SCIENCE CHINA
Chemistry

•REVIEWS•

February 2022 Vol.65 No.2: 210–223
https://doi.org/10.1007/s11426-021-1133-5

N-heterocyclic carbene-catalyzed arene formation reactions

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Received August 17, 2021; accepted October 11, 2021; published online December 8, 2021

N-heterocyclic carbene-catalyzed reactions for the formation of aromatic compounds are reviewed. The reactions are subdivided into 4 types based on their activation modes. A brief summary on the achievements and the challenges remaining in *N*-heterocyclic carbene (NHC)-catalyzed arene construction processes is provided at the end of this review. An outlook into the future research direction within this field is also given based on our own opinion and knowledge on the trends of the development of NHC organocatalysis.

***N*-heterocyclic carbene, arene construction, cycloaddition, organocatalysis**

Citation: Li T, Jin Z, Chi YR. *N*-heterocyclic carbene-catalyzed arene formation reactions. *Sci China Chem*, 2022, 65: 210–223, https://doi.org/10.1007/s11426-021-1133-5

1 Introduction

Aromatic scaffolds such as benzene, pyridine, pyrrole and others are fundamental units in various natural products and functional molecules. Nearly 90% of the best selling drugs and over 90% of the top sale agrichemicals contain at least one aromatic group (Figure 1). Therefore, the development of efficient methods for the preparations of various molecules containing one or more aromatic units is of fundamental significance in organic chemistry.

Arene formation reactions represent one class of the most direct and efficient strategies for the establishment of aromatic structures [1]. Traditionally, arene construction reactions are realized through transition-metal-catalyzed dehydrogenation of (saturated) ring systems [1c,1d], ring-closing metathesis [1a], Diels-Alder reactions [1e], and cycloaddition reactions [1b]. Recently, organocatalytic strategies have been developed for the synthesis of arene molecules and have soon attracted much interest since they avoid the use of toxic reagents, harsh conditions or expensive ligands/catalysts that had frequently been involved in the conventional arene synthesis [2]. Among the diverse organic catalysts that have been used for green and sustainable organic synthesis, *N*-heterocyclic carbenes (NHCs) are one class of the most extensively explored and efficient ones that can promote a variety of transformations for the synthesis of numerous functional molecules [3]. Although NHC organocatalysis has been developed for more than half a century, the first arene construction process promoted by NHC catalysts was reported in 2014 [4]. To date, a number of arene construction reactions have been realized through different activation modes with NHC organocatalysis. Poly-substituted arene molecules with rich functionality can be afforded in both non-chiral and enantioselective fashion. However, compared with the conventional cycloaddition reactions with NHC organocatalysis, the reaction modes and mechanisms involved in the NHC-catalyzed arene construction processes are relatively limited, with great potentials leaving to be explored.

Therefore, we consider it is the right time to provide a

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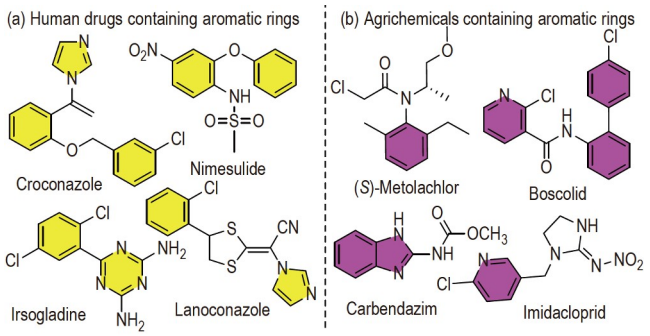


Figure 1 Examples of commercial drugs and agrichemicals containing aromatic groups (color online).

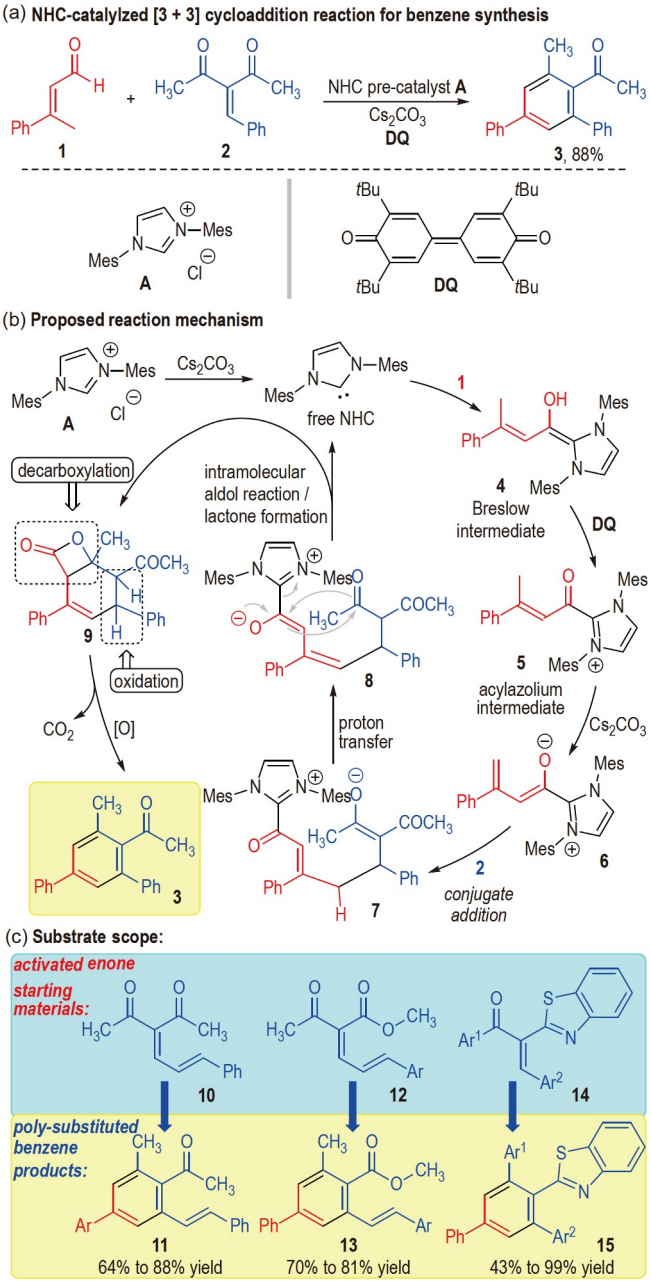
systematic summary on this highly active research field in order to clarify the future research direction for novel arene construction processes. We divided the main content of this review into 4 sections based on the activation modes involved in the NHC-catalyzed arene construction transformations: (1) arene constructions *via* dienolate activation reactions; (2) arene constructions *via* lowest unoccupied molecular orbital (LUMO) activation reactions; (3) arene construction *via* umpolung activation reactions; (4) arene construction *via* NHC-promoted hydrolysis of cyclobutenes. A brief summary on the achievements and the challenges remaining in NHC-catalyzed arene construction processes is provided at the end of this review. An outlook into the future research direction within this field is also given based on our own opinion and knowledge on the trends of the development of NHC organocatalysis.

2 NHC-catalyzed arene constructions *via* dienolate activation reactions

2.1 [3 + 3] Cycloaddition reactions for aromatic compound formation

The first NHC-catalyzed arene formation reaction was reported in 2014, when Chi and co-workers [4] disclosed an [3 + 3] cycloaddition reaction between β-methyl enal **1** and activated α,β-unsaturated ketone **2** (Scheme 1). Imidazolium-derived NHC pre-catalyst **A** is used in the presence of stoichiometric amounts of the basic additive (Cs_2CO_3) and the **DQ** oxidant to promote this aromatization process and gives the poly-substituted benzene product **3** in a 88% yield (Scheme 1a).

The reaction is believed to go through a cascade cycloaddition/decarboxylation/aromatization multi-step process (Scheme 1b). The enal substrate **1** can be attacked by the free imidazolium NHC catalyst generated from **A** under basic condition to give the Breslow intermediate **4**, which is readily oxidized by the **DQ** oxidant to give the acylazolium intermediate **5**. Intermediate **5** can be deprotonated by external bases to generate the azolium dienolate intermediate **6**.



Scheme 1 NHC-catalyzed benzene formation *via* [3 + 3] cyclization of enal and enone substrates [4] (color online).

The conjugate addition between the dienolate **6** and the activated enone substrate **2** leads to the formation of the adduct **7**, which can be isomerized to the azolium enolate **8** *via* intramolecular proton transfer processes. An intramolecular aldol reaction/lactone formation cascade process within the intermediate **8** leads to the formation of the fused bicyclic intermediate **9** with the free NHC catalyst liberated for additional catalytic cycles. Intermediate **9** is not stable in the catalytic system and can go through a decarboxylation/oxidative aromatization cascade process to afford the final product of the poly-substituted benzene molecule **3**.

This protocol has proven to be general to activated enone

substrates with various substitution patterns (Scheme 1c) [5]. For instance, the β-benzene group on the enone substrate **2** can be switched to a styryl group (to afford **10**), with the substituted 1,2-diphenylethene products **11** afforded in 64% to 88% yields. The α-acyl substituent of **10** can be replaced by methoxylcarbonyl group (to afford **12**). We also demonstrate that an α-benzothiazole substituted enone substrate **14** can be used as a suitable reactant for this benzene formation process, with the corresponding 2-phenylbenzothiazole products **15** obtained in moderate to excellent isolated yields.

Carboxylic esters have proven to be versatile substrates for the generation of acylazolium intermediates [6]. Therefore, the β-methyl-α,β-unsaturated carboxylic ester **16** can be used as a suitable starting material to react with the activated enone **2** for the synthesis of the poly-substituted benzene product **3** (Scheme 2) [7].

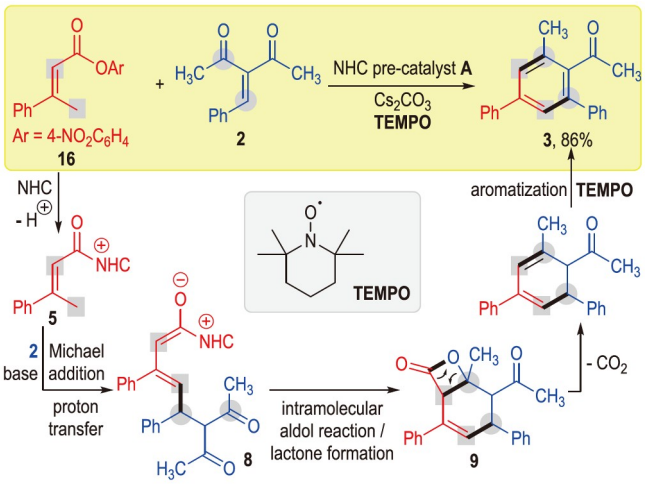
It is worth to note that although the generation of the acylazolium intermediate **5** does not need the participation of external oxidants, the aromatization step after the decarboxylation of the bicyclic intermediate **9** is an oxidative process. Therefore, diverse oxidative additives have been examined and 2,2,6,6-tetramethylpiperidinooxy (TEMPO) was found as the optimal oxidant to enhance the generation of the desired benzene product **3** with a good isolated yield.

2.2 [4 + 2] Cycloaddition reactions for aromatic compound formation

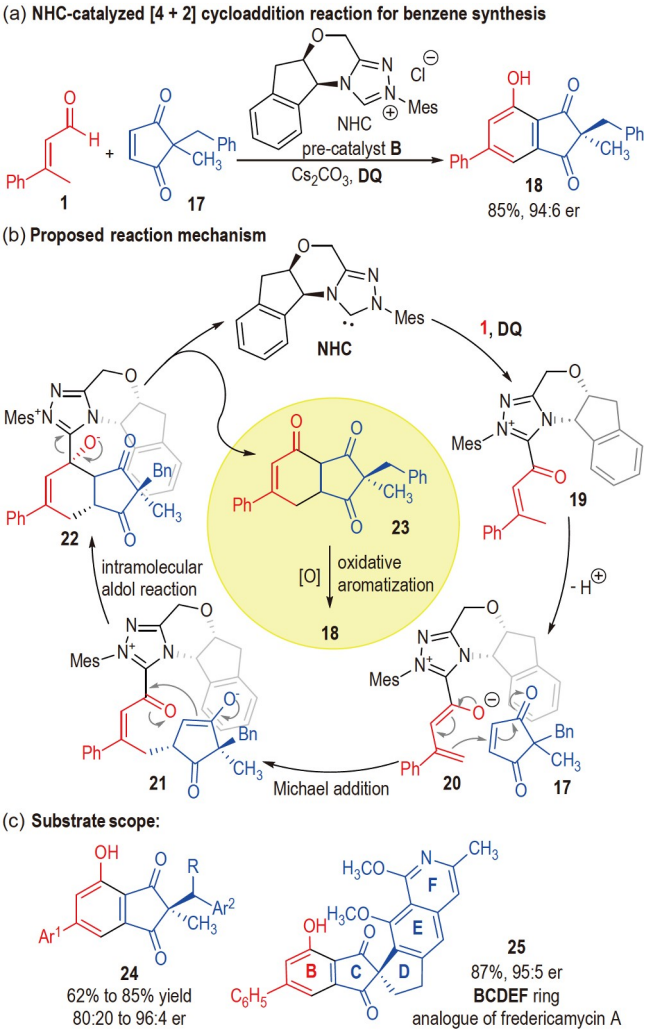
NHC-catalyzed [4 + 2] cycloaddition reactions of β-methyl-α,β-unsaturated enals with 2-membered reactants have been developed as robust tools for the construction of 6-membered ring structures. It can also be used as efficient protocols for the preparation of various benzene molecules.

In 2019, Chi and co-workers [8] disclosed an NHC-catalyzed desymmetrization reaction of cyclopentenedione **17** with enal substrate **1** *via* an asymmetric [4 + 2] cycloaddition process (Scheme 3). A multi-functionalized benzene skeleton is constructed through this reaction, with the chiral group substituted phenol product **18** afforded in a good yield and optical purity (Scheme 3a).

Mechanistically, a chiral acylazolium intermediate **19** can be generated from the oxidative reaction between the enal substrate **1** and the free NHC catalyzed derived from **B** in the presence of the **DQ** oxidant. After deprotonation, the dienolate intermediate **20** can react with the pro-chiral cyclopentenedione **17** in stereoselective fashion to give the chiral adduct intermediate **21**, which can go through an intramolecular aldol reaction to afford the intermediate **22**. Elimination of the NHC catalyst leads to the formation of the multi-ketone molecule **23**, which is not stable under the basic and oxidative catalytic condition and will be promptly transformed to the aromatic product **18** with retention of the optical purity of the previous intermediates.



Scheme 2 NHC-catalyzed benzene formation *via* [3 + 3] cyclization of carboxylic ester and enone substrates [7] (color online).



Scheme 3 NHC-catalyzed desymmetrization [4 + 2] cyclization for phenol synthesis [8] (color online).

This enantioselective desymmetrization process can tolerate various substitution patterns on both of the enal and the

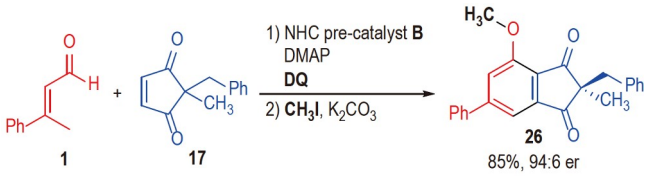
diketone substrates (Scheme 3c). The multi-functionalized chiral phenol products **24** can be afforded in generally moderate to good yields and optical purities. Interestingly, an analogue of the natural product fredericamycin A (**25**) can be obtained through our approach from known starting materials with an excellent enantioselectivity.

Soon later, Wang and co-workers [9] reported a similar protocol for the desymmetrization of the pro-chiral cyclopentenedione **17** (Scheme 4). In their protocols the phenol OH group is further methylated by CH_3I under basic condition after the NHC-catalyzed benzene formation process. The one-pot multi-step cascade reactions can finally give the poly-substituted anisole products **26** in a moderate yield and excellent enantioselectivity.

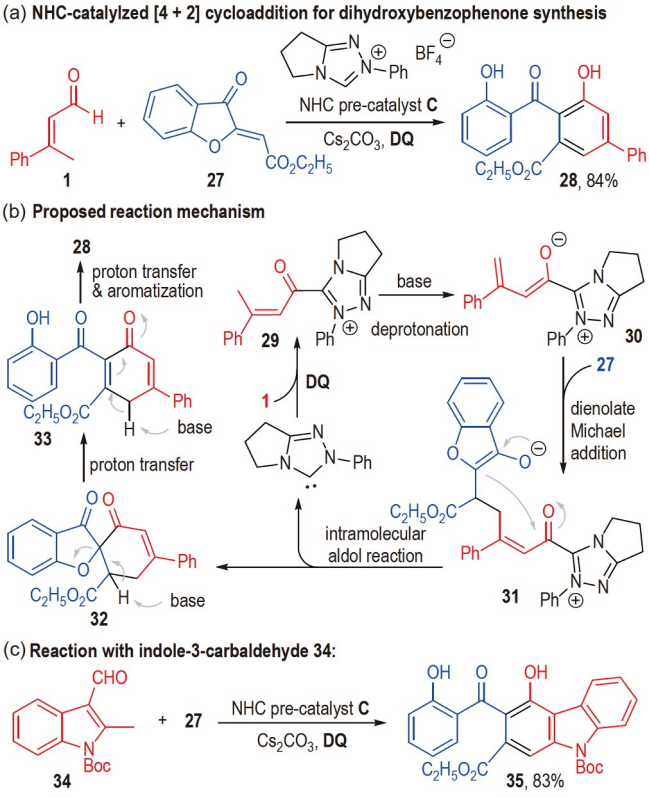
Ye and co-workers [10] reported a facile synthesis of aromatic dihydroxybenzophenones *via* an NHC-catalyzed [4 + 2] cycloaddition reaction of the enal substrate **1** and the aurone **27** (Scheme 5a). The dihydroxybenzophenone product **28** was afforded in 84% yield with the catalysis of the NHC catalyst **C** in the presence of a stoichiometric amount of a basic additive and the **DQ** oxidant.

The reaction is believed to go through a cascade dienolate Michael addition/intramolecular aldol reaction/aromatization process (Scheme 5b). The oxidative addition of the NHC catalyst to the enal substrate **1** gives the azolium dienolate intermediate **30**, which can react with the aurone **27** to afford the adduct **31**. The intermediate **31** can be cyclized *via* an intramolecular aldol reaction and gives the spirocyclic intermediate **32** with elimination of the free NHC catalyst. The spirocycle of the intermediate **32** is not stable under basic conditions and can isomerize to ketone **33** *via* proton transfer process. Aromatization process within the ketone molecule **33** leads to the formation of the final product of the dihydroxybenzophenone **28**.

It is worth noting that the enal substrate **1** can be replaced with the 2-methylindole-3-carbaldehyde **34** to react with the urone **27** under the same reaction conditions (Scheme 5c). The dihydroxybenzophenone product **35** bearing multiple fused ring structures can be obtained in a good isolated yield.



Scheme 4 NHC-catalyzed one-pot benzene formation/phenol methylation reaction [9] (color online).



Scheme 5 NHC-catalyzed dihydroxybenzophenone formation *via* [4 + 2] cycloaddition reactions [10] (color online).

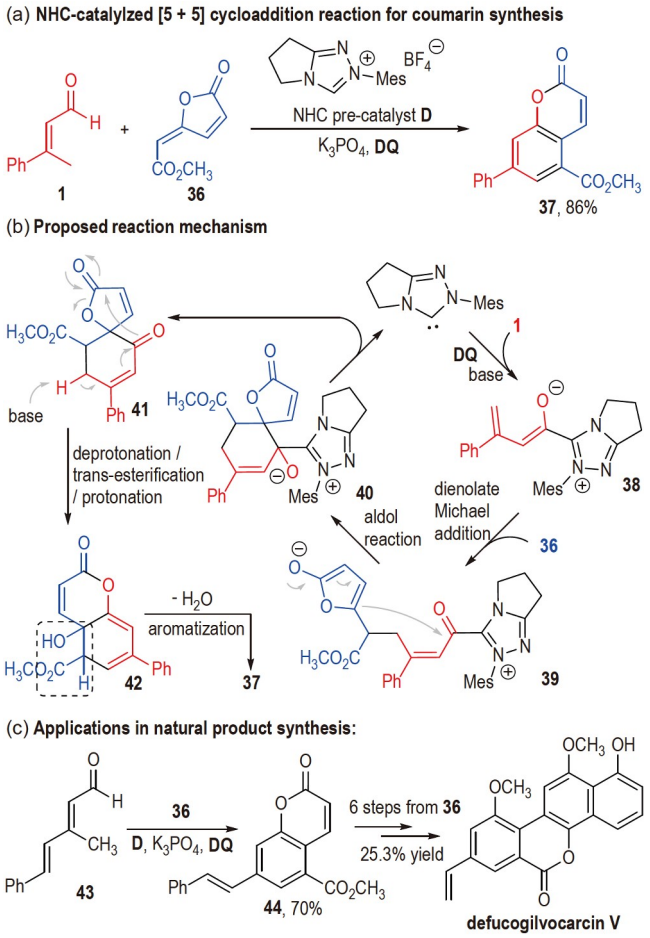
2.3 [5 + 5] Cycloaddition reactions for aromatic compound formation

Coumarins are interesting aromatic structures that are widely found as fragments in natural products. The synthesis of substituted coumarins has therefore attracted much interest.

In 2017, Chi and co-workers [11] used the furanone **36** to react with the enal substrate **1** in the formal [5 + 5] cycloaddition reaction for the synthesis of the substituted coumarin **37** (Scheme 6a).

The reaction is initiated through a similar dienolate-activation of the enal substrate **1** with the NHC organic catalyst **D** under oxidative conditions (Scheme 6b). After the dienolate Michael addition of the intermediate **38** with the furanone **36**, the afforded adduct **39** can cyclize *via* an intramolecular aldol reaction to give the spiocyclic azolium intermediate **40**. The spiro lactone intermediate **41** can be generated on the elimination of the free NHC catalyst, which can then go through an intramolecular transesterification process to give the fused lactone **42**. A dehydrative aromatization reaction within the lactone **42** leads to the formation of the desired coumarin product **37**.

Interestingly, this formal [5 + 5] coumarine formation strategy can be used as key steps in the total synthesis of various natural products (Scheme 6c). For instance, the defucogilvocarcin V can be obtained from the dienal substrate **43** *via* a 6-step synthetic protocol in a 25.3% overall yield, with the currently developed [5 + 5] aromatization reaction used as the key step for the preparation of the functionalized coumarin intermediate **44**.



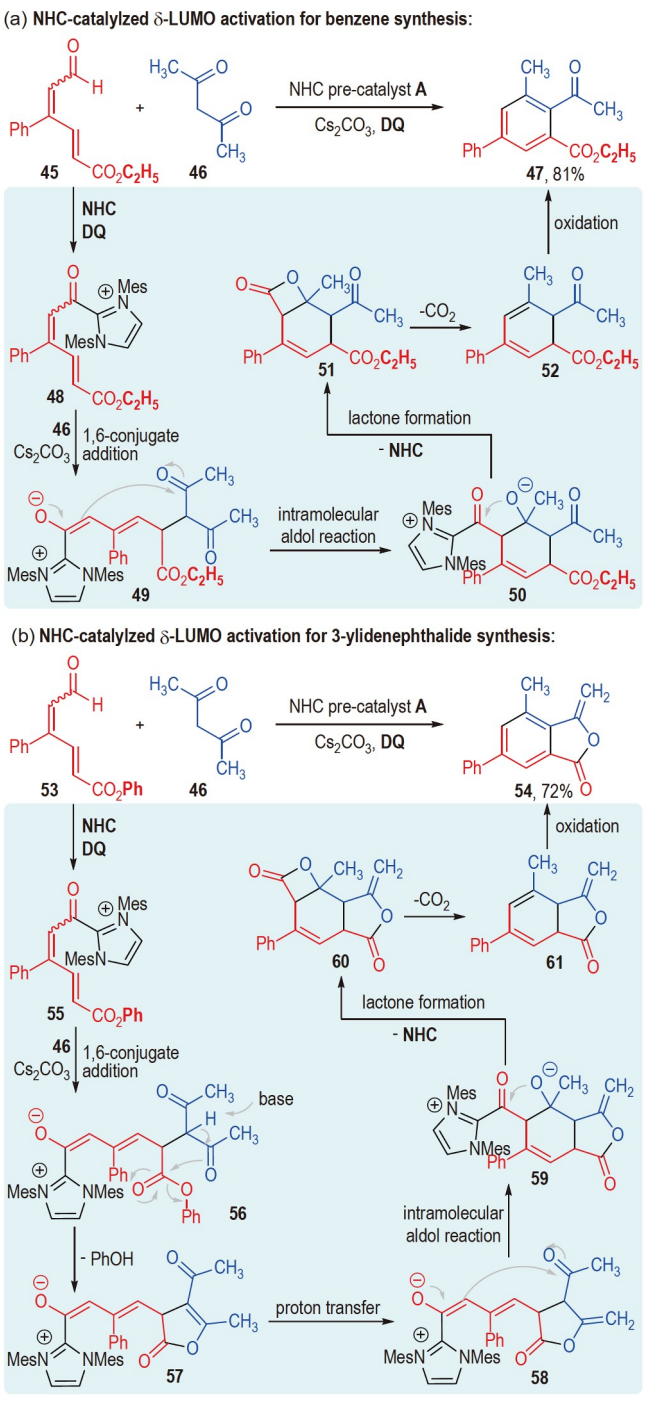
Scheme 6 NHC-catalyzed coumarin synthesis *via* [5 + 5] cycloaddition reaction [11] (color online).

3 NHC-catalyzed arene constructions *via* LUMO activation reactions

3.1 NHC-catalyzed arene constructions *via* δ-LUMO activation of α,β,γ,δ-unsaturated aldehydes

Besides the NHC-catalyzed nucleophilic activation of the enal substrates *via* azolium dienolate formation protocols, arene molecules can also be obtained *via* electrophilic lowest unoccupied molecular orbital (LUMO) activation of enals with NHC organocatalysis.

The seminal report on benzene formation reactions through NHC-catalyzed LUMO activation of enal substrates came from Chi's group in 2015 [12]. The δ-carbon of the conjugated α,β,γ,δ-unsaturated dienal **45** can be activated as an electrophile by an NHC catalyst to react with the 1,3-diketon **46** under oxidative conditions to give the poly-substituted benzene product **47** in 81% yield (Scheme 7a). The reaction is initiated by the 1,6-conjugate addition of the nucleophilic substrate **46** to the δ-carbon of the α,β,γ,δ-unsaturated acylazolium intermediate **48**. The adduct **49** can be cyclized through an intramolecular aldol reaction to afford



Scheme 7 NHC-catalyzed benzene synthesis *via* δ-LUMO activation of α,β,γ,δ-unsaturated aldehydes [12] (color online).

50, which can give the fused β-lactone intermediate **51** with elimination of the free NHC catalyst. Decarboxylation of the intermediate **51** leads to the formation of **52**, which is very unstable under the catalytic conditions and is tentative to be oxidized to give the aromatized product **47** in good yield.

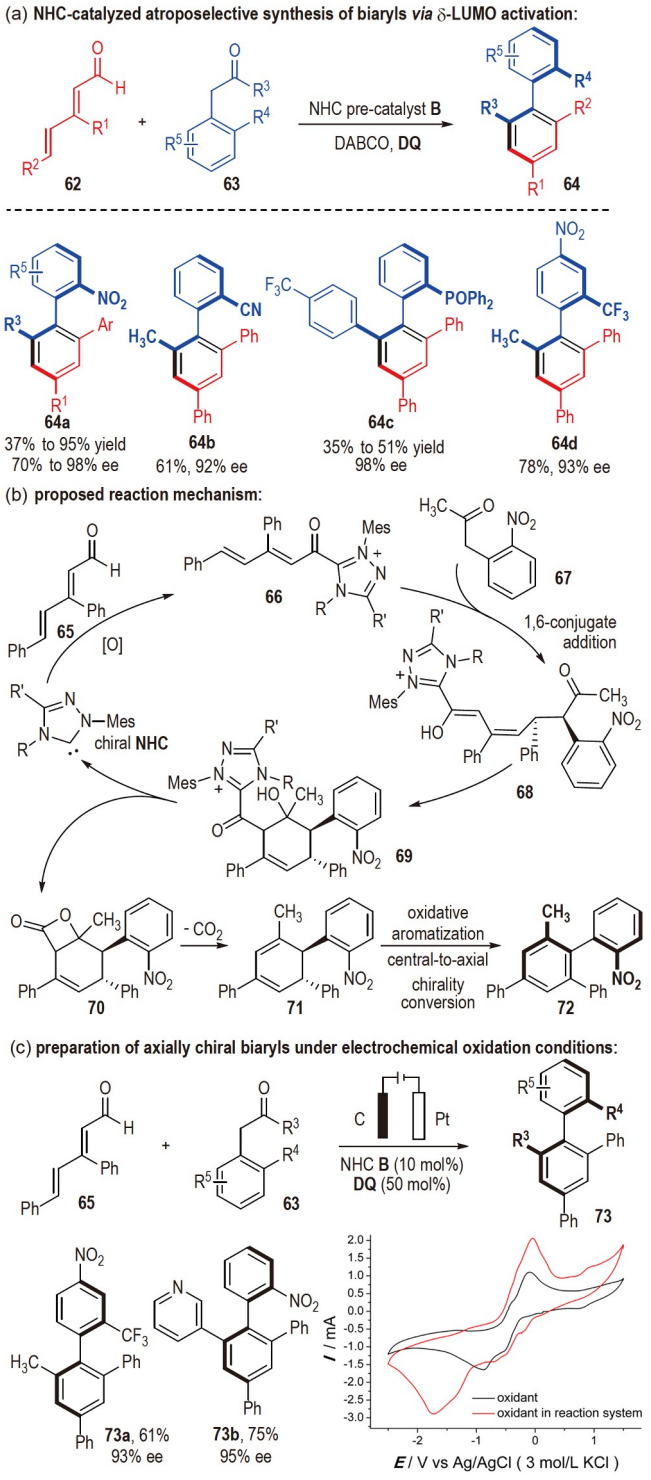
Interestingly, switching the ethyl group of the carboxylic ester moiety of the dienal substrate **45** to a phenyl group (to

afford **53**) leads to the formation of a different aromatic product **54** (Scheme 7b). A similar 1,6-conjugate addition reaction between the α,β,γ,δ-unsaturated acylazolium intermediate **55** and the 1,3-diketon **46** gives the adduct **56**, which can then go through an intramolecular *trans*-esterification reaction to afford the lactone intermediate **57**. The intermediate **57** can isomerize to **58** *via* a proton transfer process and then cyclize *via* an intramolecular aldol condensation to give the fused cyclohexene intermediate **59**. A β-lactone formation process within the intermediate **59** leads to **60** with elimination of the free NHC catalyst. Finally, the target product of the 3-ylidenephthalide **54** can be afforded through a spontaneous decarboxylation/aromatization process from **60** without any isolable intermediate observed.

Axially chiral biaryls are significant aromatic molecules with interesting applications in both synthetic and medicinal chemistry. The NHC-catalyzed arene formation protocols have provided extensive opportunities for the asymmetric catalytic preparations of atropisomeric byaryl products. In 2019, Zhu and co-workers [13] were able to synthesize a variety of optically enriched multi-functional biaryls bearing stereogenic axes through chiral NHC-catalyzed benzene formation reactions (Scheme 8). The δ-carbon of the α,β,γ,δ-unsaturated dienal substrate **62** is activated as an electrophile to react with the nucleophilic benzyl ketone **63** under the catalysis of the NHC catalyst **B** in presence of the **DQ** oxidant (Scheme 8a). Various substituents are installed on the 2-positions of the benzene rings of the benzyl ketone **63** to provide steric hindrance during the atroposelective benzene formation reaction and block the rotation of two benzene groups around the $C(sp^2)$–$C(sp^2)$ σ-bond in the biaryl product **64**. Diverse functional groups are well tolerated on both of the reaction substrates, with the target atropisomeric biaryl products afforded in generally good to excellent yields and enantioselectivities (Scheme 8a, **64a** to **64d**).

From a mechanistic view, the α,β,γ,δ-unsaturated acylazolium intermediate **66** that is generated from the oxidative addition of the dienal **65** and the chiral free NHC catalyst can react with the 2′-NO_2 phenyl acetone **67** *via* an asymmetric 1,6-conjugate addition process to give the adduct **68** bearing 2 chiral centers in enantioselective fashion (Scheme 8b). Aldol condensation within the adduct **68** leads to the formation of the chiral cyclohexene intermediate **69**, which can be cyclized *via* an intramolecular lactone formation to afford the chiral bicyclic β-lactone intermediate **70** with liberation of the free NHC catalyst. A spontaneous cascade decarboxylation/oxidative aromatization process takes place within the intermediate **70** and finally leads to the formation of the atropisomeric biaryl product **72** in an excellent enantioselectivity *via* a central-to-axial chirality conversion process.

Noteworthily, this atroposelective synthesis of biaryl molecules promoted by chiral NHCs can be carried out under electrochemical redox conditions (Scheme 8c). With a sub-



Scheme 8 NHC-catalyzed dihydroxybenzophenone formation *via* [4 + 2] cycloaddition reactions [13] (color online).

stoichiometric amount of the **DQ** oxidant used, the NHC-catalyzed atroposelective oxidative benzene formation reaction can be smoothly carried out in an electrochemical system consisting of Pt/C electrodes with the target products (*e.g.*, **73a**, **73b**) afforded in moderate yields with excellent optical purities.

3.2 NHC-catalyzed arene constructions *via* β-LUMO activation of α,β-unsaturated aldehydes

Poly-substituted benzene molecules can also be obtained *via* LUMO activation strategies with α,β-unsaturated enal substrates [14].

In 2016, Wang and co-workers [15] reported a [2 + 4] benzannulation reaction between the α,β-unsaturated enal **74** and the α-cyano-β-methylenone **75** (Scheme 9a). Poly-substituted benzonitrile **76** can be afforded in 84% yield through this transformation in the presence of a stoichiometric amount of a base and the **DQ** oxidant.

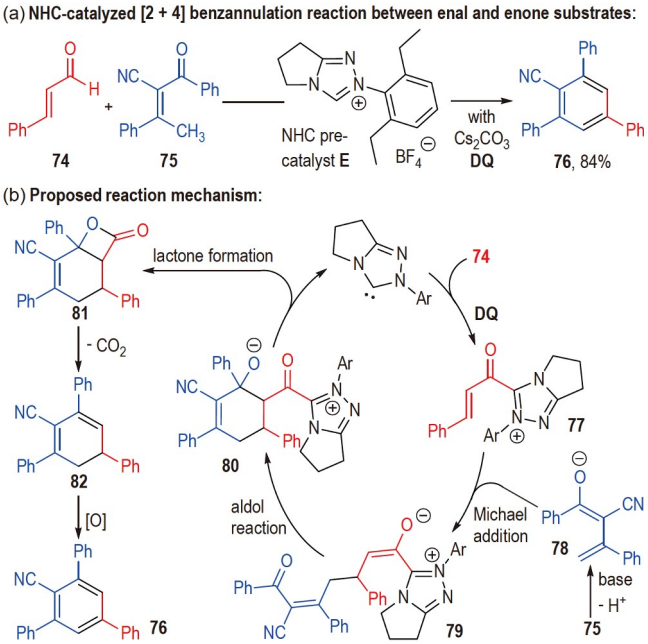
The reaction is initiated by the oxidative addition of the free NHC organic catalyst to the enal substrate **74** (Scheme 9b). Then the afforded acylazolium intermediate **77** can react with the deprotonated dienolated **78** *via* a Michael addition process to give the adduct **79**, which can then be cyclized through an intramolecular aldol condensation to give the cyclohexene intermediate **80**. A β-lactone formation process within **80** liberates the NHC catalyst and gives the bicyclic intermediate **81**, which is tentative to go through a cascade decarboxylation/oxidative aromatization process to afford the final benzonitrile product **76**.

Almost at the same time, Ye and co-workers [16] were able to realize the same [2 + 4] benzannulation reaction between the enal **74** and the enone **75** under the catalysis of the NHC catalyst **A**, with the same benzonitrile product **76** afforded in 89% yield.

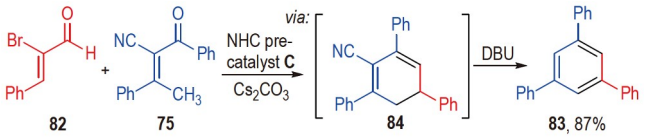
They can also facilitate the benzene formation process between the α-bromoenal substrate **82** and the α-cyano-β-methylenone **75** with the catalysis of the NHC pre-catalyst **C** in the presence of stoichiometric amounts of two strong bases (Scheme 10) [17]. Tri-aryl substituted benzene **83** can be afforded as the final product in 87% yield through a one-pot cascade process. In contrast to the benzonitrile formation reactions, the aromatization process in this transformation is realized *via* a DBU-promoted HCN elimination reaction after formation of the key intermediate **84**. It is also worth to note that the intermediate **84** can be isolated in up to 94% yield without the addition of the DBU into the catalytic system.

In 2018, Fu, Huang and co-workers [18] disclosed an NHC-catalyzed [2 + 4] benzannulation reaction between α,β-unsaturated enal **74** and the indole-derived α-ketoester **85** (Scheme 11). The fused aromatic multi-cyclic carbazole product **86** can be efficiently prepared through this process under the catalysis of the NHC catalyst **D** in the presence of a stoichiometric amount of the DBU and the **DQ** oxidant.

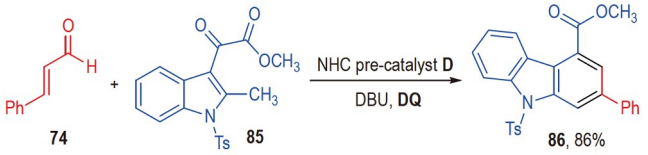
Very recently, Ye and co-workers [19] has made great success in the atroposelective [2 + 4] benzannulation reaction using the enal **74** with the catalysis of a chiral NHC under oxidative conditions (Scheme 12). A modified heteroaromatic aldehyde **87** bearing a 2-(2′-bromobenzyl) group



Scheme 9 NHC-catalyzed [2 + 4] benzannulation reaction between enal and enone substrates [15] (color online).



Scheme 10 NHC-catalyzed [2 + 4] benzannulation reaction between α-bromoenal and enone substrates [17] (color online).



Scheme 11 NHC-catalyzed [2 + 4] benzannulation reaction between enal and indole-derived α-ketoester substrates [18] (color online).

is used as the nucleophile and the atropisomeric biaryl **88** is afforded as the final product *via* a cascade cycloaddition/decarboxylation/oxidative aromatization process. Chiral NHC pre-catalyst **F** is used as the reaction catalyst and a central-to-axial chirality conversion process is involved in the late aromatization step to efficiently afford the axially chiral biaryl products in good to excellent enantioselectivities (*e.g.*, **88a**, **88b**).

3.3 NHC-catalyzed arene constructions *via* β-LUMO activation of α,β-unsaturated esters

Carboxylic esters have proven to be versatile starting materials in NHC organocatalytic reactions. These can also be

used as building blocks in the construction of various aromatic molecules.

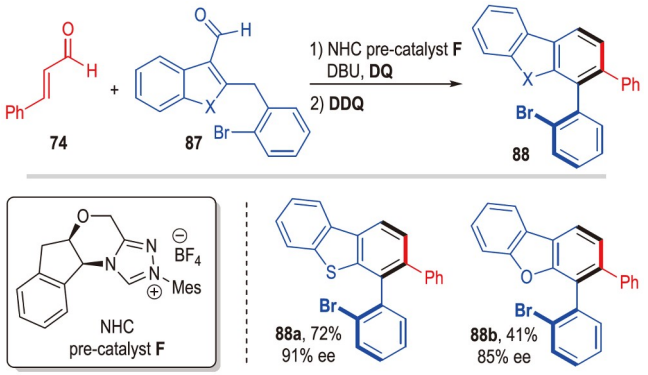
In 2015, Lupton and co-workers [20] reported an NHC-catalyzed redox isomerization of esters **89** to functionalized benzaldehydes **90** (Scheme 13a). The NHC pre-catalyst **A** or **G** used as the reaction catalyst, the poly-substituted benzaldehyde **91** can be afforded in moderate to good yields.

Mechanistically, the cinnamic acid enolate **89** can crack into the enolate anion **92** and the acylazolium intermediate **93** after the nucleophilic addition reaction with the NHC organic catalyst (Scheme 13b). A dienolate conjugate addition of the intermediate **92** to **93** gives the aldehyde intermediate **94**, which can then lead to the β-lactam product **96** *via* the formation of the bicyclic zwitterionic intermediate **95**. Zwitterionic intermediate **97** can be formed from the isomerization of the intermediate **95** or the reaction between the chiral NHC catalyst and the product **96**. The intramolecular proton transfer processes within the intermediate **97** gives the alcohol intermediate **98** bearing a delocalized negative charge. Dehydration reaction of **98** gives the Breslow intermediate **99**, which can finally lead to the formation of the target product **90** with the free NHC catalyst released for additional catalytic cycles.

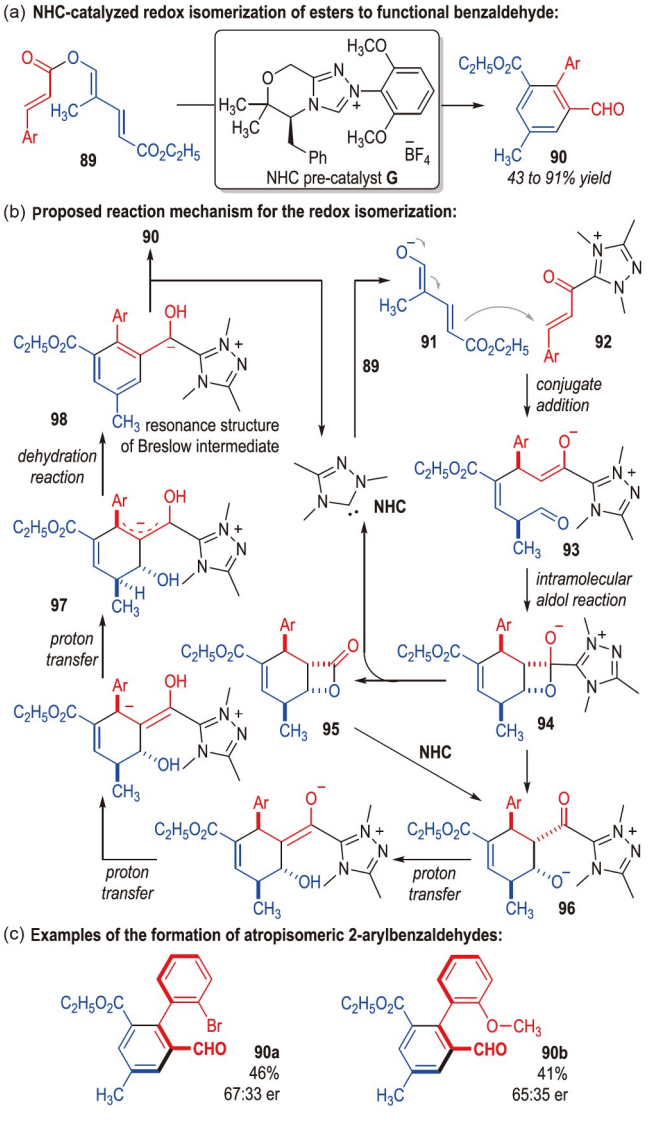
It is clear in the reaction mechanism that various central chiral intermediates can be formed with chiral NHC organic catalyst (*e.g.*, intermediates **94** to **97**) during the formation of the biaryl product **90**. In most cases, the chiral information of these intermediates is lost during the dehydrative aromatization step from the intermediate **97** to **98**. However, the central chiralities of these intermediates can be effectively transferred to the final products in the form of axially chirality. Two examples have been studied by the authors in the formation of axially chiral 2-arylbenzaldehydes (Scheme 13c, **90a**, **90b**). Noteworthily, this work represents the attempt for the asymmetric preparation of atropisomeric biaryl molecules *via* central-to-axial chirality conversion strategies in the field of NHC organocatalysis.

Propiolate **99** contains an activated alkyne group that can be used as a Michael acceptor to react with various nucleophiles to afford the cyclic products in both enantioselective and non-chiral fashion. In particular, propiolate **99** can be coupled with the imine substrate **100** under the catalysis of the NHC catalyst **D** through a one-pot cascade Michael addition/lactam formation/isomerization process (Scheme 14a) [21]. Multi-functionalized pyridine **101** is afforded as the final product in 83% yield. The acetylenic acylazolium intermediate **102** is generated during the reaction process and can react with the deprotonated imine **100** through a Michael addition to give the adduct **103** (Scheme 14b). The intramolecular lactam formation within the adduct **103** leads to the formation of intermediate **104**, which can finally give the desired pyridine product **101** through a thermodynamically favoured isomerization process.

The cascade pyridine formation protocol is proved to be versatile with a broad range of reaction substrates well tol-



Scheme 12 NHC-catalyzed atroposelective [2 + 4] benzannulation reaction between enal and arylaldehydes [19] (color online).

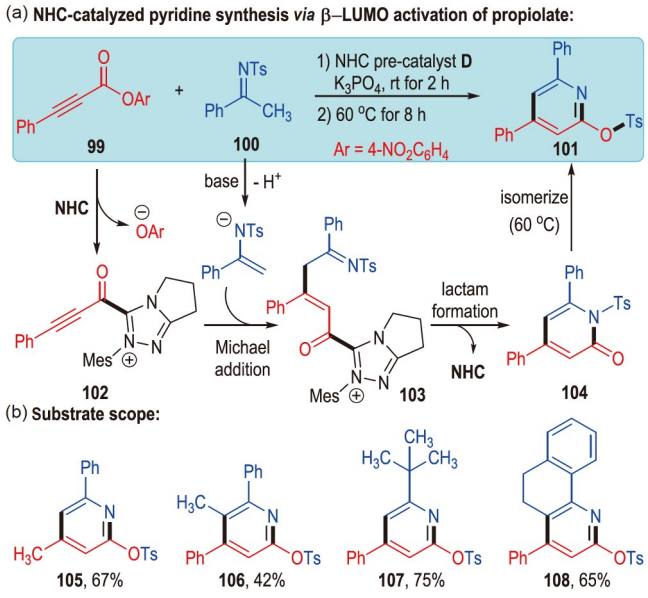


Scheme 13 NHC-catalyzed redox isomerization of esters to functionalized benzaldehydes [19] (color online).

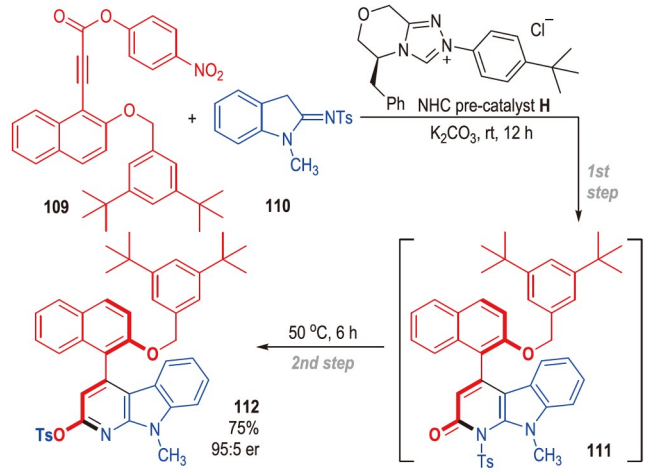
erated (Scheme 14c). For example, the phenyl group on the alkynyl aldehyde **99** can be switched to a methyl group, with the pyridine product **105** afforded in a moderate yield. The imine substrates can also tolerate various substitution patterns to give the multi-functional pyridine products in moderate to good yields (**106** to **108**).

Very recently, Du, Wei and co-workers [22] have achieved great success in the atroposelective preparation of axially chiral pyridine derivatives through an NHC-catalyzed [4 + 2] cycloaddition/isomerization cascade reaction (Scheme 15). The acetylenic ester substrate **109** bearing a bulky β-aryl group is used as the electrophile to react with the 2-sulfonamidoindoline **110**. NHC pre-catalyst **H** is used as the chiral promoter for this transformation in the presence of a stoichiometric amount of K_2CO_3. The reaction is believed to go through an atroposelective cycloaddition process, with the atropoisomeric lactam intermediate **111** afforded as the key reaction intermediate. Finally, the desired axially chiral pyridine product **112** can be obtained in a good yield with an excellent optical purity through heating the reaction mixture at 50 °C for 6 h.

It is worth noting that the authors have illustrated the origin of the stereoselectivity in this reaction *via* density functional theory (DFT) calculations. Non-covalent H-bonding interactions appeared to have great impact on the formation of the (*R*)-isomer of the afforded axially chiral pyridine molecules.



Scheme 14 NHC-catalyzed pyridine formation reaction with alkynyl carboxylic esters [21] (color online).



Scheme 15 NHC-catalyzed atropoenantioselective reaction of alkynyl carboxylic ester and 2-sulfonamidoindoline [22] (color online).

4 Arene construction *via* umpolung activation reactions

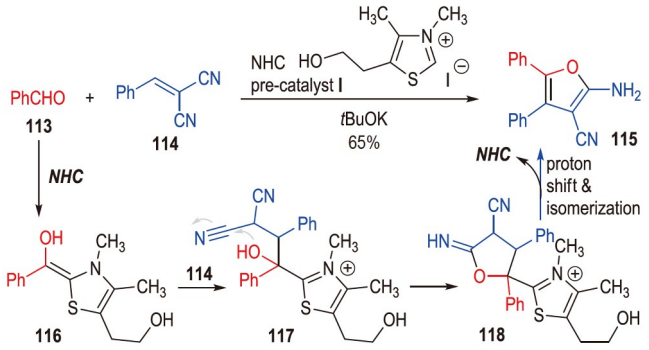
4.1 NHC-catalyzed arene constructions *via* a^1 to d^1 umpolung activation of aldehydes

The a^1 to d^1 umpolung activation represents the most basic activation mode in NHC organocatalytic reactions [23]. Benzoin and Stetter reactions are extensively explored *via* the umpolung activation of the carbonyl carbon of various aldehyde substrates [24]. Interestingly, the a^1 to d^1 umpolung activation can also be used for the synthesis of aromatic molecules. For instance, Stetter reactions can be applied to initiate various cascade processes to prepare diverse heteroaromatic compounds in one-pot operations.

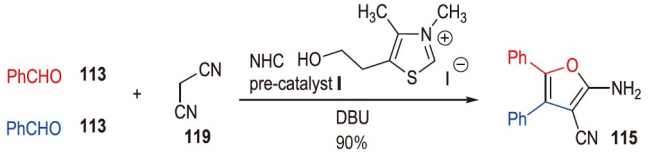
Early in the year of 2011, Hu, Ma and co-workers [25] reported a cascade Stetter-γ-ketonitrile cyclization reaction to prepare functionalized 2-aminofurans in a one-pot fashion (Scheme 16). With a sub-stoichiometric amount of the NHC pre-catalyst **I** used in the presence of the strong base of *t*BuOK, benzaldehyde **113** can be activated *via* the formation of the Breslow intermediate **116**. Michael addition reaction of **116** to the acylidenemalononitrile **114** gives the adduct **117**, which can be cyclized *via* an intramolecular nitrile addition reaction to afford the intermediate **118**. Finally, the target aminofuran product **115** can be obtained through an intramolecular proton transfer process with the liberation of the free NHC catalyst.

Almost at the same time, Yao and co-workers [26] realized the synthesis of the aminofuran **115** through a one-pot cascade process with the *in situ* formation of the acylidenemalononitrile **114** from the benzaldehyde **113** and the malononitrile **119** (Scheme 17). Pleasingly, the desired product **115** can be afforded in an excellent isolated yield with only a catalytic amount of the NHC pre-catalyst **I** used.

Recently, Tambar and co-worker [27] reported an NHC-catalyzed Hauser-Kraus annulation reaction for the synthesis of naphthalene-1,4-diol derivatives (Scheme 18). Ethyl phthaladehydate **120** was used to react with the acrylate **121** *via* a reductive [4 + 2] annulation reaction and gave the



Scheme 16 NHC-catalyzed cascade Stetter-γ-ketonitrile cyclization reaction for 2-aminofuran synthesis [25] (color online).



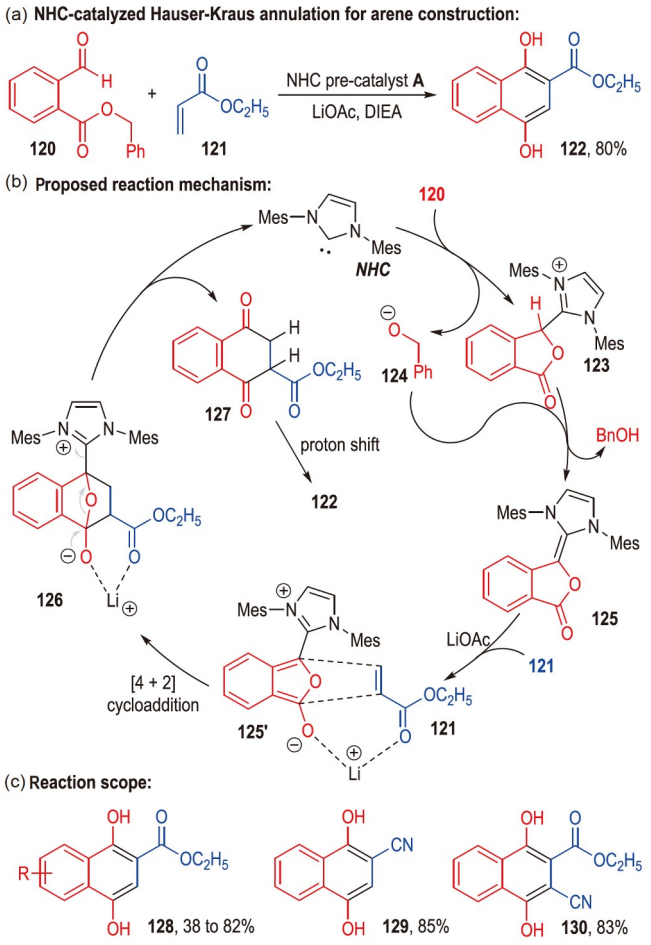
Scheme 17 NHC-catalyzed one-pot synthesis of 2-aminofuran with *in situ* formation of the acylidenemalononitrile substrate [26] (color online).

functionalized naphthalene-1,4-diol product **122** in 80% yield (Scheme 18a). The aldehyde group of the substrate **120** can be attacked by the NHC catalyst to give the zwitter ion **123** with elimination of the benzoxide **124** (Scheme 18b). A proton transfer between **123** and **124** leads to the formation of the intermediate **125**, which is in resonance with the zwitter ionic intermediate **125′**. A lithium-assisted [4 + 2] cycloaddition reaction between **125′** and the acrylate **121** gives the adduct **126**, which can crack into the quinone **127** with elimination of the free NHC catalyst. A proton shift within the quinone **127** finally gives the naphthalene-1,4-diol **122** as the final aromatic product.

It is worth to note that the lithium-assisted NHC-catalyzed Hauser-Kraus annulation reaction can tolerate a vast variety of substituents (Scheme 18c). Phthaladehydates bearing either electron-donating or electron-withdrawing groups can afford the product **128** in moderate to good yields. Electron-deficient alkenes can be used instead of the acrylate substrate **121** and afford the corresponding polycyclic arene products afforded in good yields (*e.g.*, **129**). Moreover, electron-poor internal alkenes can also work well in this transformation, with the congested substituted naphthalene-1,4-diol obtained as the products in good isolated yields (*e.g.*, **130**).

4.2 NHC-catalyzed arene constructions *via* a^1 to d^1 umpolung activation of alkenes

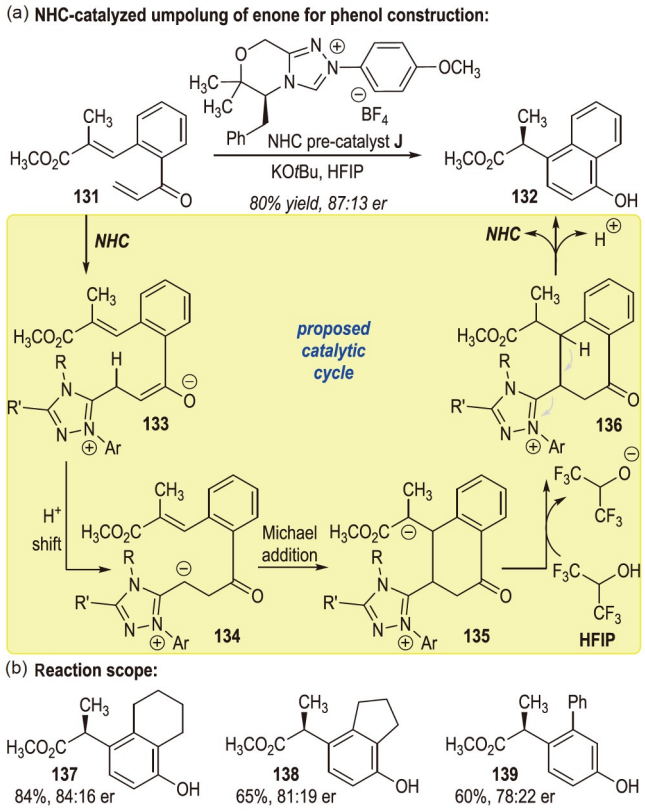
Electron-deficient alkenes can also be activated by NHC organic catalysts *via* a^1 to d^1 umpolung fashion. Specifically, the electrophilic sp^2 carbon of the alkene moiety can be ac-



Scheme 18 NHC-catalyzed Hauser-Kraus annulation for the synthesis of naphthalene-1,4-diol derivatives [27] (color online).

tivated by NHCs and behave as nucleophilic species to react with electrophiles in various addition reactions. This strategy can sometimes be used in the preparation of aromatic molecules *via* intramolecular isomerization processes.

In 2016, Lupton and co-worker [28] disclosed an NHC-catalyzed intramolecular cyclization reaction for the synthesis of naphthalenol derivatives (Scheme 19). A rationally designed α,β-unsaturated ketone **131** is used as the reaction substrate under the catalysis of the NHC catalyst **J** in the presence of the base and hexafluoroisopropanol (HFIP) additives (Scheme 19a). The optically enriched substituted naphthalenol **132** is afforded as the final product in a good yield with moderate enantioselectivity. The reaction is believed to be initiated by the addition of the free chiral NHC catalyst to the β-carbon of the enone moiety of the substrate **131**. The afforded zwitter ion intermediate **133** can go through a proton shift to give the β-nucleophilic ketone intermediate **134**, which can be add to the α,β-unsaturated carboxylic ester motif *via* an intramolecular Michael addition reaction to afford the cyclized adduct **135**. The zwitter ionic intermediate **135** can be protonated by HFIP in enantioselective fashion to give the azolium cyclohexanone



Scheme 19 NHC-catalyzed umpolung activation of α,β-unsaturated ketones for phenol constructions [28] (color online).

136. Then the cyclohexanone **136** can be deprotonated and the final naphthalenol product **132** can be obtained after an additional intramolecular proton transfer process.

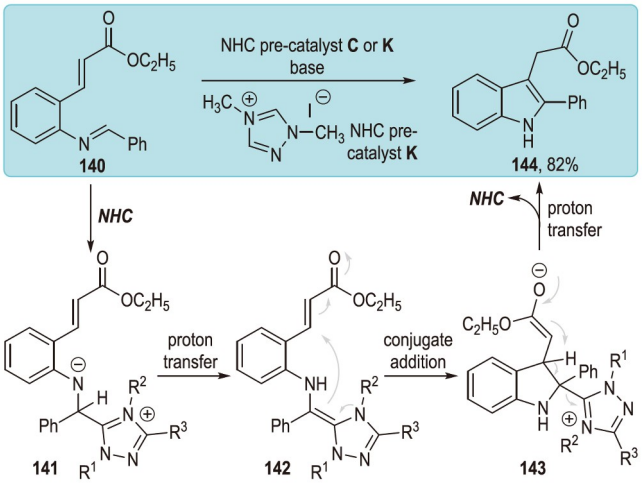
Substituted phenol derivatives bearing various substituents and substitution patterns can be efficiently obtained through this NHC-catalyzed enone activation protocol, although the enantioselectivities of the reactions were sometimes dropped (*e.g.*, Scheme 19b, **137** to **139**).

4.3 NHC-catalyzed arene constructions *via* a^1 to d^1 umpolung activation of imines

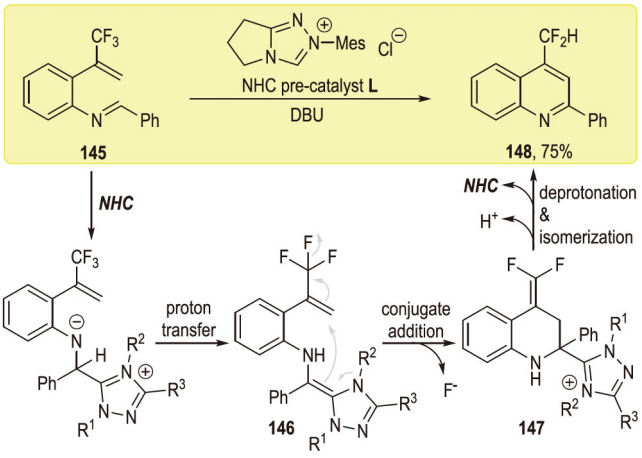
Imines are one class of the most important derivatives of carbaldehydes. Imines are analogous to aldehydes in many aspects. For instance, both of imines and aldehydes are versitile electrophiles in reactions with carbon- or heteroatom-centered nucleophiles. In principle, all the NHC-catalyzed activation modes with aldehydes could be carried out with the aldehyde-derived imine substrates. Unfortunately, there is only limited success in the umpolung activation of imine molecules with NHC organic catalysis. Challenges might exist in the distinctions between the electronic properties of the aldehyde and the imine structures.

In 2017, the groups of Biju [29] and Suresh [30] independently uncovered the NHC-catalyzed umpolung activation of imine molecules in the synthesis of indole derivatives (Scheme 20). The rationally designed aldimine **140** can be activated by a triazolium-derived NHC catalyst (*e.g.*, **C** or **K**) *via* nucleophilic addition to give the zwitter ion intermediate **141**, which can isomerize to the Breslow-typed intermediate **142**. An intramolecular conjugate addition within the intermediate **142** gives the benzopyroline intermediate **143**, and the final product **144** can be afforded after an intramolecular proton transfer process with elimination of the free NHC organic catalyst.

Soon later, Biju and co-workers [31] were able to adopt this strategy in the preparation of quinoline derivatives (Scheme 21). The activation of the aldimine **145** by NHC organic catalyst is similar to the activation of **140**. After formation of the aza-Breslow intermediate **146**, an intramolecular conjugate addition/fluoride elimination process leads to the formation of the bicyclic intermediate **147**. A cascade deprotonation/NHC elimination/proton transfer



Scheme 20 NHC-catalyzed umpolung of imine for indole synthesis [29,30] (color online).



Scheme 21 NHC-catalyzed umpolung of imine for quinoline synthesis [31] (color online).

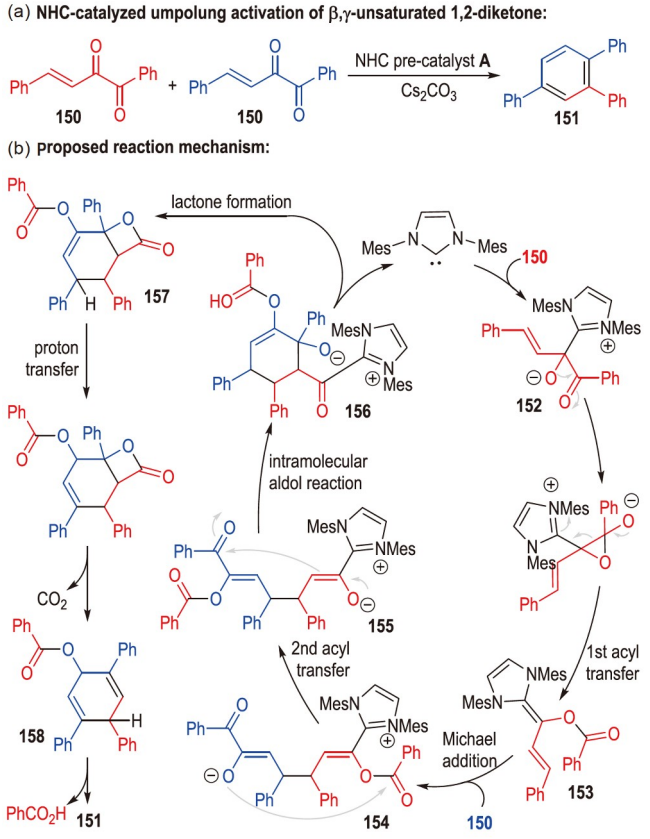
process finally gives the 4-difluoromethylquinoline **148** as the final product in 75% yield.

4.4 NHC-catalyzed arene constructions *via* umpolung activation of β,γ-unsaturated 1,2-diketones

HOMO enolate activation reactions are significant transformations realized by NHC organic catalysts. The conventional electrophilic β-sp^2 carbon of the conjugated carbonyl compound is converted into a nucleophilic species through formation of an azolium enolate intermediate. In most cases the HOMO enolate activation reactions are realized through the activation of α,β-unsaturated aldehydes by various NHC catalysts. Chi and co-workers [32] have demonstrated that saturated carboxylic esters are also promising precursors for the generation of HOMO enolate intermediates. Moreover, 1,2-diketones have also proven to be effective substrates for NHC-catalyzed HOMO enolate activation reactions, as disclosed by Fang and co-workers [33].

In 2018, Fang and co-workers [34] reported that a polysubstituted benzene molecule **151** can be efficiently obtained from an NHC-catalyzed dimerization reaction of β,γ-unsaturated 1,2-diketone substrate **150** (Scheme 22a).

The 1,2-diketone substrate **150** can be activated by the NHC catalyst *via* nucleophilic addition process to give the zwitter ion intermediate **152**. Intermediate **152** can isomerize to the acylated Breslow intermediate **153** through an intramolecular acyl transfer reaction. Michael addition reaction between the intermediate **153** and another β,γ-unsaturated 1,2-diketone **150** gives the adduct **154**, which can isomerize to **155** *via* an additional acyl transfer process. The intramolecular aldol condensation within the intermediate **155** leads to the formation of the cyclohexene intermediate **156**, which can crack into the free NHC catalyst and the fused β-lactone intermediate **157**. The cyclohexadiene intermediate **158** can be afforded from **157** *via* a proton transfer/decarboxylation cascade process, and the final product of poly substituted benzene **151** can be afforded through an additional benzoic acid elimination step.

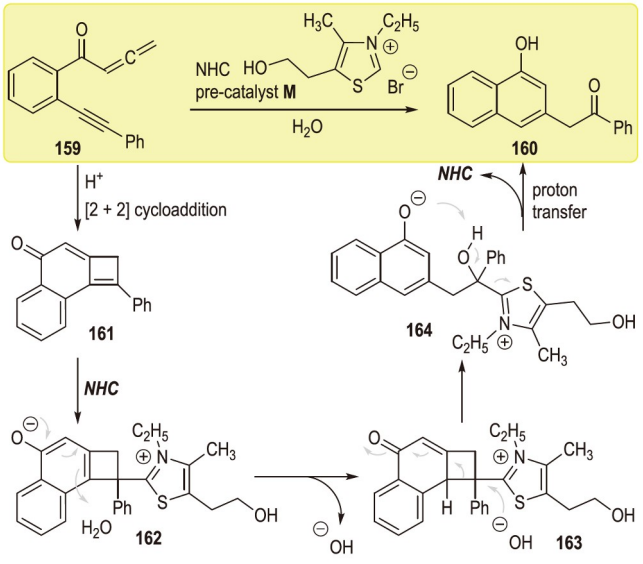


Scheme 22 NHC-catalyzed umpolung of β,γ-unsaturated 1,2-diketone for benzene construction [34] (color online).

5 Arene construction *via* NHC-promoted hydrolysis of cyclobutenes

Allenones and allenoates are reactive molecules that have been frequently used as building blocks in organic synthesis [35]. Traditionally, the β-sp^2 carbons of the allenone and allenoate substrates are electrophilic carbons that can be activated by Lewis basic catalysts to initiate various cycloaddition reactions. However, allene derivatives have rarely been used as substrates in NHC organocatalytic reactions. Limited success on the activation of electron-deficient allene molecules came from the groups of Ye [36], Yao [37], Jiang [38] and others [39].

Especially, Jiang, Tu, Li and co-workers [38] disclosed in 2017 an NHC-promoted isomerization reaction of functionalized allenone **159** for the synthesis of the naphthalenol product **160** (Scheme 23). The reaction is supposed to be



Scheme 23 NHC-catalyzed umpolung activation of allenone for naphthalenol synthesis [38] (color online).

initiated by the acid-induced [2 + 2] cyclization reaction between the allene moiety and the alkyne group of the multi-functional compound **159**. The afforded multi-cyclic cyclobutene intermediate **161** can be then attacked by the NHC catalyst to give the adduct **162**, which can be protonated by H_2O to afford the intermediate **163**. Intermediate **163** can be hydrolysed to open the 4-membered ring and gives the phenoxide intermediate **164**. Intramolecular proton transfer processes lead to the formation of the final naphthalenol product **160** with elimination of the free NHC catalyst for additional catalytic cycles.

6 Summary and outlook

A vast majority of the bioactive functional molecules consist of at least one aromatic group. The direct construction of arene structures is therefore of fundamental significance in both synthetic chemistry and biological research. Compared with the numerous structures that have been achieved with NHC organocatalytic reactions, the direct construction of arene molecules promoted by NHC catalysts has been relatively less developed.

To date, poly-substituted benzene derivatives can be efficiently afforded in both enantioselective and non-chiral forms. Heteroaromatic compounds such as indole, furan and pyridine derivatives can also be achieved with NHC organocatalysis through simple operations. Readily available and inexpensive aldehydes, aldimines, electron-deficient alkenes are typically involved in the key reaction starting materials. Moreover, numerous catalytic activation modes and reactions have been developed for the synthesis of functionalized aromatic compounds with NHC catalysts.

However, challenges and drawbacks still exist in the NHC-catalyzed arene formation reactions. On one hand, the activation modes involved in the NHC-catalyzed arene formation reactions are relatively limited. Electron-pair-transfer reactions have been dominating the NHC-catalysed poly-substituted benzene synthesis. On the other hand, chirality inductions are still challenging during the formation of the aromatic ring structures. Limited success has been achieved for enantioselective formation of arene molecules. Central-to-axial chirality conversion has been used as the main strategy in the synthesis of optically-enriched arene products.

Therefore, plenty of opportunities are remaining to be explored in NHC-catalyzed arene formation reactions. For example, single-electron-transfer (SET) reactions promoted by NHC organic catalysts are promising protocols for the construction of novel C–C bonds and might be applicable in the synthesis of arene molecules. Besides the central-to-axial chirality conversion strategy, the direct phase-selective cycloaddition reaction can in principle be applied in the construction of atropisomeric aromatic molecules. Moreover, the preparation of planar-chiral arene molecules *via* chiral NHC-catalyzed arene formation reaction is also promising and attractive directions within this highly active research field.

Conflict of interest The authors declare no conflict of interest.

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