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BF₃-Promoted, Carbene-like, C–H Insertion Reactions of Benzyne

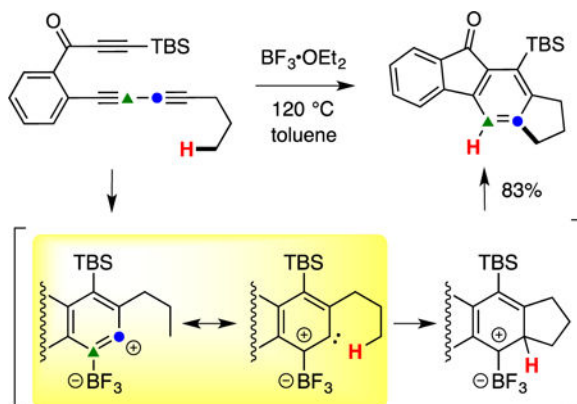
Hang Shen, Xiao Xiao, Moriana K. Hajj[†], Patrick H. Willoughby[†], and Thomas R. Hoye^{*}

Department of Chemistry, University of Minnesota, 207 Pleasant Street, SE Minneapolis, Minnesota 55455, United States.

Abstract

Boron trifluoride is observed to promote a variety of C–H insertion reactions of benzyne bearing pendant alkyl groups. Computations and various mechanistic studies indicate that BF₃ engages the strained π -bond to confer carbene-like character on the adjacent, non-coordinated benzyne carbon. This represents an unprecedented catalytic role for a non-transition metal like BF₃.

Graphical Abstract



Alkynes can, formally, be viewed as vicinal dicarbene. The importance of this resonance contributor increases for strained (e.g., cyclic) alkynes.¹ For example, dicarbene-like reactivity has been observed in the formation of spirocyclic, cyclopropane-containing carbene intermediates during the reaction of, e.g., ethylene with the alkyne in, e.g., norbornyne.^{1a,b} Various transition metal catalysts or promoters can induce alkynes to show reactivities that are an expression of 1,2-dicarbene character, including C–H insertion

^{*}Corresponding Author hoye@umn.edu.

^{†a}MKH: Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA 02138, United States

^{†b}PHW: Chemistry Department, Ripon College, 300 W Seward St., Ripon, WI 54971, United States

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures for all reactions; spectroscopic characterization data for all new compounds; details of computational methods; copies of ¹H and ¹³C NMR spectra.

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behavior.^{1c,d} In a few instances, 1,2-dicarbenoids involving two metals at each of the original alkyne carbons have even been observed.²

ortho-Benzynes, useful and versatile building blocks in organic chemistry,³ owe their high reactivity to their highly strained formal triple bond. Lee and coworkers have described C–H insertion reactions of benzyne derivatives promoted by Ag(I) that were rationalized by the intermediacy of silver carbenoid species (Figure 1a).⁴ We describe here an unprecedented boron trifluoride-catalyzed process in which carbene-like reactivity is exhibited by one of the two sp-hybridized benzyne carbon atoms. We are unaware of any example of a non-transition metal eliciting this kind of behavior. In Figure 1b we show the results of DFT calculations that foreshadow the experimental results we present below. The computed potential energy surface (PES) for the prototypical reaction between *o*-benzyne (**1**) and methane, catalyzed by BF₃, suggests the energetic accessibility of requisite intermediates and activation barriers. Specifically, the conversion of **1** + BF₃ to **2** is computed to be a nearly equienergetic event. Adduct **2** has a highly distorted geometry—the internal bond angles at C α and C β are 103° and 148°, respectively. The electronic configuration for this adduct was closed shell (stable to spin-symmetry breaking). The HOMO of **2** showed most of the pi-electron density above/below the plane of the benzyne; correspondingly, the LUMO has a large in-plane component at C β , suggesting significant phenyl cation character (cf. **2** vs. **2'**). When methane is permitted to engage **2**, the system collapses to a new adduct **3**, the result of exergonic (29 kcal•mol⁻¹) insertion of C β into the strong C–H bond of methane in a process computed to proceed through the transition structure **TS**_{2→3}, which is only 5.4 kcal•mol⁻¹ higher in energy than **2**. The 1,2-migration of the hydrogen atom in **3** proceeds as a very low-barrier (1.1 kcal•mol⁻¹) process via transition structure **TS**_{3→4} in which i) both bonds to the migrating light hydrogen atom were similar in length but ii) the C–B was only 0.01 Å longer than that in **3** (see SI for details). This TS collapsed directly to toluene (**4**) with simultaneous ejection of BF₃. The overall exergonicity of *o*-benzyne (**1**) plus methane to toluene (**4**) was computed to be >75 kcal•mol⁻¹.

One of our earliest observations suggesting the occurrence of this novel BF₃-promoted, C–H insertion process arose while studying the reaction of triyne **5** (Figure 2). When exposed to BF₃•OEt₂ (1.0 equiv) in toluene at 120 °C, the indane derivative **7a** was isolated in 82% yield. We view BF₃•OEt₂ as a pre-catalyst, providing a low equilibrium concentration of dissociated BF₃ to the reaction environment (some of which would be volatilized into the headspace of the sealed reaction vial). Further investigation showed that **7a**, the product of net C–H insertion into the methyl group of the pendant *n*-propyl substituent, occurred in competition with trapping of the intermediate benzyne **6** by the toluene solvent, giving **8a** and **8b**. This competing pathway serves as a clock reaction that allowed us to evaluate the dependency of the reaction on the initial concentration of BF₃•OEt₂ (summarized in the Figure 2 insert). With an initial load of 150 mol% of the Lewis acid, formation of the toluene adducts **8** was completely suppressed, and at 50 mol% a nearly 1:1 mixture of **7a**:**8** was observed. This dependency on catalyst loading suggests that there is a significant amount of product inhibition—that is, that the fluorenones **7a** and **8** out-compete the benzyne for engaging free BF₃.

Because of the unprecedented nature of this Lewis-acid-promoted, carbene-like C–H insertion chemistry, further studies to probe aspects of the mechanism were warranted. First (Figure 3a), we prepared the trideuterated isotopomer **5-d₃** to study whether the CD₃ group is the source of the new aromatic hydrogen atom in the product **7a**. Indeed, 95% of **7a-d₃** was measured to have three deuterium atoms (following desilylation to **9**; see SI for details). Second (Figure 3b), the deuterated triyne **5-d₃** and the non-deuterated tetrayne **10**, hexadehydro-Diels-Alder (HDDA) substrates that react at a similar rate, were simultaneously subjected to the reaction conditions and there was no evidence for crossover isotopomers in either of the products **11** or **7a-d₃**. This indicates that the reaction is intramolecular in nature. Third (Figure 3c), substrate **12**, bearing a 1,1,1-trideutero-3-pentyl substituent, was converted to the ethyl-substituted indane derivative **13**. The reaction proceeded with a small (and inverse) k_H/k_D kinetic isotope effect (KIE, see SI for details). Carbene insertions into C–H bonds frequently proceed with KIEs of low magnitude, encompassing both normal and inverse natures.⁵ Such insertions are often highly exergonic, presumably proceeding, accordingly, through relatively early transition state structures (cf. **2** to **3**, Figure 1b) with only a small degree of C–H bond rupture. Moreover, the edge-on nature of those TS geometries minimizes the contribution from the C–H stretching vibration and accentuates the importance of bending vibrations. Fourth, phenyl carbenium ions are known to promote C–H insertion reactions,⁶ and one recently reported example^{6d} of such a reaction shows a similarly small isotope effect for insertion into cyclohexane. We designed a control experiment to test whether BF₃ itself was responsible for these reactions, because a BF₃-activated Brønsted acid derived from, say, adventitious water in the reaction medium could be invoked as an alternative promoter. Tetrayne **10** was reacted under the conditions given in Figure 3b but now also containing an additional 0.5 equiv of diisopropylethylamine (DIPEA), which we presumed would buffer trace levels of Brønsted acid species such as H₂O•BF₃. As with the experiment done in the absence of amine, we again observed that **11** was formed as the major product. Finally, we did not detect any Friedel-Crafts arylation products arising from trapping by toluene, a behavior for phenyl cations recently reported by Nelson and coworkers.^{6d} In aggregate, these experiments are consistent with the mechanistic framework laid out in Figure 1b.

We returned to DFT computations for some final validation of the mechanistic framework we put forward at the outset. Specifically, we computed the BF₃-catalyzed transformation of benzyne **6** to product **7** (but with structures truncated by removal of the TBS substituent for easier computation). The results (energies and geometries) directly paralleled those given in Figure 1b for the parent reaction (see Figure S1 in SI for details).

We proceeded to study this benzyne C–H insertion reaction with, first, a series of ynone HDDA substrates (**5a-h** in Figure 4); these reactions are all variations of the **5a** to **7a** conversion described above in Figure 2. These allowed us to somewhat systematically probe the effect, primarily, of modification in the alkyl group R at the terminus of the 1,3-diyne, which proffers its C–H bond(s) to the carbenic center. In three cases two products were isolated (see boxes). Collectively, the products in Figure 4 represent all that were formed to the extent of >~5% in any of the reactions.

The reaction to produce **7b** (the non-deuterated analog of **13**, Figure 3c) behaves analogously to that giving **7a**. The formation of **7c** indicates that insertion into a methylene with concomitant formation of a five-membered ring is significantly favored over insertion into a stronger methyl C–H bond with accompanying formation of a six-membered ring.⁷ The R group in **5d** is *t*-butyl; C–H insertion still occurs even though the product, **7d**, is a benzocyclobutene. This supports the view that the insertion step passes through an early transition state geometry wherein low portion of the strong primary C–H bond cleavage and only a small fraction of the eventual ring strain has evolved. When R is an ethyl rather than *t*-butyl group as in **5e**, the unsubstituted benzocyclobutene product **7e** is still formed, but with diminished efficiency relative to that of **7d**, reflecting the lower probability of the carbene carbon to encounter an insertable C–H bond (three vs. nine methyl hydrogens to give **7e** vs. **7d**, respectively) as well as, perhaps, a Thorpe-Ingold effect that leads the methyl C–H of **5d** to more intimately sample the orbital space of the carbene center. Product **7e** is accompanied by the formation of the HF adduct **7e'**. Although we do not know the mechanism of this reaction,⁸ it is presumably slower than the insertion processes. With the exception of the reaction giving **7b** (where a trace of an HF adduct was detected by GC-MS analysis), this pathway was not observed for any of the other reactions.

Reaction of substrate **5f** proceeds via a benzyne containing a *t*-butyl instead of TBS ring-substituent. In contrast to the clean formation of **7a** for the latter, the major product from **5f** was now the methylated benzocyclobutene derivative **7f** rather than the isomeric cyclopentane **7f'**. It is possible that the more compact steric bulk of the *t*-butyl group has compressed the Ar–CH₂–CH₂Me bond angle, leading to closer proximity of the weaker methylene C–H bond to the reaction center. Consistent with this explanation, the reaction of **5g** proceeded to give the benzocyclobutene **7g** more efficiently than that of **5e** to **7e**, and no trace of the (more slowly formed) HF adduct analogous to **7e'** was detected. Finally, substrate **5h**, an analog of **5a** now bearing 4,5-dimethoxy groups, is also a competent substrate for the benzyne C–H insertion reaction. The principal product, **7h**, is analogous to **7a**, but a second product, the alkene **7h'**, was also isolated.⁹

We then explored five other HDDA polyynes substrates that differ primarily in atoms ABC (**10a-e**, Figure 5) that compose the tether between the diyne and diynophile. All give at least some amount of insertion product(s) **11**, demonstrating that the process is not unique to the phenylketone linker in substrates **5**. Moreover, products **11d** and **11e** show that a conjugated carbonyl group within the tether is not a prerequisite. We attribute the lower yield in these last two cases to the fact that the 1-pentynyl substituent is thin and that the benzyne arising from each of the substrates **10d** and **10e** each experience reduced compression between a propyl C–H bond and the carbene carbon. This slows the rate of the insertion reaction, allowing more time for competing, benzyne-consuming reactions (such as reaction with another molecule of polyynes substrate¹⁰) to ensue. Substrate **10b** contains a ^tBu group on the terminus of the diynophile and, like ^tBu-containing triynes **5f** and **5g**, gave a preponderance of a benzocyclobutene product, the lactam **11b**. Finally, the TBS containing analog **10c** gave only the cyclopentane-containing compounds **11c/c'/c''**. The second of these products reveals an interesting fluorodemethylation process. A control experiment (GCMS) demonstrated that isolated **11c** was converted to **11c'** when heated in toluene in the

presence of $\text{BF}_3 \cdot \text{OEt}_2$. Coordination of the ortho TBS and ketone groups to reversibly form a zwitterionic silicate complex would open a path for methyl group removal either by BF_3 or an adventitious, Lewis acid-activated, proton source such as water.

In conclusion, we have described an unprecedented mode of activation of an aryne. Namely, the Lewis acid BF_3 engages benzyne to promote carbene-like reactivity at the adjacent benzyne carbon atom. This work serves as another example¹¹ in which benzyne derived from the thermal HDDA cycloisomerization reaction and, therefore, in the absence of any other benzyne-generating reagents or byproducts, has allowed a fundamentally new type of transformation to be discovered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

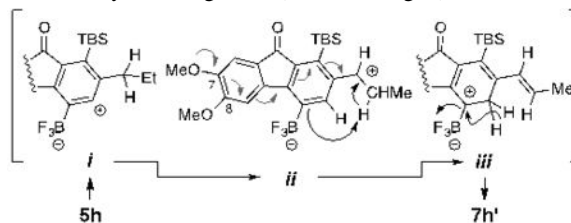
Support for this work was provided by the Institute of General Medical Sciences of the U.S. Department of Health and Human Services (R01 GM65597, then R35 GM127097) and the National Science Foundation (CHE-1665389). A portion of the NMR data were obtained with an instrument purchased with funds from the NIH Shared Instrumentation Grant program (S10OD011952). Computations were performed with resources made available by the University of Minnesota Supercomputing Institute (MSI).

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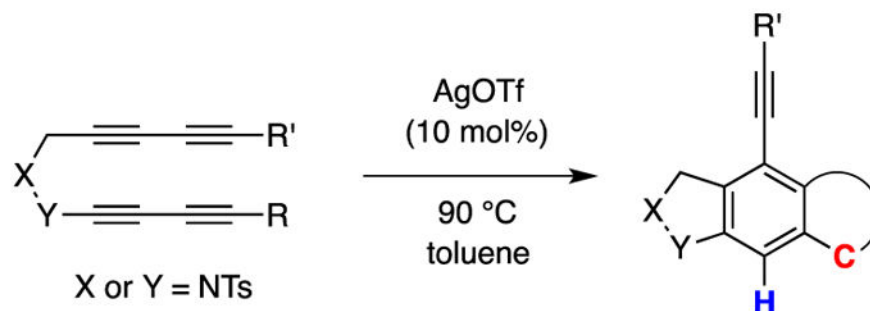
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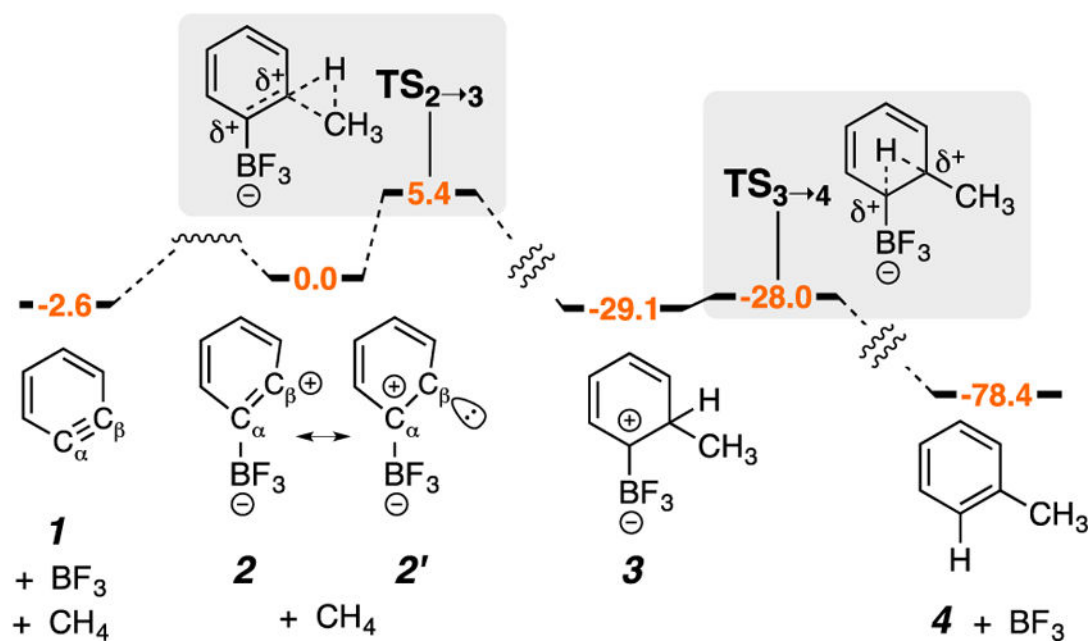
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- (8). Using HBF_4 instead of $\text{BF}_3 \cdot \text{OEt}_2$ under otherwise similar conditions, we observed formation of a larger amount of **7e'** compared to **7e**, implying that a Brønsted acid is playing a role in the net HF addition process.
- (9). An alkene product was only observed in the case of the reaction of the 4,5-dimethoxyphenone derivative **5h**. We suggest that the derived benzyne• BF_3 adduct **i** can give rise to the benzylic carbenium ion **ii**, the formation of which (more than one route can be envisioned for this transformation) is enabled by the electron donating ability of the 7-OMe substituent (cf. gray arrows). Intramolecular proton transfer restores boron carbenoid character in **iii**, which, finally, aromatizes to **7h'** via 1,2-hydride migration (cf. **3** to **4**, Fig. 1).



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a Lee et al., 2013, 2014: Ag(I)-catalyzed, C–H insertion reactions of benzynes

R,R' = C–H-containing alkyl or trialkylsilyl

b DFT PES for the prototypical BF_3 -catalyzed reactions reported here**Figure 1.**

(a) Previous work demonstrating transition metal-mediated C–H insertion of a benzyne carbon. (b) Calculated {DFT [SMD(toluene)//M06-2X/6-311+G**]} energy profile for the BF_3 -catalyzed insertion of *o*-benzyne (**1**) into H– CH_3 to give toluene (**4**). Ts = *p*-toluenesulfonyl; OTf = O_3SCF_3 ; DFT, density functional theory; PES, potential energy surface.

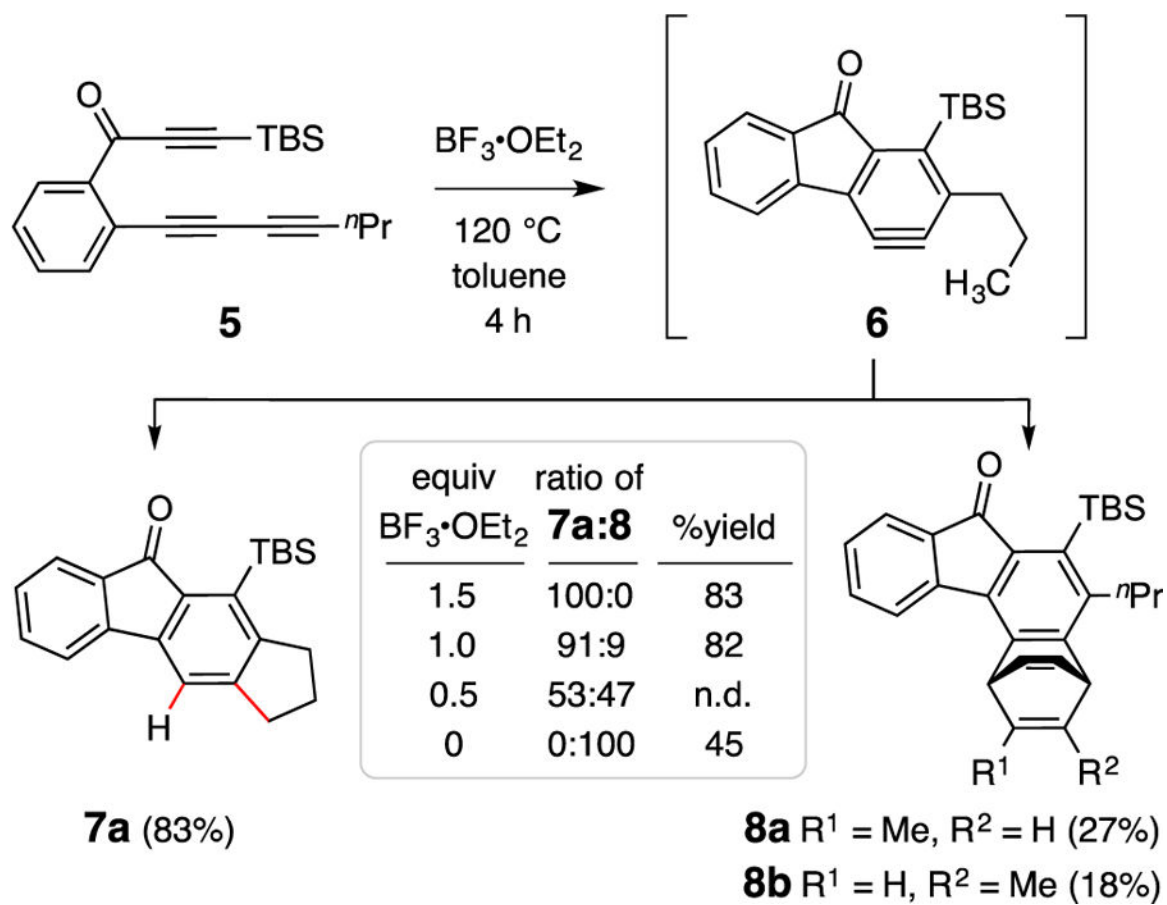
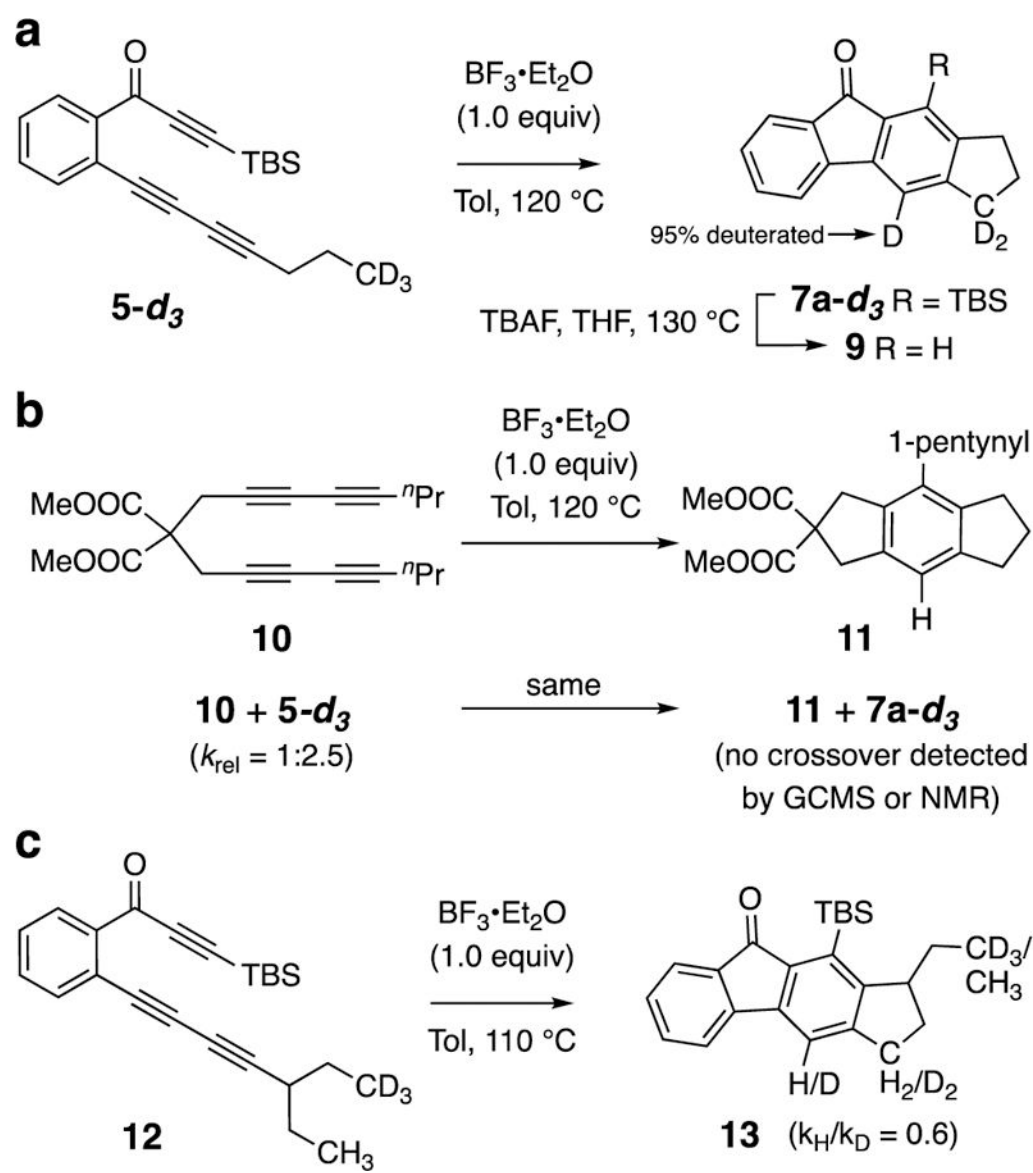
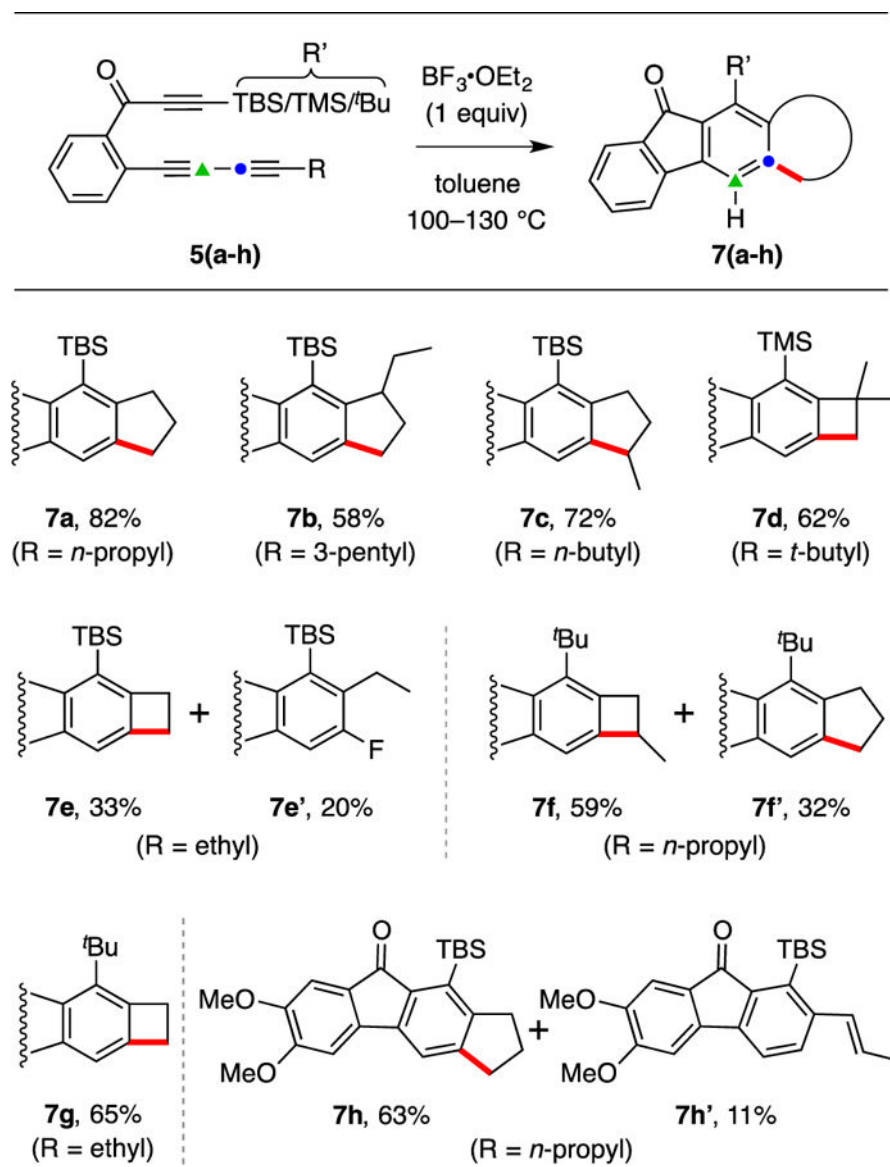


Figure 2. Results showing that the ratio of C–H insertion and Diels–Alder trapping (by PhMe solvent) products (**7a:8**) is $[\text{BF}_3]$ -dependent. TBS = *tert*-butyldimethylsilyl; ^nPr = 1-propyl; Et = ethyl; Me = methyl.

**Figure 3.**

Experiments to probe mechanistic aspects of the reaction. (a) Use of substrate **5-d₃** establishes the origin of the new aromatic hydrogen atom. (b) Crossover experiment using a mixture of substrates **10** and **5-d₃**. (c) Kinetic isotope effect measured with substrate **12**. TBAF = tetra-*n*-butylammonium fluoride; Tol = toluene.

**Figure 4.**

The major products (**7a-h**) isolated from C-H insertion experiments using tryne precursors **5a-h**. Yields are for isolated, purified (SiO₂) material. The nature of the R and R' groups present in each precursor **5** can be deduced from the structure of each resultant product **7**. TMS = trimethylsilyl; ^tBu = *tertiary*-butyl.

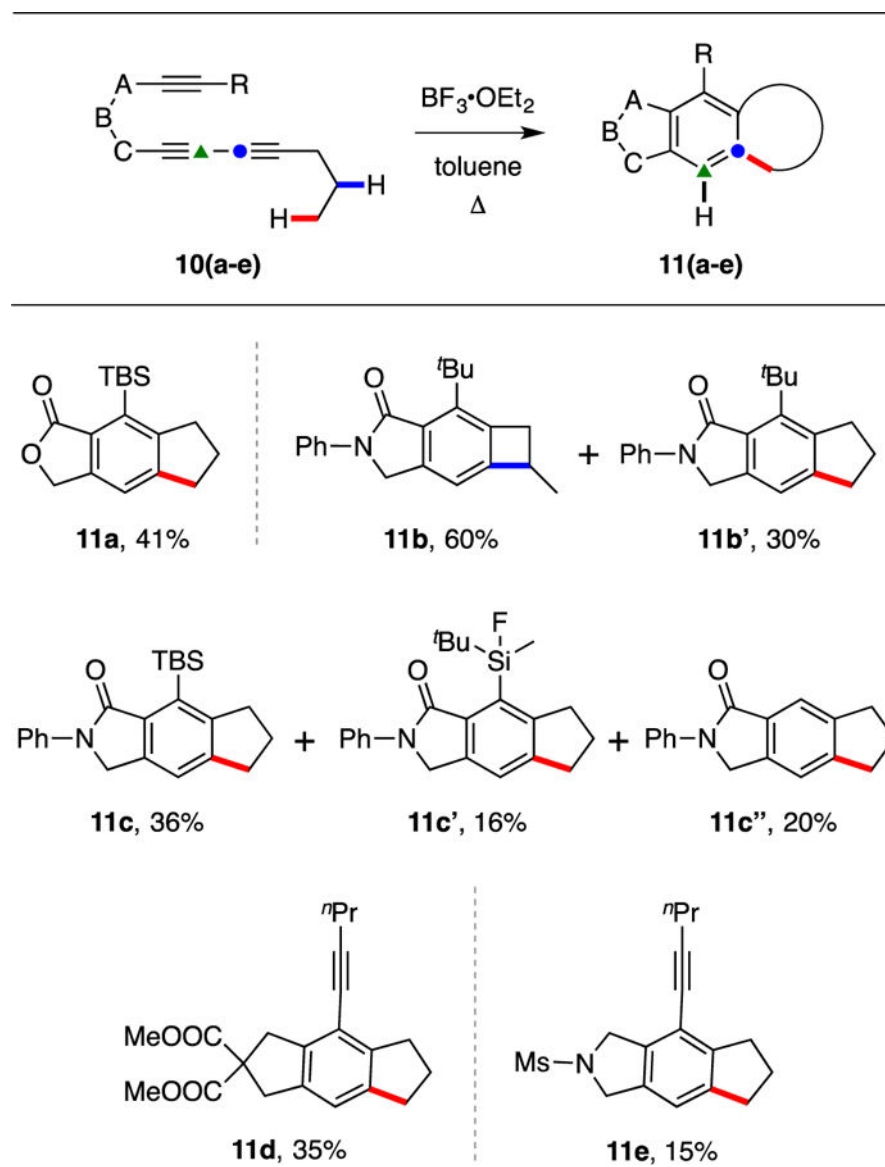


Figure 5. The major products (**11a-e**) isolated from experiments using triyne and tetrayne precursors **10a-e**, each having a different linker structure (ABC) from that in **5**. Yields are for isolated, purified (SiO_2) material. The nature of the ABC linker and the R group present in each precursor **10** can be deduced from the structure of each resultant product **11**.