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The domino hexadehydro-Diels–Alder reaction transforms polyynes to benzyne to naphthynes to anthracynes to tetracynes (and beyond?)

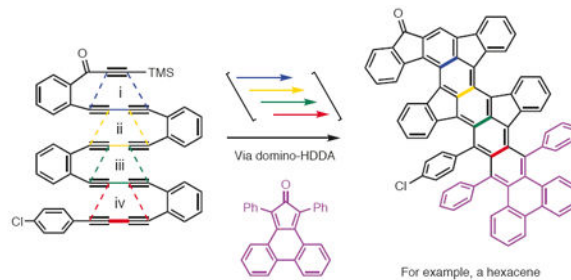
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Abstract

Polyacenes are organic compounds that have multiple, fused, aromatic rings. These highly conjugated molecules often have interesting photonic and/or electronic properties that afford them the potential for application in a host of organoelectronic devices such as sensors, light emitting diodes, photovoltaic devices, and field-effect transistors. Here we show the development and use of the title (domino-HDDA) reaction to synthesize structurally diverse polyacenes from acyclic polyyne precursors. The key event in these transformations is the successive reaction of multiple 1,3-butadiyne units with a series of *in situ*-generated, diynophilic aryne. The polyyne substrates were designed to allow for rapid engagement of each progressively larger aryne following the initiating (and rate-limiting) production of the first reactive intermediate—the benzyne. We show that aryne trapping reactions are broad in scope and that these cascade or domino processes can be quite efficient.

Abstract



Highly fused, multicyclic aromatic compounds are important for their potential utility in, for example, organic electronic and photonic applications.¹ Benzyne/aryne chemistry has

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Author contributions

X.X. and T.H. conceived the experiments, interpreted the data, and co-wrote the manuscript. X.X. executed the experiments and collected the data.

Supplementary information (SI) is available in the online version of the paper.

Competing financial interests

The authors declare no competing financial interests.

allowed chemists to construct various sub-classes and derivatives of these multi-ring compounds^{2,3,4}. The formation of benzyne—long-standing⁵ and versatile intermediates in organic chemistry (see ref 6 for a recent comprehensive listing of reviews⁶)—under purely thermal^{7,8} (or photochemical⁹) conditions by the hexadehydro-Diels–Alder (HDDA) reaction¹⁰ represents a significant development¹¹. In its simplest form, the HDDA reaction is an intramolecular cycloisomerization that converts a tethered triyne like **1** into the (much more stable¹²) fused benzyne **2** (Fig. 1a), which is typically trapped directly by any of a large host of arynophiles. If the trapping agent were to be another 1,3-diyne, then, in principle, a second aryne—a naphthyne (**3**)—could be formed.

The earliest suggestion of the possibility of a benzyne engaging a 1,3-diyne stems from a study of acetylene pyrolysis¹³. In fact, Ueda and coworkers^{14,15,16} demonstrated that by tethering a second diyne unit into a substrate (see **6**) it was possible to trap the initial benzyne to produce a naphthyne derivative (i.e., **7**), which was then trapped by benzene to give **8** in the example shown (Fig. 1b). They described eight such reactions in which naphthyne derivatives were produced and trapped to give products in yields ranging from 10–63%. One potential competing (and efficiency lowering) event in those reactions was the initial cyclization of the “left-hand” tetrayne subunit to a non-productive benzyne—i.e., ring closure to the two atoms labeled as \blacktriangle rather than \bullet . The reaction of benzyne with 1,3-butadiyne to generate naphthyne has also been studied by density functional theory (DFT) computations.¹⁷ Recently, the generation of a naphthyne through trapping of a conventionally generated benzyne (i.e., through reductive elimination of an *ortho*-iodotriflate by a Grignard reagent) by a tethered 1,3-diyne was described¹⁸.

Results and discussion

We envisioned that sequential HDDA reactions within a properly designed polyynes substrate could be used to synthesize higher acenes. We began our studies by designing a substrate—namely, **9**—that would be likely to initiate reaction by cyclizing in only one sense (Fig. 1c). That is, we were confident that **9** would efficiently close to **10**¹⁹ and presumed that it would proceed on to the naphthyne **11** prior to being trapped by an external arynophile. Indeed, when **9** was heated in the presence of 2,5-dimethylfuran, adduct **12** was the only product observed and was isolated in 85% yield following purification. The substrate **9** was prepared in three reactions from commercially available precursors (see Supplementary Section II).

We next explored the hypothesis that extension of the HDDA process to substrates containing more than one additional 1,3-diyne unit would lead to a cascade of cycloisomerizations. If so, this had the potential to greatly expand the versatility of this reaction by allowing rapid construction of complex, polycyclic arenes (polyacenes). Moreover, we judged that a key design feature of the requisite polyynes substrates would be that each additional 1,3-diyne moiety be linked to the previous by a two-atom linking unit. Accordingly, we prepared substrate **13** (5 steps, see Supplementary Section II) and heated it in the presence of furan (5 equiv). Adduct **15** obligingly formed, again as the only observed product (Fig. 2a). Presumably (see below), the sequential cyclizations implied by the labels i, ii, and iii in substrate **13** had progressed smoothly to an anthracene intermediate by way of the naphthyne **14**. Similarly, the anthracene adduct **16**, a compound discussed in a later

context, was formed when diethyl 3,4-furandicarboxylate²⁰ was used as the trapping agent. To explore whether an aromatic 2-atom linker would be compatible with a similar cascade reaction, we prepared the heptyayne **17**, now containing a pair of *o*-substituted benzene rings rather than the two-atom ethano (or dimethylene) linkers along its backbone. The domino reaction of this substrate, being initiated by an essentially identical cyclization to the benzyne intermediate (step i), proceeded at a very similar rate as the other substrates described thus far. Furan trapping led to the isolation of **19** as the major product. We speculate that this reaction was somewhat less efficient because of the potential for further reaction of the more delocalized polyacene present in **19** by its [4+2] cycloaddition with another molecule of the anthracyne **18**.

To establish the bona fide intermediacy of discreet aryne intermediates in a domino process, we explored the effect of concentration of the external trapping reagent. Furan is a particularly reactive aryneophile by virtue of its facile [4+2] cycloaddition, a feature that has been exploited from some of the very earliest investigations of benzyne reactivity²¹. Furan is also convenient to use as a bulk solvent. Several of our polyyne substrates, when heated in neat furan (ca. 14 M), led to a pair of products—the expected furan adduct of a naphthyne (cf. **12**, Fig. 1c) as well as a benzyne/furan adduct, in which the intermediate benzyne was prematurely trapped by a solvent molecule. This bifurcation was most vivid in the case of the octayne **20** (Fig. 3). When heated in neat furan, the benzyne adduct **21** was formed to the near exclusion of the naphthyne-derived product **22** (Fig. 2). In a series of experiments, this reaction was progressively starved of furan; the product ratio favored **22** to an increasing extent, in accord with the expectation that furan trapping is a bimolecular process first-order in the concentration of furan, whereas the competing benzyne to naphthyne cyclization (cf. **10** to **11**) is a unimolecular event whose rate is independent of the rate of external trapping. By contrast, we did not observe products of premature trapping by furan for any polyyne substrates containing a benzo-linker; presumably the additional degree of freedom in the ethano-linker slows the rate of each successive aryne homologation event by virtue of population of a larger number of unreactive conformers. As an aside, we note that the three-atom linker in the symmetrical octayne **20** here resides in the center of the molecule and that the domino reaction propagates in one direction only in a process that is, necessarily, desymmetrizing.

With all external aryneophiles that we have examined that are less reactive than furan, intramolecular cyclization of each aryne to its next higher homolog was faster than trapping, and no products of premature interruption of the domino process were observed. We explored most extensively the scope of the reaction by generating the series of naphthyne **24** from substrates **23** (Fig. 4a). Many types of trapping reagents (T¹–T²) are effective, providing access to a host of products **25** in good yields. The nature of the ABC tether unit in the polyyne substrates **23** can be varied widely¹¹, and the two-atom linker between adjacent diynes can include substituted arenes (cf. **25h**, **25q**, **25t–25v**) as well as ethano- and 1,2-benzo-linkers. In addition to Diels–Alder products with furan (**25a**, **25b**); [4+2] cycloaddition adducts with a pyrrole (**25c**), *o*-dichlorobenzene (*o*-DCB, **25d**), anthracene (**25e**), cyclopentadienones (**25f**, **25g**), pyrones (**25h**, **25i**), and perylene (**25j**, **25k**) are readily formed. Nucleophilic traps are efficient [carboxylic acid (**25l**), sulfide (**25m**), and amine

(**25n**) as are other types of cycloaddition reactions {[2+2] (**25o**) and 1,3-dipolar (**25p**)}. Symmetrical vicinal difunctionalization is also well accommodated [dihalogenation²² (**25q** and **25r**), dihydrogen transfer²³ (**25s** and **25t**), and dichalcogenation^{24,25} (**25u** and **25v**)].

A few additional features of these reactions are noteworthy. The furan adduct **25a** was also readily formed under photochemical-HDDA conditions⁹ (at ambient temperature). We computed the internal bond angles at the sp-hybridized carbons²⁶ in some of the naphthylene intermediates [DFT B3LYP/6-31G*] and observed a smaller degree of distortion relative to the benzyne precursors¹² (see Supplementary Fig. 1). Trapping with the cyclopentadienone **26** gave an isolable, bis-fused norbornadienone adduct (not shown, see Supplementary Section II and cf. **32**, Fig. 6) enroute to **25g**. Cheletropic ejection of CO was quite slow (relative to that in the simple *o*-benzyne adduct²⁷), consistent with the smaller gain in aromatic resonance energy produced upon forming the highly delocalized dibenzotetracene moiety in **25g**. The variability in the extent of regioselectivity observed for these reactions suggests that there is a subtle interplay between the inherent reactivity imposed by the degree of distortion of the aryne and the steric bias presented by the two different substituents flanking the aryne carbons as they are approached by trapping agents, themselves of varying size²⁸.

Finally, the two trapping reactions with perylene to give **25j** and **25k** deserve comment. The former behaves in an expected fashion—namely, benzynes are known to add to the bay region diene portion of perylene^{29,30} and to eject hydrogen thermally to rearomatize. In contrast, the naphthylene leading to **25k** (see Supplementary Section V for X-ray diffraction coordinates) differs from the one that gives **25j** by the presence of a larger benzo- rather than ethano-two atom linker, which would encounter a greater steric obstruction were it to add to the bay region diene. DFT calculations (B3LYP/6-31G*, see Supplementary Fig. 2) support this view—the transition structure for concerted addition of that naphthylene to the bay region was computed to be 1.6 kcal•mol⁻¹ higher in energy than that leading to **25k**. A lesser amount of an isomeric product in which the naphthylene added in reversed head-to-tail fashion was also formed, and the DFT energetics were consistent with that process as well.

As an aside, we have observed some surprising acid-catalyzed processes for a subset of these polycyclic acenes; these show that unusual reactivity can ensue within certain, structurally complex HDDA products. Two examples are shown in Fig. 5. When exposed to trifluoroacetic acid, the highly fused anthracene derivative **16** gave rise to the doubly oxidized analog **27**. When this (mechanistically unusual) transformation was monitored directly by NMR spectroscopy in CDCl₃, resonances associated with metastable intermediates were seen, which eventually converged largely to those of the diene **27**. This suggests that the oxidation occurs in stages, likely by way of each of the two possible monoenes. A similar experiment, in which the air in the head space of the NMR sample tube was replaced by nitrogen, resulted in a much slower conversion, implicating dioxygen as the stoichiometric oxidant. Consistent with that and because **27** is more visibly colored than its precursor, **16**, the color of the solution turned darker at the top of the NMR sample solution, closer to the air-liquid interface. Finally, in the absence of the TFA, **16** showed no sign of oxidative instability.

In a different setting, that of the fluoranthene derivative **25s**, methanesulfonic acid was used to remove the trimethylsilyl group by a protodesilylation reaction and to catalyze the introduction of a spirocyclic xanthene (cf. **28**) by a Friedel-Crafts addition/dehydration sequence³¹. Conversion of fluorenones to spirocycles of this sort has been used to confer fluorescence behavior that is rendered dormant by the ketone functional group³²; indeed, compound **28** showed emission that was cyan in color (see Supplementary Fig. 10). The one-pot conversion of **25s** to **28** was accompanied by a surprising 1,2-migration of the phenyl substituent from its hindered environment in the reactant to the much less encumbered position in **28**. The mechanism of Brønsted acid-catalyzed 1,2-phenyl (or – naphthyl) migration on a benzene (or naphthalene) framework has been studied computationally,^{33,34} which indicates that this process likely proceeds by way of *ipso*-protonation of the phenyl-bearing carbon followed by phenyl migration to the adjacent carbon atom via a phenonium ion intermediate.

Having established that trapping of domino HDDA products (Fig. 4) is robust and that the benzyne-to-naphthyne-to-anthracene cascade is viable (Fig. 2), we were motivated to further extend the domino process to see if a tetracyne could be accessed. Toward that end we prepared the nonayne **29**. The route of synthesis involved twelve (8 longest linear sequence) reactions (see Supplementary Section II) from commercially sourced chemicals. By contrast, the preparation of nearly all of the other multi-yne substrates in the work reported here required no more than seven synthesis steps.

When **29** was heated in the presence of anthracene, a pleasingly efficient transformation to the adduct **30** transpired (Fig. 6a), establishing that, indeed, a tetracyne can be generated by a domino-HDDA reaction. From ¹H NMR spectra, **30** is inferred to exist as a pair of topological isomers [crossed (cf. **31**) vs. butterfly] that interconvert slowly on the NMR time scale and whose equilibrium ratio is somewhat solvent dependent. DFT calculations [SMD(CHCl₃)/B3LYP-D3BJ/6-31G**//B3LYP/6-31G*] are consistent with these observations, were used to assign structure, and predicted that the desilylated derivative **31** would have a larger preference for one isomer (see Supplementary Figs. 3–5). Indeed, protodesilylation with methanesulfonic acid smoothly gave **31**, which was largely a single isomer (d.r. = 47:1).

In a second example (Fig. 6b), the tetracyne from **29** was trapped by the dienone **26**, producing the diketone **32**. Protodesilylation (MsOH) gave the intermediate **32-H**, which, upon thermolytic ejection of CO, smoothly provided the dibenzohexacene product **33**. In contrast to relatively unsubstituted polyacenes³⁵, none of these compounds showed signs of sensitivity to air and/or light. The most highly conjugated polyacene **33** has its longest wavelength absorption moved significantly into the infrared (Fig. 6c). Compounds that absorb near-IR light find utility in applications such as organic field-effect transistors, organic photovoltaics, and photodetectors³⁶. Again, topoisomerism was seen³⁷ (NMR) for each of **32–33**. Fortunately, evaporative crystallization of a solution of **32-H** gave material suitable for single crystal X-ray diffraction analysis (Fig. 6d). The helical twist of the fused tetracene core is clearly evident, a feature mimicked in the lowest energy topoisomer found by DFT calculations (see Supplementary Fig. 6).

In conclusion, we have established that the domino-HDDA reaction is an efficient process having considerable generality. It proceeds through a staged series of cycloisomerization events within substrates containing varying numbers of 1,3-diyne units, each separated by two-atom spacers. The cascade is initiated by a diynophilic alkyne that is connected uniquely by a three-atom tether. This reagent-free thermal reaction is remarkably robust, is broad in scope, and generates considerable structural complexity, as underscored, for example, by the nine newly formed rings present in each of **31–33**. A future challenge may be the management of potential product solubility and/or stability issues, but these have not posed significant problems to date.

Methods

General protocol for performing the domino-HDDA reactions

The headspace of a threaded vial containing the polyynes precursor in an organic solvent (initial concentration typically 0.02 M in, often, ethanol-free CHCl₃) and the indicated number of equivalents of the trapping reactant was flushed with nitrogen immediately before being sealed with a Teflon-lined cap. The reaction solution was heated at 80–130 °C for ca. 5–16 h. The product(s) was(were) separated/purified by silica gel chromatography.

Data availability

The authors declare that all relevant data supporting the findings of this study are available either within the manuscript itself and/or in the Supplementary Information. Experimental details and full spectroscopic characterization data for all new compounds, a description of the computational methods and results, UV-Vis absorption and emission spectra, a summary of the X-ray diffraction data, and copies of all proton and carbon NMR spectra are provided in the Supplementary Information. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 1818244 (**25k**), 1818243 (**28**) and 1818245 (**32-H**). Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. Additionally, the corresponding author can be contacted directly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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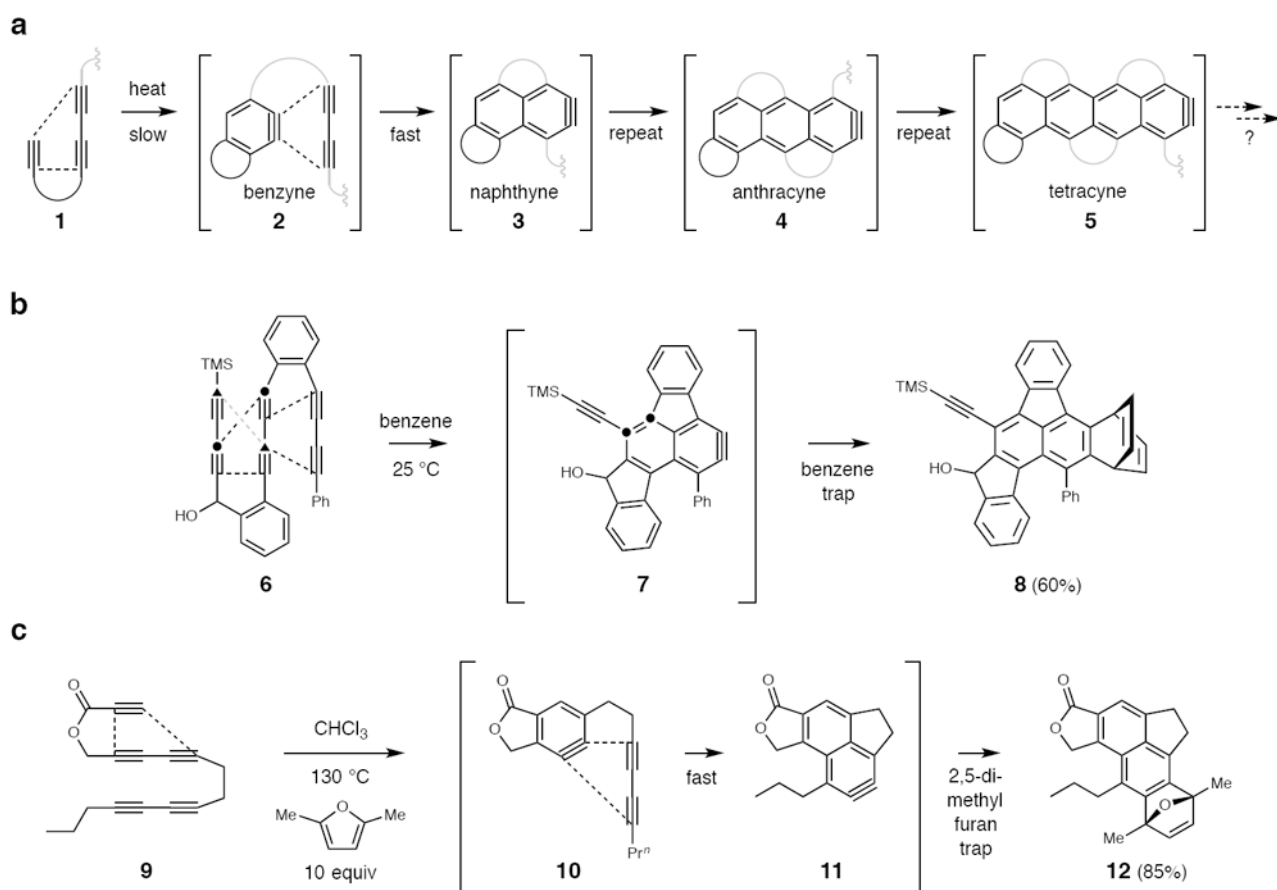


Figure 1. The domino HDDA reaction

a) Generic scheme of sequential cycloisomerizations in which a new 1,3-diyne unit adds to an aryne to produce the next higher homolog among a series of polyacynes. **b)** A known example that demonstrates feasibility. **c)** Our first example, using a substrate designed to initiate reaction by cyclizing in only one sense—that is proceeding from **9** to the initial benzyne **10** and then on to the naphthyne **11** prior to being trapped by an external arynophile. Adduct **12** was the only product observed.

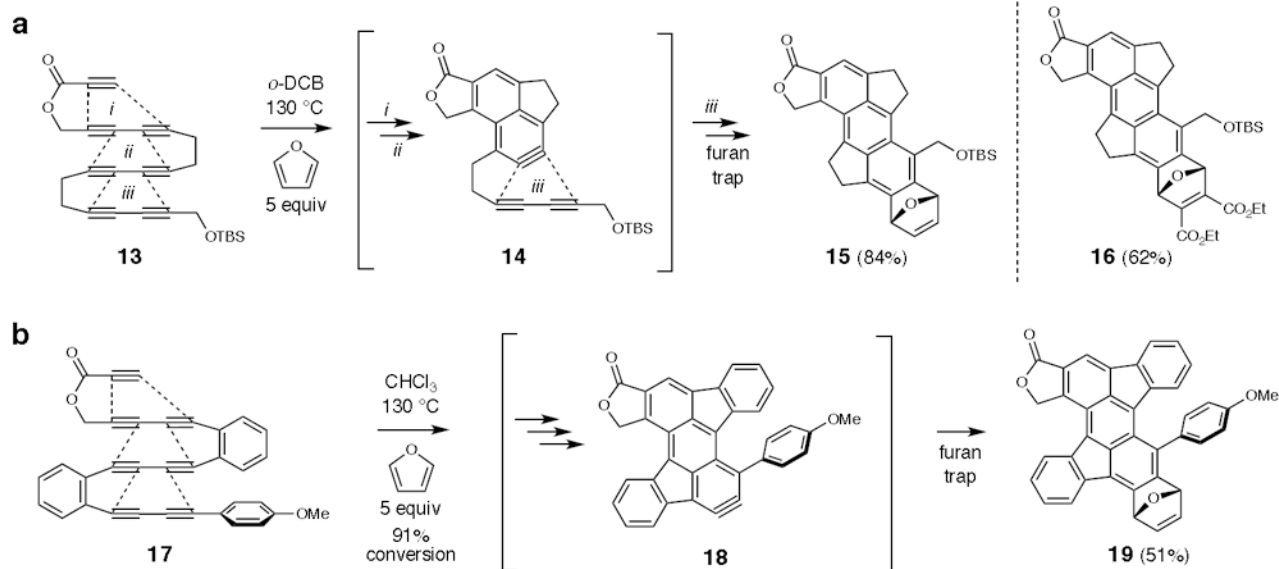


Figure 2. Benzyne to naphthyne to anthracyne

a) The first example of extension of the domino reaction to a case involving three aryne-forming reactions: i) triyne to benzyne; ii) benzyne to naphthyne; iii) naphthyne to anthracyne; and final trapping event. **b)** Substrate **17** demonstrates that benzene subunits are suitable 2-atom linkers to conjoin adjacent pairs of 1,3-diyne, a feature that results in the formation of a product having more extended conjugation of the anthracene core in the product. TBS is *tert*-butyldimethylsilyl; *o*-DCB is 1,2- or *ortho*-dichlorobenzene.

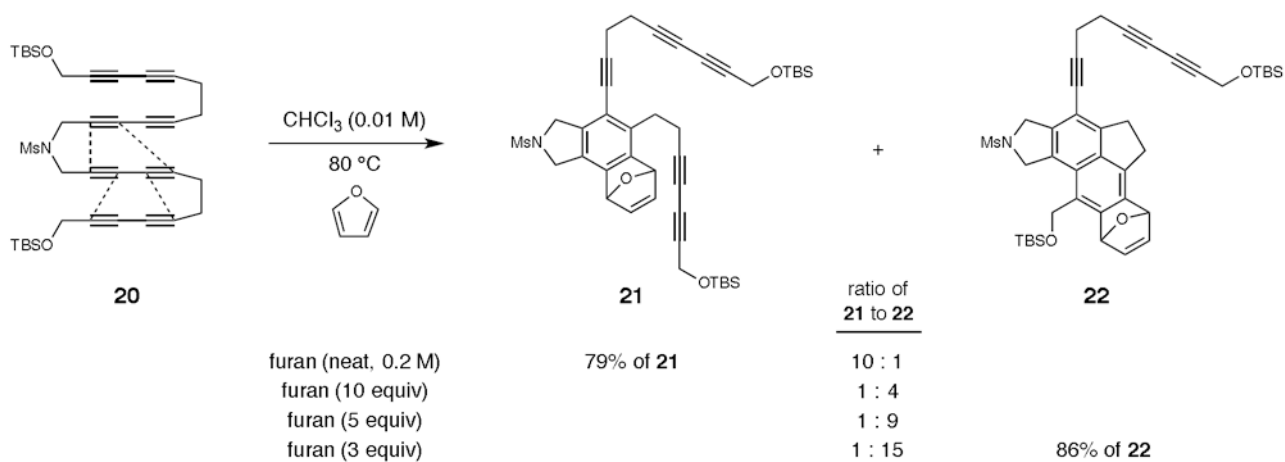


Figure 3. Polyene to benzyne to naphthene is a stepwise process

The ratio of products **21:22** is dependent on the concentration of furan, a particularly reactive aryne trapping reagent. This demonstrates that the intermediate benzyne, the precursor to **21**, has a sufficiently long lifetime that it can be trapped when the trapping event has a fast enough rate, that rate being dependent upon the inherent rate constant for the trapping event as well as on its concentration. The **21:22** branching ratio changes with [furan] used because, of course, the conversion of the benzyne to naphthene intermediate is a unimolecular event whereas trapping of either aryne by furan is bimolecular. Ms is mesyl (or methanesulfonyl).

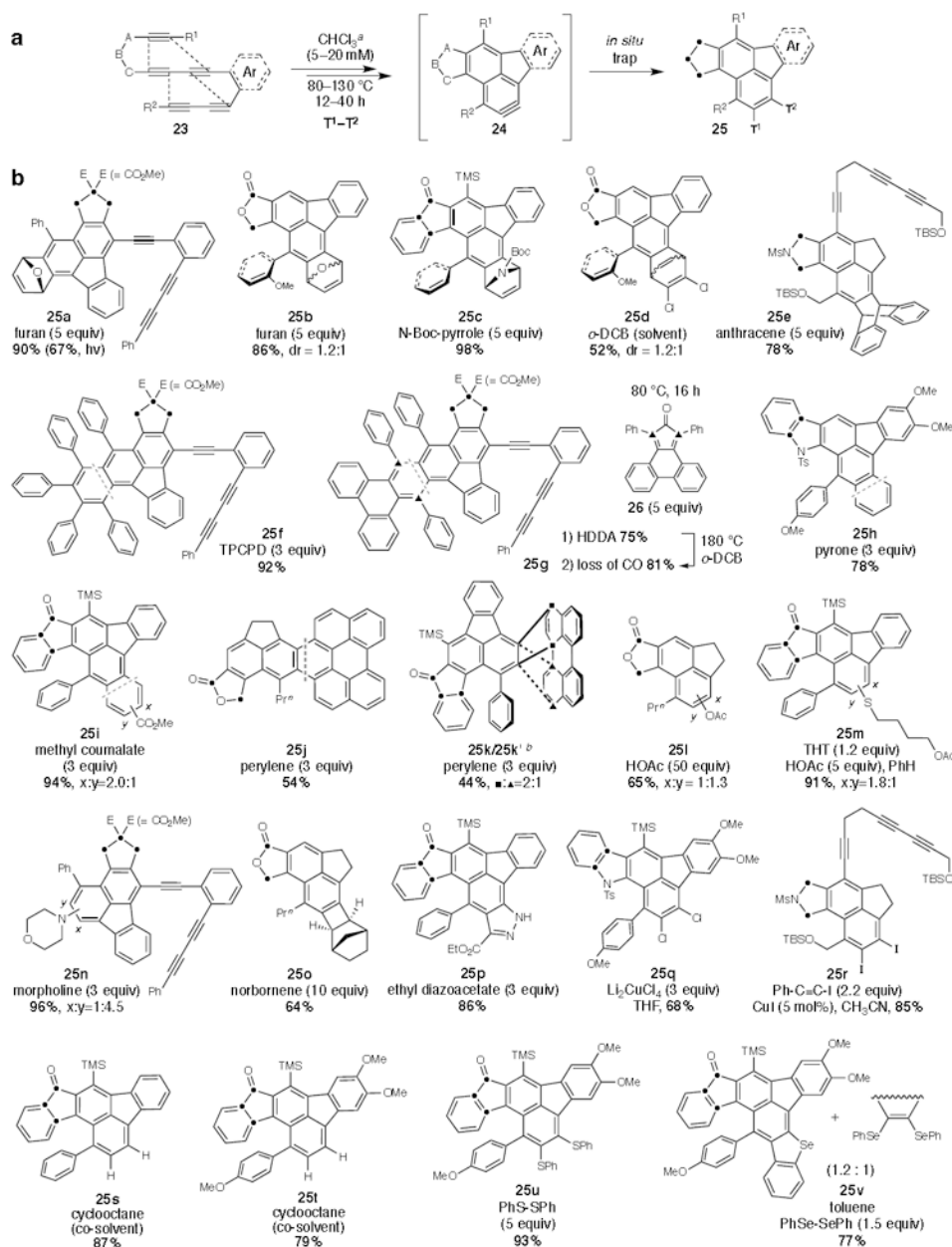


Figure 4. Examples of domino HDDA products via naphthynyl intermediates

a) Generic reaction and reaction conditions for naphthynyl generation and trapping. **b)**

Reactions that demonstrate considerable scope in the variety of naphthynyl precursors **23** as well as trapping agents (T^1 – T^2) that can be used. Variations of the three-atom (A-B-C) linker allow the formation of products containing the following types of rings newly fused to the initial benzyne intermediate: cyclopentane (cf. **25a**), butyrolactone (cf. **25b**), indanone (cf. **25c**), pyrrolidine (cf. **25e**), and indole (cf. **25h**). Variations of the classes of trapping reactions include cycloadditions {[4+2] (cf. **25a**–**25k**), [3+2] (cf. **25p**), and [2+2] (cf. **25o**)}, nucleophilic addition (cf. **25l**–**25n**), oxidative addition (cf. **25q**–**25r** and **25u**–**25v**), and reductive addition (of H₂, cf. **25s**–**25t**). Ar is aryl; Ph is phenyl; TMS is trimethylsilyl; Boc

is *tert*-butyloxycarbonyl; TPCPD is tetraphenylcyclopentadienone; Ac is acetyl; THT = tetrahydrothiophene.

^aThe reaction solvent was chloroform unless otherwise stated. ^b**25k** has the solid bonds (see X-ray diffraction data in Supplementary Section V); **25k'** is the isomeric adduct having, instead, the analogous connectivity implied by the dashed bonds.

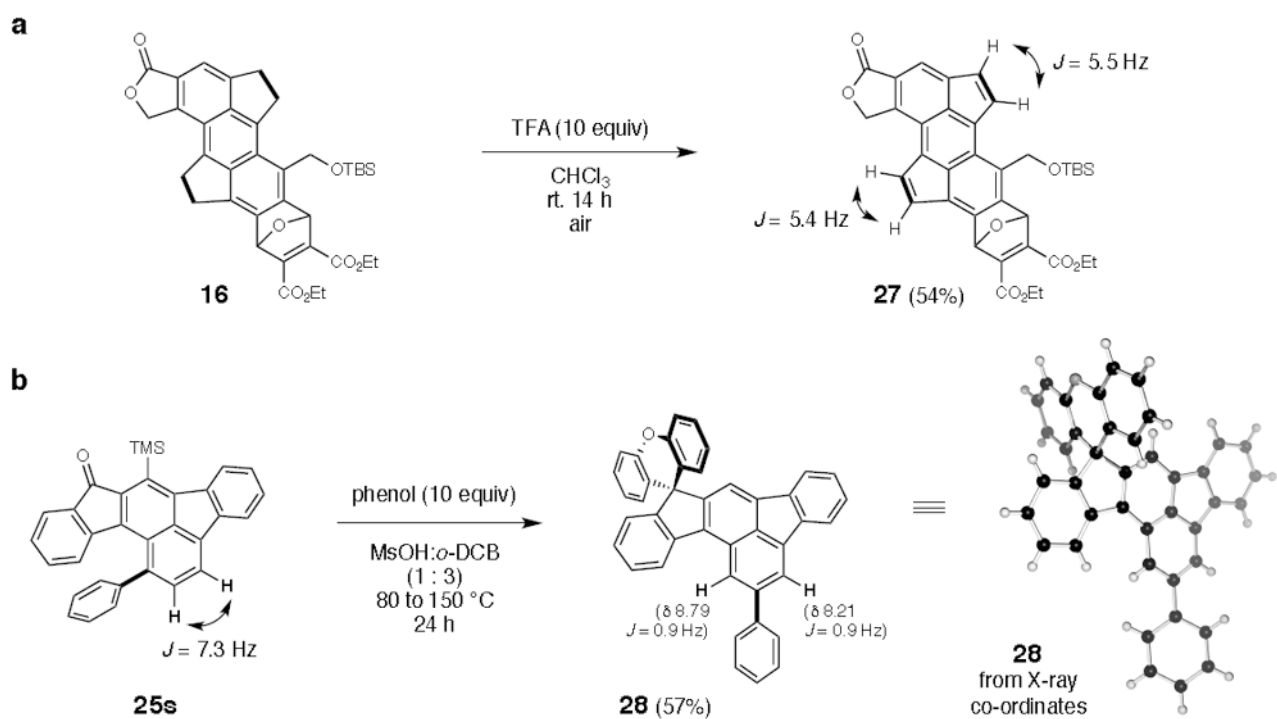


Figure 5. Unusual acid-catalyzed transformations of the products 16 and 25s

a Brønsted acid-promoted oxidation of the two bis-methylene subunits in **16** (red) to the alkenes in the pair of acenaphthylene subunits (red) in **27**. **b** Brønsted acid-promoted 1,2-migration within the phenyl group of **25s**, concomitant with formation of the deplanarizing, spirocyclic xanthenone moiety. TFA is trifluoroacetic acid.

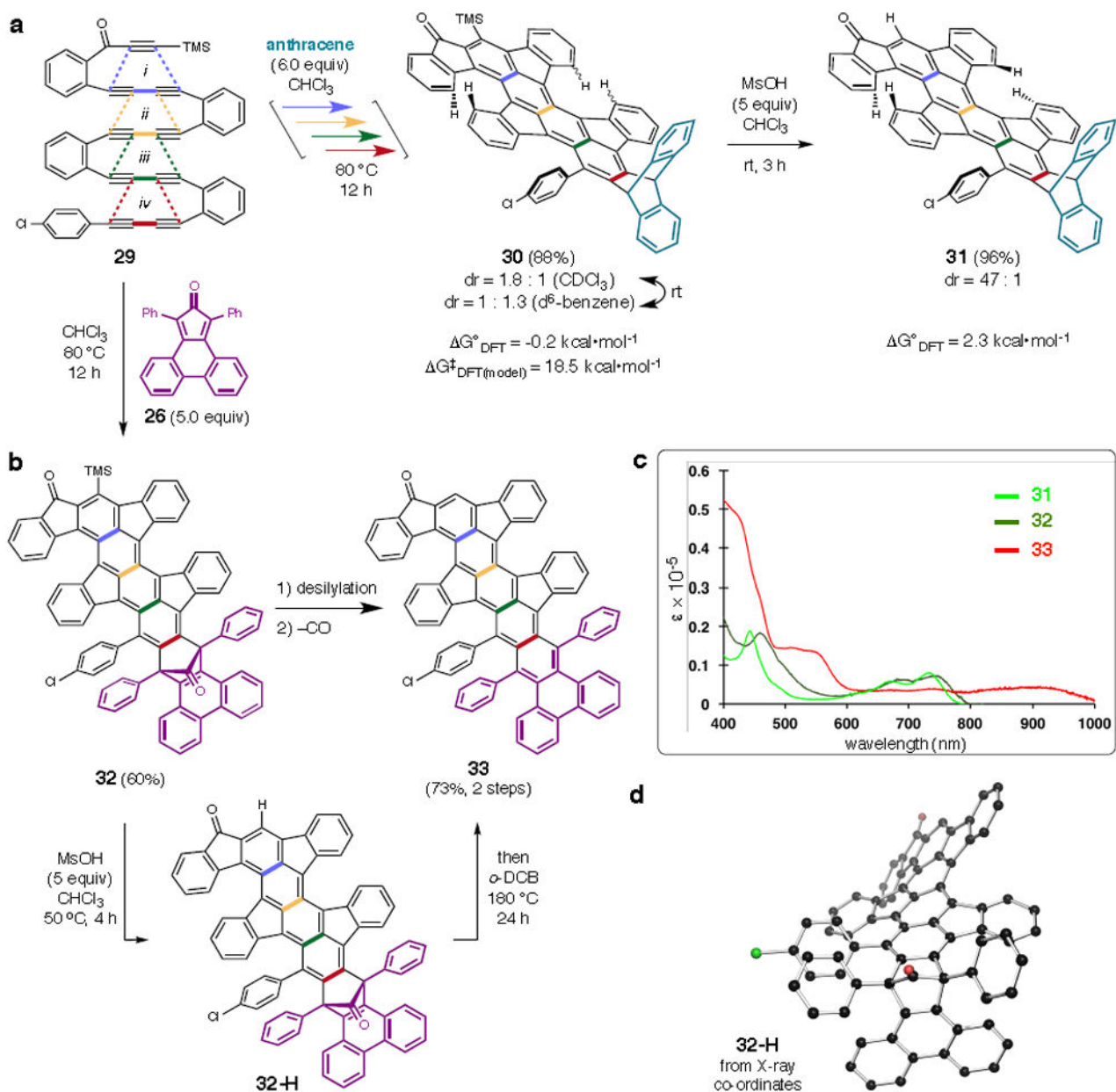


Figure 6. Benzynes to naphthynes to anthracynes to tetracynes

a) The nonayne **29** cyclizes in four serial (i–iv) events to a tetracyne that is cleanly trapped by anthracene, producing **30**. **b)** Trapping the tetracyne with the dienone **26** provides the adduct **32**, which can be more fully aromatized by thermolysis to give the dibenzohexacene **33**. **c)** Absorption spectral data for **33** vis-à-vis **31** and **32**. **d)** Geometry of the heavy atoms from the co-ordinates of the X-ray diffraction analysis of **32-H**. d.r. is diastereomeric ratio.