

# Intramolecular Oxyallyl–Carbonyl (3 + 2) Cycloadditions

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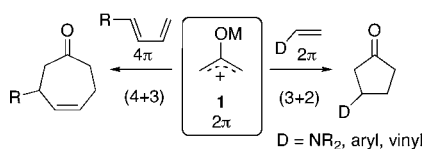
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## Supporting Information

**ABSTRACT:** Cycloadditions involving oxyallyl intermediates typically require an electron-rich diene or alkene, but we have discovered the first examples of the cycloaddition of heteroatom-stabilized oxyallyls onto carbonyl groups. An oxazolidinone-substituted oxyallyl undergoes chemoselective (3 + 2) cycloaddition onto the carbonyl group of a tethered dienone in preference to formation of the expected (4 + 3) cycloadduct. Density functional theory calculations indicated that the (3 + 2) cycloaddition takes place through a concerted, highly asynchronous mechanism. The transition state features simultaneous interactions of the oxyallyl LUMO with the carbonyl  $\pi$  and lone-pair orbitals, making this reaction “hemipseudopericyclic” (halfway between purely pericyclic and purely pseudopericyclic). Further (3 + 2) cycloadditions involving tethered phenyl ketones and a tethered enone were predicted theoretically and verified experimentally.

Oxyallyl cations (**1**) (Scheme 1) are valuable substrates for cycloaddition reactions that provide access to a variety of

## Scheme 1. Generalized (4 + 3) and (3 + 2) Cycloadditions of Oxyallyl Cations

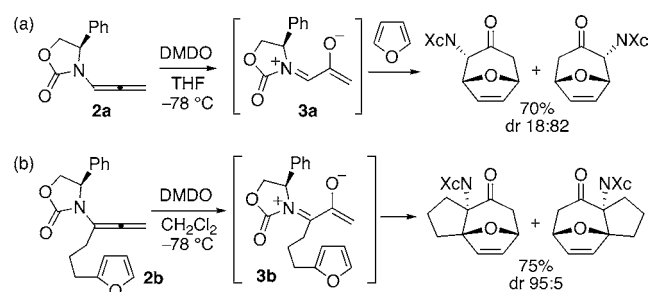


ring types.<sup>1</sup> Both  $[4\pi + 2\pi]$  and  $[2\pi + 2\pi]$  modes of cycloaddition are known under thermal conditions.<sup>2</sup> Important examples are the (4 + 3) cycloadditions with dienes leading to cycloheptenones and the (3 + 2) cycloadditions with alkenes leading to cyclopentanones, respectively. A frequent hallmark of oxyallyl cycloaddition chemistry is a requirement for an electron-rich partner (diene or alkene), since the oxyallyl cation is electrophilic. These polar cycloadditions often have stepwise mechanisms.<sup>3</sup> We have now uncovered an unprecedented type of oxyallyl cycloaddition that displays the opposite

features: a concerted intramolecular (3 + 2) cycloaddition of an oxazolidinone-substituted oxyallyl onto the carbonyl group of a dienone, enone, or phenyl ketone. While (3 + 2) cycloadditions have been reported for oxyallyls generated from  $\alpha,\alpha'$ -dibromo ketones,<sup>4–6</sup> to the best of our knowledge, such (3 + 2) cycloadditions involving heteroatom-stabilized oxyallyls have not been previously reported.

In recent years, we have explored (4 + 3) cycloadditions of oxazolidinone-substituted oxyallyls (**3**) (Scheme 2) with

## Scheme 2. Intermolecular and Intramolecular (4 + 3) Cycloadditions of Allenamide-Derived Oxazolidinone-Substituted Oxyallyls with Dienes<sup>7a,c</sup>

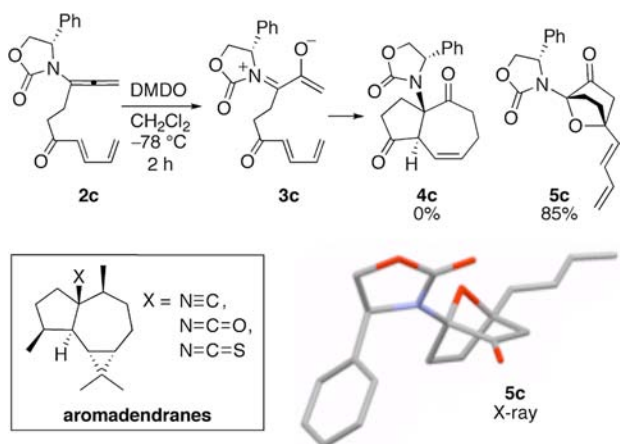


numerous classes of dienes.<sup>7</sup> Oxyallyls **3** are readily generated by oxidation of allenamides and can be trapped either intermolecularly or intramolecularly by dienes. We had intended to apply the allenamide oxidation/(4 + 3) cycloaddition sequence to access bicyclic species **4c** (Figure 1) in a planned synthesis of aromadendrane natural products.<sup>8</sup> Unexpectedly, treatment of allenamide **2c** with dimethyldioxirane (DMDO) under standard conditions led not to **4c** but to the oxabicyclic species **5c** (85%), whose identity was confirmed by X-ray crystallography. Adduct **5c** is the product of chemoselective (3 + 2) cycloaddition of the oxyallyl onto the carbonyl group of the tethered dienone.

The formation of **5c** is surprising given the fact that other oxyallyls in which the diene is connected by a three-carbon tether do undergo intramolecular (4 + 3) cycloadditions (e.g.,

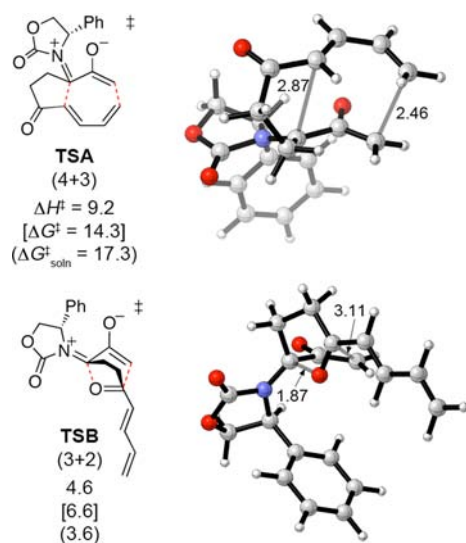
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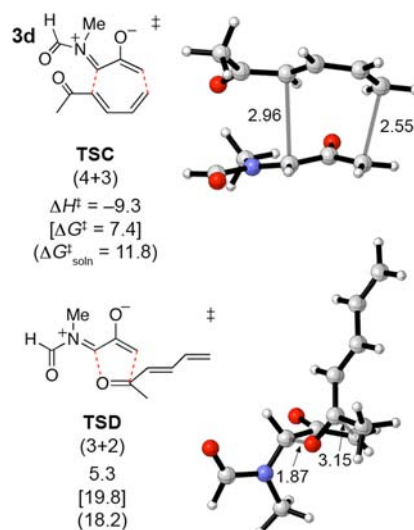
**Figure 1.** Synthesis and X-ray crystal structure of (3 + 2) cycloadduct **5c**.

Scheme 2b).<sup>7c</sup> We conducted density functional theory (DFT) calculations to explore how **5c** is formed.<sup>9</sup> Transition states (TSs) were computed for the (4 + 3) and (3 + 2) cycloadditions of **3c** leading to **4c** and **5c**, respectively, at the B3LYP/6-31G(d) level of theory.<sup>10</sup> Activation energies were then obtained from M06-2X/6-311+G(d,p) single-point calculations,<sup>11</sup> and solvent effects (CH<sub>2</sub>Cl<sub>2</sub>) were modeled through SMD calculations.<sup>12</sup> The computational results are shown in Figure 2. For comparison, we also computed TSs for intermolecular cycloadditions of a model oxyallyl (**3d**) with hexadienone (Figure 3).



**Figure 2.** Transition states for the intramolecular (4 + 3) and (3 + 2) cycloadditions of **3c** leading to **4c** and **5c**, respectively (distances in Å,  $\Delta H^\ddagger$  and  $\Delta G^\ddagger$  in kcal/mol; M06-2X//B3LYP, SMD solvation in CH<sub>2</sub>Cl<sub>2</sub>).

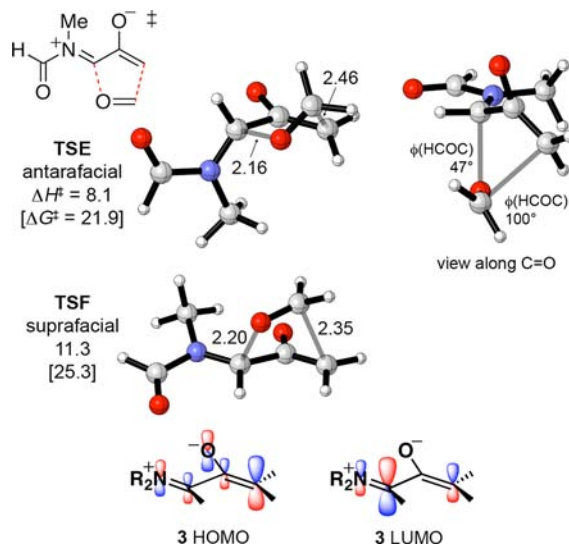
The activation energies for the intermolecular cycloadditions (Figure 3) show that the dienone has no innate preference for the (3 + 2) mode of cycloaddition. The (3 + 2) TS (TSD) is 12.4 kcal/mol higher in energy than the (4 + 3) TS (TSC) in the gas phase ( $\Delta\Delta G^\ddagger$ ) and 6.4 kcal/mol higher in solution. By contrast, the intramolecular (3 + 2) cycloaddition of **3c** (Figure 2) is favored over the (4 + 3) cycloaddition by 7.7 kcal/mol in the gas phase and 13.7 kcal/mol in solution. Both of these



**Figure 3.** Transition states for intermolecular (4 + 3) and (3 + 2) cycloadditions of oxyallyl **3d** with hexadienone.

modes of intramolecular cycloaddition are downhill by more than 40 kcal/mol ( $\Delta G_{\text{soln}}$ ). The switch in chemoselectivity displayed by **3c** reflects a 4.6 kcal/mol lower activation enthalpy and a 3.1 kcal/mol smaller entropic term ( $-T\Delta S^\ddagger$ ). While the inter- and intramolecular (3 + 2) cycloaddition TSs are geometrically very similar (except for the orientation of the diene chain), the (4 + 3) TS occurs intramolecularly at a more advanced stage of bond formation, and the carbonyl group is twisted 21° out of the diene plane (compared with 7° in TSC).

The (3 + 2) cycloadditions are concerted but highly asynchronous processes. C–O bond formation is much more advanced at the TS (1.87 Å) than C–C bond formation (3.11–3.15 Å). Addition is antarafacial with respect to **3c** or **3d** and suprafacial with respect to the carbonyl, in agreement with the orbital symmetry rules for a thermal  $[2\pi + 2\pi]$  cycloaddition.<sup>13</sup> To explore the details of the mechanism, we calculated TSs for alternative modes of (3 + 2) cycloaddition in the reaction of **3d** with formaldehyde (Figure 4). The preference for antarafacial addition over suprafacial addition (TSE vs TSF) is 3 kcal/mol.



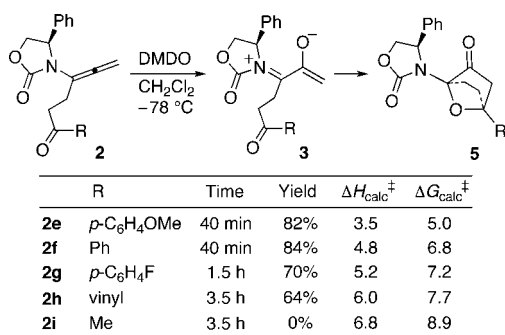
**Figure 4.** Transition states for antarafacial and suprafacial (3 + 2) cycloadditions of oxyallyl **3d** with formaldehyde.

The concerted antarafacial mechanism is favored over stepwise mechanisms by at least 10 kcal/mol.

The highest occupied molecular orbital (HOMO) and lowest unoccupied MO (LUMO) of oxallyls **3** are depicted at the bottom of Figure 4. The HOMO is enolate-like, while the LUMO has both allyl  $\pi^*$  and iminium  $\pi^*$  character.<sup>14</sup> To reach the antarafacial TS, the iminium and enolate moieties rotate into a roughly perpendicular arrangement that allows maximum overlap with the  $\pi$  orbitals of the carbonyl. Orbital interactions with  $\pi(\text{C}=\text{O})$  and  $\pi^*(\text{C}=\text{O})$ , which define the pericyclic [ $2\pi + 2\pi$ ] cycloaddition, are accompanied by a simultaneous interaction between the LUMO of **3** and a carbonyl oxygen lone pair. The latter interaction endows the reaction with pseudopericyclic<sup>15</sup> character. The contributions of pericyclic and pseudopericyclic character to TSE are approximately equal, as shown by the geometry of approach of the aldehyde viewed along the C=O bond (Figure 4). The iminium terminus of **3d** approaches at an angle of  $47^\circ$  with respect to the  $\text{CH}_2=\text{O}$  plane, halfway between the angles expected for purely pericyclic ( $90^\circ$ ) and pseudopericyclic ( $0^\circ$ ) processes. We describe this new type of reaction not as pericyclic or pseudopericyclic but as "hemipseudopericyclic".

We also explored the feasibility of intermolecular (3 + 2) cycloadditions. Reactions of **3d** with ketones, esters, and aliphatic or aromatic aldehydes are predicted to have  $\Delta H^\ddagger = 6-9$  kcal/mol and  $\Delta G_{\text{soln}}^\ddagger = 20-23$  kcal/mol (see the Supporting Information).<sup>16</sup> Unfortunately, experimental attempts to perform intermolecular (3 + 2) cycloadditions with a number of carbonyl systems, including aldehydes, ketones, esters, and amides, were thwarted by competing oxidation of the carbonyl substrates under the conditions used for generation of the oxallyl. Intramolecularity appears to be necessary for the cycloaddition to compete with these unwanted oxidation reactions.<sup>17</sup> Consistent with this, analogous (3 + 2) cycloadditions were accomplished with tethered phenyl ketones **2e-g** and tethered enone **2h** (Scheme 3). On the other hand,

### Scheme 3. Experimental and Theoretical Investigations of Other (3 + 2) Cycloadditions



methyl ketone **2i** failed to react under the same conditions. It appears that an electron-rich carbonyl substituent (R) is necessary to stabilize the cationlike character at the carbonyl carbon in the highly asynchronous TS. Calculations on **2e-i** agreed with experiment, predicting the methyl ketone to have a barrier 2 kcal/mol higher than that of **2c**, while the vinyl and phenyl ketones have lower barriers that decrease as the ketone becomes more electron-rich.

The (3 + 2) cycloadditions of **3** with carbonyl compounds are an unexpected addition to the repertoire of oxallyl reactivity.<sup>4-6</sup> Oxallyls **3** possess a reactivity profile quite

different from most other synthetically important oxallyls, which are cationic, electrophilic species. We had previously reported that oxallyls **3** are ambiphilic in (4 + 3) cycloadditions with furans.<sup>14b</sup> The cycloadditions onto carbonyls represent an even more unusual pairing and suggest tantalizing new synthetic prospects; pursuit of potential applications is underway.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, compound characterizations, NMR spectra, crystallographic data (CIF), computational methodology and data, and complete citations for ref 9. 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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(16) Amides are predicted to be more reactive than these types of carbonyl compounds. For example, cycloaddition of **3d** with dimethylacetamide is calculated to have  $\Delta H^\ddagger = 1.0$  kcal/mol and  $\Delta G_{\text{soln}}^\ddagger = 12.1$  kcal/mol.

(17) We also located a TS for an alternative mode of (3 + 2) cycloaddition in which the formaldehyde carbon binds to the oxyallyl

oxygen rather than to the oxyallyl carbon, leading to a 4-alkylidene-5-oxazolidinyl-1,3-dioxolane. This TS is much lower in energy than TSE ( $\Delta G^\ddagger = 10.7$  kcal/mol) and may represent an unwanted side reaction in certain of our attempted intermolecular cycloadditions; however, its importance depends on the carbonyl substituents. With hexadienone, for example, addition across CCO is 0.2 kcal/mol higher in energy than addition across CCC. At this stage, we have not observed any products that could be assigned to cycloadditions of ketones across CCO of oxyallyls. In all of our intramolecular examples, addition across CCO is prevented by the geometrical constraints of the tether. Analogous products from reactions of  $\alpha,\alpha'$ -dibromoketones with ketones or amides under reductive conditions have been reported.<sup>4e,f</sup>