

The hexadehydro-Diels–Alder reaction

Thomas R. Hoye¹, Beeraiah Baire¹, Dawen Niu¹, Patrick H. Willoughby¹ & Brian P. Woods¹

Arynes (aromatic systems containing, formally, a carbon–carbon triple bond) are among the most versatile of all reactive intermediates in organic chemistry. They can be ‘trapped’ to give products that are used as pharmaceuticals, agrochemicals, dyes, polymers and other fine chemicals. Here we explore a strategy that unites the *de novo* generation of benzyne—through a hexadehydro-Diels–Alder reaction—with their *in situ* elaboration into structurally complex benzenoid products. In the hexadehydro-Diels–Alder reaction, a 1,3-diyne is engaged in a [4+2] cycloisomerization with a ‘dienophile’ to produce the highly reactive benzyne intermediate. The reaction conditions for this simple, thermal transformation are notable for being free of metals and reagents. The subsequent and highly efficient trapping reactions increase the power of the overall process. Finally, we provide examples of how this *de novo* benzyne generation approach allows new modes of intrinsic reactivity to be revealed.

ortho-Benzyne (1,2-didehydrobenzene, **1**, Fig. 1a) is one of the oldest¹, most interesting, most useful and most well-studied of all reactive intermediates in chemistry. The multifaceted and often remarkably efficient reactions of benzyne with suitable trapping reagents (**1**→**3** in Fig. 1a) have long been employed in the service of synthetic chemistry. Even by 1967 many such reactions were known². Nonetheless, newly discovered benzyne reaction motifs continue to emerge, especially so within the last decade^{3–10}. This renaissance attests to the additional versatility and heralds even greater potential of this intermediate. Currently, all practical methods for producing benzyne involve the removal of two adjacent atoms or substituents (‘G’ and ‘X’; Fig. 1a) from benzenoid precursors (**2**). These protocols typically require the use of a strong base and/or access to a 1,2-disubstituted arene substrate. A complementary general method for benzyne/aryne generation would considerably expand the preparative utility of these remarkable intermediates.

The venerable Diels–Alder cycloaddition reaction¹¹ is highly regarded in synthetic chemistry^{12,13}. The prototypical event (Fig. 1b), found in every introductory organic chemistry textbook, is the combination of 1,3-butadiene (**5**) as the 4 π -component with ethylene (**4**) as the dienophile to give cyclohexene (**6**)—a product in the tetrahydrobenzene oxidation state. If, instead, an alkyne like ethyne (**7**) is the dienophile, a 1,4-cyclohexadiene (here 1,4-dihydrobenzene (**8**)) results (Fig. 1c); we suggest this be viewed as a didehydro-Diels–Alder reaction. Another known variant (Fig. 1d) involves engagement of a (yet more highly oxidized) 1,3-enyne (for example, **9**) as the 4 π -component with an alkyne (for example, **7**). It is interesting to note that the first example of this process (the thermal dimerization of phenylpropionic acid)¹⁴ was described 30 years before the initial report of Diels and Alder¹¹. The intermediate cyclic allene **10** rapidly rearranges via a [1,5] hydrogen atom shift to benzene (**11**). This process has until now been called,

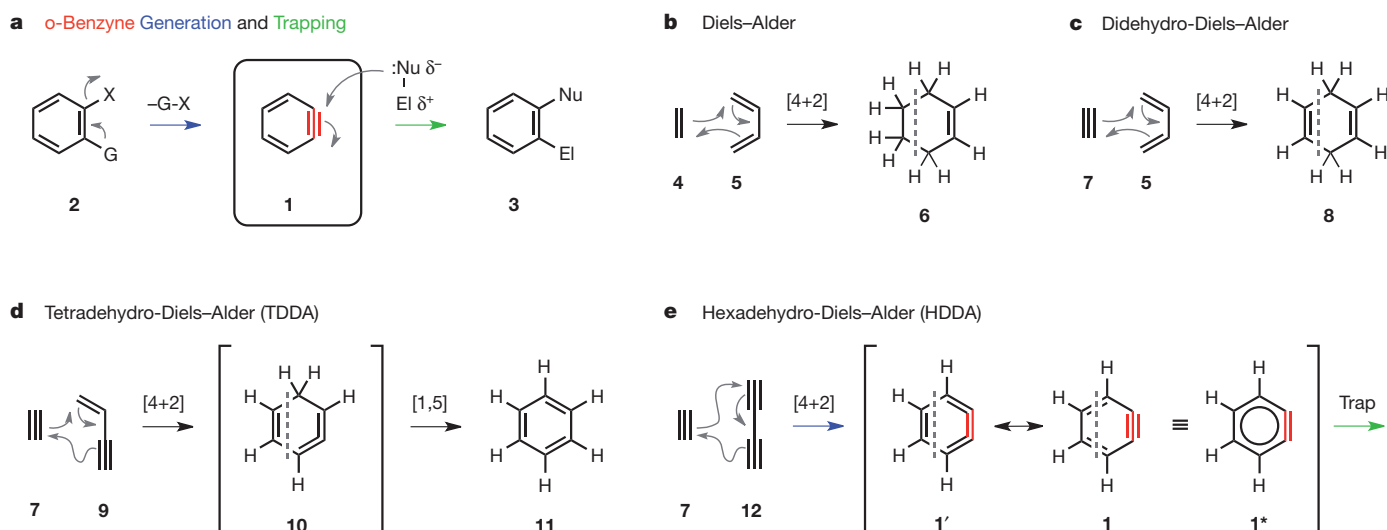


Figure 1 | Diels–Alder reactions of varying oxidation states. **a**, Generic benzyne generation (**2** to **1**) and trapping (**1** to **3**). Most commonly, G/X = H/halogen, CO₂[−]/N₂⁺, halogen/halogen, or TMS/OTf. **b–e**, Prototypes of Diels–Alder [4+2] (that is, the combination of a four-atom (or 4 π electron) component with a two-atom (or 2 π electron) component to produce a six-membered ring) reactions differing in the oxidation levels of the reactant pairs

and products: classic Diels–Alder (**b**), didehydro-Diels–Alder (**c**), tetradehydro-Diels–Alder (TDDA) (**d**), and hexadehydro-Diels–Alder (HDDA, this work) (**e**) reactions. The aromatic character of benzyne is emphasized by the resonance contributors **1** and **1'** as well as by the resonance hybrid structure **1***. TMS, trimethylsilyl; OTf, trifluoromethanesulphonate; Nu, nucleophile; El, electrophile.

¹Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455, USA.

generically, the dehydro-Diels–Alder (DDA) reaction¹⁵. In the light of the generality of the results we present here, we suggest that the transformation in Fig. 1d would be better named the tetrahydro-Diels–Alder (TDDA) reaction.

The most highly oxidized Diels–Alder variant (Fig. 1e) is the cycloaddition between a 1,3-diyne like **12** and an alkyne diynophile like **7**, which generates *o*-benzyne (compare **1'**, **1** and **1***). This hexahydro-Diels–Alder (HDDA) reaction is the subject of this Article. Given the efficiency, ease of precursor access, versatility and mild reaction conditions revealed by the examples we present here, it is remarkable that this reaction has remained essentially unexploited^{16–19}. It is interesting to speculate that this may be due in part to the fact that the most common depiction of benzyne—the resonance contributor **1** (Fig. 1e)—obscures its potential construction via a [4+2] cycloaddition reaction. It is the alternative, but rarely encountered, Kekulé depiction (**1'**) that reveals the opportunity for assembly via an HDDA process.

We report below the broad scope of a strategy that combines the versatile and efficient generation of benzynes via the HDDA reaction with various trapping reactions to yield structurally complex benzenoid products. Each substrate is a readily accessible conjugated diyne containing a remote alkynyl diynophile. These cycloisomerize in (a highly exergonic) [4+2] fashion to produce the reactive aryne intermediate. The examples demonstrate that the tandem benzyne forming/trapping sequence can be designed to proceed with excellent efficiency.

The HDDA reaction revealed

In the course of an otherwise unrelated study, we attempted to prepare the ketotetrayne **14** by oxidation of the precursor alcohol **13** with manganese dioxide (Fig. 2a). To our surprise, the major product from this experiment, formed in about 5 hours, was the (hexasubstituted) benzene derivative **15** (53% yield after purification). We quickly postulated that the benzyne intermediate **16'**/**16** was being both readily formed and efficiently trapped by the nucleophilic oxygen atom in the fortuitously poised β -siloxyethyl group. Migration of the silyl group from O to C within zwitterion **17**, a retro-Brook rearrangement, accounts for formation of **15**. This constitutes an unprecedented mode of benzyne trapping. Additionally, the process is attended by a substantial increase in structural complexity. The potential power of this transformation was immediately apparent.

We surmised that the modest yield observed in this reaction of tetrayne **14** reflected the fact that two competitive modes of [4+2] cyclization are possible. We were also keen to learn the feasibility of cyclization of analogous triynes. We therefore designed and synthesized a substrate—the ketotriyne **21** (Fig. 2b)—that could only undergo a HDDA reaction with a single regiochemical outcome. Our efforts were rewarded by its smooth transformation at room temperature to the hexasubstituted, tetracyclic indenone derivative **22** in 93% yield after chromatographic purification.

Intramolecular trapping

As the examples presented in Table 1 clearly show, the HDDA-initiated cascade has considerable scope with respect to both the cycloisomerization and the intramolecular trapping events. Each substrate is readily accessible by a convergent coupling strategy (compare Fig. 2b). All yields of purified products were $\geq 75\%$, and (with the exception of entry 8) all reactions occurred between temperatures of 20 and 120 °C. Highlights include: the presence of an electron withdrawing substituent on the diynophile enhances substrate reactivity (compare conditions for **21** to **22** (Fig. 2b) with entry 1); the activating carbonyl group can be a distal (carboalkoxy) rather than a tethering substituent (entries 2 and 3); many classical methods of aryne generation are not compatible with electron-withdrawing groups in the substrate²⁰; carbonyl activation is not a necessity (entries 1, 4 and 7); products having nitrogen-containing heterocycles annulated to the new arene ring can be prepared (entries 3–5); an ester tether (entry 6)

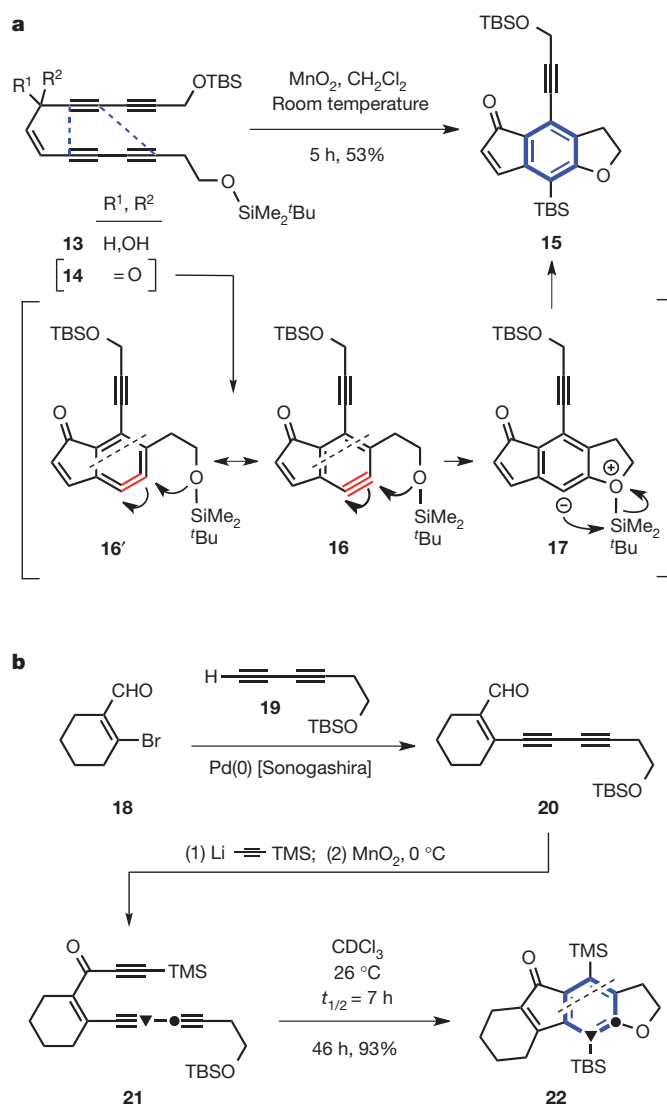


Figure 2 | Mechanistic rationale, substrate synthesis and mild conditions for our initial two HDDA reactions. **a**, Serendipitous observation of the HDDA reaction: cyclization of ketone **14** (see blue dashed lines) to putative benzyne (red) intermediate **16'**/**16** (via formation of the bonds indicated by the black dashed line in each) and subsequent trapping by the pendant silyl ether gave a hexasubstituted benzenoid (blue), the indenone **15**. **b**, Synthesis of **21** (via convergent coupling of **18** with **19**, addition of an ethynyl unit to **20**, and oxidation) and its facile, high-yielding conversion to the tetracyclic benzenoid (blue) **22**. The adjacent atoms denoted by the triangle and dot in substrate **21** map onto those of the product **22**. The half-life ($t_{1/2}$) for conversion of **21** to **22** was measured by *in situ* NMR analysis (Supplementary Fig. 1). TBS, *t*-butyltrimethylsilyl.

cyclizes more slowly than its *N*-phenyl amide analogue (entry 5), consistent with the lower concentration of the *s*-cis conformation required for ring closure; our observations are consistent with the absence of radical character in both the cycloaddition and trapping phases of the process (for example, reactions performed in chloroform solvent, an excellent hydrogen atom donor, have shown no evidence of hydrogen atom transfer (entries 4 and 9)); the new silyl ether trapping reaction has considerable generality (entries 1–3, 5, 6 and 8 and Fig. 2); other efficient internal benzyne traps include tethered alcohols (entries 4 and 7), aryl rings ([4+2] cycloaddition in entry 9), or alkenes (ene reaction in entry 10); seven-membered ring formation is feasible (entry 8), and the robust nature of the substrate and product at the high temperature required for this slower cyclization are noteworthy; and finally the silyl substituents in many of the products provide handles

Table 1 | Examples of intramolecular trapping of HDDA-generated benzenes

Entry	Substrate	Conditions	Product
1		110 °C 72 h PhMe 96%	
2		110 °C 20 h <i>d</i> ₈ -PhMe 86%	
3		120 °C 18 h PhMe 80%	
4		65 °C 20 h CDCl ₃ 95%	
5		120 °C 15 h PhMe 92%	
6		120 °C 48 h PhMe 86%	
7		95 °C 48 h PhH 87%	
8		195 °C 32 h <i>o</i> -DCB 75%	
9		85 °C 18 h CHCl ₃ 85%	
10		97 °C 22 h Heptane 83%	

Benzoid (bold black bonds) synthesis via the HDDA cycloaddition has considerable substrate scope with respect to the nature of the poly-yne tether (red) and of the intramolecular trapping moiety (blue). Ac, acetyl; Ts, *p*-toluenesulphonyl; *o*-DCB, 1,2-dichlorobenzene.

for subsequent elaboration through protonative, oxidative or halogenative desilylation or cross-coupling reactions²¹.

Intermolecular trapping

We wished to validate the feasibility of bimolecular trapping of these thermally generated benzenes. Clearly, this would add considerable versatility and power to a HDDA-initiated transformation. The triyne **23** (Fig. 3) represents a substrate that bears an innocent (non-participating) side chain. We have successfully captured the derived benzyne **24** (formed from **23** in a cyclization reaction having a half-life of ~4 h at about 85 °C) by a variety of external reagents to give adducts **25**. Highlights include: benzene as solvent forms the Diels–Alder adduct **25a** (compare entry 9 of Table 1)—although this process has been previously documented²², because of the low reactivity of simple aromatics, rarely have they been trapped by benzenes in high yield; this result also indicates that many intramolecular trapping events are faster than capture by the aromatic solvents used in earlier examples (entries 1–3 and 5–8 of Table 1); the [2+2] cycloaddition of norbornene gives **25b** in higher yield than has been observed for trapping of arynes formed by conventional methods²; *N*-phenylacetamide gives **25c**, demonstrating that a nitrogenous substituent can be conveniently installed; acetic acid²² or phenol traps **24** to cleanly provide adducts **25d** or **25e**, respectively, in processes that may share a mechanistic feature of transfer of a hydroxyl proton coincident with nucleophilic attack; this mode of reaction with acetic acid or phenol is unique and complementary to that seen with benzenes generated by non-reagent-free methods^{23,24}, and finally net trapping by hydrogen bromide was achieved using Br(CH₂)₂NH₂·HBr in THF/H₂O (20:1) as an HBr source to give **25f** (6:1 mixture of isomers).

The sense of regioselectivity observed for formation of products **25c–f** is consistent with the analyses described in refs 24 and 25, in which the relative magnitude of the computed internal bond angles of an unsymmetrical benzyne is correlated with the site of nucleophilic attack. Namely, the more obtuse angle corresponds to the more electron deficient (δ^+) of the two benzyne carbon atoms. We computed the geometry for **24** (R = CH₃) using density functional theory (DFT) at the M06-2X/6-31+G(d,p)²⁶ level to have internal angles of 135° and 119° at atoms 'a' and 'b', respectively. We are currently investigating additional substrates that should allow us to distinguish the relative impact of electronic versus ring-distortion effects on the site of attack by external nucleophiles.

To gain understanding of some of the key thermodynamic features associated with the HDDA aryne-forming step, we turned to computational analysis of the reaction of ester **26** (Fig. 4). This simple triyne was cycloisomerized and the resulting benzyne trapped in *t*-butanol (120 °C, closed tube) to produce 5-*t*-butoxyphthalide (**28**) in 68% yield. Johnson and co-workers recently reported a DFT approach to compute the energetics of the hypothetical HDDA reaction of **7** with **12** to produce *o*-benzyne (**1**, Fig. 1e)²⁷. They concluded that this benzyne-forming reaction was exothermic by 51.4 kcal mol⁻¹. Using similar DFT methodology, we have computed the free energy of reaction for the conversion of triyne **26** to the aryne **27** and found it to be -51 kcal mol⁻¹. It is remarkable that highly reactive benzyne intermediates can be accessed by a thermal process that is exothermic by ~50 kcal mol⁻¹. These very favourable reaction energetics reflect the large amount of potential energy inherent in the (albeit kinetically protected) alkyne functional group. Finally, this point is further underscored by the computed free energy of reaction—namely, -73 kcal mol⁻¹—for the trapping by *t*-butanol of the strained alkyne²⁸ in **27**. Thus, the overall transformation of **26** to **28** is computed to be exothermic by >120 kcal mol⁻¹.

Discussion

Our results show that the HDDA reaction is a general method for generating benzenes under conditions amenable to a wide variety of intra- and intermolecular trapping events. This powerful and efficient

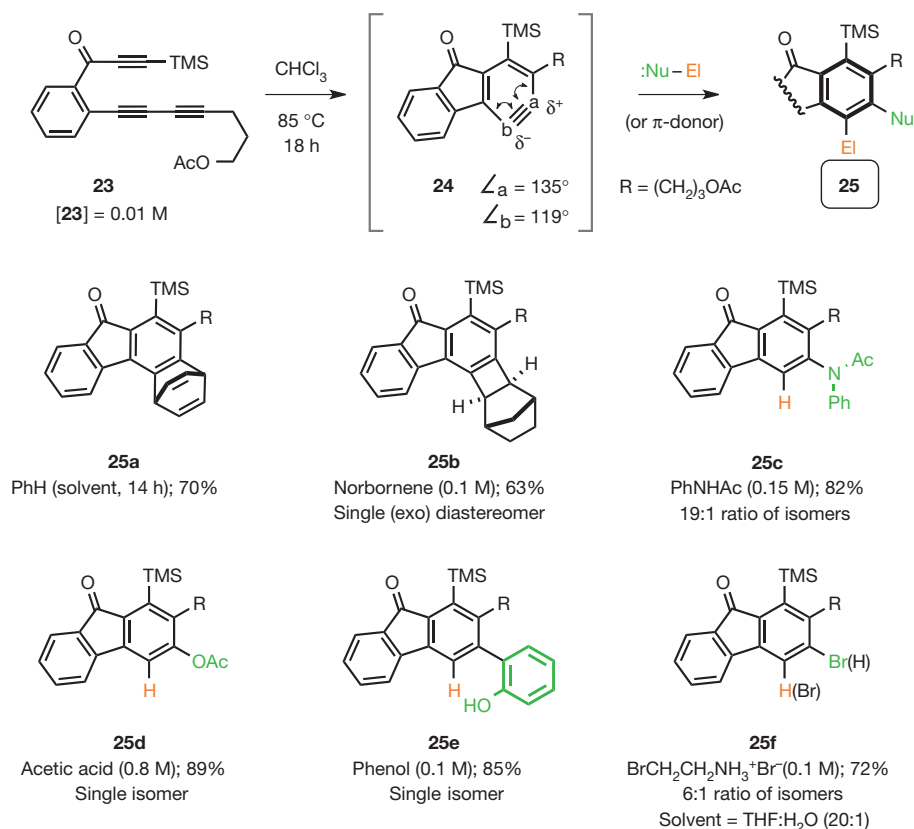


Figure 3 | Examples of intermolecular trapping of HDDA-generated benzenes. Bimolecular trapping reactions of benzyne **24** to give adducts **25a–f**. Under the structure of each of these adducts is given information on the

domino sequence comprises a fundamentally new way to synthesize benzenoid compounds—especially those having high structural complexity. Because HDDA-derived benzenes are produced in the absence of by-products and external reagents, the intrinsic reactivity of a benzyne can be more fully explored and exploited. Even at this early stage of development, many additional lines of investigation

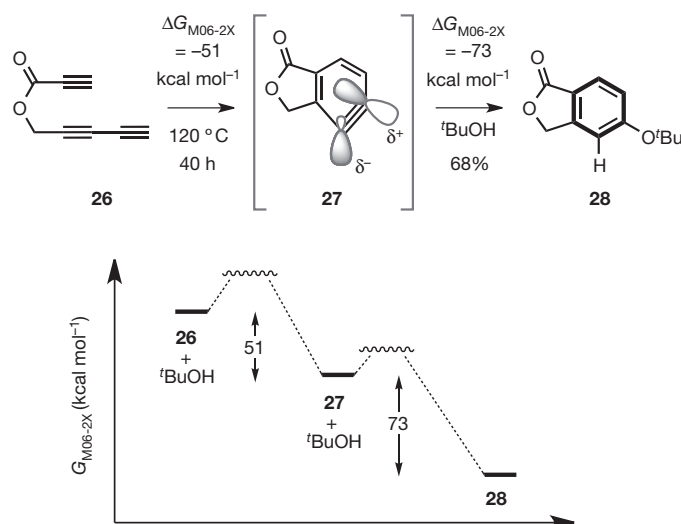


Figure 4 | Computed free energy changes for a representative HDDA-initiated cascade. Free energies of reaction ($\Delta G_{M06-2X} = G_{M06-2X}(\text{product}) - G_{M06-2X}(\text{reactant})$) were computed by DFT at the M06-2X/6-31+G(d,p) level for the aryne-generating (**26** to **27**) and *t*-butanol (*t*BuOH) trapping (**27** to **28**) reactions. These serve to highlight the favourable thermodynamics associated with both the triyne cycloisomerization and aryne trapping events.

trapping agent (and amount) and yield following purification. Stereochemical information is given for adduct **25b**. Regiochemical information is given for adducts **25c–f**. THF, tetrahydrofuran.

have revealed themselves. These include studies of mechanistic issues (concerted versus stepwise cycloaddition), substituent effects (electronic versus steric), catalysis (Lewis acid or transition metal), new modes of benzyne trapping, the use of cleavable tethers, and the feasibility of bimolecular HDDA cycloadditions. This enabling technology is well-suited for preparing compound libraries, for accessing aromatics having substitution patterns that would be otherwise challenging to prepare, and for application to target molecule synthesis (for example, drugs, natural products^{9,10}, heteroaromatics and polyacenes). Lessons of how imagery (that is, **1** (versus **1'**) from **7** + **12**) can bias our perception are also embedded in the developments described here. Finally, our results serve as a reminder that, even in the twenty-first century, serendipitous discovery (“in the course of an otherwise unrelated study”) in science can still play a pivotal role.

METHODS SUMMARY

General procedure. An oven-dried vial containing the triyne precursor in the indicated solvent (0.05 M) was closed with a Teflon-lined cap and heated at the indicated (external bath) temperature. After the indicated time the product was purified by chromatography on silica gel. Full procedural details and characterization data for all new compounds (substrates and products) and a detailed description of the computational protocols and results are provided in Supplementary Information.

Received 15 May; accepted 16 August 2012.

- Wenk, H. H., Winkler, M. & Sander, W. One century of aryne chemistry. *Angew. Chem. Int. Edn* **42**, 502–528 (2003).
- Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes* (Organic Chemistry, A Series of Monographs, Vol. 11, Academic, 1967).
- Pellissier, H. & Santelli, M. The use of arynes in organic synthesis. *Tetrahedron* **59**, 701–730 (2003).
- Dyke, A. M., Hester, A. J. & Lloyd-Jones, G. C. Organometallic generation and capture of *ortho*-arynes. *Synthesis* 4093–4112 (2006).
- Sanz, R. Recent applications of aryne chemistry to organic synthesis. A review. *Org. Prep. Proced. Int.* **40**, 215–291 (2008).

- Gilchrist, T. L. in *Science of Synthesis* Vol. 43 (ed. Hopf, H.) 151–215 (Georg Thieme, 2008).
- Chen, Y. & Larock, R. C. in *Modern Arylation Methods* (ed. Ackermann, L.) 401–473 (Wiley-VCH, 2009).
- Kitamura, T. Synthetic methods for the generation and preparative application of benzyne. *Aust. J. Chem.* **63**, 987–1001 (2010).
- Tadross, P. M. & Stoltz, B. M. A comprehensive history of arynes in natural product total synthesis. *Chem. Rev.* **112**, 3550–3577 (2012).
- Gampe, C. M. & Carreira, E. M. Arynes and cyclohexyne in natural product synthesis. *Angew. Chem. Int. Edn* **51**, 3766–3778 (2012).
- Diels, O. & Alder, K. Syntheses in the hydroaromatic series [in German]. *Justus Liebigs Ann. Chem.* **460**, 98–122 (1928).
- Onishchenko, A. S. *Diene Synthesis* (Israel Program for Scientific Translations, 1964).
- Nicolaou, K. C., Snyder, S. A., Montagnon, T. & Vassilikogiannakis, G. The Diels–Alder reaction in total synthesis. *Angew. Chem. Int. Edn* **41**, 1668–1698 (2002).
- Michael, A. & Bucher, J. E. Über die Einwirkung von Eissigsäureanhydrid auf Phenylpropionsäure. *Chem. Zentrbl.* 731–733 (1898).
- Wessig, P. & Müller, G. The dehydro-Diels–Alder reaction. *Chem. Rev.* **108**, 2051–2063 (2008).
- Bradley, A. Z. & Johnson, R. P. Thermolysis of 1,3,8-nonatriyne: evidence for intramolecular [2+4] cycloaromatization to a benzyne intermediate. *J. Am. Chem. Soc.* **119**, 9917–9918 (1997).
- Miyawaki, K., Suzuki, R., Kawano, T. & Ueda, I. Cycloaromatization of a non-conjugated polyenyne system: synthesis of 5*H*-benzo[*d*]fluoreno[3,2-*b*]pyrans via diradicals generated from 1-[2-{4-(2-alkoxymethylphenyl)butan-1,3-diyne}]phenylpentan-2,4-diyne-1-ols and trapping evidence for the 1,2-didehydrobenzene diradical. *Tetrahedr. Lett.* **38**, 3943–3946 (1997).
- Kimura, H., Torikai, K., Miyawaki, K. & Ueda, I. Scope of the thermal cyclization of nonconjugated ene-yne-nitrile system: a facile synthesis of cyanofluorene derivatives. *Chem. Lett.* **37**, 662–663 (2008).
- Tsui, J. A. & Sterenberg, B. T. A metal-templated 4 + 2 cycloaddition reaction of an alkyne and a diyne to form a 1,2-aryne. *Organometallics* **28**, 4906–4908 (2009).
- Uchiyama, M. *et al.* Generation of functionalized asymmetric benzynes with TMP-zincates. Effects of ligands on selectivity and reactivity of zincates. *J. Am. Chem. Soc.* **124**, 8514–8515 (2002).
- Chang, W.-T. *et al.* Cross-coupling with organosilicon compounds. *Org. React.* **75**, 213–746 (2011).
- Stiles, M., Miller, R. G. & Burckhardt, U. Reactions of benzyne intermediates in non-basic media. *J. Am. Chem. Soc.* **85**, 1792–1797 (1963).
- Liu, Z. & Larock, R. C. Facile *O*-arylation of phenols and carboxylic acids. *Org. Lett.* **6**, 99–102 (2004).
- Cheong, P. H.-Y. *et al.* Indolyne and aryne distortions and nucleophilic regioselectivities. *J. Am. Chem. Soc.* **132**, 1267–1269 (2010).
- Garr, A. N. *et al.* Experimental and theoretical investigations into the unusual regioselectivity of 4,5-, 5,6-, and 6,7-indole aryne cycloadditions. *Org. Lett.* **12**, 96–99 (2010).
- Zhao, Y. & Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **120**, 215–241 (2008).
- Ajaz, A. *et al.* Concerted vs. stepwise mechanisms in dehydro-Diels–Alder reactions. *J. Org. Chem.* **76**, 9320–9328 (2011).
- Johnson, R. P. & Daoust, K. J. Interconversions of cyclobutyne, cyclopentyne, cyclohexyne, and their corresponding cycloalkylidene carbenes. *J. Am. Chem. Soc.* **117**, 362–367 (1995).

Supplementary Information is available in the online version of the paper.

Acknowledgements P.H.W. thanks the National Science Foundation for a graduate research fellowship. Financial support from the National Institutes of Health (GM65597 and CA76497) is acknowledged. This work was carried out in part using hardware and software provided by the University of Minnesota Supercomputing Institute.

Author Contributions B.B. performed the initial experiments. All authors designed the experiments, analysed the data and wrote the manuscript.

Author Information Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to T.R.H. (hoye@umn.edu).