Article

Radial-hexadehydro-Diels-Alder reactions

Daniel Lee[1], Sean P. Ross[1], Xiao Xiao[1], and Thomas R. Hoye[1,2]*

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

[2]Lead contact

*Correspondence: hoye@umn.edu

SUMMARY

Polycyclic, highly fused and, perforce, highly conjugated aromatic organic compounds (PACs) have been of interest to chemists since the discovery of naphthalene in 1821. In modern decades these have attracted ever-growing attention because of their architectures, properties, and wide-ranging practical applications (cf. The Bigger Picture). Given the unabated interest in such molecules, the development of new methods and strategies for the practical synthesis of PACs having new structural motifs is important. Here we describe one-pot, purely thermal cyclizations of substrates containing sets of independent triynes, each arrayed upon a common core structure. This produces topologically unique products through sequential generation/trapping of a series of benzyne intermediates. More specifically, these all conform to processes that can be considered as radial-hexadehydro-Diels-Alder (HDDA) reactions. The late-stage and de novo creation of multiple arenes in these multi-benzyne processes constitutes a fundamentally new synthetic strategy for constructing novel molecular topologies.

Keywords: hexadehydro-Diels-Alder (HDDA), aryne, multi-yne, multiple cycloisomerizations

INTRODUCTION

Polycyclic aromatic compounds (PACs), of which polycyclic aromatic hydrocarbons (PAHs) are a subset, include both all-carbocyclic as well as mixed carbo- and heterocyclic subunits. These have attracted considerable attention as novel molecules having new properties and/or functions[1] or to serve as precursors to new graphitic materials, including nanotubes and belts.[2,3] Benzyne/aryne chemistry[4] has been utilized by researchers as a strategy for the synthesis of various classes of arenes.[5,6,7] Reactive benzyne (and aryne) intermediates have long been recognized for the versatile array of products they can afford when produced in the presence of suitable, in situ trapping agents. The thermal (or photochemical[8]) intramolecular cycloisomerization of substrates containing a conjugated 1,3-butadiyne and a tethered third alkyne (the diynophile) produces benzyne intermediates[9,10] (cf. **multi-yne** to **benzyne** (n = 1) in Figure 1A); we have termed this process the hexadehydro-Diels-Alder (HDDA) reaction.[11]

HDDA chemistry has served as a platform for new strategic developments. Examples include the pentadehydro-DA,[12] domino-HDDA,[13] and aza-HDDA[14] reactions. We now show that radial-HDDA reactions, related in part to the strategy of "expanding [polyphenylenes] in all directions,"[15] constitute a new facet of this chemistry. Our studies were designed to establish the principles of this process rather than being motivated by targeting a particular set of structures or structural classes. We considered what opportunities might arise by studying substrates having two (or more) independent sets of triyne units that react in, for example, double-, triple-, quadruple-, or sextuple-barreled fashion (n = 2, 3, 4, or 6; Figure 1B). All of these potential multi-yne substrates share the common feature of being templated on and, therefore, radiating from a central aromatic core (blue). We show here that modification of the number of triyne units gives rise to an array of substrates that readily lead to structurally

The Bigger Picture

We report hexadehydro-Diels-Alder (HDDA) reactions in which the substrates are designer multi-ynes arrayed upon a common, central template. These undergo sequential, multiple cycloisomerization (termed here radial-HDDA) reactions to produce architecturally novel polycyclic compounds in a single operation.
Diverse product topologies are accessible, ranging from highly fused, polycyclic aromatic compounds (PACs) to architectures having structurally complex arms adorning central phenylene or expanded phenylene cores.

Members of some of these structural classes are well known to play important roles in fields of, for example, organic electronic/photonic devices, organomagnets, and as building blocks in reticular chemistry [metal-organic and covalent-organic frameworks (MOFs and COFs)]. Hence, new strategic advances that complement existing approaches and/or that provide access to novel structural topologies are significant.

complex PACs in a single operation.

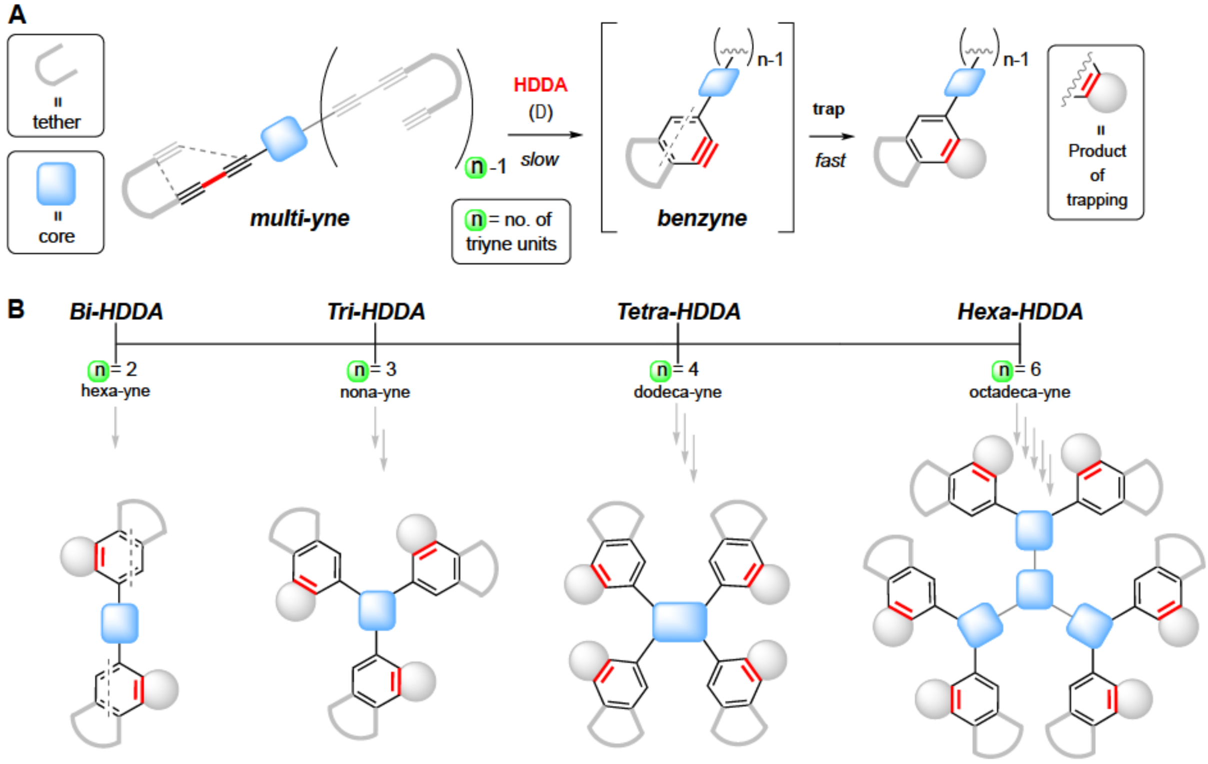

Figure 1. Generic radial-HDDA reactions. **(A)** A general formulation of the sequential polycyclization of **multi-ynes** containing two to six independent, tethered triyne units; the benzyne from each successive cycloisomerization event is rapidly captured by an in situ trapping agent to produce elaborated benzenoid products (gray balls). **(B)** General structural representations of the products arising from bi-, tri-, tetra-, and hexa-HDDA cyclization/trapping events. HDDA, hexadehydro-Diels-Alder.

RESULTS and DISCUSSION

Conventions, Preliminary Considerations, and Terminologies. In this document we have used Roman numerals to indicate presumed intermediates (or transition structures) in a reaction transformation and Arabic numerals for structures of isolable (and characterized) substances. The preparation of all multi-yne substrates is detailed in the Supplementary Information (SI). Because of their inherent symmetry, those with a greater number of triyne subunits are generally no more difficult to synthesize than their simpler analogs. For example, each of the multi-ynes **1**, **3**, and **5** is made in five reactions (four linear) from bromobenzaldehyde starting materials. Procurement of the yet higher-ynes is similarly straightforward. In reticular chemistry, the term “topicity” is used to describe the number of points of extension in the building units of MOFs or COFs: that is ditopic, tritopic, tetratopic, etc.[16] Similarly, we use here bi-, tri-, tetra-, and hexa-prefixes to denote the topicity of the multi-yne substrates and their respective products.

A mono-HDDA reaction. The thermal conversion of **1**[17] to **2** in the presence of furan via the benzyne intermediate **I** constitutes a prototypical mono-HDDA reaction (Figure 2A). There are now dozens of examples of this mono-HDDA process.[18,19,20] The tether between the diyne and diynophile in substrates is nearly always a three-atom linking unit (black dots).

Bi-HDDA reactions. Two complementary types of bi-HDDA reaction can be envisioned: an “outside-in” (Figure 2B) or an “inside-out” (Figure 2C) motif. These differ by the relative orientation of the tether with respect to the central core. Namely, in the hexayne **3** the tethering atoms are remote from that core, whereas in hexayne **5** core atoms make up part of the tether (cf. black dots in **3** vs. **5**). An example of the “outside-in” bi-HDDA process is demonstrated by the efficient conversion of hexayne **3** to the bis-fluorenone **4a** upon heating **3** in the presence of tetraphenylcyclopentadienone (TPCPD).[21,22] This overall process involves six discrete steps [i)–vi)]; only the second (and penultimate) benzyne, **II**, is shown in Figure 2B. As a complement, the "inside-out" substrate **5** undergoes cyclization in the presence of trimethylsilyl azide ($TMSN_3$)[23] to produce the indenofluorenedione **7** (Figure 2C). The discrete benzyne intermediates **III** and **IV** are shown following each of the steps in the sequence: i) the (slow) first HDDA reaction, ii) the (rapid) trapping of **III** by $TMSN_3$ to give the (isolable) mono-triazole adduct **6**, iii) the (slow) second HDDA reaction, and iv) the (rapid) trapping of **IV** by a second molecule of $TMSN_3$. Notice the significantly different and complementary topologies of the products arising from these two motifs of bi-HDDA reaction. Namely, **4a** has a bis-biaryl skeleton with a non-planar orientation around the core benzene ring whereas **7** is a highly fused heptacycle arrayed in planar fashion around the central benzene ring.

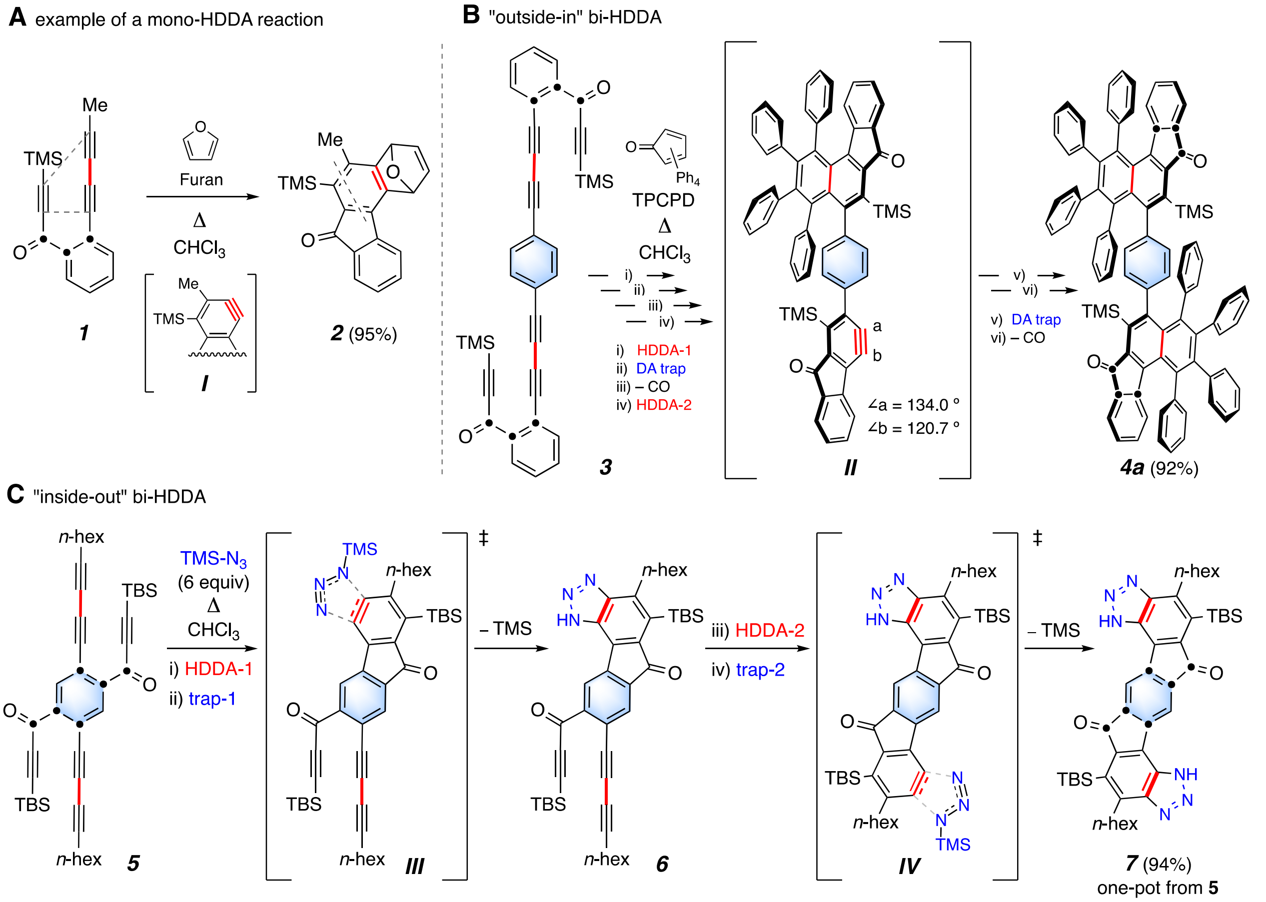

Figure 2. Mono- and bi-HDDA reactions. (**A**) A mono-HDDA reaction using furan as the benzyne trap. (**B**) An "outside-in" bi-HDDA reaction using TPCPD as the trapping reagent; the intermediate bicyclic ketone (not shown) ejects carbon monoxide to provide the aromatized naphthalene derivative under the thermal reaction conditions. (**C**) An "inside-out" bi-HDDA reaction using TMS-azide as the trapping reagent; the labile TMS group is lost during workup/purification; the desilylated compound **6** was isolated (see Supplemental Information). Note that the three-atoms of the tether (see black dots) are either remote from vs. part of the benzene core in the "outside-in" vs. "inside-out" delineations of these topologically complementary processes. TMS, trimethylsilyl; TPCPD, tetraphenylcyclopentadienone; DA, Diels-Alder; *n*-hex, *normal*-hexyl.

To demonstrate the robustness of the "outside-in" bi-HDDA reaction, we subjected hexayne **3** to an array of benzyne trapping reagents. This produced the collection of products **4b-h** (Figure 3A) in generally good to excellent yields. Products include those arising from the use of both symmetrical (**4a-d**) and unsymmetrical (**4e-h**) trapping agents. In the case of the latter, the regioselectivity was exclusive, as expected from the high degree of distortion calculated for benzyne **II** ($\Delta\angle_{a\text{-}b}$ = 13.3°, Figure 2B). That is, the electron-rich center of the trapping agent selectively engaged the more electron-deficient benzyne carbon atom (C_a), as reflected by its larger computed (DFT, see SI) internal bond angle.[24,25,26]

Modifications to the core of the multi-yne substrate are tolerated. For example, replacement of the central benzene scaffold in **3** with a 1,4-disubstituted naphthalene leads to the products **8a** and **8b** when heated in the presence of, for example, *n*-hexylamine and cyclooctane (dihydrogen redox transfer[27]), respectively (Figure 3B). Further modification of the exterior of the substrate (and product) is also possible. For example, hexayne **9** (from 1-bromo-2-naphthaldehyde) upon trapping with 2-pyrone and concomitant cheletropic ejection of CO_2,[28] leads to product **10**, which embodies five non-contiguous naphthalene substructures.

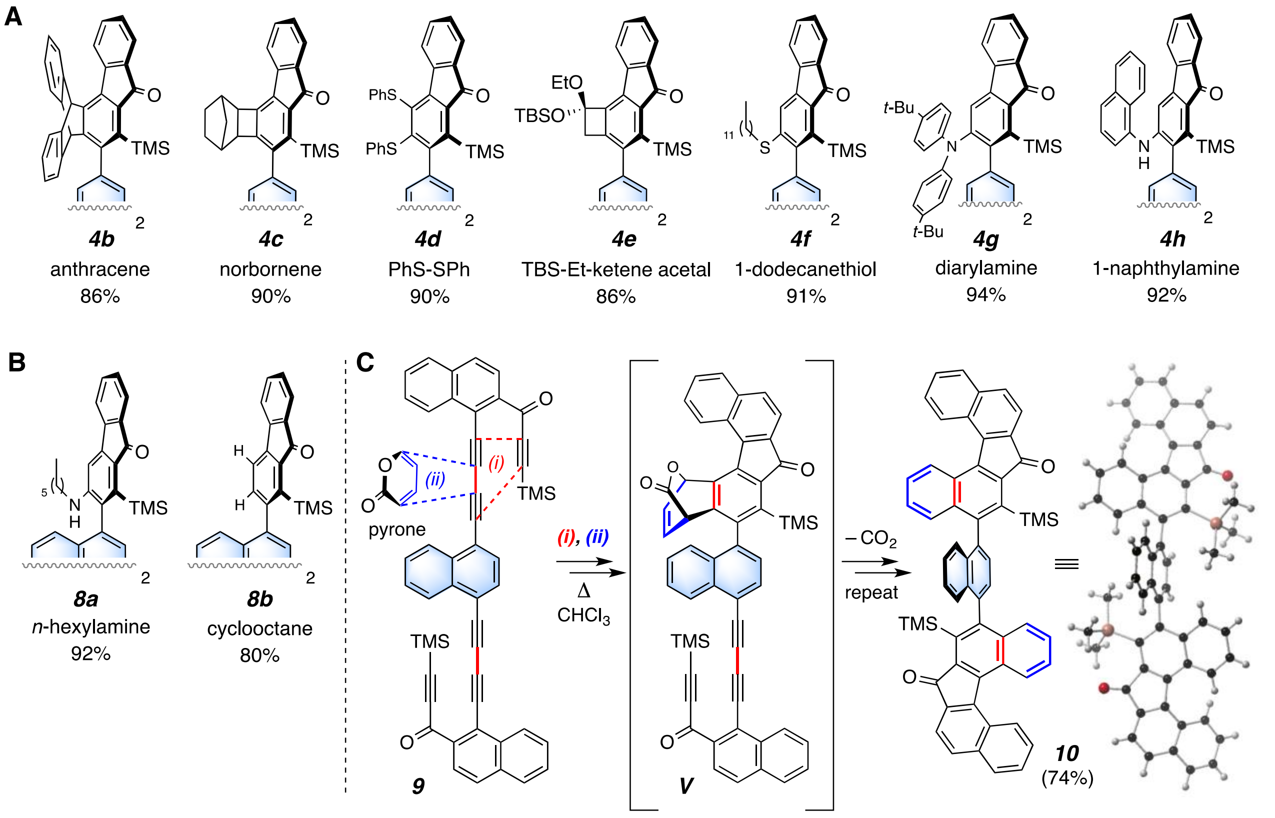

Figure 3. Trapping versatility, shown here for "outside-in" bi-HDDA reactions. (**A**) Products **4b**–**4h** arising from the hexayne substrate **3**, the same precursor used to prepare **4a** (see Figure 2B). (**B**) Products **8a** and **8b** arising from a hexayne substrate analog of **3** in which the central 1,4-phenylene subunit was replaced by a 1,4-naphthylene moiety (see **S5**, SI). (**C**) Trapping of hexayne **9** with 2-pyrone produces, by a multi-stage process in which **V** is one of the intermediates, the bis-binaphthyl product **10**. TBS, (*tert*-butyl)dimethylsilyl; Ph, phenyl; Et, ethyl; *t*-Bu, *tertiary*-butyl.

We next speculated that the “inside-out” bi-HDDA cascade could be an efficient tactic to construct more highly conjugated PACs. Incorporation of an *intra*molecular benzyne trapping unit into the substrate(s) would lead to products of higher planarity having even more π-conjugation. If successful, this approach would be complementary to existing strategies for preparing PACs of potential utility in organic electronics research.[29] To that end, we prepared the “inside-out” bi-HDDA substrates **11a-c** (Figure 4A), each containing a nucleophilic substituent in the *ortho*-position of the two terminal aryl groups. When heated in the presence of acetic acid (5 equiv), each yielded the corresponding product **12a-c,** containing newly fused benzothiophene, benzofuran, and indole moieties, respectively, adorning the central fluorenedione. The pair of sequential trapping events in each reaction is envisioned to proceed via a zwitterionic onium ion such as that indicated in intermediate **VI**. The acetic acid serves as an *in situ* proton source to quench the carbanion in that zwitterion and then to dealkylate the R group. In the case of substrate **11c**, the expected *n*-hexyl acetate byproduct was formed (by ^{1}H NMR spectroscopy) in nearly stoichiometric amount in an experiment performed in $CDCl_3$.

The nearly planar, crystalline nature of highly fused PACs such as the nonacyclic products **12** often limits their solubilities in common organic solvents.[30, 31] Notably, the *n*-hexyl substituents in analog **12c** allowed for reaction monitoring via an NMR experiment in which the cyclization of the bis-aniline substrate **11c** was performed in $CDCl_3$ at a $[\mathbf{11c}]_{t=0}$ = 7.2 mg mL^{-1} (7.0 mM). This experiment demonstrated the remarkable cleanliness of this “inside-out” bi-HDDA process (see SI) by allowing direct observation of the crude reaction mixture, which remained homogeneous even after >90% conversion to **12c**.

Enlightened by the effectiveness of the bi-HDDA reaction to afford a planar skeleton in a single operation, we pursued the synthesis of an all-carbon PAH motif (Figure 4B). This was demonstrated by preparation of the TPCPD bis-adduct **15**, having an embedded indenofluorene skeleton[32] (yellow+green substructure), The twisted aryl appendages in each of compounds **13**–**15** significantly improved their solubility. Lithium acetylide addition to the diketone **13b** (from n-$Bu_4N^+F^-$ treatment of **13a**) afforded diastereomeric diols **14**, which were then reductively deoxygenated (stannous chloride[33]) to give the indenofluorene **15** in good yield.

Lastly, we explored a hybrid strategy integrating both HDDA and traditional benzyne generation, recognizing its potential to provide highly conjugated, polycyclic, planar frameworks. Specifically, we capitalized on the 1,2-benzdiyne tactic pioneered by Li and coworkers[34] to access the nonacyclic PAC **18** (Figure 4C). Treatment of the bis-benzyne equivalent **16** with mild base in the presence of the bis-triflamide **17** generated, first, the benzyne intermediate **VII**. Nucleophilic attack by a sulfonamide anion in **17** initiated a net S_N2' event, generating intermediate **VII**. HDDA cyclization produced a transient naphthyne (not shown),[35] which was captured intramolecularly by the strategically placed methoxy group (cf. **11b** to **12b**). Repetition within the second half of **17** led to the (U-shaped PAC) **18**. This overall process proceeds via the intermediacy of six, discrete, independently formed benzyne intermediates (green, then blue, then red).

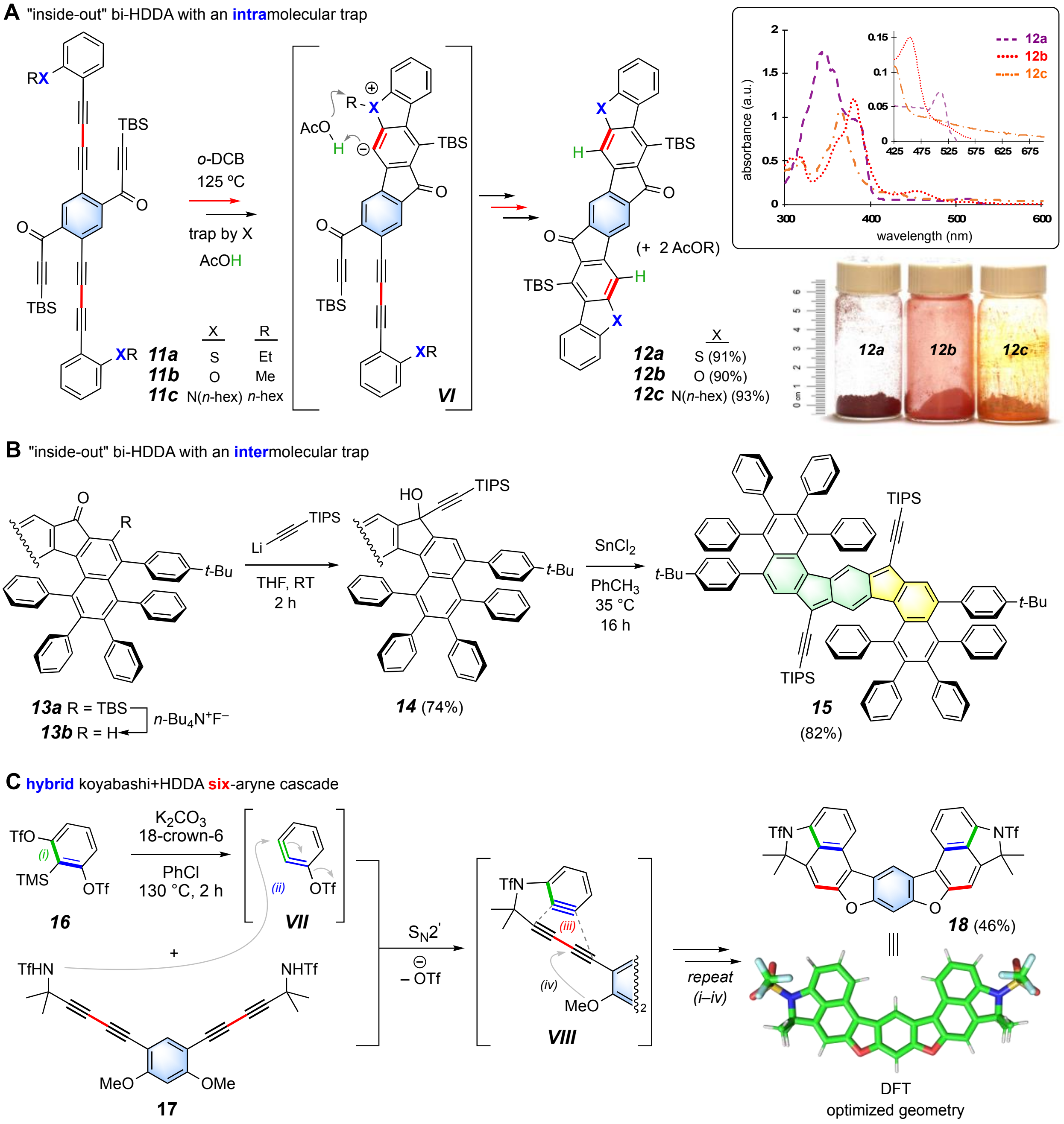

Figure 4. Extended π-conjugated PACs arising from "inside-out" bi-HDDA reactions. (**A**) *Intra*molecular trapping by a heteroatom in the 2-position of terminal phenyl substituents (cf. **VI**) results in formation of additional new rings that contain push-pull (donor-acceptor) motifs commonly found in organic semiconductor structures. The absorption spectra shown were recorded as 10^{-5} M solutions in THF ($\varepsilon_{\mathbf{12a}\ (347\ \mathrm{nm})} = 1.3\mathrm{x}10^{5}$, $\varepsilon_{\mathbf{12b}\ (380\ \mathrm{nm})} = 1.1\mathrm{x}10^{5}$, $\varepsilon_{\mathbf{12c}\ (365\ \mathrm{nm})} = 1.0\mathrm{x}10^{5}$; L mol^{-1} cm^{-1}). (**B**) *Inter*molecular trapping of an analog of **5** (cf. Figure 2), having a 4-*t*-butyl group (cf. **S18**, SI), by TPCPD gives **13a**, which provides an entry to the bis-alkynyl indeno-fluorene **15**, an architecture of interest in organoelectronic applications (see SI for UV-vis data).[30,32,33,36] (**C**) One-pot, six-benzyne cascade combining classical [steps i) and ii)] and HDDA benzyne generation [iii)] and intramolecular trapping [iv)] leads to the bis-naphthalene **18**. 18-crown-6, 1,4,7,10,13,16-hexaoxacyclooctadecane; S_N2', substitution, nucleophilic, bimolecular (with "allylic inversion"); *o*-DCB, *ortho*-dichlorobenzene; AcOR, alkyl acetate ester; TIPS, tri(*iso*-propyl)silyl; THF, tetrahydrofuran; RT, room temperature; *n*-Bu, *normal*-butyl. Tf, trifluoromethylsulfonyl; DFT, density functional theory (see SI for computational methods).

Tri-HDDA reactions. To further demonstrate the rapid complexity-building capacity of the radial-HDDA approach, we first elected to explore substrate **19**. This nonayne is built upon a 1,3,5-trisubstituted benzene template (Figure 5A). We quickly learned that these three arms did not behave independently. That is, upon heating **19** to typical reaction temperatures and times for cyclization of fluorenone precursors analogous to those in **19** (e.g., 85 °C for 24 h or 130 °C for 8 h), we observed formation of products in which two, but not the third, of the independent triyne subunits had cyclized. Long-range steric interactions were manifesting themselves in this reaction. Specifically, we speculated that at the stage of the doubly cyclized intermediate, cartooned as **IX**, the top and bottom faces of the core phenyl ring are blockaded by the substituents (blue and green) arrayed along the twisted biaryl bonds (magenta) in **IX** so as to greatly retard the rate of the third cyclization. The triynyl TBS group (gray oval) needs to enter the volume partially occupied by the meta-disposed, bulky biaryl substituents. Accordingly, upon heating a reaction mixture of **19** and 2-pyrone to substantially higher temperature – namely, 240 °C (in *o*-DCB) – we achieved clean conversion to the tri-HDDA product **20a** (Figure 5A, left). The NMR spectrum of this product was challenging to fully assign because of hindered rotation about not only the three biaryl bonds, but the C_{Ar}–Si_{TBS} bonds as well. Desilylation, however, smoothly gave the 1,3,5-triarylbenzene derivative **20b**, the spectroscopic characterization of which was straightforward.

In an interesting twist, we also showed that it was possible to differentially trap the three benzyne intermediates when the reaction was performed in the presence of a mixture of two different trapping agents, themselves of inherently different reactivity. For example, heating the nonayne **19** (at 200 °C) in the presence of essentially one equivalent of 2,5-dimethylfuran, a very fast trap of arynes, and an excess of cyclooctane, which engages benzynes by a relatively slow dihydrogen-transfer reaction,[27] afforded the unsymmetrically substituted, tri-HDDA product **21a** (Figure 5A, right). Again, this structure was more easily characterized following desilylation to the analog **21b**.

Tetra-HDDA reactions. To widen the scope of classes of radial-HDDA reactions, we pursued a substrate that could undergo four-fold cyclization. In view of the accumulating steric inhibition toward cyclization observed with substrate **19** (cf. **IX**), we designed the dodecayne **22** [Figure 5B, prepared by a 5-(linear)step reaction sequence from tetraphenylethylene]. We expected that this expanded core would remove any difficulties in the later-stage HDDA cyclizations. Indeed, when **22** was heated in the presence of either cyclooctane or 2-pyrone at 130 °C (cf. ≥200 °C for **19** to effect the final HDDA cyclization), it was smoothly and exhaustively cyclized to the tetra-HDDA product **23-HH** or **23-naph**, respectively, affirming the underlying principles of the design. As can be judged from the single crystal x-ray diffraction structure of **23-naph**, the biaryl bonds are sufficiently distant from one another to allow for uninhibited rotation, consistent with the observed sharp resonances in its ^{1}H NMR spectrum. It is also noteworthy that even though the substance has a high melting point 365–372 °C (and thermal stability; no observed decomposition), it readily dissolves in common organic solvents, a property owing to its multiple biaryl rotational degrees of freedom and associated array of conformational isomers.

Hexa-HDDA reactions. Finally, to push the radial-HDDA cascade to yet another level, we designed a six-fold HDDA reaction. An expanded core was again enlisted to accommodate the cyclization of now six sets of pendant triyne units. Specifically, the octadecayne **24**, having six triyne units (spokes) arrayed on a 1,3,5-triphenylbenzene core (hub) was devised. Heating **24** with cyclooctane afforded the hexa-cyclized product **25**, having six new fluorenones symmetrically arrayed about the core structure. An analogous reaction of **24** using pyrone as the trapping agent proceeded efficiently to provide what we judge to be the hexabenzo-analog of **24** (benzo-fusions

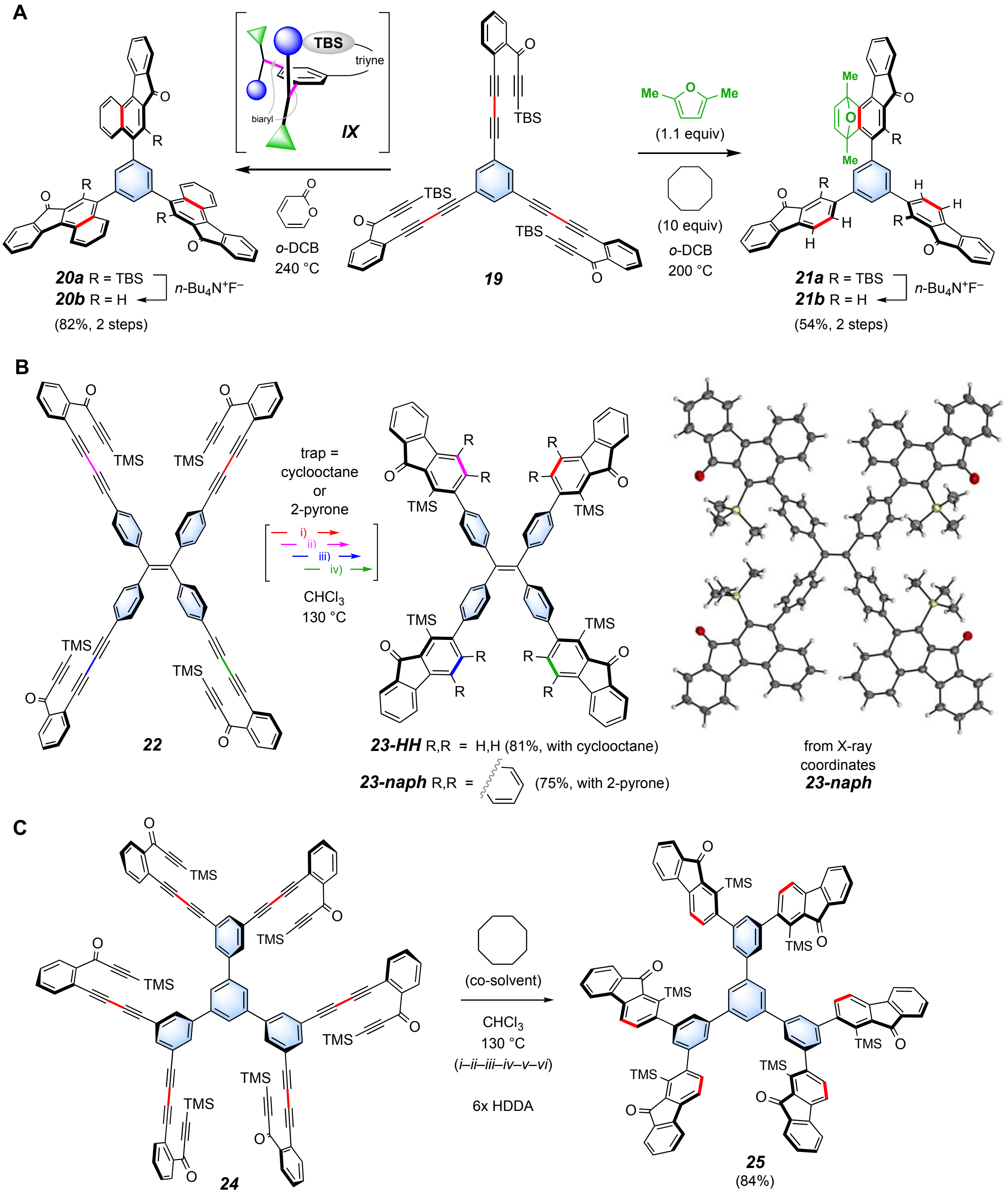

Figure 5. Tri-, Tetra-, and Hexa-HDDA. (**A**) The nonayne **19** requires heating to ≥200 °C to effect the third HDDA cyclization. (**B**) The dodecayne **22**, having an expanded core structure of considerable larger volume, sequentially cyclizes four times [cf. i) – iv)] at 130 °C. (**C**) The octadecayne **24** smoothly cyclizes six times to the hexa-fluorenone derivative **25**. naph, naphthalene.

at the six red bonds; cf. **23-HH** vs. **23-naph**), although slow rotation about the hindered biaryl bonds in that analog precluded full analysis of its NMR spectral data (see **S25** in the SI). Processes that allow the construction of such a high degree of structural complexity, accompanied by a high level of atom economy, in a single operation are rare.

Conclusion. The radial-HDDA (i.e., bi-, tri-, tetra-, hexa-) reaction described here constitutes a fundamentally new strategy for the creation of structurally complex and topologically unique polycyclic aromatic compounds (PACs). The reaction substrates have multiple (2, 3, 4, or 6) independent sets of triyne units (6 to 18 alkynes) and can be synthesized in straightforward fashion, starting from symmetrical starting materials. Simple heating of a solution of the multi-yne substrate and benzyne trapping partner, absent the need for any additional reagents or catalysts, induces a cascade of sequential HDDA reactions that rapidly builds structural complexity. The radial-HDDA approach, capitalizing on the *de novo* (and, here, late-stage) construction of arene rings, contrasts and complements many existing strategies for the synthesis of PACs.

The specific examples shown here were selected to demonstrate the variety of new architectural topologies that can be accessed. The work establishes a basis upon which future research aimed at the synthesis of functional compounds and materials can be built.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Requests for further information and data should be directed to the corresponding author (hoye@umn.edu).

Materials availability

This study did not generate new materials (other than, of course, the new chemical compounds for which experimental details for their preparation are described in the Supplemental Information.

Data and code availability

The NMR spectra can be accessed and manipulated in the .mnova file uploaded to the SI as S2.

General procedure for the radial HDDA reactions.

An oven-dried, threaded, glass culture tube containing the multi-yne precursor in organic solvent (initial concentration of 0.01–0.05 M, in, e.g., (ethanol-free) $CHCl_3$) and the indicated number of equivalents of trapping reactant(s) was closed with a Teflon-lined cap and the solution was heated at 85–130 °C for 8–24 h. The products were separated and purified by chromatography on silica gel.

SUPPLEMENTAL INFORMATION

S1. Main Supplemental PDF: i) experimental details for preparation and purification as well as characterization data for all new compounds, ii) a description of the computational methods and results, iii) a summary of the X-ray diffraction data, iv) UV–vis absorption spectra, and v) copies of all ^{1}H and ^{13}C-NMR spectra.

S2. MestReNova Files (.mnova) of NMR Spectra: ^{1}H, ^{13}C-NMR, and selected 2-D NMR spectra, assembled for each new chemical entity.

S3. Crystallographic Information Files (CIFs): Crystallographic data for the structures described in this Article have been deposited at the Cambridge Crystallographic Data Centre. The deposition numbers are CCDC 2036363 (**4a**), 2036439 (**7**), 2026027 (**10**), and 2026024 (**23-naph**). The CIFs are also included here as SI.

ACKNOWLEDGMENTS

Support for this work was provided by the National Science Foundation (CHE-1665389). The DFT calculations were performed using software and hardware available through the University of Minnesota Supercomputing Institute (MSI). Some NMR spectral data were obtained with an instrument purchased with a grant from the NIH Shared Instrumentation Grant program (S10OD011952). The authors thank Dr. V. G. Young, Jr. (University of Minnesota) for performing the X-ray diffraction analysis. X-ray diffraction data were collected on an instrument purchased with funds from the National Science Foundation (NSF/MRI 1229400). Mass spectrometry data were recorded in the Masonic Cancer Center at the University of Minnesota (Analytical Biochemistry Shared Resource) with instrumentation partially funded by a National Institutes of Health Cancer Center Support Grant (CA-77598).

AUTHOR CONTRIBUTIONS

D.L. and T.R.H co-wrote the manuscript. D.L. (Figures 2–5), S.P.R. (Figure 4A, 4B), and X.X. (Figure 4C) executed the experiments and collected and interpreted the data. All authors approved the final version of the manuscript.

DECLARATION OF INTERESTS

"The authors declare no competing interests."

REFERENCES*

1. Q. Miao, ed. (2016). Polycyclic Arenes and Heteroarenes: Synthesis, Properties, and Applications (Wiley-VCH, Verlag GmbH & Co. KGaA Weinheim).
2. K. Müllen, and X. Feng, eds. (2017). From Polyphenylenes to Nanographenes and Graphene Nanoribbons (Springer-Verlag Berlin Heidelberg).
3. Cheung, K. Y., Watanabe, K., Segawa, Y., and Itami, K. (2021). Synthesis of a zigzag carbon nanobelt. Nat. Chem. *13*, 255–259. 10.1038/s41557-020-00627-5.
4. A. Biju, ed. (2021). Modern Aryne Chemistry (Wiley-VCH, Verlag GmbH & Co. KGaA Weinheim).
5. Tadross, P. M., and Stoltz, B. M. (2012). A comprehensive history of arynes in natural product total synthesis. Chem. Rev. *112*, 3550–3577. 10.1021/cr200478h.
6. Gampe, C. M., and Carreira, E. M. (2012). Arynes and cyclohexyne in natural product synthesis. Angew. Chem. Int. Ed. *51*, 3766–3778. 10.1002/anie.201107485.
7. Peréz, D., Peña, D., and Guitián, E. (2013). Aryne cycloaddition reactions in the synthesis of large polycyclic aromatic compounds. Eur. J. Org. Chem. *27*, 5981–6013. 10.1002/ejoc.201300470.
8. Xu, F., Xiao, X., and Hoye, T. R. (2017). Photochemical hexadehydro-Diels–Alder reaction. J. Am. Chem. Soc. *139*, 8400–8403. 10.1021/jacs.7b03832.
9. Bradley, A. Z., and Johnson, R. P. (1997). Thermolysis of 1,3,8-nonatriyne: evidence for intramolecular [2+4] cycloaromatization to a benzyne intermediate. J. Am. Chem. Soc. *119*, 9917–9918. 10.1021/ja972141f
10. Miyawaki, K., Suzuki, R., Kawano, T., and Ueda, I. (1997). 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-diynyl}]phenylpentan-2,4-diyn-1-ols and trapping evidence for the 1,2-didehydrobenzene diradical. Tetrahedron Lett. *38*, 3943–3946. 10.1016/S0040-4039(97)00785-5.
11. Hoye, T. R., Baire, B., Niu, D. W., Willoughby, P. H., and Woods, B. P. (2012). The hexadehydro-Diels–Alder reaction. Nature *490*, 208–212. 10.1038/nature11518.
12. Wang, T., Naredla, R. R., Thompson, S. K., and Hoye, T. R. (2016). The pentadehydro-Diels–Alder reaction. Nature *532*, 484–488. 10.1038/nature17429.
13. Xiao, X., and Hoye, T. R. (2018). The domino hexadehydro-Diels–Alder reaction transforms polyynes to benzynes to naphthynes to anthracynes to tetracynes (and beyond?). Nat. Chem. *10*, 838–844. 10.1038/s41557-018-0075-y.
14. Thompson, S. K., and Hoye, T. R. (2019). The aza-hexadehydro-Diels–Alder reaction. J. Am. Chem. Soc. *141*, 19575–19580. 10.1021/jacs.9b11243.
15. Hammer, B., and Müllen, K. (2016). Dimensional evolution of polyphenylenes: Expanding in all directions. Chem. Rev. *116*, 2103–2140. 10.1021/acs.chemrev.5b00515.
16. Yaghi, M. O., Kalmutzki, M. J., and Diercks, S. C. (2019). Introduction to Reticular Chemistry: Metal-Organic Frameworks and Covalent Organic Frameworks (Wiley-VCH, Verlag GmbH & Co. KGaA Weinheim).
17. Chen, J., Palani, V., and Hoye, T. R. (2016). Reactions of HDDA-derived benzynes with sulfides: mechanism, modes, and three-component reactions. J. Am. Chem. Soc. *138*, 4318–4321. 10.1021/jacs.6b01025.
18. Holden, C., and Greaney, M. F. (2014). The Hexadehydro-Diels–Alder reaction: A new chapter in aryne chemistry. Angew. Chem. Int. Ed. *53*, 5746–5749. 10.1002/anie.201402405.
19. Diamond, O. J., and Marder, T. B. (2017). Methodology and applications of the hexadehydro-Diels–Alder (HDDA) reaction. Org. Chem. Front. *4*, 891–910. 10.1039/C7QO00071E.
20. Fluegel, L. L., and Hoye, T. R. (2021). Hexadehydro-Diels-Alder reaction: Benzyne generation via cycloisomerization of tethered triynes. Chem. Rev. *121*,

2413–2444. 10.1021/acs.chemrev.0c00825.

21. Wittig, G., and Knauss, E. (1958). Dehydrobenzol und Cyclopentadien. Chem. Ber. *91*, 895–907. 10.1002/cber.19580910502.
22. Fieser, L. F., and Haddadin, M. J. (1965). Isobenzofurane, a transient intermediate. Can. J. Chem. *43*, 1599–1606. 10.1139/v65-211.
23. Chen, J. H., Baire, B., and Hoye, T. R. (2014). Cycloaddition reactions of azide, furan, and pyrrole units with benzynes generated by the hexadehydro-Diels–Alder (HDDA) reaction. Heterocycles *88*, 1191–1200. 10.3987/COM-13-S(S)83.
24. Hamura, T., Ibusuki, Y., Sato, K., Matsumoto, T., Osamura, Y., and Suzuki, K. (2003). Strain-induced regioselectivities in reactions of benzyne possessing a fused four-membered ring. *Org. Lett. 5*, 3551–3554. 10.1021/ol034877p.
25. Garr, A. N., Luo, D., Brown, N., Cramer, C. J., Buszek, K. R., and VanderVelde, D. (2010). Experimental and theoretical investigations into the unusual regioselectivity of 4,5-, 5,6-, and 6,7-indole aryne cycloadditions. Org. Lett. *12*, 96–99. 10.1021/ol902415s.
26. Cheong, P. H.-Y., Paton, R. S., Bronner, S. M., Im, G.-Y. J., Garg, N. K., and Houk, K. N. (2010). Indolyne and aryne distortions and nucleophilic regioselectivites. J. Am. Chem. Soc. *132*, 1267–1269. 10.1021/ja9098643.
27. Niu, D. W., Willoughby, P. H., Woods, B. P., Baire, B., and Hoye, T. R. (2013). Alkane desaturation by concerted double hydrogen atom transfer to benzyne. Nature *501*, 531–534. 10.1038/nature12492.
28. Wittig, G., and Hoffmann, R. W. (1962). Dehydrobenzol aus 1.2.3-Benzothiadiazol-1.1-dioxyd. Chem. Ber. *95*, 2718–2728. 10.1002/cber.19620951120.
29. Fix, A. G, Chase, D. T., and Haley M. M. (2014). Indenofluorenes and Derivatives: Syntheses and Emerging Materials Applications. In Polyarenes I, J. S. Siegel, and Y. Wu, eds. (Springer-Verlag Berlin Heidelberg), pp. 160-193.
30. Frederickson, C. K., Rose, B. D., and Haley, M. M. (2017). Explorations of the indenofluorenes and expanded quinoidal analogues. Acc. Chem. Res. *50*, 977–987. 10.1021/acs.accounts.7b00004.
31. Nakagawa, T., Kumaki, D., Nishida, J.-I., Tokito, S., and Yamashita, Y. (2008). High performance n-type field-effect transistors based on indenofluorenedione and diindenopyrazinedione derivatives Chem. Mater. *20*, 2615–2617. 10.1021/cm800366b.
32. Chase, D. T., Rose, B. D., McClintock, S. P., Zakharov, L. N., and Haley, M. M. (2011). Indeno[1,2-b]fluorenes: Fully Conjugated Antiaromatic Analogues of Acenes. Angew. Chem. Int. Ed. *50*, 1127–1130.10.1002/anie.201006312.
33. Chase, D. T., Fix, A. G., Rose, B. D., Weber, C. D., Nobusue, S., Stockwell, C. E., Zakharov, L. N., Lonergan, M. C., Haley, M. M. (2011). Electron-Accepting 6,12-Diethynylindeno[1,2-b]fluorenes: Synthesis, Crystal Structures, and Photophysical Properties. Angew. Chem. Int. Ed. *50*, 11103–11106. 10.1002/anie.201104797.
34. He, J., Qiu, D., and Li, Y. (2020). Strategies toward aryne multifunctionalization via 1,2-benzdiyne and benzyne. Acc. Chem. Res. *53*, 508–519. 10.1021/acs.accounts.9b00608.
35. Xiao, X., and Hoye, T. R. (2019). One-pot, three-aryne cascade strategy for naphthalene formation from 1,3-diynes and 1,2-benzdiyne equivalents. J. Am. Chem. Soc. *141*, 9813–9818. 10.1021/jacs.9b04606
36. Anthony, J. E. (2008). The larger acenes: versatile organic semiconductors. Angew. Chem. Int. Ed. *47*, 452–483. 10.1002/anie.200604045.

*Please note that each numbered reference may contain only one citation.

---

[1] Q. Miao, ed. (2016). Polycyclic Arenes and Heteroarenes: Synthesis, Properties, and Applications (Wiley-VCH, Verlag GmbH & Co. KGaA Weinheim).

[2] K. Müllen, and X. Feng, eds. (2017). From Polyphenylenes to Nanographenes and Graphene Nanoribbons (Springer-Verlag Berlin Heidelberg).

[3] Cheung, K. Y., Watanabe, K., Segawa, Y., and Itami, K. (2021). Synthesis of a zigzag carbon nanobelt. Nat. Chem. *13*, 255–259. 10.1038/s41557-020-00627-5.

[4] A. Biju, ed. (2021). Modern Aryne Chemistry (Wiley-VCH, Verlag GmbH & Co. KGaA Weinheim).

[5] Tadross, P. M., and Stoltz, B. M. (2012). A comprehensive history of arynes in natural product total synthesis. Chem. Rev. *112*, 3550–3577. 10.1021/cr200478h.

[6] Gampe, C. M., and Carreira, E. M. (2012). Arynes and cyclohexyne in natural product synthesis. Angew. Chem. Int. Ed. *51*, 3766–3778. 10.1002/anie.201107485.

[7] Peréz, D., Peña, D., and Guitián, E. (2013). Aryne cycloaddition reactions in the synthesis of large polycyclic aromatic compounds. Eur. J. Org. Chem. *27*, 5981–6013. 10.1002/ejoc.201300470.

[8] Xu, F., Xiao, X., and Hoye, T. R. (2017). Photochemical hexadehydro-Diels–Alder reaction. J. Am. Chem. Soc. *139*, 8400–8403. 10.1021/jacs.7b03832.

[9] Bradley, A. Z., and Johnson, R. P. (1997). Thermolysis of 1,3,8-nonatriyne: evidence for intramolecular [2+4] cycloaromatization to a benzyne intermediate. J. Am. Chem. Soc. *119*, 9917–9918. 10.1021/ja972141f.

[10] Miyawaki, K., Suzuki, R., Kawano, T., and Ueda, I. (1997). 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-diynyl}]phenylpentan-2,4-diyn-1-ols and trapping evidence for the 1,2-didehydrobenzene diradical. Tetrahedron Lett. *38*, 3943–3946. 10.1016/S0040-4039(97)00785-5.

[11] Hoye, T. R., Baire, B., Niu, D. W., Willoughby, P. H., and Woods, B. P. (2012). The hexadehydro-Diels–Alder reaction. Nature *490*, 208–212. 10.1038/nature11518.

[12] Wang, T., Naredla, R. R., Thompson, S. K., and Hoye, T. R. (2016). The pentadehydro-Diels−Alder reaction. Nature *532*, 484−488. 10.1038/nature17429.

[13] Xiao, X., and Hoye, T. R. (2018). The domino hexadehydro-Diels−Alder reaction transforms polyynes to benzynes to naphthynes to anthracynes to tetracynes (and beyond?). Nat. Chem. *10*, 838−844. 10.1038/s41557-018-0075-y.

[14] Thompson, S. K., and Hoye, T. R. (2019). The aza-hexadehydro-Diels−Alder reaction. J. Am. Chem. Soc. *141*, 19575−19580. 10.1021/jacs.9b11243.

[15] Hammer, B., and Müllen, K. (2016). Dimensional evolution of polyphenylenes: Expanding in all directions. Chem. Rev. *116*, 2103–2140. 10.1021/acs.chemrev.5b00515.

[16] Yaghi, M. O., Kalmutzki, M. J., and Diercks, S. C. (2019). Introduction to Reticular Chemistry: Metal-Organic Frameworks and Covalent Organic Frameworks (Wiley-VCH, Verlag GmbH & Co. KGaA Weinheim).

[17] Chen, J., Palani, V., and Hoye, T. R. (2016). Reactions of HDDA-derived benzynes with sulfides: mechanism, modes, and three-component reactions. J. Am. Chem. Soc. *138*, 4318–4321. 10.1021/jacs.6b01025.

[18] Holden, C., and Greaney, M. F. (2014). The Hexadehydro-Diels–Alder reaction: A new chapter in aryne chemistry. Angew. Chem. Int. Ed. *53*, 5746–5749. 10.1002/anie.201402405.

[19] Diamond, O. J., and Marder, T. B. (2017). Methodology and applications of the hexadehydro-Diels−Alder (HDDA) reaction. Org. Chem. Front. *4*, 891−910. 10.1039/C7QO00071E.

[20] Fluegel, L. L., and Hoye, T. R. (2021). Hexadehydro-Diels-Alder reaction: Benzyne generation via cycloisomerization of tethered triynes. Chem. Rev. *121*, 2413−2444. 10.1021/acs.chemrev.0c00825.

[21] Wittig, G., and Knauss, E. (1958). Dehydrobenzol und Cyclopentadien. Chem. Ber. *91*, 895–907. 10.1002/cber.19580910502.

[22] Fieser, L. F., and Haddadin, M. J. (1965). Isobenzofurane, a transient intermediate. Can. J. Chem. *43*, 1599–1606. 10.1139/v65-211.

[23] Chen, J. H., Baire, B., and Hoye, T. R. (2014). Cycloaddition reactions of azide, furan, and pyrrole units with benzynes generated by the hexadehydro-Diels–Alder (HDDA) reaction. Heterocycles *88*, 1191–1200. 10.3987/COM-13-S(S)83.

[24] Hamura, T., Ibusuki, Y., Sato, K., Matsumoto, T., Osamura, Y., and Suzuki, K. (2003). Strain-induced regioselectivities in reactions of benzyne possessing a fused four-membered ring. *Org. Lett. 5*, 3551–3554. 10.1021/ol034877p.

[25] Garr, A. N., Luo, D., Brown, N., Cramer, C. J., Buszek, K. R., and VanderVelde, D. (2010). Experimental and theoretical investigations into the unusual regioselectivity of 4,5-, 5,6-, and 6,7-indole aryne cycloadditions. Org. Lett. *12*, 96–99. 10.1021/ol902415s.

[26] Cheong, P. H.-Y., Paton, R. S., Bronner, S. M., Im, G.-Y. J., Garg, N. K., and Houk, K. N. (2010). Indolyne and aryne distortions and nucleophilic regioselectivites. J. Am. Chem. Soc. *132*, 1267−1269. 10.1021/ja9098643.

[27] Niu, D. W., Willoughby, P. H., Woods, B. P., Baire, B., and Hoye, T. R. (2013). Alkane desaturation by concerted double hydrogen atom transfer to benzyne. Nature *501*, 531–534. 10.1038/nature12492.

[28] Wittig, G., and Hoffmann, R. W. (1962). Dehydrobenzol aus 1.2.3-Benzothiadiazol-1.1-dioxyd. Chem. Ber. *95*, 2718–2728. 10.1002/cber.19620951120.

[29] Fix, A. G, Chase, D. T., and Haley M. M. (2014). Indenofluorenes and Derivatives: Syntheses and Emerging Materials Applications. In Polyarenes I, J. S. Siegel, and Y. Wu, eds. (Springer-Verlag Berlin Heidelberg), pp. 160-193.

[30] Frederickson, C. K., Rose, B. D., and Haley, M. M. (2017). Explorations of the indenofluorenes and expanded quinoidal analogues. Acc. Chem. Res. *50*, 977–987. 10.1021/acs.accounts.7b00004.

[31] Nakagawa, T., Kumaki, D., Nishida, J.-I., Tokito, S., and Yamashita, Y. (2008). High performance n-type field-effect transistors based on indenofluorenedione and diindenopyrazinedione derivatives Chem. Mater. *20*, 2615–2617. 10.1021/cm800366b.

---

[32] Chase, D. T., Rose, B. D., McClintock, S. P., Zakharov, L. N., and Haley, M. M. (2011). Indeno[1,2-b]fluorenes: Fully Conjugated Antiaromatic Analogues of Acenes. Angew. Chem. Int. Ed. *50*, 1127–1130.10.1002/anie.201006312.

[33] Chase, D. T., Fix, A. G., Rose, B. D., Weber, C. D., Nobusue, S., Stockwell, C. E., Zakharov, L. N., Lonergan, M. C., Haley, M. M. (2011). Electron-Accepting 6,12-Diethynylindeno[1,2-b]fluorenes: Synthesis, Crystal Structures, and Photophysical Properties. Angew. Chem. Int. Ed. *50*, 11103–11106. 10.1002/anie.201104797.

[34] He, J., Qiu, D., and Li, Y. (2020). Strategies toward aryne multifunctionalization via 1,2-benzdiyne and benzyne. Acc. Chem. Res. *53*, 508–519. 10.1021/acs.accounts.9b00608.

[35] Xiao, X., and Hoye, T. R. (2019). One-pot, three-aryne cascade strategy for naphthalene formation from 1,3-diynes and 1,2-benzdiyne equivalents. J. Am. Chem. Soc. *141*, 9813–9818. 10.1021/jacs.9b04606.

[36] Anthony, J. E. (2008). The larger acenes: versatile organic semiconductors. Angew. Chem. Int. Ed. *47*, 452–483. 10.1002/anie.200604045.