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The hexadehydro-Diels–Alder reaction

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Summary

o-Benzynes (arynes) are among the most versatile of all reactive (short-lived) intermediates in organic chemistry. These species can be trapped to give products that are valuable from the perspective of both fine (pharmaceuticals) and commodity (agrochemicals, dyes, polymers, etc.) chemicals. Here we show a fundamentally new strategy that unites a *de novo* generation of benzyne, through the title hexadehydro-Diels–Alder (HDDA) reaction, with their *in situ* elaboration into structurally complex benzenoid products. In the HDDA reaction a 1,3-diyne is engaged in a [4+2] cycloisomerization with a third (pendant) alkyne—the diynophile—to produce the highly reactive benzyne intermediate. The metal- and reagent-free reaction conditions for this simple, thermal transformation are notable. 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.

o-Benzyne [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 (cf. **1** to **3**) 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 (cf. “G” and “X”) 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 Diels–Alder [4+2] cycloaddition reaction¹¹ is arguably the most revered of all chemical reactions^{12,13}. The prototypical event (Fig. 1b), found in every introductory organic

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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 at the tetrahydrobenzene oxidation state. If, instead, an alkyne like ethyne (**7**) is the dienophile, a 1,4-cyclohexadiene [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 (e.g., **9**) as the 4π -component with an alkyne (e.g., **7**). It is interesting to note that the first example of this process (the thermal dimerization of phenylpropionic acid)¹⁴ was described 30 years *prior* to 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 heretofore been called, generically, the dehydro-Diels–Alder (DDA) reaction¹⁵. In light of the generality of the results we present in this report, we suggest amending the moniker for the transformation in Fig. 1d to *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 dienophile like **7**, which generates *o*-benzyne (cf. **1'**, **1**, **1***). This *hexadehydro*-Diels–Alder (HDDA) reaction is the subject of this report. 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 benzyne 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 dienophile. 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 ca. 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 reaction. 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 *triyne*s. 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 Fig. 3 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 (cf. Fig. 2b). All yields of purified products were $\geq 75\%$, and (with the exception of entry 8) all reactions occurred between temperatures of 20–120 °C. Highlights include: **i**] the presence of an electron withdrawing substituent on the diyne enhances substrate reactivity [cf. conditions for **21** to **22** (Fig. 2b) vs. entry 1]; **ii**] the activating carbonyl group can be a distal (carboalkoxy) rather than a tethering substituent (entries 2 and 3); **iii**] many classical methods of aryne generation are not compatible with electron-withdrawing groups in the substrate;²⁰ **iv**] carbonyl activation is not a necessity (entries 1, 4, and 7); **v**] products having nitrogen-containing heterocycles annulated to the new arene ring can be prepared (entries 3–5); **vi**] an ester tether (entry 6) cyclizes more slowly than its *N*-phenyl amide analog (entry 5), consistent with the lower concentration of the *s*-cis conformation required for ring closure; **vii**] our observations are consistent with the absence of radical character in both the cycloaddition and trapping phases of the process; e.g., reactions performed in chloroform solvent, an excellent hydrogen atom donor, have shown no evidence of hydrogen atom transfer (entries 4 and 9); **viii**] the new silyl ether trapping reaction has considerable generality (entries 1–3, 5, 6, and 8 and Fig. 2); **ix**] 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); **x**] 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 **xi**] the silyl substituents in many of the products provide handles for subsequent elaboration through protonative, oxidative, or halogenative desilylation or cross-coupling reactions²¹.

Intermolecular trapping

We were eager 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. 4) 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 ca. 4 h at ca. 85 °C) by a variety of external reagents to give adducts **25**. Highlights include: **i**] benzene as solvent forms the Diels–Alder adduct **25a** (cf. Fig. 3, entry 9); although a precedented process²², because of the low reactivity of simple aromatics, rarely have they been trapped by benzyne in high yield; **ii**] 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 Fig.

3); **iii**] the [2+2] cycloaddition of norbornene gives **25b** in higher yield than has been observed for trapping of arynes formed by conventional methods²; **iv**] *N*-phenylacetamide gives **25c**, demonstrating that a nitrogenous substituent can be conveniently installed; **v**] 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; **vi**] this mode of reaction with acetic acid or phenol is unique and complementary to that seen with benzyne generated by non-reagent-free methods^{23,24}; **vii**] 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 of Cramer and Buszek²⁵ and of Houk and Garg²⁴ 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; M06-2X/6-31+G(d, p)²⁵] 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 vs. 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. 5). This simple triyne was cycloisomerized and the resulting benzyne trapped in *tert*-butanol (120 °C, closed tube) to produce 5-*tert*-butoxyphthalide (**28**) in 68% yield. Johnson and coworkers recently reported a density functional theory (DFT) approach to compute the energetics of the hypothetical HDDA reaction of **7** with **12** to produce *o*-benzyne (**1**, Fig. 1e).²⁶ They concluded that this benzyne-forming reaction was downhill 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 ca. 50 kcal•mol⁻¹ downhill. These very favorable free energies of reaction 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 *tert*-butanol of the strained alkyne²⁷ 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 domino sequence comprises a fundamentally new, arguably revolutionary, way to synthesize benzenoid compounds—especially those having high structural complexity. Because HDDA-derived benzyne are born in the absence of byproducts and external reagents, the intrinsic reactivity of a benzyne can be more fully explored and exploited. Even at this early stage of development, myriad additional lines of

investigation have revealed themselves. These include studies of mechanistic issues (concerted vs. stepwise cycloaddition), substituent effects (electronic vs. 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 [e.g., drugs, natural products^{9,10}, heteroaromatics, polyacenes]. Lessons of how imagery [i.e., **1**(vs. **1'**) from **7** + **12**] can bias one's perception are also embedded in the developments described here. Finally, our results serve as a reminder that even in the 21st 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 the Supplementary Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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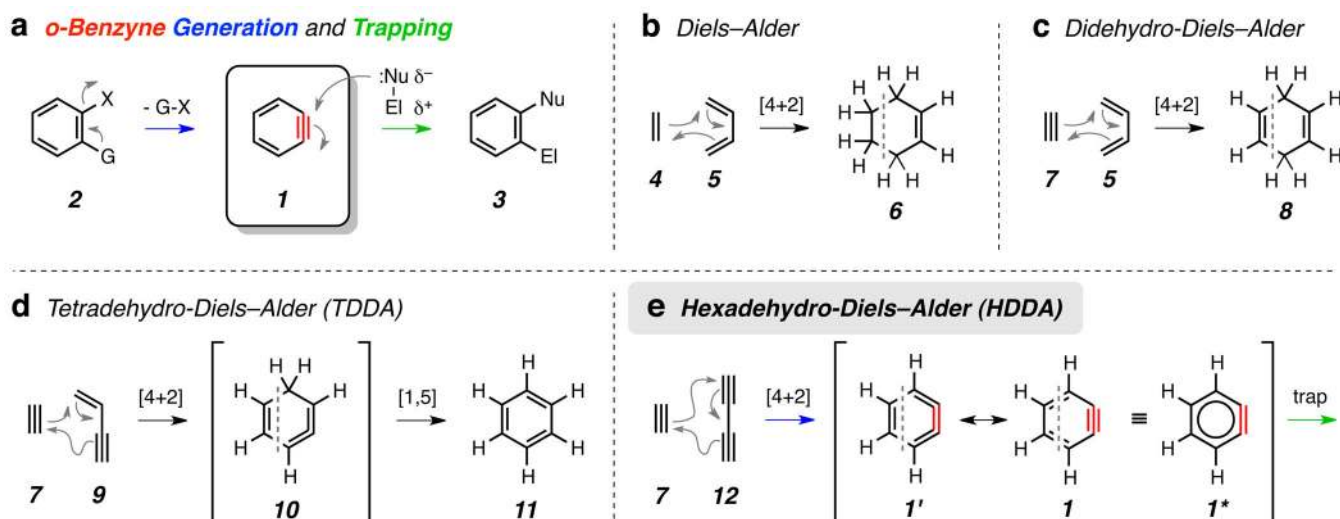


Figure 1. Diels–Alder reactions of varying oxidation states

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 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. [TMS = trimethylsilyl, OTf = trifluoromethanesulfonate, Nu = nucleophile, El = electrophile]

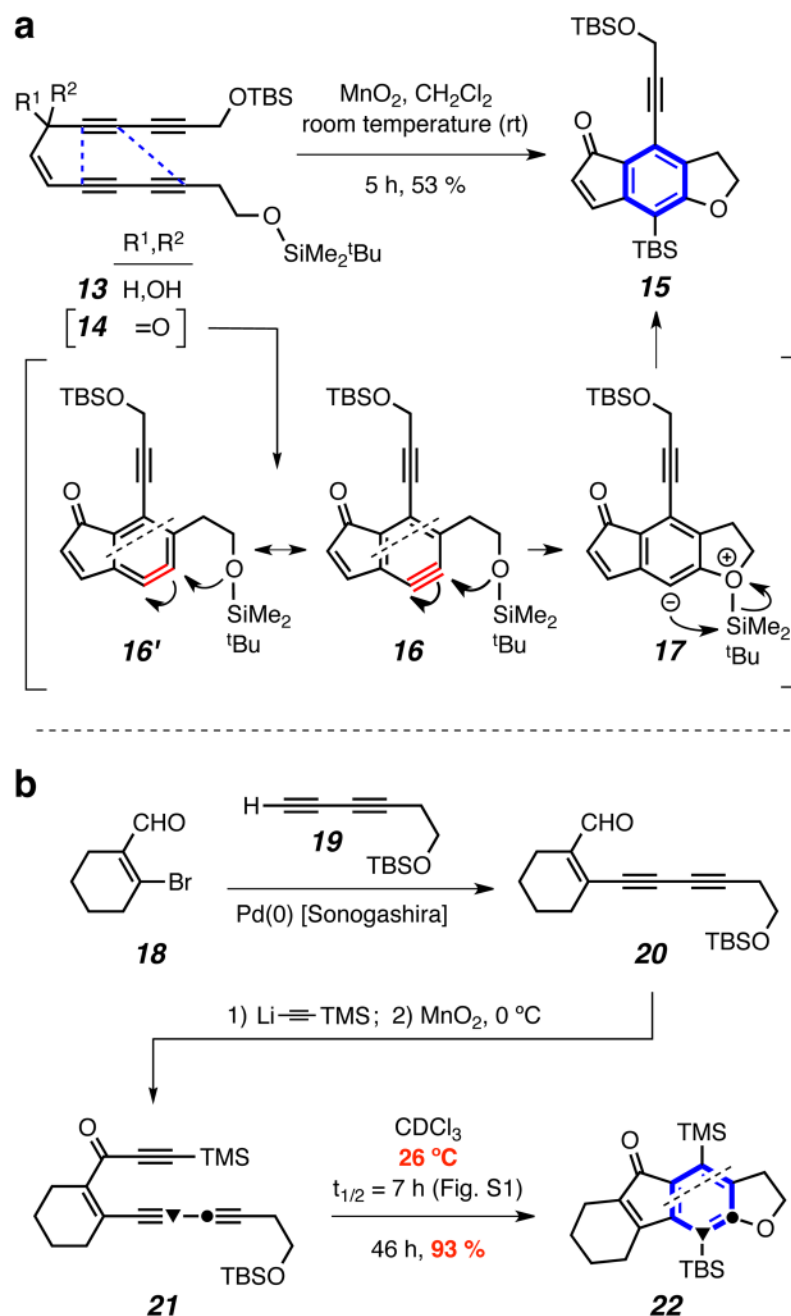


Figure 2. Mechanistic rationale, substrate synthesis, and mild conditions for our initial two HDDA reactions

a, Serendipitous observation of the HDDA reaction: cyclization of ketone **14** to putative benzyne (red) intermediate **16/16'** 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**. [TBS = *tert*-butyldimethylsilyl]

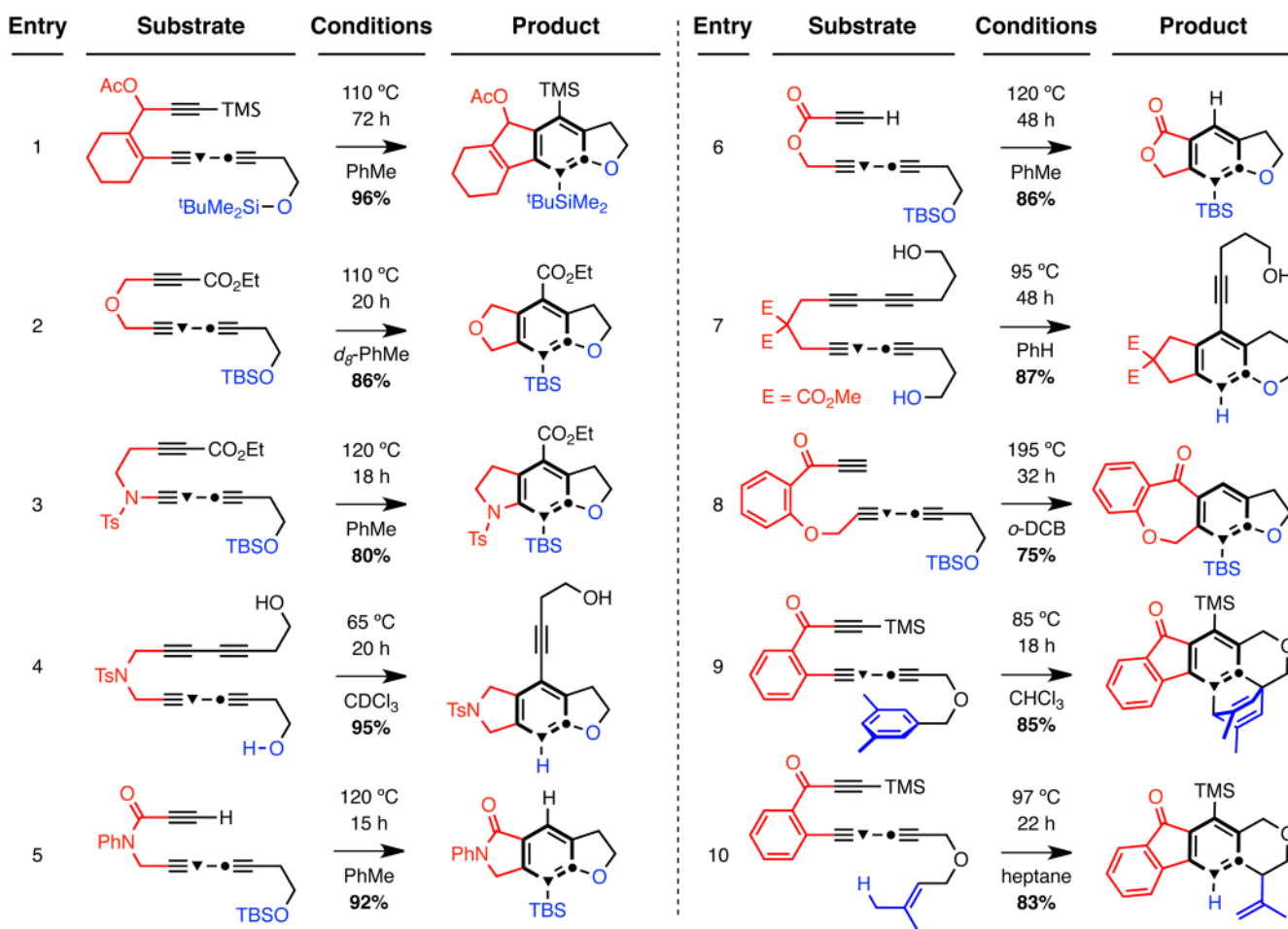


Figure 3. Examples of intramolecular trapping of HDDA-generated benzenoids
 Benzenoid (bold black bonds) synthesis via the HDDA cycloaddition has considerable substrate scope with respect to the nature of i) the poly-yne tether (red) and ii) the intramolecular trapping moiety (blue). [Ac = acetyl, Ts = *p*-toluenesulfonyl, *o*-DCB = 1,2-dichlorobenzene]

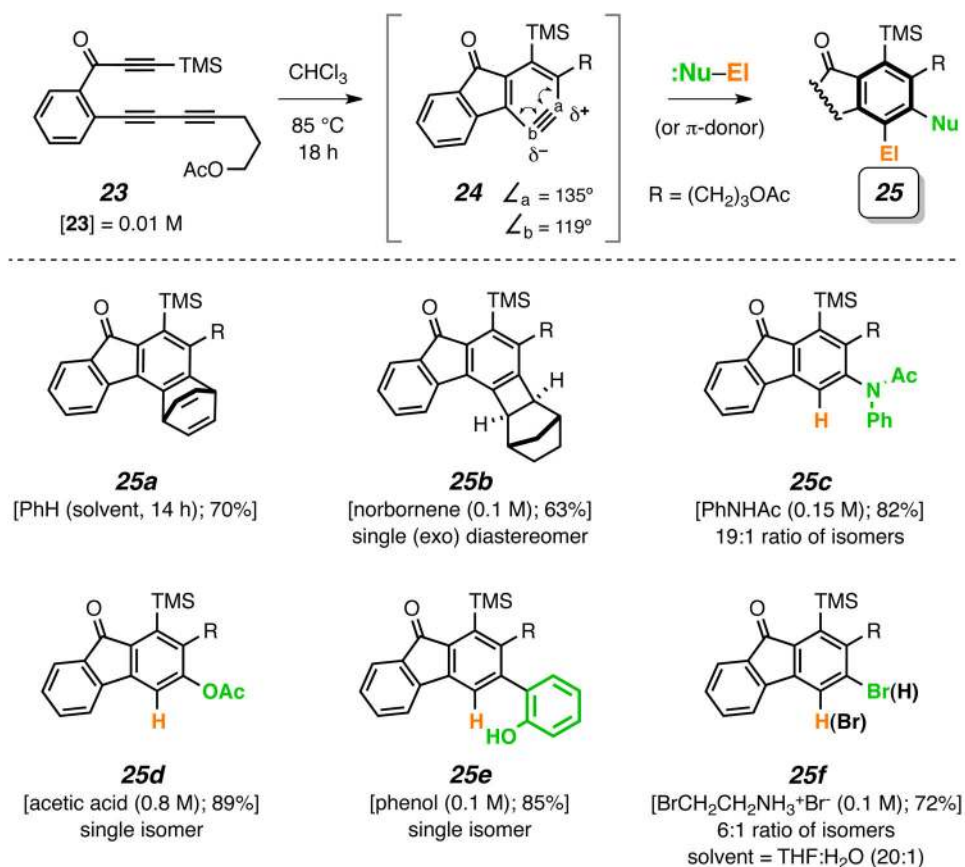


Figure 4. Examples of intermolecular trapping of HDDA-generated benzynes
 Bimolecular trapping reactions of benzyne **24** to give adducts **25a–f** [trapping agent (and amount); yield following purification]. [THF = tetrahydrofuran]

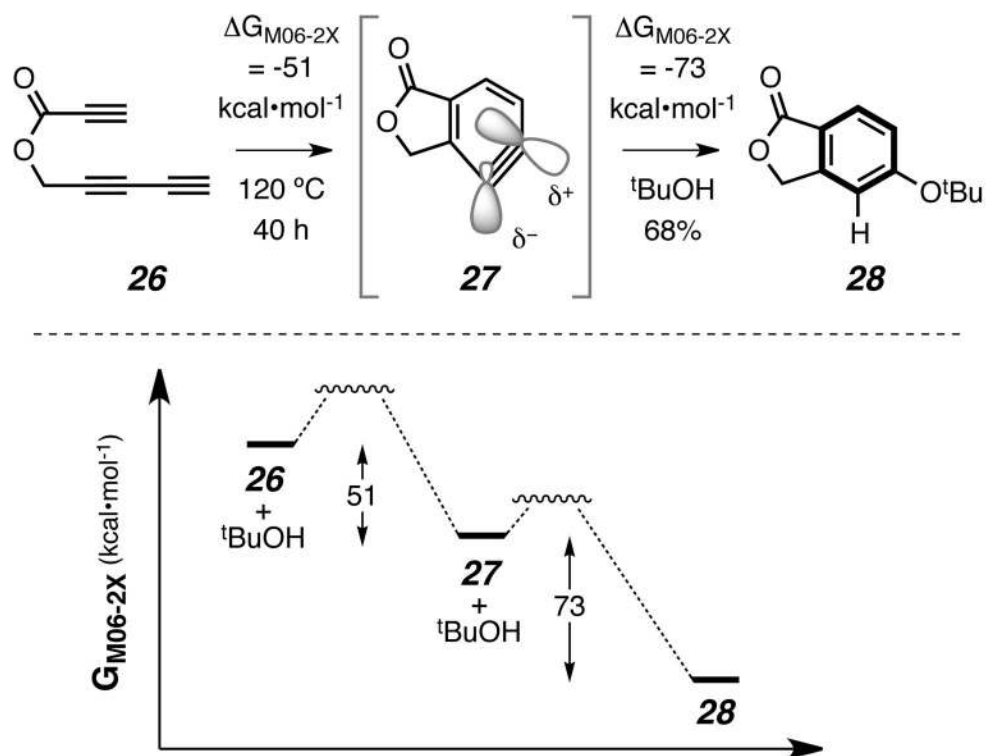


Figure 5. Computed free energy changes for a representative HDDA-initiated cascade
 Free energies of reaction [M06-2X/6-31+G(d, p)] for the aryne-generating (**26** to **27**) and *tert*-butanol ($t\text{BuOH}$) trapping (**27** to **28**) stages highlight the favorable thermodynamics associated with both the triyne cycloisomerization and aryne trapping events.