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# Recent advances of N-heterocyclic carbenes in the applications of constructing carbo- and heterocyclic frameworks with potential biological activity

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In recent years, N-heterocyclic carbenes (NHCs) have established themselves as a masterful and promising type of organocatalyst for the speedy construction of medicinally and biologically significant molecules from common and accessible small molecules. In particular, various cyclic scaffolds, including carbocycles and heterocycles, have been synthesized using NHCs *via* cycloaddition reaction. An exhaustive review focused on the chemistry of NHCs in these cyclic molecules has yet to be reported. In this contribution, a general picture of the utilization of NHCs in constructing twelve kinds of bioactive cyclic skeletons is firstly presented. We provide a systematic and comprehensive overview from the perspective of cycloaddition reactions; moreover, the limitations, challenges, and future prospects were discussed.

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## 1 Introduction

Cyclic organic frameworks, especially heterocyclic frameworks, are widely distributed motifs in numerous biologically active molecules, including natural products and pharmaceutical molecules, which occupy a crucial position in organic and medicinal chemistry.<sup>1</sup> The interest toward the discovery of novel and elegant approaches for the construction of these complex carbocycles and heterocycles has been enduring, due to their potential in the production of pharmaceutically active compounds.<sup>2</sup> Organocatalysts are tremendously attractive for assembling these bioactive cyclic compounds. So far, a variety of organocatalysts with excellent reaction performances have been discovered.<sup>3</sup>

NHC catalysis<sup>4</sup> is deemed to be a significant organic synthesis strategy, which shows the unique property of the polarity inversion for many carbonyl compounds, then produces nucleophilic acyl anion intermediates, thereby reacting with a variety of electrophilic substrates. Apart from the applications of NHCs in umpolung strategies, NHCs simultaneously function as catalysts in non-umpolung transformation.<sup>5</sup> These reactions mainly involve several types of important intermediates: Breslow intermediates, homo-enolate intermediates,  $\alpha,\beta$ -unsaturated acyl azoliums, saturated acyl azoliums, azolium enolates and azolium dienolates (Fig. 1).

In view of the unique catalytic properties, various types of reactions have been realized *via* NHC catalysis, with C–C bond and C-heteroatom formation reactions being ubiquitous, including cross-benzoin, homo-enolate, especially cycloaddition/annulation reactions.<sup>6</sup> Certainly, the flourishing development of carbene catalysis has opened the door to a new era in the construction of bioactive cyclic scaffolds.<sup>7</sup> The cycloaddition reaction has long been recognized as the most effective method for synthesizing cyclic scaffolds, leading to four- to eight-membered cyclic structure compounds being constructed. NHC-catalyzed cycloaddition/annulation reactions provide a facile and elegant access to a library of ring skeletons, such as indoles, pyrazoles, pyrroles, and fused ring compounds with important physiological activities, and important intermediates in the pharmaceutical synthesis process, or key pharmacophores as well as structural modules of drugs.<sup>8</sup>

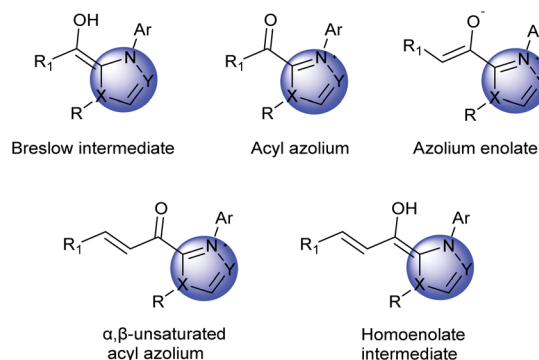


Fig. 1 Five crucial intermediates derived from NHCs.

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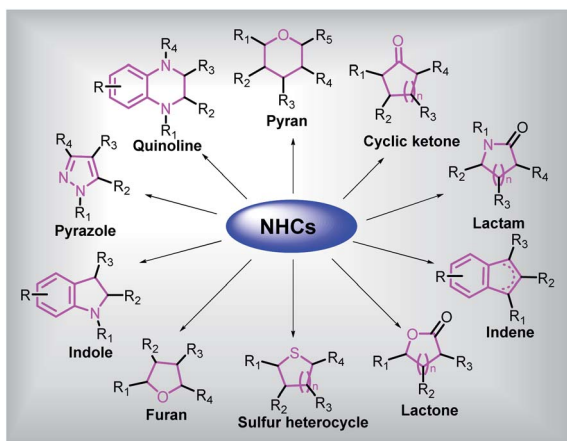


Fig. 2 A general picture of utilization of NHCs in constructing several kinds of bioactive cyclic skeletons.

We herein summarize and analyze literatures during the last ten years related to the synthesis of common biologically active cyclic organic skeletons, such as indoles, pyrazoles, pyrroles, quinolines, lactams and lactones catalyzed by NHCs, providing a comprehensive overview of the applications of NHCs to fabricate bioactive carbocycles and heterocycles, then discussing the substantial limitations, technical challenges and future prospects for the applications of NHCs in this field (Fig. 2).

## 2 Applications of NHCs in the construction of biologically active cyclic skeletons

### 2.1 Applications in the synthesis of indole derivatives

Indole skeleton compounds exist widely in various medicinal plants, most of which have been found possessing crucial biological activities and being broadly used in medicine and pesticides.<sup>9</sup> As a pharmaceutical key skeleton with extensive bioactivities, indole derivatives are attractive synthetic targets for the drug discovery.<sup>10</sup>

Owing to their complex and diverse structures, the synthesis of indole alkaloids is a hot research target in the field of organic

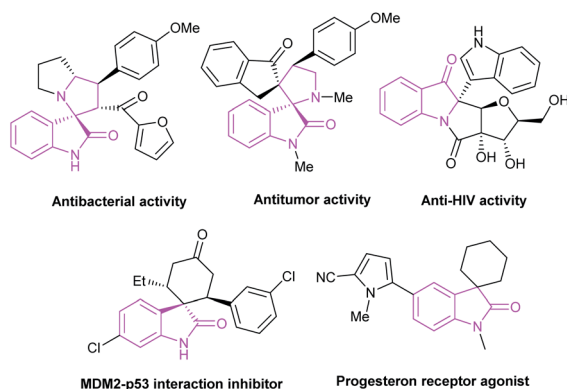


Fig. 3 Several spirocyclic indoxyl derivatives with obvious bioactivities.

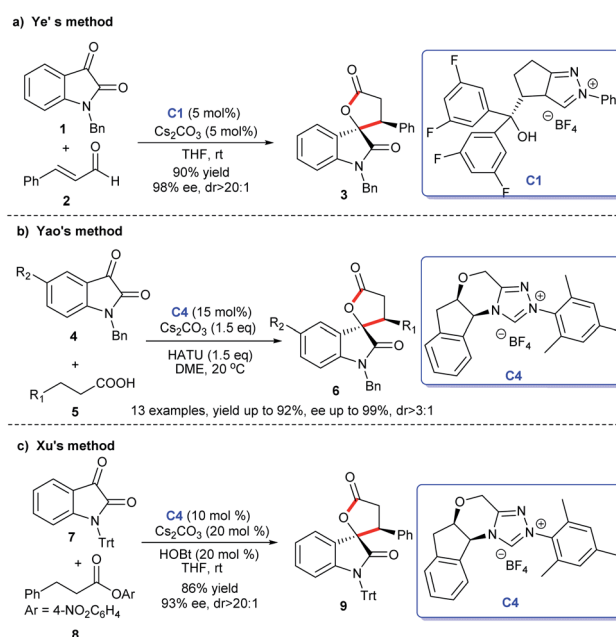
chemistry.<sup>11</sup> The construction of indole skeletons was an unprecedented challenge over a long period of time. In recent years, the emergence of NHCs has provided a powerful strategy for the synthesis of these relatively complex cyclic compounds, especially those containing chiral centers.

In the past decade, reports on the synthesis of indole derivatives catalyzed by NHCs sprang up rapidly. In this section, we summarize the synthesis protocols of indole derivative skeletons mainly include spiroindole derivatives and other indole derivatives catalyzed by chiral NHCs.

**2.1.1 Synthesis of spiroindole derivatives.** Among those bioactive indole derivatives, spiroindoles are very universal and of great quantity in nature, while the research investigating the construction of spiroindole skeletons is involving, of course, the use of NHCs as catalysts in this process.

The spirocyclic indoxyl scaffold has been found as the core structure of many bioactive molecules and pharmaceuticals (Fig. 3), and often found applications for the treatment of human cancers and neurodegenerative diseases.<sup>12</sup> In view of the biological importance, there's an urgent demand for the preparation of this type of framework. In recent years, there appears many researches on the efficient construction of NHC-catalyzed indole derivatives. In this review, we classify and explain the construction of spiroindole skeleton from the perspective of cycloaddition reaction.

**2.1.1.1 [3 + 2] Annulation to construct five-membered spirooxindole compounds.** Regarding the construction of chiral five-membered spirooxindole compounds, the [3 + 2] cycloaddition reaction demonstrates a pivotal position. For the preparation of spirooxindole skeleton compounds, isatin is employed as a very common raw material. Ye *et al.* reported NHC-catalyzed [3 + 2] annulation of enals **2** and isatins **1**, resulting in the corresponding spirocyclic oxindolo- $\epsilon$ -butyrolactones **3** in good yield



Scheme 1 Synthesis of spiroindole lactones from isatins.

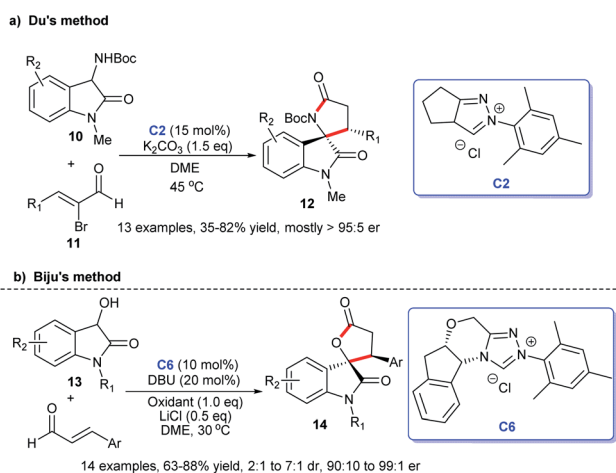


with acceptable diastereo- and enantioselectivities. Authors employed the chiral NHC bearing a proximal hydroxy group derived from *L*-pyroglutamic acid as a catalyst, the reaction taking place under mild conditions with a low catalysis loading (Scheme 1a).<sup>13</sup>

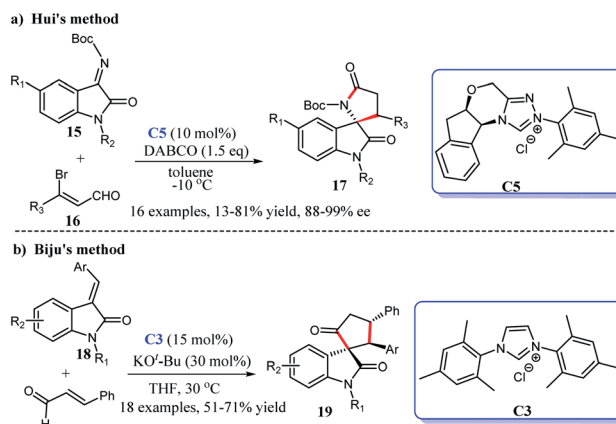
Moreover, an [3 + 2] annulation for the synthesis of spirocyclic oxindolo- $\gamma$ -butyrolactones **6** was demonstrated using substituted propionic acid **5** and isatin **4** as raw materials *via* the catalysis of chiral NHC derived from triazolium salt **C4**. This reaction was provided with good to high yields with excellent enantioselectivities (Scheme 1b). A variety of isatins with different substituents and substituted propionic acid were well tolerated under the optimized reaction conditions.<sup>14</sup>

Subsequently, the use of  $\beta$ -functionalization of saturated carboxylic esters afforded the spiroindole lactones **9**. In this [3 + 2] reaction, isatin **7** was still used as the basic material and a HOBT-assisted NHC-catalysis strategy was developed (Scheme 1c). The authors proved that the addition of HOBT achieved the enhancement of diastereoselectivity and enantioselectivities.<sup>15</sup> These reactions provided strategies for the preparations of the spiroindole lactone ring of the [3 + 2] cycloaddition reaction with isatin as the substrate.

In addition, the [3 + 2] cycloaddition reactions between C-3 saturated heteroatom substituted isatin and different types of reactive aldehydes were developed separately. In 2015, Du and co-workers demonstrated that NHC can catalyze the [3 + 2] annulation of  $\alpha$ -bromoaldehydes **11** and 3-aminooxindoles **10** leading to the synthesis of spiroindole  $\gamma$ -butyrolactams **12** (Scheme 2a). They conducted a series of experiments furnishing good substrate tolerance and high enantioselectivities. The work offered an approach for rapid access to the 3,2'-spiro-pyrrolidine oxindole skeleton.<sup>16</sup> 2017, Indian researcher Biju disclosed the enantioselective synthesis of spiro  $\gamma$ -butyrolactones **14** [3 + 2] annulation of enals with 3-hydroxy oxindoles **13** under NHC-catalysis **C6** in the presence of oxidant and LiCl (Scheme 2b). The reaction afforded good yields and excellent *er* values, among which NHC-bound homoenolate was the key intermediate in the formation of spiro compounds.<sup>17</sup>



Scheme 2 Synthesis of spiroindole lactones and lactams from isatin derivatives.



Scheme 3 Synthesis of spiroindole lactones and spirocyclopentanoneoxindoles.

After the carbonyl group at the C-3 position is modified as a C=C double bond or a C=N double bond, the isatin still shows excellent reactivity. In 2016, the interception of isatin *N*-*boc*-ketimines **15** and 3-bromoaldehydes **16** resulted in the enantioselective synthesis of spiro[indoline-3,2'-pyrroles] **17** with one quaternary chiral center *via* a chiral NHC-catalysis **C5**. A screening of various solvents, catalysis and bases achieved a mild to good yield and excellent enantioselectivities (>95 : 5 *er*) (Scheme 3a).<sup>18</sup> The same year, Biju's group published the diastereoselective synthesis of cyclopentanone-fused spirooxindoles by the [3 + 2] reaction of isatilenone derivatives **18** and  $\alpha,\beta$ -unsaturated aldehydes. In the presence of NHC generated from the imidazolium salt **C3** and base, the desired cyclopentanone-fused spirooxindoles **19** bearing an all-carbon quaternary were obtained in moderate to good yields (51-71%) (Scheme 3b).<sup>19</sup>

**2.1.1.2 [4 + 2] and [3 + 3] Annulations to construct six-membered spirooxindole compounds.** Spiro six-membered oxindoles bearing a quaternary stereo-center at the C3 position are significant moieties appearing in various biological natural products and synthetic drug molecules (Fig. 4),<sup>20</sup> and thus can

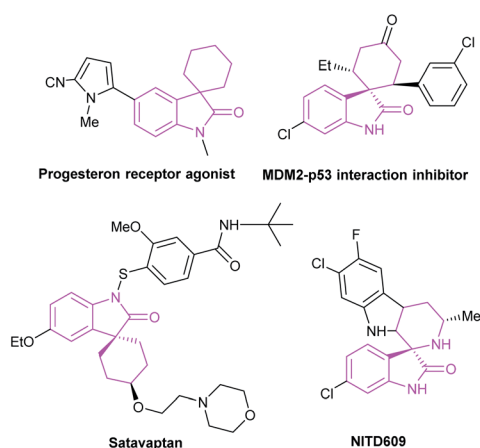
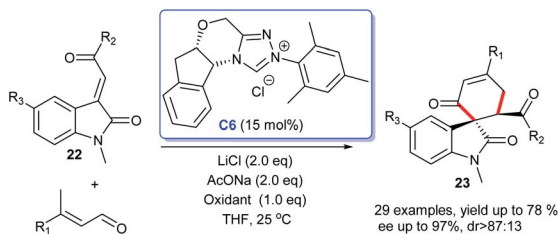


Fig. 4 Several bioactive six-membered spirooxindoles.





Scheme 4 The enantioselective synthesis of spirocarbocyclic oxindoles.

serve as a precursor to synthesize derivatives with a wide spectrum of biological activities. Enormous endeavours have been contributed for their synthesis and synthetic protocols to spiro six-membered oxindoles have been well disclosed.

In 2016, an enantioselective version of the oxidative NHC-catalyzed spirocarbocyclic oxindoles synthesis was developed by Liu's group (Scheme 4). The [4 + 2] cycloaddition of 3-alkenyloxindoles **22** with enals **21** resulted in the desired six-membered spiroindoles **23**. The use of NHC generated from salt **C6** in cooperation with AcONa and LiCl was found to be optimal for the reaction. A variety of substitution patterns on the benzene ring of 3-alkenyloxindoles as well as substitution on the enals were tolerated well under the optimized reaction condition to achieve the desired products in good yields and high enantioselectivities.<sup>21</sup> The reaction could be carried out smoothly at room temperature, which made the process highly practical.

The enantioselective synthesis of spiroindole containing a six-membered lactam ring was efficiently achieved through oxidative carbene catalysis using NHC generated from chiral triazolium salt **C7** and oxidant with LiCl as a cooperative Lewis acid (Scheme 5). In this process, treating the 2-aminoacrylates with oxindole-derived enals gave the corresponding products **26** in excellent yields (up to 98%).<sup>22</sup> Nonetheless, the drawbacks of this approach still existed, such as the optical purity hasn't been investigated and the reaction temperature could be further optimized.

In 2019, Enders and colleagues designed an interesting formal [3 + 3] cycloaddition of isatin-derived enals **24** and cyclic *N*-sulfonyl ketimines **25**. In this reaction, the NHC catalyst and DQ have proven to be indispensable for superior yields and ee values. Finally, the [3 + 3] annulation afforded highly enantioselective six-membered lactam rings fused at the C3 position of spiroindoles **26** (Scheme 6).<sup>23</sup>



Scheme 5 The enantioselective synthesis of spiroindoles containing a six-membered lactam ring.



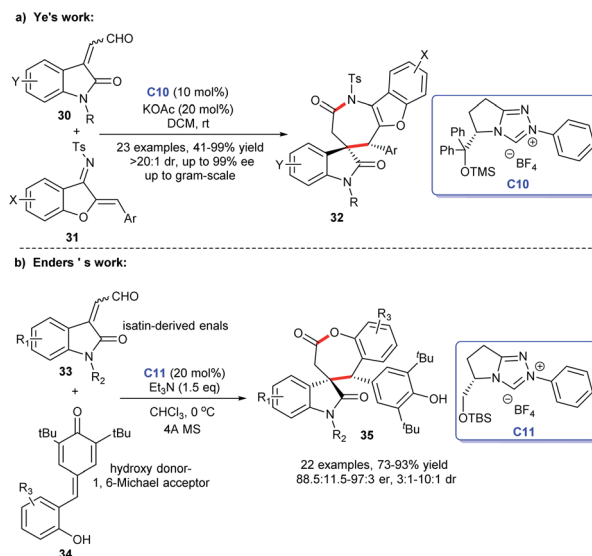
Scheme 6 The enantioselective synthesis of spiroindoles containing a six-membered lactam ring.

Subsequently, the enantioselective [3 + 3] cycloaddition of isatin-derived enals **27** with ethynyl-ethylene carbonates **28** through a cooperative NHC **C8**/Cu catalytic process was reported by Gong's group.<sup>24</sup> With these feasible approaches in hand, the six-membered lactones and lactams **29** fused at the C3 position of spiroindoles could be easily obtained.

**2.1.1.3 [3 + 4] Annulation to construct seven-membered rings fused at C3 position of spiroindole compounds.** In view of their attractive biological activities and extensive applications in human diseases, the diversified spiroindoles incited synthetic chemists' tremendous concern. Quantities of protocols have been opened up for the preparation of these compounds with four-, five-, six-, or seven-membered rings fused at the C3 position. Among them, the catalytic asymmetric synthesis of seven-membered spiroindoles was less reported relatively, mainly owing to the difficulty in forming the unstable large rings with spiro-quaternary stereocenters.<sup>25</sup>

NHC-catalyzed [3 + 4] cycloaddition reactions *via* a homo-enolate intermediate have proven to be a prominent approach to seven-membered heterocycles.

In 2018, Ye and co-workers designed an [3 + 4] annulation of aurone-derived azadienes **31** and isatin-derived enals **30** under NHC-catalysis **C10** leading to the practical and efficient



Scheme 7 The enantioselective synthesis of spirocyclic oxindole- $\epsilon$ -lactones and lactams from isatin-derived enals.





Scheme 8 The enantioselective synthesis of spirocyclic oxindole seven-membered- $\epsilon$ -lactams.

synthesis of spirocyclic oxindole-benzofuroazepinones **32** (Scheme 7a). Moreover, the cycloadducts were afforded in good yields with excellent enantioselectivities and gram-scale preparation was achieved. Numerous researches showed these oxindole-benzofuroazepinones have highly potential bioactivities, the exploitation of this preparation method provided the basis for the exploration of the biological activity of which.<sup>26</sup>

In the same year, Enders *et al.* discovered a NHC **C11**-catalyzed [3 + 4] cycloaddition of isatin-derived enals **33** and *p*-quinone methides **34** resulting in a good-yield and high-stereoselectivity synthesis of spirocyclic oxindole- $\epsilon$ -lactones **35** (Scheme 7b).<sup>25</sup>

Subsequently, on the basis of previous reports, an additional approach to spirocyclic oxindole seven-membered- $\epsilon$ -lactams was described by Gong group in 2019.<sup>24</sup> In this study, ethynylethylene carbonates **36** with enals derived from isatin were employed as suitable substrates and triazole salt **C12** and Cu(OTf)<sub>2</sub> as co-catalyst giving the corresponding products **37** in good to excellent yields with high enantioselectivities (Scheme 8).

**2.1.1.4 [2 + 2] Annulation to construct four-membered spirooxindole compounds.** Compared with other spiroindole rings, four-membered spirooxindole compounds are rarely reported relatively. With the combination of two outstanding heterocycles of indole and  $\beta$ -lactam, spirocyclic indolo- $\beta$ -lactam is one of the leading structures of some bioactive natural products, such as chartelines extracted from the marine bryozoan *Chartella papyracea* (Fig. 5). In view of the unique structure and potential bioactivities, the synthesis of spirocyclic indolo- $\beta$ -lactams is an important task for organic synthesis.<sup>27</sup>

In 2014, the first efficient and atom-economic NHC-catalyzed enantioselective synthesis for spirocyclic oxindolo- $\beta$ -lactams was disclosed by Ye's group. The reaction was achieved with isatin-derived ketimines and ketenes as substrates, the bifunctional NHC **C13** with a free hydroxyl group as catalysis (Scheme 9).<sup>28</sup> A variety of substitution pattern on the

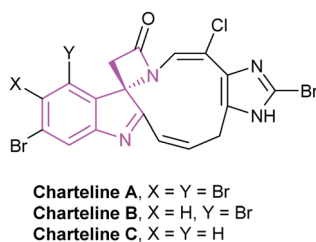
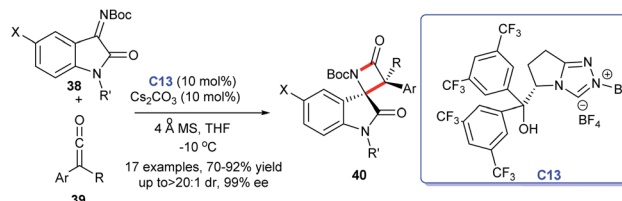


Fig. 5 Several natural products containing four-membered spirooxindoles.



Scheme 9 The enantioselective synthesis of 3-position quaternary lactam ring of spiroindoles.

benzene ring of isatin-derived ketimines **38** as well as substitutions on ketene **39** were tolerated well under the optimized reaction conditions. This process provided new channel for the preparation of 3-position quaternary lactam ring of spiroindoles **40** which was difficult to synthesize.

**2.1.2 Synthesis of indole-fused scaffolds.** Indole-fused scaffolds are a crucial pharmacologically relevant core, which is abundant in a great number of natural products with meaningful bioactivities (Fig. 6).<sup>29</sup>

Owing to their complicated structures and diverse biological activities, indole-fused heterocyclic compounds, which is the combination of indole structure with other heterocyclic scaffolds containing bioactive centers have drawn considerable attention of organic chemists.

In 2013 and 2015, Lu and co-workers completed NHC-catalyzed cycloaddition leading to the preparation of

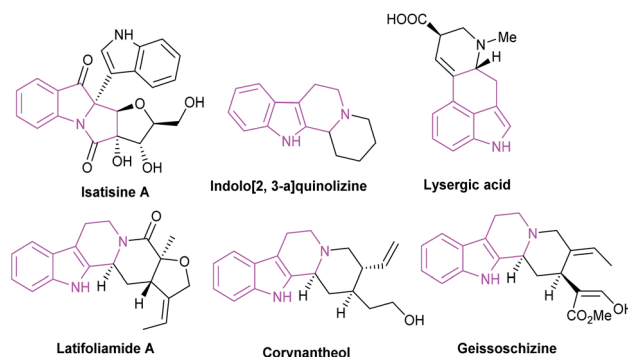
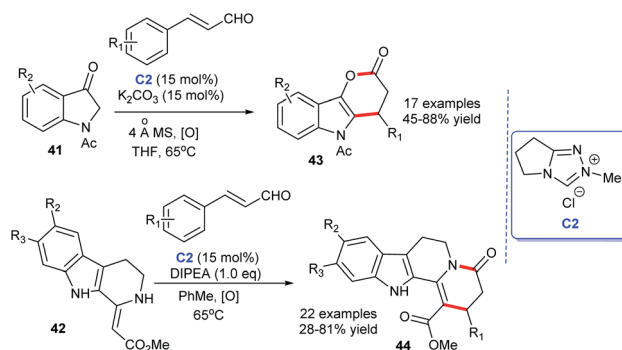
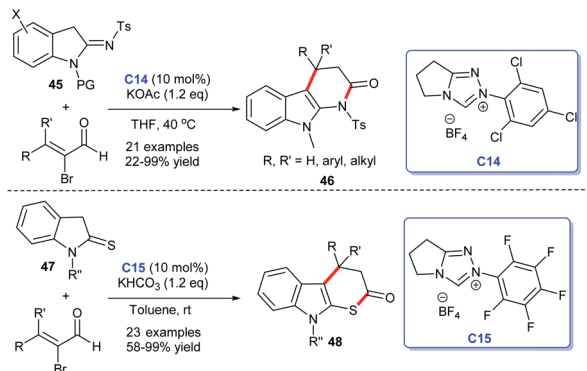


Fig. 6 Several natural products containing indole-fused scaffolds.



Scheme 10 The enantioselective synthesis of indole-fused six-membered heterocyclic rings from cinnamaldehyde derivatives.



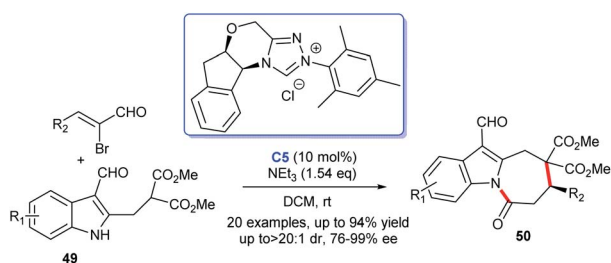


**Scheme 11** The enantioselective synthesis of indole-fused six-membered heterocycle rings from  $\alpha$ -bromocinnamaldehyde derivatives.

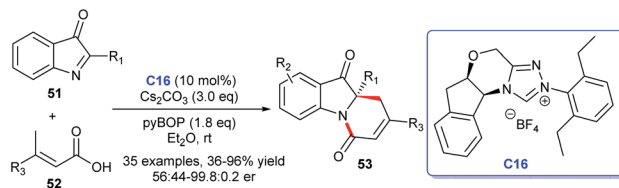
functionalized 3,4-dihydroprano[3,2-*b*] indol-2-ones **43** (ref. 30) and indolo[2,3-*a*] quinolizidines **44**,<sup>31</sup> respectively. In the presence of NHC **C2** generated from the triazolium salt and base, the desired products were obtained in moderate to good yields (Scheme 10). With this elegant approach in hand, indole-fused lactones and lactams analogs were easily prepared.

In 2017, Ye's group disclosed an [3 + 3] annulation accessing to indolo[2,3-*b*]dihydrothiopyranones from bromoenals and indoline-2-thiones **47** catalyzed by NHC **C15**.<sup>32</sup> Soon after, on the basis of the abovementioned study, the same group reported their achievements in NHC-catalyzed [3 + 3] cycloaddition, they accomplished the synthesis of dihydro-pyridinone-fused indoles **46** *via* conducting the reactions with bromoenals and indolin-2-imines **45** as raw materials for cycloaddition reactions (Scheme 11).<sup>33</sup> In the process, they developed a unified strategy for the synthesis of indole-fused six-membered heterocycles catalyzed by NHC **C14**. This reaction obtained satisfactory substrate suitabilities and good yields. However, the stereoselectivity of the reaction was not achieved.

Construction of the indole-fused heterocyclic scaffolds using NHC-activated 2-bromoaldehydes as substrate was continually studied. In 2019, the efficiently asymmetric [3 + 4] cycloaddition of 3-formylindol-2-methylmalonates **49** with 2-bromoaldehydes to functionalized azepino[1,2-*a*]indoles **50** promoted by NHC catalyst **C5** was reported. The authors pointed out that the 3-formyl group in indoles served as an essential mediated group in the generation of cycloaddition products under moderate



**Scheme 12** The enantioselective synthesis of indole-fused seven-membered lactams from  $\alpha$ -bromocinnamaldehyde derivatives.



**Scheme 13** The enantioselective synthesis of indole-fused six-membered lactams.

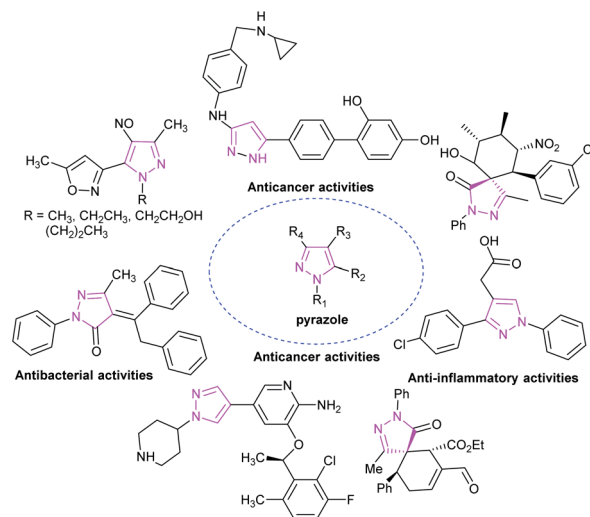
conditions (Scheme 12).<sup>34</sup> This reaction took place under mild conditions with low catalyst loading. Moreover, the reaction exhibited good substrate tolerance and excellent yields with good to excellent stereoselectivities.

Besides, by taking advantage of chiral NHC catalysis cooperated with pyBOP strategy, Du *et al.* reported the [4 + 2] annulation of  $\alpha,\beta$ -unsaturated carboxylic acids **52** bearing  $\gamma$ -H and 2-aryl-3*H*-indol-3-ones **51** to afford C2-quaternary indolin-3-ones **53** (Scheme 13).<sup>35</sup> The cycloadducts were obtained in good yields with good to excellent enantioselectivities. A wide variety of substituted 2-aryl-3*H*-indol-3-ones and  $\alpha,\beta$ -unsaturated carboxylic acids were well tolerated under the optimized reaction conditions. These synthetic methods about indole-fused scaffolds provide effective pathways for drug discovery.

## 2.2 Applications in the synthesis of pyrazole derivatives

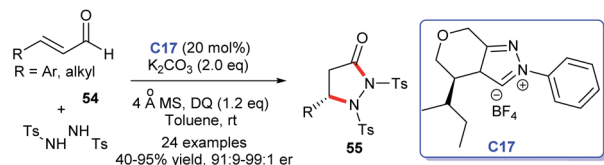
As a representative of a five-membered heterocyclic ring, the pyrazole skeleton contains two nitrogen atoms and is the core structural unit of many synthetic drugs and natural compounds. Pyrazole derivatives and related analogues display a broad scope of biological and pharmaceutical activities,<sup>36</sup> including antitumor, antibacterial, antifungal and other biological activities (Fig. 7).<sup>37</sup>

During to the characteristics of high efficiency, low toxicity, and the ability to modify multiple substituents, pyrazole skeleton has become the focus of scientific researchers around the



**Fig. 7** Bioactive compounds with pyrazole ring as the core structure.





Scheme 14 The enantioselective synthesis of pyrazolidinones.

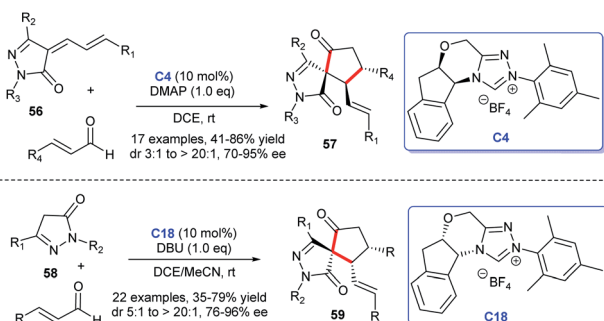
world. The synthesis of pyrazole derivatives is also a hot topic in organic synthetic chemistry. The pyrazole derivative 1-phenyl-3-methylpyrazolone was first artificially synthesized by L. Knott from ethyl acetoacetate and phenyl-hydrazine in 1883. Since then, the door to the synthesis of pyrazole derivatives has been opened, and a large number of pyrazole derivatives have been synthesized.

In recent years, the synthesis of heterocyclic compounds catalyzed by NHCs has drawn considerable attention, and reports on the synthesis of pyrazole derivatives catalyzed by NHCs are abundant.

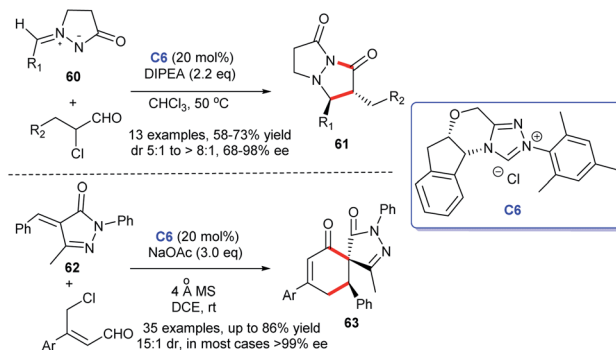
In 2016, Yang and coworkers developed a feasible approach to access to pyrazolidinone products **55** *via* NHC **C17**-catalyzed [3 + 2] cycloaddition of enals and protected hydrazine with suitable electronic properties, disclosing an enantioselective amination of enals'  $\beta$ -carbon (Scheme 14). In this reaction,  $\alpha,\beta$ -unsaturated acyl azolium intermediate derived from NHC was the core intermediate to form the new C–N bond asymmetrically.<sup>38</sup>

In the same year, Enders group reported that they obtained the five-membered spiro-pyrazolones **57** from the [3 + 2] cycloaddition of unsaturated pyrazolones **56** with enals under the catalysis of chiral NHC **C4**. The reaction showed good yields and excellent stereoselectivities.<sup>39</sup> Soon afterwards, as their continuous work in this direction, the research group published another work about NHC-catalyzed the three-component and one-pot synthesis of spirocyclic pyrazolones **59** (Scheme 15). They employed two molecules of the enal and pyrazolone **58** as substrates to obtain the products *via* a [3 + 2] cycloaddition in excellent stereoselectivities and good yields.<sup>40</sup> These reactions exhibited good substrate and functional group tolerance.

In 2018, Zhong and coworkers disclosed a highly asymmetric [3 + 2] annulation of  $\alpha$ -chloroaldehydes with 3-oxopyrazolidin-1-ium-2-ides **60** catalyzed by chiral NHC **C6**, leading to the



Scheme 15 The enantioselective synthesis of five-membered spiro-pyrazolones.



Scheme 16 The enantioselective synthesis of pyrazolones reported by Zhong and coworkers.

synthesis of a series of bicyclic pyrazolidinones **61**.<sup>41</sup> Subsequently, Zhong's group kept on reporting their research on the synthesis of pyrazole derivatives under the same catalyst chiral NHC. They framed spirocyclohexane pyrazolone skeletons **63** through [4 + 2] annulation of  $\alpha$ -arylidene pyrazolinones **62** and  $\gamma$ -chloroaldehydes without the participation of oxidant. The reaction presented great advantages in substrate tolerance and stereoselectivity. This protocol furnishes new thinking for the establishment of spirocyclohexane pyrazolone skeletons (Scheme 16).<sup>42</sup>

### 2.3 Applications in the synthesis of quinoline derivatives

Compounds with quinoline as the core structure are abundant in natural products. Quinoline is one of the leading structures processing strong biological activities and many potential medicinal values. They are widely used in new materials, pharmaceuticals, agrochemicals, *etc.*

The quinoline-based compounds are the focus of drug discovery due to their extensive physiological activities. As early as 1988, Evans assigned quinoline as a "privileged scaffold" in medicinal chemistry.<sup>43</sup> The prominent antimalarial drug quinine and compounds with anti-inflammatory and antitumor activities are based on the quinoline skeleton (Fig. 8).

For acquiring quinoline derivatives, concise and efficient chemical synthesis is the principal channel. In recent years, because of their simple preparations, stable structures, and low toxicity, NHCs have become very effective organic catalysts for

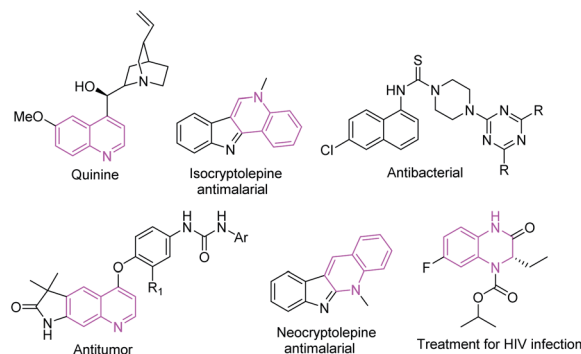
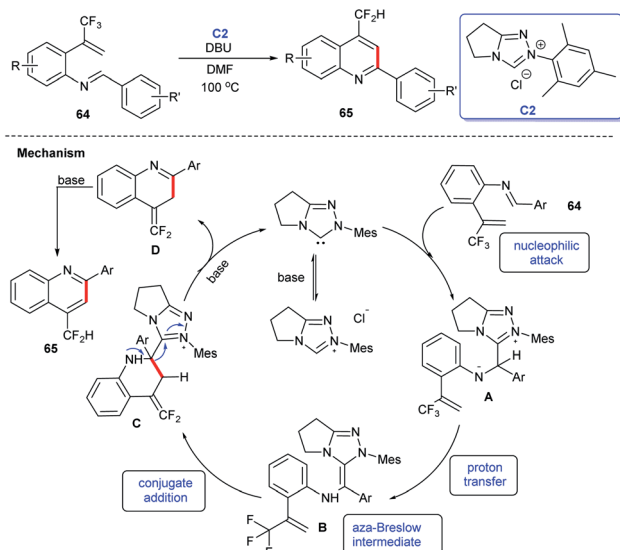


Fig. 8 Bioactive compounds with quinoline as the core structure.



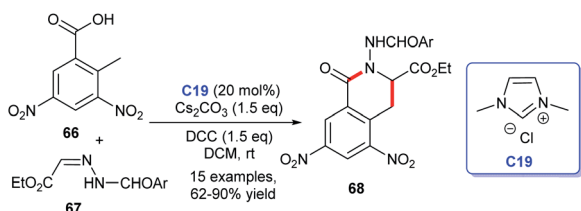


Scheme 17 The synthesis of 4-difluoromethylquinolines catalyzed by NHC and the tentative mechanism of the reaction.

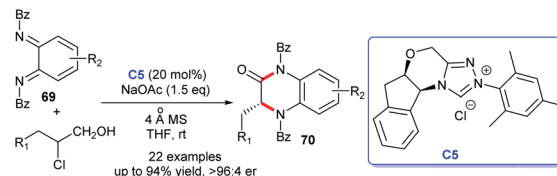
synthesizing heterocyclic skeletons. Therefore, NHCs are also diffusely employed in the construction of quinoline skeletons.

In 2018, Biju and coworkers developed a method for the synthesis of 4-difluoromethylquinolines **65** through intramolecular cyclization of aldimines **64** under the catalysis of NHC **C2**. The generation of NHC from precursor bicyclic triazolium salt in the presence of DBU as the base was the key step for the conversion. The substrate scope of the reaction was examined and a tentative mechanism in Scheme 17 for this NHC-catalyzed 4-difluoromethyl-quinolines synthesis was described as: aldimine **64** can be converted into tetrahedral intermediate **A** by combining with the NHC, then undergoes a rapid proton transfer to create aza-Breslow intermediate **B**, which could form an NHC-bound intermediate **C** by intercepting the electron-poor olefin intramolecularly. When a base excess is present, elimination of the carbonate occurs, resulting in intermediate **D**, which can undergo a 1,3-H shift and eventually lead to quinoline **65**.<sup>44</sup> In this study, it was proposed that addition of NHC catalyst **C2** to C=N of **64** resulting in formation of the Breslow intermediate, conjugate addition and tautomerization under alkaline conditions then afforded the cycloaddition products **65**.

Later, Yao *et al.* demonstrated the [4 + 2] annulation of 2-methyl-3,5-dinitrobenzoic acid **66** and acylhydrazone **67** leading to the synthesis of isoquinolinones **68** by using a cooperative



Scheme 18 The synthesis of isoquinolinones.



Scheme 19 The synthesis of dihydroquinoxaline derivatives.

NHC **C19** and DCC catalytic strategy (Scheme 18). The reaction showed good yields.<sup>45</sup>

In 2019, the asymmetric synthesis of dihydroquinoxaline derivatives was described by Chi's group. In this process, triazolium **C5** has proven to be effective for the production of highly stereoselective dihydroquinoxaline derivatives **70** in the presence of NaOAc. The aminated chloroaldehydes and cyclohexadiene-1,2-diimines were employed as suitable substrates and afforded the corresponding functional dihydroquinoxaline derivatives in excellent yields with brilliant enantioselectivities (Scheme 19).<sup>46</sup> In view of the previous synthetic routes, Chi's method showed advantages with a gentle reaction condition and widespread substrate applicability, and products with high purity were achieved.

#### 2.4 Applications in the synthesis of pyran derivatives

The pyran skeleton and its analogues are detected in numerous natural products or synthetic compounds, many of which possess significant biological activities. For instance, the most common pyran structure—tetrahydropyrans, pyrones and benzopyrones are privileged structures existing in numerous natural products and bioactive molecules (Fig. 9).<sup>47</sup> These scaffolds showed promising applications in the field of medicinal chemistry. Therefore, economical and efficient synthetic methods for these molecules are highly desirable. The bloom of NHC catalysts provides excellent routes for their acquisition.<sup>48</sup>

Ye's group demonstrated the synthesis of multiple substituted dihydropyrans **72** by [4 + 2] annulation of oxodienes **71** and nitroalkenes in the presence of NHC **C20**. The cycloaddition products were given in good yields with nice

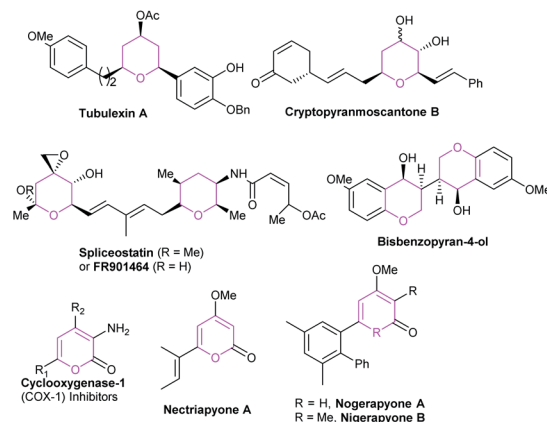


Fig. 9 Representative biologically important  $\alpha$ -pyrones.







Scheme 20 The synthesis of multiple substituted dihydropyrans.

diastereoselectivities. Furthermore, they declared that the NHC catalysis behaved good applicability to  $\beta$ -substituted nitroalkenes, which was not feasible in the presence of DABCO or phosphine (Scheme 20).<sup>49</sup>

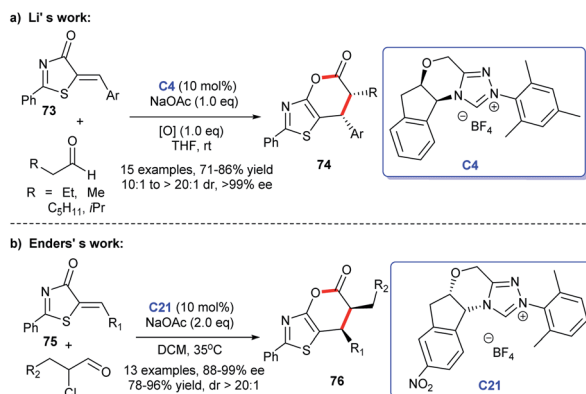
Subsequently, Li *et al.* provided a method to prepare functionalized thiazolopyrones. They received the target [4 + 2] cycloadducts *via* the reaction between aliphatic aldehydes and thiazolones 73 in the presence of NHC C21 generated from the triazolium C4 and NaOAc, the desired products 74 were obtained in moderate to good yields<sup>50</sup> (Scheme 21a). An additional approach to functionalized thiazolopyrones 76 was reported by Enders group in 2017 (Scheme 21b). In this study,  $\alpha$ -chloroaldehydes and 5-alkenylthiazolones 75 were exploited to engage in the asymmetric [4 + 2] heterocycloaddition.<sup>51</sup>

Following these pioneering reports, Zhou and co-workers constructed the bisbenzopyrone 78 scaffold through the intramolecular hydroacylation–Stetter reaction by the catalysis of NHC C22 in 2018. A sequence of bisbenzopyrones was acquired with good to excellent yields (Scheme 22).<sup>52</sup>

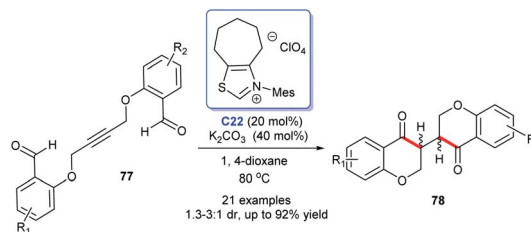
## 2.5 Applications in the synthesis of furan derivatives

Furan is a pharmacophore structure discovered in numerous natural products and thus can act as a precursor to synthesize derivatives with a wide spectrum of biological activities.<sup>53</sup> In addition, furan derivatives are widely employed in many other areas, including agriculture, materials and other fields. In view of the application importance, several methodologies were developed for the synthesis of furan derivatives, NHC-catalyzed synthesis method, of course, included.

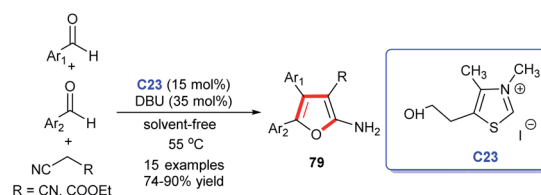
In 2011, Yao and colleagues disclosed a solvent-free cycloaddition of malononitrile (or ethylcyano-acetate) with two molecular



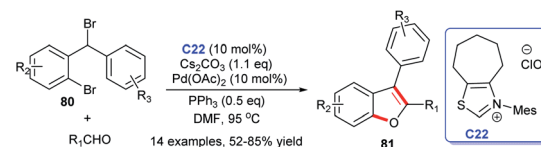
Scheme 21 The synthesis of functionalized thiazolo-pyrone.



Scheme 22 The synthesis of bisbenzopyrones.



Scheme 23 The synthesis of substituted furans.



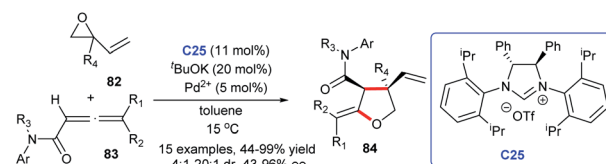
Scheme 24 The synthesis of substituted benzo[b]furans.

aromatic aldehydes catalyzed by NHC generated from the thiazolium salt C23 and DBU (Scheme 23). Finally, the substituted furans 79 were obtained efficiently, meanwhile, the reactions showed good substrate and functional group tolerance.<sup>54</sup>

On the basis of the previous study, the same group completed the construction of furans skeleton *via* the [3 + 2] annulation of aryl aldehydes with a series of substituted 2'-bromodiphenyl bromomethanes 80 by using a cooperative NHC-palladium C22 complex and PPh<sub>3</sub> catalytic strategy (Scheme 24).

This protocol exhibited the characteristics of simple operation, good substrate applicability, and good catalyst tolerance, offering a new novel strategy for obtaining benzo[b]furans.<sup>55</sup>

The enantioselective synthesis of polyfunctional chiral tetrahydrofurans was achieved through carbene–palladium complex catalysis using NHC generated from chiral imidazolium salt and <sup>t</sup>BuOK (Scheme 25) by Hou's group. The process starting from vinyl epoxides 82 and  $\alpha$ -allenic amides 83 proceeded favourably in toluene. The asymmetric [3 + 2] annulation



Scheme 25 The synthesis of polyfunctional chiral tetrahydrofurans.



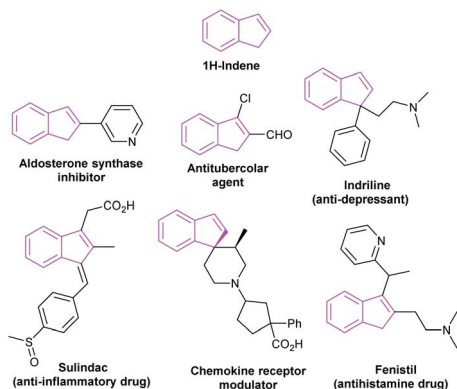


Fig. 10 Bioactive compounds with indene as the core structure.

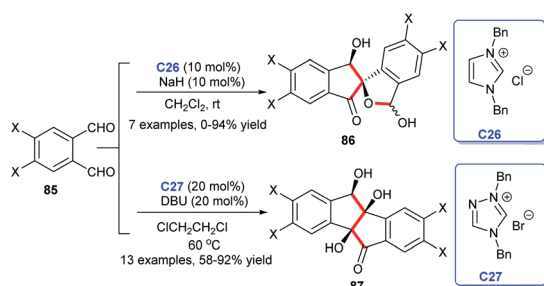
for accessing polyfunctional chiral tetrahydrofurans **84** acquired good yields with high diastereo- and enantioselectivities by NHC–Pd catalysis **C25**. They clued that chiral NHC serving as a particular ligand in this reaction.<sup>56</sup>

## 2.6 Applications in the synthesis of indenenes

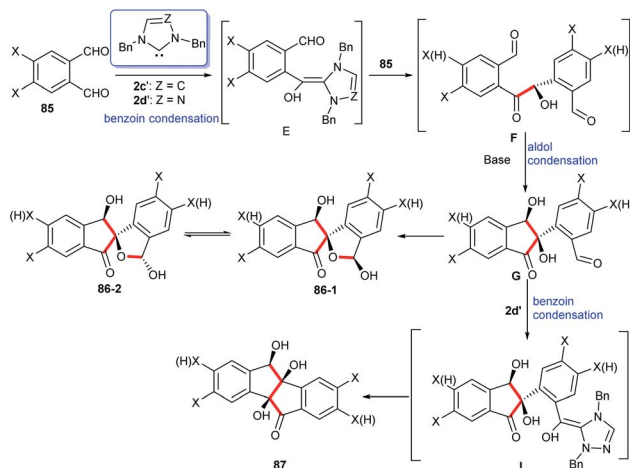
The indene skeleton was significant moieties found in many natural compounds possessing interesting bioactivities and pharmaceutical activities (Fig. 10). Moreover, indene derivatives were widely used in materials science, including new fluorescent materials and catalytic materials. In recent years, many attempts have been made to build this special skeleton by organic chemists. Herein, we summarize the NHC-catalyzed synthesis of indene derivatives.

In 2011, Cheng *et al.* described that two molecules of phthalaldehydes **85** dimerized in the presence of NHC **C26** or **C27**, leading to an asymmetry synthesis of indenones.<sup>57</sup> The adoption of different salts, bases and solvents leading to different condensation products **86** and **87** respectively. In this work, the NHC-catalysis successively mediated intermolecular benzoin condensation, intramolecular aldol reaction and benzoin condensation to obtain corresponding indenones. This work has reflected the diversity of NHC as organocatalysis (Scheme 26).

To further explain the effect of different reaction conditions on the products, the mechanism of intermolecular condensation was proposed in Scheme 27. In the reaction between imidazole or triazole carbene and phthalaldehydes **85**, they



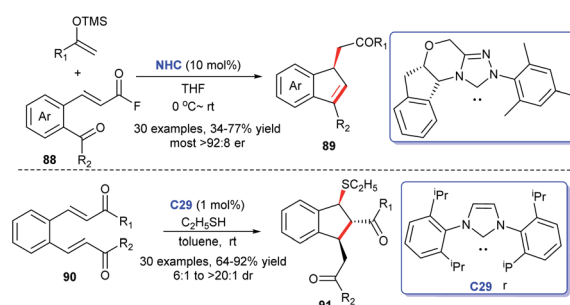
Scheme 26 The synthesis of indenones.



Scheme 27 The Proposed Mechanisms for the NHC-catalyzed reactions of phthalaldehydes.

form a benzoin condensation *via* a Breslow intermediate **E** which then gives rise to *R*-hydroxylketones **F**. There has been a possibility that the intramolecular aldol condensation of **F** may yield *cis*-dihydroxylindenone **G** due to the presence of hydrogen bonds between the two *cis*-substituted hydroxyl groups. As a result of the intramolecular addition of 2-hydroxyl to aldehyde moiety **G**, hemiacetals of spiro-indenones **86** exist in solution as a mixture of epimer **86-1** and epimer **86-2**. Accompanying with an intramolecular condensation of benzoin between two carbonyl groups the hydroxylindenones **G** are converted into the fully *cis*-trihydroxylindenone[2,1-*a*]inden-5-ones **87**.

In 2017, Lupton and coworkers disclosed an approach to obtain functionalized indenenes **89** exploiting  $\alpha,\beta$ -unsaturated acyl fluorides **88** and TMS enol ethers as raw materials with NHC catalyzing (Scheme 28). The reaction realized the efficient synthesis of highly stereoselective functionalized indenenes. Thirty-one examples were tested *via* generality investigation. The results exhibited a broad substrate scope and excellent functional group tolerance.<sup>58</sup> In 2019, He's group acquired a series of sulfenylated indanes **91** *via* sulfa-Michael–Michael cascade reaction of thiols with *o*-formyl chalcones **90** mediated by NHC **C29**.<sup>59</sup> Only 1% of NHC sufficed to promote the reaction, which made the process highly practical.



Scheme 28 The synthesis of functionalized indenenes.



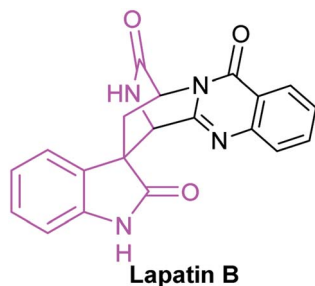


Fig. 11 The structure of natural product Lapatin B.

## 2.7 Applications in the synthesis of lactams

Great quantities of compounds containing lactam structure have outstanding biological activities. For instance, lactam skeletons are the essential pharmacophores of penicillin antibiotics. Thalidomide containing spiro-glutarimide skeleton is a widely exploited drug for cancer treatment.<sup>60</sup> **Lapatin B** bearing a  $\delta$ -lactam moiety and possessing antibacterial activity, was isolated from *Trichoderma penicillium* (Fig. 11).

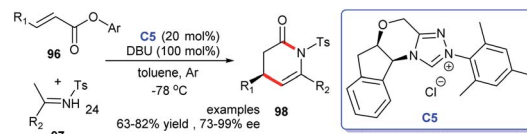
In addition, lactam skeletons are often used as intermediates to synthesize complex organic compounds. Therefore, their special properties and important applications have attracted chemists' widespread attention. With the widespread application of NHC catalysts, reports regarding to synthesis of lactam compounds catalyzed by NHC are numerous.<sup>61</sup>

**2.7.1 Synthesis of  $\beta$ -lactam scaffold.** In 2011, Ye and co-workers disclosed an efficient and atom-economic NHC-catalyzed [2 + 2] annulation reaction between *N*-sulfinylanilines **93** and ketenes **92**, achieving  $\beta$ -lactam scaffold in good yields with excellent enantioselectivities (Scheme 29).<sup>62</sup>

Only 1% of triazolium salt **C10** or **C30** and 2% of  $\text{Cs}_2\text{CO}_3$  sufficed to promote the reaction. Surprisingly, under the same other conditions, two different types of NHC precursors triazolium salts **C10** and **C30** led to the completely distinct four-membered cycloaddition products, which reflects the "smart" of NHC catalysts. However, the harsh reaction condition ( $-78^\circ\text{C}$ ) thereby prevented its large-scale synthetic applications. In addition, Xia *et al.* offered a powerful strategy for the synthesis of  $\beta$ -lactams. They utilized NHC-Pd complex to catalyze the [2 + 2] cycloaddition of imine's allyl derivatives and benzyl chlorides in the presence of  $\text{CO}$ .<sup>63</sup>



Scheme 29 The synthesis of  $\beta$ -lactams.

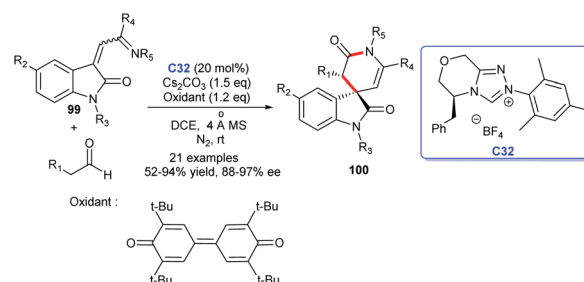


Scheme 30 The synthesis of  $\delta$ -lactams.

**2.7.2 Synthesis of  $\delta$ -lactam scaffold.** Liu and coworkers developed two routes accessing to six-membered  $\delta$ -lactams catalyzed by NHC. In 2015, they obtained target  $\delta$ -lactams *via* the [4 + 2] annulation between substituted imines and enals containing a leaving group (Scheme 30). They achieved the chiral control of remote  $\gamma$ -carbon by introducing a leaving group in the enals in the catalytic reaction.<sup>64</sup> Subsequently, they changed the substituents on the raw materials enals **96** and amines **97**, leading to the desirable [3 + 3] cycloaddition products  $\delta$ -lactams **98**.<sup>65</sup> Of course, the protocol still has the disadvantage of rigorous reaction condition.

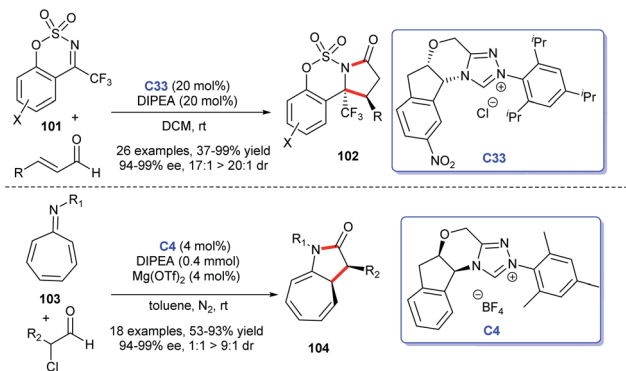
A [2 + 4] cycloaddition promoted by oxidative carbene catalysis using NHC generated from chiral triazolium salt **C32** and 3,3',5,5'-tetra-*tert*-butyldi-phenoquinone as oxidant was disclosed by Ren's group in 2019. Employing isatin derivatives **99** and aldehydes as substrates in the process could result in the enantioselective synthesis of oxindole  $\delta$ -lactams (Scheme 31).<sup>66</sup> The reaction took place under mild conditions with low catalyst loading. In view of the previous synthetic approaches, the reaction temperature was optimized, conducting to the large-scale preparation of products.

**2.7.3 Synthesis of  $\gamma$ -lactam scaffold.** In recent years, significant efforts have been made to disclose the construction of the  $\gamma$ -lactam scaffold. An efficient approach accessing to  $\gamma$ -lactams was developed by Wang *et al.* in 2020. The interception of cyclic *N*-sulfonyl  $\text{CF}_3$  ketamine **101** with  $\alpha,\beta$ -unsaturated aldehydes resulted in the enantioselective synthesis of fused *N*-heterocycle  $\gamma$ -lactams bearing two adjacent chiral centers **102**. In this process, the NHC derived from triazolium salt **C33** has proven to be effective for the [3 + 2] annulation (Scheme 32).<sup>67</sup> In 2019, Xu and co-workers exploited  $\alpha$ -chloro aliphatic aldehydes and azaheptafulvenes **103** as starting materials, affording  $\gamma$ -lactams **104** with NHC **C4** as catalysis. The reaction exhibited high yield, excellent stereoselectivities and broad substrate scope.<sup>68</sup>



Scheme 31 The synthesis of oxindole  $\delta$ -lactams.



Scheme 32 The synthesis of oxindole  $\gamma$ -lactams.

**2.7.4 Synthesis of other lactams.** In 2018, Biju *et al.* developed a method accessing to spiro-glutarimides *via* the asymmetric [3 + 3] cyclo-addition between cyclic  $\beta$ -ketoamides and  $\alpha,\beta$ -unsaturated aldehydes (Scheme 33a). NHC mediated the reaction by forming  $\alpha,\beta$ -unsaturated acylazoliums. The approach described in this paper was applied to various examples, in which different aspects were investigated. A wide variety of substrates were well tolerated under the optimized reaction conditions. In 2019, Huang *et al.* demonstrated a highly stereoselective method for obtaining spiro- $\epsilon$ -lactam oxindoles **106** with NHC catalysis C6 (Scheme 33b). They completed the [4 + 3] annulation by employing enals and oxotryptamines as substrates.<sup>69</sup> The reaction showed wide applicability to various aldehydes including aryl aldehydes, flexible oxotryptamines **107**.

## 2.8 Applications in the synthesis of lactones

The lactone ring structure is extensively distributed in a large number of synthetic and natural organic compounds, many of which exhibit significant biological activities.<sup>70</sup> For instance, venolepin is used as an antitumor drug, butyrolactone is used as a neurotransmitter, natural product, and iedomycins B shows antimicrobial activity, and so on (Fig. 12). These excellent activities of lactone ring compounds stimulated the great interest of synthetic chemists. Several routes have been developed to

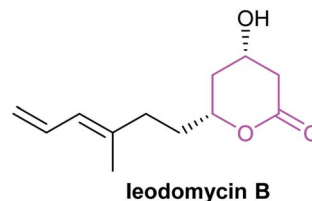


Fig. 12 The structure of natural product iedomycin B.

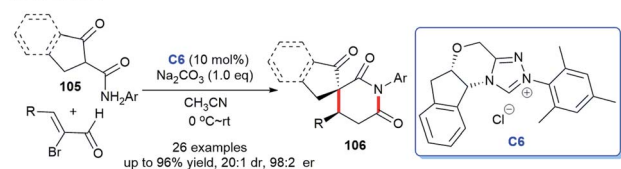
construct the lactone ring scaffold, among which, the NHCs were also found to be efficient catalysts for the lactone rings.<sup>71</sup>

Scheidt and co-workers developed an [4 + 2] annulation accessing to imidazole fused six-membered lactones **110** with imidazolidinones **109** and  $\alpha,\beta$ -unsaturated aldehydes as starting materials in 2013.<sup>72</sup> The reaction was promoted by using a cooperative NHC and AcOH catalytic strategy, with the corresponding products afforded in moderate to good yields with up to 99 : 1 er. On the basis of **110**, the same group focused on the core structure lactone, and subsequently, developed a protocol to synthesis 2-benzoxopinones **112**, *via* the NHC-catalyzed [4 + 3] cycloaddition by treating  $\alpha,\beta$ -unsaturated aldehydes with *o*-quinone methides for the formation of 2-benzoxopinones. NHC catalyzes the formation of cycloaddition products by forming homoenolate intermediates with aldehydes (Scheme 34).<sup>73</sup>

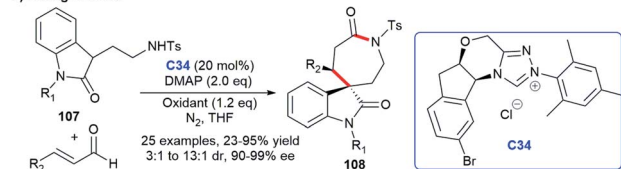
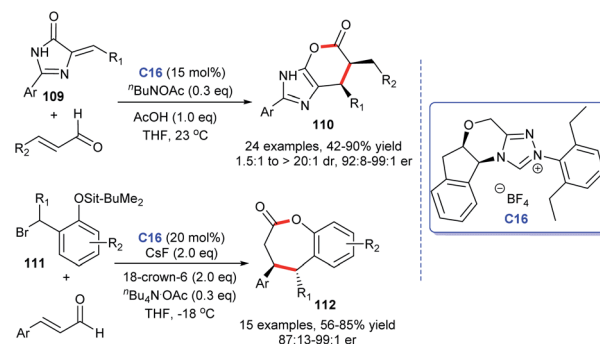
An additional approach to benzo- $\epsilon$ -lactones was described by Ye and co-workers. In the study, *o*-quinone methides **113** and enals were adopted as substrates and NHC derived from triazolium salt C35 was proven to be effective for the generation of desired seven-membered lactone rings **114** (Scheme 35).<sup>74</sup> The reaction exhibited mild reaction conditions, high yields, and good stereoselectivities. The construction of five-membered lactone rings through NHC–Lewis acid cooperative catalysis was reported by She *et al.* during the same period. They synthesized a series of butenolides by [3 + 2] cycloaddition of alkynyl aldehydes and  $\beta,\gamma$ -unsaturated  $\alpha$ -ketoesters.<sup>75</sup>

Coumarin is a typical aromatic lactone, and coumarin scaffolds were discovered in lots of natural products, including bioactive compounds. Thus, coumarins received great attention of chemists. In recent years, reports on the synthesis of coumarin skeleton compounds catalyzed by NHCs have gradually increased (Scheme 36). In 2015, Scheidt's group opened up a new synthetic strategy of dihydrocoumarins **116** under the

a) Biju's work:



b) Huang's work:

Scheme 33 The synthesis of spiro-glutarimides and spiro- $\epsilon$ -lactam oxindoles.

Scheme 34 The synthesis of lactones.



Scheme 35 The synthesis of benzo- $\epsilon$ -lactones.

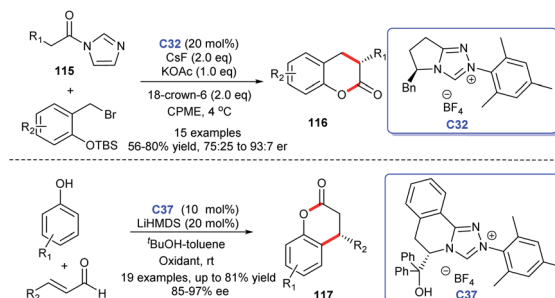
catalysis of NHCs. The study is a continuation of “a dual activation” strategy based on their previous report.<sup>76</sup> In 2017, You and co-workers demonstrated that NHC could catalyze the [3 + 3] cycloaddition of enals with phenols resulting in the synthesis of 4-aryl-3,4-dihydrocoumarins **117** in good yields with good to excellent enantioselectivities. Meanwhile, the reaction also showed good substrate applicability.<sup>77</sup> In addition, Enders's group exploited enals to react with malonates bearing an *ortho*-hydroxy phenyl with the NHC-catalysis, leading to the efficient synthesis of coumarin scaffolds **117** called cyclopenta-[*c*]-fused chromenones.<sup>78</sup>

The efficient asymmetric acquisition of  $\epsilon$ -caprolactones was developed by Glorius and co-workers in 2018. The corresponding cycloaddition products **119** were achieved in good yields with excellent enantioselectivities through cooperative catalysis of NHC-Pd and P-ligand\*. Vinyl ethylene carbonates **118** and enals were employed as substrates for the [5 + 2] cycloaddition reaction (Scheme 37). Twenty-six examples were investigated demonstrating good substrate tolerance and wide functional group applicability for the reaction.<sup>79</sup>

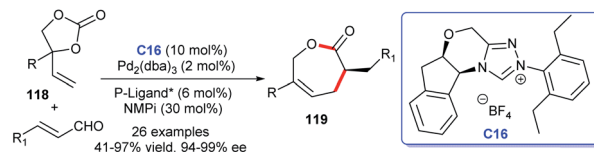
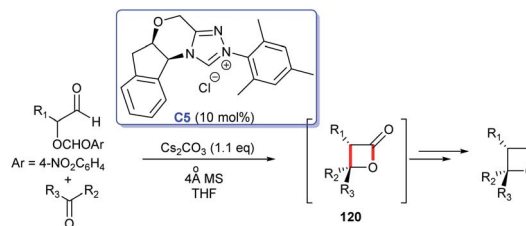
In 2015, NHC-catalyzed [2 + 2] cycloaddition to construct four-membered lactone ring was developed by Smith's group (Scheme 38). The reaction starting from perfluoroketones and  $\alpha$ -aryloxyaldehydes proceeded smoothly in THF, catalyzed by NHC generated from triazolium salt **C5**, affording the cycloadducts four-membered lactones **120**, as a precursor for the synthesis of chiral multisubstituted four-membered cyclic ethers in good yields, with excellent diastereo- and enantioselectivities.<sup>80</sup> This reaction took place under mild conditions with low catalyst loading, providing an excellent strategy for the construction of the quaternary lactone rings.

## 2.9 Applications in the synthesis of cyclic ketones

The NHC catalysis was also found to be an efficacious strategy for the preparation of cyclic ketones.<sup>81</sup> In 2017, Enders's group demonstrated the asymmetric synthesis of a variety of 3,5-diaryl



Scheme 36 The synthesis of dihydrocoumarins.

Scheme 37 The synthesis of  $\epsilon$ -caprolactones.Scheme 38 The synthesis of  $\epsilon$ -caprolactones four-membered lactones.

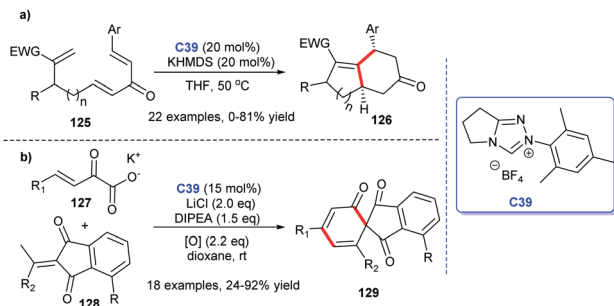
cyclohexenones **122** with the assistance of chiral NHC **C38**. They achieved the [4 + 2] cycloaddition products through the Breslow intermediate from the reaction of NHC with enals (Scheme 39a).<sup>82</sup> Subsequently, the group reported the NHC-catalyzed [3 + 2] annulation reaction for obtaining cyclopentanone derivatives.<sup>83</sup> In 2018, with the catalysis of chiral NHC **C21**, the same group synthesized cyclohexenone derivatives-tricyclic fluorene skeletons, through an intramolecular homoenolate Michael addition esterification reaction (Scheme 39b).<sup>84</sup> These reactions exhibited wide substrates applicability, medium to good yields, and excellent region- and stereo selectivities.

In 2019, Lupton and co-workers reported their new strategy for synthesizing cyclohexenones with the catalysis of NHC. They exploited acrylates **125** undergoing intermolecular [5 + 1] cycloaddition to achieve corresponding functionalized cyclopentanones **126** in moderate to good yields (Scheme 40a).<sup>85</sup> Therefore, the stereoselectivity of the reaction needs to be further explored. In the same year, a synthesis strategy regarding to spirocyclohexanones catalyzed by NHC was reported by Huang *et al.* They employed 2-ethylidene 1,3-indandiones and potassium 2-oxo-3-enoates as substrates to conduct the [3 + 3] annulation reaction. The enantioselective synthesis of spirocyclohexanones **129** was achieved through oxidative carbene catalysis using NHC generated from



Scheme 39 The synthesis of cyclic ketones.





Scheme 40 The synthesis of cyclic ketones.

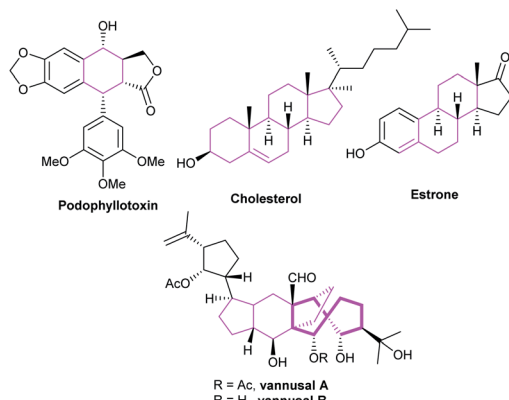


Fig. 13 Several natural products with complex carbocyclic skeletons.

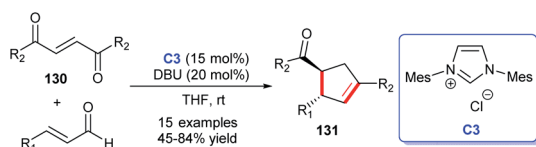
triazolium salt **C39** and oxidant with LiCl as a cooperative Lewis acid (Scheme 40b).<sup>86</sup> With these protocols in hand, spiro- and fused cyclohexanones were easily afforded.

## 2.10 Applications in the construction of several complex carbocyclic skeletons

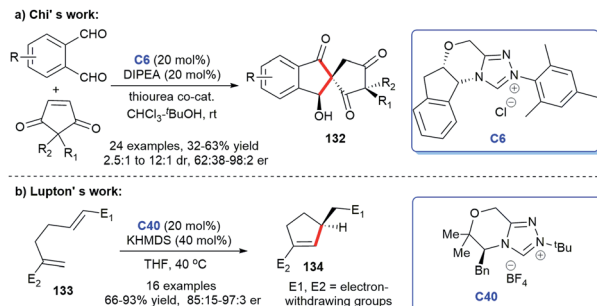
In addition to heterocyclic skeletons, carbocyclic skeletons are significant moieties discovered in natural products and biologically active molecules (Fig. 13).<sup>87</sup> Therefore, the construction of carbocyclic skeletons has achieved considerable attention.<sup>88</sup> For NHCs, there have been increasing applications in the synthesis of almost all types of cyclic compounds, and they are also widely used in the synthesis of carbocyclic skeletons.

### 2.10.1 Construction of five-membered carbocyclic skeletons.

A [3 + 2] cycloaddition, disclosed by Nair *et al.* in 2013, between enals and ene-1,4-diones **130** was promoted by NHC derived from **C3**. Simple operation and mild reaction conditions provided a powerful method for the synthesis of multi-substituted cyclopentenones **131** (Scheme 41).<sup>89</sup>



Scheme 41 The synthesis of multisubstituted cyclopentenones.

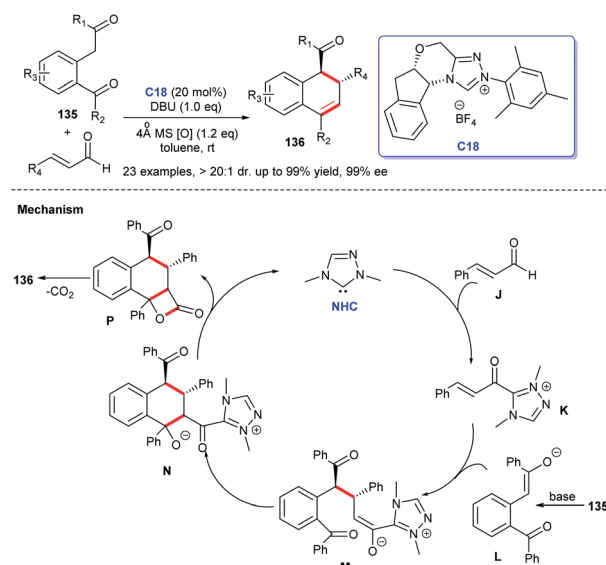


Scheme 42 The synthesis of all-carbon spirocycle scaffold.

Following these pioneering reports, in 2018, an all-carbon spirocycle scaffold **132** was constructed by one-step asymmetric [4 + 1] annulation through catalysis of NHC **C6** (Scheme 42a). In this study, they employed thiourea, which proved essential for the reaction, as a co-catalyst to unseal the reaction. The research opened the door to NHC-catalyzed synthesis of all-carbon spirocyclic skeletons for the first time.<sup>90</sup> In the same year, Lupton and co-workers synthesized a series of multi-substituted cyclopentenones **134** through intramolecular cycloaddition reaction under the catalysis of NHC **C40**. Additionally, the highly stereoselective reaction was accomplished through the  $\beta$ -azolium ylide, which was reported lesser than Breslow intermediate (Scheme 42b).<sup>91</sup>

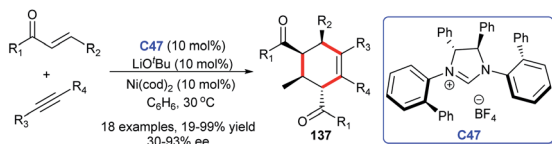
### 2.10.2 Construction of six-membered carbocyclic skeletons.

In 2017, Fang and co-workers realized the construction six-membered carbocyclic skeleton, leading to a sequence of 1,2-dihydronaphthalenes **136** via the reaction between enals and benzodiketones **135** catalyzed by oxidative NHC. They proposed a possible reaction mechanism: NHC transformed into  $\alpha,\beta$ -unsaturated acyl azolium intermediates **K** at the presence of enals **J**. Meanwhile, deprotonation of **135** under basic



Scheme 43 The synthesis of 1,2-dihydronaphthalenes and the proposed reaction mechanism.



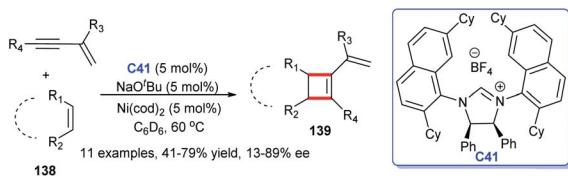


Scheme 44 The synthesis of chiral multisubstituted cyclohexenes.

conditions releases enolate **L**, which is subsequently added to **K** to yield a new enolate **M**. Within **M**, the aldol reaction can form intermediate **N**, which reacts spontaneously to form lactone **P**, which yields product **136** after decarboxylation (Scheme 43).<sup>92</sup> The reaction afforded functionalized 1,2-dihydronaphthalenes in good yields with excellent regio- and stereoselectivities. A wide variety of enals and benzodiketones were well tolerated under the optimized reaction conditions.

In 2015, a novel approach to chiral multi-substituted cyclohexenes was disclosed by Ogoshi and co-workers. In this study, a [2 + 2 + 2] cycloaddition of alkynes and two molecules of enones took place by using a cooperative NHC **C47** and Ni(cod)<sub>2</sub> catalytic strategy. The multi-substituted cyclohexenes bearing four contiguous chiral centers **137** were obtained in moderate to good yields and ee values (Scheme 44).<sup>87</sup>

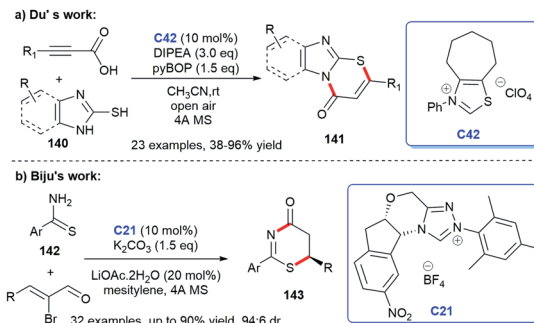
**2.10.3 Construction of four-membered carbocyclic skeletons.** In 2019, Sensuke Ogoshi *et al.* reported that they successfully constructed the four-membered carbocyclic skeleton employing NHC **C41**-Ni cooperative catalysis through [2 + 2] annulation between 1,3-enynes and  $\alpha,\beta$ -unsaturated carbonyls **138**, leading to a series of enantioenriched cyclobutenes **139** (Scheme 45).<sup>93</sup>



Scheme 45 The synthesis of cyclobutenes.



Fig. 14 Several natural products with sulfur-containing heterocyclic skeletons.



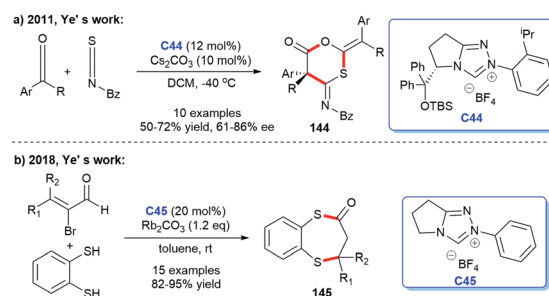
Scheme 46 The synthesis of thiazinones.

## 2.11 Applications in the synthesis of sulfur heterocycles

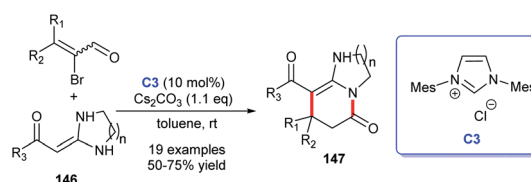
Organic sulfur-containing heterocyclic compounds exist widely in nature. They are the core fragments of many drugs and natural alkaloids, which show good biological activities in many aspects. Moreover, sulfur-containing heterocyclic compounds are broadly used in medicines, pesticides, dyes and other fields, such as the antipsychotic drug promazine, the antibacterial agent Kathon, sulfur dyes and so on (Fig. 14). Therefore, the research on sulfur-containing heterocyclic compounds has become an important part of organic chemistry. In recent years, as more and more excellent catalytic properties of NHCs have been discovered, synthetic methods of sulfur-containing heterocycles catalyzed by NHCs have also been developed.

Owing to its remarkable biological activities and challenging structure, the synthesis of thiazinone skeleton is a research hotspot in the field of NHC catalysis.

In 2018, imidazo fused thiazinones **141** was synthesized by Du *et al.* In the presence of NHC **C42** generated from the thiazolium, alkynyl acids were converted into alkynyl acylazolium intermediates, then reacted with mercaptoimidazoles **140** in

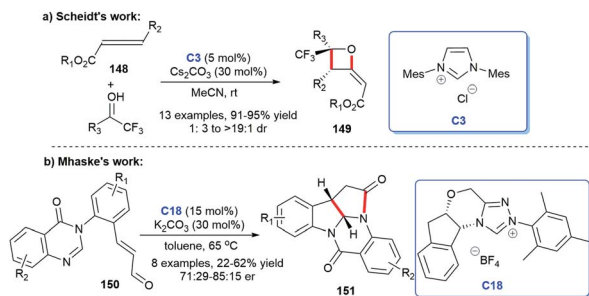


Scheme 47 The synthesis of thiazinones.



Scheme 48 The synthesis of imidazo-fused heterocyclic compounds.





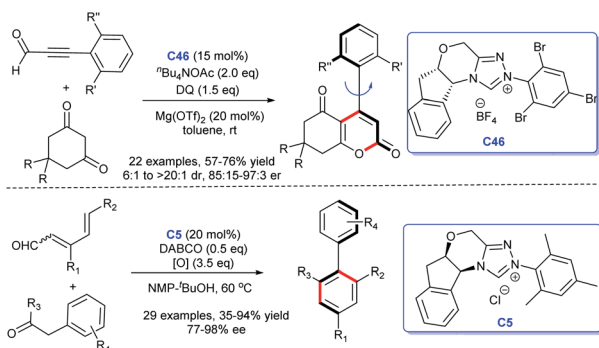
Scheme 49 The synthesis of heterocyclic compounds.

*situ* to form C–S bond, leading to the corresponding [3 + 3] cycloadducts (Scheme 46a).<sup>94</sup> In 2019, Biju and co-workers reported their [3 + 3] cycloaddition between enals and thioamides **142** catalyzed by chiral NHC **C21**, resulting in a variety of functionalized thiazinones **143** with high stereoselectivities (Scheme 46b).<sup>95</sup> Thirty-two reactions were carried out to prove the good functional group applicability.

Ye's team has also made great progress in the establishment of NHC-catalyzed sulfur-containing heterocyclic skeletons. In 2011, Ye's group reported that they completed the asymmetric synthesis of 1,3-oxathian-6-ones **144** catalyzed by chiral NHC *via* [2 + 2 + 2] cycloadditions of isothiocyanates and two molecules of ketones.<sup>96</sup> In this study, NHC generated from **C44** was proven to be the effective catalyst (Scheme 47a). In 2018, the same group developed an NHC **C45**-catalyzed [3 + 4] annulation reaction, affording benzo[1,5]di-thiepin-2-ones **145** with 1,2-benzenedithiol and bromoenals as starting materials (Scheme 47b).<sup>97</sup> This reaction provided ideas for the establishment of seven-membered sulfur-containing heterocycles.

## 2.12 Applications in the synthesis of other heterocyclic compounds

In 2011, Yao and co-workers disclosed the construction of imidazo-fused heterocyclic skeleton, which was catalyzed by NHC **C3** and a privileged motif in diverse bioactive molecules.<sup>98</sup> They employed bromoenals and HKAs as substrates, under the catalysis of NHC, to form C–C and C–N bond, leading to the acquisition of imidazo(pyrido)[1,2-*a*]pyridine and tetrahydrobenzo[*b*]imidazo[1,2,3-*ij*][1,8] naphthyridine **147** (Scheme 48).<sup>99</sup>



Scheme 50 The synthesis of atroposelective arenes.

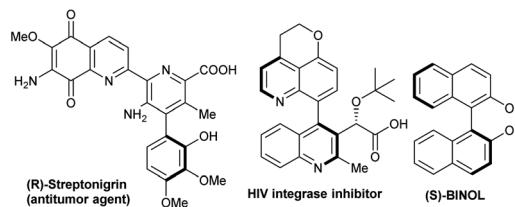


Fig. 15 Several bioactive axially chiral biaryl skeletons.

In 2018, Scheidt *et al.* developed an asymmetric NHC-catalyzed [2 + 2] cycloaddition strategy for multi-substituted oxetanes **149** (Scheme 49a).<sup>100</sup> In 2019, Jin *et al.* obtained challenging chromeno[4,3-*b*]pyrrole derivatives containing four chiral centers with the catalysis of chiral NHC.<sup>101</sup> In the same year, Mhaske and coworkers prepared deoxy-cruciferane alkaloid scaffold **151**, which was a class of biologically active skeletons, *via* intramolecular annulation reaction catalyzed by NHC **C18** (Scheme 49b).<sup>102</sup>

Axially chiral biaryl skeletons have emerged as indispensable structures in organic chemistry.<sup>103</sup> They are found in a lot of natural products, drugs, catalysts, and some important chiral ligands (Fig. 15).<sup>104</sup> As a class of smart catalysts, chiral NHC catalyzed annulation reactions provide an efficient way for the construction of axially chiral biaryl scaffolds.<sup>105</sup>

In 2018, Wang's group built axially chiral molecule scaffolds with the catalysis of NHC.<sup>106</sup> In 2019, Zhu *et al.* developed a chiral NHC **C46**-catalyzed asymmetric [4 + 2] cycloaddition, resulting in a series of atroposelective arene.<sup>107</sup> In the same year, Shi *et al.* completed the efficient synthesis of biaryl atropisomers under the cooperative catalysis of NHC **C5** and Pd (Scheme 50).<sup>108</sup> These approaches open a new avenue for the diverse synthesis of axially chiral molecule scaffolds.

## 3 Conclusions and outlook

In summary, we have reviewed the general protocols for synthesizing carbocycles and heterocycles containing indoles, pyrazoles, pyrroles, quinolines, lactams, lactones and other cyclic compounds assisted by NHCs from the perspective of cycloaddition reactions, wishing to advertise the readers of achievements and challenges that lie ahead in the field of NHC-mediated the construction of bioactive skeletons. In these studies, NHCs catalyze simple molecules to build complex heterocyclic skeletons, which is determined by the attractive features of NHCs. The current applications of smart NHCs in the catalytic synthesis of the organic framework have already unleashed a significant impact on the field of organic chemistry and medicinal chemistry. In general, high-efficient atomic utilization, mild reaction conditions, good functional group compatibility, and excellent stereoselectivity enable this NHC catalysis strategy to be applied in more aspects. Based on these outstanding advances, new challenges are likely to be conquered in the future.

From the perspective of this review, we proposed several challenging aspects, and the suggested directions for the future investigation in this area mainly include the following:





(i) The synthetic approaches of NHC catalysts are relatively miscellaneous, meanwhile, the low yield is the direction, which is urgently needed to be settled in the future.

(ii) The development of a completely innovative NHC catalyst may bring a more concise and efficient approach for the synthesis of these complex chiral cyclic skeletons;

(iii) The mechanism of NHC catalysis is expected to be further clarified, then promoting the production of chiral bioactive molecules on an industrial scale, making greater contributions to the efficient synthesis of bioactive natural products and drugs;

(iv) In addition to the applications highlighted in this review, the applications of NHCs in other fields will also be increasingly developed.

(v) Based on these previous studies, more simple and outstanding organic catalysts will be disclosed for assembling biologically active organic cyclic frameworks;

NHCs provide opportunities to create complex biologically active scaffolds from simple molecules. It is reasonable to believe that the chemistry of NHCs will continue to flourish and will lead to amazing results.

## Conflicts of interest

The authors confirm that this article content has no conflicts of interest.

## Acknowledgements

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