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Strain-promoted reactions of 1,2,3-cyclohexatriene and its derivatives

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Abstract

Since 1825¹, compounds with the molecular formula C₆H₆—most notably benzene—have been the subject of rigorous scientific investigation^{2–7}. Of these compounds, 1,2,3-cyclohexatriene has been largely overlooked. This strained isomer is substantially (approximately 100 kcal mol⁻¹) higher in energy compared with benzene and, similar to its relatives benzyne and 1,2-cyclohexadiene, should undergo strain-promoted reactions. However, few experimental studies of 1,2,3-cyclohexatriene are known^{8–12}. Here we demonstrate that 1,2,3-cyclohexatriene and its derivatives participate in a host of reaction modes, including diverse cycloadditions, nucleophilic additions and σ -bond insertions. Experimental and computational studies of an unsymmetrical derivative of 1,2,3-cyclohexatriene demonstrate the potential for highly selective reactions of strained trienes despite their high reactivity and short lifetimes. Finally, the integration of 1,2,3-cyclohexatrienes into multistep syntheses demonstrates their use in rapidly assembling topologically and stereochemically complex molecules. Collectively, these efforts should enable further investigation of the strained C₆H₆ isomer 1,2,3-cyclohexatriene and its derivatives, as well as their application in the synthesis of important compounds.

Since Faraday's isolation of an unidentified compound of the formula C₆H₆ in 1825¹, studies of benzene (**1**; Fig. 1a) and its isomers have led to notable advances in diverse areas, including the development of resonance theory^{13–15}, the discovery of aromaticity¹⁶ and the development of countless synthetic methodologies². Of the hundreds of known and postulated benzene isomers, strained isomers (for example, **2–4**) have a particularly rich history in organic chemistry. For example, Dewar benzene (**2**) and prismane (**4**), which

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Author contributions A.V.K., A.S.B. and D.C.W. designed and performed experiments and analysed experimental data. A.V.K. and D.C.W. designed, performed and analysed computational studies. N.K.G. directed the investigations and prepared the paper with contributions from all authors; all authors contributed to discussions.

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often appear in introductory textbooks, evolved from being hypothetical structures in the nineteenth century to notable synthetic targets in the twentieth century^{3,4}. Despite the nearly 200 years since the original isolation of benzene, investigation of strained isomers of benzene and their derivatives continues to provide new opportunities for discovery in modern organic chemistry⁵⁻⁷.

A strained benzene isomer that has remained largely underexplored is 1,2,3-cyclohexatriene⁸ (**5**), which was not validated experimentally until 1990. The three olefins in **5**, unlike those in benzene itself, are cumulated to give a highly strained structure. This strain, coupled with the lack of aromatic stabilization present in benzene, results in substantially higher free energy. The free energy of **5** calculated using density functional theory (DFT) compared with benzene (**1**) is +101 kcal mol⁻¹ (G_{rel}). As such, the strong ground state destabilization of **5** should yield kinetically and thermodynamically favourable reactions that are difficult or not possible for benzene (Fig. 1b). More specifically, in the case of benzene, a transformation of the type **1** → **6** would be disfavoured because of the loss of aromatic stabilization, which is expected to result in an energetic penalty in the relevant transition state and comparatively destabilize the corresponding product **6**. By contrast, analogous reactions of 1,2,3-cyclohexatriene (**5** → **7**) should be kinetically and thermodynamically favoured because of the considerable strain release along the reaction coordinate.

Conceptually, the strained benzene isomer **5** is closely related to arynes and strained cyclic alkynes (**8**) and strained cyclic allenes (for example, **9**; Fig. 2a). Each of these intermediates incorporates a functional group with a preferred linear geometry into a small ring. Although the cyclic alkynes and allenes were initially mere scientific curiosities when first validated in the 1950s and 1960s¹⁷⁻²⁰, they have now emerged as powerful tools for the construction of diverse target molecules²¹. Strained intermediates **11-14** are used in agrochemistry²², materials chemistry²³, heterocycle synthesis²⁴ and natural product total synthesis²⁵, respectively. Numerous studies pertaining to strained cyclic alkynes and strained cyclic allenes are available in the literature (about 4,600 reports and 160 reports, respectively; see Supplementary Information, part I, for details).

By contrast, 1,2,3-cyclohexatrienes (for example, **5**) have remained underexplored despite the fact that 1,2,3-trienes constrained to cyclic systems have been studied by chemists since the 1960s^{26,27}. Only four experimental studies pertaining to **5** are available in the literature. Two Diels–Alder trapping experiments involving 1,2,3-cyclohexatriene (**5**) have been reported previously⁸⁻¹⁰ using 1,3-diphenylisobenzofuran and cyclopentadiene, respectively. The intermediacy of a fused bicyclic 1,2,3-cyclohexatriene during flash vacuum pyrolysis of a linear precursor has been reported¹¹. Furthermore, a [4 + 2] cycloaddition reaction presumed to proceed between 1,2,3-cyclohexatriene (**5**) and nitrones, ultimately leading to products arising from rearrangement pathways rather than the expected primary cycloadducts, has also been reported¹². Substituted derivatives of 1,2,3-cyclohexatriene (**5**) are largely unexplored²⁸. These limitations are notable given the diverse transformations known for strained alkynes, which include (8 + 2), (7 + 2), (5 + 2), (4 + 2), (3 + 2) and (2 + 2) cycloadditions, nucleophilic trappings, ene reactions, transition metal-catalysed reactions, formal σ -bond insertions and many others. Furthermore, the lack of study of substituted trienes is notable given that substituted strained cyclic alkynes and allenes have

been studied extensively and shown to be important for enabling synthetic applications of strained intermediates²¹.

We now report an investigation of 1,2,3-cyclohexatriene (**5**) and its derivatives, which will enable further research in this long-understudied area (Fig. 2b). We describe (a) a computational comparison of 1,2,3-cyclohexatriene (**5**) to its isomer benzene (**1**) and its close relative benzyne (**20**); (b) (4 + 2), (3 + 2), (2 + 2) and nucleophilic trapping reactions (for example, **15** + **17** → **18**); (c) syntheses and trappings of new substituted cyclic 1,2,3-hexatrienes, including a geometrically distorted silyl-substituted cyclic triene that undergoes regioselective reactions; and (d) the elaboration of cyclic triene cycloadducts by leveraging the embedded 1,3-diene to rapidly access diverse product scaffolds (for example, **18** → **19**).

We performed DFT studies to directly compare the geometric and electronic structures of 1,2,3-cyclohexatriene (**5**) with those of its isomer benzene (**1**) and its relative benzyne (**20**) (Fig. 3a). Whereas the geometry of benzene is characterized by equivalent interior angles of 120°, the isomeric 1,2,3-triene (**5**) and benzyne (**20**) each show a wider internal angle at the positions depicted (131° and 127°, respectively) as a consequence of constraining two formally *sp*-hybridized carbons to a six-membered ring. This structural deformation leads to a calculated strain energy of approximately 50 kcal mol⁻¹ for both 1,2,3-cyclohexatriene (**5**) (ref. 29) and benzyne (**20**) (ref. 30). This calculated geometry for triene **5** is in good agreement with earlier reports³¹. However, to our knowledge, the electronic structure of **5** has not been reported previously. We find that the highest occupied molecular orbitals (HOMOs) of benzene (**1**), its isomer 1,2,3-cyclohexatriene (**5**) and benzyne (**20**) (ref. 31) are all localized to the conjugated π -systems, but the lowest unoccupied molecular orbital (LUMO) structures differ substantially. Unlike the LUMO of benzene, the LUMO of **5** is largely localized to the central, in-plane π -bond of the triene and is 1.5 eV lower in energy. Although the LUMO structure and energy are very different between cyclic triene **5** and benzene (**1**), there is a strong similarity in comparison with benzyne (**20**). This similarity suggests that triene **5**, unlike its well-studied isomer benzene (**1**), should share the strong electrophilicity of benzyne and its propensity to undergo cycloaddition reactions.

To initiate the experimental study of 1,2,3-cyclohexatriene (**5**), we prepared silyl triflate **21**, a readily available compound known from a 1990 study⁸, and performed trapping experiments (Fig. 3b). The use of a Kobayashi silyl triflate precursor was considered ideal, as Kobayashi precursors typically require mild fluoride sources to trigger in situ formation of the desired strained intermediate²¹. After optimization (see Supplementary Information, part I, section A, for details), we found that generation and trapping of **5** proceeded best using CsF as the fluoride source, tetrabutylammonium triflate as a fluoride-solubilizing agent³² and tetrahydrofuran (THF) as the solvent at 60 °C. Triene **5** reacts smoothly with various dienes, including an isobenzofuran, furans and a pyrrole, to provide (4 + 2) cycloadducts **27–30** in good yields (Fig. 3b, entries 1–4). We also studied (3 + 2) cycloadditions of **5**, direct products of which have not been reported in the literature¹². We found that triene **5** undergoes dipolar (3 + 2) cycloadditions with azomethine imines **31** and **32** to give cycloadducts **35** and **36**, respectively (Fig. 3b, entries 5 and 6). A formal (2 + 2) cycloaddition could also be achieved by using ketene acetal **33** as a trap, giving cyclobutane

37 (Fig. 3b, entry 7). Moreover, the use of phenoxide **34** as a nucleophile gives the direct addition product **38**. These results indicate that triene **5** is indeed a versatile intermediate capable of undergoing a range of trapping reactions despite having been minimally exploited in earlier experimental studies.

Substituted 1,2,3-cyclohexatrienes are largely unknown. To our knowledge, a single literature example suggestive of a substituted derivative of 1,2,3-cyclohexatriene (**5**) is available¹¹, which required pyrolytic temperatures (600 °C) and led to unimolecular rearrangement processes of the presumed triene intermediate, yielding a mixture of products. By contrast, substituted arynes, cyclic alkynes and cyclic allenes have been investigated extensively in both fundamental and applied studies to control regioselectivity in trappings and to synthesize complex structures^{21,33–35}. As such, we undertook the study of two new substituted 1,2,3-cyclohexatrienes (di- and monosubstituted) to validate their intermediacy and assess their synthetic potential.

To evaluate a disubstituted 1,2,3-cyclohexatriene, we prepared dimethylated silyl triflate **42**, the presumed precursor to **43**, using the sequence shown in Fig. 4a. Known brominated vinylogous ester **39** (ref. 36) was first converted to the corresponding silylated vinylogous ester **40** by a retro-Brook rearrangement of the corresponding silyl enol ether³⁷. Subsequent 1,2-addition and Stork–Danheiser transposition provided enone **41**. α -Methylation followed by triflation then delivered the desired silyl triflate **42**. This synthetic route is flexible and scalable, thus providing a roadmap for future studies of substituted cyclic trienes.

With silyl triflate **42**, we studied the generation and trapping of disubstituted triene **43** (Fig. 4b). Our previously optimized reaction conditions led to low conversion, but we found that switching the solvent to acetonitrile and increasing the loading of Bu₄NOTf facilitated full conversion and good yields in trappings of **43**. More generally, we observed that trappings of disubstituted triene **43** proceeded in higher yields and with broader scope compared with trappings of the parent compound, 1,2,3-cyclohexatriene (**5**), despite **43** bearing an increased steric profile. The results indicate the engagement of disubstituted triene **43** in (a) (4 + 2) cycloadditions with either electron-rich or electron-deficient dienes affording **50–52** (Fig. 4b, entries 1–3); (b) (3 + 2) cycloadditions using azomethine imines (**31** and **32**), nitrones (**46** and **47**), a quinolinium imide (**48**) or an isoquinolinium imide (**49**) to generate products **53–58** (Fig. 4b, entries 4–9); (c) a (5 + 2) cycloaddition of oxidopyridinium **59** to give [3.2.1]-bicycle **66** (Fig. 4b, entry 10); (d) formal (2 + 2) reactions using nucleophilic 2 π -systems, such as ketene acetal **33**, enamine **60** and thioketone **61**, to afford the corresponding cyclobutane or thietane products **67–69** (Fig. 4b, entries 11–13) and (e) nucleophilic additions using oxygen, sulfur, nitrogen or carbon nucleophiles **34** and **62–65** to give dienes **70–74**, respectively (Fig. 4b, entries 14–18). Notably, in the case of carbon nucleophiles **64** and **65**, formal C–C σ -bond insertion products were isolated, analogous to known aryne insertion reactions³⁸. Collectively, these data showcase that 1,2,3-cyclic trienes may engage in a host of trappings akin to what has long been established for arynes, but largely overlooked for cyclic trienes. Moreover, a variety of structurally distinct scaffolds are accessible, including fused polycyclic compounds, bridged structures and

complex heterocycles. All of the products bear functional handles for further manipulation, particularly the 1,3-diene motif.

Figure 5 highlights studies related to **75**, an unsymmetrical monosubstituted 1,2,3-cyclic triene bearing a triethylsilyl substituent. Silyl substituents have previously been used to study the origins of regioselectivity in aryne trappings^{39–42}, but similar studies relating to reactions of substituted 1,2,3-cyclic trienes have not been reported. The structure of **75** was optimized using DFT calculations (Fig. 5a). Polarization of the C1–Si bond towards C1 leads to rehybridization of the internal, formally *sp*-hybridized carbons of triene **75** in accordance with Bent's rule^{43,44}, which states that 'atomic s-character concentrates in orbitals directed toward electropositive substituents' and has been applied in previous studies of silyl-substituted arynes³⁹. This rehybridization strongly distorts the ground-state geometry, leading to a substantially flattened C1=C2=C3 bond angle ($\theta_{C2} = 146^\circ$) and a contracted C2=C3=C4 bond angle ($\theta_{C3} = 118^\circ$) relative to those of unsubstituted triene **5** ($\theta_{C2} = \theta_{C3} = 131^\circ$). This geometric distortion also yields a shift in the electron distribution in the substituted triene, with C2 now bearing a slight positive charge and C3 bearing a slight negative charge, consistent with the observed rehybridization. We inferred that **75** could undergo regioselective trapping given that analogous ground state distortion has previously led to regioselectivity in trapping reactions of silyl-substituted arynes³⁹.

To test this hypothesis, we prepared triethylsilyl-substituted silyl triflate **76** (see Supplementary Information, part I, section E, for details) and performed the key trapping experiments (Fig. 5b). With the large enamine **77** as the trap, adduct **78** was obtained, arising from a sterically controlled addition onto C3 of the triene, distal to the bulky triethylsilyl substituent. Conversely, with smaller phenoxide nucleophile **34** as the trap, a complete switch in regioselectivity was observed; adduct **79** was the sole product, arising from a proximal attack at C2. We proposed that this contra-steric outcome could arise from reactant pre-distortion, in which the geometric distortion in the ground state discussed above probably mirrors the geometry of the transition state, leading to the observed product. Such effects have been observed extensively in aryne chemistry and have been codified previously in the 'aryne distortion model', an application of distortion–interaction activation strain (DIAS) analysis⁴⁵, which enables the prediction of regiochemical outcomes in reactions of substituted arynes^{46–50}. DFT studies of the phenoxide trapping were performed (using a trimethylsilyl group instead of a triethylsilyl group and omitting the Na⁺ counterion) to validate the pre-distortion hypothesis (Fig. 5c). Consistent with our experiments, addition at C2 (**TS-1**) was found to be favoured over the addition at C3 (**TS-2**) by 3.1 kcal mol⁻¹ (G^\ddagger ; $E^\ddagger = 4.6$ kcal mol⁻¹, where G^\ddagger is the difference in Gibbs free energy barriers between **TS-1** and **TS-2** and E^\ddagger is the difference in electronic energy barriers between **TS-1** and **TS-2**). To explain the origin of this difference, we performed DIAS analysis to decompose E^\ddagger into two separate contributions from reactant distortion energies and interaction energies⁴⁵. With respect to distortion, $E^\ddagger_{\text{distortion}}$ for nucleophile **34** was negligible. However, $E^\ddagger_{\text{distortion}}$ for triene **80** was 1.4 kcal mol⁻¹, indicating greater distortion of triene **80** in **TS-2** compared with **TS-1**. The geometry of the triene in **TS-1** is indeed very similar to that of ground state triene **80**, thus requiring minimal geometric distortion to reach **TS-1** geometry ($\theta_{C3} = -4^\circ$; $\theta_{C2} = 0^\circ$). Conversely, arriving at **TS-2**

requires substantial geometric reorganization ($\theta_{C3} = 18^\circ$; $\theta_{C2} = -21^\circ$). This supports the notion that triene pre-distortion contributes to **TS-1** being favoured as proposed. DIAS analysis also indicates strong differences in interaction energies ($E_{\text{interaction}}^\ddagger = 3.2$ kcal mol⁻¹), which substantially contribute to the observed selectivity (see Supplementary Information, part II, section C, for details). Overall, the results shown in Fig. 5 indicate that sterics, distortion and interaction all contribute to controlling selectivity and that substituted 1,2,3-cyclohexatrienes can be used in regioselective reactions with potentially predictable outcomes.

Figure 6 shows the previously untapped value of strained cyclic trienes for the construction of complex scaffolds. Tricyclic diene **35**, prepared by azomethine imine cycloaddition of triene **5** (Fig. 3b), was elaborated to four compounds with different skeletons (**81–84**; Fig. 6a). Diene **35** underwent a Diels–Alder reaction with *N*-Ph-maleimide with high facial control guided by the *t*-butyl substituent to generate [2.2.2]-bicycle **81**. The diene of **35** can instead serve as a 2 π -component in cycloaddition reactions with either a strained cyclic allene or a nitrile oxide to generate fused polycycles **82** and **83**, respectively. These transformations occur with high regioselectivity with respect to both the diene and trap and give rise to unusual heterocyclic scaffolds. Alternatively, the diene motif of **35** can be preserved through chemoselective reduction of the N–N bond⁵¹ to deliver the 6/8 fused ring system of **84**.

The synthetic sequence shown in Fig. 6b establishes that 1,2,3-cyclic trienes can be used to quickly assemble complex scaffolds in a highly selective manner. Silyl-substituted triene **75** was trapped using enantioenriched enamine **85**. After hydrolytic workup, diene (+)-**78** was obtained regioselectively in 92% enantiomeric excess (ee). Subsequent allylation of (+)-**78** yielded diene (–)-**87** bearing a pendant alkene. Thermolysis of (–)-**87** effected a Diels–Alder (**TS-3**), retro-aldol and alkene isomerization cascade to yield (+)-**19** in 91% ee; (+)-**19** bears considerable structural complexity as shown by the 11-membered ring, a highly substituted [2.2.2]-bicycle, and three stereocentres. This concise, three-step elaboration of triene **75** to (+)-**19** demonstrates that, despite their high reactivity and minimal use in earlier experimental studies, strained cyclic trienes can be engaged in regio- and stereoselective reactions to ultimately access complex products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Experimental procedures, characterization data, computational methods and computational data are provided in the Supplementary Information. Crystallographic data are available free of charge from the Cambridge Crystallographic Data Centre under CCDC 2238912 and 2239633 (neilgarg@chem.ucla.edu). Reprints and permissions information is available at www.nature.com/reprints.

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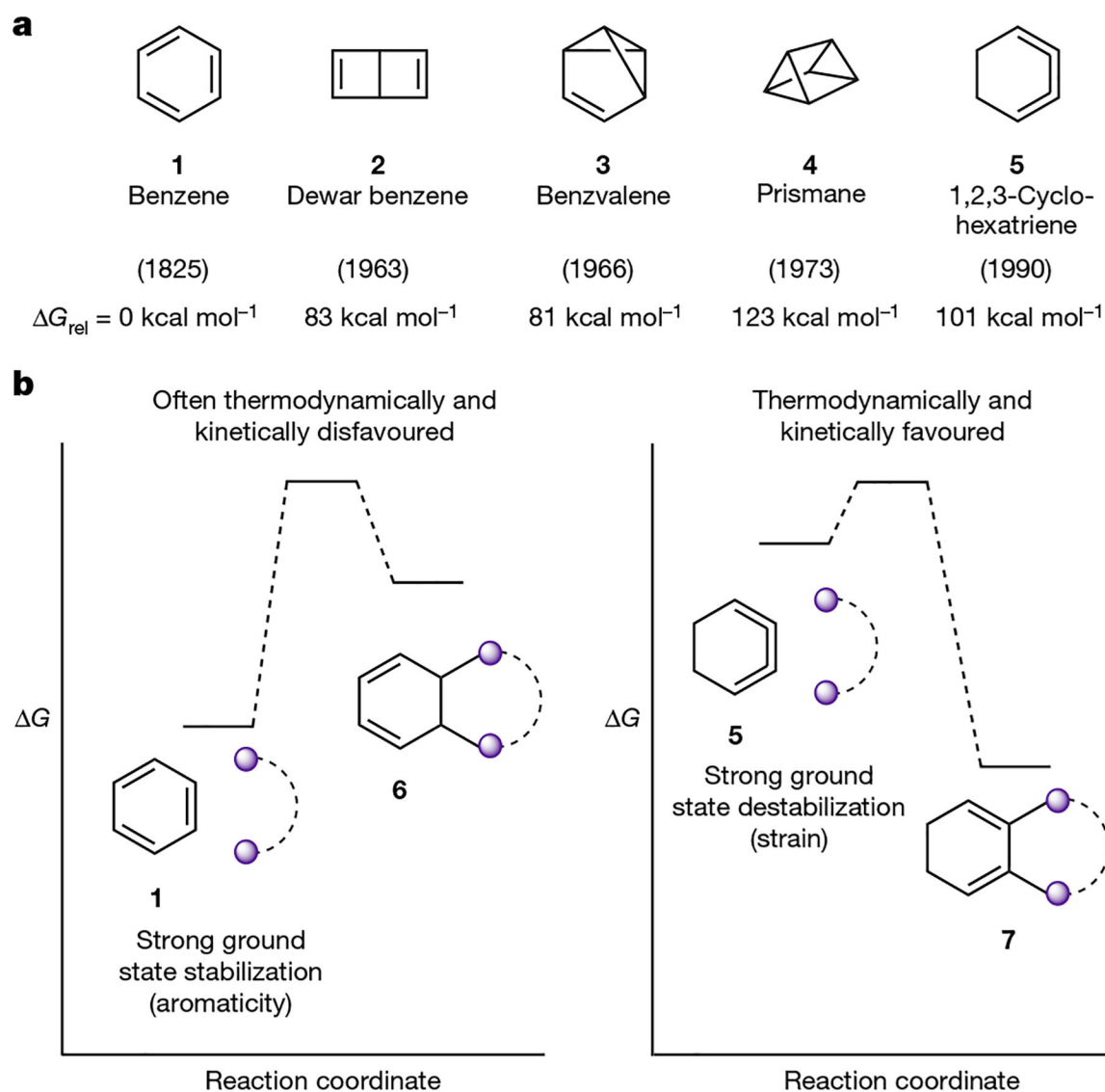


Fig. 1 | Selected strained isomers of benzene (1) and comparison of reaction coordinate diagrams.

a, Benzene (1) and its strained isomers with the year in which each was first isolated—or generated in situ in the case of 1,2,3-cyclohexatriene (5). Free energies at 298.15 K are reported relative to benzene (B3LYP-D3/6–311+G(*d,p*)). **b**, Hypothetical reaction coordinate diagrams for transformations of benzene (1) and 1,2,3-cyclohexatriene (5).

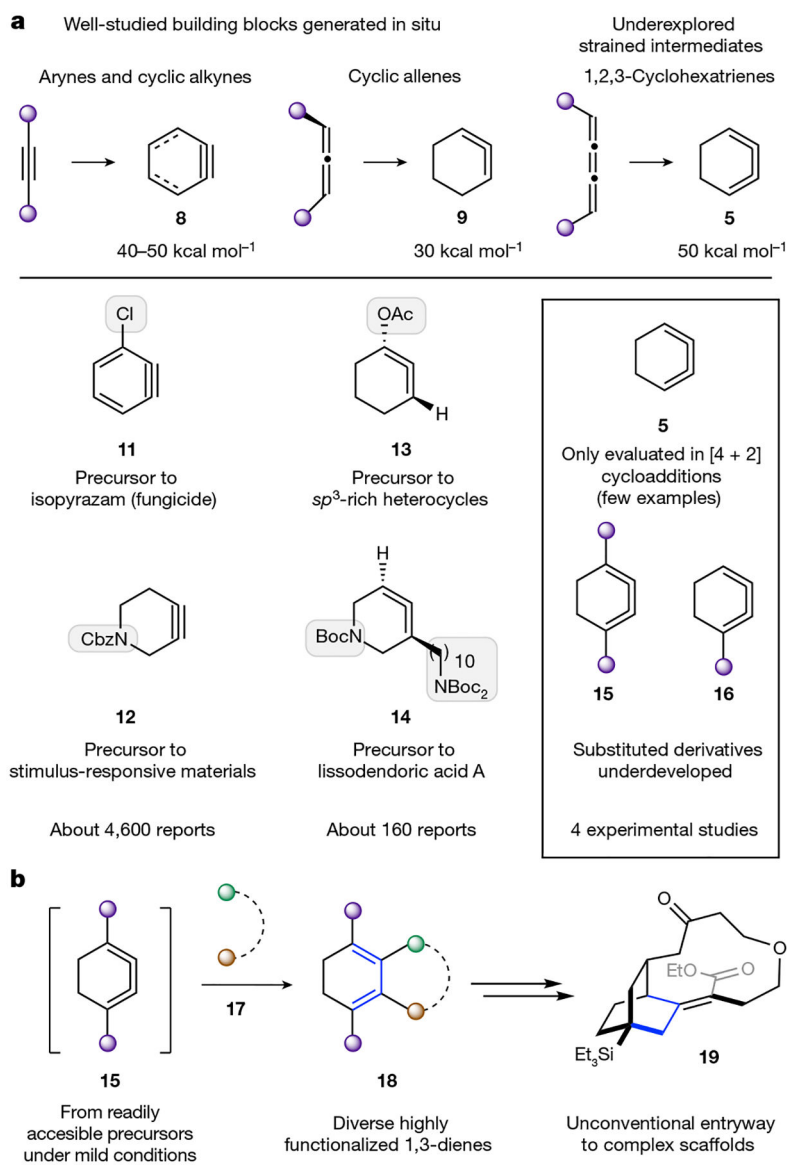


Fig. 2 | Strained cyclic intermediates and overview of the current study.

a, Representative classes of strained cyclic intermediates with synthetically useful derivatives **11–14**. **b**, Overview of our current study. Ac, acetyl; Boc, butyloxycarbonyl; Cbz, benzyloxycarbonyl; Et, ethyl.

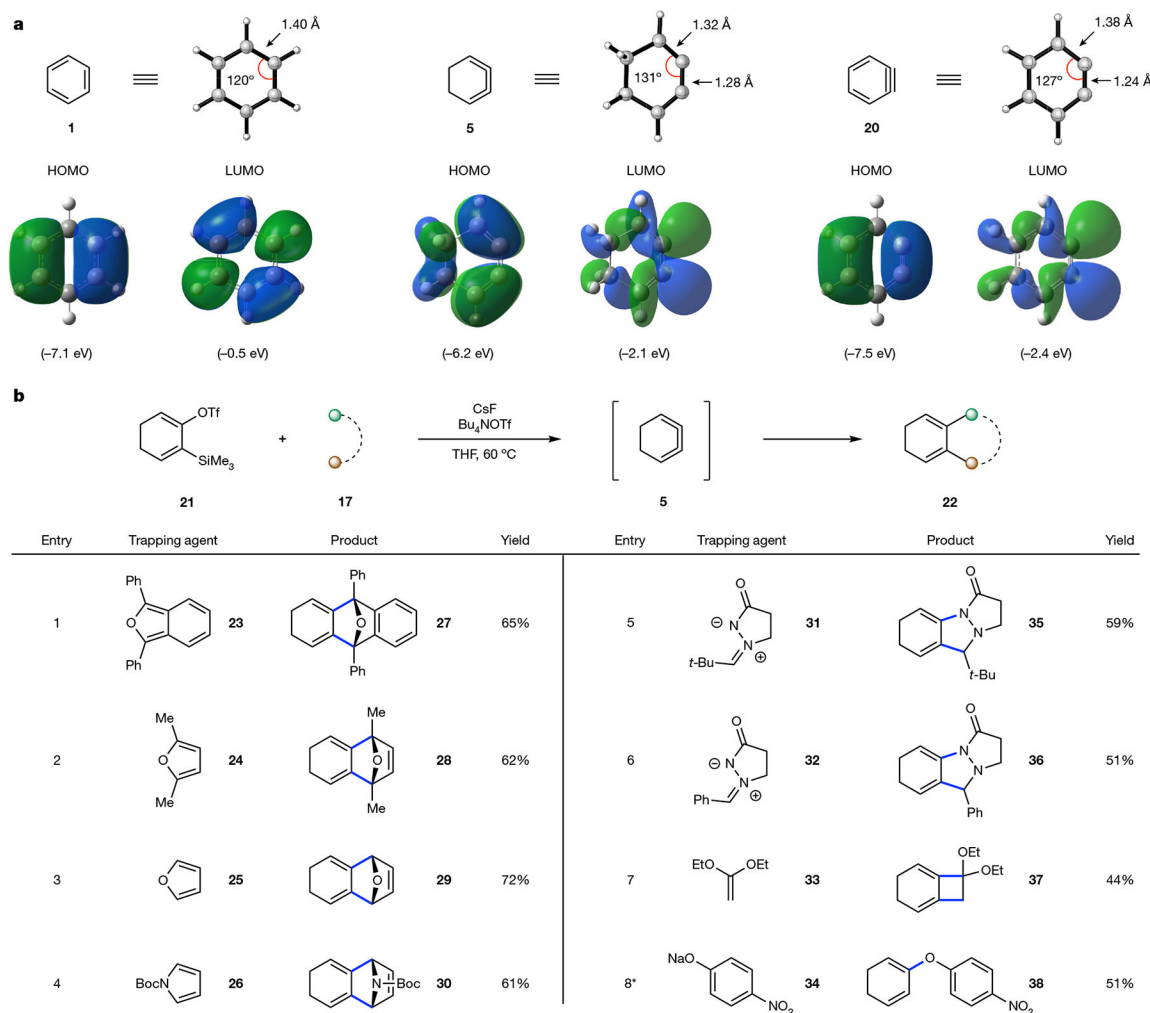


Fig. 3 | Structural analysis of benzene (1), 1,2,3-cyclohexatriene (5) and benzyne (20) and trapping reactions of strained triene 5.

a, Geometry-optimized structures and frontier molecular orbitals of benzene (1), 1,2,3-cyclohexatriene (5) and benzyne (20) (B3LYP-D3/6–311+G(*d,p*)). **b**, Reaction conditions are as follows: **21** (1 equiv.), trapping partner **17** (5–20 equiv.), CsF (10 equiv.), Bu₄NOTf (2 equiv.), THF (0.1 M), 60 °C, 24 h. Yields were determined by an average of two isolation experiments. Asterisk indicates modified reaction conditions: CsF (20 equiv.), Bu₄NOTf (4 equiv.), MeCN (0.1 M), 60 °C, 22 h (see Supplementary Information, part I, section B, for details). Boc, butyloxycarbonyl; Bu, butyl; Et, ethyl; OTf, trifluoromethanesulfonate; Me, methyl; Ph, phenyl; *t*-Bu, *tert*-butyl; THF, tetrahydrofuran.

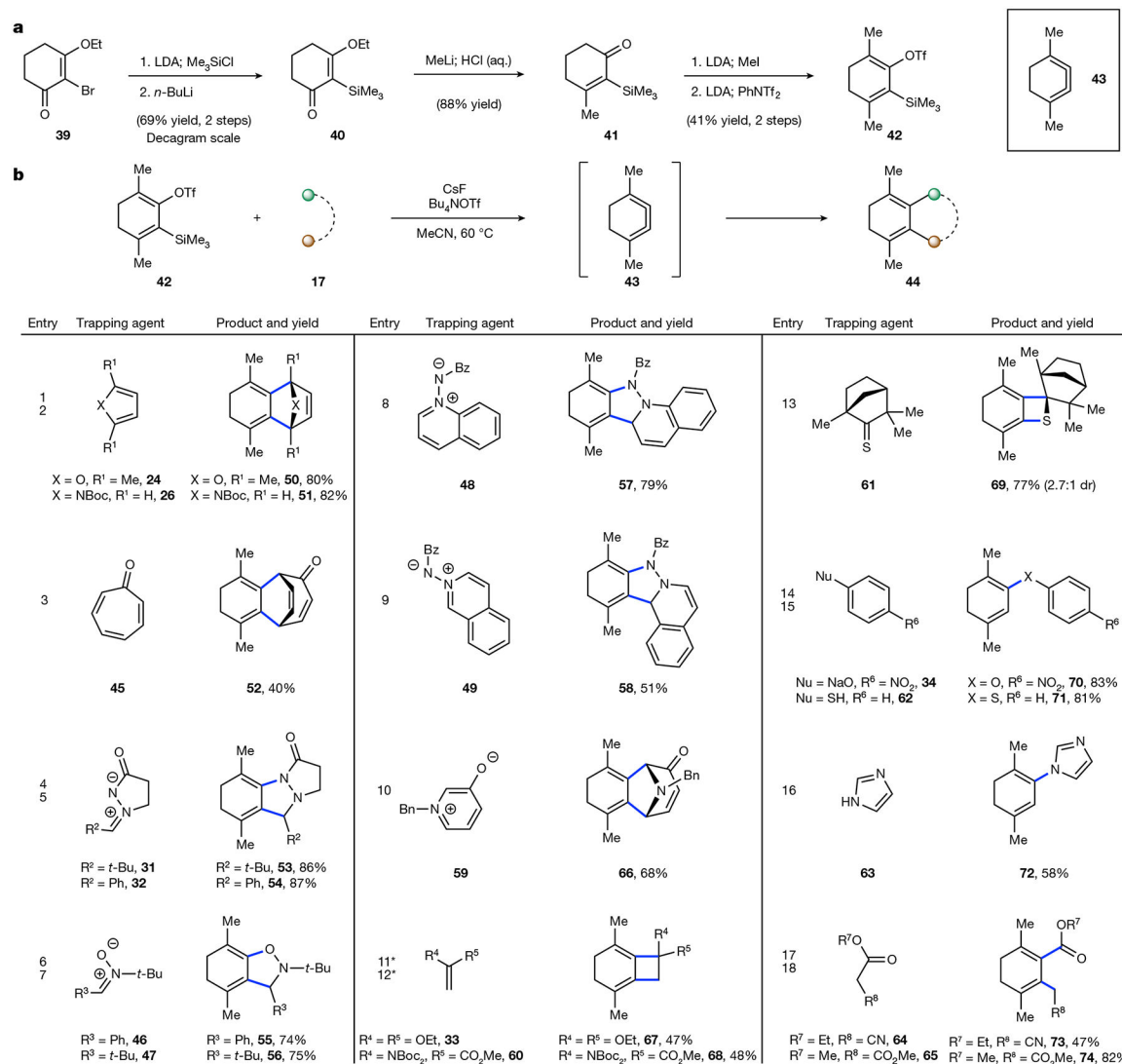


Fig. 4 | Preparation of a disubstituted cyclic triene precursor and scope of reactions.

a, Synthesis of silyl triflate **42** (see Supplementary Information, part I, section C, for reaction details). **b**, Reaction conditions are as follows: **42** (1 equiv.), trapping partner **17** (5–20 equiv.), CsF (20 equiv.), Bu₄NOTf (4 equiv.), MeCN (0.1 M), 60 °C, 24 h. Yields were determined by an average of two isolation experiments unless otherwise noted (see Supplementary Information, part I, section D, for details). Asterisk indicates yield determined by ¹H NMR with mesitylene as an external standard. Bn, benzyl; Boc, butyloxycarbonyl; Bz, benzoyl; dr, diastereomeric ratio; Et, ethyl; OTf, trifluoromethanesulfonate; LDA, lithium diisopropylamide; *n*-BuLi, *n*-butyllithium; Me, methyl; MeLi, methyllithium; Ph, phenyl; PhNTf₂, *N*-phenyl bistrifluoromethanesulfonimide; *t*-Bu, *tert*-butyl.

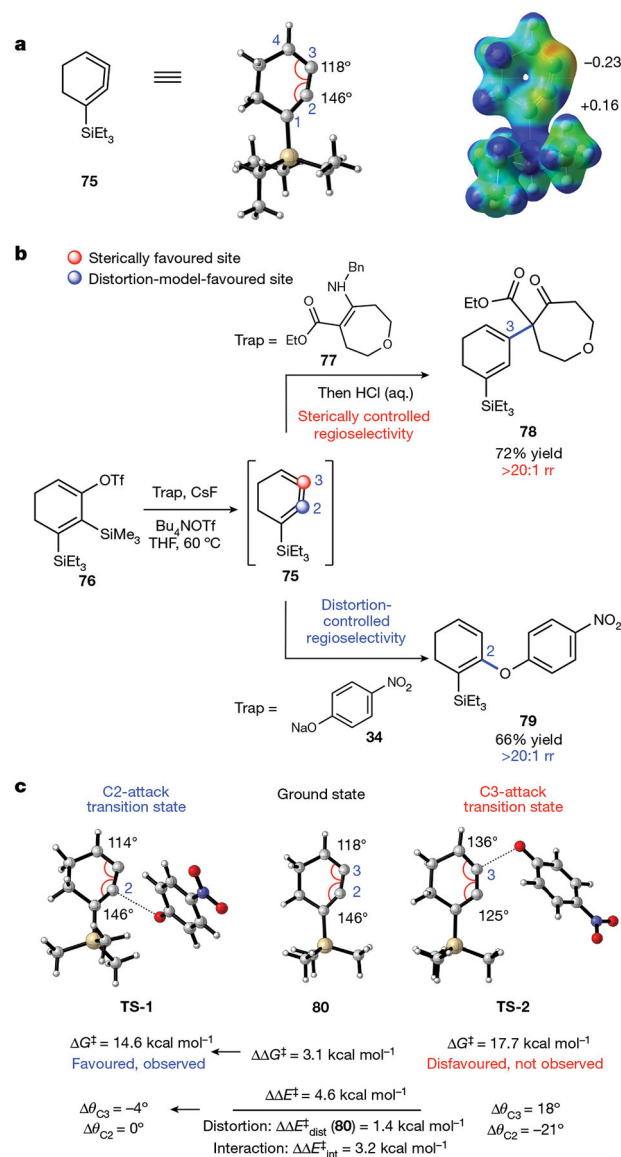


Fig. 5 | Structure and regioselective reactions of a monosubstituted cyclic triene.
a. Geometry-optimized structure of triene **75** and electrostatic potential map (B3LYP-D3/6–311+G(*d,p*)) (natural bond orbital charges shown). **b.** Yields determined by isolation experiments (see Supplementary Information, part I, section F, for reaction details). **c.** Transition state analysis at 333.15 K using a trimethyl silyl group to model the triethyl silyl group in **75** and omitting the Na cation of **34** (B3LYP-D3/6–311+G(*d,p*)/SMD(THF)) (see Supplementary Information, part II, section C, for details). Bu, butyl; Bn, benzyl; Et, ethyl; OTf, trifluoromethanesulfonate; Me, methyl; rr, regioisomeric ratio; THF, tetrahydrofuran.

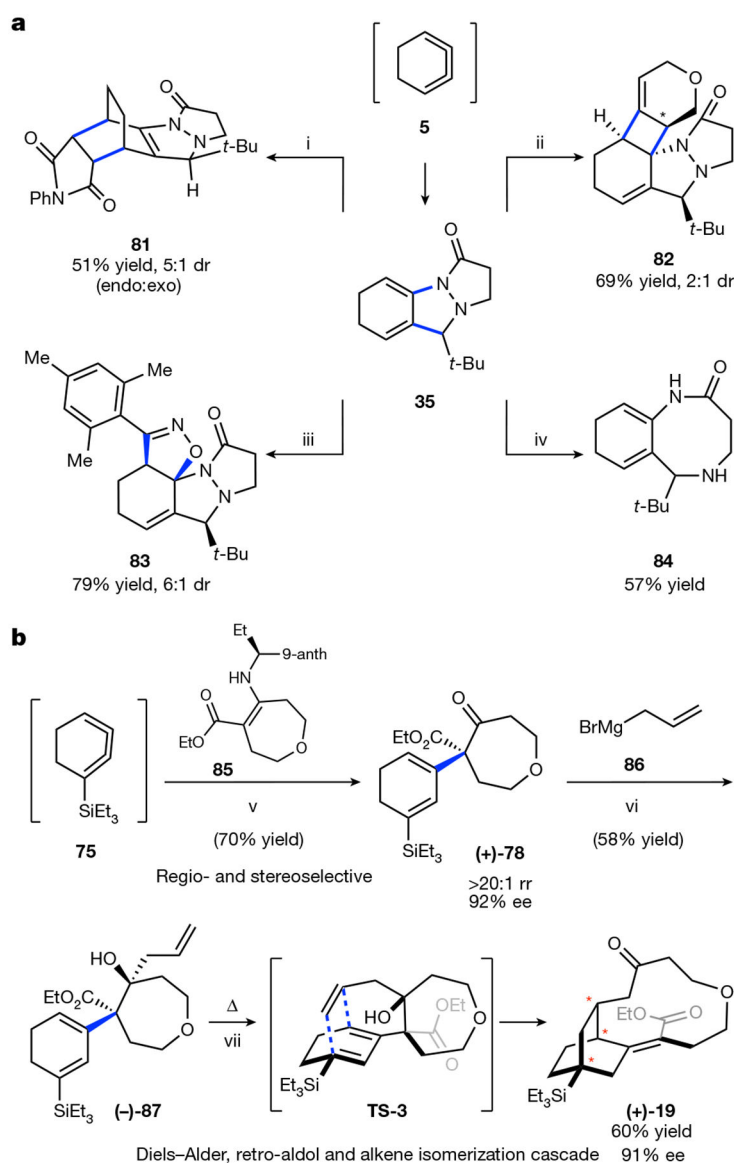


Fig. 6 | Strained 1,2,3-cyclohexatrienes in multistep synthesis.

a, Reaction conditions are as follows: i, *N*-Ph maleimide (2.5 equiv.), benzene, 80 °C, 51% yield, 5:1 dr. ii, Oxacyclic allene precursor (1.5 equiv.), CsF (5 equiv.), MeCN, 23 °C, 69% yield, 2:1 dr at the stereocentre indicated by an asterisk. iii, Mesitylene nitrile oxide (1.5 equiv.), CH_2Cl_2 , 0 °C to 40 °C, 79% yield, 6:1 dr. iv, Sodium naphthalenide (3 equiv.), THF, 0 °C, 57% yield (see Supplementary Information, part I, section G, for full reaction details). **b**, Reaction conditions are as follows: v, enamine **85** (5 equiv.), CsF (10 equiv.), Bu_4NOTf (2 equiv.), THF, 60 °C, then HCl (1 M), 23 °C, 70% yield, $>20:1$ rr, 92% ee. vi, AllylMgBr (2 equiv.), THF, -78 °C, 58% yield, $>20:1$ dr. vii, Hexadecane, 220 °C, 60% yield (see Supplementary Information, part I, section G, for full reaction details). 9-anth, 9-anthracenyl; dr, diastereomeric; Et, ethyl; Me, methyl; Ph, phenyl; rr, regioisomeric ratio; *t*-Bu, *tert*-butyl.