The venerable Diels–Alder cycloaddition reaction\(^1\) is highly regarded in synthetic chemistry\(^2,3,4\). The prototypical event (Fig. 1b), found in every introductory organic chemistry textbook, is the combination of 1,3-butadiene (5) as the 4π-component with ethylene (4) as the dienophile to give cyclohexene (6)—a product in the tetrahydrobenzene oxidation state. If, instead, an alkene 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-enzyme (for example, 9) as the 4π-component with an alkene (for example, 7). It is interesting to note that the first example of this process (the thermal dimerization of phenylpropionic acid)\(^4\) was described 30 years before the initial report of Diels and Alder\(^1\). The intermediate cyclic allene 10 rapidly rearranges via a [1,5] hydrogen atom shift to benzene (11). This process has until now been called, ortho-Benzene (1,2-didehydrobenzene, 1, Fig. 1a) is one of the oldest\(^1\), 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 known\(^2,3\). 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 benzynes 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 benzene/aryne generation would considerably expand the preparative utility of these remarkable intermediates.

**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, CO\(_2\)/N\(_2\), halogen/halogen, or TMS/OTf. b–e, Prototypes of Diels–Alder \([4+2]\) (that is, the combination of a four-atom (or 4π electron) component with a two-atom (or 2π 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), tetrahydro-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.

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generically, the dehydro-Diels–Alder (DDA) reaction\textsuperscript{15}. 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 tetradehydro-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-benzene (compare 1', 1 and 1\textsuperscript{a}). This hexadehydro-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\textsuperscript{16–19}. It is interesting to speculate that this may be due in part to the fact that the most common depiction of benzene—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 benzenes via the HDDA reaction with various trapping reactions to yield structurally complex benzoid products. Each substrate is a readily accessible conjugated diyne containing a remote alkyne diynophile. These cycloisomerize in a (highly exergonic) [4+2] fashion to produce the reactive aryne intermediate. The examples demonstrate that the tandem benzene 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 benzene intermediate 16/16 was being both readily formed and efficiently trapped by the nucleophilic oxygen atom in the fortuitously poised β-siloxethyl 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 benzene 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 ≥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 (carbalkoxy) rather than a tethering substituent (entries 2 and 3); many classical methods of aryne generation are not compatible with electron-withdrawing groups in the substrate\textsuperscript{20}; 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) 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 benzene traps include tethered alcohols (entries 4 and 7), aryl rings ([4+2] cycloaddition in entry 9), or alkynes (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...
Intermolecular trapping

We wished to validate the feasibility of bimolecular trapping of these thermally generated benzyne. 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 benzoyne 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 Dieck–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 benzyne 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 norborne 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 acid 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 benzyne generated by non-reagent-free methods24; and finally net trapping by hydrogen bromide was achieved using Br(CH2)2NH2 at 120 °C 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) 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-butoxylhalide (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 benzyne under conditions amenable to a wide variety of intra- and intermolecular trapping events. This powerful and efficient
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.

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 indicated solvent (0.05 M) was closed with a Teflon-lined cap and heated at the indicated temperature. After the indicated time the product was indicated (external bath) temperature. After the indicated time the product was indicated (external bath) temperature. After the indicated time the product was indicated (external bath) temperature. After the indicated time the product was indicated (external bath) temperature. After the indicated time the product was indicated (external bath) temperature. After the indicated time the product was indicated (external bath) temperature. After the indicated time the product was indicated (external bath) temperature. After the indicated time the product was indicated (external bath) temperature. 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29. Supplementary Information is available in the online version of the paper.

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