

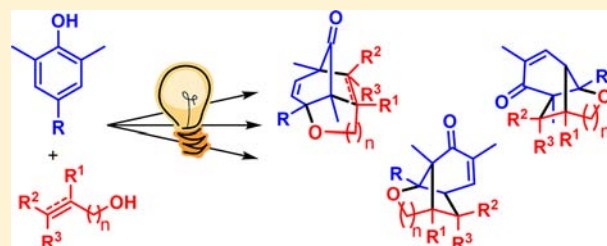
# Tandem Dienone Photorearrangement–Cycloaddition for the Rapid Generation of Molecular Complexity

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**S** Supporting Information

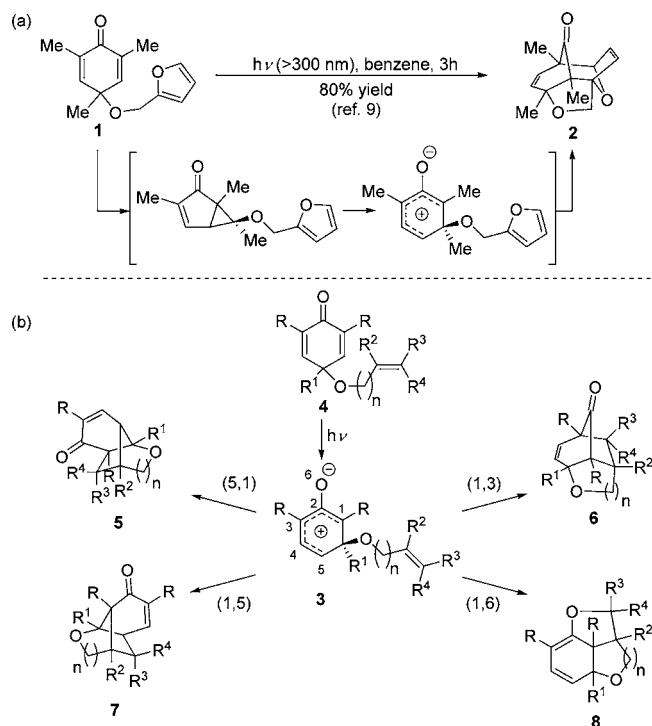
**ABSTRACT:** A tandem dienone photorearrangement–cycloaddition (DPC) reaction of novel cyclohexadienone substrates tethered with various  $2\pi$  and  $4\pi$  reaction partners resulted in the formation of polycyclic, bridged frameworks. In particular, use of alkynyl ether-tethered substrates led to  $(3 + 2)$  cycloaddition to afford strained alkenes which could be further elaborated by intra- and intermolecular cycloaddition chemistry to produce complex, polycyclic chemotypes.



## INTRODUCTION

Photochemistry is a useful tool for the generation of architecturally interesting small molecules<sup>1</sup> and is often used as a key step in the synthesis of natural products.<sup>2</sup> In light of these developments, it is surprising that photochemistry is underutilized in the development of novel scaffolds for drug development.<sup>3</sup>

**Scheme 1. (a) Tandem Dienone Photorearrangement by Schultz et al.;<sup>9</sup> (b) Possible Reaction Pathways for Intramolecular  $(3 + 2)$  or  $(5 + 2)$  Cycloaddition with Tethered Alkene Substrates**



As part of a program directed toward the synthesis of novel chemotypes, we have been interested in leveraging the powerful transformations enabled by photochemical excitation for the rapid generation of molecular diversity from simple, readily available scaffolds.<sup>4</sup> Moreover, photochemical transformations are easily parallelized with simple reactor designs<sup>5</sup> and scale-up can be readily accomplished using continuous processing technology.<sup>6</sup> Equally important, photochemical transformations provide access to products with rich topological complexity and stereochemical diversity.

We wished to investigate the photochemical rearrangement of substituted cyclohexadienones to oxallyl cations,<sup>7</sup> versatile intermediates which have found broad applicability in reaction development and complex molecule synthesis.<sup>8</sup> In 1985, Schultz and co-workers demonstrated that dienone photorearrangement of cyclohexadienone **1** led to the formation of an oxallyl cation intermediate which underwent dipolar cycloaddition with a pendant furan to afford the  $(4 + 3)$  cycloadduct **2** (Scheme 1a).<sup>9</sup> While the majority of examples conducted were intramolecular cycloadditions involving carbon-tethered alkenes, Schultz and co-workers also observed intermolecular reactions, albeit in lower chemical yields.<sup>10</sup> A limited study on the factors controlling the mode of cycloaddition showed that substituent effects (both steric and electronic) appear to play dominant roles in determining product distributions.<sup>11</sup>

With the advent of powerful strategies for the oxidative dearomatization of phenols,<sup>12</sup> we were interested in examining the potential of a modular dearomatization-photorearrangement-cycloaddition strategy to generate topologically rich molecular architectures from readily available materials (phenols and  $\omega$ -alkenols or  $\omega$ -alkynols). Specifically, we were interested in determining the factors responsible for divergent, intramolecular  $(3 + 2)$  and  $(5 + 2)$  photocycloaddition pathways of oxallyl

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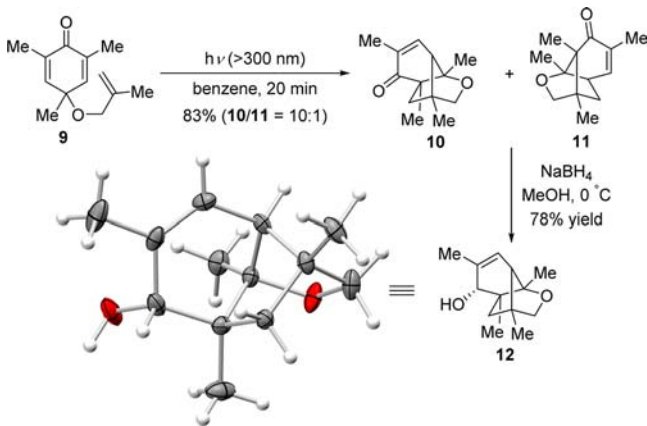
cations **3** derived from substrates **4** (Scheme 1b) to produce bridged (**5**, **6**, and **7**) or fused frameworks (e.g., **8**).

Herein, we report use of tandem dienone photorearrangement-intramolecular cycloaddition (DPC) of alkenyl and alkynyl ether-tethered cyclohexadienone substrates to produce a variety of structurally complex cycloadducts. In particular, use of alkynyl ether-tethered substrates led to (3 + 2) cycloaddition to afford strained alkenes which could be further elaborated to polycyclic chemotypes.

## RESULTS AND DISCUSSION

Our initial investigations focused on substituted cyclohexadienone substrate **9**, readily available via oxidative dearomatization of 2,4,6-trimethylphenol.<sup>13</sup> Having optimized reaction parameters (solvent/concentration/reaction time) for the conversion of **1** → **2** in a multiwelled photoreactor (Scheme 1),<sup>13</sup> we examined dienone photorearrangement–cycloaddition of alkene-tethered substrate **9** (Scheme 2). Indeed, **9** was smoothly converted to a

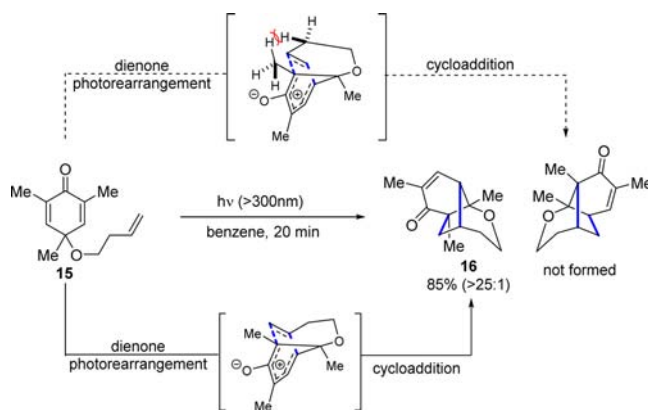
**Scheme 2. Dienone Photorearrangement–Cycloaddition of Alkene-Tethered Substrate 9**



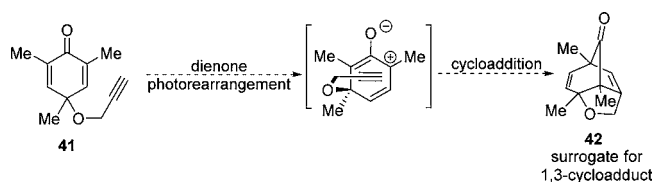
10:1 mixture of the 5,1- and 1,5-bonded products (**10** and **11**, respectively) in 83% isolated yield upon irradiation ( $\lambda > 300\text{ nm}$ ) in benzene at  $20^\circ\text{C}$  for 20 min. Interestingly, 1,3- and 1,6-cycloaddition products were not observed upon irradiation of substrate **9**. In addition, cycloadduct **10** was observed as the major regioisomeric cycloadduct. Although the reason for this outcome was unclear at the time, we observed that the selectivity was attenuated (**10**/**11** = 6:1) when the reaction mixture was not degassed prior to irradiation, presumably due to degradation of the major product under the reaction conditions. The use of polar solvents to potentially stabilize the oxyallyl cation did not change the product distribution.<sup>13,14</sup> Structural assignment of the major isomer was confirmed by X-ray crystallographic analysis of alcohol **12**, obtained as a single diastereomer from reduction of **10**:**11** with  $\text{NaBH}_4$  in methanol (Scheme 2).<sup>13</sup>

We next focused our efforts on evaluating the scope of the reaction (Table 1). Irradiation of substrate **9** with  $>300\text{ nm}$  light in degassed benzene for 20 min afforded the DPC product in a 10:1 ratio of 5,1-/1,5-bonded product in 83% isolated yield (Table 1, entry 1). In most cases, isolation of pure 5,1-products such as **10** was accomplished by a reduction/oxidation sequence.<sup>13</sup> Switching from methyl- to allyl-substituted cyclohexadienone substrate **13** provided similar regioselectivity to afford the 5,1-product **14** in 80% isolated yield (Table 1, entry 2). Elongation of the carbon spacer with an extra methylene group led

**Scheme 3. Mechanistic Rationale for Selective Formation of 5,1-Bonded Cycloaddition Products**



**Scheme 4. Mechanistic Proposal for Selective Formation of 1,3-Bonded Cycloaddition Products**



to complete regioselectivity in which case products **16** and **18** could be obtained in 85% and 78% yield, respectively (Table 1, entries 3 and 4).

Upon replacement of the methyl group in the 4-position of the cyclohexadienone substrate with aromatic substituents, a decrease in regioselectivity was observed in some cases (cf. Table 1, entry 5). Irradiation of diallyl acetal **27** provided the DPC product in 52% yield as a 9:1 mixture of regioisomers (Table 1, entry 6). Substitution of the terminal position of the alkene with an ester moiety led to selective formation of cycloadduct **30** in 80% yield (Table 1, entry 7). Photoirradiation of substrate **31** provided silyl ether product **32** in 53% yield as a 12:1 mixture of 5,1-/1,5-product (Table 1, entry 8); whereas, its corresponding *Z*-isomer gave an indiscernible mixture. Upon irradiation of cyclic alkene-substituted cyclohexadienone substrates, a decrease in yield and regioselectivity was observed (Table 1, entries 9 and 10).

As depicted in Scheme 1, irradiation of cyclohexadienone substrate **1** bearing a tethered furan led solely to the formation of (4 + 3) cycloadduct **2** in excellent yield. Substrate **37** bearing a 3-furyl ether connected to the cyclohexadienone moiety did not lead to the formation of the corresponding (4 + 3) cycloadduct. In this case, (5 + 2) cycloaddition was observed to provide a 7:1 mixture of the 5,1- and the 1,5-bonded products in 51% isolated yield (Table 1, entry 11). Substitution of the 5-position of the furyl group of substrate **1** with an ester moiety cleanly afforded the (4 + 3) cycloadduct **40** in 81% isolated yield (Table 1, entry 12).

To rationalize the observed preference for 5,1- vs 1,5-bonded products, we examined molecular models of the zwitterionic intermediate formed after dienone photorearrangement (Scheme 3).<sup>15</sup> Formation of the 1,5-bonded product appears to be disfavored due to steric hindrance between one of the methyl groups on the cyclohexadienone core and the tethered alkene. This disfavored steric interaction is particularly apparent in the case of substrate **15** which provided exclusively the 5,1-product **16** in 85% isolated yield.

Table 1. Substrate Scope for Dienone Photorearrangement–Cycloaddition<sup>a</sup>

Entry	Substrate	Major Product	Yield [%] <sup>b,c</sup>	Entry	Substrate	Major product	Yield [%] <sup>b,c</sup>
1			83 (10:1)	7			80 (>25:1)
2			80 (9:1)	8			53 (12:1)
3			85 (>25:1)	9			67 (4:1)
4			78 (>25:1)	10			73 (4:1)
5			20: 75 (10:1) 22: 63 (4:1) <sup>d</sup> 24: 60 (4:1) <sup>d</sup> 26: 60 (4:1) <sup>d</sup>	11			51 (7:1)
6			52 (9:1)	12			81 (>25:1)

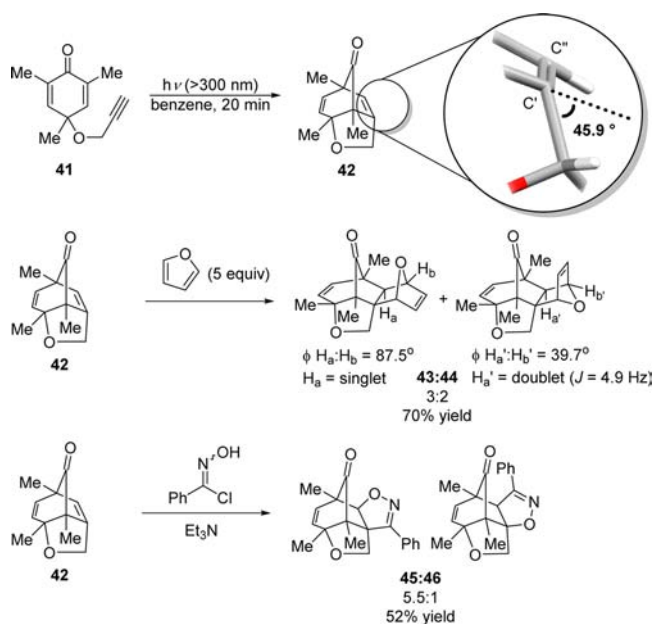
<sup>a</sup>Reaction conditions: substrate (0.25 mmol) in benzene (10 mL) degassed for 30 min followed by irradiation (>300 nm) at room temperature for 20 min. <sup>b</sup>Isolated yield. <sup>c</sup>Regioselectivity determined by <sup>1</sup>H NMR analysis of the crude reaction mixture in parentheses. <sup>d</sup>Isolated yield of the 5,1-product.

On the basis of these results, we surmised that the use of a tethered alkyne in the cycloaddition may provide a surrogate for the formation of the 1,3-bonded cycloaddition product. Examination of transition state models for dienone photorearrangement of substrate **41** (Scheme 4) shows that as a consequence of the linear geometry of the alkyne, cycloaddition to form 5,1- or 1,5-adducts is geometrically impossible.

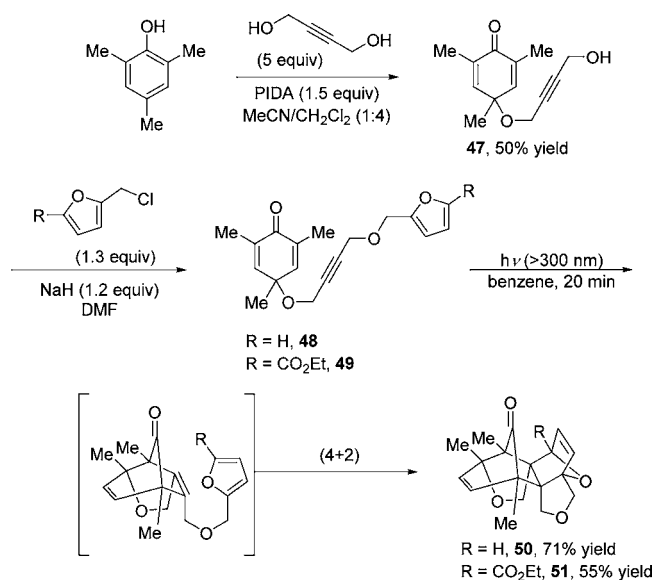
To test this hypothesis, we prepared alkyne-tethered cyclohexadienone substrate **41**<sup>16</sup> in analogous fashion to the alkene counterparts.<sup>13</sup> Photoirradiation of substrate **41** led to the formation of the (3 + 2) cycloaddition product **42** as predicted by our hypothetical transition state model (Scheme 4). Although adduct **42** was cleanly formed during the photochemical reaction as observed by <sup>1</sup>H NMR analysis of the crude reaction mixture, the product proved to be unstable to attempted chromatographic purification and other isolation attempts (Scheme 5). This

instability can be explained by the strained nature of the system which was also confirmed by DFT calculations (B3LYP/6-31g\*\*), predicting torsion angles for strained alkene **42** up to 45.9° out of the plane ( $\chi_C = 45.9^\circ$  and  $\chi_{C'} = 10.8^\circ$ , see Scheme 5).<sup>17,18</sup> We were able to leverage this high energy intermediate in cycloaddition chemistry by successfully trapping the alkene in an intramolecular (4 + 2) cycloaddition with furan providing a 3:2 mixture of regioisomers (**43/44**) in 70% isolated yield (Scheme 5).<sup>19,20</sup> Although the two diastereomeric cycloadducts were inseparable, the major isomer could be assigned on the basis of coupling constant analysis (**43**, H<sub>a</sub>, singlet, calculated dihedral angle H<sub>a</sub>:H<sub>b</sub> = 87.5° and **44**, H<sub>a</sub>', doublet, J = 4.9 Hz, calculated dihedral angle H<sub>a</sub>':H<sub>b</sub>' = 39.7°).<sup>21</sup> Intramolecular dipolar cycloaddition with in situ-generated benzonitrile oxide<sup>22</sup> afforded a 5.5:1 mixture of tetracyclic regioisomers **45/46**.

## Scheme 5. Trapping of Unstable, Strained Alkene 42 by Cycloaddition with Furan or a Nitrile Oxide



## Scheme 6. Tandem DPC/Intramolecular (4 + 2)-Cycloaddition To Afford Complex Polycyclic Chemotypes



Inspired by the successful intermolecular transformations utilizing strained alkene intermediate **42**, we envisioned that the use of alkynyl ether substrates tethered with furfuryl ethers (Scheme 6, **48** and **49**) would lead to the formation of highly complex, polycyclic structures. Oxidative dearomatization of trimethylphenol with 1,4-butanediol using PIDA followed by etherification of the resulting alkynyl **47** provided the substituted dienone substrates **48** and **49** in two steps. Photoirradiation of **48**, **49** for 20 min cleanly afforded polycyclic compounds **50** and **51** in good isolated yield as single diastereomers. The structural assignment of **50** was confirmed by X-ray crystallographic analysis (Figure 1).<sup>13</sup> It is noteworthy that four new bonds are formed in the tandem DPC/(4 + 2) sequence which produces a highly complex architecture, containing six rings and seven stereogenic centers.

Figure 1. X-ray crystal structure of polycyclic compound **50**.<sup>13</sup>

## CONCLUSION

In summary, we have employed a dienone photorearrangement–cycloaddition (DPC) sequence for the synthesis of highly functionalized, bridged tri- and tetracyclic frameworks. Photoirradiation of alkynyl ether-tethered cyclohexadienones led to the favored production of 5,1-bonded (5 + 2) cycloaddition products. Alternatively, use of alkynyl ether-tethered substrates led to (3 + 2) cycloaddition to afford strained alkenes which could be further elaborated by both inter- and intramolecular cycloaddition chemistry to produce complex polycyclic adducts. Further studies on reactions of strained alkenes produced by DPC as well as biological studies of the chemotypes and derived adducts are currently in progress and will be reported in due course.

## ASSOCIATED CONTENT

## Supporting Information

Experimental procedures and spectral data including <sup>1</sup>H NMR, <sup>13</sup>C NMR, and HRMS for all new compounds and X-ray structure analysis of compounds **12** and **50**. 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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