. DFT computations suggest that the slowest step following benzyne generation is the 4π-electrocyclic ring-opening of the alkynylbenzocyclobutene to a 1,3-dien-5-yne (an alkynylxylylene) intermediate. The activation energy for the subsequent 6π-electrocyclic ring-closure is lower than for related acyclic dienynes because of the aromaticity that is being regained in the transition structure. Finally, the isolation of the benzocyclohexadienone products rather than their phenolic tautomers is notable.



Strain plays an essential role in chemical reactions. On one hand, accumulation of strain enroute to products, either in intermediates or transition structures, can prevent a transformation from proceeding; on the other, the presence of strain in reactants can often accelerate a conversion and sometimes confer unusual reactivity. The latter is prominent in species containing distorted π bond(s) such as in strained cyclic alkenes (e.g., **1a**-**b**, Figure 1a), alkynes (e.g., **2a**-**b**), and cyclic allenes (e.g., **3a**-**c**). Derivatives of cyclobutene (**1a**),[1] trans-cyclooctene (**1b**),[2] and cyclooctyne (**2a**)[3] can be handled on the laboratory working timescale, yet will often readily undergo cycloaddition reactions, even at ambient temperature, useful in, for example, bioorthogonal conjugation reactions.[4] In contrast, benzyne (**2b**),[5] 1,2-cyclohexadiene (**3a**),[6] and 1,2,4-cyclohexatriene (**3b**)[6b,7] and their derivatives are reactive intermediates having short lifetimes and high reactivities. Among species **1a**-**3b**, derivatives of the 1,2,4-cyclohexatriene **3b** are the least investigated. An even more strained isomer of **3b** is 1,2,3-cyclohexatriene (**3c**), the reactivity of which has only very recently succumbed to systematic study.[8]

1,2,4-Cyclohexatriene (**3b**) derivatives are central to the studies being described here. These reactive intermediates were first generated in designed fashion from **4**[9] or **5**[10] as indicated in Figure 1b. The transient nature of species **6** was deduced from the products of various trapping events involving nucleophilic addition or cycloadditions with various alkenes and dienes **7**. Two earlier processes, each not originally recognized as proceeding via a 1,2,4-cyclohexatriene derivative, are the Hopf rearrangement of 1,3-hexadien-5-yne (**8**, Figure 1c)[11] and the cycloisomerization of an enyne with a second alkyne in a tetradehydro-Diels-Alder (TDDA) reaction[12] (see **10** to **11**, Figure 1d for a recent example of a TDDA cyclization). Notably, the prototypical Hopf cyclization required a quite high temperature (274 °C) to proceed. In addition, 1,2,4-cyclohexatrienes can aromatize to their more stable, isomeric benzenoid analogs[7] (e.g., **3b** to **9**) or undergo strain-promoted group migration events[13] (e.g., **11** to **12**).

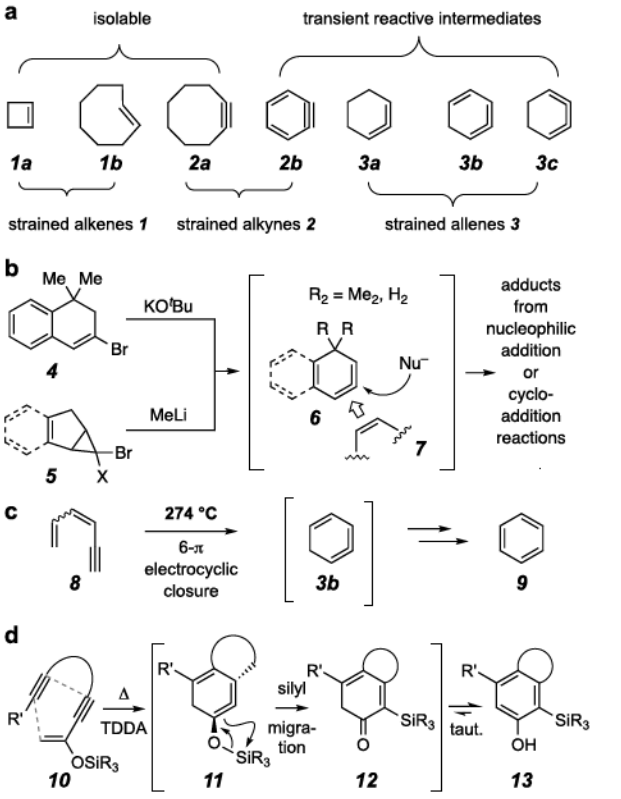


Figure 1. (a) Selected, prototypical strained cyclic molecules containing distorted π-bond(s).[14] (b) Designed generation of 1,2,4-cyclohexatrienes. (c) Hopf cyclization, which requires high temperature. (d) A strain-promoted silyl group migration.

Arynes are known to react with olefins in a net (2+2) cycloaddition to give benzocyclobutenes,[15] another class of strained hydrocarbons. We were curious whether such adducts could be integrated into a reaction manifold involving a Hopf-like cyclization to a cyclic allene. Specifically (Figure 2), we hypothesized that a benzyne would engage a silyoxyenyne such as **14** to initially produce a benzocyclobutene **17**, electrocyclic ring-opening and reclosure of which would lead to the siloxyallene **19** via the *o*-xylylene **18**. Intermediate **19** would be expected to undergo a 1,3-silyl migration to give the α-silylated enone **15**,[13] which might tautomerize (or not) to its phenolic isomer **16**. We are unaware of any transformation in which the skeletal carbon atoms of a 1,2,4-cyclohexatriene originate from two different reactants and show here the realization of such reactions.

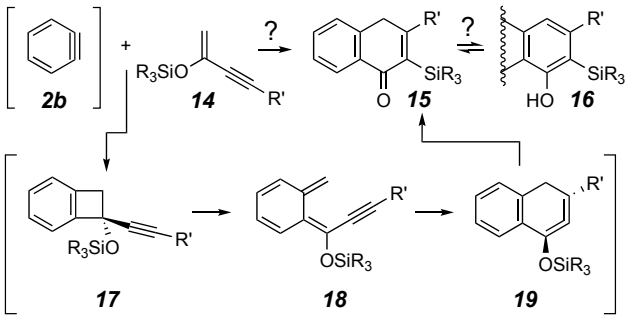


Figure 2. Proposed cascade sequence that converts a benzyne to benzocyclohexadienone (cf. **15**) via alkynylbenzocyclobutene (cf. **17**), *o*-xylylene (cf. **18**), and cyclic allene (cf. **19**) intermediates.

STo test the viability of this hypothesis, we used DFT computation employing benzyne **2b** and trimethylsiloxyenyne **20** as the model reactants (Figure 3). The net (2+2) cycloaddition between these two species leads to benzocyclobutene **21** with a large exergonicity, typical of many benzyne trapping reactions.[5d,f] This is computed to be a stepwise process via a zwitterionic intermediate [see Figure S1 in the Supporting Information (SI)]. From there (see the red portion of the PES) 4π-electrocyclic ring-opening results in formation of xylylene **22** via **TS-1**. The alternative ring-opening to give the isomeric xylylene having the alkyne oriented to the outside of the xylylene and distal to the methylene carbon was computed to be formed via a transition structure (TS) with a significantly higher energy (7.9 kcal mol^{-1}; see Figure S2 in the SI). The dienyne **22** subsequently undergoes the Hopf cyclization with a relatively low activation barrier (ca. 20 kcal mol^{-1}) and gives rise to the strained cyclic allene intermediate **23** via **TS-2**. TMS migration via a 1,3-retro-Brook rearrangement produces the cyclohexadienone **24** via **TS-3**. In this case, the isomeric naphthalenol derivative **25** is computed to have a lower Gibbs energy compared to the napthalenone **24**. We also computed the relative energy of (an analog of[16]) dienone **39** (Figure 5d) vs. its phenolic tautomer and observed the enone to be more stable in this more complex polycyclic setting (by 1.9 kcal mol^{-1}; see **S6** vs. **S5** in Figure S3 in the SI).

For comparison (cf. red vs. blue in Figure 3), we also computed the potential energy surface (PES) of an analogous process using the simpler, monocyclic cyclobutene analog **21'**. Without the benzannulation present in **21**, the landscape of the two PESs differs significantly. The absence of an energy penalty from dearomatization allows the ring-opening within **21'** to proceed with a lower activation barrier (22.9 vs 25.5 kcal mol^{-1}), and this elementary step becomes significantly exergonic. However, without rearomatization as the driving force for the next event, the subsequent 6π-electrocyclization within **22'** is kinetically and thermodynamically disfavored ($\Delta G^{\neq}$ = 34.4 kcal mol^{-1}, $\Delta G°$ = 8.5 kcal mol^{-1} from **22'** to **23'** vs. $\Delta G^{\neq}$ = 20.7 kcal mol^{-1}, $\Delta G°$ = -13.8 kcal mol^{-1} from **22** to **23**). Most notably, this shows that benzannulation should play an important role in enabling a low-

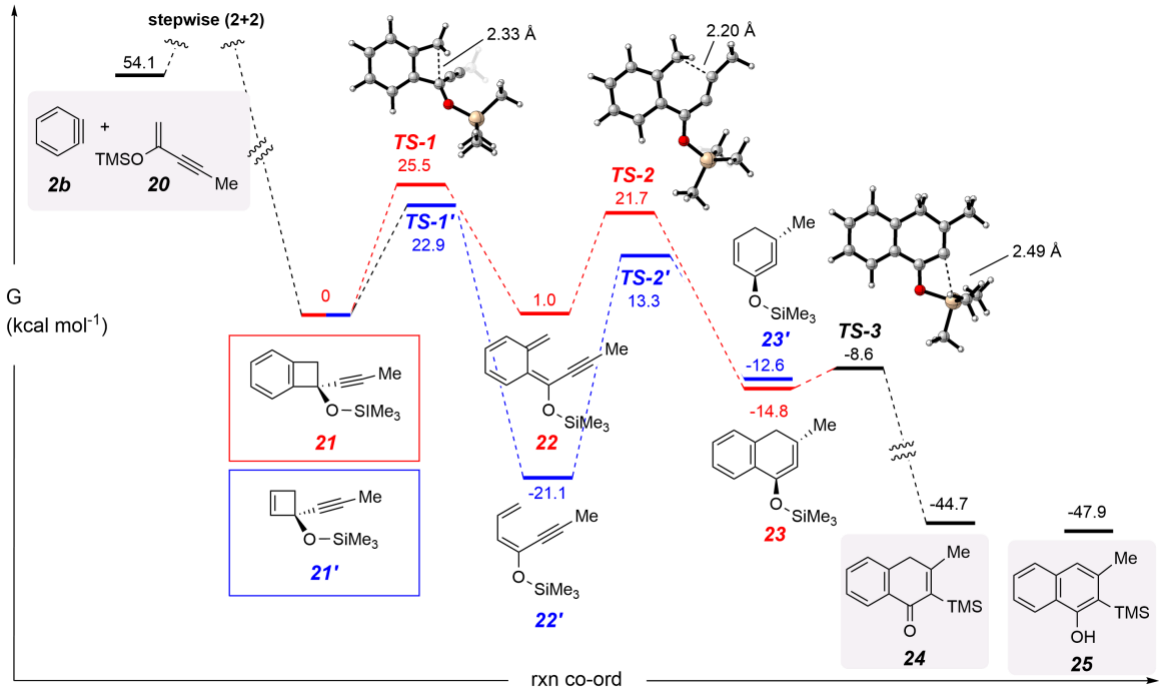
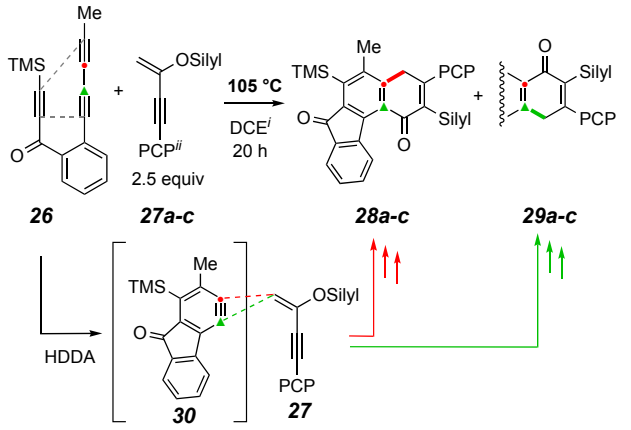


Figure 3. Computed potential energy surface for the formation of the benzocyclohexadienone **24** from *o*-benzyne (**4**) and the siloxyenyne **20**. DFT:[SMD (dichloroethane)/B3LYP-GD3BJ/6-311++G(d,p)

barrier Hopf cyclization. A rate acceleration effect for the Hopf cyclization (of single molecules) on a gold surface was also recently reported .[17]

Encouraged by these theoretical results, we initiated our experimental work with the reaction between benzyne precursor **26** and the family of siloxyenynes **27**[18] (Figure 4). Use of only a small excess of each of these enynes was sufficient for reasonably efficient capture of the benzyne. All of these reactions showed full conversion (no **26** by TLC) after 20 hours at 105 °C (vs. $t_{1/2}$ of ca. 90 min at 274 °C for **8** to **9**,[11a] Figure 1c), reflecting the rate enhancement provided by rearomatization of the alkynyl-*o*-xylylene. Surprisingly, regardless of the size of the silyl groups, the resulting cyclohexadienone moiety in both regioisomeric products **28** and **29** remained intact, even after chromatographic purification.

Structural elucidation (e.g., nOe studies, see SI) of the cyclohexadienone products showed that the skeleton of the major product **28** arose from initial trapping of benzyne **30** by the alkene methylene in enyne **27** at C● (red dashed line). The minor product **29** also arises from a benzocyclobutene wherein the methylene has engaged C▲ (green dashed line) in the initial trapping process.



27	Silyl	28 : 29[iii]	yield of 28[iv]	yield of 29[iv]
a	TBS	3.6 : 1	52%	14%
b	TES	3.8 : 1	54%	15%
c	TIPS	4.5 : 1	66%	13%

Figure 4. Efficient reactions between benzyne **30** and siloxyenynes **27**.

[i]DCE = 1,2-dichloroethane. [ii]PCP = *para*-chlorophenyl. [iii] From integration of the well-separated benzylic CH_2 resonances in each compound in the ^1H NMR spectrum of the crude product mixture. [iv]Yield of purified product.

After obtaining this first set of results, we explored several additional pairs of reactants (Figure 5). First, replacing the benzyne precursor **26** by the tetrayne **31** still produced a cyclohexadienone, now **32**, in high yield (Figure 5a). Second, reaction of **26** with the trisubstituted enyne **33** gave the cyclohexadienone adduct **34**, although with lower efficiency than with the less substituted alkene **27c** (Figure 5b). Third, the presence of the acetoxy group in the enyne **35** impacted the outcome significantly (Figure 5c). Although this was not a particularly efficient trapping agent, the benzocyclobutene derivative **36** was identified as the major product when heated with **26** under conditions (105 °C, 20 h) in which the silyl enol ether analogs underwent ring opening enroute to the final product. A model DFT analysis of the relative ease of ring-opening of a siloxy- vs. acetoxy-containing alkynylbenzocyclobutene showed the latter to have a significantly higher activation barrier than the former (33.7 vs. 25.5 kcal mol^{-1}; Figure S4 in the SI).

A third class of benzyne precursor was also examined (Figure 5d). The triyne **37** proceeds to give the benzyne **38**, which now contains a bulky trimethylsilyl substituent adjacent to C●. This steers the attack by the electron-rich enol ether methylene carbon in **27c** predominantly to C▲,[19] thus reversing the orientation of the benzocyclohexadienone in product **39** relative to that seen in the methylated analog **28c**. DFT computations suggest that the steric hindrance imposed by the larger TMS group is responsible for this reversal in regioselectivity (see SI, Figure S5 and related discussion).

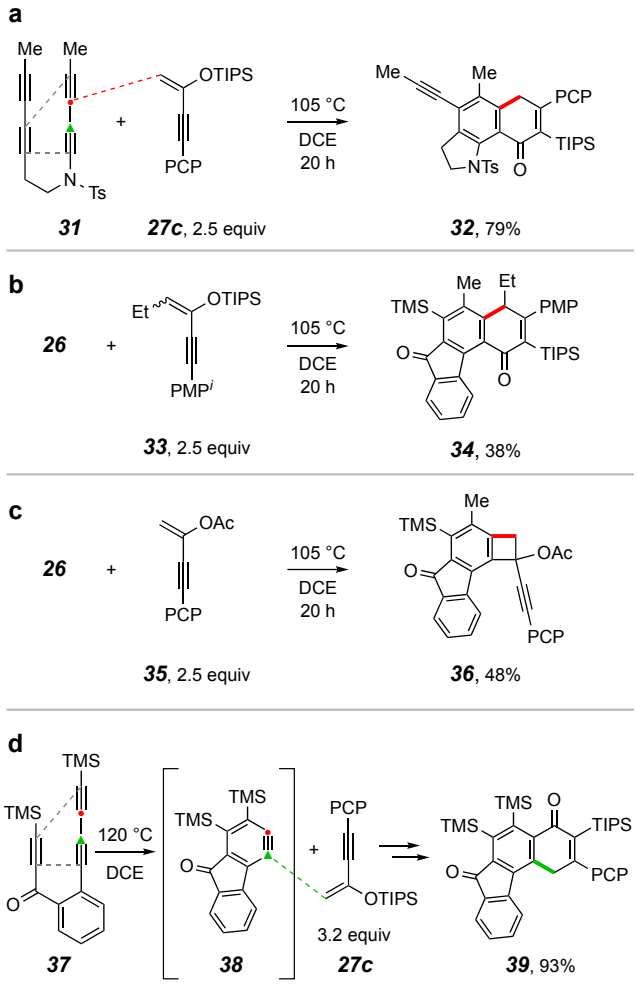


Figure 5. (a) Tetrayne **31** produced the cyclohexadienone **32** efficiently. (b) Trisubstituted siloxyenyne **33** engaged benzyne precursor **26** and provided the cyclohexadienone **34**. (c) The enol ester **35** engaged benzyne precursor **26** but produced, principally, the benzocyclobutene **36**. (d) Benzyne **38** was trapped by the enol ether with a reversed regioselectivity to provide the structurally complementary cyclohexadienone **39**. [i]PMP = *para*-methoxyphenyl.

We used **39** to probe the question of whether the enone could be isomerized to its phenolic tautomer. A solution of **39** in $CDCl_3$ was treated with DBU (ca. 20 equiv); there was no observable change (^1H NMR) at ambient temperature after 3 days, but when the sample was heated, slow exchange of H for D at the methylene CH_2 was observable. After 20 hours at 85 °C, the exchange had proceeded to produce an ~1:4:5 mixture of the CH_2 : CHD : CD_2 isotopomers. No evidence for the isomeric phenol tautomer was seen. Although not definitively, this observation strongly suggests that **39** is more stable than its phenolic tautomer.

We also showed that various substituents at the remote terminus of the alkyne were compatible with this process (Figure 6a). Enynes **40** containing an unsaturated substituent (C_{sp2}- or C_{sp}-) R group (such as aryl, carbonyl, alkenyl, alkynyl, or heteroaryl) all performed well. A limitation is that several substrates in which R was an alkyl or trialkylsilyl substituent gave a complex array of products that were not further pursued.

We next prepared the bis-enyne substrate **42** to probe the viability of its engaging two benzyne species (Figure 6b). When **42** was heated in the presence of 2.5 equiv of the triyne substrate **37**, the projected bis-cyclohexadienone **43** was formed in 58% isolated yield.

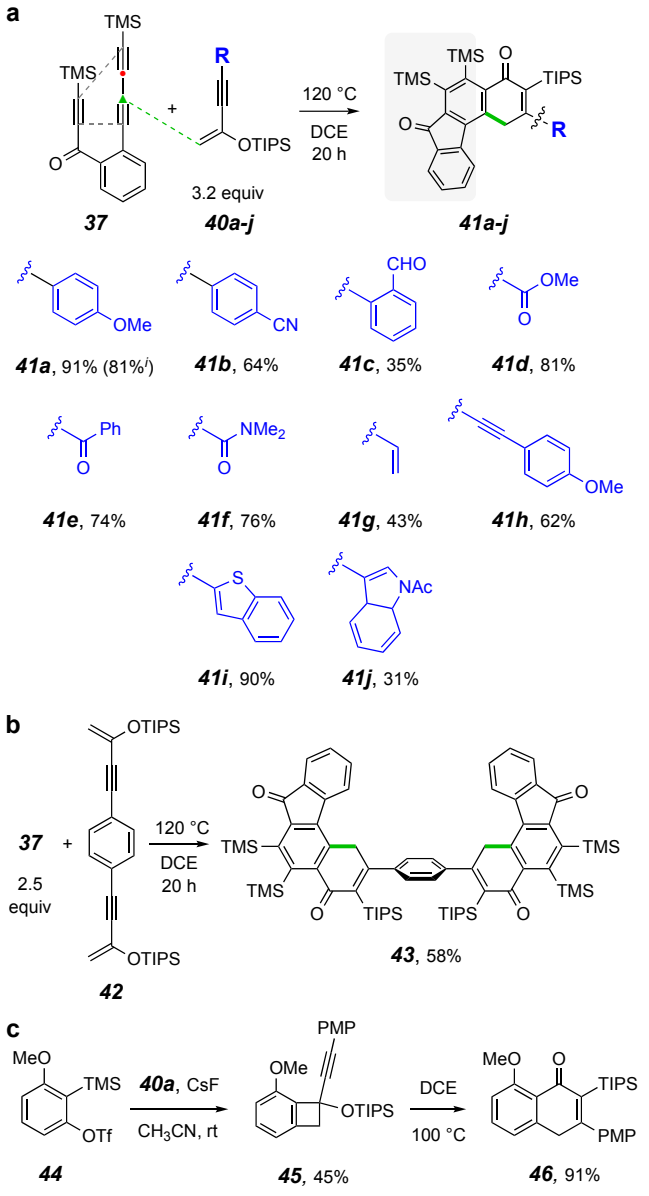


Figure 6. (a) A variety of unsaturated functionalities (aryl, carbonyl, alkenyl, alkynyl, heteroaryl) can be incorporated into the cyclohexadienone product. (b) Formation of a bis-cyclohexadienone derivative (**43**). (c) An example showing that a benzocyclobutene (the isolable adduct **45**, derived from the Kobayashi benzyne precursor **44**) will also efficiently participate in strain-promoted rearrangement to a cyclohexadienone derivative (**46**).

[i] Isolated yield from a 1 mmol reaction using 1.8 equiv of the enyne.

Finally, we demonstrated that a simple monocyclic benzyne precursor can also engage a siloxyenyne and undergo a net ring expansion (Figure 6c). The Kobayashi benzyne precursor **44**[20] reacted with enyne **40a** in the presence of CsF to produce the benzocyclobutene **45** in a highly regioselective manner**.** Reaction of **45** at 60 °C for 3 hours gave no evidence of a rearranged product. However, heating at 100 °C for 3 hours led to full consumption of **45** and efficient formation of the cyclohexadienone product **46**[21] (91%). This clearly indicates the intermediacy of the benzocyclobutene enroute to the cyclohexadienone product.

In summary, we have discovered a one-step, multi-stage reaction cascade that proceeds via cyclic (and thereby strained) alkyne, alkene, and allene intermediates. The process begins with the HDDA cycloisomerization of a linear polyyne to produce a benzyne intermediate (cf. **30**, Figure 4), which engages an electron-rich 1-alkynyl-1-siloxyalkene substrate (cf. **27**, Figure 4) to efficiently provide a semi-stable alkynylbenzocyclobutene intermediate [cf. E_{act} for **21** to **22** (Figure 3)]. Subsequent 4π-electrocyclic opening converts the strained cyclobutene derivative into an *o*-xylylene intermediate [cf. **22** (Figure 3)] that cyclizes to a cyclohexa-1,2,4-triene. A low barrier silyl migration within this strained allene [cf. **23** to **24** via **TS-3** (Figure 3)] leads to the final benzocyclohexadienone product. A variety of unsaturated substituents (aryl, carbonyl, alkenyl, alkynyl, and heteroaryl) at the distal alkyne terminus of the enyne substrate are tolerated (Figure 6).

DFT computations of a model reactant pair have given a PES for this cascade having both kinetically and thermodynamically favorable energetics (Figure 3). The slowest step after benzyne formation enroute to product is the 4π–electrocyclic ring opening, as supported experimentally by the isolation of the benzocyclobutenes **36** (Figure 5c) and **45** (Figure 6c). Rearomatization of the xylylene lowers the barrier for the Hopf cyclization compared to simpler dienynes (cf. **22'** to **23'**, Figure 3). Overall, these results constitute a strain-driven, multi-step process culminating in the formation of polycyclic benzocyclohexadienone derivatives.

ASSOCIATED CONTENT

Supporting Information

A PDF with details for i) the preparation and spectroscopic characterization (including copies of ^{1}H and ^{13}C NMR spectra) for all new compounds (**27a–c, 28a–c, 29a–c, 32–36, 39, 39-deuterated, 40a–j, 41a–j, 42**, **43**, **45**, and **46**) and ii) DFT energies and geometries for the structures in Figure 3 (PDF).

A .zip file of a master .mnova file of the NMR worked up data for all new compounds.

AUTHOR INFORMATION

Corresponding Author

* Thomas R. Hoye – Department of Chemistry, 207 Pleasant St., SE, University of Minnesota, Minneapolis, MN 55455, United States; orcid.org/0000-0001-9318-1477; Email: hoye@umn.edu

Author

Qian Xu – Department of Chemistry, 207 Pleasant St., SE, University of Minnesota, Minneapolis, MN 55455, United States; orcid.org/0000-0002-8655-8683

Notes

Neither of the authors has any conflict of interest with this work.

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[19] A similar steric directing effect has been observed for attack by bulky nucleophiles on 3-triethylsilyl-1,2-benzyne: (a) Bronner, S. M.; Mackey, J. L.; Houk, K.; Garg, N. K. Steric effects compete with aryne distortion to control regioselectivities of nucleophilic additions to 3-silylarynes. *J. Am. Chem. Soc.* **2012**, *134,* 13966–13969. (b) Medina, J. M.; Mackey, J. L.; Garg, N. K.; Houk, K. N. The role of aryne distortions, steric effects, and charges in regioselectivities of aryne reactions. *J. Am. Chem. Soc.* **2014**, *136,* 15798–15805.

[20] 3-Methoxy-*o*-benzyne (derived from **44**) selectively engages nucleophiles via attack at C1: Shi, J.; Li, L.; Li, Y. o-Silylaryl triflates: A journey of Kobayashi aryne precursors. *Chem. Rev.* **2021**, *121,* 3892–4044.

[21] In a separate experiment, **46** was heated in $CDCl_3$ in the presence of DBU. No evidence of a phenolic tautomer or of deuterium incorporation into **46** was seen; after 3 and 20 h at 100 °C, only partial or full decomposition of **46** was observed.