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# Tandem Cycloadditions

## Introduction

Chemists are constantly working to discover new and improved reactions. One of the primary motivating goals of this research is the development of cleaner, more efficient transformations to shorten syntheses and save money on chemicals. The strategy of using reactions in tandem is also aimed at shortening syntheses.

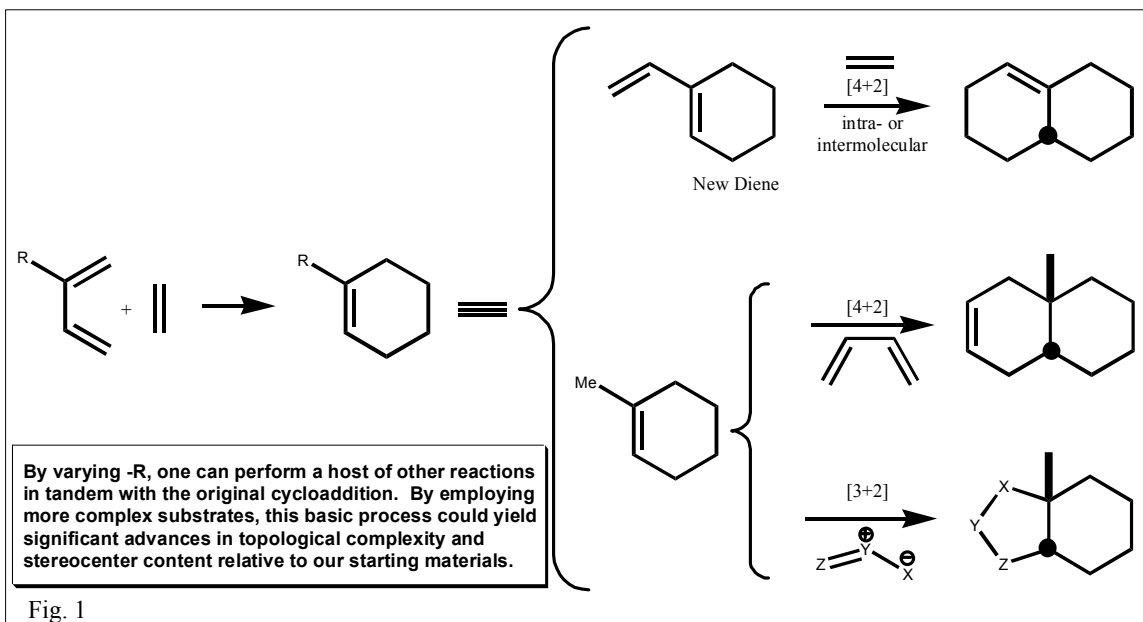
Tandem reactions are commonly referred to under the nebulous phrase “multistep one-pot reactions.” However, more rigorous definitions have been suggested.<sup>1</sup> Ho’s definition is probably the most descriptive: tandem reactions are “combinations of two or more reactions whose occurrence is in a specific order, and if they involve sequential addition of reagents the secondary reagents must be integrated into the products.”<sup>2</sup>

Tandem reactions have several advantages over a series of individual reactions. First, they allow construction of complex structures in as few steps as possible. In theory, they also eliminate the need for a purification step (or steps). Since the intermediates are not isolated it becomes easier to work with sensitive or unstable intermediates. Finally, employing reactions in tandem will save on cost and amounts of reagents, solvents, and reduce the amount of waste that is generated.

Chemists have grouped tandem reactions into three categories. The first is “cascade or domino” reactions in which both or all reactions take place without the need for additional reagents or a change in reaction conditions. Everything that is necessary for both reactions is incorporated into the starting materials. The second class, “consecutive” reactions, is where the intermediate formed in the first reaction has the necessary functionality, but additional energy must be added in order to overcome an activation barrier. The last class is “sequential,” where the functionality for the second

reaction has been created but additional reagents must be added in order for the second reaction to occur.

Among the numerous types of known organic reactions available to use in tandem, cycloadditions are particularly attractive.<sup>3-4</sup> While there are many types of cycloadditions known, this abstract will focus only on the Diels-Alder<sup>5</sup> and 1,3-dipolar cycloaddition<sup>6</sup> (also known as [3+2] cycloadditions). Cycloadditions utilize olefins to generate new alkenes that can be reacted further (Fig 1). Cycloadditions can often be run under mild conditions, and are amenable to Lewis acid catalysis. Cycloadditions are also capable of creating multiple carbon-carbon bonds, rings, and stereocenters in a single step. By properly controlling the reaction conditions and carefully choosing your substrate it is possible to obtain high levels of regio- and stereochemical control.

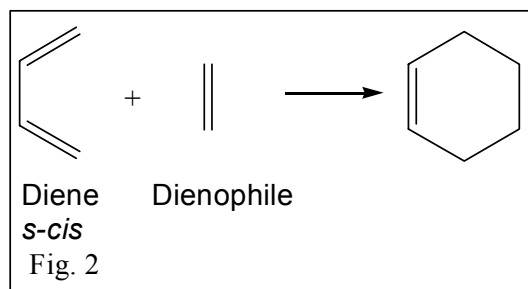


It is also important to be aware of the limitations of tandem cycloadditions. The Diels-Alder and 1,3-dipolar cycloadditions yield only 6- and 5-membered rings respectively. While these are common ring sizes, it is not possible to directly generate larger or smaller rings with these reactions. Difficult cycloadditions may actually require harsh conditions such as extreme heating or pressure. Obviously, sensitive or unstable substrates may not be able to withstand these conditions. Finally, the products generated in these reactions are usually racemic. This is because addition can occur on opposite faces of the double bond or dipole, yielding different stereoisomers.

## Review of Cycloadditions

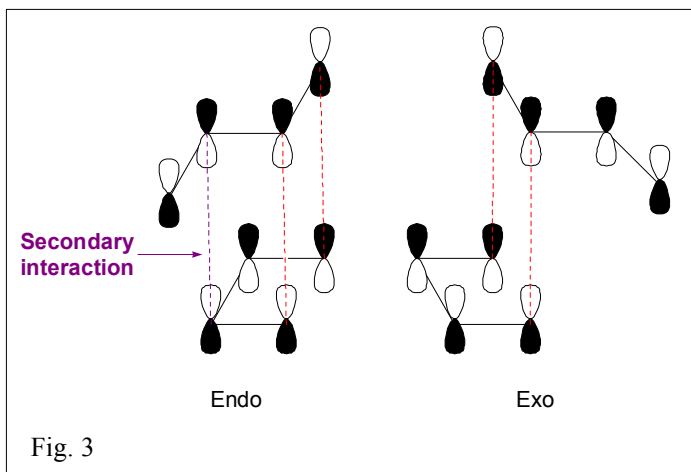
### I. Diels-Alder

The Diels-Alder cycloaddition is the reaction between a conjugated diene and an alkene / alkyne commonly known as the dienophile (Fig. 2). The diene portion must adopt the *s-cis* conformation to be reactive.



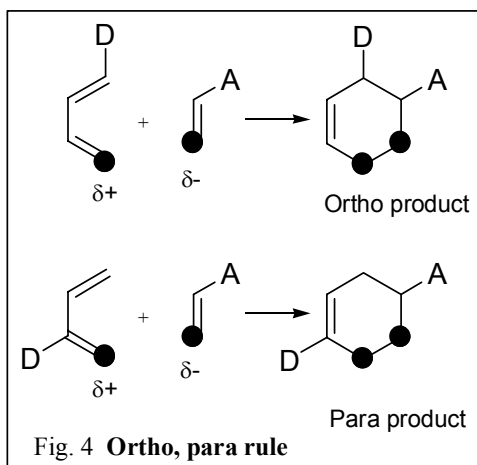
The reaction is a concerted  $6\pi$  electron process designated as  $[\pi 4_s + \pi 2_s]$ . The numbers refer to the number of electrons in the two reactants respectively, and the subscript "s" designates the orbital overlap as suprafacial. Normally the  $4\pi$  component is electron rich relative to the  $2\pi$  component, and addition occurs by overlap of its HOMO with the relatively electron deficient LUMO of the dienophile. There are two possible orientations of the diene overlapping with the dienophile which determine the stereochemical outcome of the reaction (Fig. 3). The *endo* approach is usually favored due to secondary orbital overlap between the diene and the electron withdrawing

substituent on the dienophile.



The regiochemistry of the Diels-Alder cycloaddition can be predicted by examining the orbital coefficients of the diene and dienophile. This can usually be done by simply drawing resonance structures. When an electron donor is at the

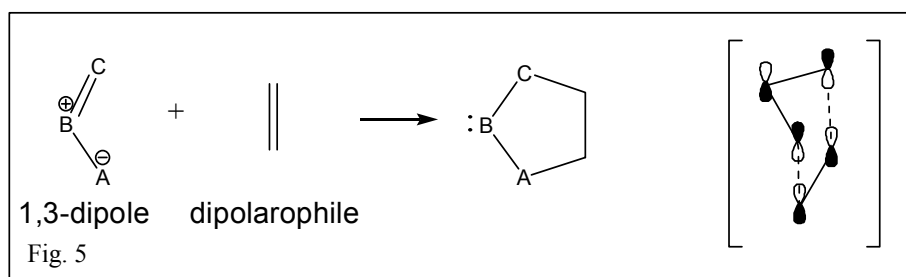
terminal position of the diene the relative positions of the electron withdrawing and electron donating substituents is ortho. A para product results if the donating group is located at an internal position on the diene. This regiochemistry is often referred to as the ortho, para rule (Fig. 4).



The Diels-Alder reaction is amenable to catalysis by pressure or Lewis acids. Lewis acids increase the rate of addition, and regio and stereo selectivity of the reaction. Coordination of the Lewis acid to the electron withdrawing substituent on the dieneophile increases its electron withdrawing capacity. This results in the lowering of the HOMO/LUMO energy gap.

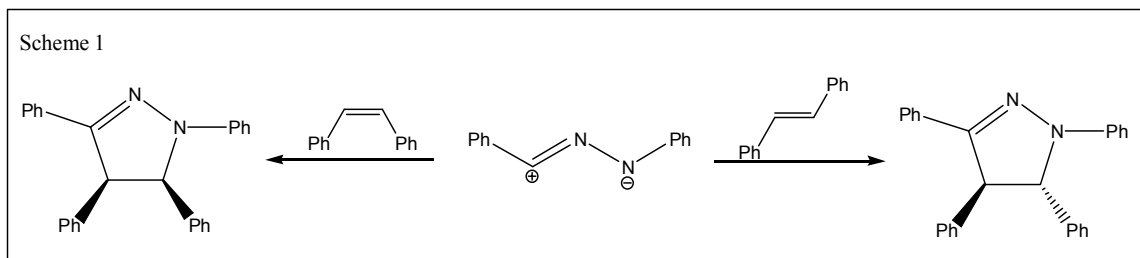
## II. 1,3-Dipolar Cycloaddition

The 1,3-dipolar cycloaddition is a reaction between a 1,3-dipole and an alkene / alkyne known as a dipolarophile (Fig. 5). Like the Diels-Alder, it is also a concerted  $[\pi 4_s + \pi 2_s]$  process. The 1,3-dipolar cycloaddition is also referred to as a [3+2] cycloaddition. The [3+2] nomenclature refers to the number of atoms in the two reacting molecules, i.e. a three-atom unit and a two-atom unit. By analogy, the Diels-Alder reaction could also be called a [4+2] cycloaddition. The 1,3-dipolar cycloaddition is also amenable to Lewis acid catalysis.



The prediction of stereochemistry and regiochemistry for the 1,3-dipolar cycloaddition is more complicated than for the Diels-Alder. The stereochemistry of the reaction is a syn addition with respect to the dipolarophile (Scheme 1). Unsymmetrical

reactants often lead to a mixture of diastereomers because the secondary interactions of the endo orientation are often weak or negligible. Therefore, steric factors and coordination of Lewis acids play a large role in determining the most favorable orientation of addition.



Determination of regiochemistry requires the estimation of orbital energies. The relative energies will determine if the interaction is between  $\text{HOMO}_{\text{dienophile}}/\text{LUMO}_{\text{diene}}$  or vice versa. This is important because the orbital energies vary at different positions along the 1,3-dipole depending on if its reacting molecular orbital is the HOMO or LUMO.

### Strategies for Tandem [4+2]/[4+2] Cycloadditions

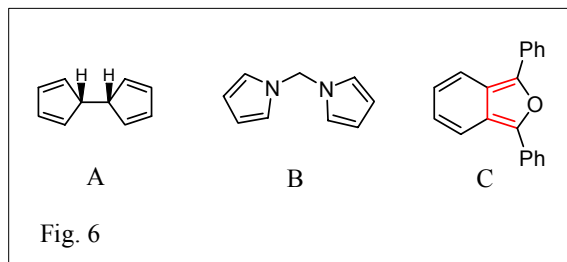
One of the most obvious strategies in designing a tandem Diels-Alder cycloaddition is to incorporate two or more of the same reactive functionality on a single substrate. Two approaches to this strategy are to incorporate either bis-dieneophiles or bis-dienes into the reaction. A third strategy is known as diene-transmissive.

#### A. Bis-Dieneophile Strategies

The first strategy uses acetylene or substituted acetylenes as the dieneophile. After the first cycloaddition the alkyne will be transformed into an alkene which is then available to undergo a further cycloaddition reaction.<sup>7</sup> Nonacetylinic dieneophiles have also been developed,<sup>8</sup> and their use has been applied to the synthesis of various fused ring skeletons such as hydrofluorenones.<sup>9</sup>

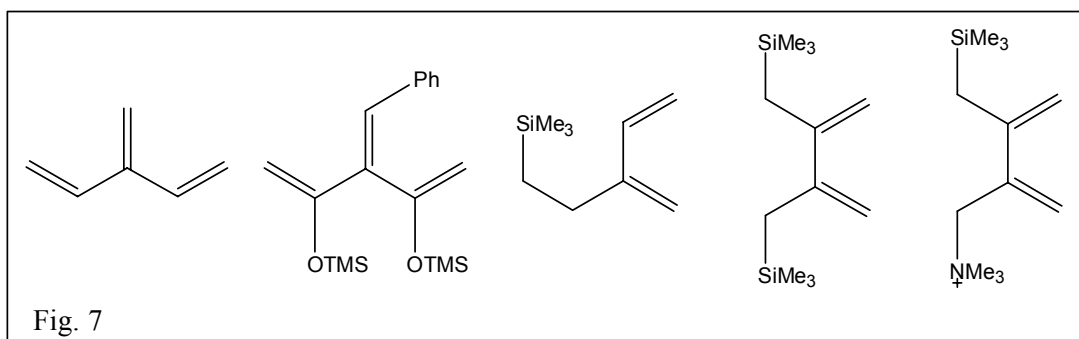
## B. Bis-Diene Strategies

One of the earliest strategies for the incorporation of bis-dienes was to use bicyclic dienes. These compounds were often employed in the synthesis of norbornanes (Fig. 6 A-B).<sup>10-11</sup> They have also been used in the synthesis of caged compounds (Fig. 6C).<sup>12</sup>

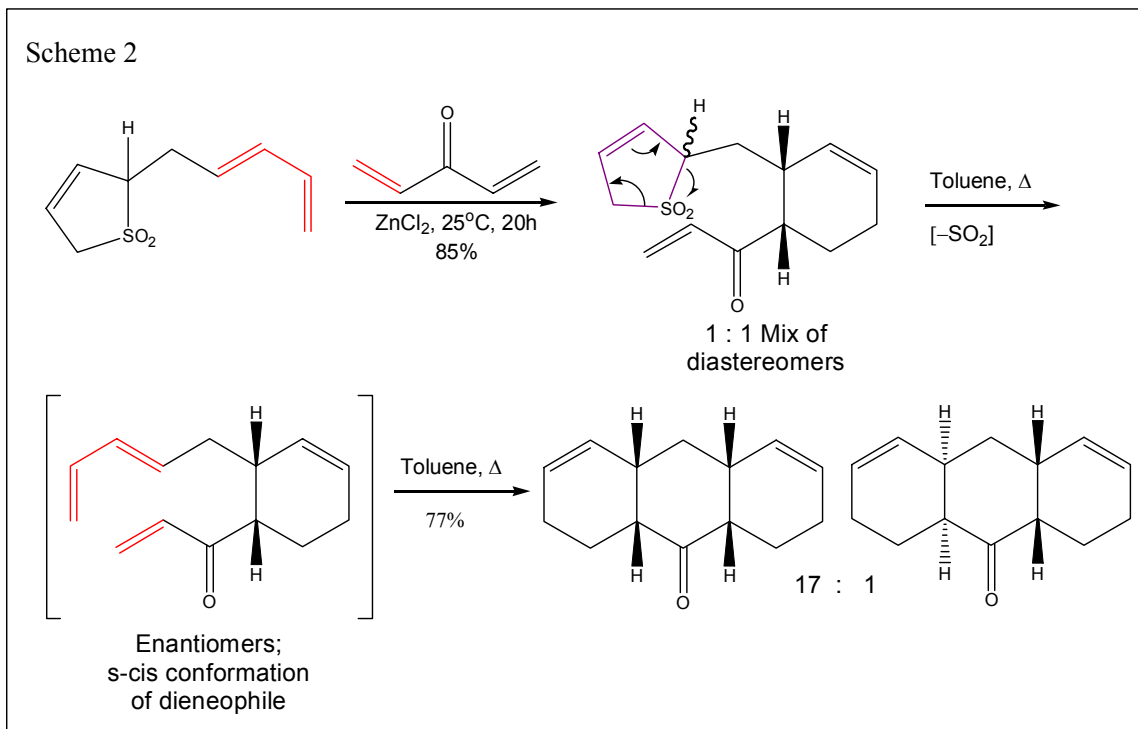
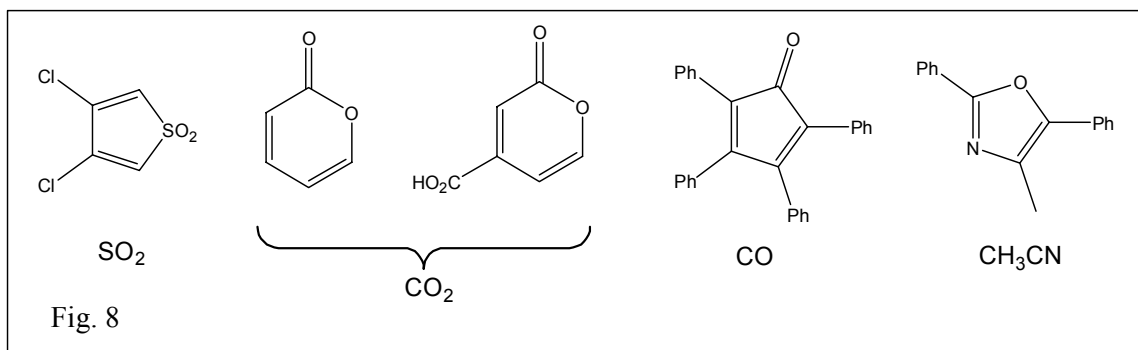


An exocyclic bis-diene strategy has been utilized by Vogel and co-workers towards the synthesis of 11-Deoxydaunomycinone.<sup>13</sup>

A sound strategy for incorporation of bis-diene functionality is the use of 3-methylene-1,4-pentadiene and its synthetic equivalents (Fig 7). Due to the instability of the parent compound, the second diene equivalent usually has to be generated *in situ*. Desilylation is a common tactic for generating the second diene.<sup>14</sup>



The masked bis-diene strategy is probably the most attractive. One of the diene functionalities is masked, which allows for selectivity in the first cycloaddition. Unmasking of the second diene unit is done by the thermal extrusion of a small molecule (Fig. 8). A representative example from Winkler and coworkers is shown in Scheme 2.<sup>15</sup>



Acyclic bis-dienes have also been employed in synthesis. Kraus and coworkers used an acyclic bis-diene strategy for the synthesis of the fluorenone ring system.<sup>16</sup> Important to this strategy was the use of electron withdrawing and donating groups to tune the reactivity of the dienes to make one more reactive than another. The temporary masking of one diene and Lewis acid catalysis can also be used in conjunction with acyclic bis-dienes to allow better control of reactivity. This methodology has been used by Winkler and coworkers to generate a tricyclic ring system wherein they could tune the stereochemical outcome of their products by adding a Lewis acid.<sup>15</sup> Winkler later applied this methodology to the synthesis of the ABC rings of the taxane skeleton.<sup>17</sup>

### C. Diene Transmissive

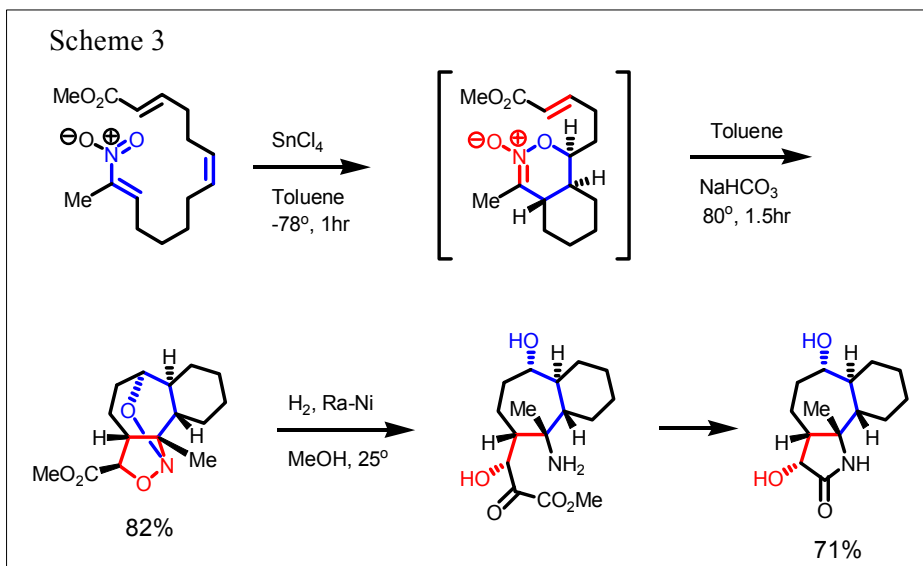
The term diene transmissive, coined by Tsuge,<sup>18</sup> involves the reaction of cross-conjugated trienes where the diene functionality is transmitted in order during the reaction. This strategy was used for the synthesis of nor-steroid and triterpenoid skeletons by Fallis and coworkers.<sup>19</sup> This is an exceptional example of substrate control used to generate a single stereoisomer. Schreiber and coworkers developed a split-pool library synthesis<sup>20</sup> based upon earlier work by Fallis.<sup>21</sup> The Schreiber lab noticed that tri- and tetra-substituted alkenes did not undergo the planned tandem reaction. Instead, they were able to isolate the mono adduct, and use this as a point to incorporate diversity in their library. Using commercially available starting materials they were able to synthesis a split-pool library containing approximately 31, 000 unique members.

### Tandem [4+2]/[3+2] and [3+2]/[4+2] Cycloadditions

The literature is full of examples of tandem [4+2]/[3+2] and [3+2]/[4+2] cycloadditions. These have been carried out in different permutations of intermolecular and intramolecular fashions. Examples include the synthesis of azanorbornadiene derivatives<sup>22</sup>, cycloaddition of a nitrile amine to cyclooctatetraene<sup>23</sup>, and the synthesis of various caged compounds<sup>24</sup>. A unique sequence developed by Grigg and coworkers generates the dipole and dipolarophile for the [3+2] cycloaddition *in situ*.<sup>25</sup> This strategy is accomplished by an oxime on the Diels-Alder adduct doing a Michael addition to methyl vinyl ketone. Boger and coworkers have used a tandem Diels-Alder/Retro [3+2]/[3+2] scheme towards the synthesis of the Vindoline skeleton in which all six stereocenters were established.<sup>26</sup>

Denmark and coworkers have developed a whole series of tandem [4+2]/[3+2] cycloadditions using nitroalkenes. The nitroalkene first reacts in an inverse electron demand, hetero-Diels-Alder reaction, generating a nitronate. The nitronate then functions as the dipole in the subsequent 1,3-dipolar cycloaddition to give a nitrosoacetal. Hydrogenolysis can be used to cleave both N-O bonds, yielding various tricyclic systems (Scheme 3).<sup>27</sup> They have also utilized chiral auxiliaries appended to the dienophile in the Diels-Alder cycloaddition. The auxiliary can be recovered in good yields upon

hydrogenolysis. The use of chiral auxiliaries and different bulky Lewis acids have allowed them access to both sets of stereoisomers in a controlled manner.<sup>28-29</sup>



## Conclusions

If properly planned and executed, tandem cycloadditions can drastically reduce the number of synthetic steps required for a synthesis. Numerous examples in the literature show that tandem cycloaddition sequences can provide a facile route into complex natural product skeletons. Tandem cycloadditions are also ideally suited for diversity oriented synthesis where the goal is the generation of structural and topological complexity in as few transformations as possible.

The biggest drawback to using tandem cycloadditions lies in the fact that you often get mixtures of diastereomers, whose purification and unambiguous structural assignments may not be trivial. Hidden in these papers is also the fact that a mixture of diastereomers also includes their enantiomers. This complicates matters even more, especially if you desire only one specific stereoisomer.

Future tandem cycloadditions should be able to overcome these short-comings through the use of chiral Lewis acid catalysts or chiral auxiliaries appended to the starting materials. However, the biggest innovation in this field remains the active imagination of chemists to develop novel combinations of tandem organic reactions.

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