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Progress in organocatalytic asymmetric (4+3) cycloadditions for the enantioselective construction of seven-membered rings

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Chiral seven-membered ring systems such as seven-membered carbocycles and heterocycles are widely found in natural products and pharmaceuticals. Therefore, the catalytic enantioselective construction of such frameworks has evoked considerable interest in the field of chemistry. Among the various approaches, organocatalytic asymmetric (4+3) cycloadditions are highly effective for the enantioselective construction of seven-membered rings. Over the past two decades, substantial efforts have been devoted to this field and chemists have developed various organocatalytic asymmetric (4+3) cycloadditions. This review summarizes the progress in organocatalytic asymmetric (4+3) cycloadditions from 2003 to early 2022 and provides insights into challenging issues faced in this research field, enabling the future development of this field.

organocatalysis, (4+3) cycloaddition, seven-membered rings, four-atom building blocks

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1 Introduction

Chiral seven-membered rings, including seven-membered carbocycles and heterocycles, are widely found in the structures of several natural products and pharmaceuticals, serving as important motifs (Figure 1) [1–6]. Therefore, the catalytic enantioselective construction of seven-membered rings has aroused considerable interest in the field of chemistry. However, owing to unfavorable entropic factors and transannular interactions [7,8], catalytic enantioselective construction of a seven-membered ring is quite challenging.

Catalytic asymmetric (4+3) cycloaddition reactions have proven to be powerful methods for enantioselective construction of seven-membered rings. Over the past two decades, substantial efforts have been made in this field and chemists have developed various catalytic asymmetric (4+3) cycloadditions, including those involving transition metal catalysis, organocatalysis, and cooperative organometal catalysis (Figure 2a). In 1994, Davies and co-workers [9] presented the first transition metal-catalyzed asymmetric (4+3) cycloaddition in the presence of a chiral rhodium (II) complex, achieving enantioenriched seven-membered carbocycles (Figure 2b). Nine years later, in 2003, Harmata [10] used a chiral secondary amine as an organocatalyst to accomplish the first organocatalytic asymmetric (4+3) cycloaddition, affording chiral seven-membered carbocycles with an *oxo*-bridged bond (Figure 2c). Afterward, in 2016, Glorius and co-workers [11] established a cooperative organocatalysis/transition metal catalysis system to enable asymmetric (4+3) cycloaddition using chiral *N*-heterocyclic carbene (NHC) and palladium as co-catalysts, providing a

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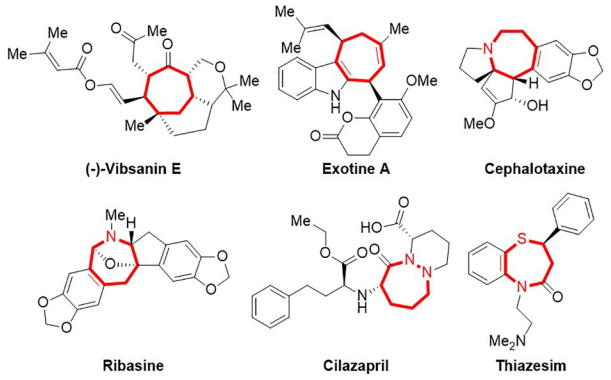


Figure 1 Selected natural products and pharmaceuticals containing a chiral seven-membered ring (color online).

new strategy for synthesizing chiral benzazepine derivatives bearing a chiral seven-membered *N*-heterocyclic motif (Figure 2d). Based on these pioneering work, numerous interesting findings on catalytic asymmetric (4+3) cycloadditions have been reported successively, considerably advancing the development of this research field.

In 2006, Harmata [12] published a review on the initial developments in the field of enantioselective (4+3) cycloaddition reactions. Afterwards, a series of reviews concerning (4+3) cycloadditions were published [13–22], promoting the rapid development of this research field. In 2020, Lautens and co-workers [16] published an account summarizing their contributions to transition metal-catalyzed (4+3) cycloadditions for constructing racemic and enantioenriched seven-membered rings. In addition, Swamy and co-workers [17] described the advancements in (4+3) annulation/cycloaddition reactions from the perspective of various classifications of catalysts. However, these reviews mainly focused on nonenantioselective (4+3) cycloadditions and transition metal-catalyzed (4+3) cycloadditions. By contrast, no review focusing on organocatalytic asymmetric (4+3) cycloadditions has been published so far. Therefore, a timely and systematic summary of the organocatalytic asymmetric (4+3) cycloadditions is highly desirable and valuable, considering that asymmetric organocatalysis, the subject of the Nobel Prize in Chemistry, 2021 [23], is a very important research field [24,25].

In this review, we summarize the recent advances in organocatalytic asymmetric (4+3) cycloadditions for the construction of enantioenriched seven-membered rings, enabling the future development of this research field. For clarity, this review is organized according to different types of four-atom building blocks (Figure 3) in organocatalytic asymmetric (4+3) cycloadditions, which are classified into four categories: four-carbon (4C) building blocks, *oxa*-four-atom building blocks, *aza*-four-atom building blocks, and other four-atom building blocks.

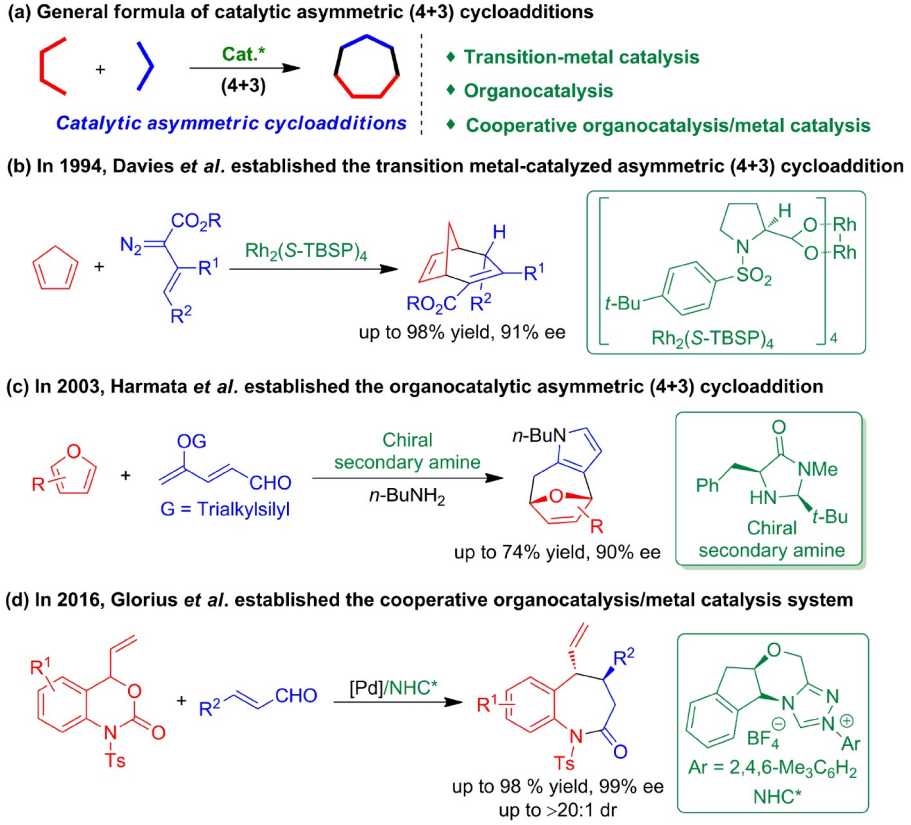


Figure 2 Profile and history of the catalytic asymmetric (4+3) cycloadditions (color online).

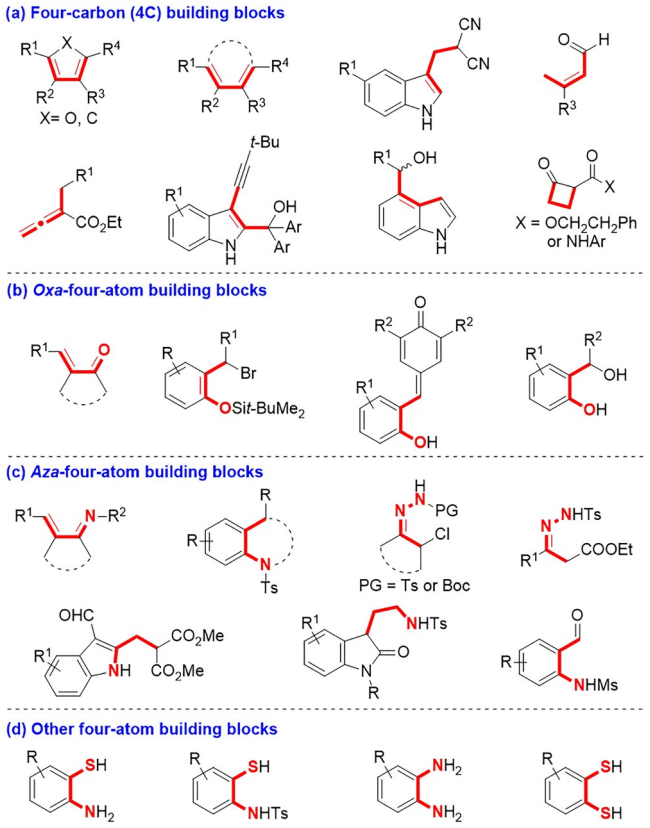
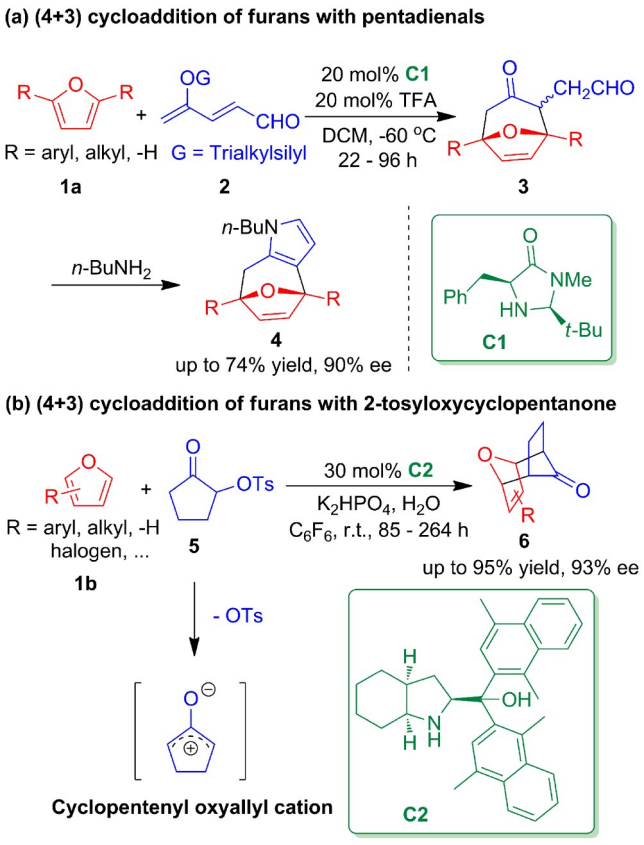


Figure 3 Four-atom building blocks in organocatalytic asymmetric (4+3) cycloadditions (color online).



Scheme 1 Chiral amine-catalyzed asymmetric (4+3) cycloadditions of substituted furans by Harmata and co-workers [10,29] (color online).

Further, this review summarizes the different classes of four-atom building blocks used in organocatalytic asymmetric (4+3) cycloadditions and provides insights into their reactivity and activation mode under asymmetric organocatalysis, thereby empowering chemists to design more innovative (4+3) cycloadditions and discover their applications in synthesizing natural products and pharmaceuticals. Moreover, this review provides in-depth insights regarding the challenges faced in this field, which will encourage chemists to design new competent four-atom building blocks for realizing organocatalytic asymmetric (4+3) cycloadditions, thus promoting the development of cycloaddition reactions and asymmetric organocatalysis.

2 Organocatalytic asymmetric (4+3) cycloadditions involving 4C building blocks

2.1 Cyclic dienes as 4C building blocks

In 2003, Harmata and co-workers [10] reported the organocatalytic asymmetric (4+3) cycloaddition reactions (Scheme 1a). In the presence of an amine-type organocatalyst **C1** and trifluoroacetic acid (TFA), substituted furans **1a** as 4C building blocks underwent enantioselective (4+3) cycloadditions with pentadienals **2**, yielding chiral seven-membered cycloadducts **3**. However, cycloadducts **3** were difficult to separate using various chiral high performance liquid chromatography (HPLC) columns. Therefore, cycloadducts **3** were treated with butylamine to obtain the corresponding *N*-butylpyrroles **4**, which could be separated using chiral HPLC columns and showed overall high enantioselectivities (up to 90% ee). Harmata and co-workers suggested that organocatalyst **C1** formed an iminium ion with pentadienals **2**, thereby influencing the enantioselectivity of the (4+3) cycloaddition. Notably, this synthetic methodology was later applied by Lin, Sun *et al.* [26–28] for synthesizing numerous natural products, demonstrating the power of organocatalytic asymmetric (4+3) cycloaddition reactions for the preparation of natural products.

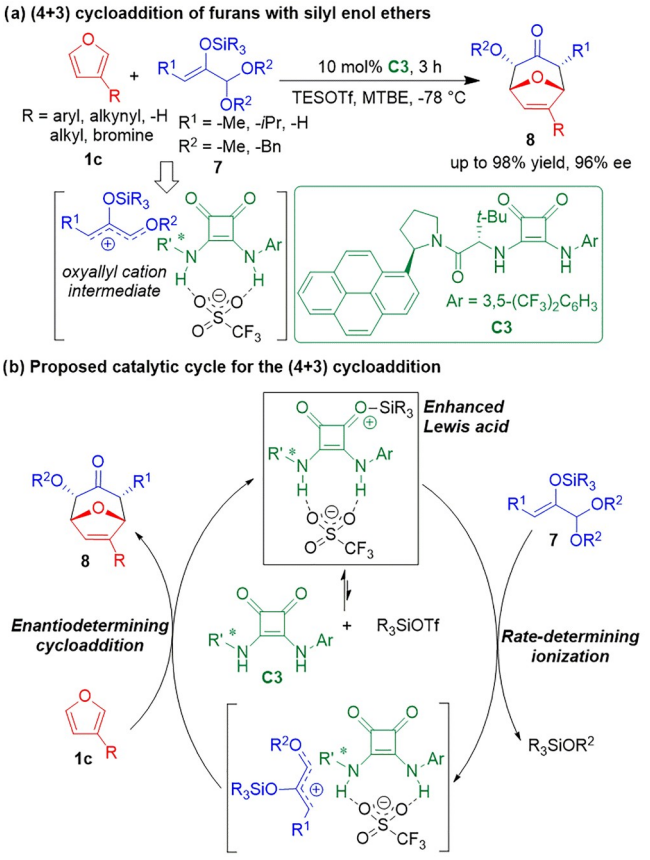
After 14 years, in 2017, the same group used substituted furans **1b** as 4C building blocks in organocatalytic asymmetric (4+3) cycloaddition reactions with 2-tosyloxycyclopentanone **5** using a chiral amino alcohol **C2** as the catalyst (Scheme 1b), yielding chiral seven-membered cycloadducts **6** in high yields and excellent enantioselectivities [29]. In their study, 2-tosyloxycyclopentanone **5**, as a three-atom partner, was able to generate an active cyclopentenyl oxyallyl cation [30–32] with the removal of *p*-toluenesulfonate ion (TsO^-). Based on the previous work of MacMillan [30] on oxyallyl cation catalysis, chiral amino alcohol

C2 was suggested to exhibit hydrogen-bonding interactions with *oxy*-allyl cation, which played a crucial role in controlling the enantioselectivity of the reaction.

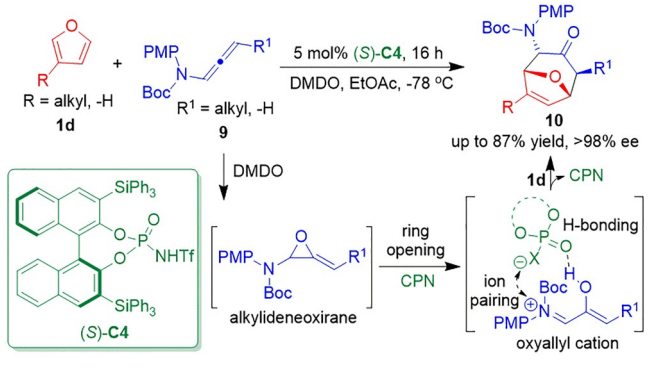
In 2017, Jacobsen and co-workers [33] disclosed a new catalytic mode of Lewis acid enhancement *via* hydrogen-bond donors such as thioureas and squaramides. Using this catalytic mode, they established a chiral squaramide **C3**-catalyzed asymmetric (4+3) cycloaddition of substituted furans **1c** with silyl enol ethers **7** to afford bicyclic products **8** with good yields and high enantioselectivities (Scheme 2a). In this approach, chiral squaramide **C3** interacted with silyl triflates to form a stable complex with high Lewis acidity. This Lewis acidic complex controlled the enantioselectivity of this (4+3) cycloaddition reaction by enabling the formation of chiral catalyst-associated oxyallyl cation intermediates [34]. Based on the mechanistic studies, they proposed a catalytic cycle (Scheme 2b), wherein the complex of silyl triflate-chiral squaramide acted as the resting state of the catalyst with Lewis acidity to facilitate acetal ionization. The subsequent reaction of oxyallyl cation intermediates with furans was the post rate-determining step, which afforded (4+3) cycloadducts. Different trialkyl silyl triflate promoters exhibited similar enantioselectivities, indicating that the enantioselectivity-determining step occurred after the formation of the oxyallyl cation and involved the reaction with furan. This work not only established organocatalytic enantioselective (4+3) cycloaddition of furans with silyl enol ethers but also presented a new catalytic mode and powerful catalytic strategy in asymmetric organocatalysis.

In the same year (2017), Vicario, Uria and co-workers [35] used chiral phosphoramide (CPN) (*S*)-**C4** as a suitable organocatalyst to promote the enantioselective (4+3) cycloaddition reaction of substituted furans **1d** with oxyallyl cations that were generated *in situ via* oxidation of allenamides **9** (Scheme 3), providing convenient access to a wide range of potentially valuable chiral seven-membered cycloadducts **10** with good yields and high diastereo- and enantioselectivities. In detail, allenamides **9** was oxidized into alkylideneoxiranes using dimethyldioxirane (DMDO) as the oxidant [36,37]. Then, the oxyallyl cation intermediate was formed *via* ring opening of the alkylideneoxirane intermediate in the presence of CPA, which activated the oxyallyl cation intermediate *via* a bifunctional mode of cooperative hydrogen-bonding and ion-pairing interactions, enabling the enantioselective (4+3) cycloaddition with substituted furans **1d** to afford the final adducts **10**.

Notably, in the aforementioned cases involving substituted furans **1a**–**1d** as cyclic dienes, chiral organocatalysts activated other three-atom partners by forming iminium intermediates or hydrogen-bonding interactions. Owing to the high reactivity of substituted furans, this mono-activation mode was able to control both the reactivity and enantioselectivity of the desired (4+3) cycloadditions, constructing



Scheme 2 Chiral squaramide-catalyzed asymmetric (4+3) cycloaddition of substituted furans with silyl enol ethers, reported by Jacobsen and co-workers [33] (color online).



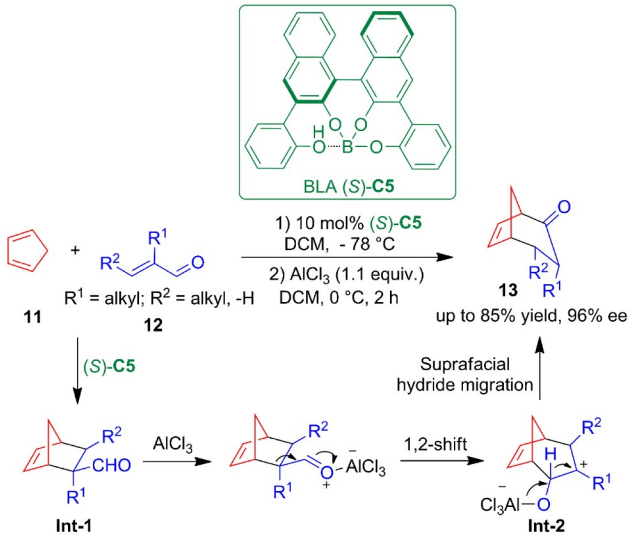
Scheme 3 CPA-catalyzed asymmetric (4+3) cycloaddition of substituted furans with allenamides by Vicario, Uria and co-workers [35] (color online).

bridged seven-membered rings with optical purity.

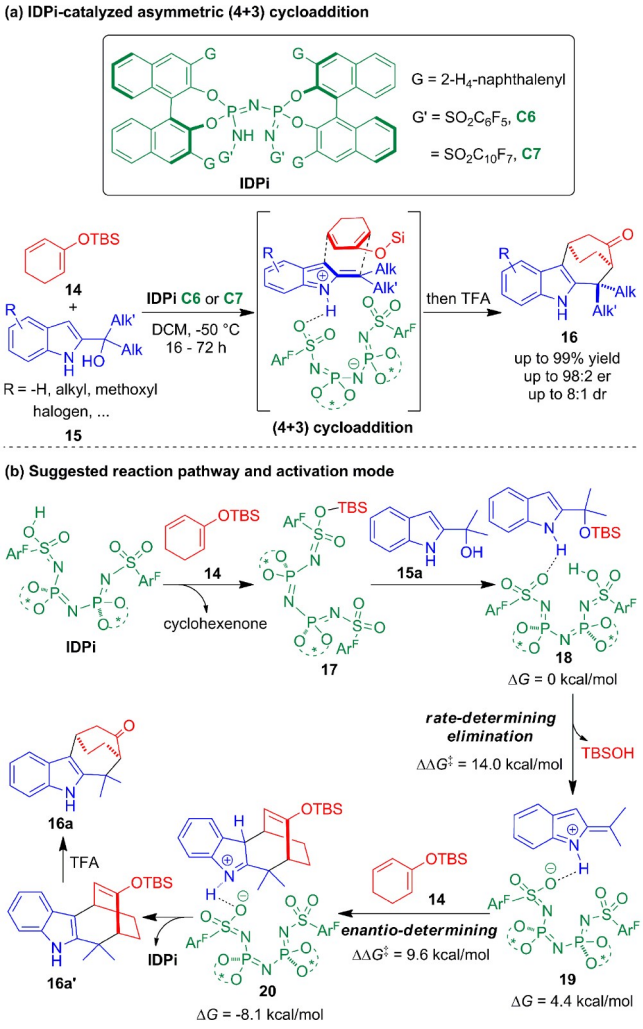
In addition to substituted furans, cyclopentadiene [9] as a typical cyclic diene could also serve as a 4C building block in catalytic asymmetric (4+3) cycloadditions. However, owing to the low reactivity of cyclopentadiene, its use in organocatalytic (4+3) cycloadditions is quite challenging. In 2006, Davies and co-workers [38] established a formal asymmetric (4+3) cycloaddition reaction of cyclopentadiene **11** with

unsaturated aldehydes **12** *via* a tandem Diels-Alder reaction/ring-expansion process [39,40], realizing the catalytic enantioselective construction of bicyclo-[3.2.1]octenones **13** in the presence of Yamamoto's Brønsted acid-assisted chiral Lewis acid (BLA) catalyst (*S*)-**C5** (Scheme 4). In detail, first, cyclopentadiene **11** reacted with unsaturated aldehydes **12** in the presence of the chiral catalyst (*S*)-**C5** to afford the enantioselective (4+2) cycloadduct **Int-1**, which could undergo an aluminum chloride-induced 1,2-alkyl shift to form the tertiary carbocation **Int-2** with the corresponding alkoxide at the endo position. Then, **Int-2** underwent suprafacial hydride migration to afford the endo (4+3) cycloadduct **13**. This formal (4+3) cycloaddition offered a useful method for constructing enantioenriched bicyclo[3.2.1]octenone scaffolds.

Organocatalytic asymmetric construction of chiral indole-based scaffolds, particularly chiral indole-fused rings, has become an important objective in chiral indole chemistry [41]. To achieve this objective, developing organocatalytic asymmetric cycloadditions of 2-indolylmethanol has proven to be an effective method [42–45]. However, dialkyl-substituted 2-indolylmethanols have rarely been used in organocatalytic asymmetric cycloadditions owing to considerable challenges in accomplishing regioselective and enantioselective cycloadditions of dialkyl-substituted 2-indolylmethanols. To address these challenges, List and co-workers [46] recently used an imidodiphosphorimidate (IDPi) **C6** or **C7** as a competent organocatalyst to enable regioselective and enantioselective (4+3) cycloaddition of dienolsilane **14** with dialkyl-substituted 2-indolylmethanols **15** (Scheme 5a). After the removal of the silyl group using TFA, the (4+3) cycloaddition reaction afforded bicyclo [3.2.2]cyclohepta[*b*]indole scaffolds **16** bearing three stereogenic centers in high yields and excellent enantioselectivities. In this organocatalytic asymmetric (4+3) cycloaddition, dienolsilane **14**, as a cyclic diene, played an important role by acting as a 4C building block and performing a silyl transfer reaction. As shown in Scheme 5b, the IDPi organocatalyst **C6** or **C7** initially reacted with dienolsilane **14** through a silyl transfer reaction to generate the active silylium Lewis acid **17**. The intermediate **17** then transferred the silyl group to 2-indolylmethanol **15a** and generated complex **18** *via* hydrogen-bonding interaction. Subsequently, complex **18** transformed into intermediate **19** *via* the C–O bond cleavage to release TBSOH, which was the rate-determining elimination step. Subsequently, an enantioselective (4+3) cycloaddition occurred between intermediate **19** and dienolsilane **14** to produce cycloadduct **20**, which rapidly underwent rearomatization to form intermediate product **16a′**. The removal of the silyl group from **16a′** by TFA generated the final product **16a**. Notably, this study overcame the issues in achieving regioselective and enantioselective (4+3) cycloadditions of dialkyl-substituted



Scheme 4 BLA-catalyzed asymmetric formal (4+3) cycloaddition of cyclopentadiene with unsaturated aldehydes by Davies and co-workers [38] (color online).



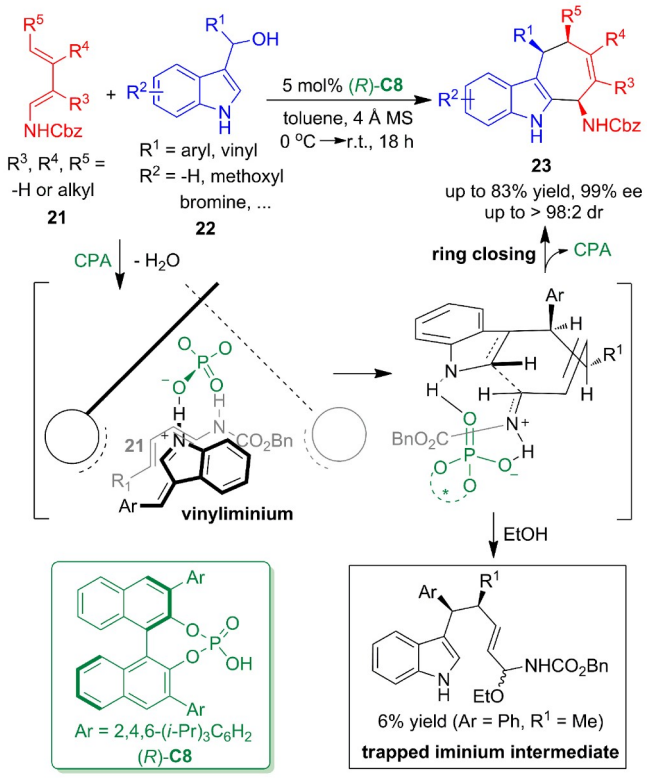
Scheme 5 IDPi-catalyzed asymmetric (4+3) cycloaddition of dienolsilane with 2-indolylmethanols by List and co-workers [46] (color online).

2-indolylmethanols, representing a breakthrough in 2-indolylmethanol-related enantioselective transformations [47].

2.2 Acyclic dienes as 4C building blocks

Although a pioneering work on the organocatalytic asymmetric (4+3) cycloadditions of cyclic dienes was established in 2003 [10], acyclic dienes have been rarely applied as versatile 4C building blocks to such (4+3) cycloadditions. In 2016, Shi and co-workers [48] used Nazarov reagents as diene precursors in a formal (4+3) cycloaddition with 3-indolylmethanols in the presence of hydrobromic acid to obtain an all-carbon seven-membered ring in a diastereoselective manner. However, this formal (4+3) cycloaddition could not occur when using chiral Brønsted acid as the catalyst. In 2018, Masson and co-workers [49] established a CPA (*R*)-**C8**-catalyzed asymmetric (4+3) cycloaddition reaction of 3-indolylmethanols **22** using 1,3-diene-1-carbamates **21** as acyclic dienes, thereby providing an efficient method for the enantioselective synthesis of multisubstituted cyclohepta[*b*]indoles **23** bearing three stereogenic centers in good yields and excellent diastereo- and enantioselectivities (Scheme 6). The mechanism proposed for this (4+3) cycloaddition is a stepwise process, involving the formation of a vinyliminium intermediate *via* dehydration of 3-indolylmethanol **22** in the presence of CPA (*R*)-**C8**. This vinyliminium intermediate formed an ion pair with the CPA anion. Simultaneously, the Lewis basic phosphoryl oxygen atom of CPA formed a hydrogen bond with the NH group of dienecarbamate **21**, thereby promoting an enantioselective addition reaction to the vinyliminium intermediate. Subsequently, a ring-closing step occurred under the catalysis of CPA to afford the final cycloadducts **23**. They used ethanol as the capture agent in the reaction, which afforded the trapped iminium intermediate in 6% isolated yield, providing evidence for the stepwise pathway of the (4+3) cycloaddition. This reaction represents the first catalytic asymmetric (4+3) cycloaddition of 3-indolylmethanols, providing a stereoselective method for constructing chiral indole-fused seven-membered carbocycles.

In addition to electron-rich dienes (as exemplified by 1,3-diene-1-carbamates), electron-deficient dienes could serve as competent 4C building blocks in organocatalytic asymmetric (4+3) cycloadditions. In 2018, Jørgensen and co-workers [50] used chiral diphenylprolinol silyl ether **C9** as a suitable organocatalyst to realize a formal (4+3) cycloaddition of electron-deficient dienes **24** with indene carbaldehydes **25**, affording a broad substrate scope of tetracyclic products **26** in overall good yields and high diastereo- and enantioselectivities (Scheme 7a). In the reaction process, the condensation of indene carbaldehydes **25** with the chiral catalyst **C9** generated amino isobenzofulvenes (as the reactive species in the cycloaddition reaction) [51,52] with conjugate

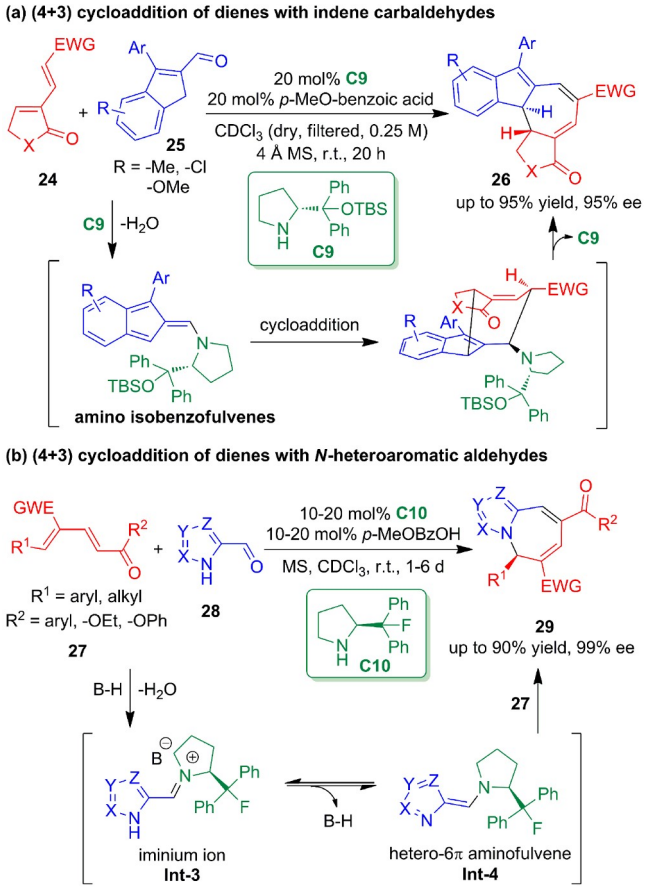


Scheme 6 CPA-catalyzed asymmetric (4+3) cycloaddition of 1,3-diene-1-carbamates with 3-indolylmethanols by Masson and co-workers [49] (color online).

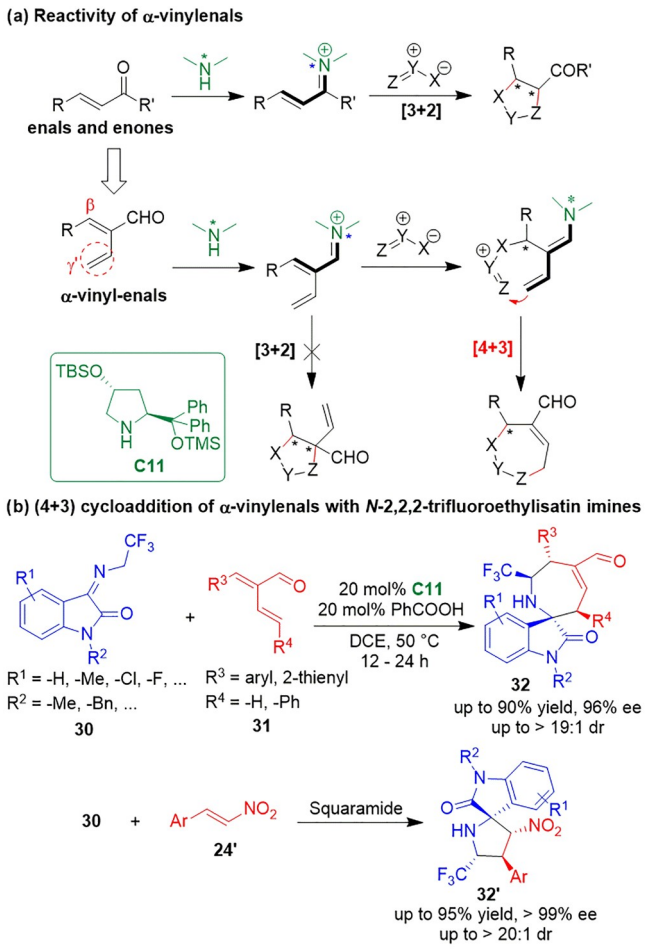
10π electrons. Considering the electrons involved in the cycloadditions, this reaction could be named as catalytic enantioselective (10+4) cycloaddition.

Subsequently, Jørgensen and co-workers [53] used electron-deficient dienes **27** as 4C building blocks and conducted a formal (4+3) cycloaddition reaction with heteroaromatic aldehydes **28** (including pyrrole-, imidazole-, and pyrazole-substituted formaldehydes) under the cooperative catalysis of a chiral aminocatalyst **C10** and *p*-anisic acid (*p*-MeOBzOH), which could also be referred to as organocatalytic asymmetric hetero-(6+4) cycloaddition, considering the electrons involved in the reaction (Scheme 7b). In addition, several control experiments were performed for mechanistic studies, and two types of intermediates **Int-3** and **Int-4** could be observed. Heteroaromatic aldehyde **28** rapidly generated the iminium ion intermediate **Int-3** under the influence of the racemic Brønsted acid, which was subsequently transformed into the reactive hetero-6π aminofulvene intermediate **Int-4** to participate in the cycloaddition reaction. Furthermore, computational studies suggested that this cycloaddition mechanism was a stepwise process, and the key step for stereoselective control was the formation of the second C–C bond rather than the formation of the first C–N bond.

Because α,β-unsaturated carbonyl compounds such as enals and enones serve as 2C building blocks in the



Scheme 7 Chiral amine-catalyzed asymmetric formal (4+3) cycloaddition with electron-deficient dienes by Jørgensen and co-workers [50,53] (color online).

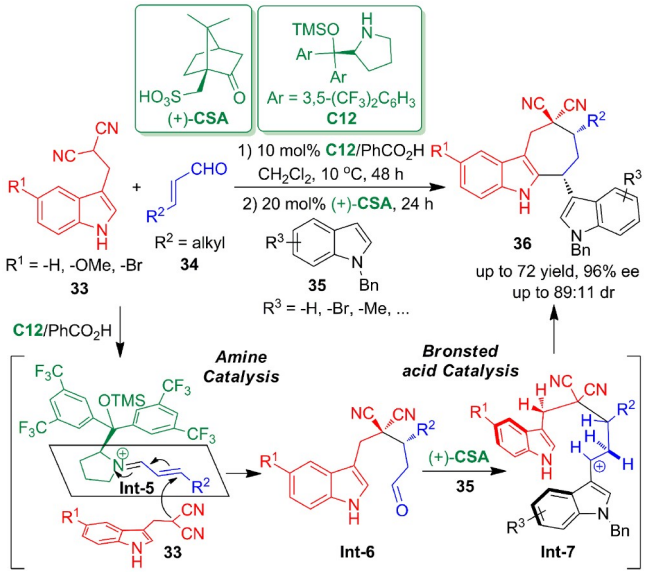


Scheme 8 Chiral amine-catalyzed asymmetric (4+3) cycloaddition of α-vinylenals, reported by Chen and co-workers [55,56] (color online).

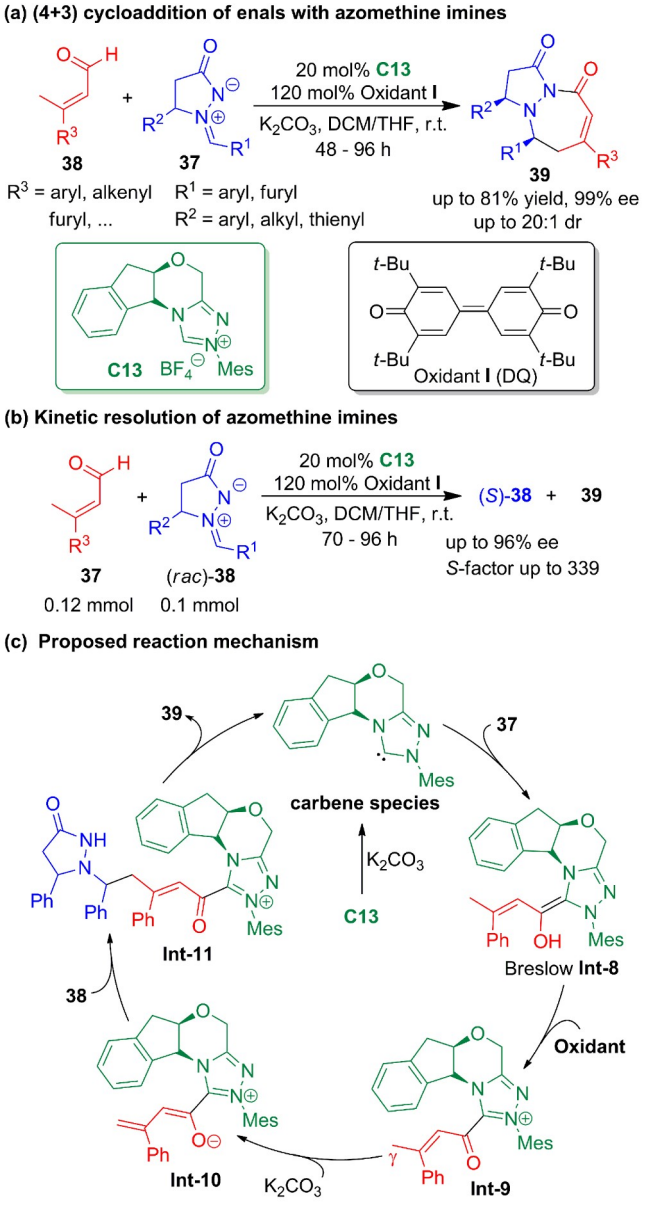
asymmetric (3+2) 1,3-dipolar cyclization reactions with 1,3-dipoles [54] (Scheme 8a), vinyl enals or vinyl enones with an extended conjugated double bond have gained the interest of chemists and were designed as 4C building blocks for organocatalytic asymmetric (4+3) cycloadditions. In 2020, Chen and co-workers [55] designed a type of α-vinyl α,β-unsaturated aldehydes (α-vinyl enals) by introducing α-vinyl group into enal substrates. These α-vinyl-enals could react with 1,3-dipoles under the catalysis of chiral secondary amines to undergo a β,γ′-regioselective asymmetric (4+3) cycloaddition, avoiding the traditional asymmetric (3+2) annulation pathway. They used *N*-2,2,2-trifluoroethylisatin-derived imines **30** that could readily isomerize to azomethine ylide-type species as the active three-atom reactants to interact with α-vinyl enals **31** under the cooperative catalysis of the chiral amine **C11** and benzoic acid, thereby synthesizing a series of spirooxindoles **32** containing a seven-membered azepane motif in overall high yields and good to excellent enantioselectivities (Scheme 8b). Notably, *N*-2,2,2-trifluoroethylisatin-derived imines **30** proved to be a competent 1,3-dipoles in squaramide-catalyzed asymmetric (3+2) cycloaddition with nitroalkenes **24′** for the synthesis of enantioenriched spirooxindoles **32′** containing a five-membered pyrrolidine scaffold [56].

2.3 Other 4C building blocks

Besides cyclic and acyclic dienes, other reactants could serve as 4C building blocks in organocatalytic asymmetric (4+3) cycloadditions for the construction of chiral seven-membered carbocycles. In 2013, Hong and co-workers [57] reported that malononitrile-based indoles **33** could serve as 4C building blocks in a catalytic asymmetric formal (4+3) cycloaddition reaction with α,β-unsaturated aldehydes **34** and *N*-Bn-protected indoles **35** (Scheme 9). This (4+3) cycloaddition involved a sequential Michael/double Friedel-Crafts alkylation reaction of malononitrile-based indoles **33** with α,β-unsaturated aldehydes **34** and *N*-Bn-protected indoles **35** under the catalysis of the chiral amine **C12** and chiral Brønsted acid (+)-**CSA** *via* a stepwise one-pot process, resulting in the enantioselective synthesis of cyclohepta[*b*]-indoles **36**. Specifically, first, α,β-unsaturated aldehydes **34** were activated by chiral amine catalyst **C12** and PhCOOH to



Scheme 9 Chiral amine and (+)-CSA cooperative catalysis realizing asymmetric formal (4+3) cycloaddition by Hong and co-workers [57] (color online).

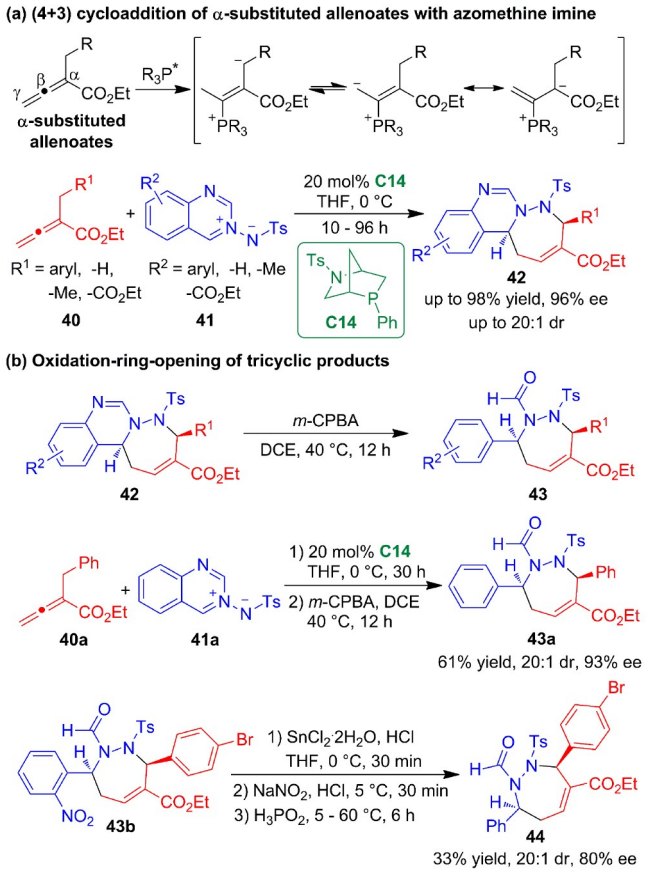


Scheme 10 Chiral NHC-catalyzed asymmetric (4+3) cycloaddition of enals by Chi and co-workers [58] (color online).

generate the corresponding iminium cation **Int-5**, followed by the nucleophilic Michael addition of malononitrile-based indoles **33** to generate the enantioenriched intermediate **Int-6**. Then, **Int-6** reacted with indoles **35** under the activation of chiral Brønsted acid (+)-**CSA** *via* the Friedel-Crafts alkylation process to form another cation, **Int-7**, which underwent an intramolecular stereoselective cyclization to afford cyclohepta[*b*]indoles **36** in moderate to good yields and high enantioselectivities.

In 2014, Chi and co-workers [58] used enals **37** as 4C building blocks and developed the first chiral NHC-catalyzed asymmetric (4+3) cycloaddition of enal substrates with azomethine imines **38** in the presence of oxidant **I**, realizing the synthesis of a series of dinitrogen-fused seven-membered heterocyclic products **39** in overall good yields and high diastereo- and enantioselectivities (Scheme 10a). Notably, the kinetic resolution [59] of racemic azomethine imines *rac*-**38** in this organocatalytic (4+3) cycloaddition was also investigated by modulating the relative equivalents of enals **37** under standard conditions. They found that enantioenriched azomethine imines (*S*)-**38** could be effectively obtained in good yields and high selectivity factors (*S*-factor up to 339) (Scheme 10b). In the suggested reaction mechanism (Scheme 10c), the chiral NHC catalyst **C13** generated highly reactive carbene species in the presence of a base, which immediately reacted with enal **37** to form the Breslow intermediate **Int-8**. Subsequently, an NHC-bounded ester intermediate **Int-9** was generated in the presence of oxidant **I** [60], which was transformed to vinyl enolate **Int-10** as a 1,4-dipolarophile *via* deprotonation of the γ-carbon [61]. Then, **Int-10** underwent an asymmetric (4+3) cycloaddition with azomethine imine **38** *via* the formation of intermediate **Int-11** to afford the desired product **39** with the regeneration of active carbene species. In addition, the origin of the kinetic resolution of racemic azomethine imines *rac*-**38** was explained by the different reactivity of the two enantiomers of azomethine imine **38** to the chiral vinyl enolate **Int-10**. This study demonstrates that enals can function as competent 4C building blocks in asymmetric (4+3) cycloadditions catalyzed by NHC, considerably contributing in developing the chemistry of 1,3-dipolar cycloadditions and NHC catalysis.

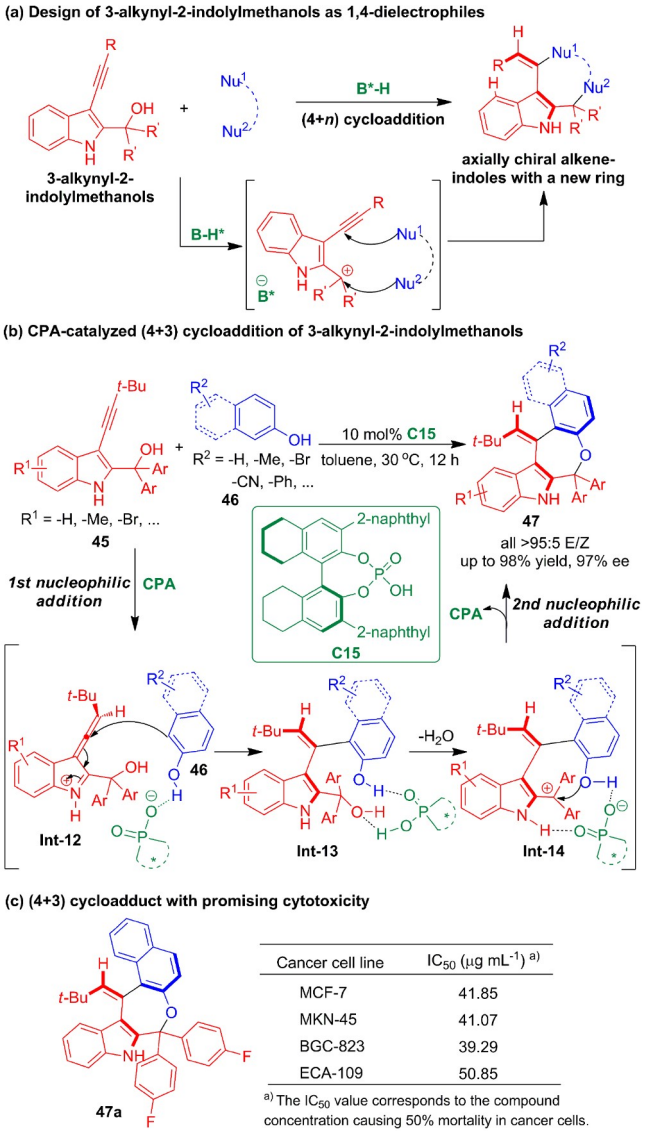
α-Substituted allenoates can be activated by chiral organic phosphine catalysts to form phosphonium (di)enolate zwitterions [62], which can be used as 4C or 2C building blocks in cycloaddition reactions *via* competing (4+*n*) or (2+*n*) pathways (Scheme 11a). Therefore, it is difficult to control



Scheme 11 Chiral phosphine-catalyzed asymmetric (4+3) cycloaddition of α-substituted allenoates by the Guo group [63] (color online).

the chemoselectivity of cycloadditions involving α-substituted allenoates. In 2016, Guo's group [63] developed a chiral phosphine **C14**-catalyzed asymmetric (4+3) cycloaddition reaction of α-substituted allenoates **40** with azomethine imines **41**, affording a wide range of chiral seven-membered ring-fused quinazoline-based tricycles **42** in overall excellent yields and high diastereo- and enantioselectivities. In addition, as shown in Scheme 11b, products **42** were used in synthesizing enantioenriched diazepine derivatives **43** in the presence of *meta*-cholorperoxybenzoic acid (*m*-CPBA) *via* an oxidation-ring-opening process. Moreover, they investigated the synthesis of compound **43a** through a sequential cycloaddition/oxidation/ring-opening process in a one-pot manner, where product **43a** could be obtained with a 61% yield, 20:1 dr, and 93% ee. Furthermore, the nitro group (NO_2) was removed from **43b** *via* a sequential three-step reaction, affording the target compound **44** with a 33% yield, 20:1 dr, and 80% ee.

In previous reports on organocatalytic asymmetric (4+3) cycloadditions, seven-membered rings were always constructed with central chirality. Recently, catalytic asymmetric synthesis of molecules with axial chirality has become an important area of studies [64–66]. Particularly, organocatalytic asymmetric approaches have proven to be effective methods for constructing axially chiral scaffolds [67–70]. Nevertheless, the construction of axially chiral scaffolds *via* organocatalytic asymmetric (4+3) cycloaddition was unknown until 2020, when Shi's group [71] reported a CPA-catalyzed asymmetric (4+3) cycloaddition reaction for the construction of an indole-fused seven-membered ring bearing an alkene-indole with axial chirality (Scheme 12). In this study, 3-alkynyl-2-indolylmethanols were designed as a new type of indole-based platform molecules [72] that could act as 1,4-dielectrophiles and 4C building blocks to react with dielectrophiles under the catalysis of B*–H, thereby constructing axially chiral alkene-indoles with simultaneous generation of a new ring (Scheme 12a). Based on this design, they accomplished the catalytic asymmetric (4+3) cycloaddition of 3-alkynyl-2-indolylmethanols **45** with 2-naphthols or phenols **46** under the catalysis of CPA **C15**, and the

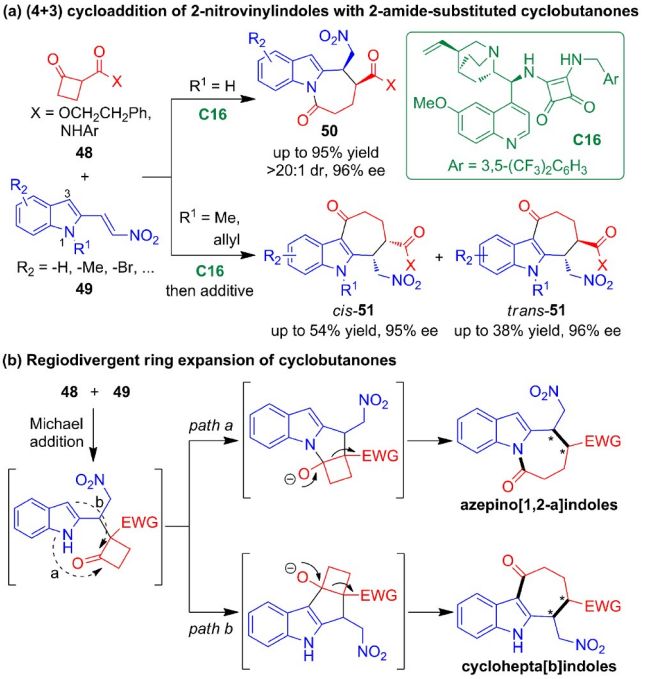


Scheme 12 CPA-catalyzed asymmetric (4+3) cycloaddition with 3-alkynyl-2-indolylmethanols by Shi's group [71] (color online).

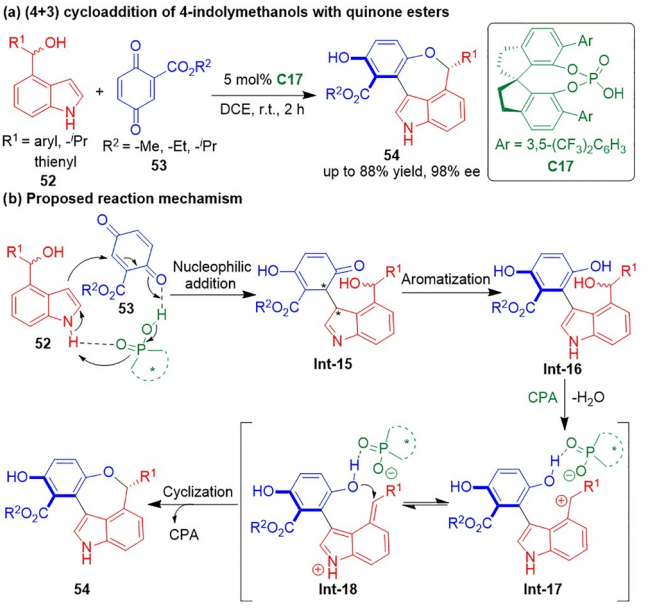
desired seven-membered heterocycles **47** bearing axial chirality were obtained in excellent yields and high (*Z*/*E*)- and enantioselectivities (Scheme 12b). Using theoretical calculations, they suggested that this (4+3) cycloaddition involved a double nucleophilic addition process. The first step involved an intermolecular nucleophilic addition of 2-naphthol or phenol **46** to the allene intermediate **Int-12,** which was generated *in situ* from 3-alkynyl-2-indolylmethanol **45** in the presence of CPA [73], resulting in the formation of adduct **Int-13**. Then, **Int-13** was activated by CPA **C15** to produce the carbocation intermediate **Int-14**, which subsequently underwent intramolecular nucleophilic addition to yield the final product **47**. Moreover, the investigation on the potential bioactivity of some products revealed that product **47a** exhibited some cytotoxicity toward different types of cancer cell lines (Scheme 12c), indicating the potential application of this class of axially chiral alkene-indole products. Notably, this reaction not only added new content to catalytic asymmetric (4+3) cycloadditions and provided a powerful method for constructing seven-membered heterocycles bearing axial chirality but also represented the first catalytic asymmetric construction of axially chiral alkene-indole frameworks, advancing the development of axially chiral indole chemistry.

In addition to 3-alkynyl-2-indolylmethanols, cyclobutanones could be used as 4C building blocks in organocatalytic asymmetric (4+3) cycloadditions. In 2020, Deng and co-workers [74] used cyclobutanones **48** as 4C building blocks and established an organocatalytic asymmetric formal (4+3) cycloaddition of such substrates with 2-nitrovinylindoles **49** in the presence of chiral bifunctional amino catalyst **C16** *via* an enantioselective Michael addition/three-atom ring-expansion sequence (Scheme 13a). The reaction could afford the regiodivergent cycloadducts **50** or **51** by controlling the nucleophilicity of the N1 or C3 site of the indole ring. Notably, it was necessary to use the strong Lewis acid $BF_3{\cdot}Et_2O$ as an additive for the C3-nucleophilic reaction to occur. Specifically (Scheme 13b), reactants **48** and **49** first underwent a Michael addition step. Then, the N1 and C3 sites of the indole ring were selectively added to the carbonyl group of the cyclobutanone moiety to generate the corresponding polycyclic intermediate, which afforded azepino[1,2-*a*]indoles or cyclohepta[*b*]indoles *via* an enantioselective spontaneous fragmentation process.

4-Indolylmethanols [75] can also be utilized as 4C building blocks to undergo a (4+3) cycloaddition reaction with suitable three-atom reactants. In 2021, Lin and co-workers [76] established an enantioselective (4+3) cycloaddition reaction of 4-indolylmethanols **52** with 1,4-benzoquinone esters **53** in the presence of CPA **C17**, synthesizing chiral indole derivatives **54** with good yields and moderate to high enantioselectivities (Scheme 14a). Moreover, they proposed a reaction mechanism (Scheme 14b). Initial activation of 4-



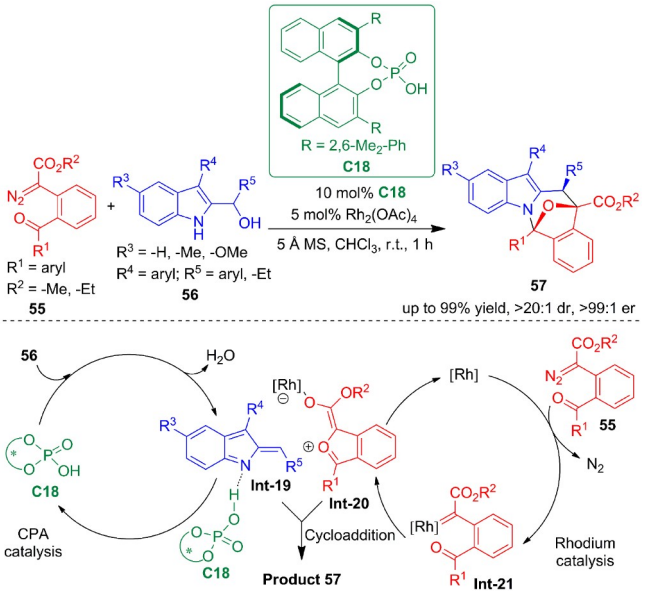
Scheme 13 Chiral bifunctional amino-catalyst-catalyzed asymmetric formal (4+3) cycloaddition of cyclobutanones, reported by Deng and co-workers [74] (color online).



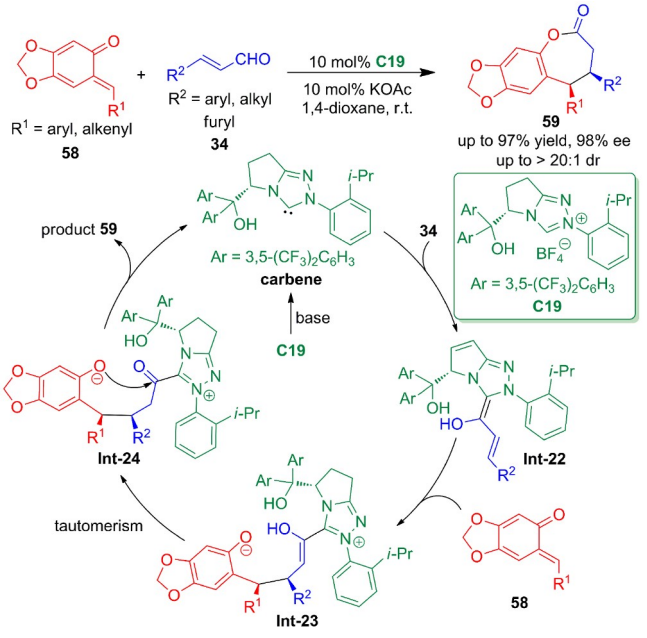
Scheme 14 CPA-catalyzed asymmetric (4+3) cycloaddition of 4-indolylmethanols by Lin and co-workers [76] (color online).

indolylmethanol **52** and 1,4-benzoquinone ester **53** by CPA **C17** resulted in an enantioselective nucleophilic addition to generate **Int-15**, which rapidly transformed into **Int-16**. Subsequently, **Int-16** was converted to carbocation **Int-17** and vinyliminium **Int-18** *via* dehydration, which underwent intramolecular cyclization to generate the final product benzoxepino[5,4,3-*cd*]indole **54**.

Cooperative catalysis of organocatalyst with metal catalyst has proven to be a powerful catalytic strategy in asymmetric catalysis, which can enable unconventional transformations with excellent control of the enantioselectivity. Based on this strategy, in 2021, Schneider's group [77] developed a stereoselective formal (4+3) cycloaddition of α-diazo esters **55** with C3-substituted 2-indolylmethanols **56** *via* the cooperative catalysis of rhodium and CPA **C18**, affording a series of *oxa*-bridged azepino[1,2-*a*]indoles **57** containing three stereogenic centers in good yields and high stereoselectivities (Scheme 15). In this reaction, α-diazo esters **55** functioned as the 4C building blocks, capable of producing highly reactive carbonyl ylides *in situ*. In addition, they hypothesized that the reaction was enabled by the cooperative catalysis of rhodium and CPA **C18** in separate catalytic cycles. In the catalytic cycle of CPA **C18**, the dehydration of C3-substituted 2-indolylmethanol **56** resulted in the formation of the hydrogen-bonded intermediate **Int-19**. Simultaneously, in the catalytic cycle [78–80], Rh-catalyzed decomposition of α-diazo ester **55** and subsequent intramolecular trapping of the metal carbine complex **Int-21** by the carbonyl group generated the carbonyl ylide **Int-20**. Then, the transient intermediates **Int-19** and **Int-20** generated by two catalytic cycles were subjected to a formal (4+3) cycloaddition to afford the target product **57**. This approach not only provides an effective stereoselective method for constructing indole-fused seven-membered rings but also serves as a model for asymmetric organo/metal cooperative catalysis.



Scheme 15 Rh/CPA-catalyzed asymmetric (4+3) cycloaddition of α-diazo esters by Schneider's group [77] (color online).



Scheme 16 Chiral NHC-catalyzed (4+3) cycloaddition of *o*-QMs by Ye's group [89] (color online).

3 Organocatalytic asymmetric (4+3) cycloadditions involving *oxa*-four-atom building blocks

3.1 *Oxa*-dienes as four-atom building blocks

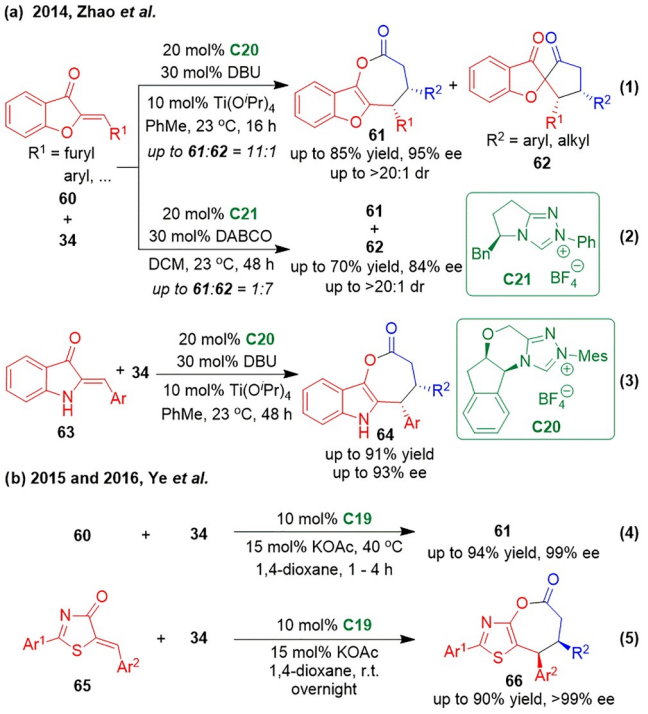
Oxa-dienes are the commonly used four-atom building blocks [81,82] that have been extensively applied to organocatalytic asymmetric (4+3) cycloadditions for constructing seven-membered oxygen-containing rings in an enantioselective manner. *o*-Quinone methides (*o*-QMs) belong to a class of versatile building blocks, especially for catalytic asymmetric cycloadditions [83,84]. However, most of the transformations of *o*-QMs focused on catalytic asymmetric (4+2) cycloadditions [85–88]. However, organocatalytic asymmetric (4+3) cycloadditions involving *o*-QMs remained unknown until 2013. In that year, Ye's group [89] used *o*-QMs as the four-atom building blocks to realize the first chiral NHC-catalyzed (4+3) cycloaddition of *o*-QMs **58** with α,β-unsaturated aldehydes **34**, realizing a series of benzo-ε-lactones **59** in good yields, excellent enantioselectivities, and moderate to good diastereoselectivities (Scheme 16). Notably, both β-aryl- and β-alkyl-enals could be used in this reaction, with β-alkyl-enals as the compatible reaction partners, providing the corresponding products with excellent diastereoselectivities (all > 20:1 dr). In the proposed reaction mechanism, the active carbene species was initially released from the chiral catalyst **C19** in the presence of a base to activate enals **34**, thus generating the vinyl Breslow intermediate **Int-22**. **Int-22** then reacted with *o*-QMs **58** *via* Michael addition to generate **Int-23**, which could be converted to **Int-24** *via* tautomerization. Finally, **Int 24** underwent intramolecular lactonization to produce the desired cycloadducts **59**. This study not only demonstrates the

efficacy of chiral NHC catalysis in developing asymmetric (4+3) cycloadditions but also provides a protocol for constructing oxygen-containing seven-membered rings with optical purity.

Besides *o*-QMs, some heterocycle-based enones [90] can act as *oxa*-dienes in organocatalytic asymmetric (4+3) cycloadditions to produce chiral seven-membered oxygen-containing heterocyclic compounds. In 2014, Zhao and co-workers [91] used enones **60** and **63** as the four-atom building blocks in chiral NHC-controlled divergent cycloadditions with enals **34**, leading to the formation of (4+3) cycloadducts **61** and **64** in overall good yields and high diastereo- and enantioselectivities (Scheme 17a). In detail, when the chiral NHC catalyst **C20** was used in this reaction, benzofuran-containing ε-lactones **61** were obtained as the major products, along with a small amount of spiro-heterocycles **62** as by-products (Eq. (1)). Meanwhile, compounds **62** could be obtained as the major products by replacing **C20** with the chiral catalyst **C21** under the related conditions (Eq. (2)). The reaction of enones **63** (as heterodienes) with enals **34** in the presence of **C20** could produce the target indole-containing ε-lactones **64** with almost no byproduct formation (Eq. (3)).

Nearly at the same time, Ye and co-workers [92] reported the construction of benzofuran-containing ε-lactones **61** in good yields and high diastereo- and enantioselectivities *via* chiral NHC-catalyzed (4+3) cycloaddition of enones **60** with enals **34** in the presence of chiral bifunctional catalyst **C19** bearing a free hydroxyl group, where the competitive (3+2) cycloadducts were not formed in the presence of bifunctional NHC catalyst (Scheme 17b, Eq. (4)). Moreover, they conducted several control experiments and suggested that the (3+2) cycloadducts are thermodynamically favored and could be generated from the kinetically favored (4+3) cycloadducts in the presence of a nonbifunctional NHC catalyst. Based on continuous studies on chiral NHC-catalyzed cycloadditions, Ye and co-workers [93] also used alkenyl thiazolones as building blocks and achieved an organocatalytic asymmetric (4+3) cycloaddition of 5-alkenyl thiazolones **65** with enals **34** in the presence of chiral catalyst **C19**, obtaining enantioenriched thiazole-fused ε-lactones **66** in good yields and excellent diastereo- and enantioselectivities (Eq. (5)). In 2021, Li and co-workers [94] investigated the possible mechanism and origin of stereoselectivity of such a (4+3) cycloaddition reaction between 5-alkenyl thiazolone and enal *via* density functional theory (DFT) calculations, which provided valuable insights for a comprehensive understanding of this class of reactions.

In 2020, Chen and co-workers [95] developed a chiral tertiary amine-catalyzed asymmetric regioselective (4+*n*) cycloaddition reaction of isatin-derived Morita-Baylis-Hillman (MBH) carbonates [96,97] with *o*-QMs. When MBH carbonates **68** were subjected to a γ-regioselective (4+3)

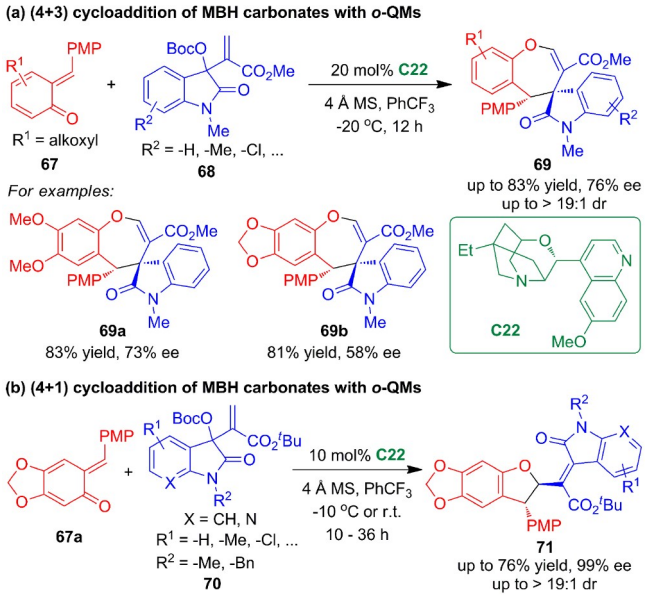


Scheme 17 Chiral NHC-catalyzed (4+3) cycloaddition with heterocyclic enones by the groups of Zhao *et al*. [91] and Ye *et al*. [92,93] (color online).

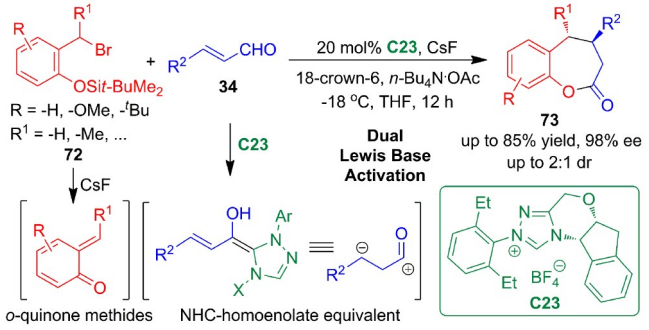
cycloaddition with *o*-QMs **67** under the catalysis of **C22**, several chiral oxepane spirooxindoles **69** could be obtained in good yields and moderate enantioselectivities (Scheme 18a). Interestingly, when the ester group of MBH carbonates was changed from methyl acrylate (–CO_2Me) to *t*-butyl acrylate (–$CO_2{}^t$Bu), an interesting α-regioselective (4+1) cycloaddition of MBH carbonates **70** with *o*-QMs **67a** was realized under similar catalytic conditions, affording a series of 2,3-dihydrobenzofuran derivatives **71** in moderate to good yields and excellent enantioselectivities, revealing that the switchable regioselectivity and chemoselectivity of this reaction were closely related to the steric hindrance of the ester group of MBH carbonates (Scheme 18b).

3.2 *oxa*-diene precursors as four-atom building blocks

Besides the stable *oxa*-dienes as a class of easily available four-atom building blocks, the precursors of *oxa*-dienes [98–102] can be applied to various organocatalytic asymmetric (4+3) cycloadditions. In 2013, the Scheidt group [103] used *tert*-butyldimethylsilyl (TBS)-protected phenol substrates **72** as *oxa*-diene precursors, which can form transient *o*-QM intermediates in the presence of fluoride, in an enantioselective (4+3) cycloaddition reaction with α,β-unsaturated aldehydes **34** catalyzed by the chiral NHC catalyst **C23**, synthesizing a series of 2-benzoxopinones **73** in overall good yields and excellent enantioselectivities (Scheme 19). In this approach, the dual activation of the two substrates was



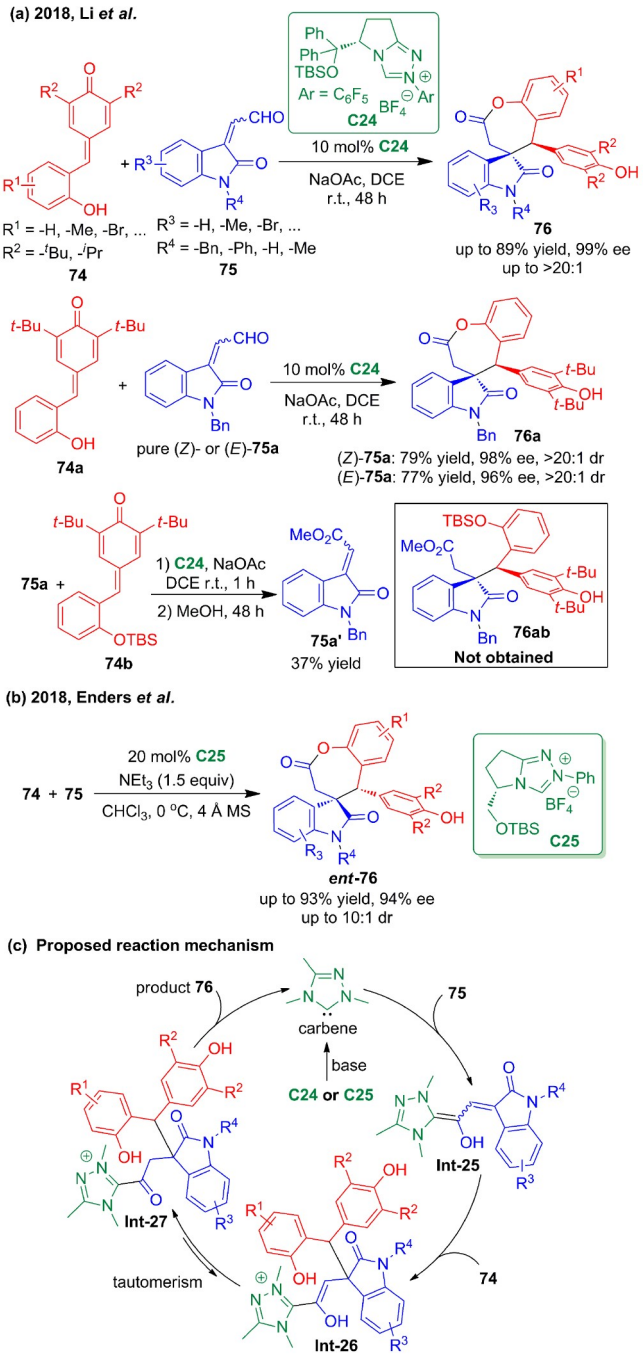
Scheme 18 Chiral tertiary amine-catalyzed (4+*n*) cycloaddition of *o*-QMs by Chen's group [95] (color online).



Scheme 19 Chiral NHC-catalyzed (4+3) cycloaddition of TBS-protected phenol substrates by Scheidt's group [103] (color online).

achieved by combining two Lewis bases in the reaction simultaneously. In the (4+3) cycloaddition, two reactive species were identified as the highly electrophilic *o*-QMs derived from substrates **72** under the activation of CsF and the nucleophilic NHC homoenolate derived from enals **34** under the activation of **C23**. This work represents a pioneering effort in chiral NHC-catalyzed asymmetric (4+3) cycloaddition and provides a proof of concept for dual activation.

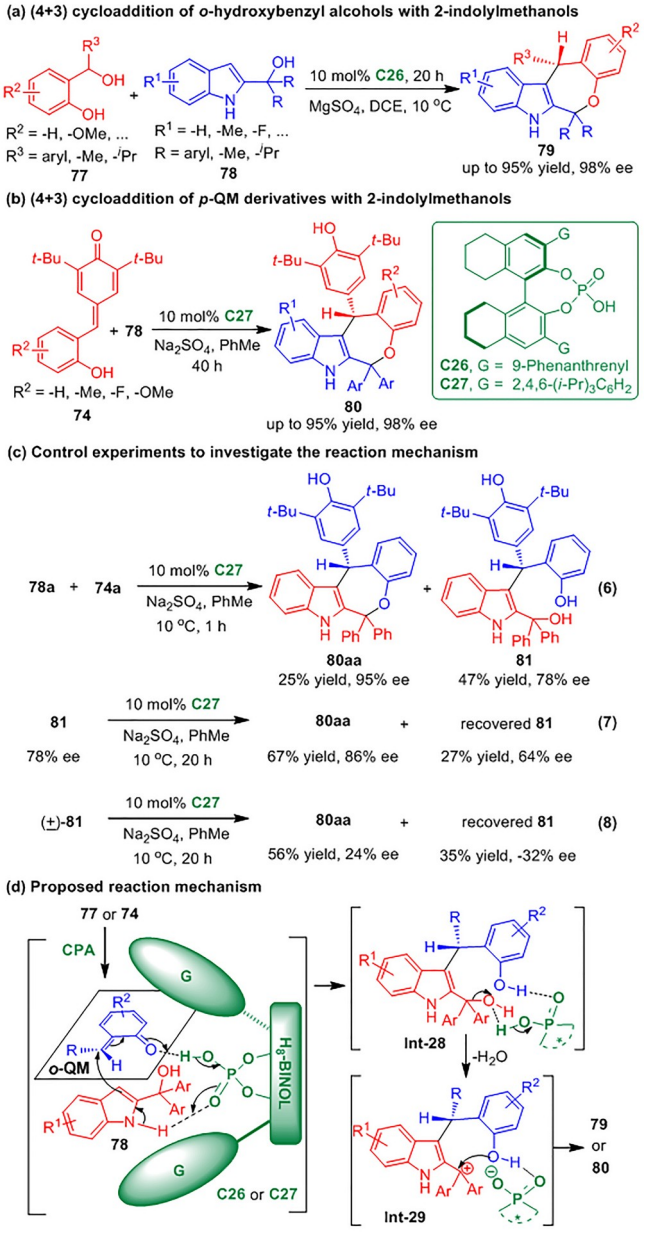
As the variants of *o*-QMs, *ortho*-hydroxyphenyl substituted *para*-quinone methides (*p*-QMs) have been used as a class of suitable *oxa*-four-atom building blocks in organocatalytic asymmetric (4+3) cycloadditions for constructing oxygen-containing heterocyclic frameworks. In 2018, Li's group [104] realized the enantioselective (4+3) cycloaddition of *p*-QMs **74** with isatin-derived enals **75** in the presence of the chiral NHC catalyst **C24**, affording chiral spiro-oxindole-ε-lactones **76** in good yields and excellent enantioselectivities (Scheme 20a). Notably, the (*Z*/*E*)-configuration of the double bond in isatin-derived enals **75** did not affect the enantioselective cycloaddition process, and the target spirobenzoxopinone **76a** could be obtained from pure (*Z*)- or (*E*)-**75a** as a starting material with nearly the same yield and stereoselectivity. In addition, the esterification product **75a′** was obtained instead of a possible adduct **76ab** using substrate **74b** bearing TBS-protected group as a reactant in the control experiment, which suggested that *p*-QMs **74** did not



Scheme 20 Chiral NHC-catalyzed (4+3) cycloaddition of *p*-QMs by the groups of Li *et al.* [104] and Enders *et al.* [105] (color online).

directly react with isatin-derived enals **75** in the (4+3) cycloaddition process. Almost at the same time, Enders' group [105] reported the asymmetric (4+3) cycloaddition of *p*-QMs **74** with isatin-derived enals **75** using chiral NHC **C25** as a suitable catalyst, leading to the formation of the desired products **ent-76** in high yields and excellent stereoselectivities (Scheme 20b). Meanwhile, two research groups of Li and Enders independently proposed a similar reaction mechanism (Scheme 20c). Initially, the addition of chiral carbene species generated from **C24** or **C25** to the isatin-derived enal **75** generated the corresponding Breslow intermediate **Int-25**, which reacted with *p*-QMs **74** through 1,6-Michael addition to produce **Int-26**. Subsequently, **Int-26** was isomerized into the acyl azolium intermediate **Int-27** to furnish the final product **76** *via* intramolecular lactonization.

Recently, chemists have taken a keen interest in *o*-hydroxybenzyl alcohols as *oxa*-diene precursors, as this class of reactants can *in situ* generate highly reactive *o*-QM intermediates *via* dehydration in the presence of an acid. In spite of the rapid development of catalytic asymmetric reactions involving *o*-hydroxybenzyl alcohols [83–88,106–111], the catalytic asymmetric (4+3) cycloaddition of *o*-hydroxybenzyl alcohols remained unknown until 2019, when Shi's group [112] established the first organocatalytic asymmetric (4+3) cycloaddition of *o*-hydroxybenzyl alcohols **77** with 2-indolylmethanols **78** catalyzed by CPA **C26** (Scheme 21a). A series of indole-fused, oxygen-containing, seven-membered heterocycles were synthesized in high yields and with excellent enantioselectivities using this method. Additionally, the catalytic enantioselective (4+3) cycloaddition of *p*-QMs **74** as four-atom building blocks with 2-indolylmethanols was investigated (Scheme 21b). Specifically, they performed the desired (4+3) cycloaddition of *p*-QMs **74** with 2-indolylmethanols **78** in the presence of CPA **C27**, realizing the synthesis of indole-fused seven-membered heterocycles **80** and expanding the applicability of CPA-catalyzed asymmetric (4+3) cycloaddition involving 2-indolylmethanols. To further understand the reaction mechanism, a series of control experiments were conducted (Scheme 21c). Interestingly, a kinetic resolution was observed in the reaction. When **78a** was reacted with **74a** under standard conditions for 1 h, a substantial amount of compound **81** (47% yield, 78% ee) and a small quantity of product **80aa** (25% yield, 95% ee) were produced (Eq. (6)). Subsequently, intermediate **81** with 78% ee was subjected to standard reaction conditions for 20 h, resulting in the final product **80aa** (67% yield, 86% ee) with a small number of recovered **81** (27% yield, 64% ee, Eq. (7)). These results confirm that compound **81** was an intermediate of the (4+3) cycloaddition and that kinetic resolution was possible. To confirm this hypothesis, they employed racemic **81** as the starting material for the reaction under standard conditions for 20 h, obtaining product **80aa** in 56% yield with 24% ee and recovering **81** in 35% yield

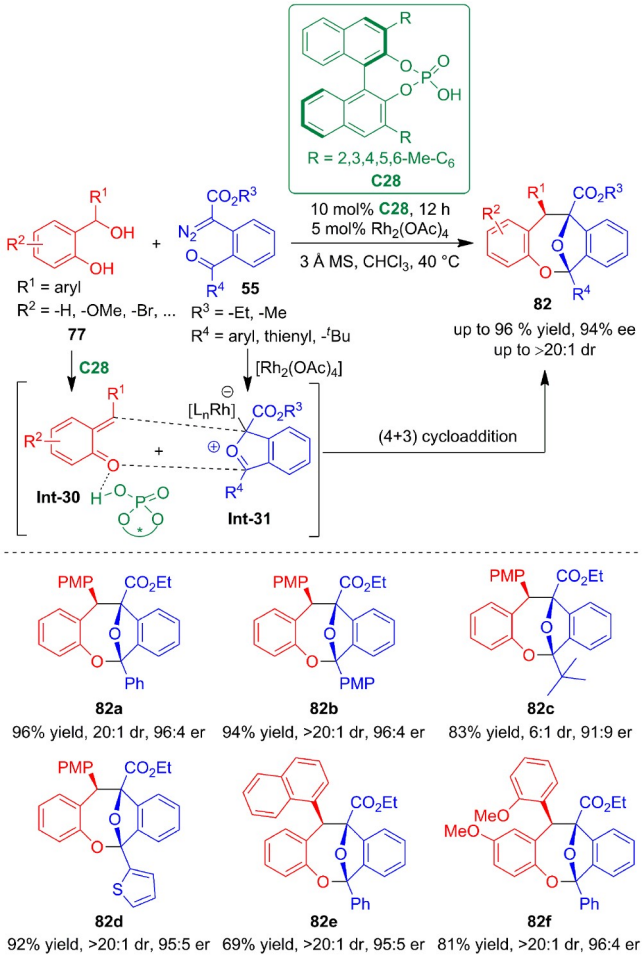


Scheme 21 CPA-catalyzed asymmetric (4+3) cycloaddition of *o*-hydroxybenzyl alcohols by the Shi group [112] (color online).

with 32% ee (Eq. (8)). These experimental results confirm that intermediate **81** underwent a moderate degree of kinetic resolution during the second step of intramolecular cyclization. Based on the experimental results, a potential reaction mechanism was proposed (Scheme 21d). In the presence of CPA, *oxa*-diene precursors **74** or **77** were transformed into the corresponding *o*-QM intermediate. Then, substrate **78** reacted with highly reactive *o*-QM species under the activation of CPA **C26** or **C27** by forming hydrogen bonds to produce intermediate **Int-28**, which underwent dehydration to produce the carbocation intermediate **Int-29**. Finally, **Int-29** was converted to the target product **79** or **80** *via* an intramolecular cyclization process under the influence of CPA

anion. Notably, this is the first catalytic asymmetric (4+3) cycloaddition of 2-indolylmethanols, which contributes a new perspective to chiral indole chemistry.

In the same year, Schneider's group [113] published an elegant work on the asymmetric (4+3) cycloaddition of *o*-hydroxybenzyl alcohols **77** as four-atom building blocks with α-diazo esters **55** under the cooperative catalysis of Rh/CPA (Scheme 22). Numerous *oxa*-bridged heterocycles **82** with two quaternary and one tertiary stereogenic centers were obtained in high yields and with excellent diastereo- and enantioselectivities *via* this method. In this (4+3) cycloaddition, the *o*-QMs **Int-30** generated from *ortho*-hydroxybenzyl alcohols **77** in the CPA catalytic cycle were four-atom reaction species activated by CPA *via* hydrogen-bonding interactions. Meanwhile, carbonyl ylides **Int-31** were formed from α-diazo esters **55** in the $Rh_2(OAc)_4$ catalytic cycle, which served as three-atom reaction species. The formation of only catalytic amounts of both types of reaction species allowed the (4+3) cycloaddition to proceed despite the instability and short lifetime of such species. This work provides an additional excellent example of the catalytic asymmetric (4+3) cycloaddition of *o*-hydroxybenzyl alcohols under the cooperative catalysis of chiral organocatalyst with metal complex, which offers a powerful strategy for constructing structurally complex *oxa*-bridged seven-membered heterocycles with optical purity.



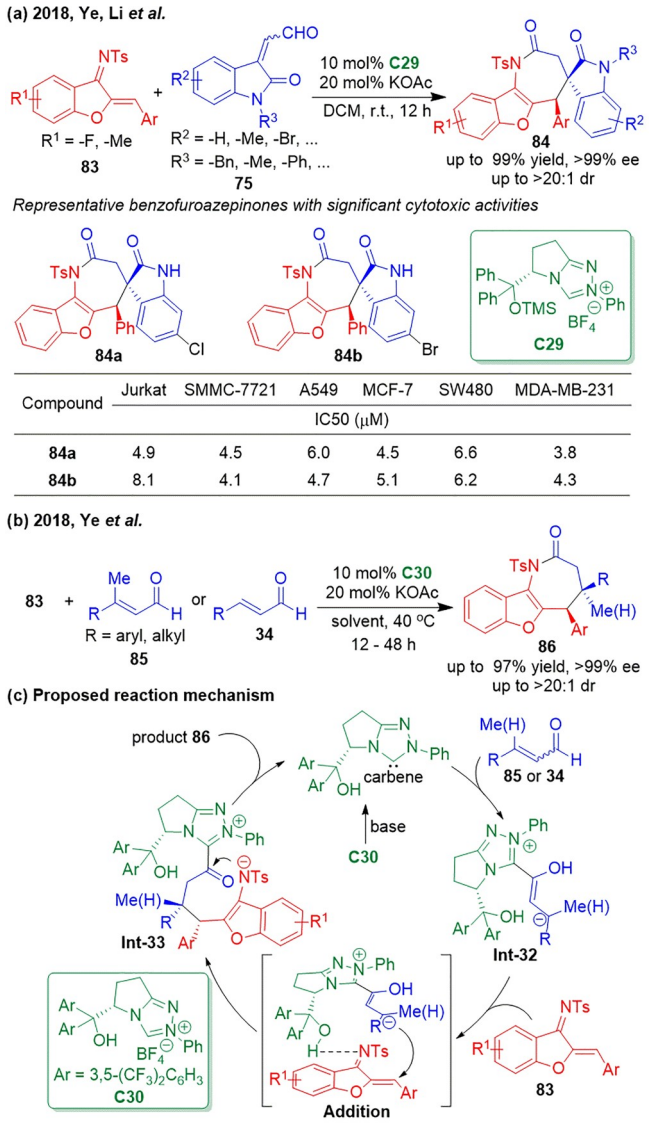
Scheme 22 Rh/CPA-catalyzed asymmetric (4+3) cycloaddition with *o*-hydroxybenzyl alcohols by Schneider's group [113] (color online).

4 Organocatalytic asymmetric (4+3) cycloadditions involving *aza*-four-atom building blocks

4.1 *Aza*-dienes as four-atom building blocks

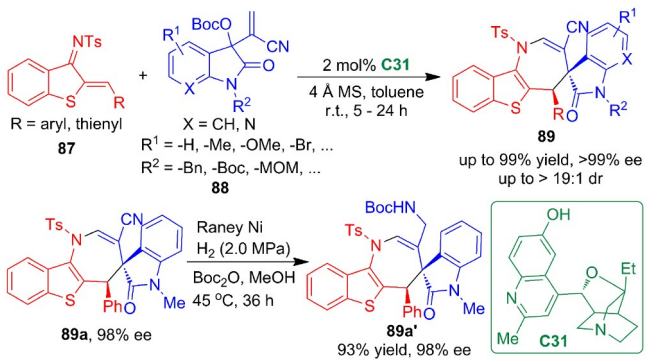
Aza-dienes, which are structurally similar to *oxa*-dienes, have proven to be a versatile class of four-atom building blocks [114–116] that can be employed in organocatalytic asymmetric (4+3) cycloadditions for the optically pure synthesis of seven-membered nitrogen-containing heterocyclic frameworks. In 2018, Ye, Li and co-workers [117] utilized aurone-derived *aza*-dienes **83** as compatible four-atom building blocks in the chiral NHC-catalyzed (4+3) cycloaddition with isatin-derived enals **75**, achieving the catalytic enantioselective synthesis of spirocyclic oxindole-based benzofuroazepinones **84** in good yields and excellent diastereo- and enantioselectivities (Scheme 23a). Additionally, some azepinones **84** bearing indole-fused seven-membered rings were evaluated for their *in vitro* cytotoxicity against several human tumor cell lines. Compounds **84a** and **84b** exhibited significant inhibitory activity against these tested cell lines. Afterward, the same group [118] employed β,β-disubstituted enals **85** and β-monosubstituted enals **34** as suitable partners to react with aurone-derived *aza*-dienes **83** through chiral NHC **C30**-catalyzed (4+3) cycloaddition for the enantioselective construction of benzofuroazepinones **86**, wherein the bifunctional chiral catalyst **C30** with a free hydroxy group plays an important role (Scheme 23b). In their proposed reaction mechanism (Scheme 23c), the chiral catalyst **C30** initially generates an active carbene species *via* the action of a base, which then reacts with acyclic enals **85** or **34** to produce the corresponding homoenolate **Int-32**. Then, the adduct **Int-33** is produced by the nucleophilic addition of **Int-32** to *aza*-diene **83** *via* the hydrogen-bonding interaction between the hydroxy group of **C30** and **83**. Finally, the intramolecular lactamization of **Int-33** results in the formation of (4+3) cycloadducts **86** and the release of active carbene species. Furthermore, in 2020, Li and co-workers [119] used DFT calculations to investigate the catalytic mechanisms and origins of the stereoselectivity of the NHC-catalyzed (4+3) cycloaddition between an aurone-derived *aza*-diene and an isatin-derived enal, shedding light on the possible reaction mechanism.

In 2020, Chen's group [95] employed 2-alkylenebenzo[*b*]thiophen-3(2H)-one-derived *aza*-dienes **87** as four-atom building blocks in the organocatalytic asymmetric (4+3) cycloaddition of isatin-derived MBH carbonates **88** in the



Compound	Jurkat	SMMC-7721	A549	MCF-7	SW480	MDA-MB-231
	IC50 (μM)					
84a	4.9	4.5	6.0	4.5	6.6	3.8
84b	8.1	4.1	4.7	5.1	6.2	4.3

Scheme 23 Chiral NHC-catalyzed (4+3) cycloaddition of aurone-derived *aza*-dienes by Ye's group [117,118] (color online).



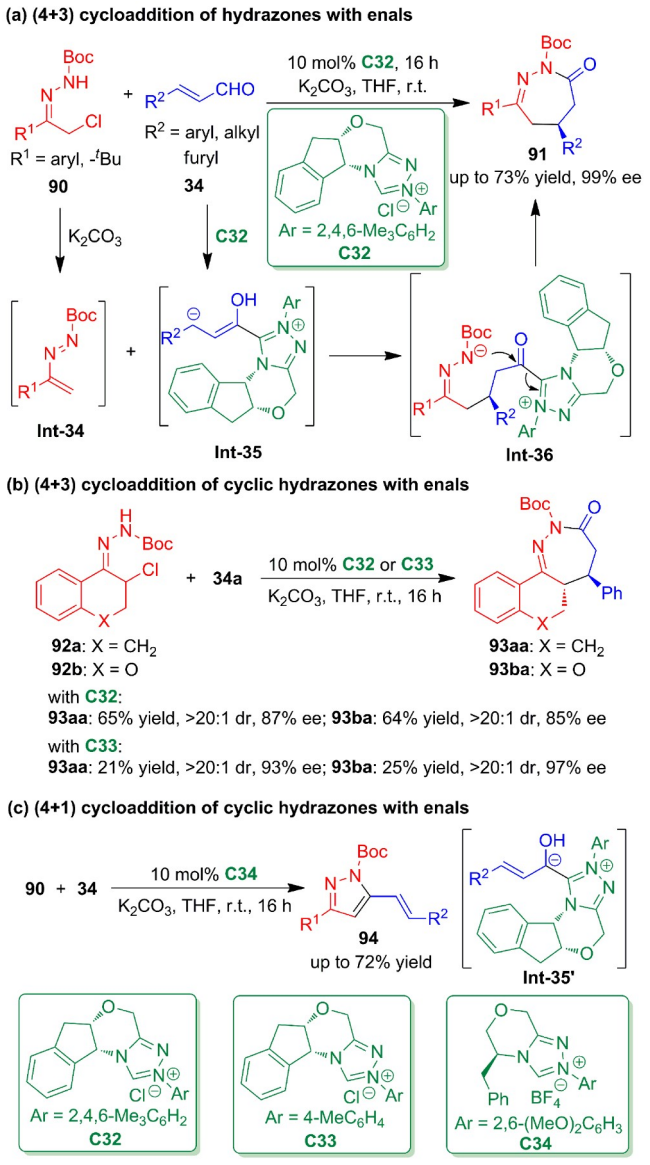
Scheme 24 Chiral tertiary amine-catalyzed asymmetric (4+3) cycloaddition of *aza*-dienes by Chen's group [95] (color online).

presence of the chiral tertiary amine catalyst **C31**, thereby achieving the enantioselective synthesis of chiral azepane-based spirooxindoles **89** in good yields and with excellent diastereo- and enantioselectivity (Scheme 24). Additionally, the selective synthetic transformation of product **89a** through hydrogenation and subsequent protection in the presence of Raney Ni and $(Boc)_2O$ was investigated, and the corresponding derivative **89a′** was obtained in high yield and with a retained ee value.

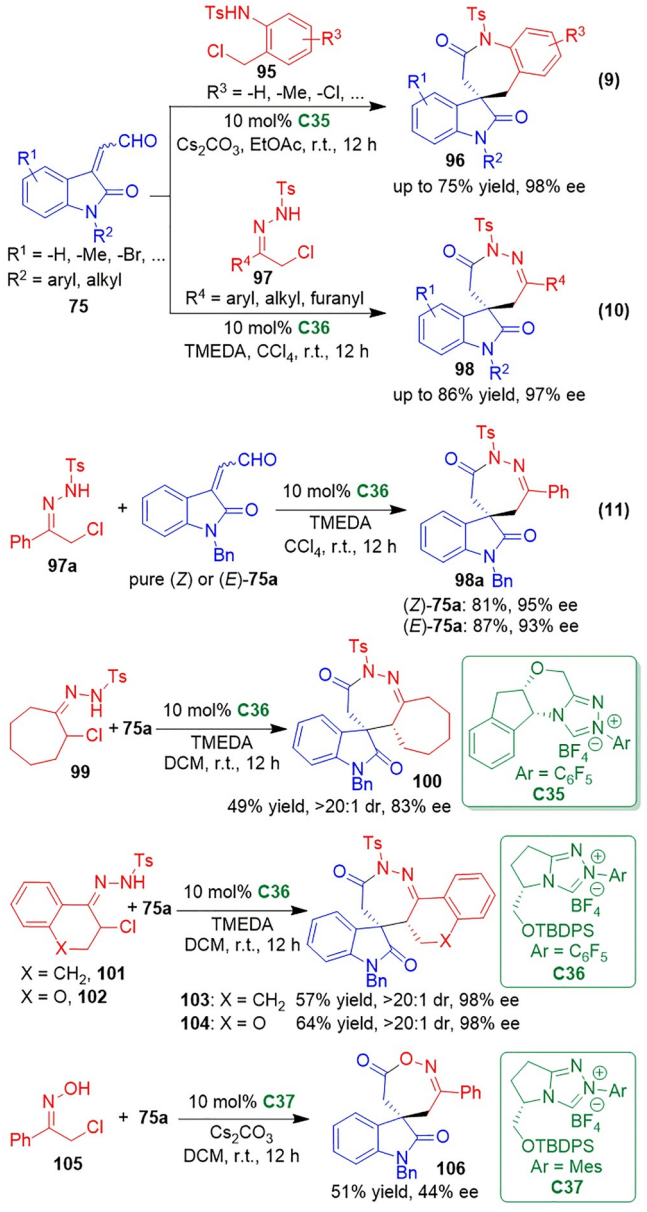
4.2 *Aza*-diene precursors as four-atom building blocks

In the organocatalytic asymmetric (4+3) cycloaddition reactions, *aza*-diene precursors [120–122] that can *in situ* form highly reactive *aza*-diene species are valuable four-atom building blocks. In 2013, Glorius and co-workers [123] developed substituted hydrazones **90** as *aza*-diene precursors in the catalytic asymmetric (4+3) cycloaddition with α,β-unsaturated aldehydes **34** in the presence of organocatalyst **C32**, thereby synthesizing a series of enantioenriched 1,2-diazepine derivatives **91** (Scheme 25a). Specifically, hydrazones **90** could allow the azoalkenes **Int-34** to undergo direct conjugate addition [124] with the homoenolates **Int-35** generated from α,β-unsaturated aldehydes **34**, leading to the formation of intermediates **Int-36**. The target product **91** could then be obtained by lactamizing **Int-36** intramolecularly. Additionally, cyclic hydrazones **92a** and **92b** were employed in this (4+3) cycloaddition as four-atom building blocks, yielding the polycyclic products **93aa** and **93ba** (Scheme 25b). It was found that steric hindrance from the *N*-substituted aromatic ring of the chiral NHC catalysts affected the yields and enantioselectivities of the final products. Further, a regioselective formal (4+1) cycloaddition of substituted hydrazones **90** with enals **34** in the presence of the NHC catalyst **C34** resulted in moderate to good yields of pyrazoles **94**, which may undergo the process of acyl anion **Int-35′** formation (Scheme 25c). This is the first chiral NHC-catalyzed asymmetric (4+3) cycloaddition using *aza*-diene species as four-atom building blocks, demonstrating the potential of chiral NHC catalysis in asymmetric (4+3) cycloadditions.

In 2016, Enders and co-workers [125] employed structurally diverse *aza*-diene precursors in chiral NHC-catalyzed asymmetric (4+3) cycloadditions with isatin-derived enals for the enantioselective synthesis of seven-membered nitrogen-containing spiro-heterocycles bearing a quaternary all-carbon stereocenter (Scheme 26). In this work, *aza*-*o*-quinone methides or azoalkenes as highly reactive species generated *in situ* from *N*-(*ortho*-chloromethyl)aryl amides **95** or α-halogeno hydrazones **97** were subjected to cycloadditions with enals **75** in the presence of the chiral NHC catalysts **C35** or **C36**, resulting in the synthesis of a variety of spirobenzazepinones **96** or spiro-1,2-diazepinones **98** in high yields and with good to excellent enantioselectivities (Eqs.



Scheme 25 Chiral NHC-catalyzed (4+3) cycloaddition of hydrazones by the Glorius group [123] (color online).

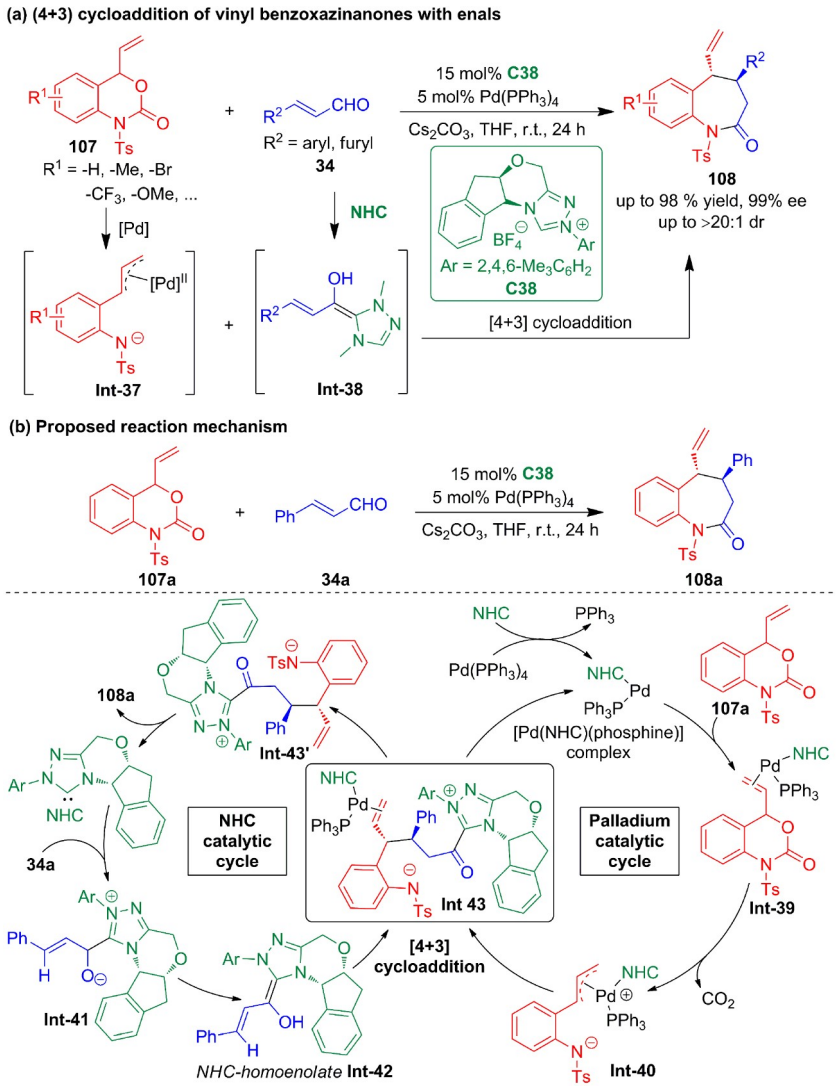


Scheme 26 Chiral NHC-catalyzed (4+3) cycloadditions of hydrazones by the Enders group [125] (color online).

(9), (10)). Notably, pure (*Z*)-**75a** and (*E*)-**75a** were examined as reactants for the catalytic enantioselective synthesis of product **98a** under standard conditions, where identical product **98a** was obtained in similar yields and enantioselectivities. These results revealed that the (*Z*/*E*)-configuration of isatin-derived enals **75** had little effect on the catalytic enantioselective (4+3) cycloaddition (Eq. (11)). Moreover, several cyclic hydrazones **99** and **101**–**102** were shown to be compatible reaction partners in this asymmetric transformation for the synthesis of polycyclic spiro-1,2-diazepinones **100** and **103**–**104**, thereby expanding the applicability of this synthetic method. Surprisingly, α-chloro oximes **105** were applicable to the reaction under similar conditions, although the desired spiro-1,2-oxazepinone **106** could only be obtained in moderate yield and enantioselectivity.

4.3 Other *aza*-four-atom building blocks

In 2016, Glorius *et al.* [11] established an enantioselective (4+3) cycloaddition of vinyl benzoxazinanones **107** with enals **34** through the cooperative activation of a chiral NHC organocatalyst **C38** with a palladium co-catalyst, thereby synthesizing a series of benzazepine derivatives **108** in good yields and with excellent enantioselectivities (Scheme 27a). In the reaction, vinyl benzoxazinanones **107**, which could generate a highly electrophilic allyl-palladium (II) complex **Int 37** upon decarboxylation, served as four-atom building blocks [126], whereas enals **34**, which could generate a nucleophilic NHC homoenolate **Int 38**, acted as three-atom reactants. In this work, the concept of cooperative activation

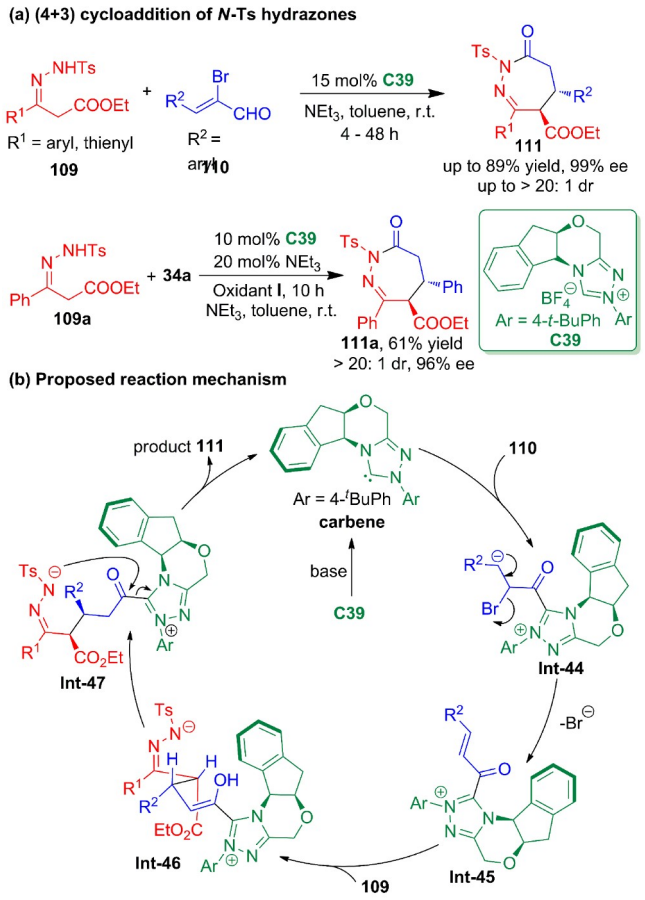


Scheme 27 NHC/Pd-catalyzed (4+3) cycloaddition of vinyl benzoxazinanones by the Glorius group [11,127] (color online).

was achieved through the simultaneous generation of two reactive species, **Int 37** and **Int 38**, in a combined catalytic system, which significantly broadened the scope of NHC organocatalysis by opening metal-catalyzed reaction pathways for the homoenolate intermediates.

A year later, the same group reported detailed mechanistic studies on a cooperative NHC organocatalysis/palladium catalysis system of vinyl benzoxazinanone **107a** with enal **34a** (Scheme 27b) [127]. They suggested a plausible reaction mechanism for catalytic (4+3) cycloaddition of vinyl benzoxazinanone **107a** with enal **34a** based on the experimental results of a mechanistic study. In the palladium catalytic cycle, the mixed [Pd(NHC)(phosphine)] complex was initially formed due to the combination of NHC and $Pd(PPh_3)_4$. This complex subsequently underwent coordination with vinyl benzoxazinanone **107a** to produce **Int-39**, which could transform into the electrophilic palladium complex **Int-40** upon decarboxylation. In the NHC catalytic cycle, the addition of chiral NHC to enal **34a** formed NHC homoenolate **Int-42**, which underwent conjugate addition with palladium complex **Int-40** to produce **Int-43**. Then, the mixed [Pd(NHC)(phosphine)] complex was regenerated, and the acyl azolium **Int-43′** obtained underwent *N*-acylation cyclization to generate the target product **107a** with the release of NHC.

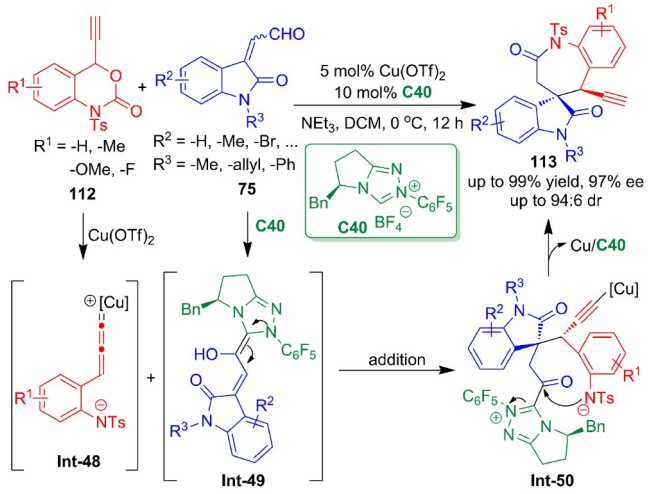
Notably, α-ester hydrazones are structurally very similar to α-halogeno hydrazones, and have been utilized as a class of useful four-atom building blocks in organocatalytic asymmetric (4+3) cycloaddition reactions. In 2017, Hui *et al.* [128] used α-ester hydrazones **109** as suitable reactants in the NHC-catalyzed asymmetric (4+3) cycloaddition of 2-bromoenals **110**, achieving the synthesis of tetrahydro-1*H*-1,2-diazepines **111** in good yields and excellent stereoselectivities (Scheme 28a). Meanwhile, an NHC-catalyzed asymmetric (4+3) cycloaddition of α-ester hydrazones **109a** with *E*-cinnamaldehyde **34a** in the presence of oxidant **I** was established, delivering the target tetrahydro-1*H*-1,2-diaze-



Scheme 28 Chiral NHC-catalyzed (4+3) cycloaddition of α-ester hydrazones by Hui and co-workers [128] (color online).

pines **111a** in 61% yield, >20:1 dr, and 96% ee. Additionally, they proposed a possible mechanism for this cycloaddition (Scheme 28b). Under the influence of a base, a highly reactive carbene species is initially generated from the chiral catalyst **C39**. Then, this species reacts with 2-bromoenals **110** to produce the corresponding Breslow intermediate **Int-44**, which undergoes tautomerization and debromination to transform into α,β-unsaturated acyl azolium **Int-45**. Subsequently, a direct Michael addition of **109** to **Int-45** produces **Int-46**, which is isomerized to **Int-47**. Finally, the desired product is generated by the intramolecular lactamization of **Int-47** with the regeneration of the active carbene species.

In 2019, Gong *et al*. [129] established an enantioselective (4+3) cycloaddition of ethynyl benzoxazinanones **112** with isatin-derived enals **75** *via* NHC/cooper cooperative catalysis, resulting in the construction of chiral spirobenzazepinones **113** in good yields and excellent enantioselectivities (Scheme 29). In this approach, ethynyl benzoxazinanones **112** functioned as four-atom building blocks [130], which could be converted to copper-allenylidene **Int-48** *via* $Cu(OTf)_2$ catalysis. In contrast, azolium homoenolate **Int-49** was generated from isatin-derived enal **75** in the presence of the chiral NHC catalyst **C40**, which was

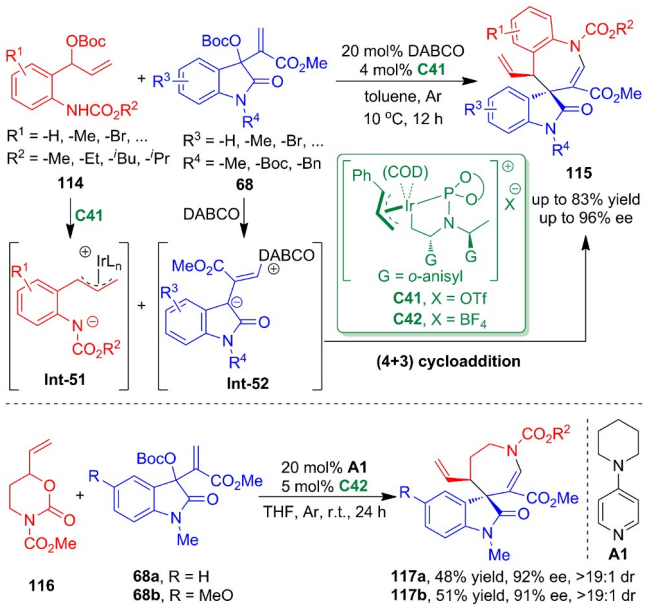


Scheme 29 NHC/cooper-catalyzed (4+3) cycloaddition of ethynyl benzoxazinanones by Gong and co-workers [129] (color online).

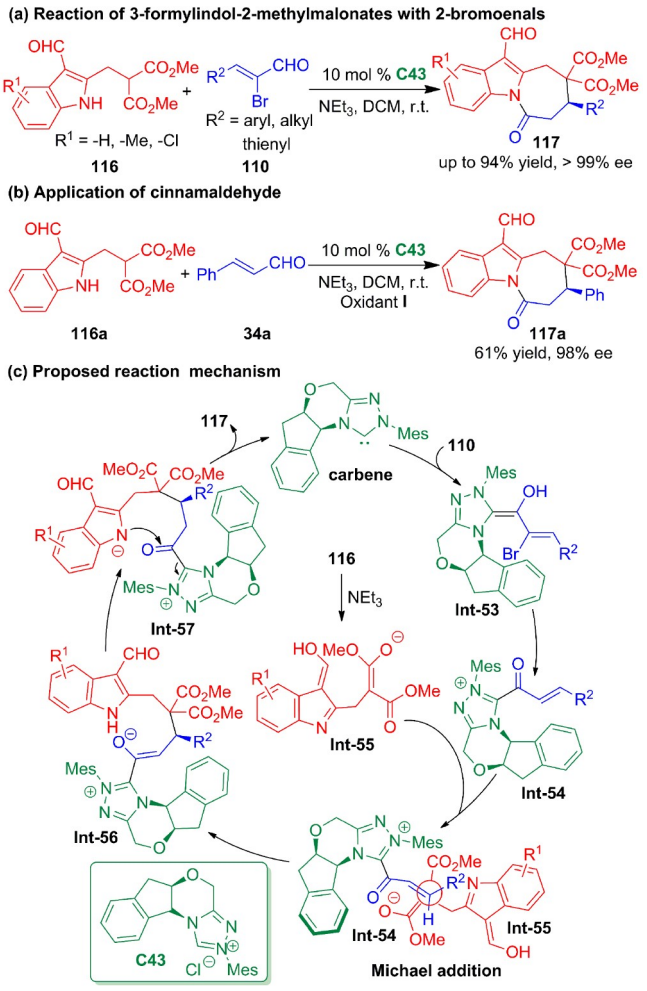
capable of undergoing enantioselective addition with **Int-48** to form adduct **Int-50**. With the release of NHC and copper catalysts, the subsequent *N*-acylation cyclization and protonation of **Int-50** produced product **113** with the release of the NHC and copper catalysts. Notably, NHC **C40** not only acted as an organocatalyst to activate enals but also as a copper ligand to modulate metal catalysis in the NHC/copper-catalyzed (4+3) cycloaddition. This strategy presents an exceptional synergistic effect of NHC and copper catalysis, in which both catalysts activate the substrates and the chiral NHC controls the stereochemistry perfectly.

As a class of four-atom building blocks, carbamate-functionalized allyl carbonates can be activated by transition metal catalysts [131]. In 2019, Chen *et al*. [132] employed carbamate-functionalized allyl carbonates **114** in an asymmetric (4+3) cycloaddition with isatin-derived MBH carbonates **68** under the cooperative catalytic system of achiral Lewis basic tertiary amines and chiral iridium (Ir) complexes, resulting in a series of spirooxindoles **115** in moderate to good yield and excellent enantioselectivities (Scheme 30). In the (4+3) cycloaddition reaction, carbamate-functionalized allyl carbonates **114** in the presence of the chiral catalyst **C41** can transform into highly reactive 1,4-π-allyl iridium dipoles **Int-51**, and substrates **68** can be activated by achiral triethylenediamine (DABCO) to generate zwitterionic allylic ylides **Int-52** serving as three-atom reactants. To further demonstrate the compatibility of this cooperative catalytic strategy, they also developed a similar (4+3) cycloaddition of isatin-derived MBH carbonates **68a**/**68b** with cyclic vinyl carbamate **116** *via* the synergistic action of chiral complex **C42** and achiral 4-(piperidin-1-yl) pyridine **A1** as the catalysts, yielding spirooxindoles **117a** and **117b** in moderate yields and excellent stereoselectivities.

In the same year, Hui *et al*. [133] reported a chiral NHC-catalyzed asymmetric (4+3) cycloaddition of 3-formylindol-



Scheme 30 DABCO/Ir-co-catalyzed (4+3) cycloaddition of carbamate-functionalized allyl carbonates by Chen and co-workers [132] (color online).

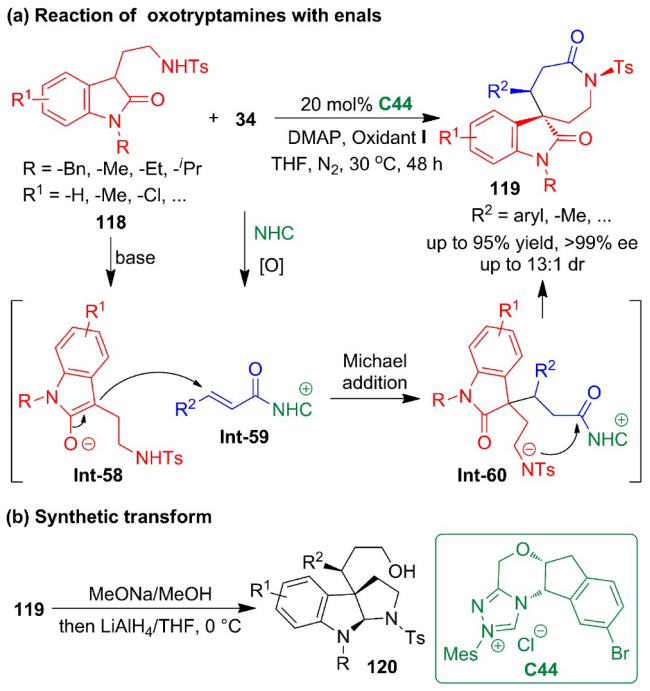


Scheme 31 Chiral NHC-catalyzed asymmetric (4+3) cycloaddition of 3-formylindol-2-methylmalonates by Hui and co-workers [133] (color online).

2-methylmalonates **116** with 2-bromoenals **110**, affording a series of functionalized azepino[1,2-a]indoles **117** in good yields and excellent enantioselectivities, wherein substrates **116** served as four-atom building blocks (Scheme 31a). Moreover, cinnamaldehyde **34a** could be used as a three-atom reaction partner in the presence of oxidant **I** to produce the target product **117a** with 61% yield and 98% ee (Scheme 31b). To determine the possible activation mode, they performed several control experiments to investigate the reaction mechanism, which revealed that the 3-formyl group in the indole moiety of substrates **116** was required for this cycloaddition and acted as a mediator. In the suggested reaction mechanism (Scheme 31c), the carbene species from **C43** reacted with 2-bromoenals **110** to generate the Breslow intermediate **Int-53**, which underwent tautomerization and debromination to become the α,β-unsaturated acyl azolium **Int-54**. Meanwhile, the starting materials **116** produced **Int-55** through deprotonation and proton transfer in the presence of NEt_3. **Int-55** then interacted with **Int-54** *via* a Michael addition reaction to produce the enolate **Int-56**. Subsequently, **Int-57** was derived from the tautomerization of **Int-56** and underwent intramolecular lactamization to yield products **117** accompanied by the release of carbene species. Furthermore, Li *et al.* [134] conducted theoretical research on such a NHC-catalyzed (4+3) cycloaddition between malonate and 2-bromoenal, affording useful insight into the reaction mechanisms.

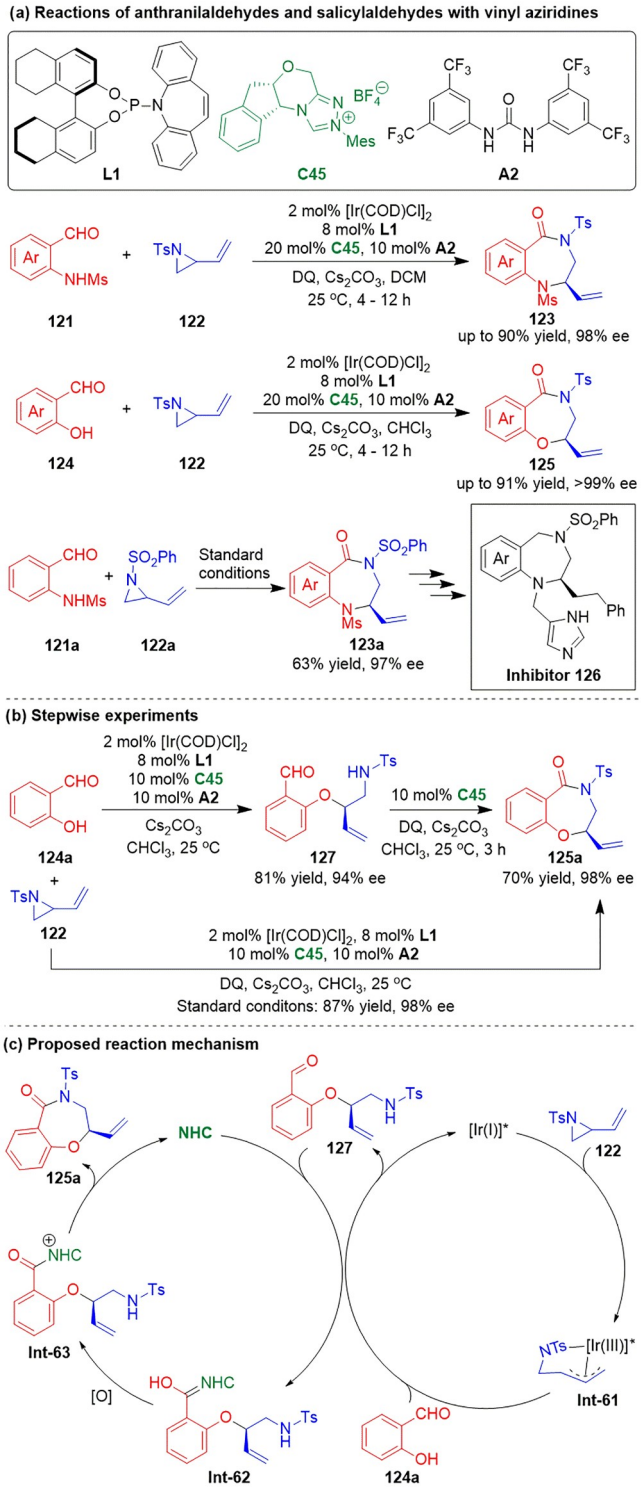
In 2019, Huang *et al.* [135] utilized oxotryptamines as four-atom building blocks in an organocatalytic asymmetric formal (4+3) cycloaddition (Scheme 32a). Specifically, they developed a chiral NHC-catalyzed formal (4+3) cycloaddition of oxotryptamines **118** with enals **34** in the presence of catalyst **C44** and oxidant **I**, offering an enantioselective metal-free strategy to access chiral spiro-ε-lactam oxindoles **119** in high yields, enantioselectivities and acceptable diastereoselectivities. In the reaction, oxotryptamine **118** underwent deprotonation to generate intermediate **Int-58** under basic conditions, and enal **34** was activated by the chiral catalyst **C44** in the presence of oxidant **I** to produce the acyl azolium intermediate **Int-59**. Then, an enantioselective Michael addition of **Int-58** to **Int-59** produced **Int-60**, which by intramolecular cyclization yielded the desired product **119**. Notably, chiral spiro-ε-lactam oxindoles **119** could be readily converted into the corresponding enantioenriched hexahydropyrroloindoles **120** through a ring-opening reaction and subsequent reductive cyclization (Scheme 32b).

Gong *et al.* [136] recently utilized anthranilaldehyde **121** and salicylaldehyde **124** as four-atom building blocks and developed an NHC/Ir/urea co-catalyzed formal (4+3) cycloaddition with vinyl aziridines **122** for the synthesis of optically pure 1,4-benzodiazepinones **123** and 1,4-benzox-



Scheme 32 Chiral NHC-catalyzed (4+3) cycloaddition of oxotryptamines by Huang, Fu and co-workers [135] (color online).

azepinones **125** (Scheme 33a). Notably, the enantioenriched 1,4-benzodiazepinone **123a** was capable of being converted into a selective inhibitor **126** of mitochondrial F1F0 ATP hydrolase. Moreover, in the multistep experiments, the produced chiral aldehyde intermediate **127** with 94% ee underwent intramolecular cyclization under the catalysis of NHC **C45** to yield 1,4-benzoxazepinone **125a** with 98% ee, revealing the slight kinetic resolution process that exists in the chiral NHC-mediated lactamization step (Scheme 33b). They proposed a plausible catalytic cycle for the asymmetric (4+3) cycloaddition based on the experimental results (Scheme 33c). The initial generation of the (η^3-allyl)iridium (III) species **Int-61** was accomplished by oxidative addition of the [Ir(I)]* complex to vinyl aziridine **122**, followed by the asymmetric allylic etherification of **Int-61** with salicylaldehyde **124a** to generate the key intermediate **127**. The addition of chiral NHC to **127** then produced the Breslow intermediate **Int-62**, which was oxidized by oxidant quinone (DQ) to produce the acyl azolium intermediate **Int-63**. Through intermolecular lactamization of intermediate **Int-63**, the target product **125a** was obtained and the NHC catalyst was regenerated for the subsequent catalytic cycle.



Scheme 33 NHC/Ir/urea-co-catalyzed (4+3) cycloaddition of anthranilaldehydes and salicylaldehydes by Gong and co-workers [136] (color online).

5 Organocatalytic asymmetric (4+3) cycloadditions involving other four-atom building blocks

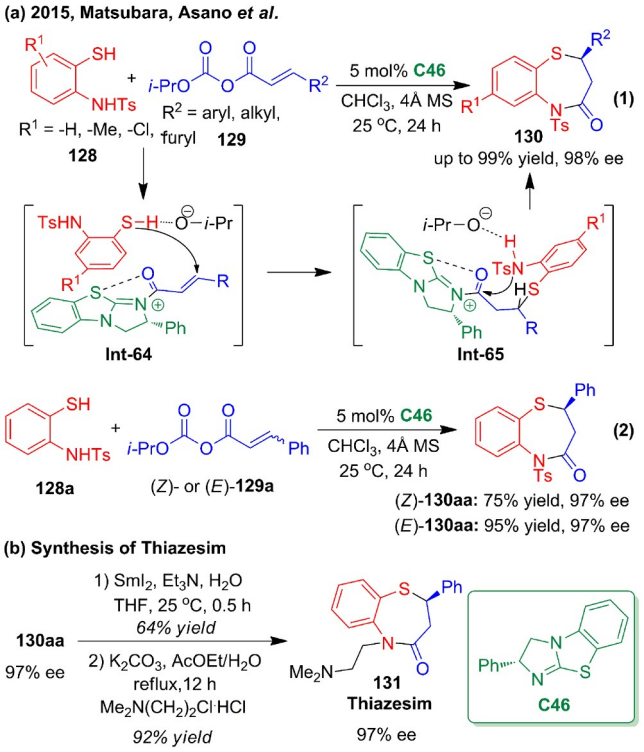
5.1 *o*-Aminothiophenols as four-atom building blocks

In synthetic transformations, 1,4-diheteroatom reactants bearing double nucleophilic sites serve as effective four-atom building blocks. Aminothiophenols, as 1,4-diheteroatom building blocks, have been used in organocatalytic asymmetric formal (4+3) cycloaddition to construct optically

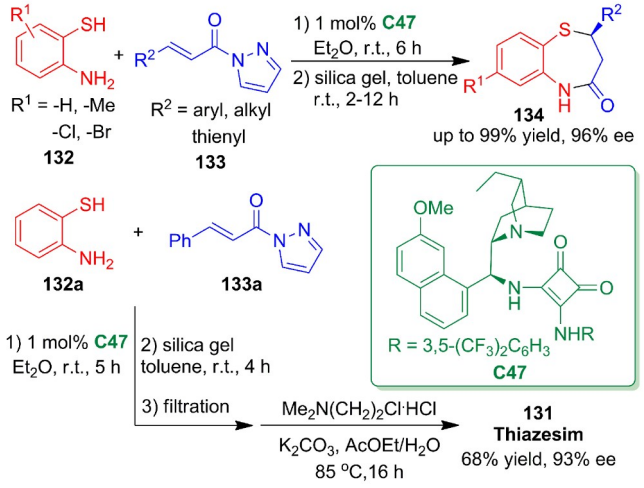
active 1,5-benzothiazepine frameworks [137]. In 2015, Matsubara, Asano and co-workers [138] established the first highly enantioselective (4+3) cycloaddition of aminothiophenols **128** with α,β-unsaturated carboxylic acid derivatives **129** in the presence of the chiral isothiourea catalyst **C46** through two sequential chemoselective nucleophilic addition processes, leading to the formation of 1,5-benzothiazepines **130** in good yields and high regioselectivity and stereoselectivity (Scheme 34a). In detail, α,β-unsaturated acyl ammonium **Int-64** was initially generated by combining **129** and **C46**. Then, a chemoselective sulfa-Michael addition between **128** and **Int-64** produced the intermediate **Int-65**, which was then transformed into the target product **130** *via* an intramolecular lactamization reaction. In addition, the (*Z*)- and (*E*)-olefin configurations of substrate **129a** were investigated for this cycloaddition, which yielded (*Z*)-**130aa** and (*E*)-**130aa** with the same configuration and enantioselectivity but in slightly different yields. Notably, the obtained cycloadduct **130aa** could smoothly undergo two sequential deprotection and alkylation steps to become the optically active antidepressant thiazesim **131** (Scheme 34b).

Two years later, an enantioselective (4+3) cycloaddition for the direct synthesis of *N*-unprotected 1,5-benzothiazepine was developed by Lattanzi *et al*. [139] (Scheme 35). In the reaction, *N*-unprotected aminothiophenols **132** were used as four-atom building blocks [140] to react with α,β-unsaturated *N*-acyl pyrazoles **133** through an organocatalytic formal (4+3) cycloaddition under the catalysis of chiral hydroquinine-derived squaramide **C47**, delivering 2-aryl/alkyl-substituted products **134** in generally good to excellent yields and enantioselectivities. Additionally, the preparation of the chiral antidepressant thiazesim **131**, which was obtained directly from the initial reactants **132a** and **133a**, was carried out with ease using this methodology. The reaction sequence for the formal (4+3) cycloaddition was sulfa-Michael addition and lactamization.

Moreover, in 2017, several other efficient methods for the synthesis of structurally diverse benzothiazepine derivatives were established by employing aminothiophenols **132** or **128** as four-atom building blocks in organocatalytic asymmetric formal (4+3) cycloadditions. For example, Bernardi, Fochi and co-workers [141] reported an asymmetric formal (4+3) cycloaddition of *N*-unprotected aminothiophenols **132** with *trans*-chalcones **135** in the presence of chiral organocatalyst **C48** for the synthesis of 2,3,4,5-tetrahydro-1,5-benzothiazepines **136** *via* a one-pot sulfa-Michael addition and subsequent diastereoselective reductive amination process (Scheme 36a). Shortly thereafter, Du, Lu and co-workers [142] accomplished an enantioselective formal (4+3) cycloaddition of *N*-unprotected aminothiophenols **132** with 2-bromoenals **110**, catalyzed by chiral NHC **C49**, for the direct synthesis of *N*-unprotected 1,5-benzothiazepines **134** (Scheme 36b). Additionally,

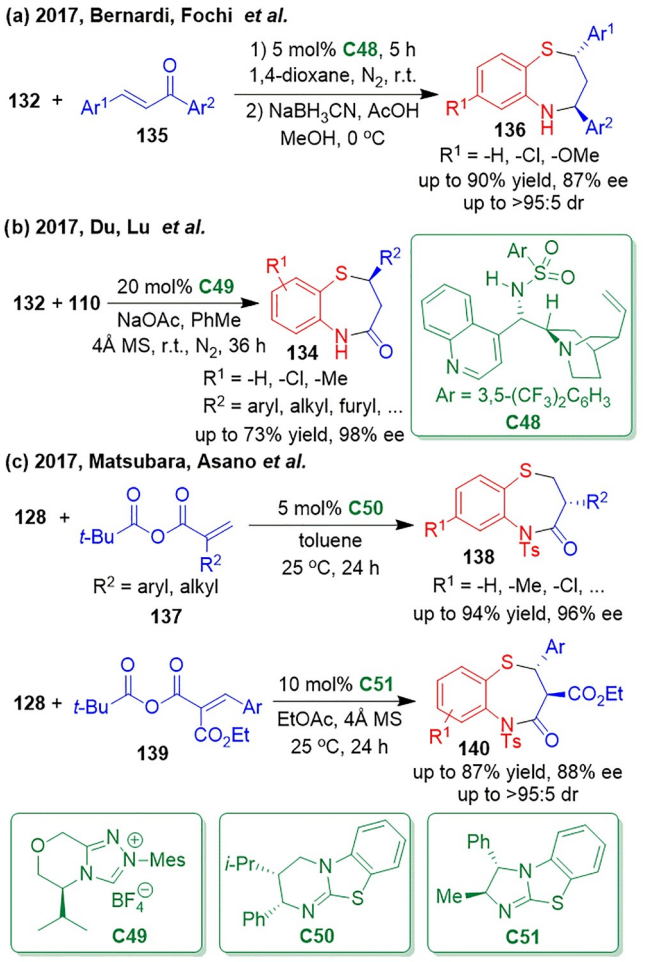


Scheme 34 Chiral isothiourea-catalyzed formal (4+3) cycloaddition of aminothiophenols by Matsubara, Asano and co-workers [138] (color online).

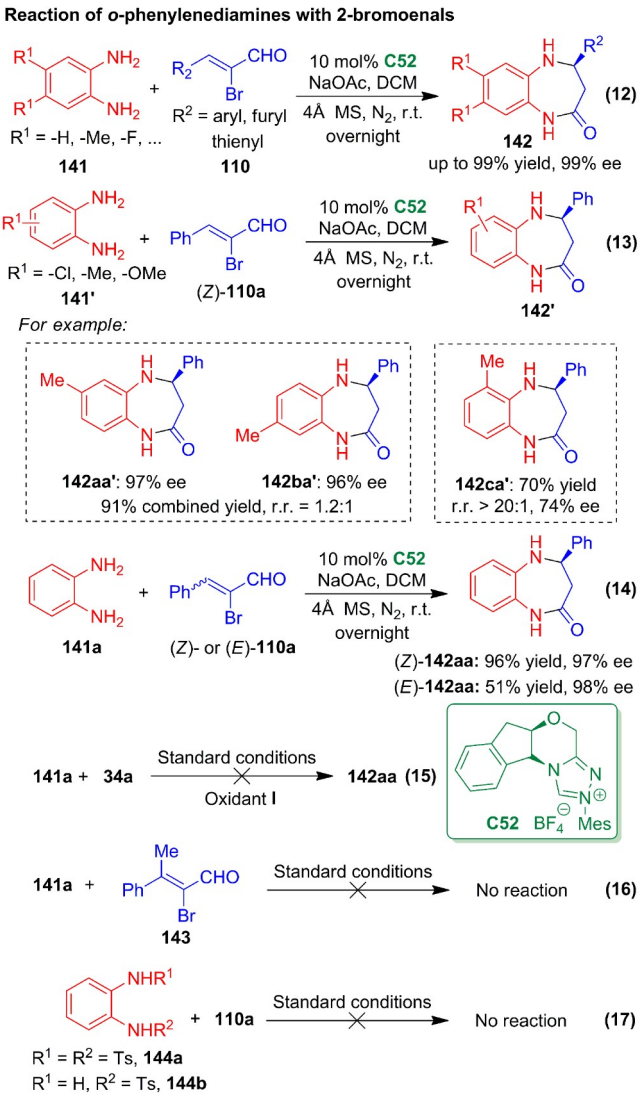


Scheme 35 Chiral squaramide-catalyzed (4+3) cycloaddition of aminothiophenols by Lattanzi and co-workers [139] (color online).

Matsubara, Asano and co-workers [143] developed an isothiourea-catalyzed enantioselective formal (4+3) cycloaddition of aminothiophenols **128** with various α,β-unsaturated substrates **137** or **139**, resulting in the synthesis of structurally diverse 1,5-benzothiazepines **138** and **140** in moderate to good yields and enantioselectivities (Scheme 36c).



Scheme 36 Organocatalytic asymmetric formal (4+3) cycloaddition of aminothiophenols by the groups of Bernardi *et al*. [141], Du *et al*. [142] and Matsubara *et al*. [143] (color online).



Scheme 37 Chiral NHC-catalyzed asymmetric formal (4+3) cycloaddition of *o*-phenylenediamines by Du, Lu and co-workers [147] (color online).

5.2 *o*-Phenylenediamines and 1,2-benzenedithiol as four-atom building blocks

o-Phenylenediamines, which are structurally similar to aminothiophenols, have also been utilized as 1,4-diheteroatom building blocks in organocatalytic asymmetric (4+3) cycloadditions for the construction of optically active nitrogen-containing seven-membered heterocyclic frameworks. In 2014, Shi's group [144–146] established the first catalytic asymmetric formal (4+3) cycloaddition of *o*-phenylenediamines *via* multicomponent reactions with cyclic 1,3-diones and aldehydes or isatins catalyzed by CPA. By this approach, structurally rigid seven-membered chiral heterocycles including dibenzo[1,4]diazepines, benzodiazepine-based spirooxindoles, and cyclopenta[1,4]diazepines, were prepared in high enantioselectivities and good yields.

Later, in 2018, Du, Lu and co-workers [147] developed an NHC-catalyzed formal (4+3) cycloaddition of *o*-phenylenediamines **141** with 2-bromoenals **110** in the presence of chiral catalyst **C52** (Scheme 37), constructing 1,5-benzodiazepin-2-one frameworks **142** in moderate to high yields with excellent enantioselectivities (Eq. (12)). Remarkably, when several unsymmetrical *o*-phenylenediamines **141′** were employed in this reaction, regioselectivity was observed in the formation of cycloadducts **142′** (Eq. (13)). Under standard conditions, the regioisomers **142aa′** and **142ba′** were produced with a combined yield of 91% and a regioselectivity of 1.2:1, while the regioisomer **142ca′** could be obtained with a yield of 70%. In contrast, (*Z*)- and (*E*)-olefin configurations of 2-bromoenals **110a** had no evident effect on the enantioselectivity of product **142a** (Eq. (14)). Additionally, cinnamaldehyde **34a** and β,β-disubstituted 2-bromoenal **143** were tested in this NHC-catalyzed reaction, but neither produced the desired products (Eqs. (15), (16)). Moreover, *N*-protected *o*-phenylenediamines **144a** and **144b** were tested in the reaction, but they failed, indicating that the

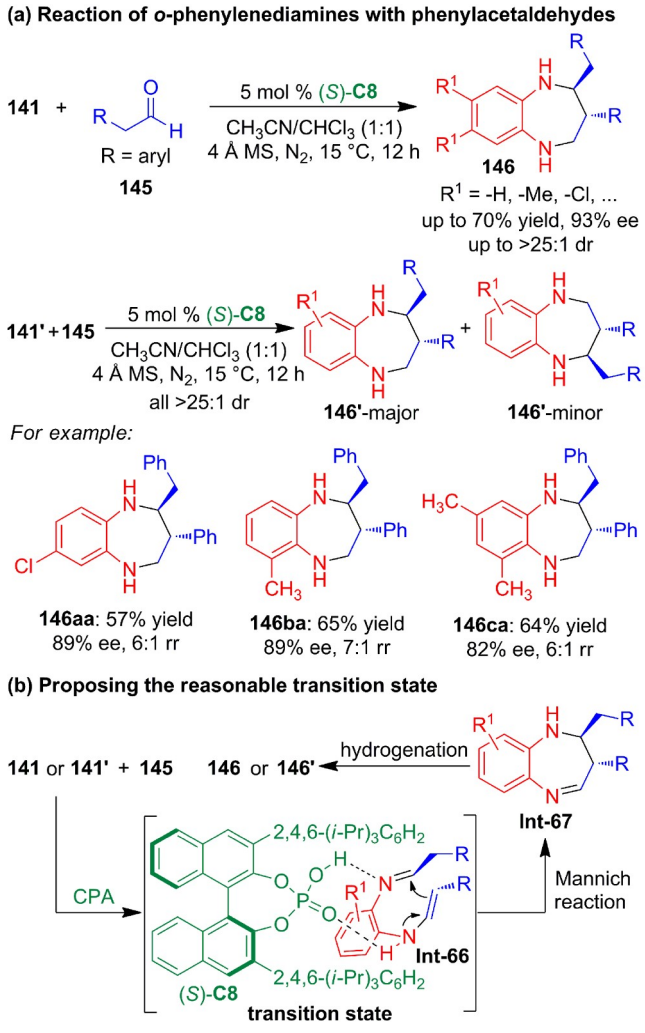
protecting group on the structure of *o*-phenylenediamines was essential to this cycloaddition (Eq. (17)).

In 2021, Tang, Li and co-workers [148] reported a CPA-catalyzed asymmetric formal (4+3) cycloaddition of *o*-phenylenediamines **141** with phenylacetaldehydes **145**, enabling the enantioselective preparation of chiral 1,5-benzodiazepines **146** with moderate yields, good enantioselectivities, and excellent diastereoselectivities (Scheme 38a). Furthermore, when several unsymmetrical *o*-phenylenediamines **141′** were added to this CPA-catalyzed reaction under standard conditions, the corresponding 1,5-benzodiazepines were obtained with acceptable regioselectivities. Additionally, they found that the reaction likely occurred *via* an intramolecular Mannich and subsequent transfer hydrogenation process and that the chirality of the target product may have been formed during the Mannich reaction step (Scheme 38b). In particular, the intramolecular enamine and imine motifs of **Int-66** were simultaneously activated by CPA through hydrogen-bonding interactions to undergo a Mannich reaction and form **Int-67** with two adjacent chiral centers, which were subsequently hydrogenated to form the final products.

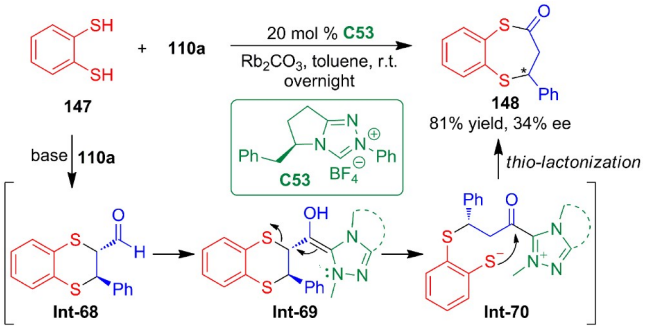
In addition to aminothiophenols and *o*-phenylenediamines, 1,2-benzenedithiols containing two nucleophilic sulfur atoms can be used as four-atom building blocks in organocatalytic asymmetric formal (4+3) cycloaddition to prepare chiral seven-membered sulfur-containing heterocycles. In 2018, Ye *et al*. [149] used 1,2-benzenedithiol **147** for NHC-catalyzed asymmetric formal (4+3) cycloaddition with bromoenal **110a** in the presence of chiral catalyst **C53**; they obtained enantioenriched benzo[1,5]dithiepin-2-one **148** with 81% yield and 34% ee (Scheme 39). Additionally, they proposed a reaction mechanism based on the kinetic investigation results, which indicate that this formal (4+3) cycloaddition occurred *via* base-promoted (4+2) annulation and a subsequent carbene-catalyzed ring-expansion process. Specifically, the cycloadduct **Int-68** was initially formed by base-promoted (4+2) annulation of 1,2-benzenedithiol **147** with bromoenal **110a**, and immediately interacted with NHC catalyst **C53** to form the corresponding Breslow intermediate **Int-69**. **Int-69** then underwent C–S bond cleavage to produce acyl azolium **Int-70**, which subsequently underwent intramolecular thio-lactonization to yield the final cycloadduct **148**.

6 Summary and outlook

Organocatalytic asymmetric (4+3) cycloadditions have advanced rapidly over the past few decades, providing efficient and enantioselective approaches for accessing optically pure seven-membered rings, which are prevalent in the structures of natural products and pharmaceuticals. However, challenging problems remain to be resolved in this research field. These issues include but are not restricted to: (1) The four-atom and three-atom building blocks involved in organocatalytic asymmetric (4+3) cycloaddition are still rather limited, particularly those containing multiple heteroatoms and functional groups or activation groups, resulting in the



Scheme 38 CPA-catalyzed (4+3) cycloaddition with *o*-phenylenediamines by Tang, Li and co-workers [148] (color online).



Scheme 39 Chiral NHC-catalyzed asymmetric formal (4+3) cycloaddition of 1,2-benzenedithiol by Ye and co-workers [149] (color online).

restriction of the constructed chiral seven-membered rings. Consequently, it is highly desirable to develop a new class of four-atom building blocks that can be easily activated by chiral organocatalysts to undergo asymmetric (4+3) cycloadditions. (2) Currently, organocatalytic asymmetric (4+3) cycloaddition reactions are confined to the traditional thermal reaction strategy. In contrast, reactions based on the combination of asymmetric organocatalysis with visible-light photoredox catalysis or electrochemical synthesis have not yet been established, although these combined catalytic strategies have proven to be potent means of achieving unconventional transformations. Therefore, it will be a new direction to develop new types of organocatalytic asymmetric (4+3) cycloadditions with the combination of visible-light photoredox catalysis or electrochemical synthesis. (3) Even though the frameworks of the chiral seven-membered ring are present in a large number of natural products and pharmaceuticals, the applications of organocatalytic asymmetric (4+3) cycloadditions as key steps in the synthesis of natural products or pharmaceuticals are underdeveloped. Therefore, it is necessary to investigate and demonstrate the power and potential of organocatalytic asymmetric (4+3) cycloadditions in the synthesis of natural products or pharmaceuticals. Undoubtedly, substantial efforts are required to address these difficult issues. We believe that the research field of organocatalytic asymmetric (4+3) cycloadditions will develop to a new horizon and find more synthetic applications due to the efforts of synthetic chemists.

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Conflict of interest The authors declare no conflict of interest.

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