Intramolecular Capture of HDDA-derived Benzynes:
i) 6- to 12-Membered Ring Formation,
ii) Internally (*vis-à-vis* Remotely) Tethered Traps, and
iii) Role of the Rate of Trapping by the Benzynophile

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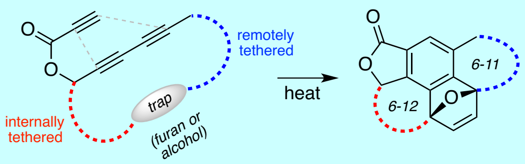
Supporting Information Placeholder

ABSTRACT: Reported here are studies that have established novel features of the hexadehydro-Diels-Alder (HDDA) reaction of substrates containing tethered trapping moieties. Products having new structural motifs can be created. i) Medium-sized fused rings can be produced by varying the length of the tether. ii) The tether can emanate from an atom within the linker unit that joins the 1,3-diyne and diynophile. iii) The importance of the rate of trapping by the benzynophile is established.



Triyne substrates containing, minimally, a conjugated 1,3-diyne and a diynophile linked by a three atom (ABC) linker (cf. subunit in the gray box in **1** and **4**) undergo thermal cycloisomerization to a reactive benzyne intermediate (cf. **2**).[1] This can be viewed as a hexadehydro-Diels-Alder (HDDA) reaction[2,3] because the triyne reactant is at a higher oxidation state—it lacks six hydrogen atoms—than the diene+dienophile subunits typical of classical Diels-Alder reactions. These benzynes can then be trapped intramolecularly (and ***in situ***) by appropriately reactive functional groups, resulting in the rapid construction of polycyclic products (cf. **3**). To date the attachment of an intramolecular trapping moiety (T–T') has always been i) of such a length that the resulting new ring is either 5- or 6-membered (cf. blue in **3**) and ii) tethered to the terminus ("remotely tethered") of the 1,3-diyne (Fig. 1a).

We now report results of studies that address the following two questions. **Q1.** Will a longer remote tether still allow for efficient trapping reactions to produce medium-sized rings [cf. blue in **5** (and **4**)]? **Q2.** Can substrates be designed in which the trapping group is tethered within the ABC linker ("internally tethered") so as to produce, for the first time, polycycles with a topologically novel motif [cf. red in **6** (and **4**)]?

For convenience in the synthesis of the HDDA substrates, we chose for this study to use triynes in which ABC was a 3-atom ester linker (**7**, Table 1), although we know of no reason why the results would not readily translate to many, if not all, of the (ca. 20)[4] linker motifs that are known to support HDDA cyclizations. As the trapping functionality (T–T'), we used either a primary alcohol[5] or a furan,[6] representative of the classes of i) nucleophilic and ii) cycloadditive aryne trapping agents, respectively.

The half-life for disappearance of ester **7e** (Table 1) was observed to be 7 hours when heated in toluene at a bath temperature of 130 °C in a sealed reaction vessel. Because trapping reactions are always fast relative to the rate of formation of HDDA benzynes (e.g., **7** to **8**), one can confidently assume that the rate of cycloisomerization for all triynes reported here will be very similar. Consequently, all reaction mixtures were heated at 130 °C for the same total reaction time (48 h, ca. 7 half-lives).

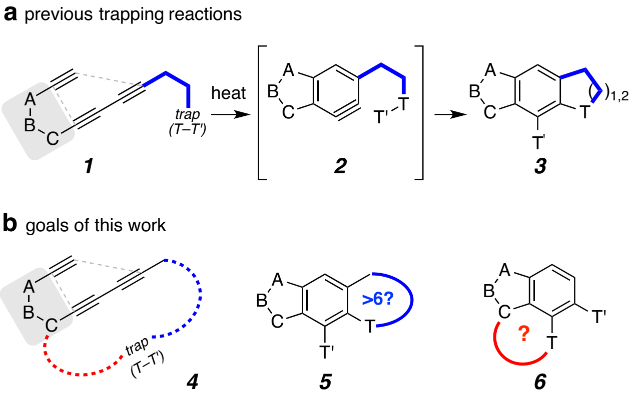
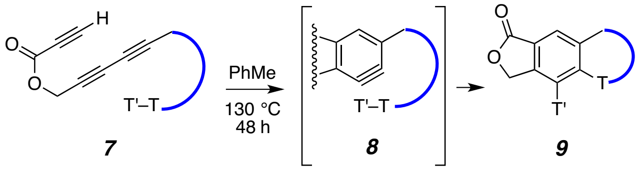
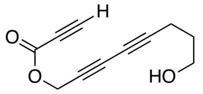
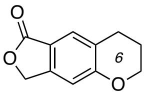
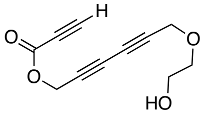
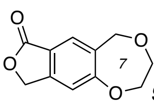
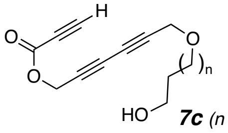
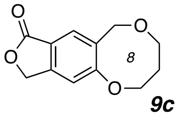
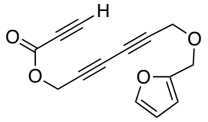
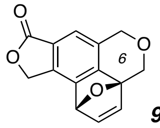
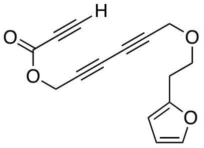
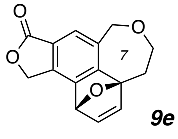
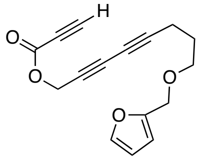
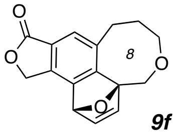
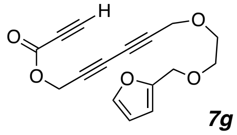
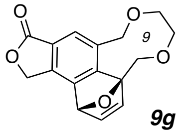
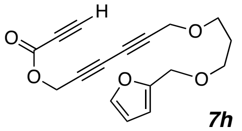
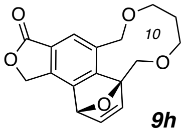
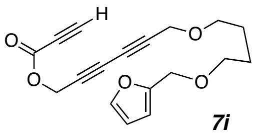
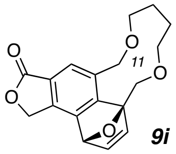


Figure 1. a. The known mode of intramolecular trapping of HDDA-generated benzynes. **b.** This work addresses two principal questions: **Q1.** can ring sizes >6 be produced (blue) and **Q2.** is the motif having the trap tethered within the ABC linker (red) an effective substrate?

Q1. Substrates bearing the trapping functionality tethered to the remote terminus of the 1,3-diyne are shown in Table 1. The benzynophile is a hydroxyl group in alcohols **7a-c** and a furan in **7d-i**. Unsurprisingly,[2] alcohol **7a** efficiently gave the pyran derivative **9a** (entry 1). The analogs **7b** and **7c** have their hydroxyl group

Table 1. Reactions of triynes 7, having varying tether lengths (blue) to the trapping functionality (hydroxyl or furanyl), give phthalide derivatives 9 with a variety of ring sizes (blue)



entry	ester triyne substrate	product (isolated yield)^a
1	 **7a**	 **9a** (95%)
2	 **7b**	 **9b** (80%)
3	 **7c** (n = 1)	 **9c** (20%)
4	 **7d**	 **9d** (88%)
5	 **7e**	 **9e** (70%)
6	 **7f**	 **9f** (81%)
7	 **7g**	 **9g** (42%)
8	 **7h**	 **9h** (47%)
9	 **7i**	 **9i** (41%)

^{a} % yield is of chromatographically purified material.

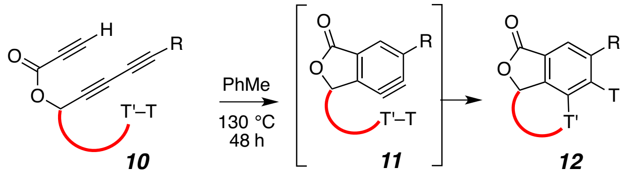
located one and two atoms more distant from the benzyne, respectively. The first (entry 2) gave **9b**, containing a fused 7-membered ring, in very good yield. However, **7c** (entry 3) produced the 8-membered homolog in only 20% (isolated) yield. The ^{1}H NMR spectrum of the crude product mixture clearly showed that this reaction gave rise to a more complicated array of products; the reaction solution was also darker in color—a qualitative indicator that we associate with oligomerization events in which the benzyne engages additional copies of the starting triyne substrate in unproductive manners when a trapping reaction is not sufficiently rapid. We examined the next higher homolog (i.e., **7c** where n = 2), which would have produced a product having a newly fused 9-membered cyclic ether, but there was no clear evidence of formation of that product (^{1}H NMR). An aliphatic aldehyde resonance suggested that one competing event was dihydrogen transfer[7] from the primary alcohol.[5]

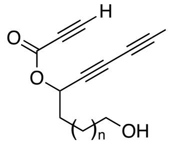
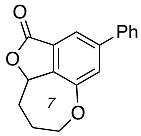
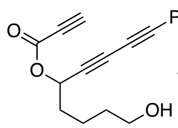
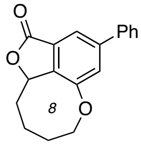
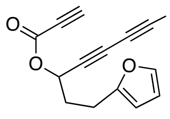
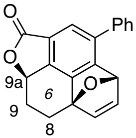
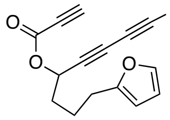
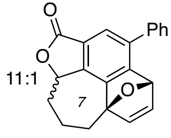
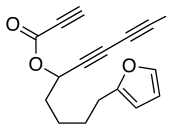
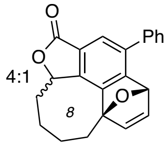
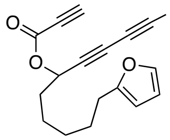
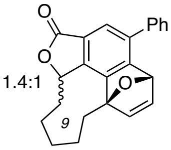
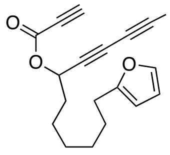
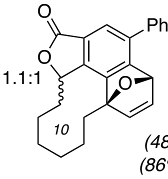
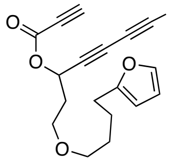
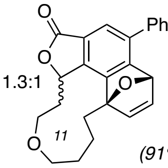
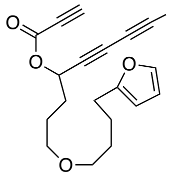
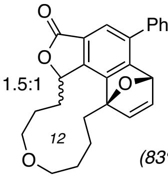
We then turned to a series of furan-containing substrates (entries 4–9). Again a newly fused six-membered ring could be formed with high efficiency; **7d** cyclized to **9d** as the only observed product. The homologs **7e** and **7f** behaved similarly well, as judged by the yields of formation of **9e** and **9f**, respectively, as well as analysis of the GC-MS and NMR spectra of the crude product mixture. We extended the tether length to 6, 7, and 8 atoms, respectively, in **7g**–**7i**. The reaction solutions (in toluene) of each of these substrates showed that a portion of the product mixture after full conversion of the triyne was insoluble. Solvent removal and trituration with methylene chloride retrieved the soluble portion of crude mass, from which each of products **9g**–**9i** was isolated. This suggests that competition between ***intra***molecular vs. ***inter***molecular furan trapping of each copy of the benzyne committed that intermediate either to **9** or to oligomeric counterparts, respectively.

We have observed that external trapping of benzynes by furans (via 4+2 cycloaddition) is significantly faster than trapping by alcohols (via nucleophilic addition). This is consistent with the collective results shown in Table 1. The internal furan trap allows the formation of larger rings to proceed, whereas capture of the reactive benzyne by the alcohol hydroxyl group is not fast enough to as effectively outcompete other side reactions.

Q2. All previous examples of HDDA reactions having internally bound trapping groups have had that functionality attached via the remote terminus of the 1,3-diyne subunit. The examples in Table 2 are the first instances in which the point of attachment of the tethered benzynophile has been ***within*** the linker connecting the diyne and diynophile subunits (red arc in **10**). Alcohol **10a** (entry 1) was the first substrate in which we observed efficient cycloisomerization, here to the tricycle **12a** (via **11**). The one carbon shorter and longer homologs (**10a**, n = 0 and **10b**, respectively), which would have produced a pyran analog of **12a** or the oxocane **12b**, gave rise, instead, only to an array of toluene-trapped, Diels-Alder (DA) adducts of the benzyne[8] (evidence for five of the six possible isomers by ^{1}H NMR, GC-MS, and HRMS analyses). This implies that the benzyne intermediate in those instances has a sufficiently long lifetime to allow the bimolecular trapping by toluene (a relatively slow process) to intervene. That is, alcohol trapping to form the strained 6-membered or medium-sized cyclic ethers was not fast enough to outcompete the toluene 4+2 cycloaddition. However, using the even less benzynophilic ***o***-dichlorobenzene[8] as the reaction solvent, we observed competitive formation of the benzoxocene **12b** (entry 2) along with (three) DA adducts of *o*DCB (GCMS). Again, effectively increasing the lifetime of the benzyne intermediate by use of the less reactive

Table 2. Triynes 10 of varying tether lengths (red), all attached *within* the three atom ester linker, give phthalide derivatives 12



entry	ester triyne substrate[a]	product (isolated yield)[b]
1	 **10a** (n = 1)	 **12a** (70 %)
2[c]	 **10b**	 **12b** (30 %)
3	 **10c**	 **12c** (77%)
4	 **10d**	 **12d** (95%)
5	 **10e**	 **12e** (97%)
6	 **10f**	 **12f** (78%)
7	 **10g**	 **12g** (48%, 0.1 M) (86%, 0.01 M)
8	 **10h**	 **12h** (91%, 0.01 M)
9	 **10i**	 **12i** (83%, 0.01 M)

[a] Entries 1-6 were done using an initial triyne concentration of 0.1 M.

[b] % yield is of chromatographically purified material.

[c] Reaction performed at 130 °C in *o*-dichlorobenzene.

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solvent allowed an otherwise slow trapping reaction—the formation of **12b**—to be revealed.

Having defined some of the limits of effective intramolecular capture by a primary alcohol, we turned attention to the series of substrates **10c-10i**, each containing a tethered furan trap—the inherently more reactive benzynophile. The successful formation of intramolecularly trapped products from each of these substrates demonstrates the ability to form a wide variety of both 'normal' as well as medium-sized fused rings for situations where the benzyne trapping reaction is sufficiently fast.

In all of the adducts **12c-12i** (entries 3–9), a pair of diastereomeric products can arise, differing in the relative configuration of the newly created stereocenters in the oxabenzonorbornene subunit with respect to the preexisting one in the chiral substrate. In the case of **10c** we observed only one adduct, **12c**. In all other instances, a pair of chromatographically separable diastereomers was formed with the diastereomeric ratios indicated beside the lactone stereocenter in structures **12d**–**12i**. As the size of the ring increased, there was a general trend toward a reduced level of diastereoselectivity.

It proved non-trivial to assign the structure to any one of these diastereomers. For the case of **12c**, we used DFT [SMD/M06-2X/6-31+G(d,p) in toluene] to compute the free energy of both **10c** and its C9a-epimer (structure not show). Diastereomer **12c** was considerably (8.7 kcal•mol^{-1}) more stable. Presuming that this very large difference in product stability is reflected even somewhat in the two diastereomeric transition states, albeit early ones given the high exergonicity for the Diels-Alder trapping of the benzyne by the furan,[9] we tentatively assigned **12c** as the structure of this product. Although we could decipher all proton-proton spin-spin couplings among the five protons attached to C8, C9, and C9a, those values did not allow for a clear distinction between the two possible diastereomeric lactones. Likewise, no definitive NOE interactions were observed. We turned to an X-ray diffraction analysis to definitively determine that the structure[10] of **12c** was as shown in entry 3.

Experiments using triynes **10c**–**10g** were performed at a starting substrate concentration of 0.1 M. In the case of **10g** (entry 7), the yield of product **12g** fell, relative to the analogs with a shorter tether, to 48% under these conditions. As described above for some of the less reactive alcohol-containing substrates, we again hypothesized that intermolecular trapping of the benzyne by a second furan-containing molecule and ensuing oligomerization was responsible for this reduced efficiency. Indeed, by performing the experiment with a [**10g**]$_0$ = 0.01 M (also used for the yet longer homologs **10h** and **10i**) a high yield of **12g** was restored.

In conclusion, we have demonstrated that i) medium-sized rings can be produced in concert with intramolecular trapping reactions of HDDA-generated benzynes; ii) the trap can be tethered to an atom within the linker moiety connecting the 1,3-diyne and its diynophile in the substrate for the HDDA cycloisomerization; and iii) less efficient trapping reactions, by virtue of (a) inherently lower reactivity of the trapping functionality (e.g., alcohol vs. furan trap), (b) the usual challenges posed by larger, medium-sized ring formation, and/or (c) competing bimolecular trapping by a second substrate molecule can be at least partially rescued by use of a less reactive solvent and/or a lower concentration of triyne substrate.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.

Experimental details for the preparation of new compounds; spectroscopic data for their characterization, including copies of ^{1}H and ^{13}C NMR spectra, of new compounds.

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Notes

The authors have no competing financial interests to declare.

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[1] (a) Bradley, A. Z.; Johnson, R. P. *J. Am. Chem. Soc.* **1997**, *119*, 9917–9918. (b) Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **1997**, *38*, 3943–3946. (c) Tsui, J. A.; Sterenberg, B. T. *Organometallics* **2009**, *28*, 4906–4908. (d) Yun, S. Y.; Wang, K.-P.; Lee, N.-K.; Mamidipalli, P.; Lee, D. *J. Am. Chem. Soc.* **2013**, *135*, 4668–4671.

[2] Hoye, T. R.; Baire, B.; Niu, D. W.; Willoughby, P. H.; Woods, B. P. *Nature* **2012**, *490*, 208–212.

[3] For reviews of dehydro-Diels-Alder reactions, see: (a) Wessig, P.; Müller, G. *Chem. Rev.* **2008**, *108*, 2051–2063. (b) Li, W.; Zhou, L.; Zhang, J. *Chem. Eur. J.* **2016**, *22*, 1558–1571.

[4] For a review of the hexadehydro-Diels-Alder reaction, see: Diamond, O. J.; Marder, T. B. *Org. Chem. Front.* **2017**, *4*, 891–910.

[5] Willoughby, P. H.; Niu, D.; Wang, T.; Haj, M. K.; Cramer, C. J.; Hoye, T. R. *J. Am. Chem. Soc.* **2014**, *136*, 13657–13665.

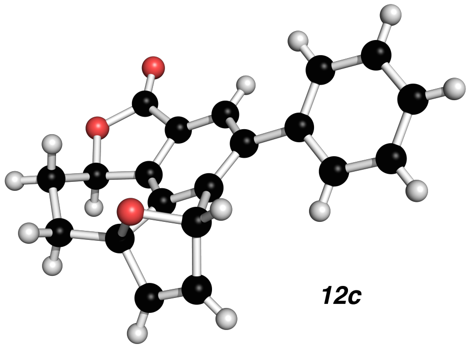
[6] Wittig, G.; Pohmer, L. *Angew. Chem.* **1955**, *67*, 348–348.

[7] Niu, D.; Willoughby, P. H.; Baire, B.; Woods, B. P.; Hoye, T. R. *Nature* **2013**, *501*, 531–534.

[8] (a) Aromatic solvents are not inert bystanders toward benzynes. In the absence of a sufficiently fast trapping event, they will add in 4+2 cycloaddition fashion to the benzyne. This type of reactivity is higher for more electron rich arenes: Tabushi, I.; Yamada, H.; Yoshida, Z.; Oda, R. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 285–290. (b) A reviewer asked whether an even more inert, non-aromatic solvent might lead to further improvement. Accordingly, we heated **10b** in $Cl_2CHCHCl_2$ (TCE), a solvent we have not previously used for HDDA cyclizations, and monitored reaction progress by ^{1}H NMR analysis of aliquots. Qualitatively, the transformation to **12b** was cleaner than the 42% isolated yield observed in *o*-DCB would suggest; we plan to explore the utility of TCE in future experiments.

[9] Although we could locate a transition structure (TS) by DFT calculations for the intramolecular DA reaction leading from the benzyne to **12c**, repeated attempts to identify the diastereomeric TS were unsuccessful.

[10] PyMol rendering of **12c** from the coordinates resulting from its x-ray diffraction analysis:



12c