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Recent advances in metal-free catalytic enantioselective higher-order cycloadditions

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Higher-order cycloadditions (HOCs) present notable benefits for the synthesis of complex molecules, particularly those featuring medium size and multiple rings. The research on HOCs has experienced remarkable advancements since the influential exchange between Woodward and Hoffmann. In recent decades, significant progress has been achieved in enantioselective metal-free catalytic HOCs. These methodologies have facilitated the regulation of peri- and enantioselectivity during ring formation. With the diversification of activation modes, the variety of intermediates used in HOCs has also been greatly expanded. This review focuses on strategies for metal-free catalytic construction of chiral frameworks. To our knowledge, there are still many unknowns to be discovered in enantioselective HOCs.

1. From classical cycloadditions to higher-order cycloadditions

Cycloaddition reactions are a class of powerful organic transformations.[1] These reactions involve the formation of cyclic compounds from two or more reactants, often accompanied by the generation of multiple new carbon–carbon bonds.

Classical cycloadditions, usually referring to cyclisations with electrons less than or equal to 6π, have been widely utilized to form cyclic products.[2] These reactions occur *via* the simultaneous formation of two or more new bonds, typically with the concomitant loss of one or more π-bonds. The most well-known classical cycloaddition is the Diels–Alder reaction,[3,4] which involves the reaction of a conjugated diene with an alkene or alkyne to build a six-membered ring. Other important examples include 1,3-dipolar cycloaddition (*e.g.*, diazo compounds react with alkenes or alkynes) and [2 + 2] cycloaddition (*e.g.*, two

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alkenes or alkynes react with each other to form a quaternary ring).[5]

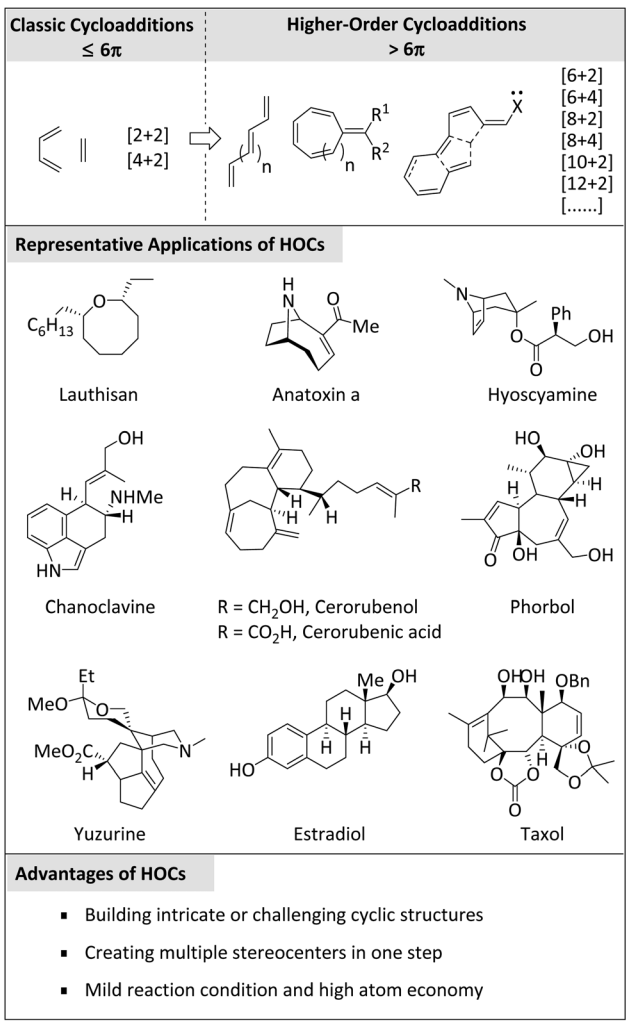
In 1965, Hoffman and Woodward conducted an important academic exchange, after which Houk experimentally verified the feasibility of the [6 + 4] cycloaddition reaction.[6,7] Almost simultaneously, Inoue, Morrison, and their colleagues independently demonstrated the viability of this new class of cyclic reactions.[8,9] Thus, the concept of higher-order cycloadditions was established and subsequently developed rapidly. Higher-order cycloadditions (HOCs)[10] generally refer to reactions in which more than six π-electrons participate, such as [6 + 2], [6 + 4], [8 + 2], [8 + 4], [10 + 2], [12 + 2] cycloaddition, *etc*. These reactions have attracted much attention due to their ability to produce complex polycyclic structures (*e.g.* natural products, pharmaceuticals, or valuable intermediates)[11–55] (Scheme 1).

While HOCs offer many advantages, many issues, such as steric hindrance, mechanical complexity, and selective control, are often encountered in their investigation. To overcome these problems, researchers continue to uncover new solutions to further promote the field of HOCs.

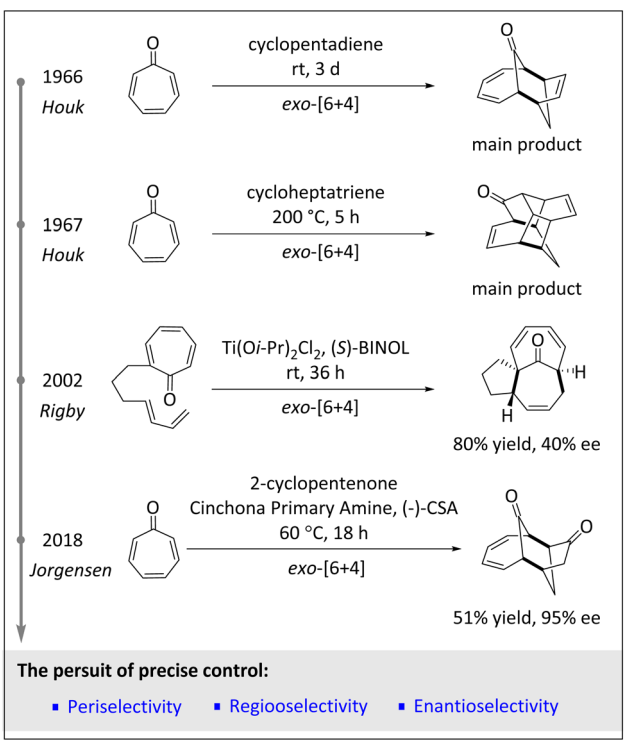
2. From racemic HOCs to asymmetric HOCs

The development of asymmetric HOCs has always been an important topic in synthetic chemistry. Racemic HOCs typically rely on heat to drive and enable reactions. Thermal HOCs involve the reaction of three or more molecules without the use of a catalyst. While these reactions can be used to synthesize complex molecules, there are some important questions. In fact, one of the main problems with thermal HOCs is that they are often difficult to be controlled. Since reactions usually proceed at high temperatures, side reactions, decomposition, or incomplete transformations are prone to occur. Furthermore, thermal HOCs often require long reaction times or high pressures to achieve reasonable yields.[9] Another significant challenge for thermal HOCs is regioselective control.[8] In short, considering the high temperature, long reaction time and purification problem, the application of HOCs in industry is extremely challenging.[56] In 2002, Rigby and co-workers reported an intramolecular [6 + 4] cycloaddition of Ti (IV)-assisted diene-tethered tropones for the construction of spirocyclic oxindoles,[57] indicating both high peri- and diastereoselectivity. Subsequently, the same team successfully synthesized the ingenane sesquiterpene core with high peri- and diastereoselectivities as well as moderate enantioselectivities *via* the use of a chiral Lewis acid catalyst (Scheme 2).

The emergence of organocatalysis has paved an alternative way for obtaining new intermediates and achieving excellent stereoselectivities. Before chiral amino catalysts were applied



Scheme 1 Brief introduction of higher-order cycloadditions.



Scheme 2 The brief history of higher-order cycloadditions.

to this field, enantioselective HOCs were very rare.[57,58] The Hayashi group first employed diphenylprolinol silyl ether as the organocatalyst to accomplish the asymmetric intramolecular [6 + 2] cycloaddition of fulvenes, resulting in the formation of valuable linear triquinane derivatives with high yields and exceptional enantioselectivities.[59] In 2018, the Jørgensen group[60] utilized cinchona alkaloid-derived amino catalysts to efficiently promote [6 + 4] and [8 + 2] cycloadditions, exhibiting excellent diastereo- and enantioselective control (>20 : 1 dr, ≥95% ee). Additionally, the periselectivities are well regulated by the combination of the ring size of the 2-cycloalkenone and the substituents of the heptafulvenoid.

Since then, organocatalytic HOCs have entered a new stage of rapid development. With the support of catalytic modes of enamine, imine, enolate and ion-pair catalysis, high efficiency and selectivity are regularly observed. In addition, computational chemistry interventions help researchers more accurately predict and design new asymmetric HOC reactions.

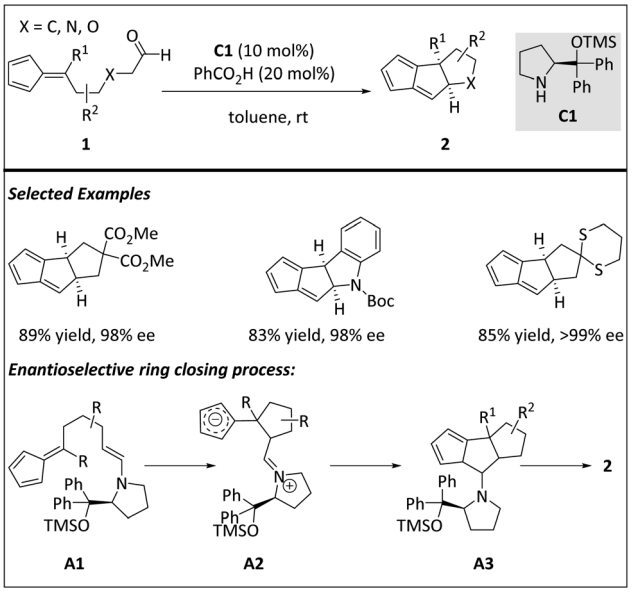
This review provides an overview of asymmetric organocatalytic HOCs. We summarize and classify HOCs according to the activation mode and discuss the fundamentals of reaction control. It also includes key advances in understanding and application, as well as challenges and opportunities for further development. Specifically, we focus on the design and formation of new synthons, the understanding of reaction pathways, and their application in natural product and drug synthesis. Overall, this review aims to provide a perspective on the current state of the art in asymmetric HOCs and highlights the exciting potential for future developments in this field.

3. Organocatalytic activation modes

The development of asymmetric HOCs is generally classified according to the types of intermediates formed by different catalysts.

3.1 Enamine catalysis

Hayashi and co-workers reported an effective intramolecular [6 + 2] cycloaddition reaction for the synthesis of linear triquinane derivatives by employing diphenylprolinol silyl ether as the chiral organocatalyst (Scheme 3).[59] The combination of linear aldehyde **1** and chiral aminocatalyst **C1** offers **A1**, a HOMO-raising 2π component. The electron rich 2π addend then reacts with a 6π fulvene core *via* **A2** to generate a triquinane structure **A3**. A systematic theoretical study of the reaction mechanism was carried out for a deeper understanding. DFT calculations show that the intermolecular [6 + 2] cycloaddition between the fulvene and the C=C bond of enamine is formed by the stepwise addition of the zwitterionic intermediate. In contrast, the intramolecular [6 + 2] cycloaddition to form a *cis*-fused triquinone backbone is carried out through a highly asynchronous transition state and a synergistic mechanism. The 6π fulvene functional group and 2π enamine moiety adapt the gauche–syn conformation during ring generation. The energy profiles also provide a plausible explanation



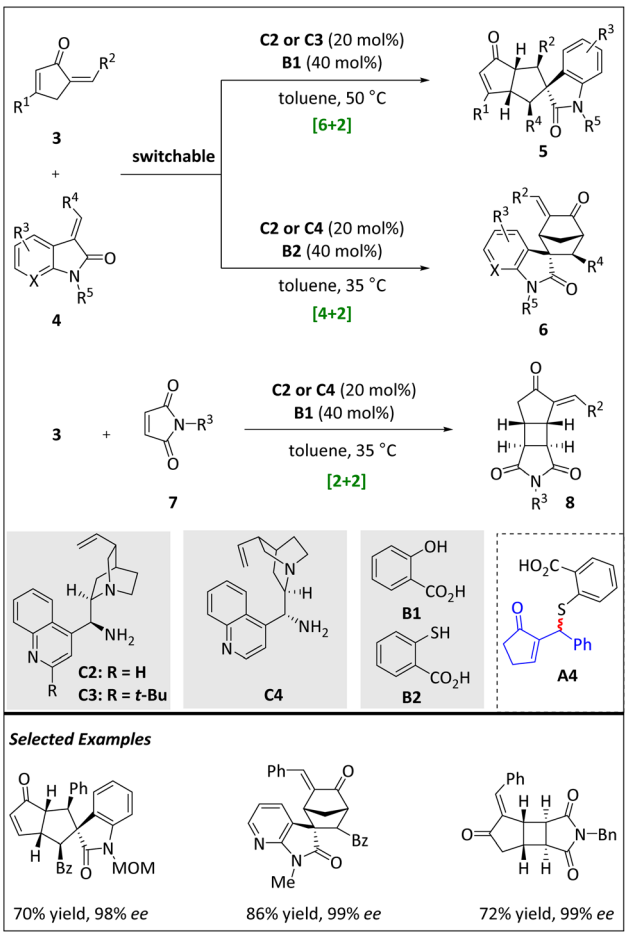
Scheme 3 Enantioselective synthesis of tricyclopentanoids *via* an intramolecular [6 + 2] cycloaddition reaction.

for the exclusive formation of the *cis*-fused triquinane skeleton. A detailed discussion on enantioselectivity control of this [6 + 2] process is also included.

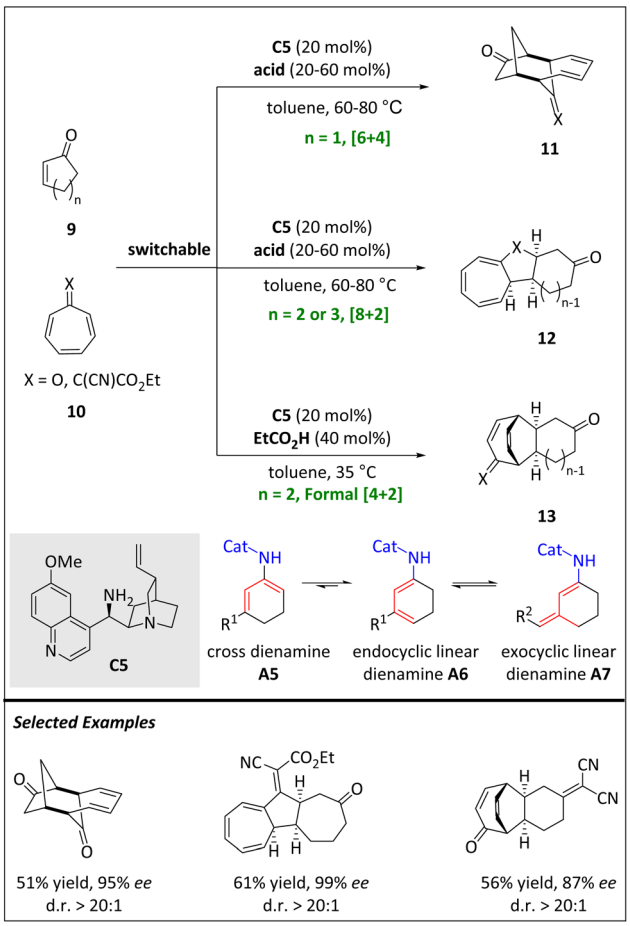
In 2017, Zhou and Chen *et al.* reported a series of [*n* + 2] (*n* = 2, 4, 6) intermolecular cycloadditions of alkylidene-2-cyclopentenones (Scheme 4).[61] When 3-olefin(7-aza)oxindole is used as a raw material, the primary amine catalysts **C2–C4** derived from cinchona alkaloids work with different Brønsted acids to facilitate the occurrence of switchable [6 + 2] HOC and [4 + 2] cyclization. When **3** reacts with maleimide **7**, an intriguing, γ-regioselective [2 + 2] cycloaddition process produces fused cyclobutanes. As mentioned before, the peri- and stereoselectivities are difficult to control in HOCs. The switching of different ring sizes is an absolute challenge.[62–65]

The generated highly reactive 6π component, 4-aminofulvene intermediate, then reacts with activated 2π alkene **4** to efficiently accomplish γ,β′-regioselective [6 + 2] HOCs. An array of bicyclic skeletons with five consecutive stereogenic centers is obtained through this pathway. Under the same reaction conditions, HOMO-raising trienamines react with suitable *N*-benzyl maleimide **7** to afford a number of tricyclic cyclobutanes in moderate yields but with excellent diastereo- and enantioselectivities. DFT calculations reveal that the previous regioselective [6 + 2] cycloaddition may occur through a stepwise Michael–Michael reaction mechanism, resulting in the formation of more thermodynamically stable [6 + 2] products. On the other hand, the [2 + 2] reaction is promoted through a kinetically favourable pathway by means of *ipso*, γ-regioselective [4 + 2] cycloaddition between maleimides and the HOMO-raised 4-aminofulvenes.

When acid **B1** is replaced by thiol acid **B2**, amine **C2** or **C4** successfully catalyzes the α,γ-regioselective [4 + 2] cycloaddition, affording a bridged structure **6** in high yields with



Scheme 4 Switchable asymmetric [6 + 2], [4 + 2] and [2 + 2] cycloadditions.



Scheme 5 Stereoselective intermolecular [6 + 4], [8 + 2] and formal [4 + 2] *via* aminocatalysis.

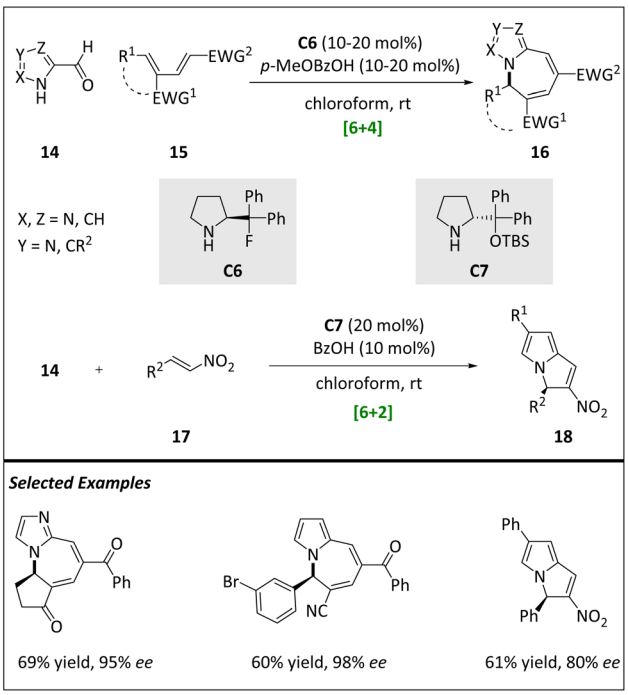
excellent diastereo- and enantioselectivities (Scheme 4). A brief mechanistic study reveals that acid **B2** can add directly to **3** in an α,β′-regioselective manner, leading to the formation of enone with a racemic sulfide moiety **A4**. Upon isomerization of the C=C bond, the [4 + 2] cycloaddition reaction mediated by dienamine is effectively promoted by the addition of olefin **7** and catalyst **C4**.

In the same year, the Jørgensen group developed a series of stereoselective cycloadditions (*e.g.* [6 + 4], [8 + 2] and formal [4 + 2]) through two types of dienamine intermediates (Scheme 5).[60] When the catalyst cinchona alkaloid-derived primary amine **C5** activates 2-cyclic enone **9**, a mixture of dienamine species, including cross dienamine, endocyclic linear dienamine, and exocyclic linear dienamine, is formed. The kinetically generated cross-dienamine intermediates drive the occurrence of [6 + 4] HOC and exhibit excellent stereoselectivities and moderate yields. Meanwhile, the carbonyl group of tropone **10** has proven to be a necessary functionality. By replacing 2-cyclopentenone with 2-cyclohexaenone, an inverse electron demand [4 + 2] cycloadduct is obtained. Notably, catalytic γ-functionalization by endocyclic linear dienylamines has not been reported. The authors hypothesize that [4 + 2] cycloadducts are made by an initial [8 + 2] cycloaddition followed by a rearrangement.

The thermodynamic distribution favours the transformation of 3-alkyl-2-cycloalkenones into endo- or exocyclic linear dienamines, while 2-cycloalkenones form endocyclic linear dienamines.[66] However, the cross dienamine is usually not observed in small amounts. Interestingly, the thermodynamic distribution of the dienamine mixtures is not reflected in the aminocatalytic reactions. Instead, 3-alkyl-2-cycloalkenones react through cross-dienamines or exocyclic linear-dienamines, while 2-cycloalkenones react through cross-dienamines. The control of periselectivities in cycloadditions is determined both by the ring size of 2-cycloalkenones and the substitution patterns of heptafulvenes.

In 2019, Houk and Jørgensen *et al.* presented an elegant work on asymmetric hetero-[6 + 4] and [6 + 2] HOCs.[67]

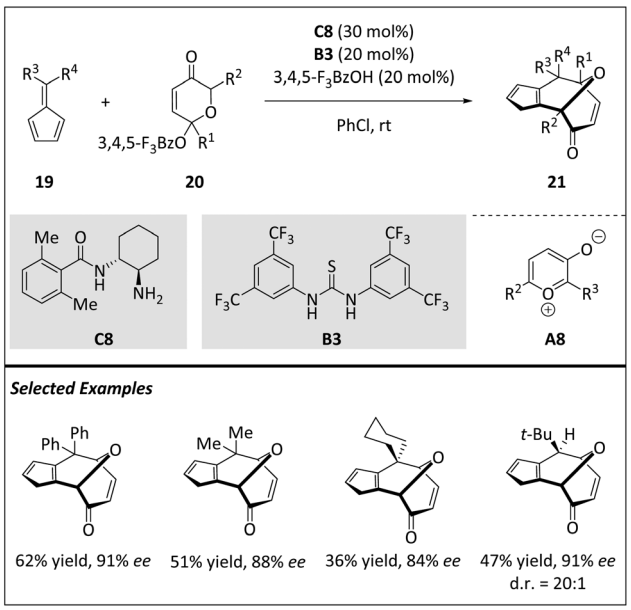
Specifically, formyl aldehydes derived from pyrroles, imidazoles, and pyrazoles can react with amino-catalyst **C6** or **C7** to generate electron-rich hetero-6π aza- and diazafulvenes. This component then undergoes chemo-, regio-, and stereoselective cyclization of electron-deficient diene **15** and nitroalkene **17** (Scheme 6). The hetero-[6 + 4] cycloaddition of pyrrole systems



Scheme 6 Stereoselective intermolecular hetero-[6 + 4] and [6 + 2] cycloadditions.

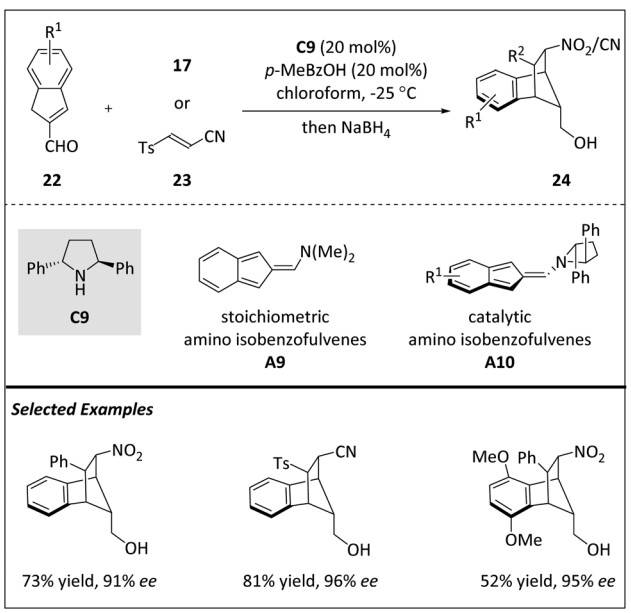
with dienes allows for a wide variation of both reaction partners, ultimately yielding pyrrolo-azepine products with high yields and excellent enantioselectivities. Importantly, the authors also extend this hetero-[6 + 4] cycloaddition protocol to imidazoles and pyrazoles, resulting in the production of imidazolo- and pyrazolo-azepines. This activation mode also achieves success in hetero-[6 + 2] cycloadditions of pyrroles with nitroolefins, synthesizing pyrrolizidine alkaloid scaffolds. DFT calculations showcase that the stereoselectivity is dominated by the stepwise addition and ring closing step. Various substrates and catalysts have an effect on enantioselectivity.

Due to high ring-strain and entropy, the formation of an eight-membered ring presents a challenging task. Although cyclooctanoid terpenes are an important class of structurally diverse natural products, the total synthesis of cyclooctane scaffolds lacks general synthetic methods. McLeod and Jørgensen *et al.* reported the first enantioselective 1,3-dipolar [6 + 4] cycloaddition of pyrylium ions **A8** with fulvenes **19** *via* primary amine organocatalysis (Scheme 7).[68] This method enables the rapid and stereoselective production of cyclooctane rings **21**. The diverse functional groups and transannular bridges facilitate the transformation of multiple stereoselective structures into complex structures, demonstrating the versatility of the core for a range of cyclooctanoid natural products. Computational studies of both catalytic and non-catalytic reactions indicate a stepwise mechanism, which agrees with the experimental results regarding regio- and stereochemical outcomes. The reaction exhibits excellent diastereoselectivity and facilitates a set of transformations, allowing for the efficient assembly of complex scaffolds.



Scheme 7 Asymmetric intermolecular 1,3-dipolar [6 + 4] cycloadditions *via* pyrylium ions.

Jørgensen and co-workers also disclosed a unique [8 + 2] cycloaddition of indene-2-carbaldehydes **22** and olefins **17** or **23** through an unprecedented catalytic amino isobenzofulvene intermediate **A10** (Scheme 8).[69] In 1968, Hafner and Bauer first used stoichiometric isobenzofulvenes in cycloaddition.[70] By introducing an amino moiety into exocyclic carbon, isobenzofulvene becomes more stable. It was found that the depicted amino isobenzofulvenes **A9** produced a blend of [10 + 2] cycloadducts when they reacted with *N*-phenylmaleimides. In the



Scheme 8 Peri- and stereoselective intermolecular [8 + 2] cycloadditions *via* an isobenzofulvene intermediate.

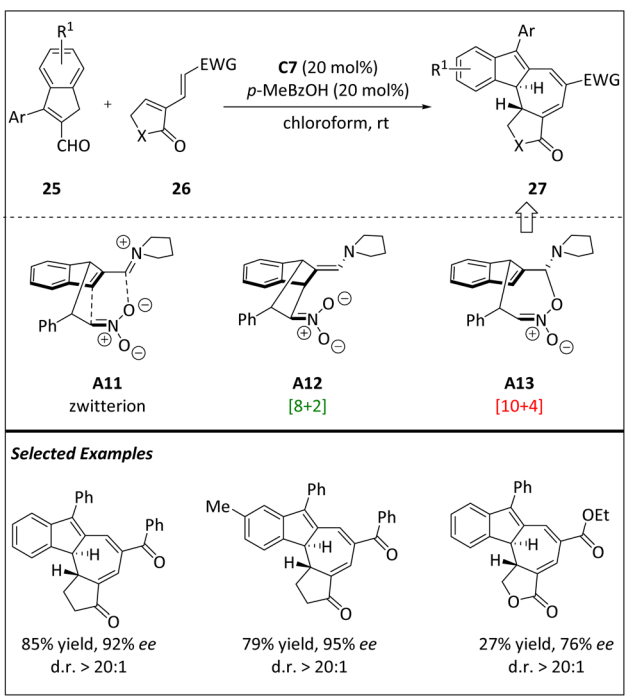
presence of chiral **A10**, a number of enantioenriched benzonorbornenes, which serve as common scaffolds in commercial pesticides and neurotransmitter analogs, are generated by [8 + 2] cycloadditions. In such a highly peri-, diastereo-, and enantioselective cyclization process, the C_2-symmetric catalyst **C9** is the key factor determining the stereochemistry of five contiguous centers. DFT analysis showed that an energetically feasible [10 + 4] cycloaddition pathway is plausible and the proposed zwitterionic structure can ultimately result in the [8 + 2] cycloaddition product.

According to the computational results of [8 + 2] cycloaddition, the [10 + 4] cycloadduct has the potential to be prepared through the kinetically preferred intermediate **A13**. The Jørgensen group realized this hypothesis by choosing electron-deficient diene **26** as the 4π component (Scheme 9).[69] Initially, the diphenylproline methylsilyl ether **C7** catalyzes the reaction between indane-2-carbaldehyde **25** and diene **26**, resulting in a mixture consisting of a small amount of presumed [8 + 2] cycloadducts and a separable quantity of [10 + 4] cycloadducts. However, by blocking the 3-position of indene-2-carbaldehydes, a single diastereoisomer **27** is obtained with a higher yield and high enantioselectivity. Both experimental and computational data show that the observed stereoselectivity is dominated by the formation of aminoisobenzofulvenes under kinetic control. The high yields, along with significant peri-, diastereo-, and enantioselectivities, and a broad scope of substrates make this technique extremely useful in the construction of intricate enantioenriched frameworks.

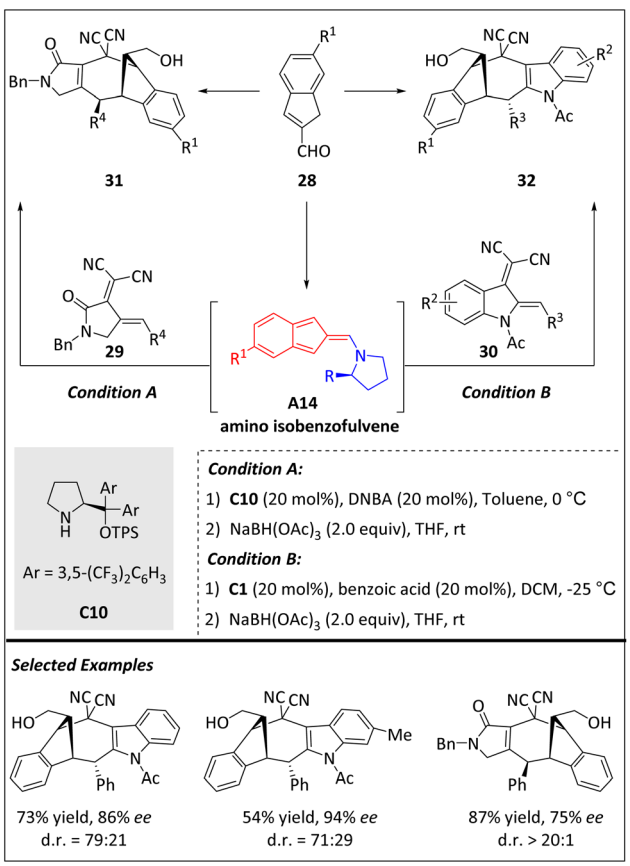
Although the asymmetric [8 + 4] cycloaddition of isobenzofurane can potentially be used for the direct construction of chiral bicyclo[4.2.1]nonane, the asymmetric version has not been achieved. Indeed, when Jørgensen *et al.* accomplished the asymmetric [8 + 4] cycloaddition reaction between indenhydrin-2-carboxaldehyde and methylene oxalate, they encountered several challenges in achieving isobenzofurans.[71] For example, (1) how to achieve periselectivity between 8π and 10π-components of isobenzofulvene? (2) how to ensure chemoselectivity among Michael addition and [8 + 2] and [8 + 4] cycloadditions? and (3) how to control the stereochemistry?

Later on, Zhao and Deng *et al.* developed a new method for asymmetric [8 + 4] cycloaddition of isobenzofuvene **A14** and electron-deficient dienes (IQDMs) with the assistance of secondary amine catalysts (Scheme 10).[72] This strategy efficiently offers indole cyclic bicyclo[4.2.1]nonane **32** with good yields, good enantioselectivities and moderate diastereoselectivities. In addition, the pyrrolidone-3,4-diene **29** is also well tolerated, yielding cyclic bicyclo[4.2.1]nonane **31** with good yields, high enantioselectivities and excellent diastereoselectivities.

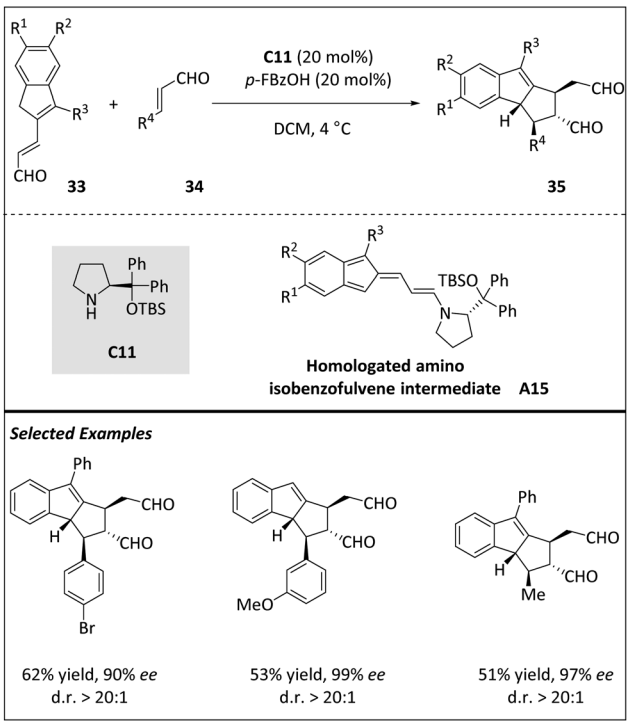
Jørgensen and coworkers reported a novel stereoselective [10 + 2] cycloaddition between homologated indenecarbaldehydes **33** and α,β-unsaturated aldehydes **34**, resulting in the assembly of tetrahydro-cyclopenta[*a*]indenes (Scheme 11).[73]



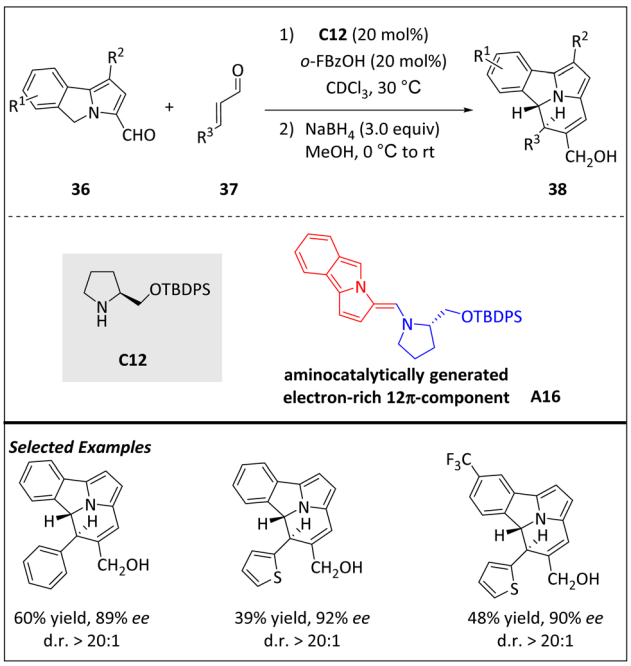
Scheme 9 Asymmetric intermolecular [10 + 4] cycloadditions *via* the isobenzofulvene intermediate.



Scheme 10 Asymmetric intermolecular [8 + 4] cycloadditions *via* the amino isobenzofulvene intermediate.



Scheme 11 Asymmetric intermolecular [10 + 2] cycloadditions *via* the homologated amino isobenzofulvene intermediate.



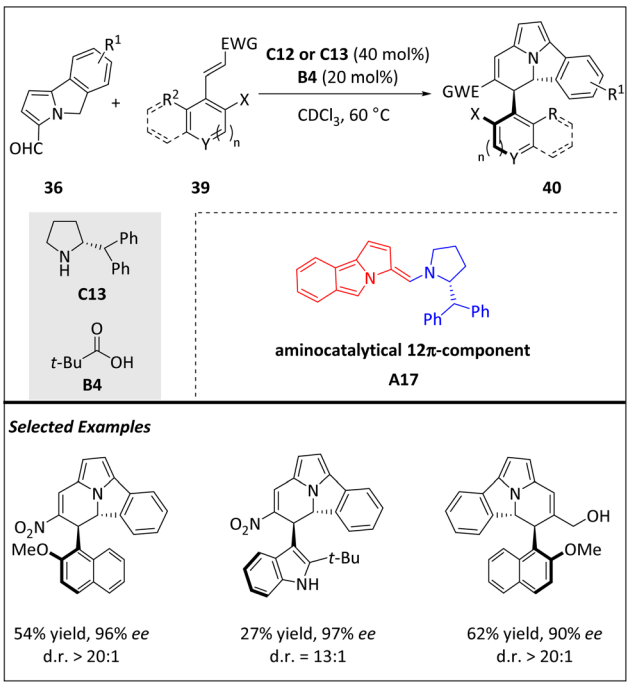
Scheme 12 Asymmetric intermolecular [12 + 2] cycloadditions *via* the aminocatalytical 12π intermediate.

The process involves the organocatalytic generation of homologated amino isobenzofulvene intermediate **A15**. Kinetic studies, DFT calculations, and isolation of intermediates suggest that a stepwise cycloaddition mechanism involving the Curtin–Hammett scenario is plausible. The stereo-determining step was the irreversible ring closure process, and the initial formation of precyclization intermediates is rapid and reversible. The reaction scope is thoroughly investigated, and the observed selectivity supports the mechanistic conclusions. This study contributes to the further development of cycloadditions with more than 6π-electrons, suggesting that these reactions tend to react selectively with specific partners based on electron effects and substrates.

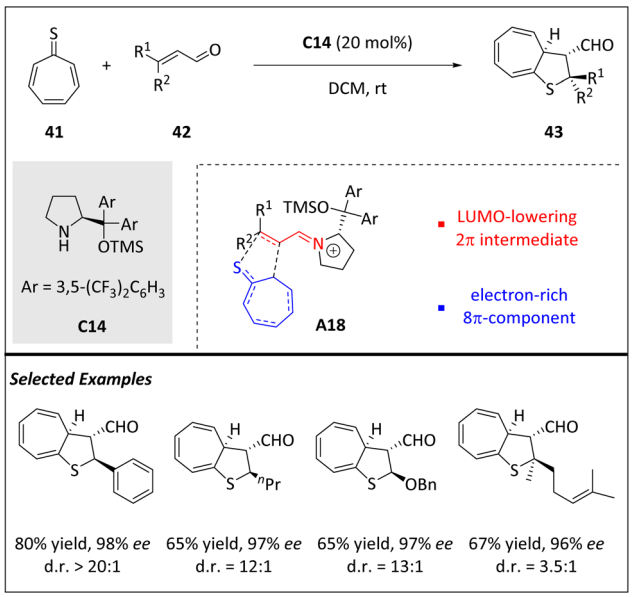
A one-step and direct organocatalytic process has been developed by Jessen and Jørgensen *et al.* for the enantioselective construction of a chiral cycl[3.2.2]azine core (Scheme 12).[74] This is the first enantioselective example of [12 + 2] cycloaddition of a tricyclic skeleton with a central ring-junction nitrogen atom. The electron-rich 12π component intermediate **A16** can be obtained from 5*H*-benzo[*a*]pyrrolizine-3-carbaldehyde **36** in the presence of aminocatalyst **C12**. Intermediate **A16** acts as a nucleophile and subsequently as an electrophile through the exocyclic position, enabling higher-order cycloadditions with electron-poor 2π-components to construct the cycl[3.2.2]azine core. It is worth noting that even-membered ring syntheses based on higher-order cycloadditions are uncommon but can be achieved in this case.

Although partial erosion of the diastereomeric ratio occurred during purification, one-pot reduction of the formyl group of cycloadducts preserves the stereochemical information. DFT calculations reveal that the observed high stereoselectivity relies on the energetic barrier of ring closure. Minor modifications to the reaction conditions allow for the introduction of *trans*-benzo[*a*]cycl[3.2.2]azines from α,β-unsaturated ketoesters and nitroolefins. Fully unsaturated and photoluminescent benzo[*a*]cycl[3.2.2]azines are also obtained in the presence of vinyl sulfones.

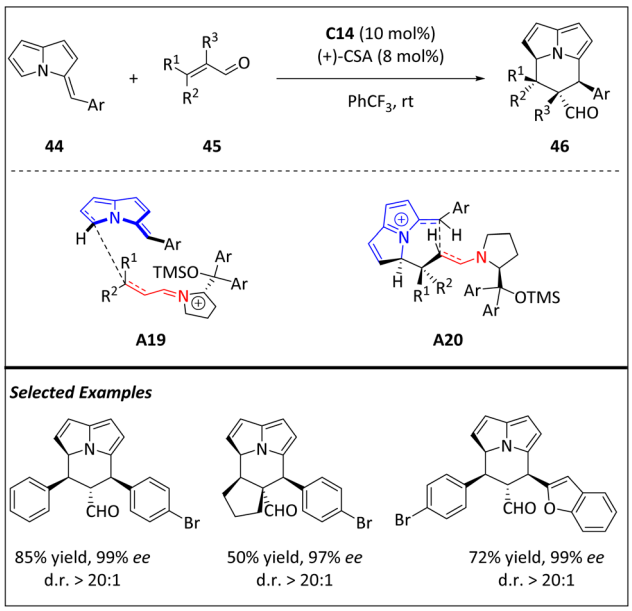
The higher-order cycloaddition reaction is not only useful in constructing multiple asymmetric centers in complex ring systems but also enables the atroposelective establishment of $C(sp^2)$–$C(sp^3)$. Most recently, the Jørgensen group developed a novel [12 + 2] HOC to access enantioenriched atropisomeric scaffolds that exhibit a stable $C(sp^2)$–$C(sp^3)$ stereogenic axis along with two chiral centers (Scheme 13).[75] Electron-rich aminocatalytic 12π intermediates **A17**, which were generated from 5*H*-benzo[*a*]pyrrolizine-3-carbaldehydes **36** with **C12** or **C13**, react with electron-poor olefins **39**, resulting in the formation of cycl[3.2.2]azine-based frameworks **40**. This approach is highly versatile, accommodating a wide range of substrates and producing various chiral products. The rotational barrier of parent compounds has been determined through experimentation, and both atropisomers have been separated and identified following thermal equilibration. The conformational stability of compounds with different substitution patterns is also evaluated, with a half-life of over 640 years. Additionally, the isolation of these unique compounds provides empirical evidence of the principle behind central-to-axial chirality conversions through a simple oxidative transformation. DFT calculations and the isolation of a reactive intermediate demon-



Scheme 13 Enantioselective intermolecular [12 + 2] cycloadditions for the construction of C(sp^2)–C(sp^3) atropisomers.



Scheme 14 Asymmetric intermolecular [8 + 2] cycloadditions *via* the LUMO-lowering strategy.



Scheme 15 Asymmetric intermolecular [8 + 2] cycloadditions *via* iminium-ion catalysis.

strate that the reaction's stereoselectivity is controlled by the Curtin–Hammett principle, with a single transition state (the elimination step) governing both the atropo- and enantio-induction.

3.2 Iminium catalysis

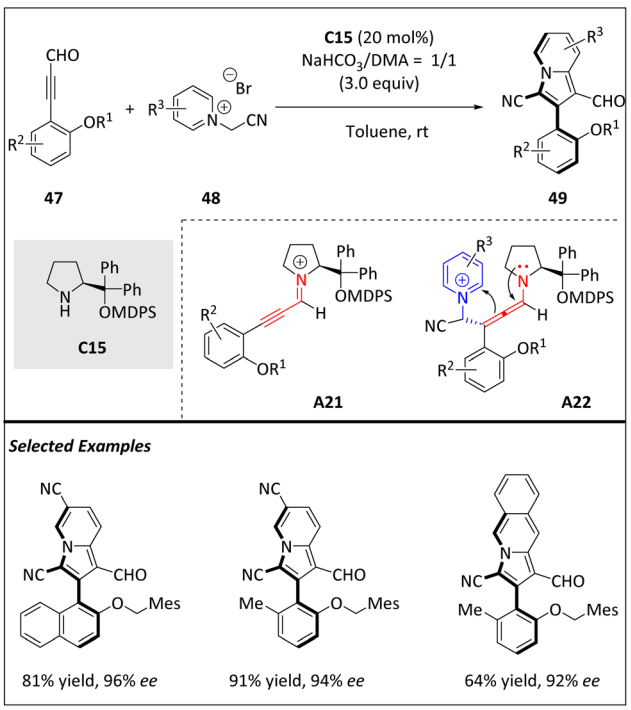
Lately, there has been growing interest in utilizing higher-order cycloadditions as a versatile platform to develop novel asymmetric transformations. Notably, organocatalytic activation strategies have gained attention in this regard. Among these, chiral amines have shown remarkable efficacies when utilizing a HOMO-raising activation pattern. The strategy of LUMO-lowering through iminium ion intermediates has greatly contributed to the development of asymmetric HOC as well.

In 2019, Albrecht and coworkers successfully utilized LUMO-activated iminium ions to react with tropothione **41** through an efficient [8 + 2] cycloaddition (Scheme 14).[76] In this finding, **41** has proven to be a highly stable and valuable reactant that readily engages in enantioselective higher-order cycloadditions. Unlike tropone and derivatives, which behaved as 8π or 6π-components and participate through their LUMOs as electron-poor systems, tropothiones act as electron-rich 8π-components based on their HOMOs. The stereochemistry is controlled by aminocatalytic LUMO-activation of the carbonyl reactant.

A rational design utilizing novel (*E*)-3-benzylidene-3*H*-pyrrolizines in iminium-ion-catalyzed [8 + 2] cycloaddition reactions proposed by Jessen and Jørgensen has facilitated the efficient and highly stereoselective synthesis of chiral cycl[3.2.2]azines (Scheme 15).[77] The protocol is capable of diverse enals, enolizable aldehydes, and substrates with extended conjugation. The resulting product has an electron-rich alkenylpyrrole and an electron-deficient carbonaldehyde moiety, both of which can be selectively modified without altering the stereochemical information in the [8 + 2] cycloaddition. The addition of electron-rich substrate **44** at its 5-position to the nonshielded face of iminium-ion substrates results in the formation of the first two stereocenters (**A19**). The tetrahydrocycl[3.2.2]azine scaffold, which contains four consecutive stereocenters (**A20**),

is then completed by ring closure through nucleophilic addition to the electrophilic pyrrolizine moiety. The aminocatalyst is then liberated through hydrolysis. The investigation of the acid-catalyzed isomerization pathway of cycloadducts emphasizes the importance of maintaining the balance between the loading of amino catalysts and acid additives.

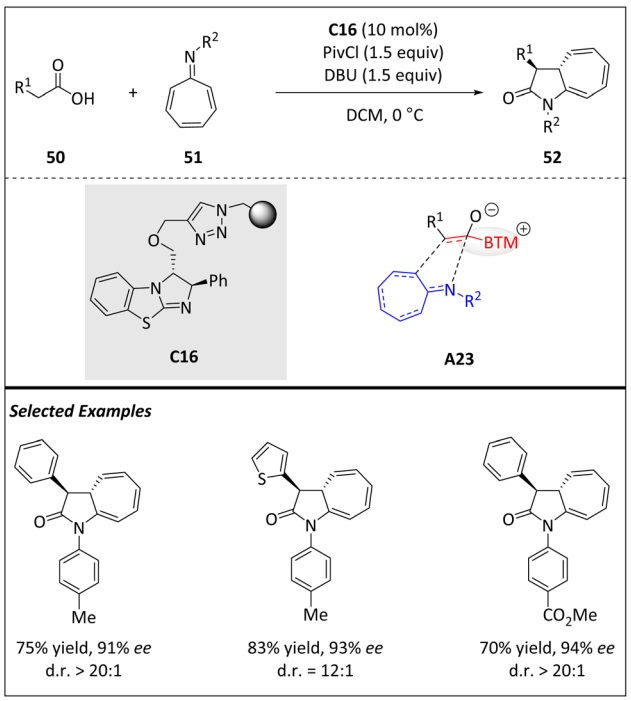
Yang and Wang *et al.* uncovered a new atroposelective [8 + 2] cycloaddition between pyridinium/isoquinolinium ylides and ynals (Scheme 16).[78] Significantly, this approach demonstrates a fresh illustration of the organocatalyzed atropoenantioselective higher-order cycloaddition, furnishing diverse axially chiral 3-arylindolizines **49** with exceptional yields and enantioselectivities. Due to their valuable photochemical properties and diverse therapeutic indications, 3-arylindolizines are recognized as one of the most significant heterocyclics. It is proposed that the chiral amine catalyst **C15** first reacts with alkynaldehyde **47** to the alkynylamine cationic intermediate **A21** through dehydration. Subsequently, the Michael addition of **A21** with **48** builds axially chiral allenamine **A22**. Next, intramolecular cyclization of **A22** leads to the formation of axial chiral heterodiaryl intermediates, which are then hydrolyzed into product **49** and release catalyst **C15** for the next catalytic cycle. The axially chiral **49** derivatives obtained in this reaction offer a wide range of functional groups, providing numerous opportunities for chemical transformations and drug discovery.



Scheme 16 Atroposelective intermolecular [8 + 2] cycloadditions *via* iminium-ion catalysis.

3.3 Enolate catalysis

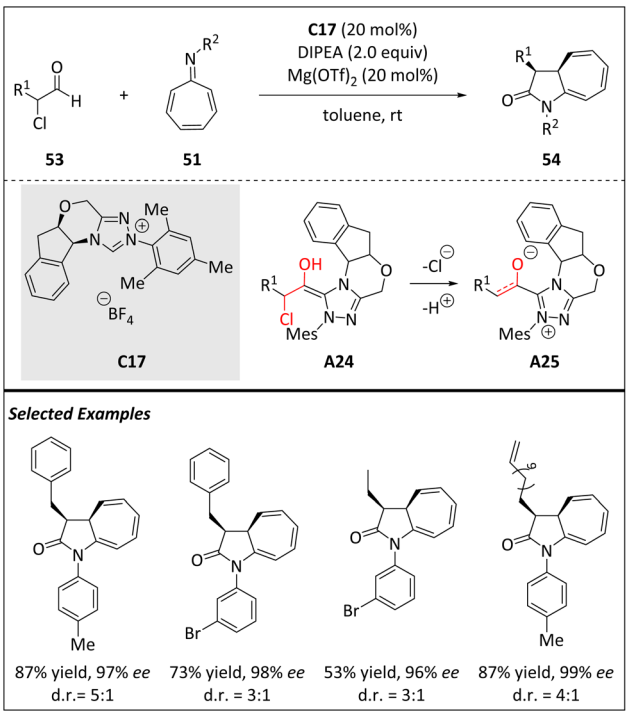
In 2017, Pericàs and colleagues presented a nice approach to produce cycloheptatriene fused pyrrolidone rings **50** with high enantioselectivities (Scheme 17).[79] It involves an isothiourea-catalyzed periselective [8 + 2] cycloaddition of chiral ammonium enolates **A23**, which are *in situ* generated from carboxylic acids **50** and azaheptafulvenes **51**. This straightforward process yields architecturally polycyclic structures.



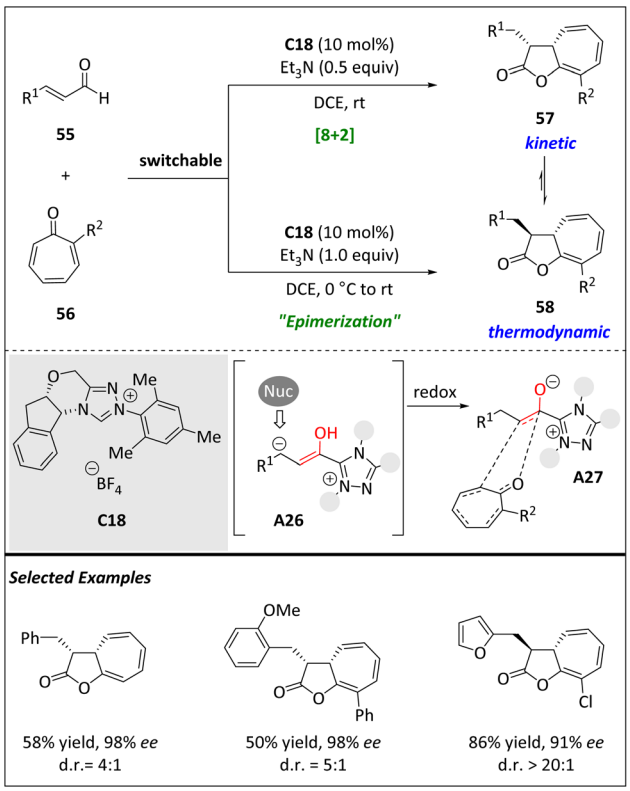
Scheme 17 Stereoselective intermolecular [8 + 2] cycloadditions *via* isothiourea catalysis.

In terms of practicality, the ability to recycle the immobilized isothiourea catalyst **C16** is highly desirable as it reduces costs and improves overall efficiency. In order to achieve this goal, catalyst **C16** is recovered through simple filtration and reused by adding fresh reactants after every single run. Surprisingly, no significant decrease in stereoselectivity is observed and only a slight yield decreases over the first four runs. The recycling experiments showcase an accumulated turnover number (TON = 44.7). Mechanistically, the mixed anhydride is produced *in situ* by the reaction of **50** with pivaloyl chloride. The corresponding acyl ammonium species is generated from the anhydride and isothiourea **C16**.

In 2019, a similar asymmetric [8 + 2] NHC-catalyzed cycloaddition reaction of azaheptafulvenes **51** with α-chloro aliphatic aldehydes **53** has been developed by Xu and coworkers (Scheme 18).[80] This reaction yields *cis*-cycloheptatriene-fused γ-lactams **54** with excellent enantioselectivities, moderate to good diastereoselectivities, and good yields. The resulting cycloadducts can easily transform into valuable structures under mild reaction conditions. In contrast to Pericas's method, the α-alkyl substituted reactants are well tolerated and a series of diastereo-cycloadducts are obtained. The proposed mechanism involves the formation of the Breslow intermediate **A24** *via* the addition of NHC catalyst **C17** to aldehyde



Scheme 18 Stereoselective intermolecular [8 + 2] cycloadditions *via* NHC catalysis.

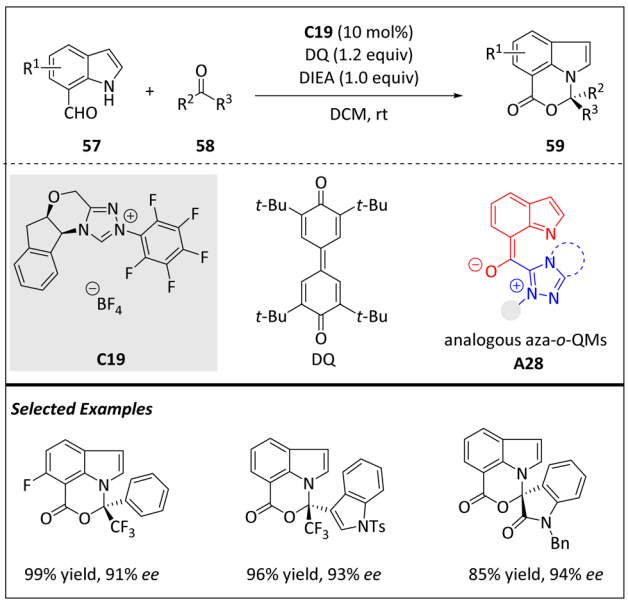


Scheme 19 Diastereodivergent asymmetric intermolecular [8 + 2] cycloadditions *via* NHC catalysis.

53. Intermediate **A24** is then dechlorinated and deprotonated to produce NHC-bound enolate intermediate **A25**. Next, Mg $(OTf)_2$ coordinates with the oxygen atom of intermediate **A25** and the nitrogen atom of azaheptafulvene **51** to form a transition state. Finally, intramolecular lactamization produces cycloheptatriene-fused γ-lactam **54** and regenerates catalyst **C17**.

The development of chiral catalysts has led to an expanding toolbox capable of covering various chemical spaces through numerous transformations. However, the emphasis is usually placed on selectivity rather than versatility. The Pericas group utilized the NHC catalyst to exploit the distinctive reactivity of enals compared to tropones, resulting in high enantiomeric purity of cyclohepta[*b*]furan-2-ones *via* higher order cycloadditions (Scheme 19).[81] In fact, the same group has recently published findings that demonstrate the ability of isothiourea catalysts to facilitate highly stereo- and periselective [8 + 2] annulations of azaheptafulvenes, producing [5.3.0] bicyclic products. However, a certain number of restrictions remained, such as the ineffectiveness of tropones and the tolerance solely of arylacetic acids as the 2π component. Consequently, they began to explore whether NHC catalysts could also facilitate these higher order cycloadditions. In this case, the Breslow intermediate **A26** smoothly yields azolium enolate **A27**, which acts as the 2π component in a redox-neutral process. Moreover, the reaction can be directed towards different diastereomers by modifying the reaction conditions, resulting in a shift from kinetic to thermodynamic control. The process is well tolerated with substituted tropones and the resulting cycloaddition products can be modified *via* hydrogenation or methanolysis. DFT computational kinetic modelling has provided strong support for the experimental results in terms of periselectivity and stereoselectivity.

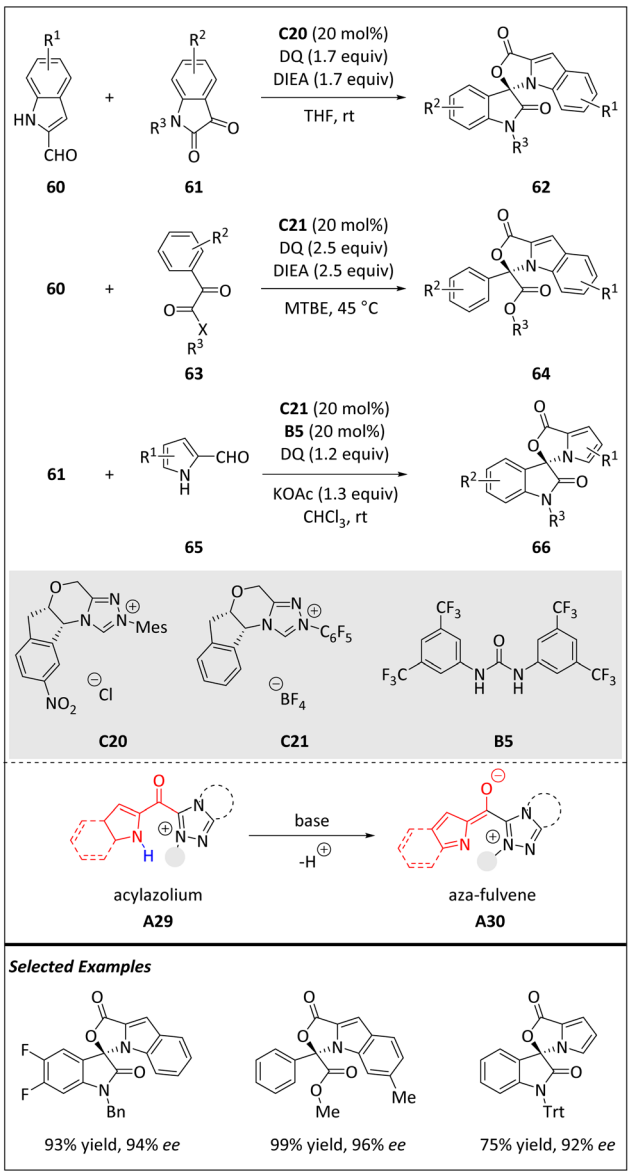
In 2019, Chi and co-workers disclosed an enantioselective [10 + 2] cycloaddition by employing indole-7-carbaldehyde as the 10π electron component with the aid of chiral NHC catalysts (Scheme 20).[82] The process involves the formation of an acyl azolium ester intermediate, which then transforms into an aza-*o*-quinone methides (aza-*o*-QMs)-containing intermediate **A28** through proton transfer. The subsequent procedure entails a [10 + 2] annulation between **A28** and a reactive ketone substrate **58**, yielding acetal product **59** with good yield and favourable enantiomeric ratios. The products obtained through this method contain pyrroloquinazoline or oxazinoindole scaffolds that are commonly found in bioactive molecules. The method demonstrates the ability of NHCs to activate the aldehyde group at a remote site of the indole molecule and control the stereoselectivity. Unlike previous studies where nitrogen or oxygen atoms are attached to benzene as reaction sites, the reactive nitrogen atom is located within the aldehyde substrate's aromatic ring in this method. To expand the versatility and practicality of this protocol, isatin derivatives for the assembling of spiro-cyclics are disclosed. The asymmetric aminals and *N*,*O*-acetal units in the cycloadducts hold significant synthetic values.



Scheme 20 Enantioselective intermolecular [10 + 2] cycloadditions *via* the 10π aza-*o*-QM intermediate.

Zhang and Wang carried out a theoretical investigation on such an asymmetric [10 + 2] HOC process.[83] According to the computational results, the stereoselectivity is primarily influenced by the ring-forming step between the aza-*o*-QMs intermediate **A28** and ketone **58**, resulting in a predominantly *R*-configured product. The researchers identify a weak interaction, which is analyzed qualitatively and quantitatively as LP···π, C–H···F, C–F···O, and C–F···F interactions in terms of NCI and AIM analyses.

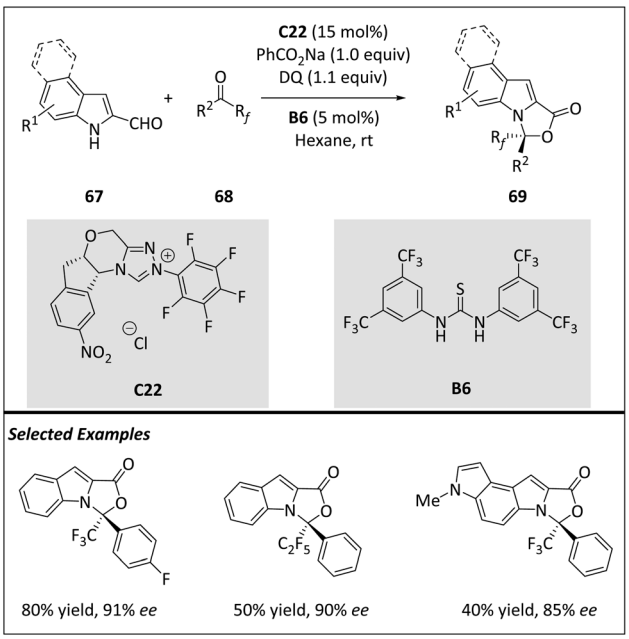
Simultaneously, Chi and coworkers uncovered a novel method to activate nitrogen atoms in heteroarenes for achieving enantioselective [10 + 2] HOCs (Scheme 21).[84] The acylazolium intermediate **A29** is generated through the carbene-addition step under an oxidant. This oxidation step eliminates the electron density from the indole (or pyrrole), resulting in a less nucleophilic overall π-system in contrast to the arylaldehyde substrate. For example, the carbon, located in the 2- or 3-position, is a possible nucleophilic center. Conversely, the nitrogen atom is selectively activated and serves as the reactive center through **A29** deprotonation, resulting in the formation of the azafulvene intermediate **A30**. The activation achieved *via* carbene catalysis leads to the creation of novel aza-fulvene acylazolium intermediates that selectively react with ketones, forming *N*,*O*-acetals with exceptional yields and enantiomeric ratios. The chiral *N*,*O*-acetal products display promising antibacterial properties against Ralstonia solanacearum and hold significance in the advancement of novel chiral agrichemicals for safeguarding plants. This study marks the initial NHC-catalyzed activation of nitrogen atoms incorporated into aromatic π-rings, thereby expanding the potential of carbene catalysis in accomplishing asymmetric reactions associated with aromatic skeletons. The [10 + 2] cycloaddition of **60** with indoline-2,3-dione **61** was also reported by the Hui group.[85]



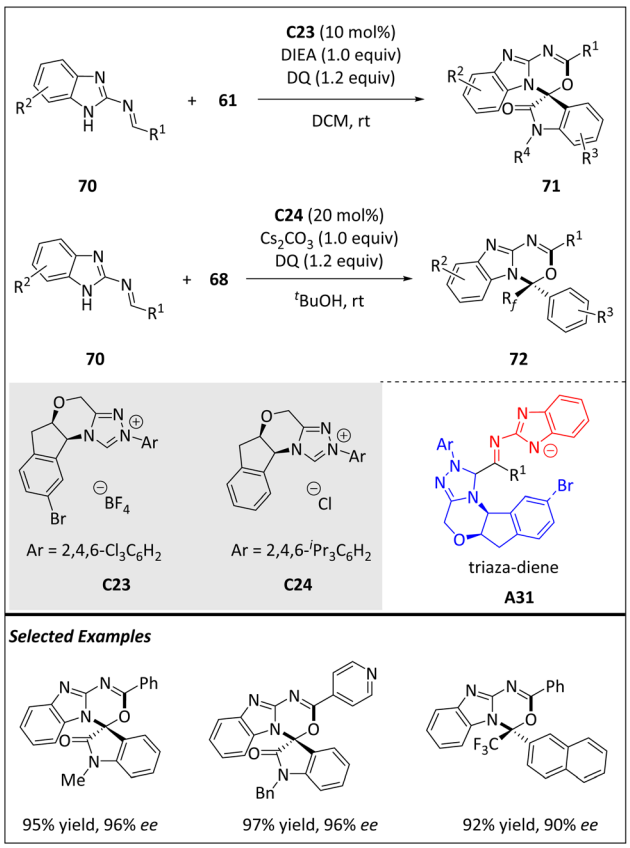
Scheme 21 Enantioselective intermolecular [10 + 2] cycloadditions *via* the 10π aza-fulvene intermediate.

Peng and Wang *et al.* independently reported a novel catalytic and enantioselective [10 + 2] higher-order cycloaddition of trifluoromethyl ketone derivatives with indole-2-carbaldehydes (Scheme 22), highlighting the potential of synthesized molecules due to the significance of polycyclic structures and the incorporation of "F"-containing fragments.[86]

The Wang group efficiently constructed enantioenriched polycycles with fluorinated substituents *via* an NHC-bound aza-benzofulvene intermediate **A30**, marking the first use of NHC-bound aza-arylfulvene intermediates in catalytic and enantioselective [10 + 2] or [14 + 2] reactions. Kinetic studies reveal that the reaction shows nearly first-order depending on catalyst **C22** and zero-order relying on substrates **67**, **68**, and 3,3′,5,5′-tetra-*tert*-butyl diphenoquinone (DQ). An intrinsic



Scheme 22 Asymmetric intermolecular [12 + 2] cycloadditions *via* the aminocatalytical 12π intermediate.



Scheme 23 Enantioselective hetero-[10 + 2] cycloadditions *via* the triaza-diene intermediate.

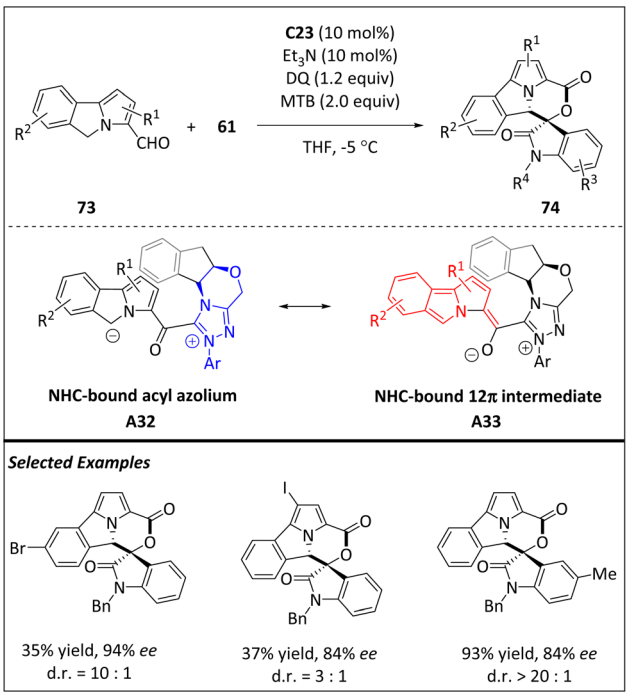
reaction coordinate calculation (IRC) of the transition state is conducted, indicating a concerted asynchronous process where the covalent bond between the **C1** of trifluoroacetophenone and the **N1** of indole is formed first. Additionally, DFT calculations enable accurate prediction of and a thorough understanding of enantio- and stereo-control. Similar HOC reactions were also discovered by the Biju group.[87]

In 2021, Yang and Chi *et al.* reported a process that utilizes carbene catalysis to activate nitrogen atoms through covalent interactions (Scheme 23).[88] This approach enables the asymmetric synthesis of heterocycles, (benz)imidazole-derived imines **70** and activated ketones **61** or **68** *via* a highly enantioselective HOC manner. The process requires the use of the chiral **C23** or **C24** catalyst and an oxidant (DQ or MnO_2) to obtain the desired skeletons. At the onset of the reaction, catalyst **C23** or **C24** is introduced to an aldimine substrate derived from (benz)imidazole. The following steps involve oxidation and proton transfer, forming triaza-diene intermediate **A31**. In a previous report, the reactive nucleophilic heteroatoms are situated at the γ-position relative to the carbonyl groups of the substrates. These intermediates (*e.g. o*-QMs,[89,90] aza-*o*-QMs **A28**[91,92] and aza-fulvene **A30**) are comparable to vinyl enolate intermediates, bearing a heteroatom at the γ-position. This is the first success in applying a triaza-diene intermediate for asymmetric HOCs. Building upon a relaxed 2D potential energy surface (PES) scan, the concerted synchronous [10 + 2] cycloaddition pathway is ruled out. Alternatively, a highly asynchronous concerted mechanism is identified with the aid of DFT calculations.

Most recently, the enantio- and diastereoselective [12 + 2] higher-order cycloaddition between 5*H*-benzo[*a*]pyrrolizine-3-carbaldehydes **73** and isatine-derivatives **61** has been developed by Chi *et al. via* NHC-catalyzed remote C(sp^3)–H activation (Scheme 24).[93] The reaction allows the rapid construction of a sophisticated tricyclic core bearing a morpholine moiety under mild conditions and easily accessible starting materials. Specifically, aldehydes **73** react with carbene catalyst **C23** to generate the Breslow intermediate. Then, the NHC-bound acyl azolium intermediate **A32** is obtained from the Breslow intermediate *via* oxidation. Deprotonation of intermediate **A32** gives rise to a carbon anion, which then undergoes tautomerization to form 12π species **A33**. Upon addition of **A33** to 2π electrophile **61**, the target product is formed.

3.4 Ion-pairing catalysis

Gao and Guo *et al.* reported the phosphine-catalyzed [8 + 2]-annulation of heptafulvene **75** with allenoates **76**, yielding bicyclo[5.3.0]decane-fused spirobarbiturates **77** in moderate to excellent yields (Scheme 25).[94] By using chiral Kwon's phosphine catalyst **C25**, enantioenriched products are obtained in moderate to high yields and with excellent enantioselectivities. The reaction involves the formation of the β-phosphonium dienolate intermediate **A34**, which is generated from the conjugate addition of phosphine to allenoate **76**. This intermediate then attacks heptafulvene-barbiturate **75**, which has never been used as an 8π component in an [8 + 2] cycloaddition before. A subsequent intramolecular Michael addition leads to

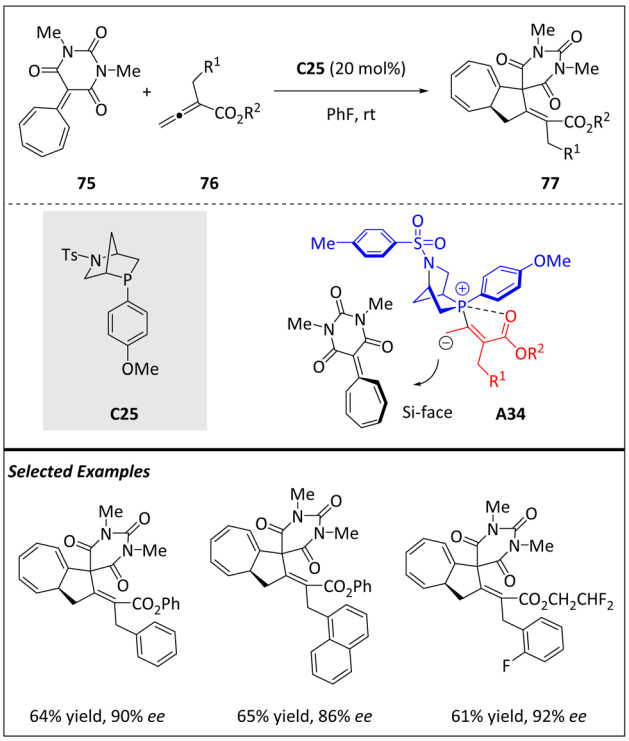


Scheme 24 Enantioselective [12 + 2] cycloadditions *via* the NHC-bound 12π intermediate.

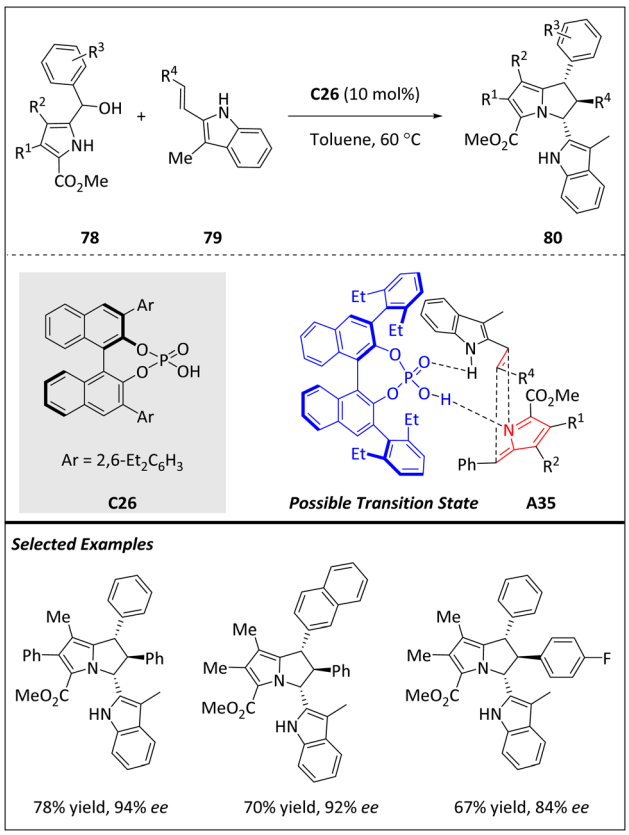
product **77**. In addition, the β-phosphonium dienolate intermediate **A34** undergoes *Si*-face attack to form **75**, ultimately generating (*S*)-tricyclic products.

Kallweit and Schneider have developed a one-step process (Scheme 26) for synthesizing densely substituted 2,3-dihydro-1*H*-pyrrolizines **80**, which are often found in many biologically active natural products.[95] The process involves an organocatalytic [6 + 2]-cycloaddition between 1*H*-pyrrole-2-yl carbinols **78** and 2-vinylindoles **79**, catalyzed by a BINOL-derived phosphoric acid **C26**. The reaction proceeds *via* the formation of chiral hydrogen-bonded 2-methide-2*H*-pyrroles **A35** and results in the formation of single diastereomers with excellent enantioselectivity and good yields. The resulting 2,3-dihydro-1*H*-pyrrolizines bear three contiguous stereogenic centers, making them highly valuable synthetic targets for developing new biologically active compounds.

In the presence of chiral **C26**, carbinols **78** can be successfully dehydrated to form chiral hydrogen-bonded 2-methide-1*H*-indoles, which subsequently react with various nucleophiles to produce both open-chain and annulated indole-based heterocycles. The intermediate 2-methide-2*H*-pyrroles **A35** plays a vital role in the biosynthesis of porphyrines, myrmicarin alkaloids and (+)-roseophilin. However, their applications in synthetic chemistry have been restricted due to the instability of pyrrol-2-yl-carbinols and the high reactivity of the



Scheme 25 Enantioselective [8 + 2] cycloadditions *via* the phosphine-bound 2π intermediate.



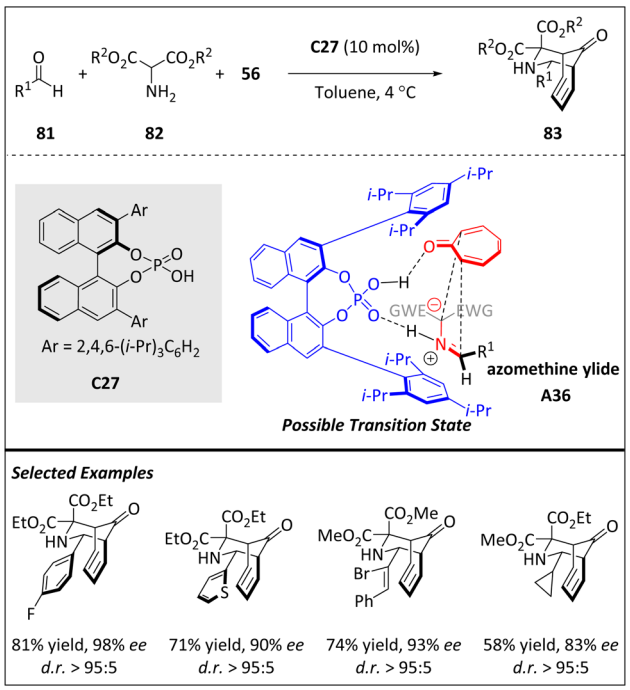
Scheme 26 Enantioselective [6 + 2] cycloadditions catalyzed by phosphoric acid *via* 2-methide-2*H*-pyrroles.

pyrrole nucleus towards electrophilic attack. To address these challenges, the authors hypothesize that introducing an electron-withdrawing group at the **C5** position of the pyrrole nucleus would effectively block this site and prevent oligomerization through electronic deactivation. By attenuating the reactivity of pyrrole, the full synthetic potential of 2-methide-2*H*-pyrroles can be realized.

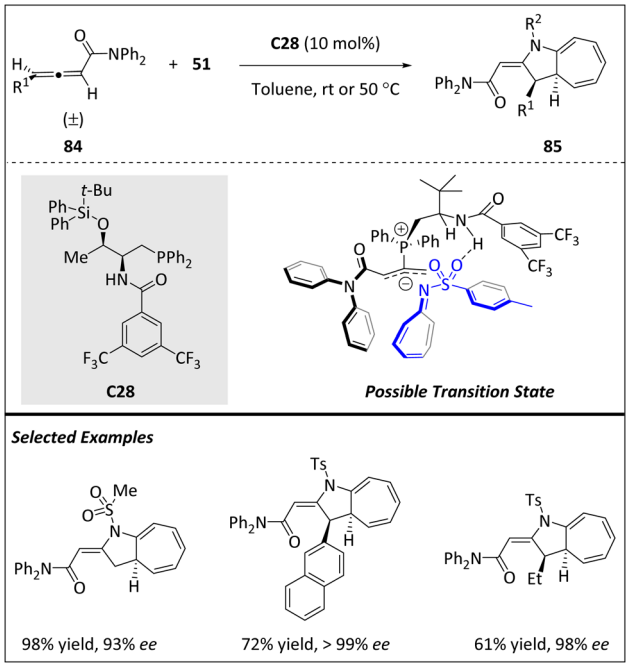
In the control experiment, no conversion is observed when subjected to the reaction with **78**, indicating the crucial role of the free *N*–H moiety for double hydrogen bonding as described previously. A plausible transition state is also proposed to explain the observed diastereo- and enantioselectivity (Scheme 26). In fact, the lower 3-aryl group in the BINOL backbone shields the bottom side of the **A35** effectively and the incoming dienophile is guided to the top face.

As mentioned above, the ability of tropone **56** to serve as a 2π, 4π, 6π, or 8π component makes it a fascinating and challenging cyclic polyene.[96] By reacting with 1,3-dipoles, a variety of fused or bridged polycycles can be prepared smoothly. Enantioselective transition metal catalysis has been reported to facilitate stereoselective 1,3-dipolar higher-order cycloadditions of tropone (or heptafulvene derivatives).[97–102] However, there is a noticeable lack of organocatalytic 1,3-dipolar higher-order cycloadditions of tropones in the literature. Using chiral phosphoric acids as catalysts for 1,3-dipolar cycloadditions of azomethine ylides **A36** with electron-deficient 2π components provides a reliable protocol for the preparation of enantio-enriched pyrrolidines. In 2020, Jørgensen and coworkers reported the first example of chiral phosphonic acid (CPA)-catalyzed 1,3-dipolar [6 + 4] cycloaddition of **56** with **A36** (Scheme 27).[103] This approach relies on the distinctive reactivity of iminomalonate esters, which are obtained through the condensation of aldehydes **81** with 2-aminomalonates **82**. The desired dipoles **A36** are produced through a CPA-facilitated prototropic shift. The resulting structural motif forms the central core of bioactive Lycopodium and Daphniphyllum alkaloids. A proposed transition state explained the relative and absolute configuration of compound **83**. The CPA catalyst **C27** plays multiple roles in the reaction.

In 2020, Vicario and Manzano *et al.* reported a phosphine-catalyzed enantioselective [8 + 2] HOC reaction using racemic γ-substituted allenes **84** and azaheptafulvenes **51** (Scheme 28).[104] This reaction offers a direct and straightforward approach for synthesizing aza-azulenoid scaffolds. By optimizing the reaction conditions, a wide range of mono- and disubstituted cycloadducts with good yields and precise control over peri-, regio-, diastereo-, and enantioselectivity were successfully afforded. In contrast to previous reports regarding **84** as the C4-component, in this study, they demonstrated the exceptional role of these allenes as excellent 2π components. The suggested mechanism entails a nucleophilic assault by catalyst **C26** on allenic amides **84**, leading to the generation of an intermediate known as an allyl phosphonium ylide. This intermediate undergoes a selective reaction guided by a three-dimensional distribution, facilitated by an H-bond association, ultimately determining the stereochemical outcome.

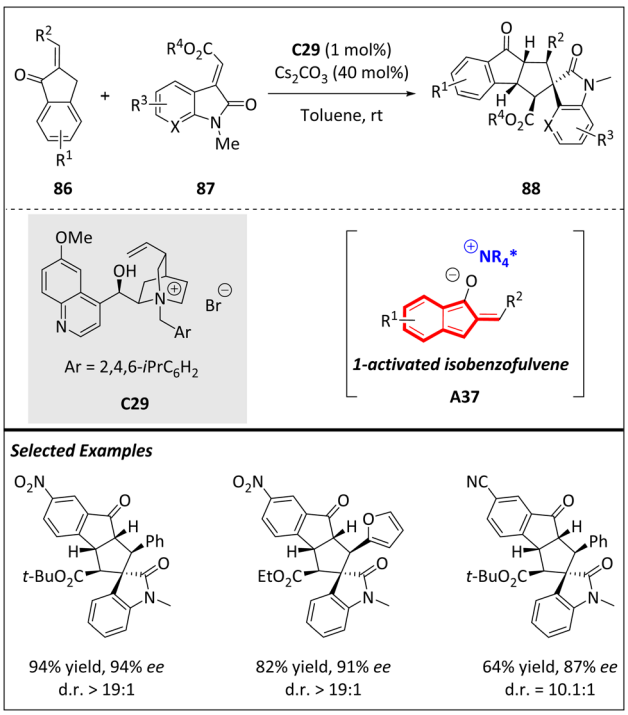


Scheme 27 Enantioselective 1,3-dipolar [6 + 4] cycloadditions catalyzed by phosphoric acid.



Scheme 28 Enantioselective [8 + 2] cycloadditions catalyzed by phosphine.

The Chen group has developed an asymmetric higher order [10 + 2] cycloaddition by employing 2-alkyl-idene-1-indanones and electron-deficient alkenes (Scheme 29). Previously, 2-benzylidene-1-indanone could transform into a 1-hydroxyl isobenzofulvene anion intermediate, and subsequently carried out a [10 + 2]



Scheme 29 Enantioselective [8 + 2] cycloadditions catalyzed by phosphine.

cycloaddition with alkenes. By introducing chiral phase-transfer catalysis, they successfully generated a novel 1-activated isobenzofulvene, enabling the realization of an asymmetric version of this transformation. The incorporation of various alkenes, such as **86**, 2-alkyl-idene-benzofuran-3(2*H*)-one, 2-alkyl-idene-1,3-dione, and α,β-unsaturated ketones, significantly enhanced the structural diversity and versatility of the resulting products.[105]

To address the challenges of diastereo- and enantioselectivity issues, a newly designed cinchona-based ammonium salt with a bulky substituent was disclosed. Surprisingly, this catalyst indicates high efficiency even at low loadings (1 mol%), even if the reactive site is physically distant from the chiral ion pair complex. This finding represents a rare instance of achieving asymmetric higher-order cycloaddition using an isobenzofulvene-based 10π intermediate.

In a recent study, Zhao and Yuan along with their colleagues developed a dearomative higher-order [10 + 2] cycloaddition of 2-alkylidene-1-indanones and 3-nitroindoles.[106] Utilizing benzyl triethyl ammonium chloride (TEBA) as the phase-transfer catalyst under basic conditions, a broad array of polycyclic cyclopenta[b]indoline derivatives were prepared under mild conditions, achieving excellent results (up to 99% yield and >20 : 1 dr).

4. Summary and outlook

Higher order cycloadditions (HOCs) offer distinct advantages in the synthesis of complex molecules, particularly those with medium size and multiple rings. The field of asymmetric HOC has witnessed significant progress since the influential exchange between Woodward and Hoffmann. In the last few decades, significant advancements have been made in the field of asymmetric HOC, particularly through the utilization of organocatalysis. These approaches have facilitated the control of peri- and enantioselectivity in the ring formation process. Diverse optically pure functional structures were smoothly prepared, showcasing attractive applications in synthetic chemistry and biological studies. This review highlights various activation strategies employed in constructing chiral skeletons in the presence of organocatalysts. However, novel activation modes, including radical-type cycloaddition[107] and transition metal/organocatalyst dual systems, have limited progress. Additionally, the control of axial, planar, spiro, and other forms of chirality through asymmetric HOCs remains very rare. In summary, there is ample room for future development in the field of asymmetric higher order cycloadditions. Advancements in this area would greatly enhance the value of precise control and efficient assembly in synthetic chemistry.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgements

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