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Photochemically driven tandem process in the construction of a biscyclopropylcage from 2,5-dimethoxy-*p*-benzoquinone and terminal acetylenes

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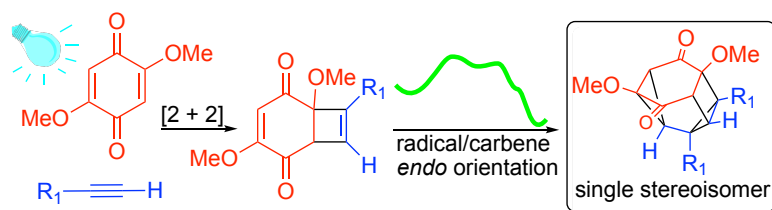
ABSTRACT: A photochemical two-step one-pot synthesis of novel biscyclopropyl-box-shaped compounds via reaction of 2,5-dimethoxy-para-benzoquinone and monosubstituted alkynes is reported. The reaction mechanism for a process in which six new C–C bonds are formed is explored by means of experimental and computational techniques. The whole process occurs with complete selectivity and only one densely decorated diastereomer is obtained, such degree of control and substitution makes for a rather powerful and complexity-building process.

Photochemical reactions provide a way to obtain compounds with structural complexity that cannot be accessed otherwise. High-energy excited electronic states permit bond forming events that are out of reach with thermal methods.[1] In fact, light-mediated reactions have proven to be key steps in the synthesis of numerous natural products.[2] In this regard, cyclobutenes represent an interesting organic framework susceptible to further transformations enabling the generation of complex polycyclic compounds.[3-5] Cage-like rigid molecules[6,7] are of particular interest due to their unique properties and potential applications in the field of biology or medicinal chemistry.[8,9]

In the search for new methodologies to form C-C bonds that would be of difficult access by conventional methods, we explored the photoaddition of alkynes to *p*-benzoquinones to obtain functionalized fused cyclobutenes en route to more complex molecular scaffolds.[10,11]

We anticipated competition between C=C and C=O bonds to provide acylquinomethanes (**D**) through unstable spiro-oxetene intermediates (**C**), or cyclobutene adducts (**E**) (Scheme 1). Therefore, based on the results reported by Portnay in 1969,[12] we considered 2,5-dimethoxy-*p*-benzoquinone a good starting point.

Firstly, we initiated the studies with 2,5-dimethoxy-*p*-benzoquinone as **A** and phenylacetylene as **B** to render fused cyclobutenes **E** and **F**, which could undergo further stereo-controlled rearrangements. The irradiation of a mixture of dimethoxy-benzoquinone and alkyne suspended in acetonitrile in N₂ atmosphere using a Hanovia UV lamp (450 W) rendered two different species in a 1:8 ratio (entry 1, Table 1).

Scheme 1: Chemoselective photoaddition of p-benzoquinones and alkynes
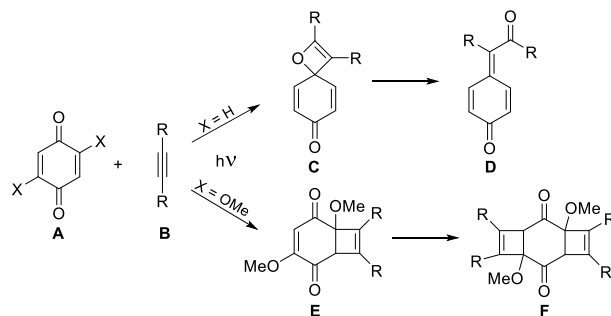
The more polar compound was quickly identified as monoadduct **3a** (Figure 1a). Of the two possible regioisomers (**3a** and **3a'**, Figure 1a) only **3a** was observed due to the regioselectivity of the photochemical event likely governed by the formation of the most stable diradical,[13] one radical ipso to the strongly electron donating methoxy group and the other one at the benzylic carbon atom in a stepwise [2+2] process.[14]

The major compound exhibited spectral signatures that did not match with the regioisomer **3a'** or the expected double-adduct (**F**). The ^{1}H-NMR (Figure 1b) showed two new sets of doublets between 3.74 and 2.85 ppm, absence of alkene resonances and 10 aromatic protons. These data pointed to the incorporation of two alkyne molecules, a fact that was confirmed by MS. To help us elucidate the structure, phenylacetylene-D was submitted to the same reaction conditions. In this case, the signals at 3.74 and 3.25 ppm disappeared and the

doublets at 3.27 and 2.85 ppm showed as singlets (Figure 1c), suggesting that perhaps a broad rearrangement occurred at the molecular scaffold to afford a complex and unanticipated pentacyclic[4.4.0.0^{3,9}.0^{5,7}.0^{2,10}]decandione **4a** (see the SI for numbering and full name). Gratifyingly, the proposed structure was confirmed by single crystal X-ray diffraction analysis (Figure 1d).
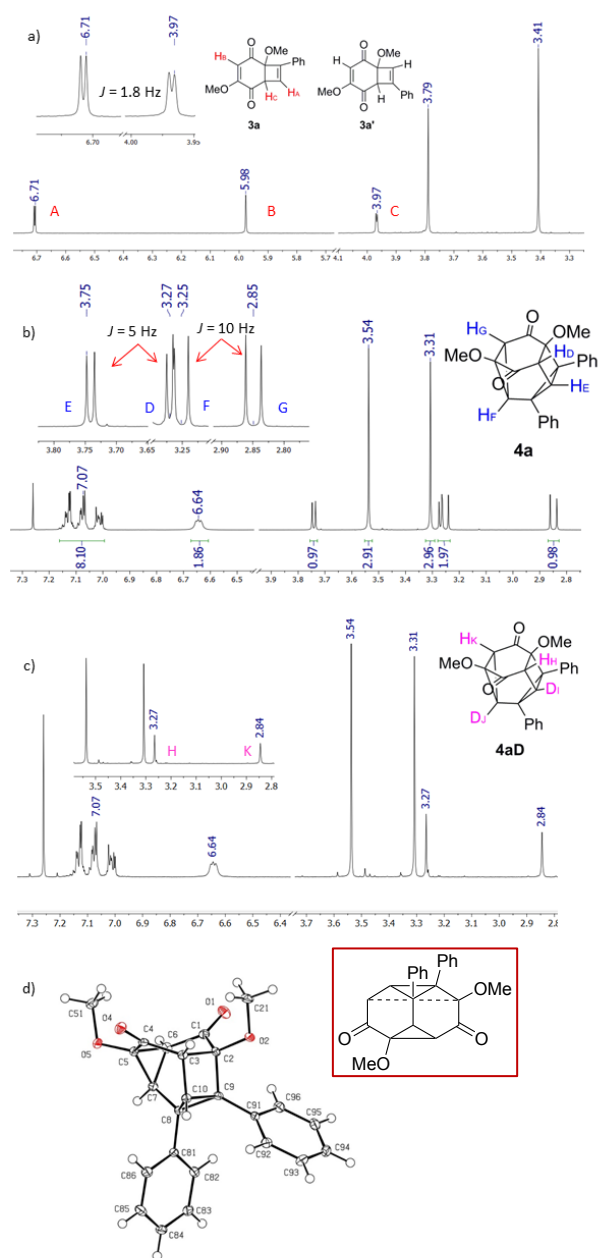

Figure 1. a) Structures of the two possible regioisomers of the phenylacetylene monoadduct **3a** or **3a'** and the ^{1}H-NMR spectra. b) ^{1}H-NMR spectra of **4a**. c) ^{1}H-NMR spectra of **4aD**. d) Crystal structure of **4a** (ellipsoid contour at 50% probability levels).

A photochemical two step-one pot reaction afforded a box-shaped compound, **4a**, in 49% yield containing a 1,1'-bicyclopropane unit (entry 2, Table 1), which was obtained as a result of four new C-C bonds being formed from monoadduct **3a**. Furthermore, the whole process occurred with high selectivity and only one diastereomer was obtained, which is quite remarkable considering that 8 carbon atoms out of the 10 that

make up the cage scaffold are chiral. This degree of control would be very difficult through conventional means. The overall mechanism for this process therefore needs to explain not only the product formation, but also this extraordinary selectivity.

Precedents of biscyclopropyl systems formation dates back to 1968 when Woods and coworkers prepared a tetracyclic-octane upon irradiation of cyclohexan-1,4-diene and internal acetylenes.[15] More recently, Alabugin´s group improved these results via the participation of acetylene triplet excited states by using alkynes with effective ISC.[16,17]

To explain our results, we decided to carry out a combined experimental-computational exploration. Initially, at least two possible mechanistic pathways can be proposed to reach to the cage system: 1- Formation of the expected double adduct **F** or the adduct involving the cyclobutene fragment double bond and subsequent rearrangements or 2- a double cheletropic-type reaction between the alkyne and intermediate **E**. Neither double adducts described above were ever observed during the course of our experiments. Given the regio- and stereocontrol of this reaction we suspected the operating mechanism was likely based on a concerted reaction. To tentatively explore the ground state surface for this process we searched for a potential pericyclic transition state responsible for this double cheletropic addition. However, this exploration was unsuccessful. A scan of the bond cleavage started from the molecular cage shows a cusp-type energy profile which strongly suggests that the concerted process is forbidden under symmetry rules (Figure 2). This is actually in agreement with the need for photochemical activation.
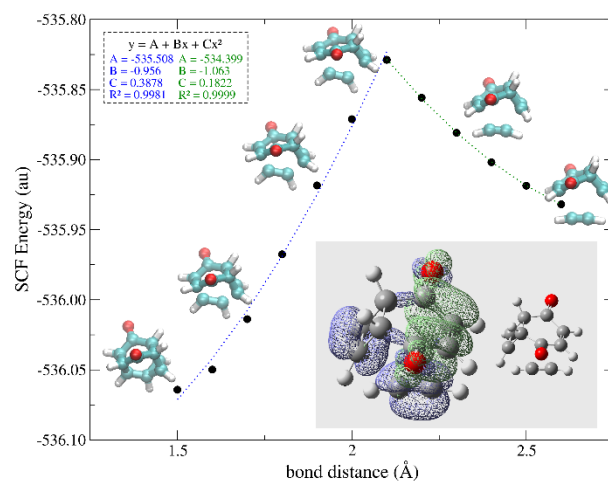

Figure 2. SCF energies vs bond distance for a relaxed scan assuming the concerted and synchronous bond formation of the four C—C bonds. Quadratic fits in blue and green to illustrate the cusp-like shape of the plot. Inset: electron density difference between the ground state and the lowest lying excited state with non-zero oscillator strength for the starting complex (at an isovalue of 0.0025 au) alongside with a smaller copy of the molecule in the same orientation for reference.

Next, we probed the photoactivation starting with a weakly bound Van der Waals complex of the alkyne and monoadduct **E** obtained from the aforementioned scan via TDDFT.[18] Interestingly, upon vertical excitation towards the S1 state a nearby and energy accessible transition state was found (Figure 3). However, this key transition state is not of concerted nature and is responsible for the formation of a single C–C bond between the alkyne and the monoadduct at its cyclobutene

moiety, thus producing a diradical species, **TS1$_{S1}$**. Following the intrinsic reaction coordinate downhill,[19] we located a surface crossing area between S1 and the ground state (S0). Surprisingly this crossing occurs in the vicinity of a transition state in the ground state surface responsible for the diradical collapse process and the formation of the cyclopropyl system onto the cyclobutene ring. This step produces a fleeting carbene intermediate, **INT1$_{S0}$**, that, due to stereoelectronic effects during the formation of the initial cyclopropane ring, is initially oriented away from the molecular scaffold and therefore not prone to react. A low-lying transition state, **TS3$_{S0}$**, however, activates its rotation to face the remaining double bond in the polycyclic system and once fully rotated an extremely asynchronous addition occurs.

The boomerang mechanism proposed by Alabugin and coworkers involving intersystem crossing (ISC) to the triplet state was also computed.[16] Interestingly the triplet state is compatible not only with this mechanism, but also with a reaction path similar to that described above for the singlet state (Figure 3). In the three alternatives the reaction would be facile since the reaction profile is mostly downhill from the initial vertical excitation. If we consider the dynamics of a reaction occurring on the singlet surface however, the reaction would be essentially barrierless due to the fleeting intermediates involved and it therefore seems unnecessary to summon ISC to the triplet state and back to obtain the final cage. This is certainly speculative but is supported by the radically different behaviour of this reaction and those reported by Alabugin. In this reaction terminal alkynes render the final product swiftly whereas Alabugin enhances the ISC process via disubstituted alkynes.

In summary, it seems that all the bond forming steps in this process are highly disconnected in terms of their timing (and their location on the potential energy surface).[20] The photoactivation process allows for the initial C–C bond formation with the consequential production of a very high energy excited intermediate that quickly relaxes onto a high energy area of the ground state surface. Once back at the ground state a cascade of radical and carbene mediated processes are responsible for the formation of the remaining three C–C bonds in a sequential fashion.
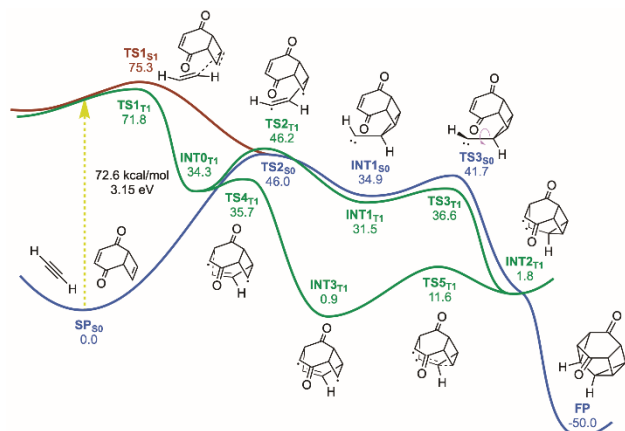

Figure 3. Computed reaction profile for the endo approach of ethyne onto an unsubstituted model of adduct **E**. In yellow the vertical excitation, in blue the ground state surfaces for the endo trajectory, the excited triplet (green) and singlet (red) state chemistry.

Given the extremely facile and exothermic nature of the final carbene addition step, the selectivity of the process is dictated by the initial C–C bond formation which seemingly occurs at the more reactive benzylic site of the phenylacetylene fragment in an endo orientation. We hypothesize that an initial exo approach would result in a highly unstable carbene intermediate that, unable to quickly add intramolecularly to a double bond, reverts back to the starting materials via a retrocheletropic step (see the SI). This process would therefore not have deleterious effects on the reaction yield or its selectivity. Once armed with this mechanistic picture, we realized that the overall process of the formation of the 6 C–C bonds from the quinone system can be divided in two drastically different steps, an orbital symmetry controlled [2+2] cycloaddition and a cascade governed by electron deficient species (radical and carbene intermediates).

These characteristics invited us to test experimentally how the overall reaction responds to alkynes with different electronic and steric demands. Such exploratory reactions were run under the same conditions that have been used with **2a**, and the results are summarized in Table 1.

When internal alkynes were used, such as **2c** or **2d** no reaction took place and starting materials were recovered (entries 4 and 5, Table 1). Diphenylacetylene **2b** showed some reactivity rendering only the corresponding monoadduct **3b** in low yield (entry 3, Table 1); similarly, tert-butylacetylene **2e** rendered only **3e** (entry 6, Table 1).

To better understand the electronic effect of the substituents in the aromatic ring, the *para*-substituted aryl groups **2f** (*p*MeO-) and **2g** (*p*NO$_2$-) were used.

Table 1. Photoaddition products in the presence of alkynes of different nature.

entry	Alkyne	R$_1$	R$_2$	Products	Yield (%)
1	2a(D)	Ph	H/D	3a/4a	5/40
2	2a	Ph	H	3a/4a	-/49[a]
3	2b	Ph	Ph	3b/4b	8/-
4	2c	CO$_2$Me	CO$_2$Me	3c/4c	-
5	2d	TMS	Me	3d/4d	-
6	2e	C(CH$_3$)$_3$	H	3e/4e	28/-[b]
7	2f	4-OMePh	H	3f/4f	70/-[c]
8	2f	4-OMePh	H	3f/4f	50/12
9	2g	4-NO$_2$Ph	H	3g/4g	15/-

Reaction conditions: A suspension of **1** (1 eq) and alkyne **2** (9 eq) in acetonitrile (0.03 M for **1**) was irradiated for 11 h at RT and N$_2$ atmosphere: [a] 12 h; [b] 22 h; [c] 3.5 h.

Thus, when the mixture of 2,5-dimethoxybenzoquinone (**1**) and **2f** was irradiated benzoquinone **1** was totally consumed and monoadduct **3f** and biscyclopropyl-box **4f** were obtained in 50 and 12% yield, respectively (entries 7 and 8, Table 1). 1H-NMR monitoring of the progress of reaction (Figure 4a) showed the disappearance of **1** after 3.5 h, which led to monoadduct **3f** being isolated in 70% yield (entry 7, Table 1). In the case of **2g**, the reaction to monoadduct **3g** is slower and after 3 hours of reaction **3g**:**1** ratio was 1.2:1 (Figure 4b). When the mixture was irradiated for 11 hours only **3g** was

isolated (table 1, entry 9). It seems therefore that the best polarity match for the [2+2] cycloaddition involves using an electron rich alkyne. On the contrary, when electron poor alkynes are employed, both the [2+2] and the radical cascade are severely hampered. These results seem reasonable when considering that both sequential reactions ultimately involve species with electron deficient carbon atoms.
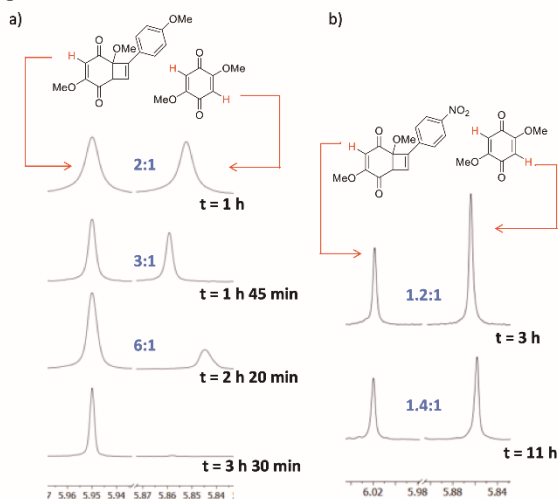

Figure 4. a) Reaction progress monitored by ^{1}H-NMR between **1** and a) **2f** and b) **2g**. The ratio in blue was calculated considering protons in red.

In summary, we have developed a two-step one-pot photochemical reaction to access a highly complex pentacyclic decandione cage in which six new C–C bonds are formed with high selectivity from readily available starting materials, such as 2,5-metoxy-*p*-benzoquinone and substituted alkynes. DFT calculations allowed us to gain insight into the mechanism, in which the overall process seems to be directed by a [2+2] cycloaddition and a subsequent double formal cheletropic addition. The latter actually spans into a cascade of separated single C-C bond formation steps involving radical and carbene intermediates. We also observed that an alkyne bearing an aromatic ring is necessary to obtain the box-shaped product and that the nature of its substituents greatly influence the outcome of the reaction. These biscyclopropylcages are sufficiently decorated with functional groups to ignite further transformations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, spectroscopic characterization, X-ray data and theoretical calculations (pdf). FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds: 3a, 3aD, 3b, 3e-3g, 4a, 4aD, 4f.

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