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Expanding the Frontiers of Higher-Order Cycloadditions

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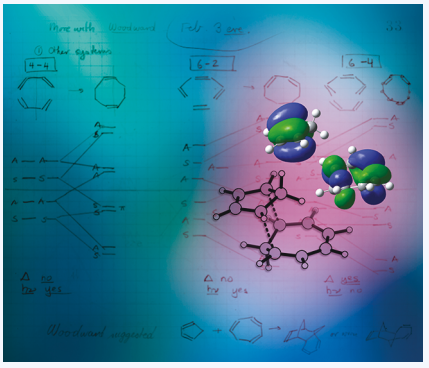
CONSPECTUS: The concept of pericyclic reactions and the explanation of their specificity through orbital symmetries introduced a new way of understanding reactions and looking for new ones. One of the 1965 Woodward−Hoffmann communications described "the (as yet unobserved) symmetry-allowed 6 + 4 combination", the prediction of a new field of "higher-order" cycloadditions, involving more than six electrons. Later these authors predicted *exo*-stereoselectivity for the [6 + 4]-cycloaddition. Chemists rushed to test this prediction (for the most part successfully). For more than half a century, chemists have hunted for additional higher-order cycloadditions. The application of catalysis within organic chemistry allows the accomplishment of previously unattainable reactions, including higher-order cycloadditions.



The many examples of [8 + 2], [6 + 4], and cycloadditions of even higher electron-counts discovered since the Woodward−Hoffmann rules were introduced illustrate the difficulty in predicting which of these transformations will occur when two highly unsaturated molecules react. Periselectivity has been a challenge, and the development of enantioselective variants has been elusive. While progress was made, the rise of organocatalysis in asymmetric synthesis has led to a surge of interest in stereoselective versions of higher-order cycloadditions. Through organocatalytic activation of conjugated cyclic polyenes and heteroaromatic compounds, asymmetric [8 + 2]-, [6 + 4]-, and [10 + 4]-cycloadditions have been realized by our groups. In this century, [6 + 4]-cycloadditions have been found also to occur in enzyme-catalyzed reactions for the biosynthesis of spinosyn A, heronamide, and streptoseomycin natural products. A whole new class of enzymes, the pericyclases that catalyze pericyclic reactions, has been discovered.

A remarkable aspect of these recent developments is the cross-disciplinary research involved: from organic synthesis to computational studies integrated with experimental studies of reaction mechanisms, intermediates, and dynamics, to understanding mechanisms of enzyme catalysis and engineering of enzymes.

This Account describes how our groups have been involved in the expansion of the higher-order cycloaddition frontiers. We describe both the history and recent progress in higher-order cycloadditions, and how these advances have been made by our collaborative experimental and computational studies. Progress in asymmetric organocatalysis, incorporating enantioselective higher-order cycloadditions in organic synthesis, and the stereoselective synthesis of important scaffolds will be highlighted. Experimental progress and computational modeling with density functional theory (DFT) has identified ambimodal cycloaddition pathways and led to the realization that multiple products of pericyclic reactions are linked by common transition states. Molecular dynamic simulations have provided fundamental understanding of factors controlling periselectivity and have led to discoveries of a group of enzymes, the pericyclases, which catalyze pericyclic reactions such as [6 + 4]-cycloadditions.

1. INTRODUCTION

The introduction of orbital symmetry selection rules for cycloadditions in 1965 classified these reactions in terms of electronic characteristics and opened a path to expand the scope beyond six-electron processes.[1−3] In the days around January 28, 1965, the first molecular orbital calculations on the crucial (forbidden) [2 + 2]-cycloaddition were carried out by Hoffmann, joining earlier calculations he had done on the [4 + 2]-cycloaddition.[4,5] Further developments took place at great speed in the early days of 1965, facilitated by the drawing of energy level correlation diagrams.[6,7] Already on February 3, 1965, orbital correlation diagrams for [4 + 4]-, [6 + 2]-, and [6 + 4]-cycloadditions appear in Hoffmann's notebook (Figure 1). As two notations on this page indicate, clearly there was a contemporaneous discussion with Woodward, who suggested the experimental study of the [6 + 4]-cycloaddition of cyclopentadiene with cycloheptatriene (Figure 1, bottom).[4] The concept of higher-order cycloadditions grew from these roots.

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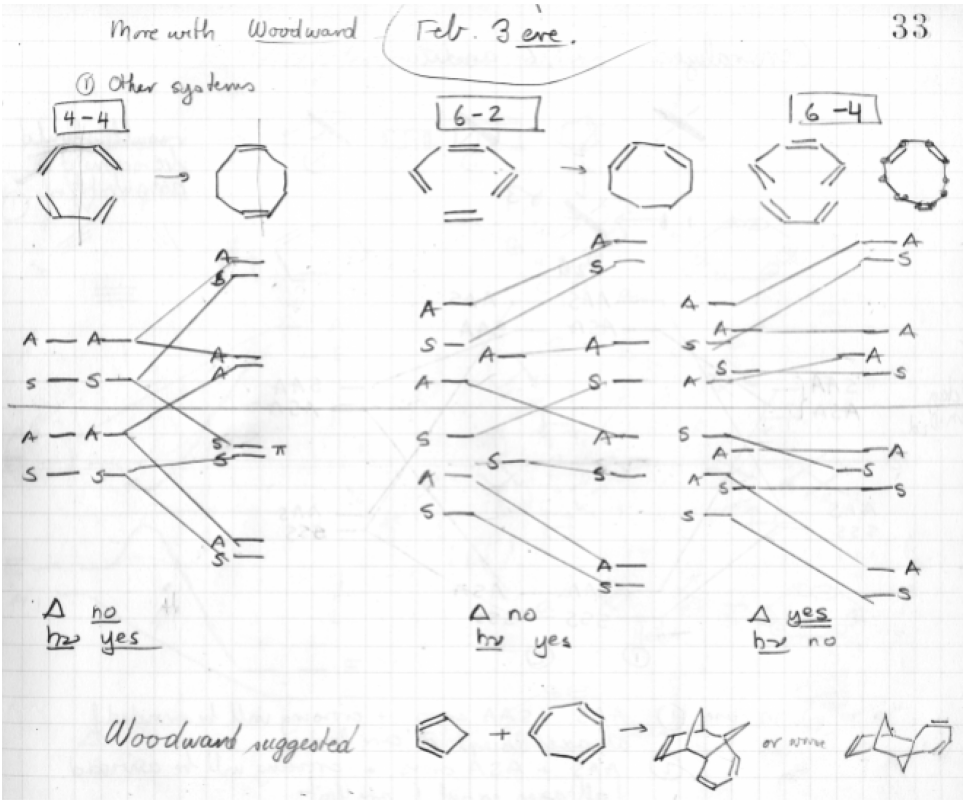

Figure 1. Page 33 from notebook 16, dated February 3, 1965, by Hoffmann where the orbital correlation diagrams for [4 + 4]-, [6 + 2]-, and [6 + 4]-cycloadditions were first described. Below these is a suggestion by Woodward of a [6 + 4]-cycloaddition of cyclopentadiene with cycloheptatriene.[4]

Shortly after, Woodward proposed that Houk should pursue this reaction for his Ph.D.[8] While this particular reaction proved to be too complex for methods and instrumentation at the time, a number of [6 + 4]-cycloadditions of related trienes and dienes were discovered by Houk in the Woodward laboratory.[9−11] The first example of a [6 + 4]-cycloaddition was published independently by Cookson[12] and Itô (Figure 2).[13] Woodward and Hoffmann predicted the reaction to be *exo*-selective,[2] a prediction amply demonstrated in thermal [6 + 4]-cycloadditions.[14]

Cycloadditions such as Diels−Alder are well-known robust synthetic routes to cyclic systems.[15] The Diels−Alder cycloaddition constructs six-membered rings from a 1,3-diene and an alkene in a highly regio- and stereoselective manner. These reactions are generally concerted, with six π-electrons undergoing bonding changes in the transition state (TS).[1−3,15] Higher-order cycloadditions involve more than six π-electrons in bonding changes during the reaction, allowing for the synthesis of medium-size rings.[3,16]

Many concerted Diels−Alder reactions are *asynchronous*, as proposed on the basis of substituent effects by Dewar and Pierini[17] and shown by experimental and computed isotope effects for an asynchronous transition state by Houk and Singleton.[18] Most higher-order cycloadditions display a pronounced asynchronicity in the TS structure and exhibit both dynamically concerted and stepwise trajectories, sometimes even fully stepwise processes. The boundary between concerted and stepwise reactions is not "hard", as now known from molecular dynamics (MD) simulations. Carbon−carbon vibrations take about 30 fs, and the passage through a TS occurs in about 60 fs. Houk and co-workers defined 60 fs as

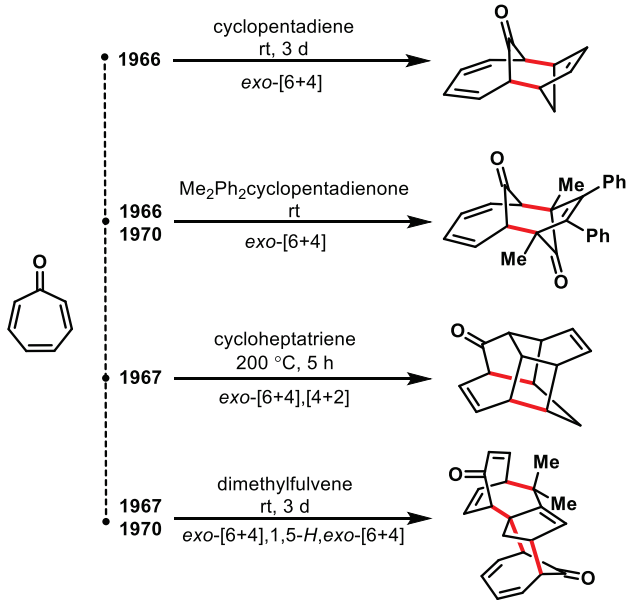

Figure 2. First examples of thermal [6 + 4]-cycloadditions.[9−13] Bonds formed through higher-order cycloadditions are highlighted in red.

the boundary between dynamically concerted and dynamically stepwise reactions.[19] When the second bond forms more than 60 fs after the first, the reaction is dynamically stepwise. While the Woodward−Hoffmann rules strictly only apply to concerted processes, the orbital interactions causing a reaction to be orbital symmetry-allowed may be maintained along a

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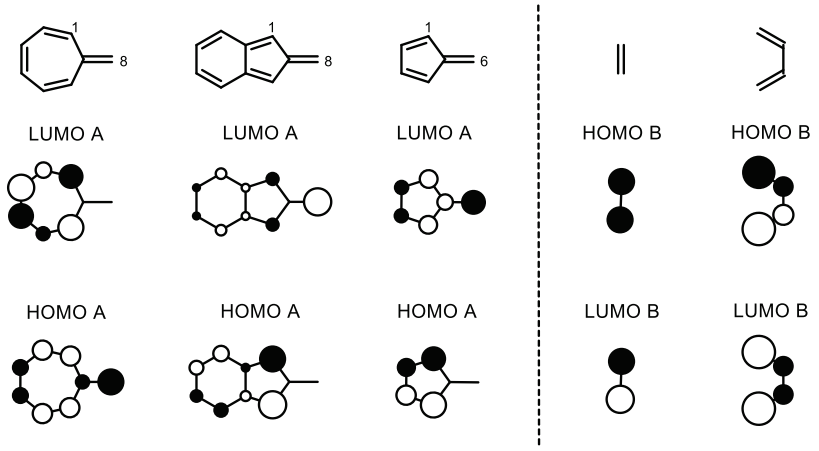

Figure 3. FMOs of some conjugated polyenes involved in higher-order cycloadditions.

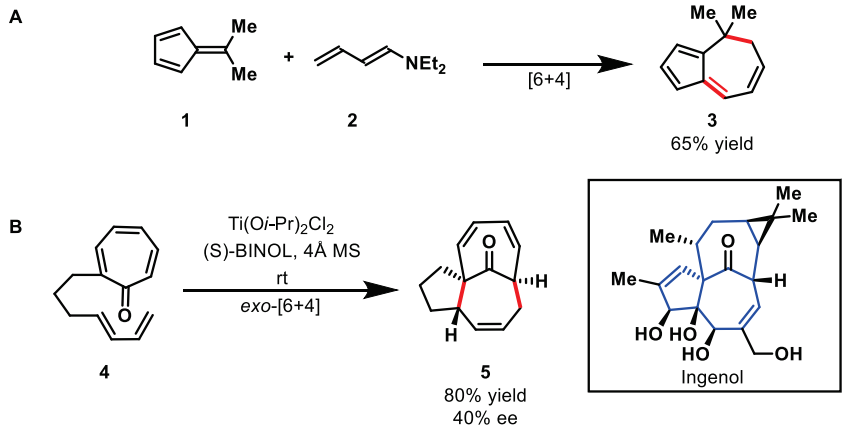

Figure 4. Early examples of [6 + 4]-cycloadditions.

dynamically stepwise pathway, leading only to allowed products.

2. EARLY EXAMPLES OF HIGHER-ORDER CYCLOADDITIONS

In the 1960s, only a few higher-order cycloadditions were known. Unlike [6 + 4]-cycloadditions, which were unknown when Woodward and Hoffmann predicted their existence,[3] the first [8 + 2]-cycloaddition, disclosed by Doering and Wiley[20] as a method to trap heptafulvene, predated the treatise on the conservation of orbital symmetry. These two classes of reactions, representing 10π-electron cycloadditions, demand the utilization of extended polyene systems, which can be highly reactive and may have a complex distribution of conformations. Some of these problems are attenuated through the usage of cyclic polyene substrates.[21] However, high reactivity has historically led to a lack of periselectivity; for example, tetraenes can react as 8π-, 6π-, 4π-, and 2π-components. While both cycloadditions are thermally allowed by frontier molecular orbital (FMO) symmetry considerations,[3,22] $[_{\pi}8_{s} + _{\pi}2_{s}]$-cycloadditions proceed with *endo*-selectivity;[23] as compared to the *exo*-selectivity observed for $[_{\pi}6_{s} + _{\pi}4_{s}]$-cycloadditions.

Early experimental studies of the origins of periselectivity in higher-order cycloadditions were reported by the groups of Garst, Liu, and Houk.[24−27] The rationales of observed selectivities were based on Fukui's FMO theory. The FMOs of several relevant species are shown in Figure 3. Fulvenes are commonly used as 6π-addends in cycloadditions due to their defined geometry and reactivity. This was exploited in 1976 in the [6 + 4]-cycloaddition of dimethylfulvene **1** with diethylaminobutadiene **2** (Figure 4A) in which the [6 + 4]-periselectivity was rationalized by FMO theory (Figure 3).[28] Note, all allowed cycloadditions involve HOMO−LUMO interactions, such that the interacting orbitals have the same local symmetry and bonding interactions can occur simultaneously at both pairs of termini. The LUMO of fulvene (Figure 3) has a large coefficient on the exocyclic carbon explaining the propensity of fulvenes to react across positions 1 and 6 with electron-rich species. The most nucleophilic terminus of the dimethylaminobutadiene attacks the exocyclic carbon (Figure 4A). After completion of the [6 + 4]-cycloaddition and loss of diethylamine, compound **3** is formed.

In an example of an enantioselective higher-order cycloaddition, Rigby et al. demonstrated the titanium(IV)-assisted intramolecular [6 + 4]-cycloaddition of a diene-tethered tropone **4** (Figure 4B).[29] The use of a chiral Lewis acid facilitated the synthesis of the ingenane sesquiterpene core **5** with high peri- and diastereoselectivity and modest enantioselectivity. They also reported a chromium(0)-promoted [6 + 4]-cycloaddition of thiepine dioxide and an enantiomerically pure diene in the total synthesis of (+)-estradiol.[29b]

3. [6 + 4]- AND [6 + 2]-CYCLOADDITIONS

In 1967, Houk discovered the 2:1 adduct of dimethylfulvene **1** to tropone **4** in the Woodward laboratory, but the structure of

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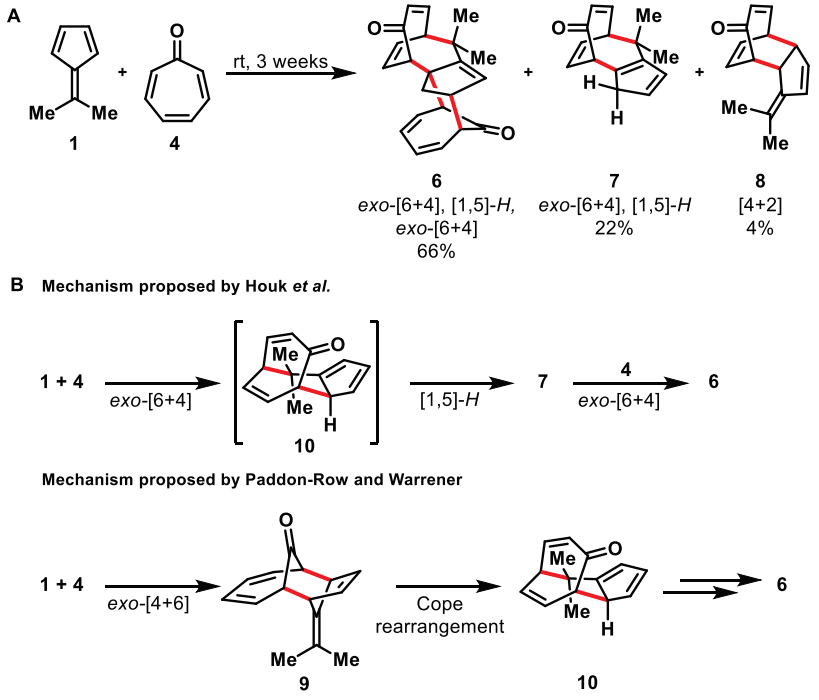

Figure 5. (A) Product distribution of the reaction between fulvene **1** and tropone **4**. (B) Mechanistic proposals for the formation of product **6**.

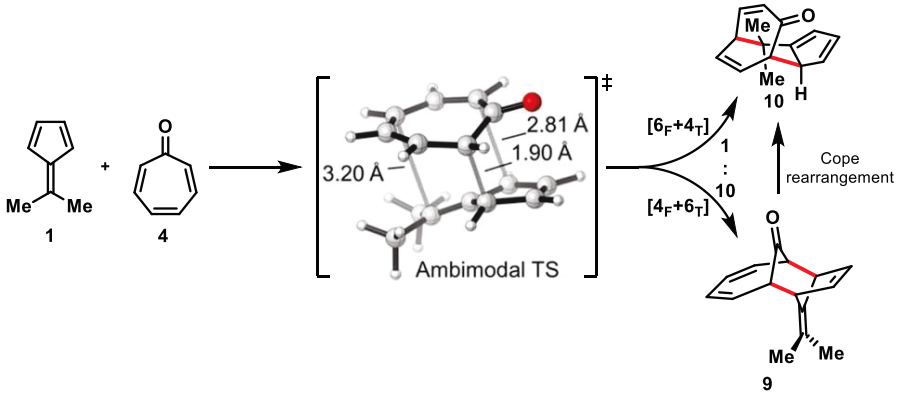

Figure 6. Ambimodal TS leading to both [6 + 4]-adducts **9** and **10**.

the adduct was finally disclosed in 1970 (Figure 5A);[11,30] an intermediate **7** and a trace of Diels–Alder product **8** were also observed. Based on these observations, a mechanism for this reaction was proposed. A [6 + 4]-cycloaddition of dimethylfulvene [6π] to tropone [4π] initially forms **10**, followed by a [1,5]-hydrogen shift to yield the thermodynamically more stable cyclopentadiene **7**, which subsequently undergoes a second [6 + 4]-cycloaddition with tropone [6π] to form the double [6 + 4]-cycloadduct **6**. Paddon-Row and Warrener proposed an alternative mechanism: the initial cycloaddition involves a different [6 + 4]-cycloaddition in which fulvene acts as the 4π-component to give **9**, and a subsequent [3,3]-sigmatropic shift (Cope rearrangement) produces the formal [6 + 4]-adduct **10** (Figure 5B).[31]

Nearly 50 years later, in 2017, the mechanisms and selectivities of the cycloadditions of dimethylfulvene **1** to tropone **4** were investigated in the Houk laboratories with density functional theory (DFT) calculations and quasi-classical direct MD simulations.[32] Computations revealed that the initial cycloaddition proceeds via an ambimodal TS, which can lead to both of the proposed [6 + 4]-adducts **9** and **10** through a post-TS bifurcation (Figure 6). These adducts can interconvert through a Cope rearrangement.

The phenomenon of bis-pericyclic, or more generally ambimodal, TS for pericyclic reactions was first discovered for dimerization of cyclopentadiene by Caramella.[33] Such a TS can lead to multiple products without intervening minima or secondary barriers, because the reaction path bifurcates after the TS. The reaction between dimethylfulvene **1** and tropone **4** constitutes an important example of a [6 + 4]-/[4 + 6]-ambimodal cycloaddition, and this feature of higher-order cycloadditions is now known to be rather general.

The emergence of organocatalysis makes novel reactive intermediates accessible and offers the opportunity for exceptional stereoselectivity. Prior to the 2017 publication by the Jørgensen group,[34] only two enantioselective higher-order cycloadditions had been reported, the example by Rigby previously discussed and a metal-catalyzed *aza*-[8 + 2]-cycloaddition.[35] In the organocatalytic reactions, it was demonstrated that 2-cycloalkenones **11** and **12** could be activated by cinchona alkaloid-derived aminocatalysts (**13** or **14**) to afford reactive cross- and linear-dienamines, **15** and **16**,

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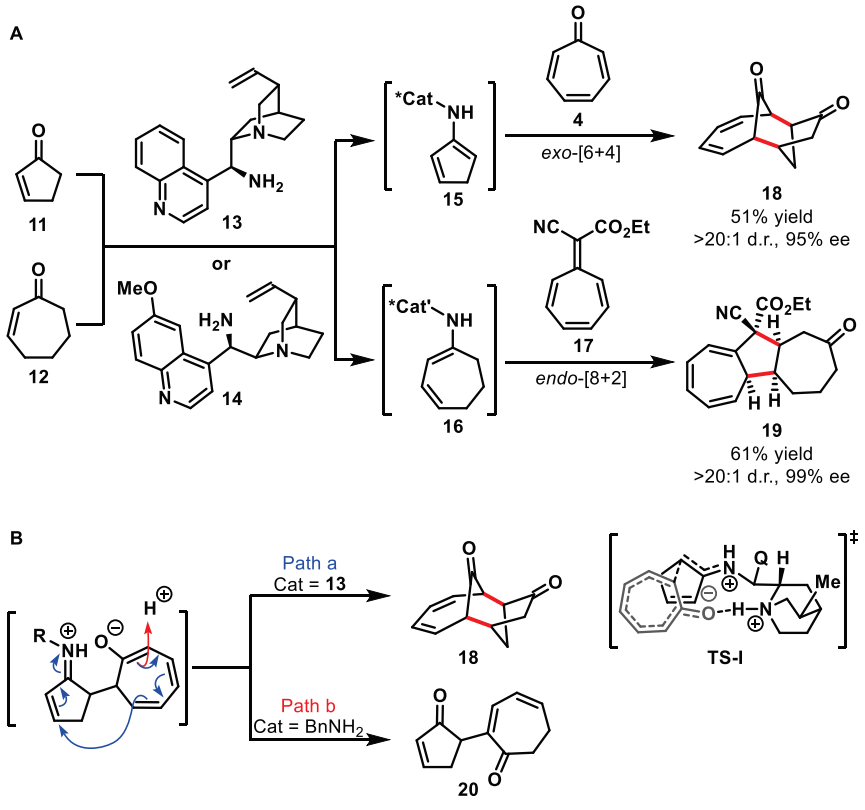

Figure 7. (A) First organocatalytic higher-order cycloadditions. (B) Mechanistic rationale for the organocatalytic [6 + 4]-cycloaddition. Cat = catalyst; Q = 4-quinolinyl.

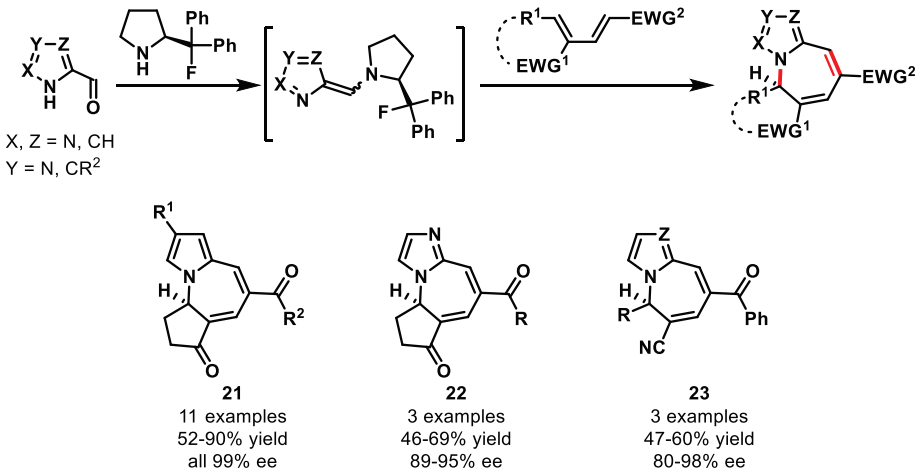

Figure 8. Organocatalytic hetero-[6 + 4]-cycloadditions of 2-formyl-substituted heteroaromatic compounds.

respectively. These intermediates undergo peri-, diastereo-, and enantioselective reactions with heptafulvenoids to provide the corresponding [6 + 4]- and [8 + 2]-cycloadducts, **18** and **19**, respectively (Figure 7A). These cycloadducts were typically obtained with exceptional diastereo- and enantiocontrol (>20:1 dr, ≥95% ee). The excellent periselectivity was controlled by the ring-size of the 2-cycloalkenone in combination with the substituents of the heptafulvenoid. Further investigation of the reaction pathway of the [6 + 4]-cycloaddition was performed through combined computational and experimental study (*vide supra*).[36]

In the presence of aminocatalyst **13**, cyclopentenone **11** was calculated to form cross-dienamine intermediate **15** over the corresponding linear-dienamine under acidic conditions. Dienamine **15** proceeds in the [6 + 4]-cycloaddition through a stepwise mechanism (Figure 7B, path a), although the conversion of intermediates to products has only small barriers. In fact, the distinction between concerted and stepwise is further blurred in such examples. Even when there is a shallow potential energy minimum on the potential surface, the intermediate here maintains the geometry related to the first TS, and the intermediate has a lifetime far too short to be trapped by anything other than the intramolecular formation of the second bond. More subtle factors control why the [6 + 4]-pathway is lower in energy than a [4 + 2]-pathway. The [8 + 2]-pathway is endothermic and disfavored. These results were consistent with the high periselectivity, or in this case, selectivity of the stepwise processes, observed exper-

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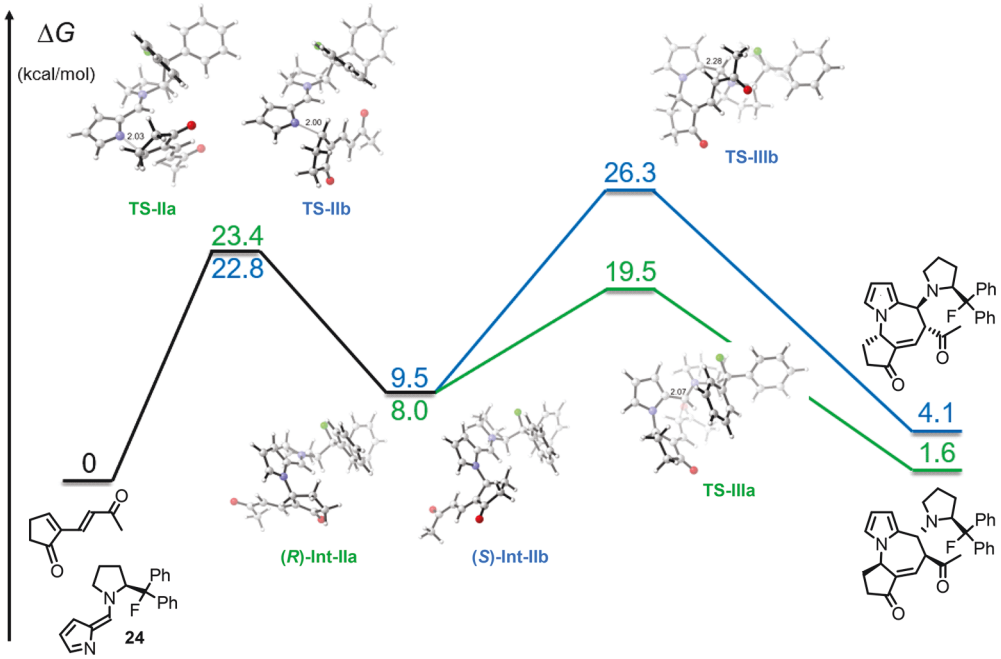

Figure 9. Lowest energy reaction profile for the hetero-[6 + 4]-cycloaddition.

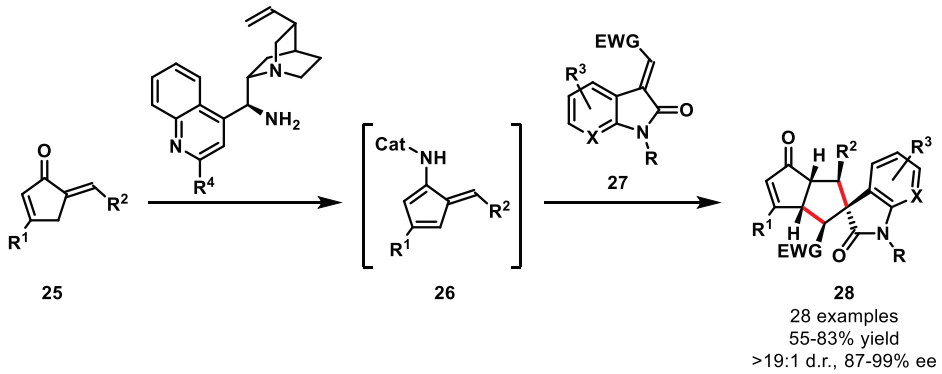

Figure 10. An organocatalytic [6 + 2]-cycloaddition of aminofulvenes **26** and 3-olefinic-(7-aza)oxindoles **27**.

imentally. A crown-like macrocyclic TS featuring a strong hydrogen bond between the protonated tertiary amine in **13** and the tropone was found computationally (Figure 7B, **TS-I**). Modulating the acid loading to the reaction revealed this hydrogen-bonding interaction to be crucial to both enantioselectivity and yield. Further support for the computed stepwise mechanism was achieved with the isolation of a noncyclized byproduct **20** when benzylamine was used as catalyst instead of **13** (Figure 7B, path b).

More recently, organocatalytic hetero-[6 + 4]- and -[6 + 2]-cycloadditions have been reported, providing rapid access to the biologically relevant pyrrolo-azepine core (Figure 8).[37] The reaction takes advantage of the ability of 2-formyl-substituted heteroaromatic compounds to condense with a secondary amine catalyst to generate 6π-addends, aminoazafulvenes, which undergo cycloadditions with electron-deficient 4π- and 2π-components. Highly enantioselective [6 + 4]-cycloadditions proceed for a series of heteroaromatic compounds such as pyrroles, imidazoles, and pyrazoles (Figure 8).

The reaction was shown to proceed via the aminofulvene **24** (Figure 9), generated from the corresponding iminium ion; both were observed by ^{19}F-NMR. Computational studies account for the excellent stereoselectivity obtained for the hetero-[6 + 4]-cycloadducts **21** (Figure 8). These studies indicate a stepwise [6 + 4]-cycloaddition, first by attack of the nitrogen lone-pair electrons onto the 4π-component through **TS-IIa** and **TS-IIb**, of similar energy, resulting in the formation of the diastereomeric intermediates **(*R*)-Int-IIa** and **(*S*)-Int-IIb**. Formation of **(*R*)-Int-IIa** is the rate-determining step toward the observed major stereoisomeric product. By contrast, the activation barrier of **(*S*)-Int-IIb** toward the observed minor product has a free energy significantly higher than the barrier of its formation, and therefore, by the Curtin–Hammett principle,[38] high enantioselectivity is achieved.

The Woodward–Hoffmann rules, which govern the boundaries of *allowed* cycloadditions, strictly only apply to concerted pericyclic reactions. As the [6 + 4]-cycloaddition of aminofulvene intermediates occurs via a stepwise mechanism, [6 + 2]-cycloadditions of these 6π-components is also possible. Though *forbidden* in concerted reactions, stepwise [6 + 2]-cycloadditions have precedent; in 1985, the intramolecular [6 + 2]-cycloaddition of fulvenes with enamines to construct tricyclopentanoids was reported by the Houk group.[39] An organocatalytic enantioselective variant of the intramolecular [6 + 2]-cycloaddition was published decades later by Hayashi et al.[40]

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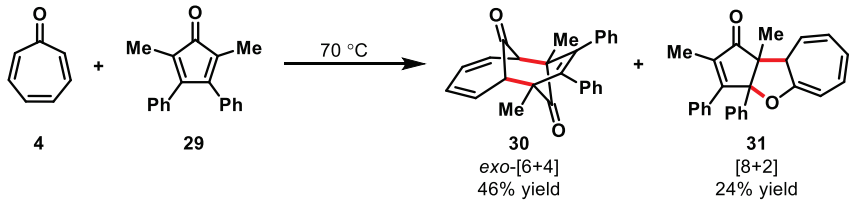

Figure 11. Early example of a [8 + 2]-cycloaddition as a side product in the reaction of tropone with a cyclopentadienone.

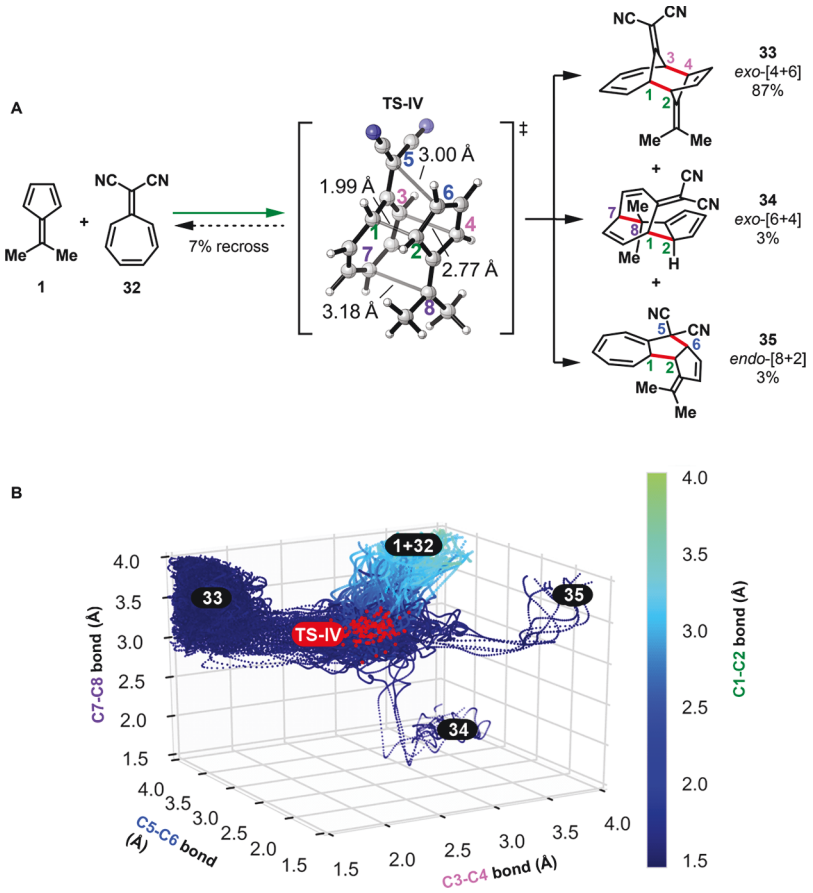

Figure 12. (A) Theoretical product distribution of a tripericyclic reaction (MD yields). (B) Trajectories initiated both forward and backward from **TS-IV**.

The first enantioselective *intermolecular* [6 + 2]-cycloaddition was reported in 2017 by Chen et al. (Figure 10).[41] The 4-aminofulvenes **26** were generated *in situ* from α'-benzylidene-2-cyclopentenones **25** catalyzed by cinchona alkaloid-derived amines and reacted with electrophilic 3-olefinic 7-azaoxindoles **27**. The fused bicyclic products **28** were isolated in generally good yields and with excellent stereocontrol.

The aminofulvene intermediates **26** are reminiscent of the 6-aminoazafulvenes, derived from condensation of 2-formyl heteroaromatic compounds with a chiral secondary amine catalyst, which reacted with electron-poor dienes in [6 + 4]-fashion (Figure 8). Indeed, these 6-aminoazafulvenes were also found to participate in stepwise [6 + 2]-cycloadditions with nitroolefins.[37] These enantioselective organocatalytic reactions afforded the corresponding pyrrolizidines in modest yield and good enantioselectivity (73−91% ee).

4. [8 + 2]- AND [10 + 4]-CYCLOADDITIONS

After Doering and Wiley's trapping of heptafulvene with dimethyl acetylenedicarboxylate (DMAD),[20] Boekelheide et al. reported the [8 + 2]-cycloaddition of indolizine with DMAD.[42,43] Notwithstanding sporadic reports involving other polyene ring systems, heptafulvenes and their hetero-analogues and isobenzofulvenes are the two most common classes of substrates that undergo [8 + 2]-cycloadditions. Heptafulvenes can be electron-rich or electron-deficient depending on the exocyclic substituent; the exocyclic substituent exerts a significant controlling influence upon the stereo-, peri-, and regioselectivity of the cycloaddition.[44] Electron-rich heptafulvenes typically react as an 8π-component, while the more stable electron-deficient heptafulvenes exhibit broader reactivity (*vide infra*).

The earliest example of the [8 + 2]-cycloaddition of a heteroheptafulvene employed tropone with dichloroketene[45] and was quickly followed by an analogous example using diphenylketene.[46] Despite these examples, tropone usually

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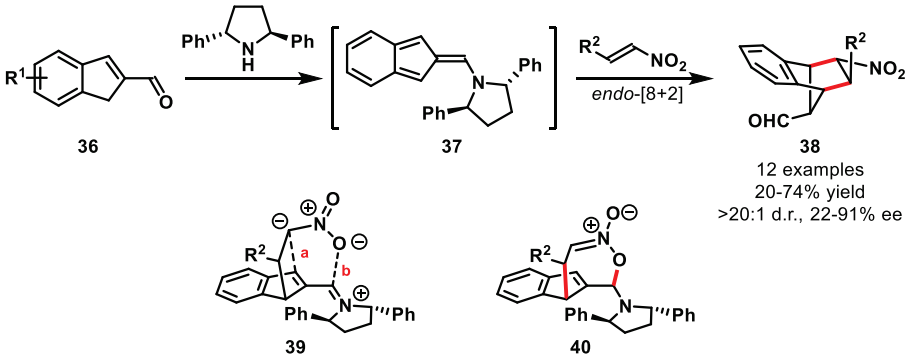

Figure 13. Organocatalytic [8 + 2]-cycloaddition with proposed zwitterionic intermediate **39** displaying reaction paths a and b leading to the [8 + 2]-cycloadduct **38** and potential [10 + 4]-cycloadduct **40**.

reacts as a 6π- or 4π-component but can react competitively as an 8π-component as demonstrated by Houk (Figure 11).[10] More electron-rich aza-heptafulvenes and tropothione, by contrast, undergo efficient [8 + 2]-cycloadditions with electron-deficient alkenes under mild conditions.[47]

In 1992, Liu and Ding further studied the effects of the exocyclic substituent of heptafulvene on selectivity through the reactions between 8,8-dicyanoheptafulvene **32** or 8-cyano-8-(methoxycarbonyl)heptafulvene and dimethylfulvene **1**.[48] They observed the formation of both [8 + 2]- and [6 + 4]-cycloadducts and hydrogen-shift derivatives. Most recently, the Houk group explored these reactions with DFT computations and quasi-classical direct MD simulations. The calculations revealed that both [8 + 2]- and [6 + 4]-cycloadducts are formed from a single tripericyclic transition state (**TS-IV**).[49] The transition structure (**TS-IV**, Figure 12A) for the reaction of **1** with **32** is highly asynchronous with four partially formed σ-bonds, as compared with the three partially formed bonds observed in the ambimodal TS for the reaction between tropone and dimethylfulvene (Figure 6). Quasiclassical trajectories initiated from **TS-IV** lead to three different cycloadducts, **33**, **34**, and **35** (Figure 12B), confirming the ambimodal nature of the TS. Cope rearrangements convert **33** to the more thermodynamically stable **34** and **35**. The initial distribution of adducts **33**, **34**, and **35** is determined by post-transition-state dynamics, while the observed products are the result of thermodynamic control.[51]

While Houk and Liu expanded the scope of [8 + 2]-cycloadditions to intramolecular examples,[50] progress on stereoselective variants was not realized until the 21st century. The first catalytic enantioselective [8 + 2]-cycloaddition of azaheptafulvene and diethyl 2-benzylidenemalonate with a chiral nickel complex was reported by Feng et al.[35] Pericas et al. demonstrated that azaheptafulvenes undergo smooth enantioselective formal [8 + 2]-cycloaddition by the stepwise addition of chiral ammonium enolates (derived from activated carboxylic acids and isothioureas).[51] In a subsequent report, *N*-hetereocyclic carbenes were used to catalyze the diastereodivergent [8 + 2]-cycloaddition of tropone derivatives and α,β-unsaturated aldehydes.[52] The reactions proceeded in good yield and high enantioselectivity, albeit with modest diastereoselectivity for most examples. An aminocatalytic [8 + 2]-cycloaddition employing α,β-unsaturated aldehydes and the inherently unstable tropothione has recently been disclosed.[53]

Isobenzofulvenes (IBFs), while less studied, also display a propensity to react as an 8π-component (this may also be considered a 4π-component if the fused benzo is not included in the electron count, but it does indeed experience bonding changes in the reaction). Hafner and Bauer reported the first synthesis of a dimethylamino-IBF derivative and its subsequent reaction with maleic anhydride in both [8 + 2]- and [10 + 2]-fashions.[54] Later, Watson and Warrener were able to prepare dimethyl- and diphenyl-isobenzofulvene, which react exclusively in [8 + 2]-cycloadditions with classical 2π-dienophiles with high *endo*-selectivity.[55] The low stability of the parent chain significantly retarded further investigation into these systems. Catalytic generation of highly reactive intermediates and their controlled subsequent utilization has recently been of high interest to the Jørgensen group, as the employment of the IBF core in higher-order cycloadditions presented exciting challenges. Organocatalytic *in situ* formation of amino-IBF **37** from stable, easily accessible indene-2-carbaldehydes **36** allows for facile [8 + 2]-cycloaddition with nitroolefins (Figure 13).[56] This constitutes the first catalytic formation and application of the reactive IBF core. The [8 + 2]-cycloadducts **38** were generally obtained in good yield and with excellent enantioselectivity.

DFT calculations were performed to elucidate the origin of stereoselectivity of the reaction. Zwitterionic intermediate **39** was found, resulting from initial Michael addition of intermediate **37** onto the nitroolefin. Subsequent ring-closure of **39** through pathway a (Figure 13) furnished the [8 + 2]-cycloadduct **38**. Unexpectedly, intermediate **39** was found computationally to be in equilibrium with a ring-closed oxazepine-*N*-oxide [10 + 4]-cycloadduct **40**, formed by ring closure through pathway b, possibly indicating the existence of a post-transition-state bifurcation. While never observed experimentally, cycloadduct **40** encouraged development of further higher-order cycloadditions.

IBFs can be utilized as 10π-components to undergo [10 + 4]-cycloadditions with high periselectivity. Two instances of *in situ* generation of 8,8-dimethylisobenzofulvene through electrocyclic fragmentation have been reported.[57,58] This highly reactive species was shown to undergo a [10 + 4]-cycloaddition with tropone to deliver an *exo*-adduct.[57] Furthermore, an *endo*-[10 + 4]-cycloaddition, established through modeling and confirmed by NOE data, of 8,8-dimethylbenzofulvene and a 1,3-dipole has been reported in low yield.[58] It was observed that the periselectivity necessary for the formation of the oxazepine *N*-oxide, indicated by computations, could be harnessed by changing the 4π-component. The catalytic reaction of the IBF derived from **41** with an all-carbon diene facilitated the irreversible formation of [10 + 4]-cycloadducts (Figure 14).[59] Judicious

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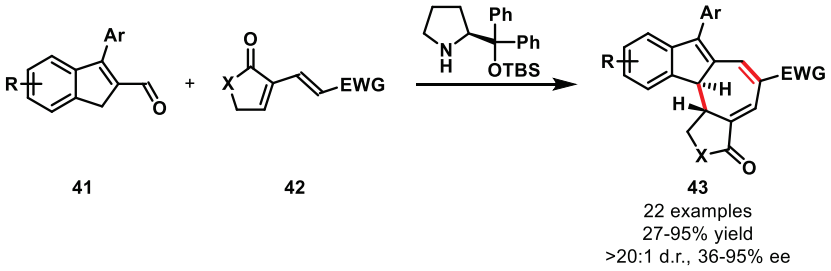

Figure 14. Organocatalytic [10 + 4]-cycloaddition.

placement of electron-withdrawing groups allowed for both conjugate addition and E1cB elimination of the aminocatalyst postcyclization. Oxadendralenes **42** were found to be exemplary in this regard. Thus, the first catalytic [10 + 4]-cycloaddition was accomplished, facilitating the stepwise formation of tetracyclic compounds **43** in high yields with excellent peri- and enantioselectivity through asymmetric aminocatalysis. Only *exo*-products were found, in accordance with the Woodward–Hoffmann rules.

Deriving inspiration from the straightforward formation of a dihydrobenzoazulenic core, fully aromatic benzoazulenes could be prepared in a single synthetic step from amino-IBFs. To accommodate elimination postformation of the seven-membered ring, the presence of a leaving group in the position of initial conjugate addition was necessary. Two classes of all-carbon 4π-components were identified as productive toward the synthesis of benzoazulenes.[60] Electron-deficient chromone derivatives delivered phenolic products in generally high yields, utilizing pyrrolidine as catalyst. Application of pyrone as a cyclic 4π-component exemplified the possibility to synthesize benzoazulenes in moderate yields through concomitant release of the aminocatalyst and CO_2. Stereocenters are absent from the benzoazulene products, but *exo*-selectivity is assumed in analogy to the previous [10 + 4]-cycloaddition conducted under similar conditions. The general reactivity of amino-IBFs toward 4π-components is remarkable, as they react with different classes of dienes to give [10 + 4]-cycloadducts with extremely high periselectivity. These transformations can be classified as aminocatalytic *aromative reactions*, in which a key high-energy intermediate, the IBF, is stabilized through partial aromaticity. This interesting phenomenon curbs the promiscuity inherent in the reactivity of polyene systems, and may be the key to unlocking currently unknown higher-order cycloadditions.

5. EVEN HIGHER-ORDER CYCLOADDITIONS

While simple orbital symmetry considerations place no upper limit of electrons that can be redistributed in concert, polyene systems of extended conjugation often demonstrate uncontrollable reactivity. Stability issues or a tendency to form complex mixtures of conformational and configurational isomers can present very real limits to the synthetic value of such components. Because of these challenges, cycloadditions involving more than 10π-electrons have only rarely been found synthetically viable. IBFs have been shown to react with high periselectivity with up to 18π-electrons. 8,8-Dimethylisobenzofulvene reacts with tropone in an *exo*-[8 + 6]-cycloaddition,[31] while *endo*-[10 + 8]-cycloadditions have been reported either by dimerization[61] or with isobenzofuran (Figure 15).[62]

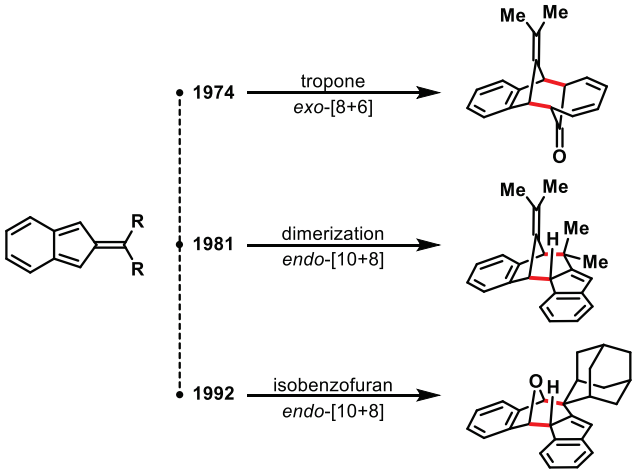

Figure 15. Examples of higher higher-order cycloadditions.

6. ENZYME-CATALYZED HIGHER-ORDER CYCLOADDITIONS

The Woodward–Hoffmann rules spurred the development of cycloaddition chemistry, and there was long speculation that nature might also use enzymes to catalyze cycloadditions for biosynthesis. Since the discovery of the first Diels–Alderase in 1995,[63] a broader class of enzymes have been coined: "pericyclases" are those enzymes that catalyze pericyclic reactions.[64] Today, Diels–Alderases are well-established in biosynthesis, with numerous examples;[65] lovastatin nonaketide synthase (LovB)[66] and PvhB catalyze the intramolecular Diels–Alder reaction to form *trans*- and *cis*-decalins, respectively.[67] The Houk group has proposed enzyme-catalyzed [6 + 4]-cycloadditions,[68−70] but examples have only recently been characterized.[71]

In 2010, Capon and co-workers isolated heronamides A–C from *Streptomyces* sp. and proposed a mechanism for their biosynthesis.[72] The polyene macrolactam heronamide C is the precursor to the heronamides A and B (Figure 16A). Capon et al. proposed that heronamide C **46** underwent a 12π-electrocyclization to yield heronamide B **45** and an S_N2 cyclization followed by a [6 + 4]-cycloaddition to form heronamide A **44**. In the following years, Kakeya et al. discovered that the latter reaction was possible at room temperature.[73] These results prompted a computational investigation from the Houk group on the nature of the putative [6+4]-cycloaddition step in the synthesis of heronamide A **44**.[69] DFT calculations indicate that the model intramolecular cycloaddition of **47** proceeds through an ambimodal **TS-V** that leads directly to **48** and an unobserved Diels–Alder side product **49** (Figure 16B). This computational study indicates that the [6 + 4]-cycloaddition

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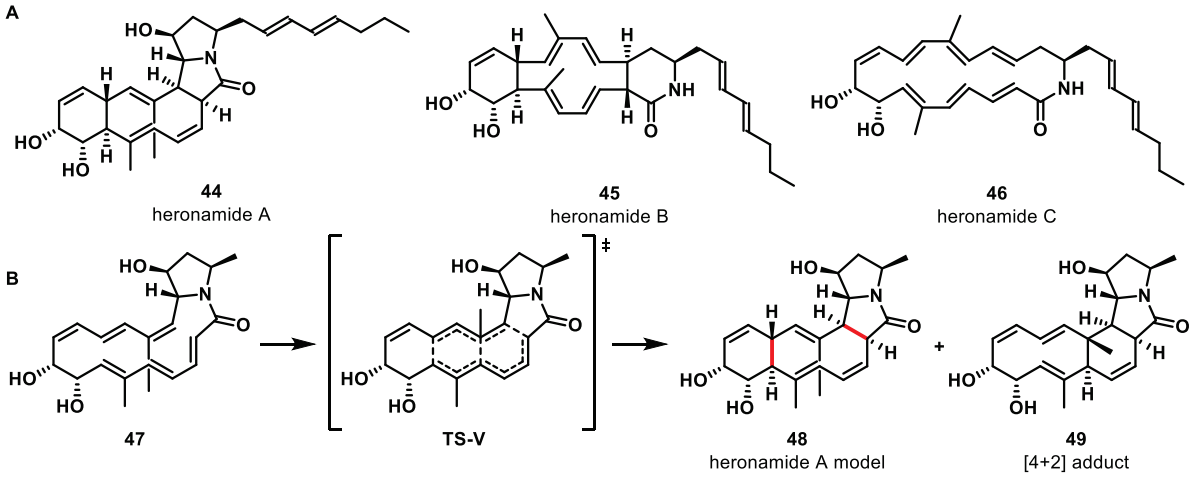

Figure 16. (A) Heronamides A–C. (B) Proposed cycloaddition step in the formation of heronamide A.

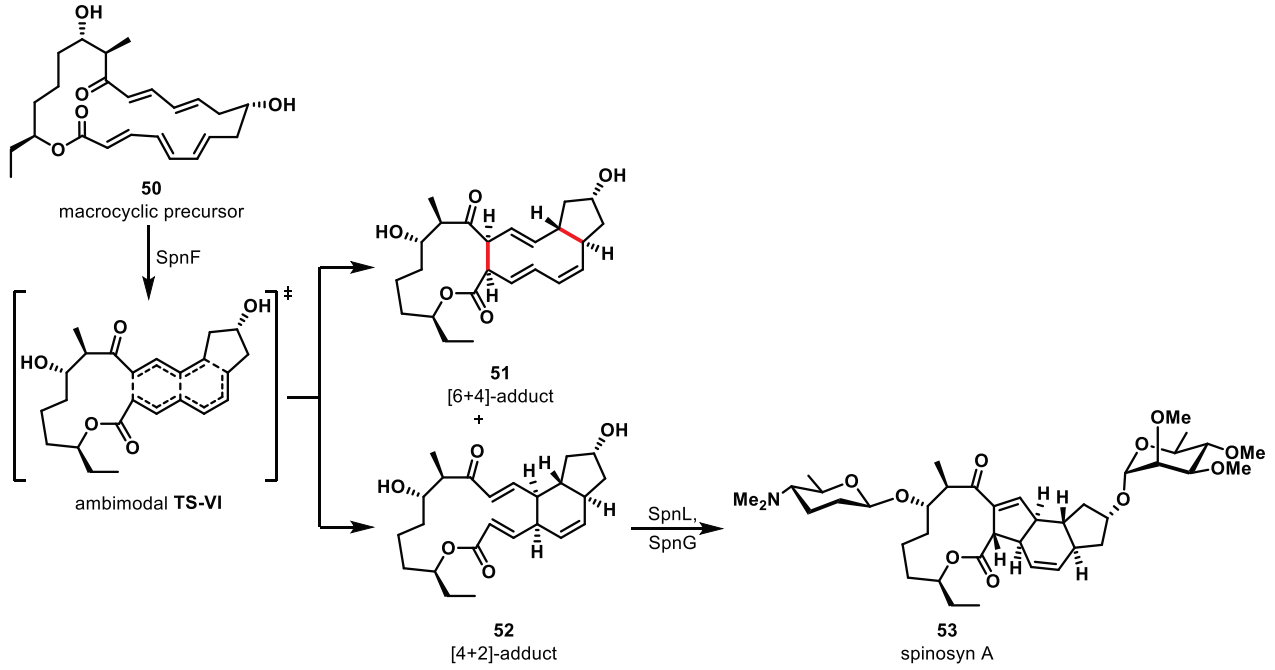

Figure 17. Final steps of the proposed biosynthesis of spinosyn A, depicting the ambimodal TS that leads to the [6 + 4]- and [4 + 2]-adducts.

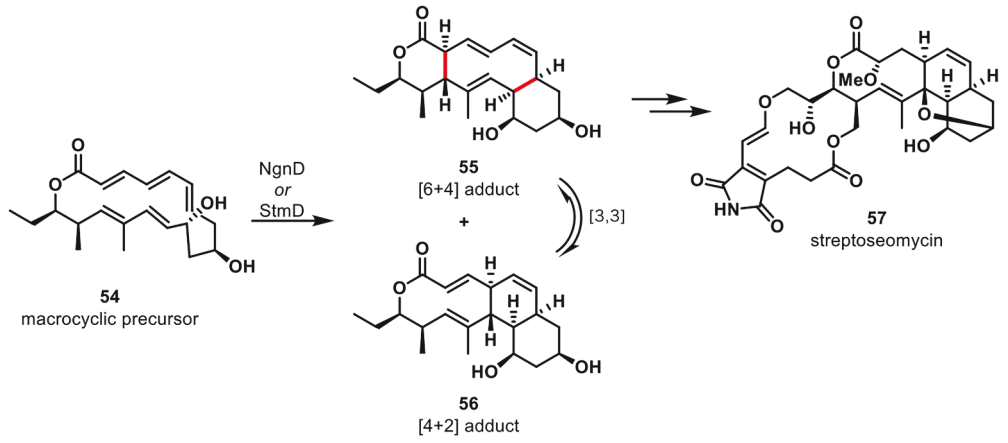

Figure 18. Cycloaddition step in the biosynthesis of streptoseomycin.

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occurs spontaneously in the biosynthesis of heronamide A and may not require enzyme catalysis.

In 2011, the first monofunctional enzyme, SpnF, was discovered to catalyze a Diels–Alder reaction involved in the biosynthesis of spinosyn A (Figure 17).[74] Previously characterized Diels–Alderases were found to catalyze multiple reactions and thus obscured the rate of reaction enhancement. SpnF accelerates the nonenzymatic Diels–Alder reaction 500-times to form the 5,6-bicyclic system of spinosyn A. Following publication of the SpnF crystal structure,[75] multiple computational papers proposed possible mechanisms of enzymatic activity.[76,77] Extensive quantum mechanical and dynamic simulations from Houk, Singleton et al. demonstrated that the reaction proceeds through an ambimodal TS, similar to that in the heronamides, which leads directly to the observed Diels–Alder adduct and an unobserved [6 + 4]-adduct.[70] In this case, the [6 + 4]-adduct is less thermodynamically stable and is readily converted to the Diels–Alder adduct via a Cope rearrangement. MD simulations indicate that the [6 + 4]-adduct is initially formed in 1% of the cases, while the majority of trajectories form the Diels–Alder adduct.[68]

The first unambiguous enzymatic [6 + 4]-cycloaddition has recently been reported in the biosynthesis of streptoseomycin and related macrolactone natural products, based on experiments and computational work.[71] Related to the previous examples, this macrocyclic precursor **54** undergoes an ambimodal [6 + 4]/[4 + 2]-cycloaddition, catalyzed by the homologous enzymes NgnD or StmD (Figure 18). This is the first example of the [6 + 4]-adduct being directly observed in an enzymatic reaction. Initially, the [6 + 4]-adduct **55** is the major product; an equilibrium is then established between **55** and the [4 + 2]-adduct **56** via a Cope rearrangement. The [6 + 4]-adduct **56** is converted to the natural product streptoseomycin **57** enzymatically.

The biosyntheses of the natural products heronamide A, spinosyn A, and streptoseomycin involve bipericyclic [6 + 4]- and [4 + 2]-cycloadditions. The catalysis of higher-order cycloadditions by enzymes may only be the tip of the iceberg; many other reactions of this type are likely catalyzed by as yet unknown pericyclases.

7. CONCLUSION AND PERSPECTIVE

As there is generally a thermodynamic driving force for a cycloaddition, it should not matter much whether a prospective reaction proceeds in a concerted or stepwise fashion. Yet often orbital symmetry-allowed reactions are the ones chosen, or rather orbital symmetry-forbidden ones are avoided. This holds for larger electron counts, as it does for smaller ones. This Account shows that these guiding principles are a rich source of reactions.

The history of higher-order cycloadditions seems to affirm the reactivity–selectivity paradigm;[78] the high reactivity of many extended polyene systems has made achieving selectivity difficult. This lack of periselectivity has hindered substantial development; in effect, the amount of work published to date on stereoselective variants of these important reactions is miniscule. Many of the recent publications in this area show that selectivity is readily achievable with judicious choice of reaction partners. Thus, a "balancing act" is necessary and catalysis offers ample opportunities for further developing this field. Where stoichiometric reactions have failed to yield the desired product in useful quantities, catalytic generation of reactive intermediates presents a unique opportunity and allows a degree of control that has only begun to be exploited.

While experimental and theoretical studies have individually advanced the field of higher-order cycloadditions, both approaches prosper from the interplay and collaboration between them. The study of the dynamics in this field has opened up a whole new world of ambimodal pericyclic reactions and the realization that several higher-order cycloadditions can share a common transition state. When reactions are allowed, catalysis can promote these processes: both natural evolution and our laboratories have achieved this. There are more higher-order cycloadditions in nature's wonderland, just waiting to be found.

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Notes

The authors declare no competing financial interest.

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Mathias Kirk Thøgersen received his B.Sc. in chemistry from Aarhus University in 2016 and is currently conducting Ph.D. studies in the group of Professor Karl Anker Jørgensen focusing on the experimental investigation and development of organocatalytic stereoselective higher-order cycloadditions.

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Karl Anker Jørgensen received his Ph.D. from Aarhus University in 1984. He was a postdoctoral researcher with Professor Roald Hoffmann at Cornell University (1985). In 1985, he became Assistant Professor at Aarhus University, and in 1992, he was promoted to Professor. His research interests are the development, understanding, and application of asymmetric catalysis mainly in the field of organocatalysis.

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K. N. Houk was a graduate student with R. B. Woodward at Harvard in 1965−1968, then on the faculties of Louisiana State University, University of Pittsburgh, and UCLA since 1986, now as Saul Winstein Research Chair in Organic Chemistry. He was Senior Editor of *Accounts* from 2005 to 2015. He is a Visiting Lecturer at Nanjing Agricultural University.

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Roald Hoffmann was born in Złoczów, Poland, now Zolochiv, Ukraine. He eventually came to the US at age 11. It was not easy to get here then, not easy now. He took advantage of every opportunity the US offered and eventually found himself a Junior Fellow in the Society of Fellows at Harvard. In the wonderful environment the Society of Fellows offered (essentially a well-paying, for its time, independent postdoc) his collaboration with R. B. Woodward began. Jeff Seeman is writing a remarkable cultural history of physical organic chemistry of the time: this is the period in which this work originated.

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