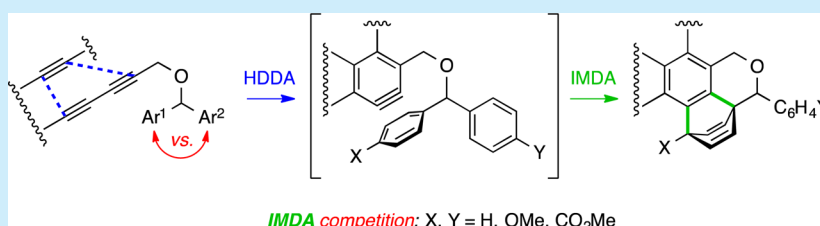


Intramolecular [4 + 2] Trapping of a Hexadehydro-Diels–Alder (HDDA) Benzyne by Tethered Arenes

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S Supporting Information



ABSTRACT: We report here the efficient, intramolecular trapping in a Diels–Alder (DA) sense of thermally generated benzyne by one of two pendant arene rings. A more electron-rich ring (*p*-methoxyphenyl) reacted substantially faster than a simple phenyl ring, which was, in turn, slightly more reactive vs a 4-carbomethoxyphenyl ring. Photoinduced di- π -methane rearrangement of the initial DA adducts gave rise to unusual isomeric polycyclic adducts.

Benzene (and its substituted derivatives) are generally unwilling partners in typical Diels–Alder (DA) [4 + 2] cycloaddition reactions. In fact, a solvent such as benzene, toluene, xylene, or 1,2-dichlorobenzene is often used as an effectively inert solvent medium for DA reactions between other pairs of diene/dienophile reactants. The energetic penalty of dearomatization of the benzenoid ring is typically too costly to permit it to participate in cycloaddition. *o*-Benzyne (**1**) and its substituted derivatives comprise one of the very few classes of dienophiles with sufficient reactivity to engage a benzenoid as a diene. The first example of the reaction of 1,2-dehydrobenzene (**1**) with benzene produced benzobarrelene (**3a** or **3b** with X = H) in $\leq 12\%$ yield (along with biphenyl and benzocyclooctatetraene).¹ This accentuates the inherent difficulty in DA reactions of arenes, even when a highly energetic benzyne is conscripted as the dienophile.

In 1977 Yoshida, Oda, and co-workers reported² the relative reactivity of **1** with several monosubstituted benzenoid derivatives (i.e., **2**) through sets of bimolecular competition experiments (Scheme 1). The reactivity pattern was that more electron-rich arenes reacted faster; however, the range of relative rates varied only from ca. 15 for the fastest (anisole) to 1 for the slowest (trifluoromethylbenzene). Anisole was also the only trapping agent that showed a propensity to favor addition across the C1/C4 positions of the arene ring (to give **3a**); the other derivatives favored formation of the C2/C5 adduct **3b**. In all of these experiments the aromatic trapping agents were used as the solvent; the sole isolated yield reported (for the anisole case) were 32% and 8% for **3a** (X = OMe) and **3b** (X = Me), respectively.

The cycloisomerization of triynes such as **4** (and **7**) to give benzyne such as **5** (and **8**) by a simple thermal process³ has considerable generality (Scheme 2).⁴ We have termed this cyclization a hexadehydro-Diels–Alder (HDDA) reaction. The

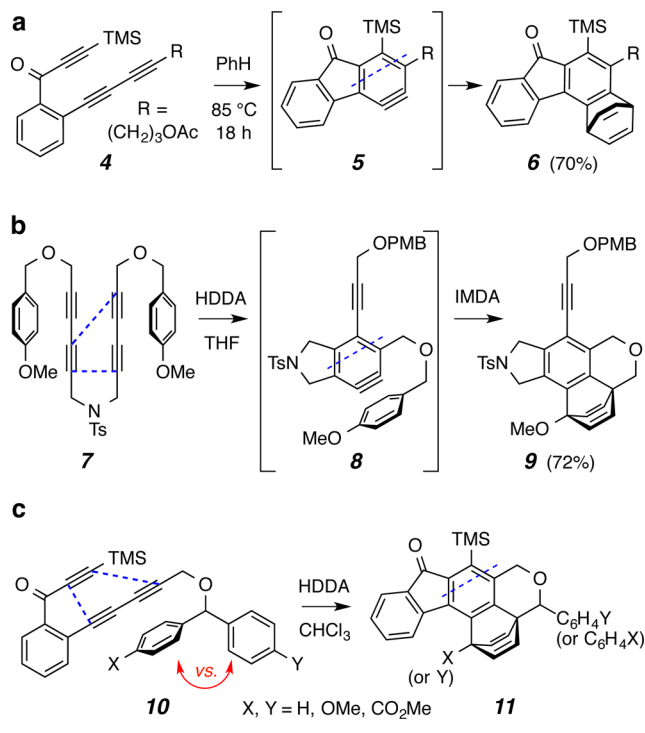
Scheme 1. Reported Bimolecular Diels–Alder Reactions between *o*-Benzyne (**1**) as the Dienophile and Various Monosubstituted Benzene Derivatives **2** as the Diene Partner To Give [4 + 2] Adducts **3a–b**

X	k_{rel} (vs. PhH)	3a	3b
Yoshida et al. (ref 2)			
OMe	7.93	83	17
Me	4.25	29	71
H	1.00	n.a.	n.a.
CO ₂ Me	0.99	~0	~100
Cl	0.79	18	82
CF ₃	0.58	~0	~100

reactive benzyne intermediates can be trapped in many useful ways, including by reaction in a [4 + 2] Diels–Alder sense with an aromatic benzenoid ring in either a bimolecular (e.g., **5** to **6**)⁴ or unimolecular (e.g., **8** to **9**)^{4,5} fashion. To understand in more detail the influence on reactivity of substituents on the aromatic ring acting in the role of the diene, we designed a substrate that would pit two aromatic rings in competition for the benzyne dienophile. Specifically, we have prepared and studied the reactivity of a number of substrates of general structure **10**, having two aryl groups that bear substituents of differing electronic character, yet otherwise were equally well-poised to engage in intramolecular [4 + 2] trapping of the HDDA-

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Scheme 2. Examples of HDDA-Generated Benzyne Reacting with Arenes Either (a) Bimolecularly or (b) Unimolecularly and (c) the Substrates Designed for the Intramolecular Competition Reactions Reported Here

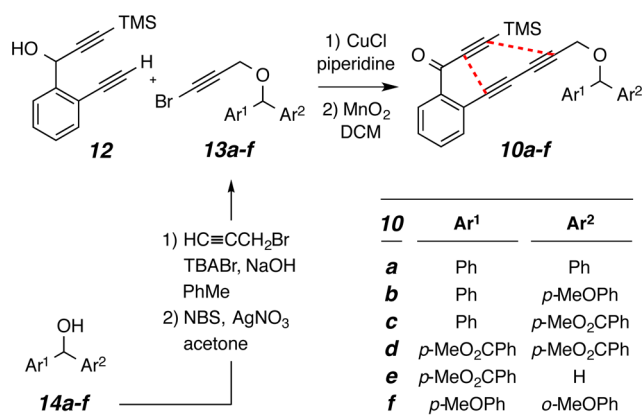


generated benzyne. The ratio of the constitutionally isomeric products **11** (where $X \neq Y$) formed upon heating **10** in an inert solvent would then provide a direct indication of the impact of substituents X vs Y on the rate of the intramolecular Diels–Alder (IMDA) trapping reaction.

The substrates examined in this study were triynes **10a–f**. Their preparation by cross-coupling of the diyne **12**⁶ and bromoalkynes **13** (derived from the known benzhydryl derivatives **14**) is outlined in Scheme 3 [see the Supporting Information (SI) for details].

The rate-limiting step in the conversion of **10** to **11** (Scheme 2c) is the initial HDDA cycloisomerization reaction; the subsequent Diels–Alder trapping event by the pendant arene is relatively rapid. We have reported that the half-life for the

Scheme 3. General Route Used for the Synthesis of HDDA Triyne Substrates **10**



HDDA reaction of a triynone similar to that of **10** is ca. 4 h at 85 °C.⁴ Accordingly, we heated each of **10a–f** in an 80–85 °C bath in a sealed vial containing a solution of the triyne for ca. 48 h in CDCl₃. This solvent has proven repeatedly to be inert toward HDDA-generated benzyne, underscoring the fact that these benzyne should not be considered to engage in reaction processes that are radical in character. Analysis of the ¹H NMR spectra of the reaction mixture itself was used to judge the product ratios in the cases where competitive reaction pathways were detected.

The diphenyl-containing triyne **10a** gave the trapped adduct **11a** (Figure 1) in 70% yield following chromatographic

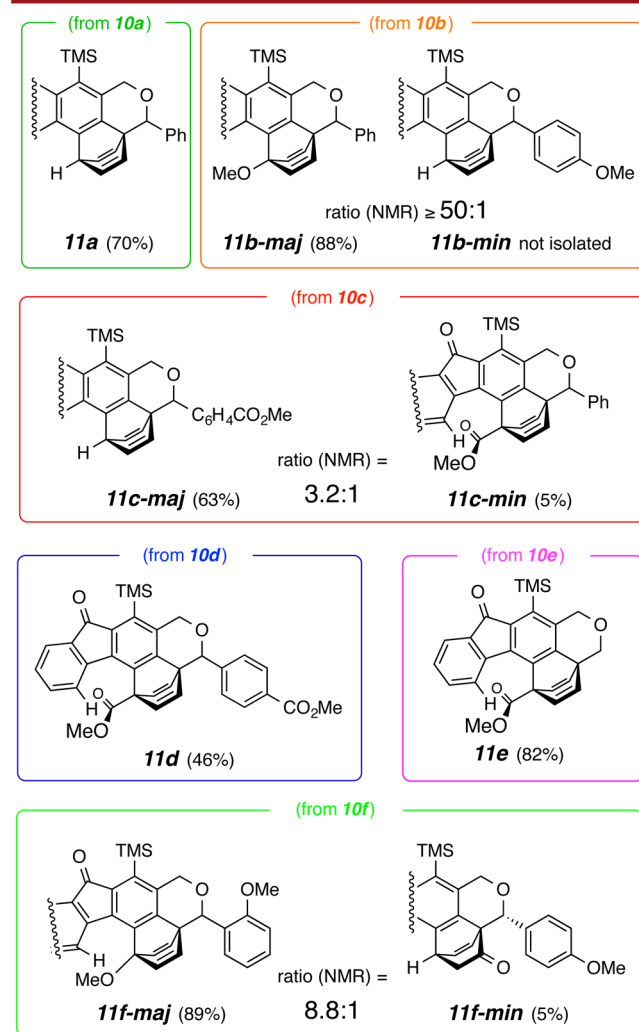


Figure 1. Products from competitive IMDA trapping within benzyne intermediates **15**, derived from **10a–f**.

purification.⁷ Hence, a simple phenyl ring is an efficient and competent trap for the benzyne intermediate (cf. **5**, $R = \text{CH}_2\text{OCHAr}^1\text{Ar}^2$). The first substrate we studied with two different pendant arenes was the mono-*p*-methoxy benzhydryl ether **10b**. It produced a single isolable IMDA adduct, namely, **11b-maj** in 88% yield. We did not definitively detect the isomeric, phenyl-trapped adduct **11b-min** (¹H NMR). Thus, the more electron-rich arene is considerably more reactive (cf. $k_{\text{anisole}}/k_{\text{benzene}} = 8$, Scheme 1).

We then studied the monocarbomethoxy monophenyl ether **10c**. In this substrate an electron-poor arene is pitted against the

parent phenyl ring. The major product in this case was the phenyl-trapped adduct **11c-maj**, isolated in 64% yield. The minor component **11c-min** was also isolated following careful separation by HPLC (product ratio = 3.2:1 by ^1H NMR analysis of the reaction mixture). An interesting behavior was observed for **11c-min** (as well as for the analogous **11d** and **11e**, which also contain a bridgehead carbomethoxy group). Several resonances in both the ^1H and ^{13}C NMR spectra were broadened when recorded at ambient temperature. We attributed this to slow rotation about the bridgehead to carbonyl carbons in these hindered esters. These resonances sharpened considerably when the ^1H spectrum was recorded at 100 °C (see SI), consistent with this hindered rotation hypothesis. Similarly, when the bis-ester-containing substrate **10d** (or the monoester **10e**) was heated (in the dark, see below), only the primary Diels–Alder adduct **11d** (or **11e**) was observed.

We also examined, in one instance, the effect of the substitution pattern. Substrate **10f** contains both a *para*- and an *ortho*-methoxyphenyl substituent. When heated in 1,2-dichloroethane at 85 °C for 2 days, **10f** produced both **11f-maj** and the ketone **11f-min**⁸ (8.8:1 ratio from ^1H NMR analysis) in 89% and 5% isolated yield (MPLC separation). Oda et al. reported facile *in situ* hydrolysis of a primary enol ether product arising from anisole trapping to its ketone, the process we also presume that gives rise to **11f-min**. They also observed a similar preference for formation of the bridgehead rather than the alkenyl methoxylated isomer (cf. Scheme 1).

We examined whether DFT calculations are effective at rationalizing the observed selectivities. Specifically, we have computed the transition state (TS) structures for the competing IMDA trapping reactions of the benzyne derived from **10b**, **10c**, and **10f**. These lead via **TS15** (Figure 2a) to the major and minor products of **11b**, **11c**, and **11f**. Also given in Figure 2a are the differences in computed free energy of activation ($\Delta\Delta G^\ddagger$) along with the associated computed and experimentally observed product ratios. DFT does a good job of accounting for the relative energies of the competing TS structures for the trapping of the benzyne. The geometries of those TSs all indicated a high degree of asynchronicity in these concerted IMDA reactions (Figure 2b).

We were also successful in using DFT to account for the sense of diastereoselectivity (i.e., *anti*) observed in the formation of **11f-min**⁸ (cf. Figure 1). The TS **TS15f-min-anti** was favored by 1.8 kcal·mol^{−1} over the alternative **TS15f-min-syn** (Figure 2b), presumably reflecting the greater steric congestion in the latter, which possesses *cis*-(and *endo*)oriented methoxy and aryl groups.

We observed that some of the IMDA products containing bridgehead substituents on their benzobicyclo[2.2.2]octatriene units underwent facile photoinduced rearrangement reactions (Figure 3). Either ambient laboratory light or exposure of a chloroform solution to a 75 W incandescent light source was sufficient to induce these changes in these typically yellow fluorenone compounds. Specifically, the primary HDDA-IMDA products **11c-min**, **11d**, and **11e** gave rise via di- π -methane rearrangement⁹ to the cyclopropane-containing products **16c**, **16d**, and **16e**, respectively. Irradiation of **11f** in CDCl_3 produced a structure whose ^1H NMR spectrum was consistent with the cyclopropane **16f**, which, upon chromatographic purification on silica gel, cleanly gave rise to the ketone **17f**. The structure assignments for **16c** and **17f** were confirmed by single crystal X-ray analysis. The hydrogen locations in the renderings in Figure 3 are idealized, and some have been omitted for clarity.

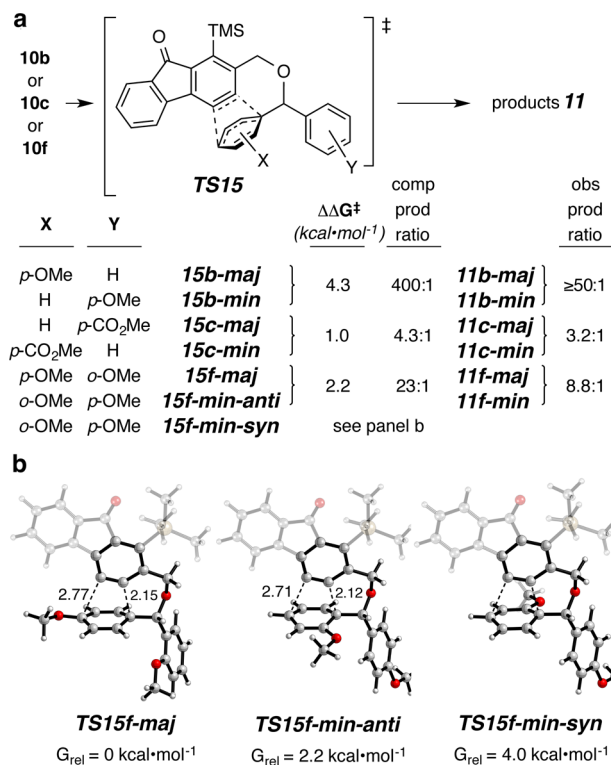


Figure 2. (a) DFT calculation [M06-2X/6-31G(d) with SMD (chloroform)] of the relative TS energies for the competitive IMDA reactions proceeding via **TS15** to **11-maj** vs **11-min**. (b) DFT geometries and relative energies for the TSs accounting for the preferential formation of **11f-maj** as well as the observed *anti* relative configuration in **11f-min** from **10f**.

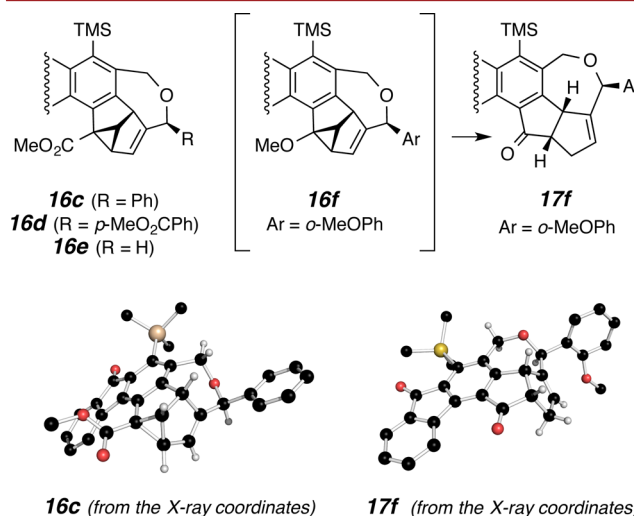


Figure 3. Di- π -methane rearrangement products from light-induced transformations of the primary HDDA-IMDA products **11c-min**, **11d**, **11e**, and **11f-maj**.

Interestingly, products of trapping by a parent phenyl ring, i.e. **11a** and **11c-maj**, did not show evidence of the di- π -methane rearrangement, likely reflecting the greater steric strain in those dibenzobarrelenes having a non-hydrogen bridgehead substituent.

Finally, a pendant naphthalene substituent was shown to efficiently capture the HDDA benzyne. Triyne **18** gave the Diels–Alder adduct **19** in high yield following chromatographic

purification (Figure 4). The *in situ* ^1H NMR spectrum of this reaction mixture is indicative of the cleanliness of this transformation.

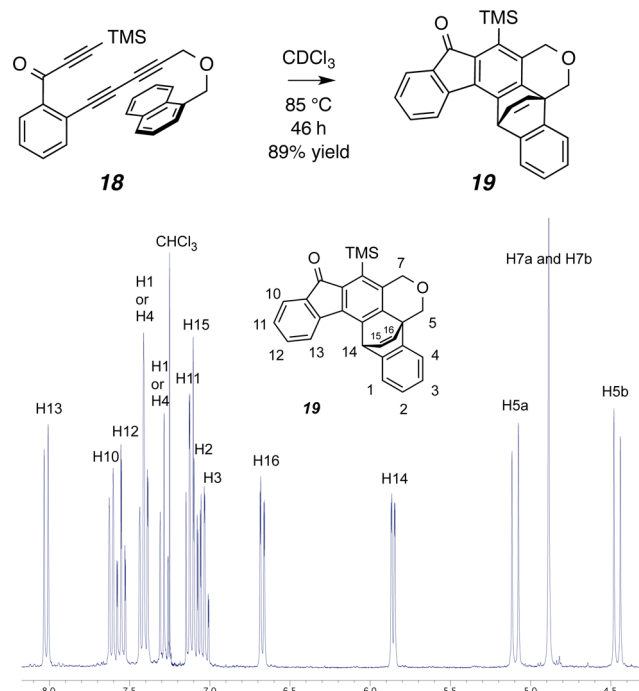


Figure 4. ^1H NMR spectrum of the product mixture produced directly upon heating **18** in CDCl_3 at 85°C .

In conclusion, we have studied intramolecular Diels–Alder reactions between various pendent aromatic groups to trap thermally generated benzyne. The arene functions as the 4π dienic component, and the HDDA benzyne, as the 2π dienophile. More electron-rich arenes are more reactive dienes, consistent with the view of the benzyne as an electrophilic partner. DFT calculations were effective in accounting for the observed product ratios for three substrates containing two different and competing arenes. The transition state structures for these reactions show a substantial degree of asynchronicity (Figure 2b). Adducts containing a bridgehead carbomethoxy substituent show hindered rotation about the ester carbonyl to the barrelene bridgehead C–C bond. Some of the initial Diels–Alder adducts—yellow, dibenzobarrelene, fluorenone-containing derivatives—underwent smooth di- π -methane rearrangement when exposed to ambient light. Finally, a pendant naphthalene substituent is a particularly effective diene. Collectively these results provide guidance about what types of substituents can be selected to enhance bimolecular Diels–Alder trapping of arynes by structurally more complex arenes, a topic that is under further study here.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, copies of ^1H and ^{13}C NMR spectra for all isolated compounds, ORTEP renderings, and DFT computational methods. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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