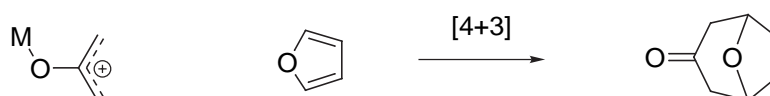


## [4+3] Cycloadditions of Oxyallyl Species

### Introduction

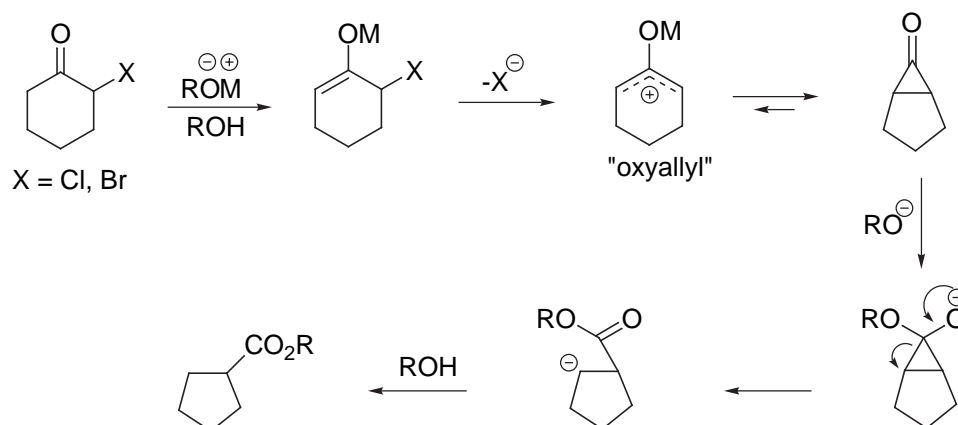
The construction of seven-membered carbocycles via [4+3] cycloaddition has emerged as a powerful synthetic tool in recent years.<sup>1</sup> The success of this transformation depends in large part on the generation of a suitable three-carbon species capable of undergoing cyclocondensation with a 1,3-diene. Allylic cations substituted at the 2-position with an oxygen substituent, termed "oxyallyls", are perhaps the most useful three-carbon unit discovered to date for use in this reaction. Cycloaddition with a suitable diene such as furan affords cycloheptenone derivatives of the general type shown (Figure 1).



**Figure 1. [4+3] Cycloaddition of an Oxyallyl with Furan**

### Discovery

Cyclopropanones were first implicated as reaction intermediates in the Favorskii rearrangement (Figure 2) through the <sup>14</sup>C labeling experiments of Loftfield.<sup>2</sup> Around the same time, Aston and Newkirk



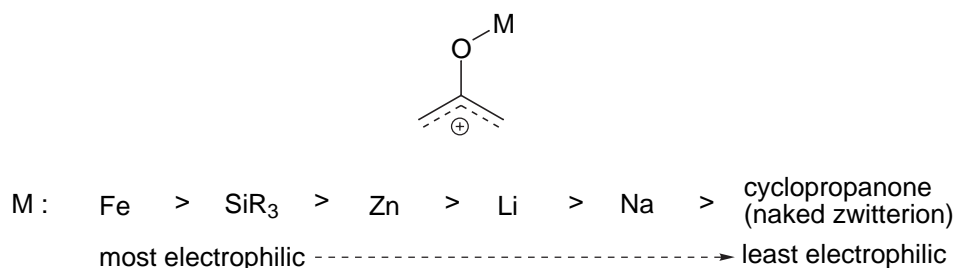
**Figure 2. The Favorskii Rearrangement**

proposed that oxyallyls were formed as transient intermediates in this reaction.<sup>3</sup> It was later established that cyclopropanones existed in tautomeric equilibrium with their much less stable oxyallyl forms, with

interconversion proceeding via a disrotatory pathway.<sup>4</sup> Fort later provided kinetic data in support of these oxyallyl intermediates<sup>5</sup> and found that these reactive species underwent [4+3] cycloaddition in the presence of furan.<sup>6</sup>

### Generation of Oxyallyls

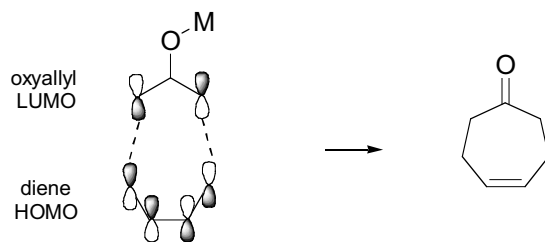
There are several established methods for generating these reactive species. The method chosen has a dramatic effect on the electrophilicity, and hence reactivity, of the resulting oxyallyl. The electrophilicity is a function of the covalency of the O-M bond, as shown in Figure 3.<sup>7</sup> Reaction of  $\alpha,\alpha'$ -dichloro- and dibromoketones with reducing agents such as  $\text{Fe}_2(\text{CO})_9$ , Zn/Cu, and Cu/NaI results in the corresponding metal-coordinated oxyallyl.<sup>8</sup> The  $\text{Fe}_2(\text{CO})_9$  reagent has seen wide use, and the highly covalent nature of the iron-oxygen bond in the oxyallyl so formed makes it one of the most electrophilic species of its kind. Basic conditions, such as those employed in the Favorskii rearrangement, have seen extensive application as well. Föhlisch<sup>9</sup> developed conditions employing the  $\text{CF}_3\text{CH}_2\text{ONa}/\text{CF}_3\text{CH}_2\text{OH}$  system which, because of its attenuated nucleophilicity, suppresses the Favorskii rearrangement for the purpose of promoting [4+3] cycloaddition. The use of Lewis acids to induce oxyallyl formation has also been reported. The silver (I)-promoted ionization of allylic halides<sup>10</sup> and the Lewis acid activation of allylic acetals<sup>11</sup> and 2-silyloxyacroleins<sup>12</sup> are some of the more useful methods published to date. Lewis acid-induced Nazarov cyclization of a dienone has also been shown to generate a suitable oxyallyl for [4+3] cycloaddition.<sup>13</sup> Photochemical methods employing dienone precursors are also known,<sup>14</sup> and oxyallyls have been identified as intermediates in certain photochemical rearrangements.<sup>15</sup>



**Figure 3. Oxyallyl Electrophilicity**

### Mechanism and Scope of Oxyallyl [4+3] Cycloaddition

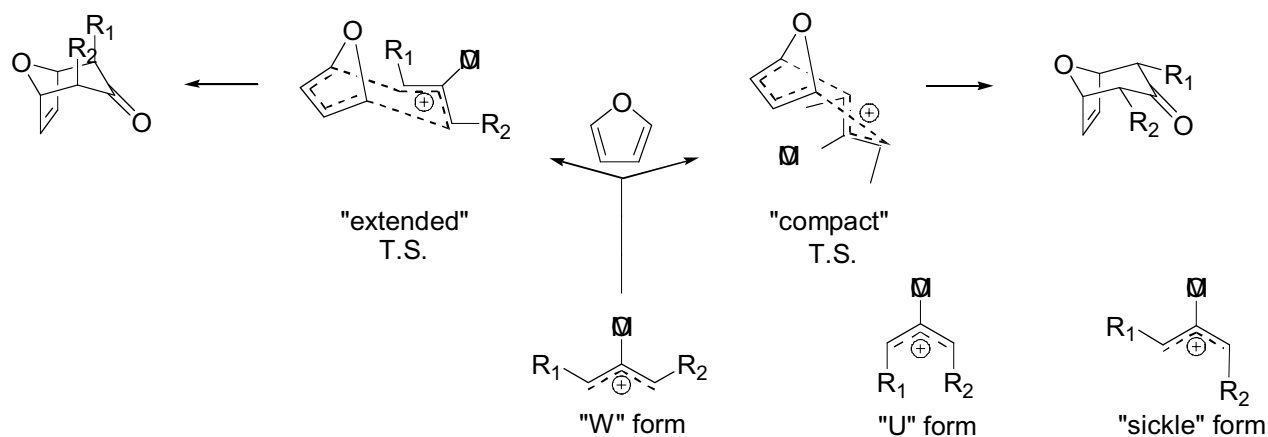
The [4+3] cycloaddition is classified as a  $[2\pi(3C) + 4\pi(4C)]$  process, with the interacting molecular orbitals being the diene HOMO and the oxyallyl LUMO (Figure 4). As with the Diels-Alder



**Figure 4. HOMO/LUMO Interactions for Concerted [4+3] Cycloaddition**

reaction, regioselectivity is subject to control by frontier molecular orbitals, although the reactants in [4+3] processes typically have similar orbital coefficients at the reaction termini.<sup>16</sup> For this reason, the extent of regioselection is normally less pronounced for [4+3] processes. Several examples have been reported, however, in which excellent facial selectivity was achieved through the use of chiral substituents on either the diene<sup>17</sup> or oxyallyl<sup>18,19</sup> component.

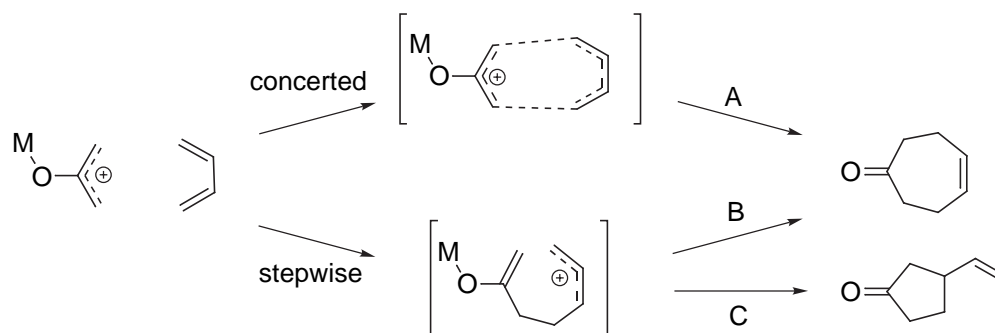
The [4+3] oxyallyl cycloaddition also tends to exhibit high levels of *endo* selectivity, another trait it shares with the Diels-Alder reaction. The terms “compact” and “extended” have been used to describe the *endo* and *exo* transition states, respectively, for [4+3] processes (Figure 5). In general, increasing the



**Figure 5. Extended and Compact Transition States**

electrophilicity of the oxyallyl leads to lower selectivity for the “compact” mode of reaction.<sup>20,21</sup> Since substituted oxyallyl species retain their well-defined conformations during concerted cycloaddition, the nature of these transition states can often be discerned from the relative stereochemistry of the product. Of the three possible conformations, acyclic oxyallyls prefer the “W” form while most cyclic species are constrained to exist in the “U” form. The “sickle” form is favored in only a few cases, and is thought to have manifested in an intramolecular cycloaddition of a cyclodecanone-derived oxyallyl reported by Harmata.<sup>22</sup>

The reaction of oxyallyl species with dienes is commonly classified according to one of the three pathways shown below in Figure 6. Pathway A is a concerted [4+3] cycloaddition, pathway B is the stepwise formation of a [4+3] product, and pathway C gives the formal [3+2] adduct via the cation implied in pathway B. It has been suggested that pathway B actually proceeds via Claisen rearrangement of a 3*H*-dihydrofuran intermediate.<sup>23</sup> Highly electrophilic oxyallyl species show a greater propensity to react in a stepwise fashion.<sup>20,21</sup>



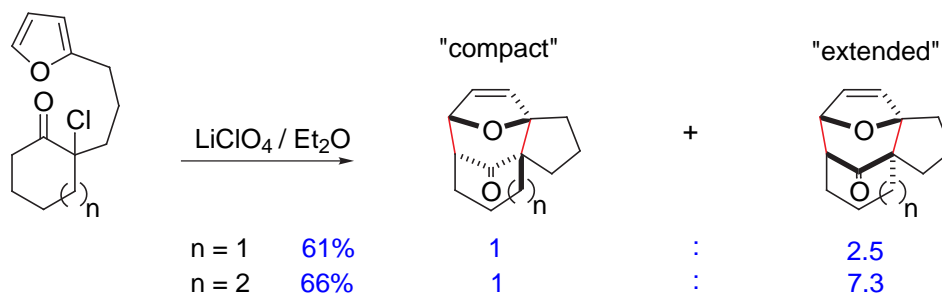
**Figure 6. Pathways for Reaction of Oxyallyls with Dienes**

Suitable diene partners in this cycloaddition consist mainly of those constrained to exist in the *s-cis* conformation. Cyclic diene components such as furan and cyclopentadiene are particularly well suited for [4+3] reaction with oxyallyls for this reason. Few useful examples employing acyclic 1,3-butadiene derivatives are known due to the low equilibrium concentration of *s-cis* conformers. However, cycloaddition of an ( $\eta^4$ -butadiene)-iron(0) complex was reported to give the expected cycloadduct in high yield since the diene is restricted by complexation to exist in the *s-cis* conformation.<sup>21</sup> Dienes such as benzene and *N*-alkyl pyrroles are prone to react by stepwise pathways and can give significant amounts of substitution products, especially when highly electrophilic oxyallyls are employed. Fulvene-derived *O,O*-ketene acetals have been reported to give products of [6+3] cycloaddition with oxyallyls via a stepwise pathway.<sup>24</sup>

### *Intramolecular Cycloaddition*

Many examples of intramolecular [4+3] cycloadditions, wherein the oxyallyl and diene components are connected by a tether, have been reported.<sup>25</sup> Acyclic dienes generally perform better in intramolecular cyclizations than they do in the intermolecular cases, and several useful examples have been reported.<sup>22,25</sup> The usual preference for a “compact” transition state is often suppressed by conformational restraints imposed by the tether, and preferential formation of “extended” products has

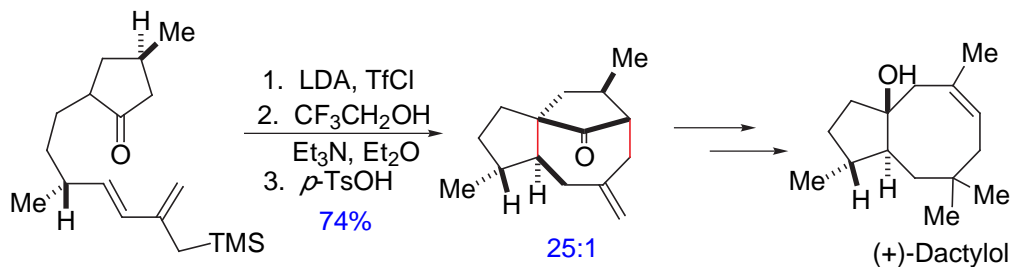
been reported in some cases. An example of this, reported by Harmata and coworkers,<sup>22</sup> is depicted in Figure 7.



**Figure 7. Intramolecular Cycloaddition**

### Synthetic Applications

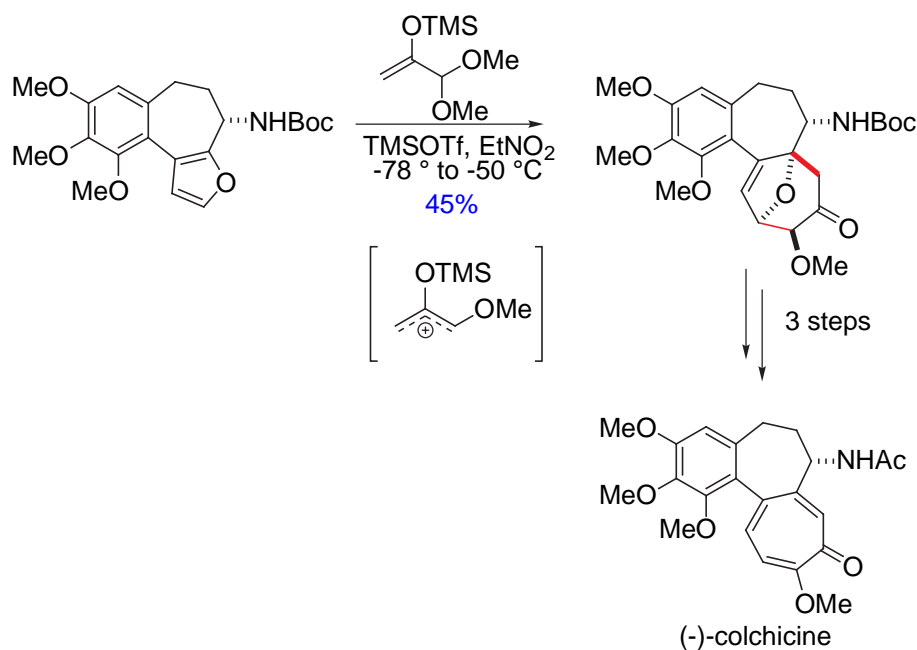
The [4+3] oxyallyl cycloaddition has seen extensive application in the realm of natural product synthesis. Rapid access to the azabicyclo[3.2.1]octane framework of the tropane alkaloids using this methodology has been reported.<sup>26</sup> More recently, a synthesis of the sesquiterpene (+)-dactyol was accomplished by Harmata which featured an intramolecular [4+3] cycloaddition to construct the cyclooctane ring system (Figure 8).<sup>27</sup> Although the methyl-bearing asymmetric center originally present on the oxyallyl component is eventually planarized, it served the purpose of setting the two ring junction stereocenters of the natural product by effecting facial discrimination in the key cycloaddition step.



**Figure 8. Synthesis of (+)-Dactyol**

Another recent natural product synthesis exploited the utility of this reaction in constructing the methylated tropolone ring of (-)-colchicine (Figure 9). Cha reported that the key cycloaddition step proceeded with excellent regioselectivity to establish the desired methyl ether regioisomer in modest yield.<sup>28</sup> Subsequent transformation of the bicyclic cycloadduct to the tropolone system was readily accomplished via Lewis acid activation of the bridgehead oxygen in the presence of triethylamine. The regioselectivity in the [4+3] step is significant since most previous syntheses of alkylated tropolone-containing targets employed a late-stage alkylation of the corresponding enol ketone. Since this enol

ketone exists as a roughly equimolar mixture of two tautomeric forms, a mixture of regioisomeric products invariably results. The [4+3] route delivers the desired regioisomer exclusively, avoiding altogether the complication of enol ketone tautomerization.



**Figure 9. Synthesis of (-)-Colchicine**

### Summary

The [4+3] cycloaddition of oxyallyls has emerged as a powerful tool in organic synthesis. It bears many similarities to the well-known Diels-Alder reaction in terms of orbital symmetry and *endo/exo* selectivity, although the regioselectivity in the [4+3] process is somewhat lower than in the analogous [4+2] process. Facial discrimination can be achieved through the use of chiral substituents on either the oxyallyl or diene component. Many intramolecular examples of [4+3] cycloaddition are also known, providing ready access to a variety of polycyclic skeletons. Consequently, this methodology has found much application in the synthesis of medium-ring carbocycles. The potential for further development of this process appears promising due to the tunable nature of oxyallyl reactivity.

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