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Benzocyclobutadienes: An unusual mode of access reveals unusual modes of reactivity

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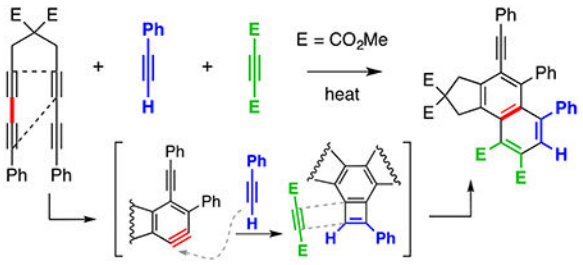
Abstract

The reaction of an aryne with an alkyne to generate a benzocyclobutadiene (BCB) intermediate is rare. We report here examples of this reaction, revealed by Diels-Alder trapping of the BCB by either pendant or external, electron-deficient alkynes. Mechanistic delineation of the reaction course is supported by DFT calculations. A three-component process joining a benzyne, first, with an electron-rich and, then, an electron-poor alkyne was uncovered. Reactions in which the BCB functions in a rarely observed role as a 4π diene component in Diels-Alder reactions are reported. The results also shed new light on aspects of the hexadehydro-Diels-Alder reaction used to generate the benzynes.

Graphical Abstract

Benzocyclobutadiene (BCB) has been accessed via a [2+2] cycloaddition of a benzyne and an alkyne. The BCB generated by this method exhibited rare reactivity—namely, as a 4π component in a Diels–Alder reaction to furnish highly substituted polyaromatic compounds as the product. DFT calculations revealed many mechanistic details of this cascade process.



Keywords

benzocyclobutadiene; cyclization; benzyne; Diels–Alder; alkyne cascades

***o-B*enzyne (1)** and its analogs have been widely studied and used in organic synthesis. The major classic reaction modes of the distorted triple bond involve nucleophilic addition and

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Conflict of interest

The authors declare no conflict of interest.

[4+2] or 1,3-dipolar cycloadditions.[1] Another highly reactive intermediate benzocyclobutadiene (**2**, BCB) is not nearly as explored due to its relative inaccessibility.[2] Moreover, reactions of BCBs, once formed, are often not highly selective and give rise to an array of products. In principle, BCB can be generated by reaction of a benzyne with an alkyne via a net [2+2] cycloaddition. However, reports of such transformations are extremely rare.[3,4] This is surprising because the reaction of a benzyne with an alkyne is computed to be significantly exergonic (cf. 58.5 kcal•mol^{-1} for **9** to **10**, Figure S1 in the SI) and to proceed with a low activation energy.[5] Therefore, the paucity of reports of alkyne + benzyne [2+2] reactions may reflect inefficiency in the subsequent manifold of reactions into which an initially formed BCB intermediate enters rather than inherent difficulty in its generation. In the initial discovery, Stiles *et al.* (Figure 1a) rationalized the formation of dibenzocyclooctatetraenes **3** by dimerization of BCB intermediates **2**.[3] In the only other example of this type of process to our knowledge, Shindo and Alabugin recently reported the reaction of various benzynes with electron-rich ynolates **4** to give triptycenes **6**, which they proposed to arise via initial formation of formal [2+2] adducts **5** (Figure 1b).[4]

The hexadehydro-Diels–Alder (HDDA) reaction provides a reagent-free and fully atom-economical method for producing a benzyne intermediate from a poly-yne substrate,[6] which can be immediately trapped by an *in situ* arynophile.[7] The formation of benzyne is the rate-limiting step in an HDDA generation/trapping cascade,[8] which means that the benzyne is present in only a low steady-state concentration along with a larger amount of the poly-yne precursor, depending upon the stage of conversion. Therefore, in the absence of a trapping reagent, we presume that the HDDA-benzyne engages one of the several alkynes in the substrate, generally in a non-selective fashion to generate a host of BCB intermediates, resulting in intractable product mixtures. Thus, we were surprised to observe that heating the triyne **7** in the absence of any trapping partner gave one major product (^{1}H NMR spectrum of the crude product mixture)—the dimer **8**, which was isolated in 45% yield (Figure 1c). Five alkyne units in two molecules of **7** had been transformed into a naphthalene core bearing one ^{t}Bu-ethynyl substituent. This purely thermal process raises a number of intriguing mechanistic questions.

Our proposed mechanism for this unexpected transformation is shown in Figure 2. The consumption of **7** proceeded with a comparable half-life to that of a similar triyne substrate in a typical HDDA cycloisomerization.[9] Thus, formation of the HDDA benzyne **9** derived from triyne **7** presumably began the process. To form the observed regioisomer of naphthalene **8**, benzyne **9** would need to selectively undergo a [2+2] cycloaddition with one of the three triple bonds in **7** and with a preference for one of two possible orientations. This would produce the BCB intermediate **10**, which could then be trapped regioselectively in a [4+2] cycloaddition as the 4**π** component by the intramolecularly tethered propiolate dienophile to afford the hemi-Dewar naphthalene **11**. Intermediate **11** would be expected to rapidly open to **8**.[10]

To explore some of the generality of the reaction, we prepared a series of analogs of ester **7**, differing in the substituents at the termini of the diyne and diynophile (**12**, Figure 3). Notably, a cyclopropyl group remains intact (**13d**), presumably because the spin of the diradical intermediates is substantially delocalized, thereby slowing the rate of the potential

ring-opening reaction.[11] Aryl substituents (**13i**–**13o**) are compatible. The presence of a TMS group in the aryl-substituted triynes led to improved yields and facilitated the solubility and handling of some of the products. Some of the products exhibited blue fluorescence upon exposure to a 365 nm light source (see SI for two examples).[12]

DFT calculations were performed to inform the mechanistic thinking (Figure S1). Conversion of **7** to **9** is seen to be exergonic by 47.7 kcal•mol^{-1}.[9,13] The reaction of **9** with a second molecule of **7** to form the BCB intermediate **10** was seen to be a stepwise net [2+2] cyclization proceeding through a diradical (**S17**).[5],[14] Because an alkyne is a strong radical-stabilizing group,[15] the lowest energy transition structure (TS) was computed to be that implied by arrows “a” (Figure 2). The subsequent conversion of **10** to the hemi-Dewar naphthalene **11**, a formal Diels-Alder cycloaddition, was also computed to be stepwise (cf. arrows “b”).[16] A TS for the concerted process was located but found to have a 24.8 kcal•mol^{-1} higher barrier compared to the diradical pathway. Finally, the fragmentation of **11** was computed to afford naphthalene **8** via a low barrier TS (9.2 kcal•mol^{-1}). Notably, the overall transformation that converts the five C≡C bonds in two molecules of **7** to the naphthalene **8** is computed to be 199 kcal•mol^{-1} (!) exergonic.

To bring additional light to bear on our hypothesized mechanism, hetero-dimerization experiments were carried out. The HDDA precursors **14a–d** and triynes **7a–d** (Figure 4a) have the indicated mismatched half-lives for their rates of cycloisomerization. We presumed that, when heated together at 80 °C, triyne **7** would remain essentially intact, while tetrayne **14** would cyclize to the benzyne **15**. In the event, **15** was trapped by **7** to give **16a–d** in a process paralleling the benzocyclobutadiene trapping stage in the homodimerization of **7**. Similarly, two faster-reacting poly-ynes were also tested with the propiolate derivative **7d** (Figure 4b); these gave rise to the polyaromatic compounds (**18**, **20**). The product fluorenone **18** is noteworthy because it arises from a naphthyne intermediate, formed by way of a domino-HDDA, double cycloisomerization[17] of a pentayne precursor (see SI). Additionally (Figure 4c), the propiolate diyne **7e** captured the benzyne derived from **14a** to give **21**, a product suggesting that the bulky mesityl substituent had steered the intramolecularly linked propiolate to approach the BCB in an unusual orientation (see the dashed line) to afford a net [2+2+2] product along with a minor isomer that derives from the normal pathway (ca. 5:1, see SI).

We next hypothesized that an initial stepwise [2+2] reaction between a benzyne and a simple alkyne (but one bearing a radical stabilizing group) would also form a BCB intermediate, which might then be trapped preferentially by a second, electron-deficient alkyne. This was first demonstrated (Figure 5a) in a three-component reaction involving the HDDA-precursor **22**, the (relatively) electron-rich 2,4-hexadiyne (**23a**), and electron-poor dimethyl acetylenedicarboxylate (**24**). The naphthalene derivative **25a** (38%) was produced; its structure was assigned on the basis of nOe and HMBC analyses (see SI). This reaction most likely proceeds through three reactive intermediates: the benzyne **26**, the BCB **27**, and the hemi-Dewar naphthalene **28**. Similarly, we surmised that simple arylethynes **23b**–**d** might also serve as effective initial alkyne traps for the benzyne (Figure 5b). Indeed, heating **22** with one of **23b**–**d** and **24** gave **25b**–**d**. Each of these reactions could have produced 8

constitutionally isomeric, 3-component adducts, but the only such product observed (direct LC-MS analysis of the reaction mixture) was that having the skeleton common to **25b**–**d**.

We then showed it is not essential to use an alkyne as the electron-deficient BCB trapping agent for this transformation. For example, reactions of **22** with **23a**/**23b** in the presence, now, of maleimide **29** as the third component led to dihydronaphthalene products **25e**/**25f** (Figure 5c). To demonstrate that these reactions are not unique to only the benzyne **26**, the ester-linked triyne HDDA substrate **7d** was also examined. When heated in the presence of DMAD (**24**) and 2,4-hexadiyne (**23a**), this gave **25g** (Figure 5d), the direct analog of product **25a**. Interestingly, when this reaction was performed in the absence of **24**, a three component product was still observed—namely, **25h**. This 2:1 adduct has incorporated two equivalents of 2,4-hexadiyne (**23a**) and the benzyne from **7d**. The regioselectivity of this process supports the view that net [4+2] trapping of the BCB is a highly asynchronous event with considerable diradical character—the non-participating, second alkyne in **23a** is a powerful radical stabilizing group.[15]

Finally, we have observed that the high, strain relief-driven reactivity of a benzyne is not a prerequisite for cyclobutadiene formation.[18] In particular, when heated in the presence of DMAD (**24**), the tetrayne **30** (Figure 6) gave the adducts **33a** and **33b** as the only tractable products. These most likely arise from a [4+2] reaction between the fused cyclobutadiene (CB) **32** and **24**. It is surprising that the tetrayne **30**, which contains a four-atom tether between its internal alkynes, gives a CB to the exclusion of a benzyne.[19] This is the first time we have gained insight to why there is a nearly absolute requirement that HDDA substrates contain a three-atom tether linking the diyne and diynophile moities—a four-atom linker is more capable of accommodating formation of a fused cyclobutadiene (cf. **32**) and the diradical (cf. **31**) does so (black arrow) in preference to cyclizing at the distal terminus of the propargylic radical (gray arrow), even though the resulting benzyne is computed to be (see SI) 30.5 kcal•mol^{-1} more stable than the isomeric CB **32**. Additionally, trapping of **32** with *N*-phenylmaleimide (**34**) was explored. Initially, a mixture of multiple stereoisomeric products, composing what we surmised to be 2:1 adducts from DA reaction of the maleimide with **35**, was observed. This complication was avoided when the reaction was performed in the presence of manganese dioxide, an oxidant that effectively intercepted diene **35** by its conversion to the phthalimide **36**.[20]

In conclusion, we have described a series of polyalkyne cascade processes via benzocyclobutadiene (BCB) intermediates. These demonstrate the feasibility of generating BCBs from certain (thermally generated) benzynes and appropriate alkyne trapping partners. A rare mode of BCB trapping—namely, as a 4**π** component in DA reactions—was also uncovered. This results in the production of alkynyl naphthalene derivatives under purely thermal conditions. DFT calculations support a stepwise formation of the BCB and guided us in the design of several multicomponent reactions. These results provide new mechanistic insights about thermal alkyne chemistry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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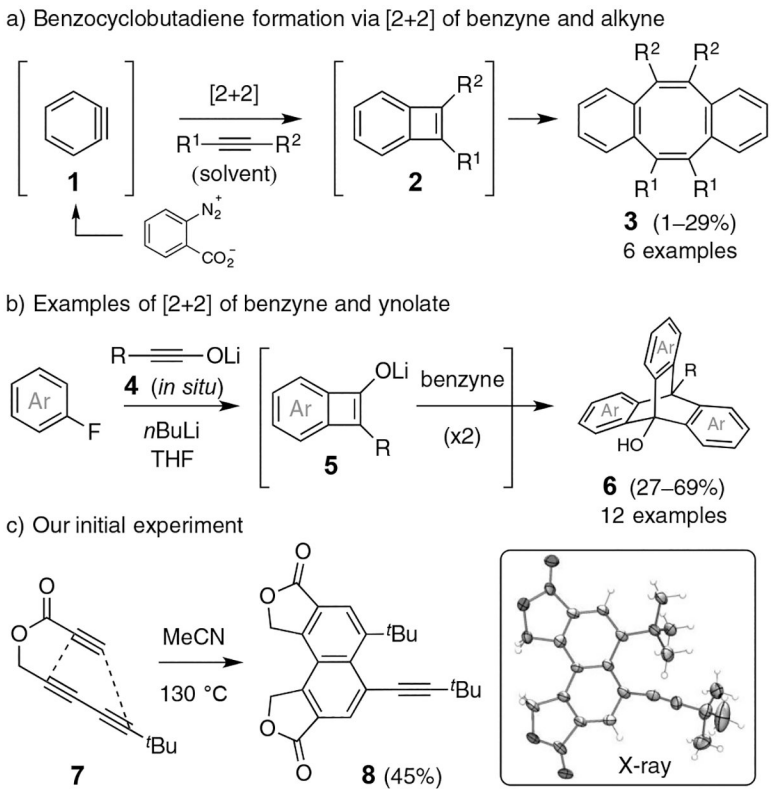


Figure 1.

Only previous examples of benzyne + alkyne net [2+2] cyclization (a, b) and our first encounter: dimerization of **7** (c).

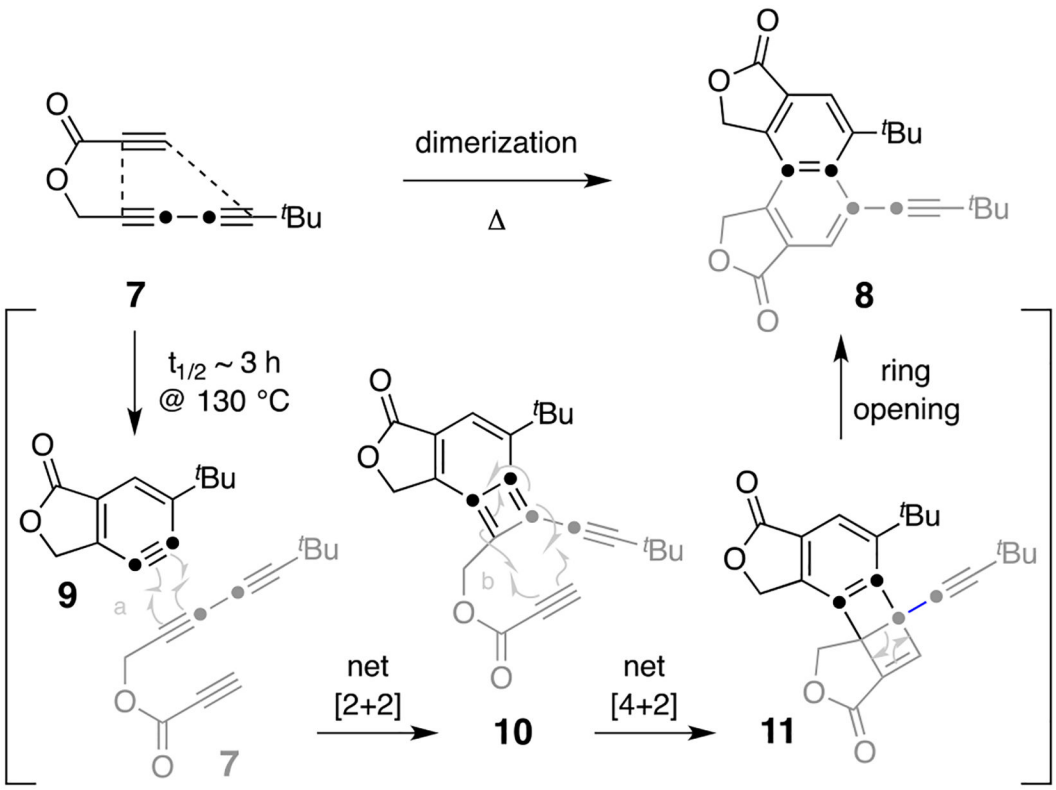


Figure 2.
Proposed mechanism for dimerization of triyne **7** to the alkynylnaphthalene derivative **8**.

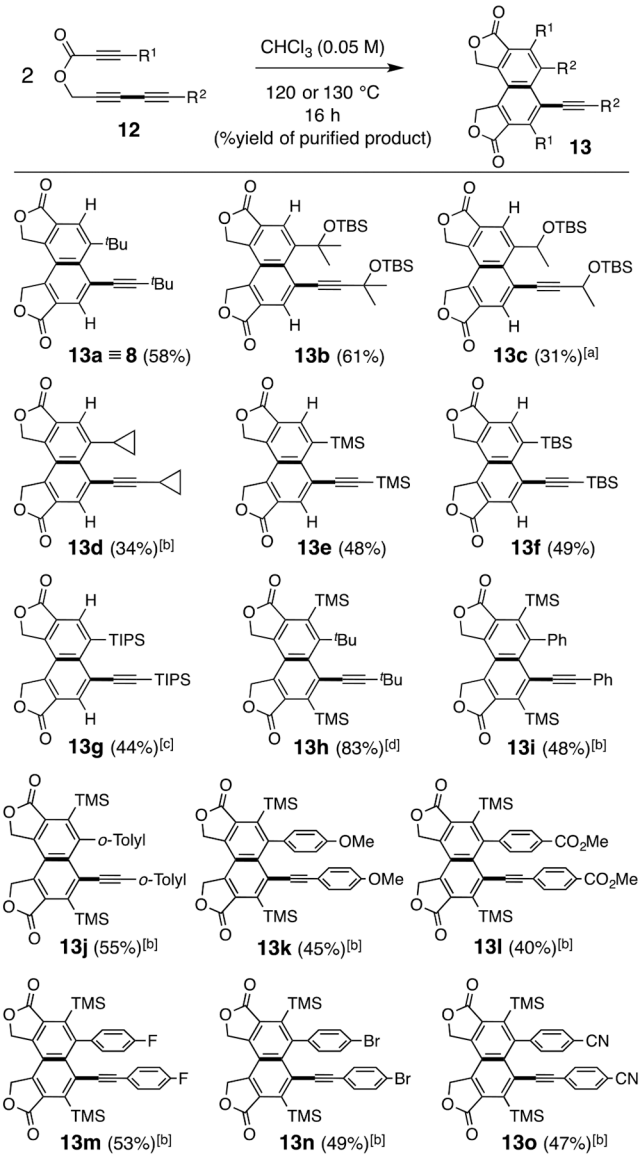
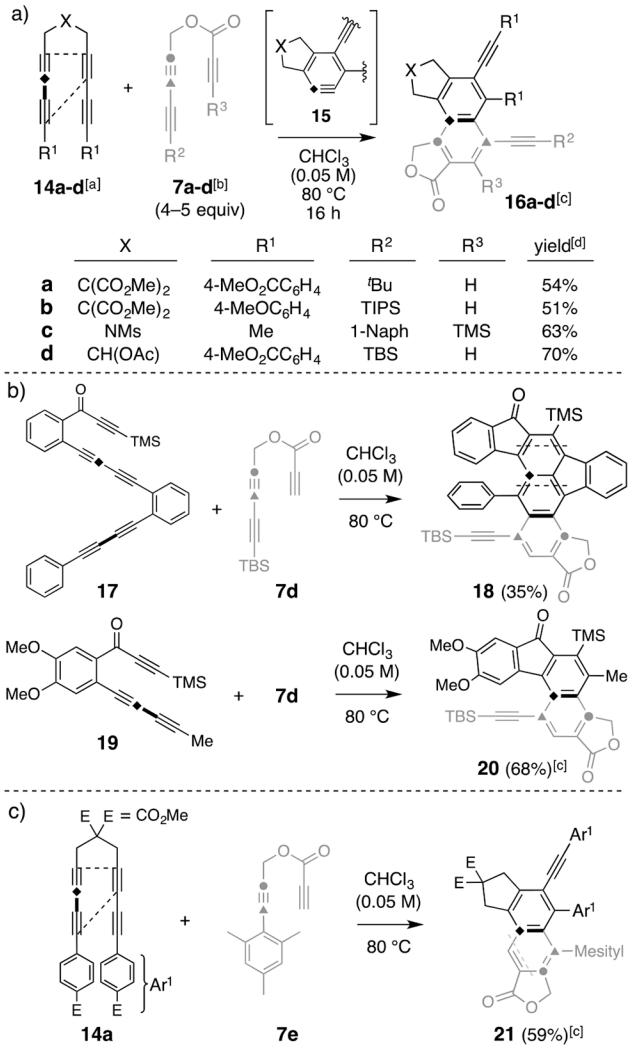


Figure 3.

Examples of dimerizations of ester-tethered triynes **12**. [a] dr = 1:1. [b] a small amount of a regioisomer (see SI for **13i'**) was observed (^{1}H NMR analysis of the crude product mixture). [c] 140 °C, 48 h. [d] 150 °C, 24 h. TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl, TIPS = triisopropylsilyl.



[a] $t_{1/2}$ = ca. 3 h @ 80 °C. [b] $t_{1/2}$ = ca. 3 h @ 130 °C [c] Each of products **16c**, **20**, and **21** was accompanied by a minor regioisomer (see SI). [d] Yields are for chromatographically purified compounds.

Figure 4.

Hetero-dimer formation between a fast-reacting HDDA substrate (e.g., **14**) and propiolate **7** and its analogs. Ms = methanesulfonyl.

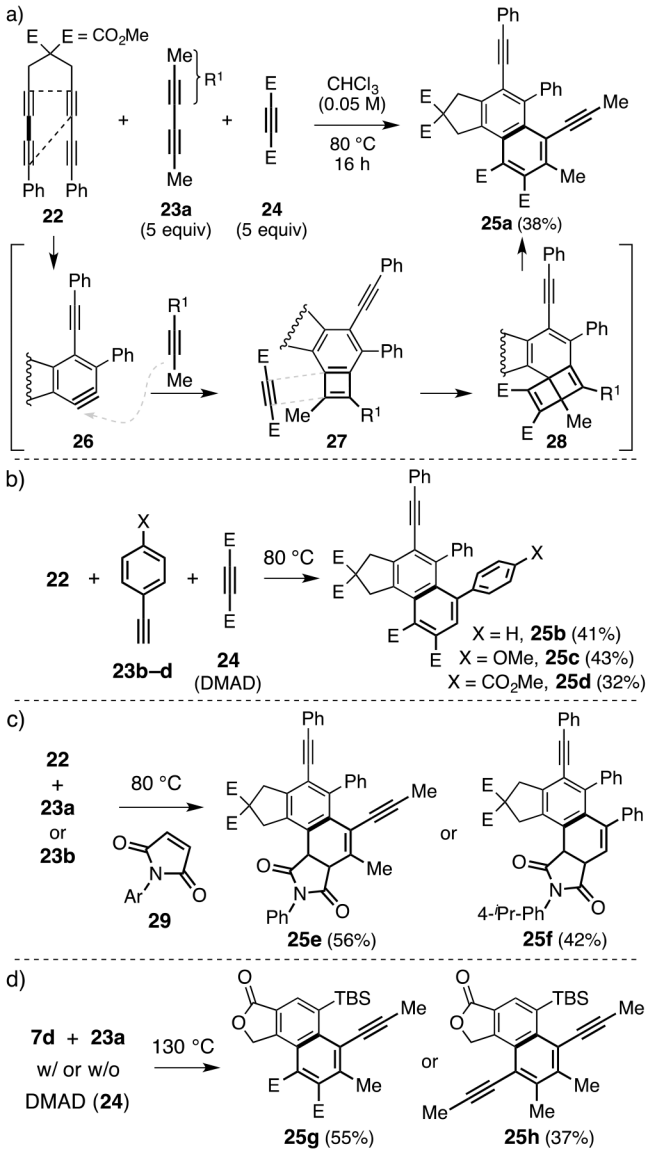
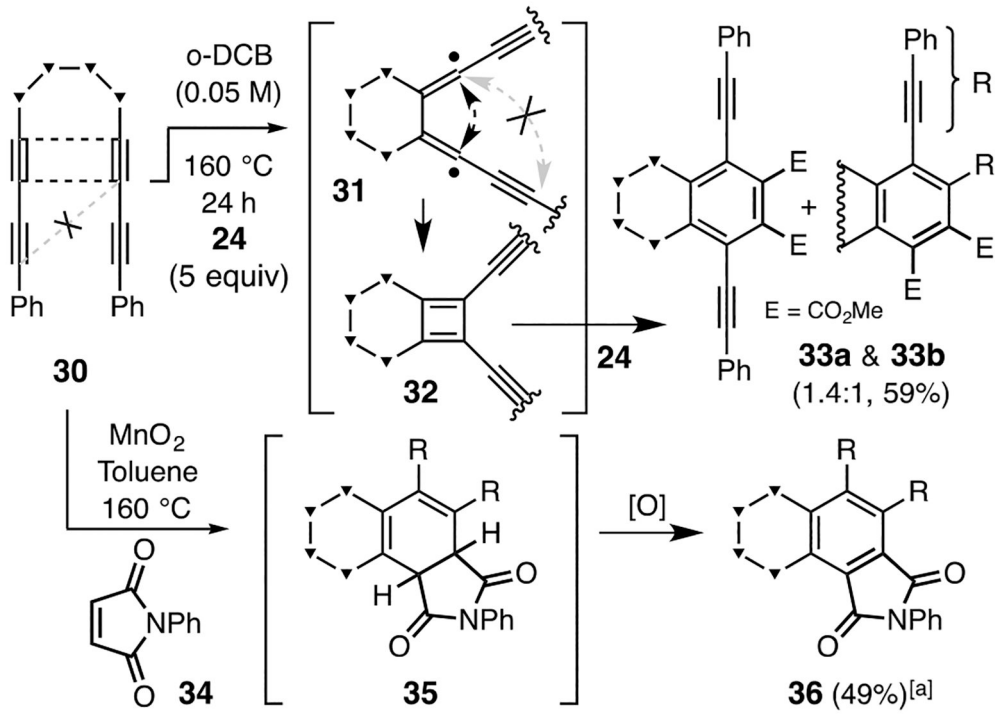


Figure 5.

Three-component reactions: benzyne + electron-rich alkyne + BCB “dienophile”. Five equivalents of each (relative to the HDDA substrate) were used in each experiment. DMAD = Dimethyl acetylenedicarboxylate.



[a] a small amount of a (symmetrical) regioisomer (see SI) was also observed.

Figure 6.

A four-atom tether thwarts the HDDA reaction by allowing for faster formation of the CB **32**.