

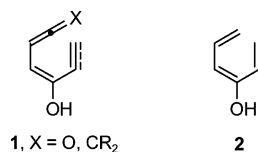
## Remarkably Facile Hexatriene Electrocyclizations as a Route to Functionalized Cyclohexenones via Ring Expansion of Cyclobutenones

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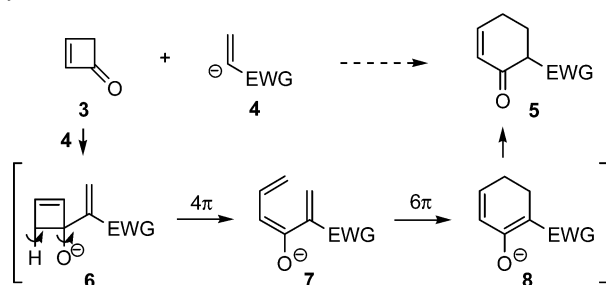
Cascade electrocyclic reactions based on cyclobutene ring expansion have been used for the synthesis of a variety of carbocyclic systems.<sup>1</sup> Transformations of cyclobutenones to the six-membered carbocycles typically involve  $6\pi$ -electrocyclic ring closure ( $6\pi$ -ERC) of reactive intermediates of type **1**, which incorporate an  $sp$  carbon at the terminus of the  $6\pi$  system to facilitate the ring closure reaction.<sup>2</sup> As a consequence, these reactions produce products containing all  $sp^2$ -hybridized ring carbons, such as phenols and quinones. Reactions of cyclobutenones leading to the synthetically more versatile cyclohexenones by  $6\pi$ -ERC of the parent 3-oxy hexatrienes (**2**) have not been reported.<sup>3</sup>



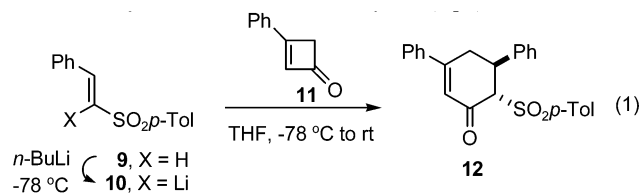
In this Communication we describe a cascade reaction sequence that leads to highly functionalized cyclohexenones starting from reaction of cyclobutenones with  $\alpha$ -lithio- $\alpha,\beta$ -unsaturated sulfones and amides. The hexatriene–cyclohexadiene cyclization steps presumed to be involved in these transformations are among the most facile hexatriene electrocyclizations reported thus far.

We imagined that reaction of enone **3** with vinyl anion **4** containing an electron-withdrawing group at the anionic carbon, followed by a charge-accelerated four-electron conrotatory ring opening of the cyclobutene, would generate a hexatriene intermediate **7** (Scheme 1).<sup>4</sup> The  $6\pi$ -ERC of **7** was expected to be exceptionally facile because bond reorganization leads to the more stable enolate **8**. This cyclization can also be formally considered as an intramolecular Michael addition of an extended enolate to an electron-deficient alkene. We reasoned that  $\alpha$ -lithiated  $\alpha,\beta$ -unsaturated sulfones would be convenient nucleophiles for the proposed reaction. These compounds can be generated by the reaction of readily available  $\alpha,\beta$ -unsaturated sulfones with alkyllithiums or lithium amides.<sup>5</sup>

### Scheme 1. Proposed Transformation of Cyclobutenones into Cyclohexenones

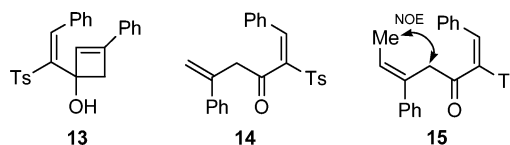


Initial experiments demonstrated that treatment of sulfone **9** with  $n$ -BuLi at  $-78$  °C, followed by addition of cyclobutenone **11** and warming the reaction mixture to room temperature, produced the desired cyclohexenone **12** in 81% yield (eq 1). The structure of **12**



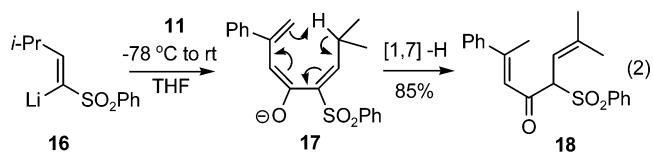
with the two substituents at the adjacent stereocenters *trans* and pseudoaxial was unequivocally established by X-ray crystallographic analysis. Notably, reaction of **11** with  $\beta$ -(*E*)-lithiostyrene stopped after the cyclobutene ring opening,<sup>6</sup> indicating that the presence of an electron-withdrawing sulfonyl group in **10** was essential for the  $6\pi$ -ERC to occur. The mild conditions for the formation of **12** are noteworthy, because  $6\pi$ -ERC of hexatrienes typically requires thermal activation.<sup>7</sup> The observed reactivity is comparable to that of methylenepropenyldienecyclohexadienes, which undergo fast thermal  $6\pi$ -electrocyclic reactions proceeding at room temperature.<sup>8</sup>

We believed that quenching the reaction between **10** and **11** at low temperature ( $-78$  °C) would allow for the isolation of reaction intermediates. Indeed, this reaction produced alcohol **13** (61%) and a ring-opened compound **14** (23%), the conjugated acids of the two intermediates postulated in the reaction. Treatment of **13** with LDA (1.2 equiv,  $-78$  °C to room temperature) cleanly furnished cyclohexenone **12** in 94% isolated yield.<sup>9</sup> As expected, the reaction of **10** with 4-methyl-3-phenylcyclobutenone produced the ring-opened compound **15** as a single isomer at the double bond, indicating that the cyclobutene ring opening was conrotatory with an outward rotation of the oxide group.<sup>10</sup>



Having established proof of principle for the proposed cascade, we next investigated the scope of the process (Table 1). Nucleophiles containing aromatic, heteroaromatic, and *tert*-alkyl substituents were well tolerated (entries 1–4). Entry 4 illustrates the potential of this reaction for the formation of cyclohexenones with quaternary carbon centers.

Interestingly, the sulfones containing allylic hydrogen atoms in a *trans* relationship to the sulfonyl group displayed a different mode of reactivity. Thus, the addition of **16** to **11** did not produce a cyclohexenone but instead gave rise to the formation of an open-chain enone **18** in 85% yield (eq 2). Apparently, this compound results



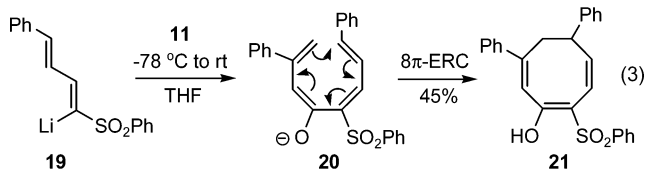
**Table 1.** Synthesis of Cyclohexenones from Cyclobutenones<sup>a</sup>

entry	vinyl lithium	enone	product	yield
1				86
2				57
3				73
4 <sup>b</sup>				63
5 <sup>c</sup>				80
6				52
7 <sup>c</sup>				72

<sup>a</sup> Conditions: THF, -78 °C to room temperature, 1–3 h. <sup>b</sup> Reaction mixture was heated at 65 °C for 1 h. <sup>c</sup> In equilibrium with 10–15% of the cis isomer.

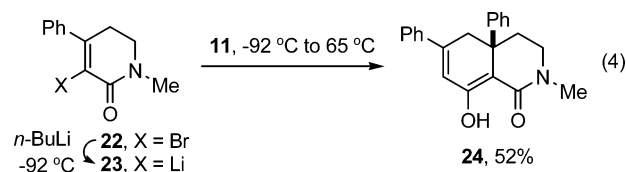
from the competitive [1,7]-sigmatropic hydrogen shift in intermediate **17**. While the driving force for the [1,7]-H shift is also the formation of a stable enolate of a  $\beta$ -ketosulfone, this process effectively contends with  $6\pi$ -electrocyclization. This is in line with the general observation that [1,7]-H shifts are faster than  $6\pi$ -ERC when both of these processes are operative.<sup>8</sup>

Sigmatropic rearrangement can be circumvented by employing a cyclopropyl-substituted sulfone (entry 5), which undergoes clean electrocyclic reaction despite the presence of an allylic hydrogen. In this particular case, the [1,7]-H shift is disfavored as it leads to a highly strained methylene cyclopropane. The sigmatropic rearrangement is geometrically impossible for *Z*-sulfones, and both cyclic and acyclic *Z*-sulfones afford cyclohexenones through  $6\pi$ -ERC (entries 6 and 7).<sup>11</sup> Not unexpectedly, reaction of dienyl sulfone **19** with **11** proceeded via an  $8\pi$ -ERC to produce **21** (eq 3),<sup>12</sup> which exists in the enol form both in the solid state and in solution.



The overall conversion outlined in Scheme 1 is not limited to nucleophiles containing the sulfonyl activating group. Amides are

also good candidates for this reaction (eq 4). Thus, reaction of **11** with **23**, generated from bromide **22** by bromine/lithium exchange, furnished the hydroisoquinoline derivative **24** in 52% isolated yield.



In summary, we demonstrated nucleophilic addition/ $4\pi$ -ring opening/ $6\pi$ -ring closing cascade reactions between cyclobutenones and  $\alpha$ -lithio- $\alpha,\beta$ -unsaturated sulfones and amides leading to functionalized cyclohexenones. Strategic incorporation of electron-withdrawing groups at the C-2 of the 3-oxido hexatrienes significantly lowers the activation energy of the  $6\pi$ -electrocyclizations, which proceed under mild conditions.

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**Supporting Information Available:** Experimental procedures, characterization data for all new compounds, and X-ray data (in CIF format) for **12**, **21**, and bicyclic sulfone (Table 1, entry 6). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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