Benzyne Cascade Reactions via Benzoxetenonium Ions and their Rearrangements to o-Quinone Methides

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Abstract

A new thermal isomerization of polyynes is described. Benzyne intermediates substituted by a C(RR')OR" substituent adjacent to one of the benzyne sp-hybridized carbons give rise to products in which the OR" moiety has migrated to the proximal benzyne carbon. This process likely proceeds via sequential formation of multiple reactive intermediates: an initial thermally generated benzyne, a strained benzoxetenonium ion, and an *o*-quinone methide. As some examples demonstrate, the overall transformation can be quite efficient. The mechanism of this novel reaction is further supported by experiments and DFT calculations.

Graphical abstract
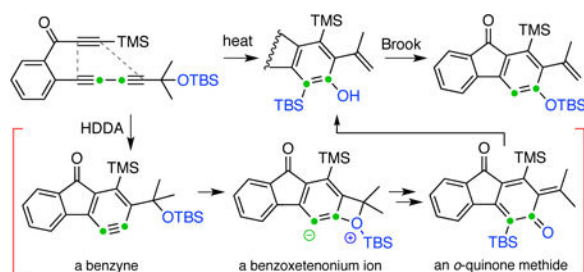
Quinone methides (QMs) are reactive intermediates of interest from the perspectives of preparative, mechanistic, and structural organic chemistry as well as their roles in chemical biology (e.g., biosynthetic pathways, prodrug cleavage, and electrophilic capture of biological nucleophiles).[1] QMs are often generated by eliminative processes of phenol derivatives or by photochemical reactions (including reversible generation in photochromic molecules). Besides these two methods, benzyne, itself a versatile reactive intermediate, can also generate *o*-QMs by reaction with the C=O π-bond in carbonyl-containing functional groups (Figure 1a).[2] For example, Yoshida and co-workers demonstrated a coupling

reaction of two arynes with aldehydes to give 9-arylxanthene derivatives through QM intermediates. They, as well as Miyabe's group, have also reported insertion reactions of arynes into formamide to afford coumarin derivatives following in situ trapping of the *o*-QM by esters, nitriles, and ketones.

We now report a reaction (Figure 1b) that represents an alternative mechanistic paradigm for producing *o*-QMs in which a thermally generated benzyne derivative bearing a benzylic ether group can produce a four-membered benzoxetenonium 1,3-zwitterion (middle structure in the brackets in Figure 1b) by an intramolecular nucleophilic attack to the strained aryne bond. Electrocyclic ring-opening of the oxetene ring[3] affords an *o*-substituted *o*-QM intermediate, and a subsequent hydrogen atom migration gives a formal C—O bond insertion product. In this process, the steric bulk of the R^1 group is crucial, possibly facilitating passage through the strained four-membered ring transition state geometry that leads to the strained four-membered zwitterion.[4] Indeed, when R^1 is a hydrogen, the reaction proceeds through other pathways. [5] The highly substituted benzyne intermediate is accessed conveniently from a triyne precursor via a cycloisomerization event, namely, the hexadehydro-Diels-Alder (HDDA) reaction,[6] and therefore, the overall cascade is essentially a net thermal isomerization of the triyne.

The first time we encountered this unusual transformation was upon heating the ynone substrate **1a**. The fluorenone derivative **2a** was produced in excellent yield (Chart 1). We proposed a mechanism to account for this outcome, which is shown in Figure 2. Initially, triyne **1a** undergoes a HDDA reaction to generate benzyne **3**, which is trapped by the pendant benzylic silyl ether to give the benzoxetenonium species **4**. Silyl migration to the anionic carbon in this zwitterion (a retro-Brook-like rearrangement) could occur at this stage, although the stereoelectronic features for that process appear to be much more favorable following ring-opening to the *O*-silylated *o*-QM **5**. Moreover, that electrocyclic opening itself might be expected to be quite rapid because it is accompanied by delocalization of the cationic portion of the zwitterion (cf. the computed **TS2** in Figure 3, which suggests that this process is barrierless). A [l,5]-hydrogen atom shift in the neutral QM[7] **6** yields the *o*-silylated phenol 7. We presumed that under the reaction conditions for this experiment (150 °C, 14 h), this species had rearranged (see later discussion) to the observed product **2a.** Similar thermal Brook rearrangements of *o*-silylated phenols have been reported.[8] Due to the size of each of the two substituents at OR^2 the termini of triyne **1** (blue and red colors), the ease of these HDDA cycloisomerizations—necessarily the rate-limiting step in each case—required more elevated temperatures to form the benzyne compared to analogous ynone-triyne substrates.[9] The transformation was shown to be general, as evidenced by the examples of substrates **1b-h** leading to **2b-h**. Propargylic substitution other than geminal dimethyl in **1** is tolerated (cf. **2d**-**e**). The R^2 group can be alkyl in addition to a silyl substituent (**2f**). When it is acetyl (cf. **1h**), two products, **2h** and **2h**', were observed. The latter could arise by either an intermolecular transfer or an intramolecular, Fries-like process.

DFT calculations [SMD(PhCl)/B3LYP-D3BJ/6– 311+G**//B3LYP/6–31G*, Figure 3] were used to further explore the mechanistic thinking laid out in Figure 2. A slightly simplified and symmetrized [e.g., TMS instead of TBS and an ester linker (cf. **8a**, later)] set of

structures was used. The HDDA-produced benzyne **A** is seen to cyclize to the benzoxetenonium ion **B** with a very low barrier (**TS1**, 3.5 kcaL·mol^{-1}), although this strained species is 1.7 kcaL·mol^{-1} higher in free energy than the benzyne. This proceeds by way of an extremely facile, indeed, barrierless, electrocyclic ring-opening to afford the more stable zwitterion **C**. Subsequent retro-Brook reaction within the zwitterion **C** results in formation of the *o*-QM **D** via another low-barrier process (**TS3**, G = 4.0 kcal·mol^{-1}). A 1,5-hydrogen atom shift in *o*-QM **004** gives the phenol **E** via **TS4** (G = 10.2 kcal·mol^{-1}). The keto tautomer **F** is seen to be less stable than the phenol by only 12.3 kca·mol^{-1}, although we do not know the specifics of the mediator that is promoting this symmetry-forbidden 1,3-hydrogen atom migration. By contrast, processes like the 1,3-silyl migration of **F** to the silyl ether product **G** are known to be symmetry allowed and concerted (cf. **TS5**, G = 21.2 kcal·mol^{-1}).[10] Finally, note that when the R group attached to the oxonium ion is not a silyl substituent (e.g., Et in **2f**), Et migration is not observed. Instead, a protonation/deprotonation sequence via the benzylic carbenium ion **H** is presumed to lead to products like **I** (i.e., **2f**).

To address the question of whether the transformation of **1** to **2** is tolerant of triyne precursors containing other types of linkers, we examined the HDDA substrates **8a-d** (Chart 2). Once again we observed that the benzyne formation step in these substrates is slower than expected based on analogous triynes that we have previously studied having the same linker but a less bulky substituent (CH$_2$R) on the terminal diyne.[9] The trapping nucleophile is not limited to oxygen. The tertiary amino group in substrate **8b** migrated to give **9b** in an analogous fashion to the reaction of the ethoxylated analog (cf. **1f** to **2f**), now by accessing a four-membered benzazetene species. In the case of **8c**, the silylated phenol product **9c** was formed cleanly (cf. **2h'**). We do not have a good explanation for the reluctance of this compound to undergo the Brook rearrangement (it remained intact even following recording of the melting point (= 235–237 °C).

^{1}H NMR spectroscopy was used to monitor the progress of the reaction of **1a** (Figure 4a). The consumption of **1a** proceed with a half-life that is estimated to be 47 min at 150 °C in chlorobenzene. As a comparison, the cyclization half-life of another ynone substrate with the same linker structure is ca. 5 h at 80 °C.[9] Intriguingly, at an early stage (30 min) of conversion, we observed quite clean the formation of phenol 7. As the reaction proceeded (60 and 110 min), the signal of silyl ether **2a** started to appear and increase. Eventually (350 min), most of 7 was isomerized to the thermodynamically more stable constitutional isomer **2a**. This NMR study clearly suggests that phenol 7 indeed is a metastable intermediate, the initially formed product arising from rearomatization of the *o*-QM **6,** which then undergoes rearrangement to **2a**.[8]

Finally, to rule out the possibility of a bimolecular silyl or alkyl group transfer, we carried out a crossover experiment using triynes **8a** and **10**, whose cyclization half-lives are comparable. No evidence of either of the two possible crossover products was observed after full consumption of both **8a** and **10** (Figure 4b). This supports the mechanism in which an intramolecular retro-Brook rearrangement of **5** produces o-QM **6** (Figure 2).

In conclusion, we have shown that certain polyyne substrates can efficiently undergo a tandem thermal isomerization via an *o*-QM intermediate. This represents a new pathway of formation of this class of intermediate. The scope of the reaction was briefly demonstrated (Charts 1-2), and a plausible mechanistic pathway was proposed (Figure 2). Furthermore, DFT calculations and mechanistic studies provided additional support of the proposed mechanism (Figure 3–4). This represents another example of the HDDA reaction serving as a platform to support fundamentally new types of reactivity.

Supplementary Material

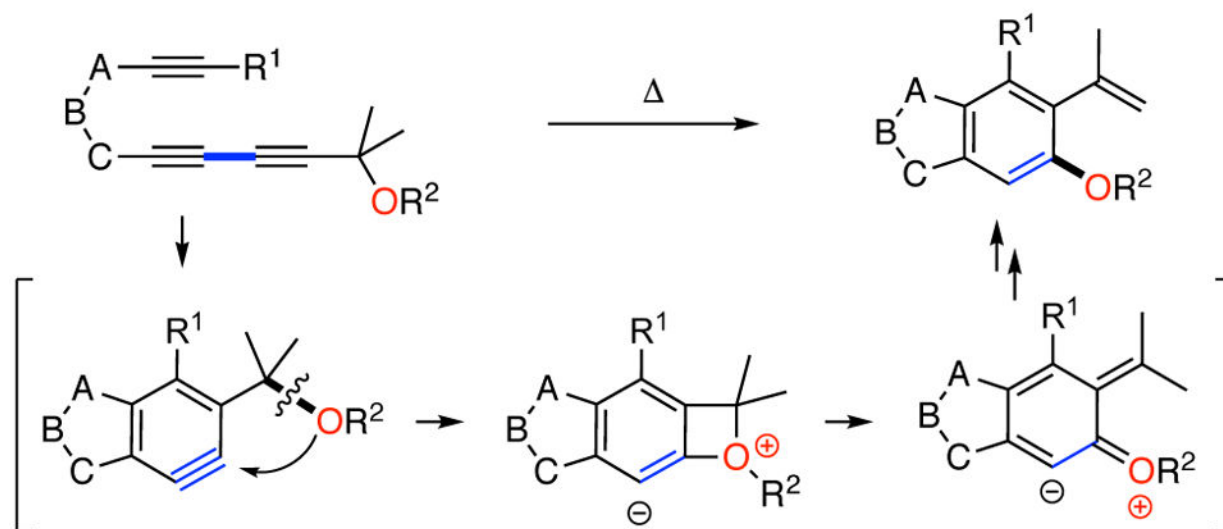Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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a previous examples of benzynes leading to *o*-quinonemethides

Yoshida et al. 2004

Miyabe et al. 2011
Yoshida et al. 2011

Miyabe et al. 2011
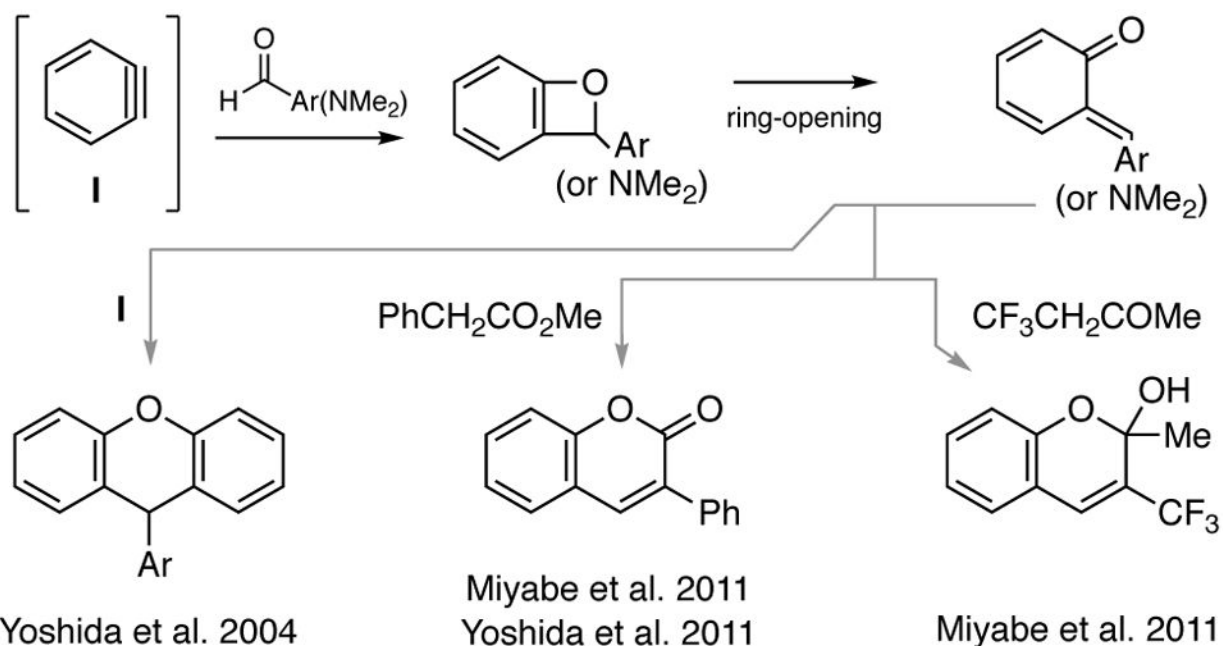
b a new route from benzynes to *o*-quinonemethides

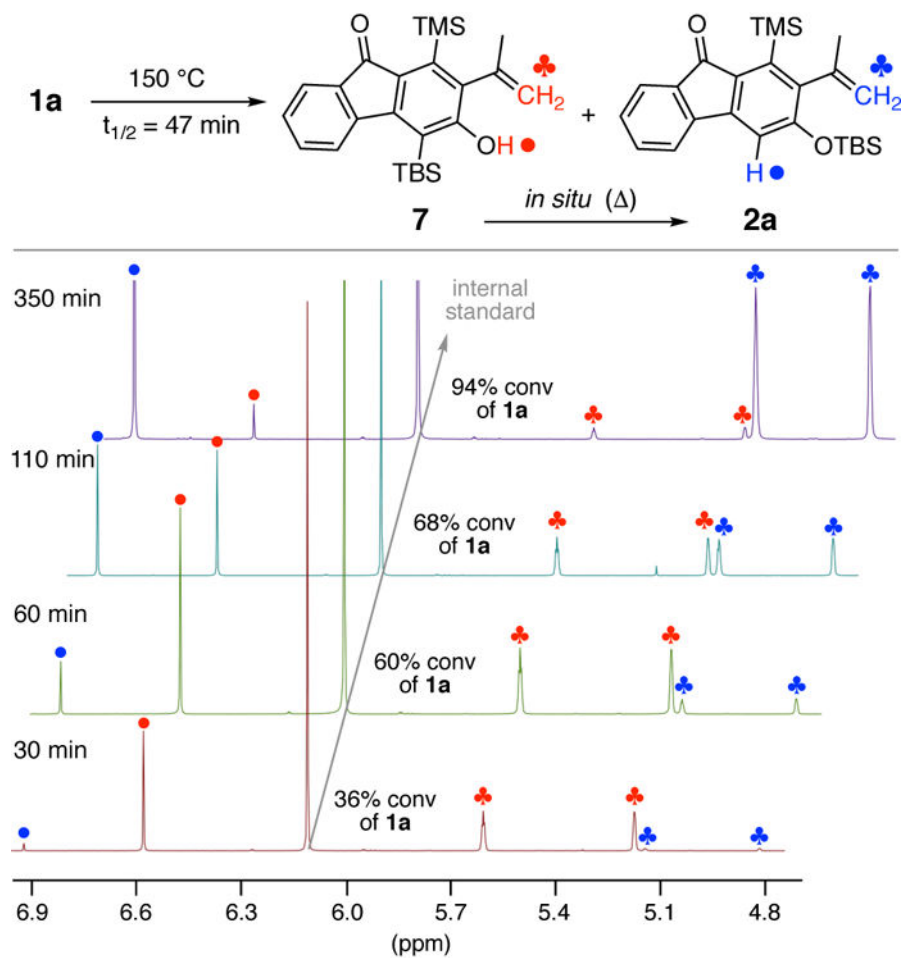**Figure 1.**
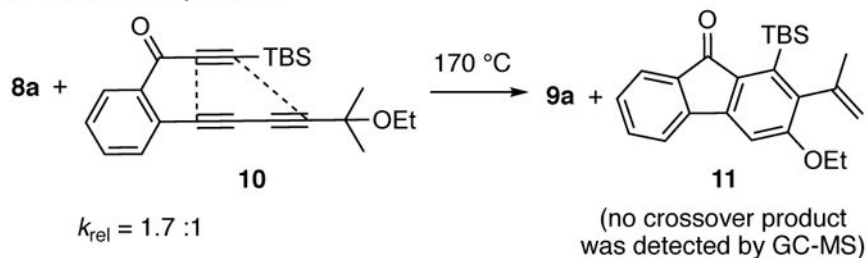Generation of *o*-quinone methides via benzynes.
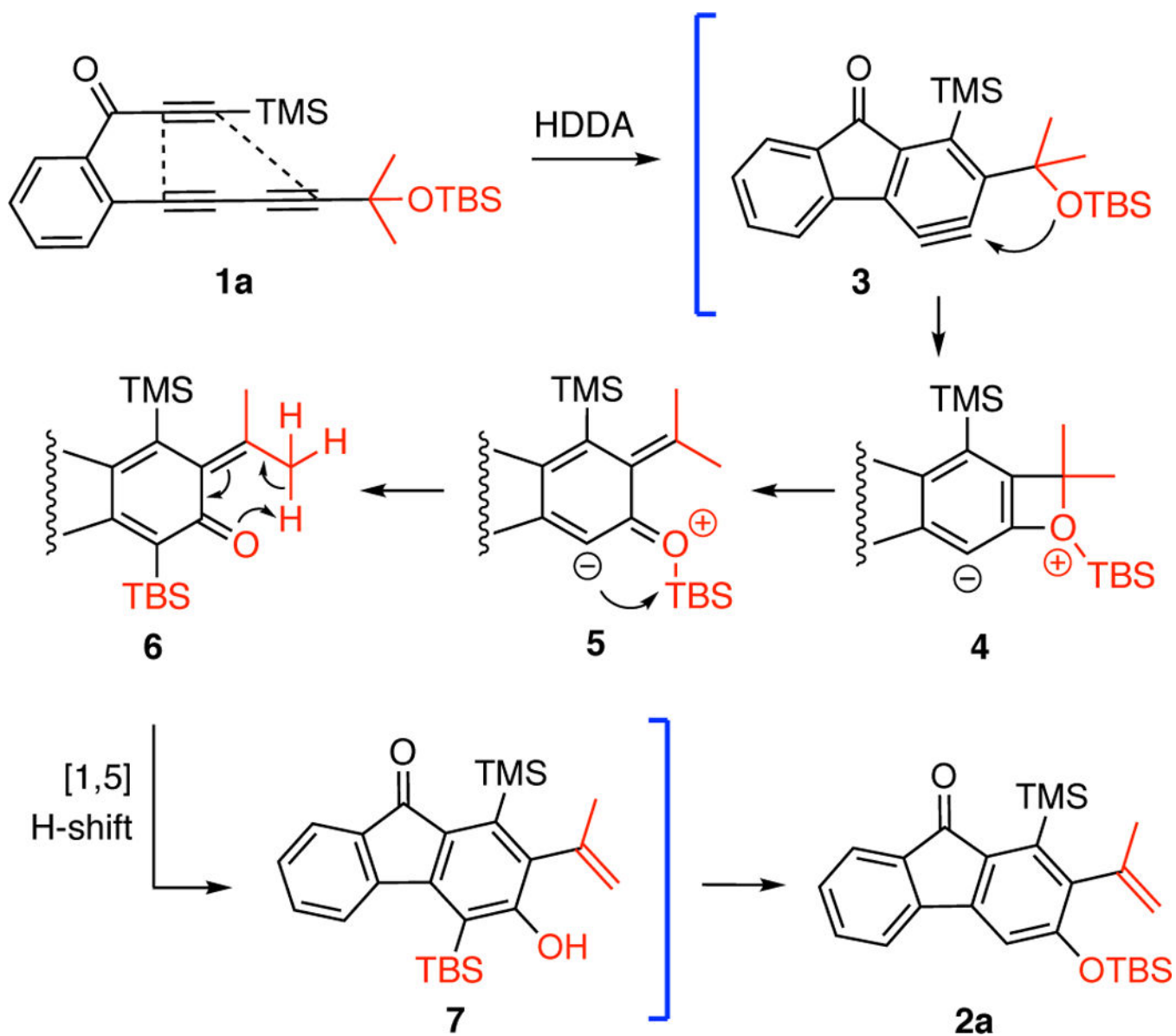
Figure 2.
A proposed mechanism for the conversion of **1a** to **2a**.
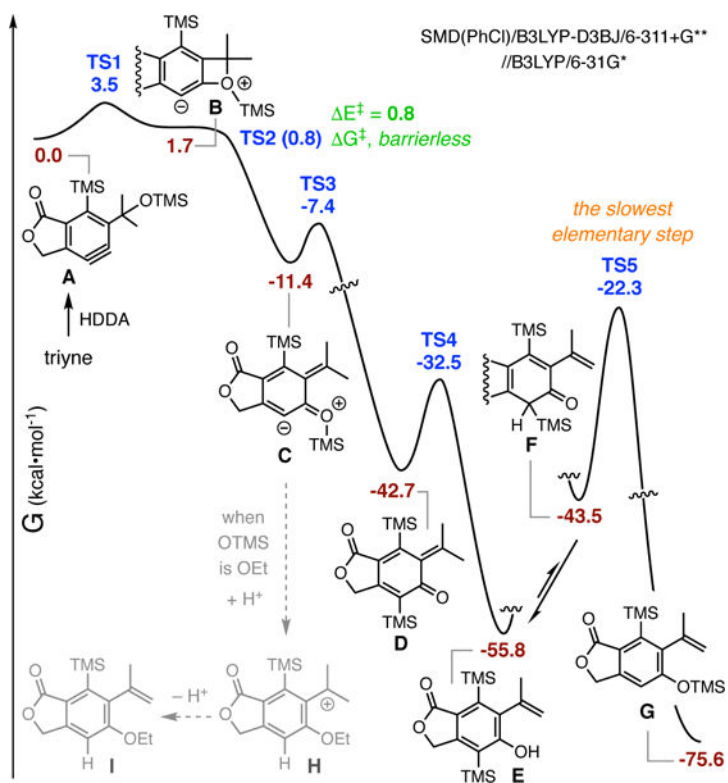
Figure 3.
Computed energy profile (See Figure S1 in Supporting Information for more details).

Figure 4.
^{1}H NMR monitoring and crossover experiment. [a]1,3,5-Trimethoxybenzene was used as an internal standard (IS) to monitor the conversion of **1a**; the indicated %conversions were measured by integration of a unique aromatic resonance for **1a** vs. the IS.
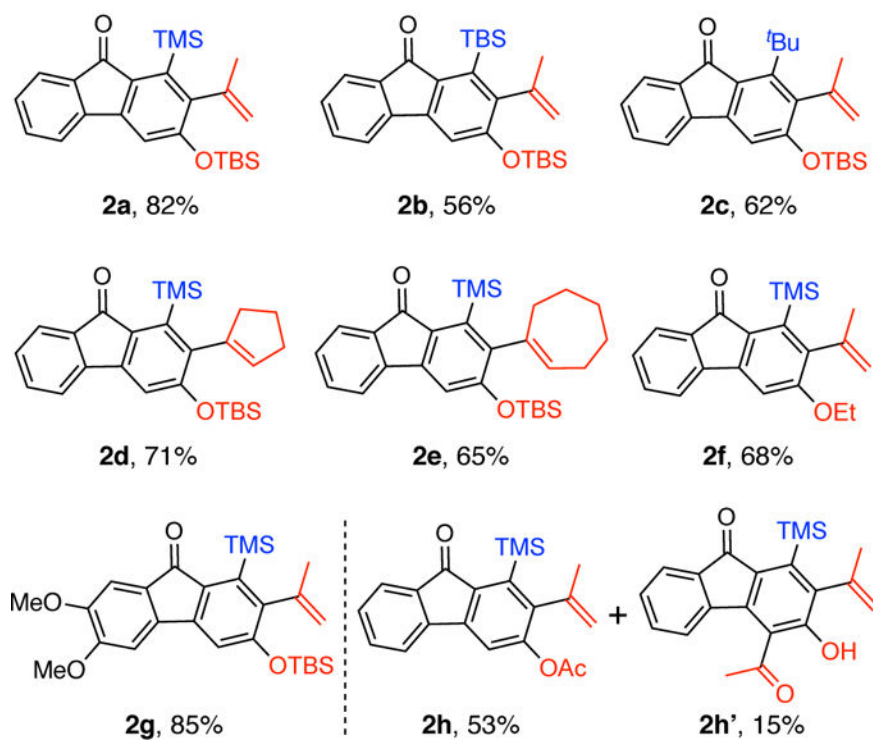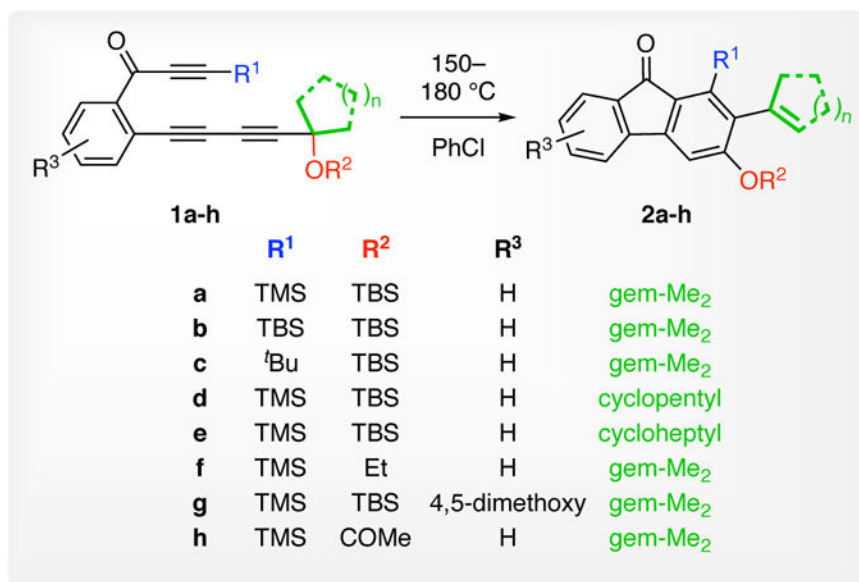
Chart 1.
The major products (2a-h) isolated from reactions of triyne precursors 1a-h.[a]
[a] Yields are for isolated, purified (SiO₂) material.
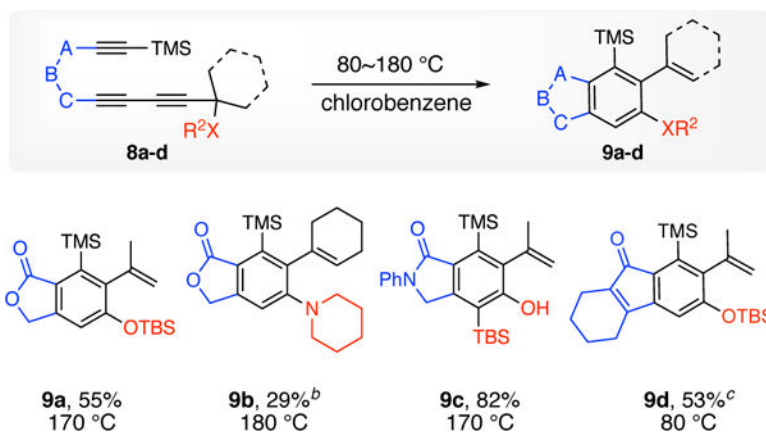
Chart 2.

The major products (9a-d) isolated from triyne precursors 7a-d[a].

[a]Yields are for isolated, purified (SiO$_2$) material. [b]DCB was the reaction solvent; **9b** was the major compound seen in the crude product mixture (^{1}H NMR analysis). [c]Chloroform was the reaction solvent.