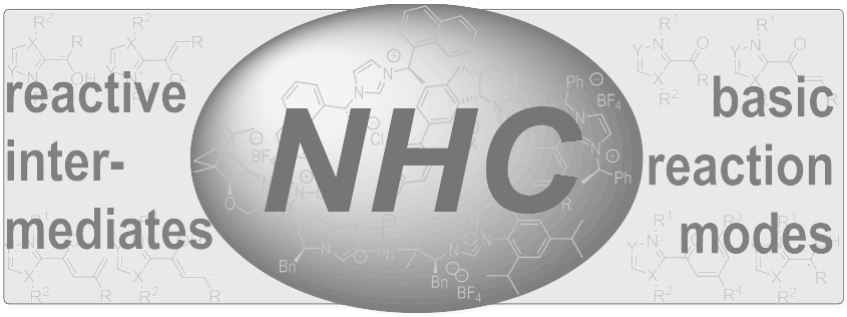
N-Heterocyclic Carbene Organocatalysis: Activation Modes and Typical Reactive Intermediates

Xingkuan Chen,[‡,a] Hongling Wang,[‡,b] Zhichao Jin,[b] and Yonggui Robin Chi*[,b,c]

[a] *Department of Chemistry, Jinan University, Guangzhou, Guangdong 510632, China*
[b] *Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Huaxi District, Guiyang, Guizhou 550025, China*
[c] *Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore*



N-Heterocyclic carbene (NHC) organocatalysis has been developed as an important approach in modern organic synthesis. Versatile activation modes within NHC organocatalysis have been established with countless transformations being realized in both efficient and selective fashion. We would like to provide an overview on the key progresses achieved within this field in the past two decades. Since numerous excellent reviews have been documented within this area, we will mainly focus on the scientific development of this research field based on the basic reaction modes and typical reaction intermediates.




Prof. Xingkuan Chen (top left) received his Ph.D. from Nanyang Technological University in 2017 under the supervision of Professor Robin Chi. After three years Postdoctoral stay with Prof. Chi, he joined Jinan University in 2019 to start his independent research career. His current research interest includes the asymmetric organocatalysis and the synthesis of bioactive molecules.

Hongling Wang (top right) received her bachelor's degree in organic chemistry from Shenyang University of Chemical Technology in 2014. She is now pursuing her PhD in Guizhou University under the joint-supervision of Prof. Zhichao Jin and Prof. Robin Chi. Her current studies include the development of new chiral oxidants, radical reactions, and new transformations catalyzed by NHC for access to agricultural chemicals.

Prof. Zhichao Jin (bottom left) received his MSc degree from East China University of Science and Technology in 2011 under the guidance of Prof. Jinxing Ye, and PhD from Nanyang Technological University in 2015 under the guidance of Prof. Robin Chi. After a two-year postdoctoral stay with Prof. Yixin Lu at National University of Singapore, he started his independent career at Guizhou University in 2017. His current research interest includes the development of novel catalytic activation modes and bioactive molecules for agricultural applications.

Prof. Yonggui Robin Chi (bottom right) received his undergraduate training from Tsinghua University and Hong Kong Baptist Univeristy during 1998—2002. He obtained PhD in Chemistry at University of Wisconsin-Madision under the guidance of Prof. Sam Gellman in 2007. After a two-year postdoctoral stay at Univeristy of California-Berkeley with Prof. Jean Frechet, he started his independent career at Nanyang Technological University and was quickly promoted to full professor. His current research, supported with students and researchers from Nanyang Technological University and Guizhou University, focuses on the development of new basic activation modes and reactions mediated by organic catalysts, efficient transformations for rapid construction of sophisticated molecules, selective modification of Chinese medicines and biomacromolecules, green reactions and processes for industrial applications, and functional molecules for applications in medicines, agricultural chemicals, and materials.

*E-mail: robinchi@ntu.edu.sg
[‡] X.C. and H.W. contributed equally to this work.

Contents

1. Introduction 1168
   1.1. General structures of *N*-heterocyclic carbenes 1168
   1.2. General properties of *N*-heterocyclic carbenes 1168
   1.3. Major applications of NHCs in organocatalysis 1169
2. Activation of Aldehydes for Access to Breslow and Homoenolate Intermediates 1169
   2.1. Characterization of the Breslow intermediate 1169
   2.2. Progresses in the benzoin and Stetter reactions 1170
   2.3. Hydroacylation of alkenes and alkynes 1172
   2.4. Annulation reactions of homoenolate intermediates 1174
   2.5. Non-annulation reactions of homoenolate intermediates 1175
   2.6. Cooperative catalysis with NHC-bounded homoenolate intermediates 1176
3. Activation of Ketenes and Aldehydes for Access to Enolate, Dienolate, and α,β-Unsaturated Acylazolium Intermediates 1177
   3.1. Activation of ketenes for access to enolate intermediates 1177
   3.2. Activation of ketenes for access to dienolate intermediates 1178
   3.3. Activation of aldehydes for access to enolate intermediates 1178
   3.4. Activation of aldehydes for access to dienolate intermediates 1180
   3.5. Activation of aldehydes for access to α,β-unsaturated acyl azolium intermediates 1181
4. Activation of Carboxylic Esters for Access to Homoenolate, Enolate, Dienolate, and α,β-Unsaturated Acylazolium Intermediates 1183
   4.1. Activation of esters for access to enolate intermediates 1183
   4.2. Activation of esters for access to homoenolate intermediates 1185
   4.3. Activation of esters for access to α,β-unsaturated acyl azolium intermediates 1187
   4.4. Activation of esters for access to dienolate intermediates 1188
5. Single-Electron-Transfer Activations and Radical Intermediates 1190
   5.1. Inspiration from bioorganic chemistry 1190
   5.2. Pioneering SET reactions in NHC organocatalysis 1191
   5.3. SET reactions with oxidants in NHC organocatalysis 1191
   5.4. NHC-catalyzed decarboxylative alkylation of aldehydes 1192
   5.5. SET reactions through cooperative NHC/photoredox catalysis 1193
6. Activation of Michael Acceptors, Styrenes and Imines 1194
7. Conclusions and Perspectives 1195

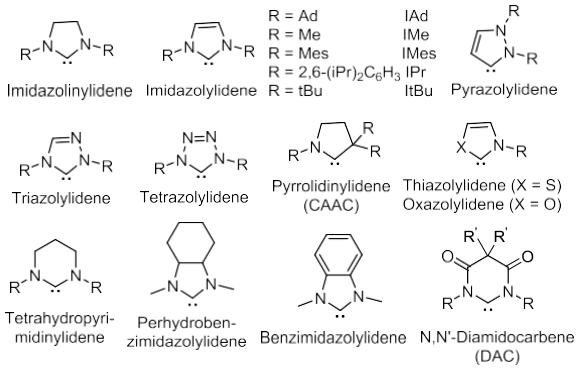
1. Introduction

Since Bertrand[1] and Arduengo[2] *et al*. successfully isolated and characterized the free carbene in 1991, *N*-heterocyclic carbene (NHC) has opened a new chapter in organic chemistry. The impact of strong σ-electron-donating properties allows for very strong NHC-metal bond formations and prevents decomposition of the catalyst. The most prominent examples are the second and third generations of the Grubbs' olefin metathesis catalysts.[3] On the other hand, NHCs are also playing important roles in nucleophilic organocatalysis. Metal-free catalytic processes are interesting approaches because of their facile reaction processes, excellent selectivities, environmental friendliness and versatile activation modes. This review provides a concise overview of *N*-heterocyclic carbenes in organic catalysis and highlights the extensive applications of the basic activation modes and reaction intermediates.

1.1. General structures of *N*-heterocyclic carbenes

N-Heterocyclic carbenes (abbreviated as NHCs or carbenes) are defined as heterocyclic species containing a carbene carbon and at least one α-nitrogen atom in the ring structure.[4] As a typical structural property, all carbenes are neutral and have bivalent carbon atoms with electron sextet. Within these criteria, there are many different classes of carbene compounds with various substitution patterns, ring sizes and degrees of heteroatom stabilizations. Typical subclasses of NHCs are presented in Scheme 1. With a wide variety of catalysts reported, several methods have been described for their synthesis and the synthesis of pre-carbenes has been reviewed in previous reports.[5]

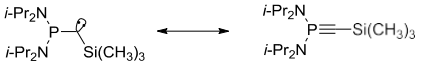
Scheme 1 Structures of typical NHCs. Ad = Adamantyl; Mes = Mesityl; *t*Bu = *tert*-Butyl; iPr = Isopropyl.



1.2. General properties of *N*-heterocyclic carbenes

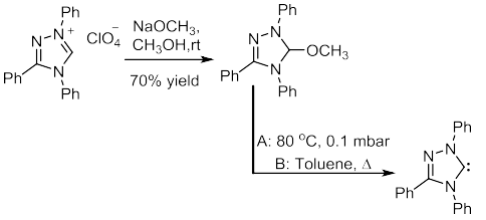
The bivalent carbon atom with a six-electron valence shell had been considered as highly reactive intermediates and rendered free carbenes inherently unstable in organic transformations. Much effort has been devoted into the isolation of stable carbenes. In 1988, Bertrand and coworkers reported the preparation of the first isolable carbene[1] stabilized by favorable interactions with adjacent phosphorus and silicon substituents (Scheme 2). But the real breakthrough facilitating forays into catalytic applications came from Arduengo *et al*. with isolation of "free" IAd[2] (see Scheme 1).

Scheme 2 Phosphinocarbene reported by Bertrand group



Inspired by Arduengo's initial report, a variety of stable NHCs have been synthesized.[6] In 1995, Enders, Teles and coworkers reported the synthesis of the crystalline triazolin-5-ylidene carbene starting from the triazole precursor (Scheme 3).[7] It is worth mentioning that the compound of triazolin-5-ylidene was the first commercially available carbene.

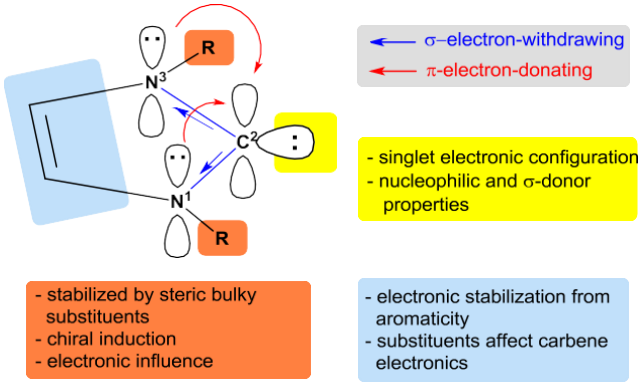
Scheme 3 The first commercially stable carbene



Based on the results of these investigations, dramatic progress

has been achieved in understanding NHCs' intrinsic properties. In 2014, Glorius and coworkers summarized the general properties of the NHC catalysts (Scheme 4).[8]

Scheme 4 General properties of NHCs.



The σ-electron-withdrawing and π-electron-donating effects of the nitrogen atoms contribute to the stabilization of the singlet carbene structure. Besides, the carbene carbon C^2 is in a singlet state configuration, leaving the p_π orbital of the C^2 center empty. This allows the adjacent nitrogen atoms to stabilize the carbene by donating π-electrons into the vacant p_π orbital, while lowering the energy of the occupied σ-orbital simultaneously by exerting σ-electron withdrawing effects on the carbene center. The stable carbene benefits from aromaticity. Different aromatic frameworks of the carbene catalysts affect their electronic properties. Moreover, the different groups attached to the nitrogen atoms adjacent to the C^2 centers offer additional stabilization, although this effect is inferior to the electronic stabilization provided by the nitrogen atoms. The bulky substituents of NHCs also help to introduce chiral induction.

1.3. Major applications of NHCs in organocatalysis

During the past 20 years, we have witnessed tremendous development in the field of NHC organocatalysis. The story can be ascribed to Ukai's demonstration that thiazolium salts catalyzed the benzoin reaction[9] and Breslow's determination of its mechanism in 1958.[10] In 1966, Sheehan and Hunneman have carried out the benzoin reaction in enantioselective fashion using chiral thiazolium pre-NHC catalysts.[11] Since then, NHC organocatalysis has emerged as a powerful strategy in organic synthesis. Many carbonyl compounds can be activated by NHC organic catalysts, such as aldehydes, esters, ketones, anhydrides and acyl halides. Typical reaction intermediates generated from the NHC catalysts are summarized in Scheme 5. The acyl anion intermediate (Breslow intermediate) can tautomerize to homoenolate and enolate intermediates via proton transfer processes. It can also be converted to the acyl azolium intermediate under oxidative conditions.

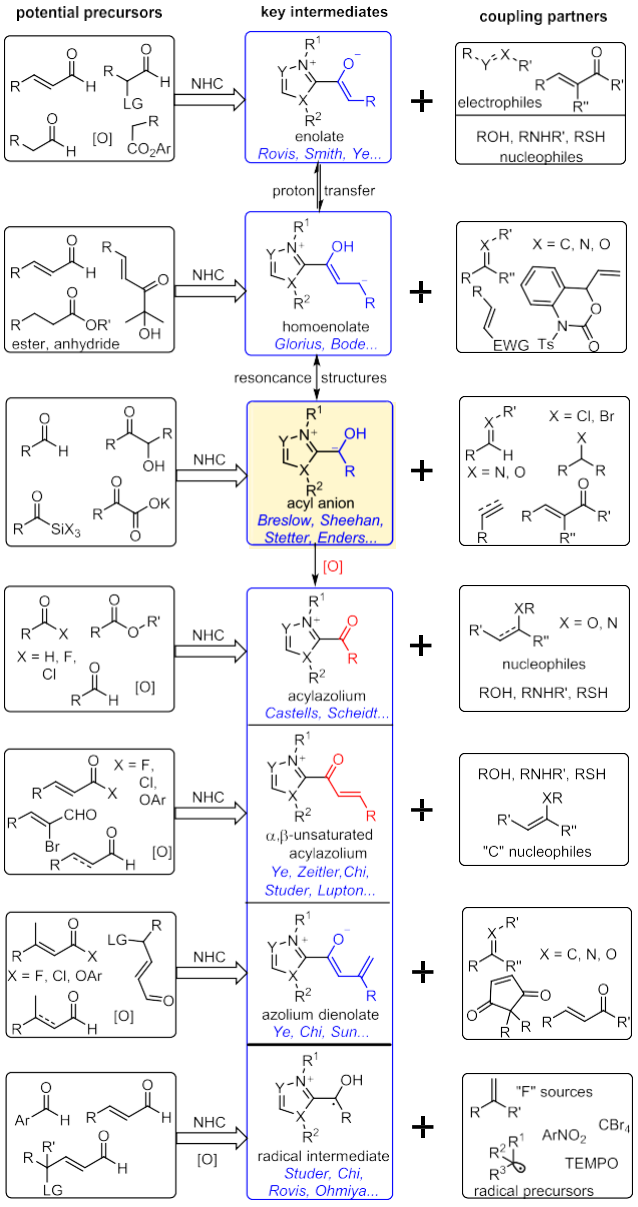
2. Activation of Aldehydes for Access to Breslow and Homoenolate Intermediates

Aldehydes are one of the most frequently used reaction substrates in NHC organocatalysis. Various aldehyde activation modes have been developed with NHCs used as the main reaction catalysts. Significant efforts have also been made to disclose the reaction mechanisms involved in the aldehyde activations enabled by NHC organic catalysts.

2.1. Characterization of the Breslow intermediate

One of the mostly investigated reactions catalyzed by NHCs

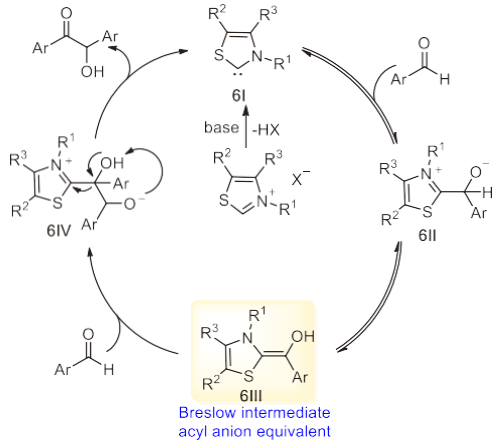
Scheme 5 NHC-bounded reactive intermediates, potential precursors and typical coupling partners



was the benzoin reaction. The benzoin reaction involves an initial attack of the NHC onto an aldehyde carbonyl carbon, and the conversion of an electrophile to a nucleophile. This process was exemplified as "Umpolung", a concept first reported by Wittig in 1951[12] and later popularized by Seebach.[13] The widely accepted reaction mechanism of the benzoin reaction was proposed by Breslow in 1958 (Scheme 6).[10] In this mechanism, the thiazolium salt is deprotonated to form a "free" carbene **6I**, which then attacks the carbonyl group of an aldehyde and gives the intermediate **6II**. The intermediate **6II** undergoes a 1,2-proton shift to generate the Breslow intermediate **6III**, which then attacks another aldehyde and gives the alkoxide intermediate **6IV**. Finally, a proton transfer in the intermediate **6IV** affords the benzoin product and the carbene catalyst is regenerated for additional catalytic cycles.

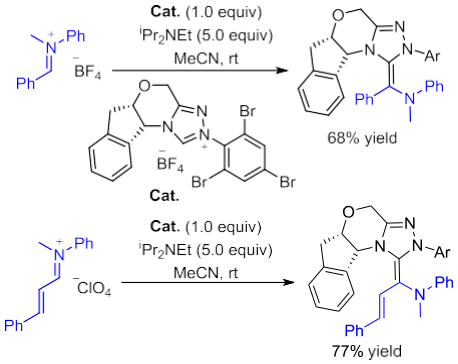
The Breslow intermediate has been involved in a lot of reactions. Some of the Breslow intermediates bearing crowed structures and related derivatives have been isolated and characterized.[14]

Scheme 6 Mechanism of the benzoin reaction proposed by Breslow



In 2012, Rovis' group reported some stable and isolable analogues of the Breslow intermediate derived from chiral triazolylidene carbenes (Scheme 7).[15] The reactions of the NHC precatalyst with iminium salts in the presence of base give the aza-Breslow intermediates in 68% and 77% yields, respectively. In this article, NMR characterization and *X*-ray crystal structures were presented.

Scheme 7 Synthesis of aza-Breslow analogues



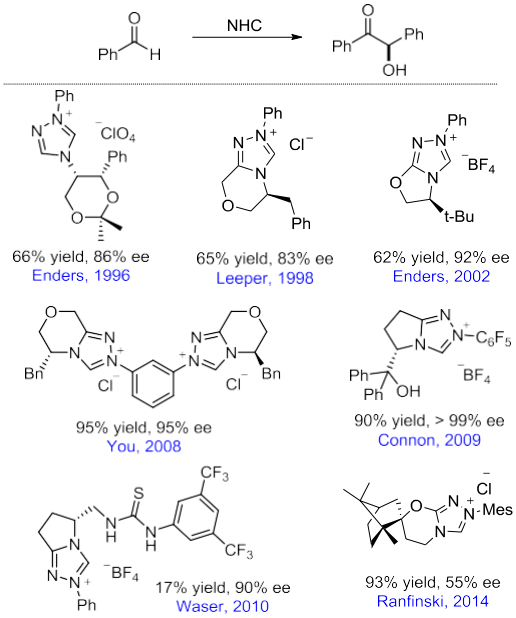
Besides, Rovis *et al*. have reported the oxidation potentials and UV-Vis spectra of the aza-Breslow intermediates.[15] According to their calculations, classical Breslow intermediate preferred *Z*-geometry, however, solid-state analysis showed a preference for the *E*-enertriamine geometry. It is worth mentioning that ^{1}H NMR showed a mixture of four compounds. The authors hypothesized that two enetriamine geometries were presented along with C—N bond rotamers.

2.2. Progresses in the benzoin and Stetter reactions

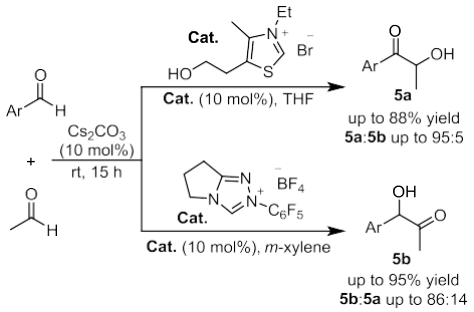
Homo-benzoin reaction implies the benzoin reaction between two molecules of the same aldehyde.[16] Several efficient and selective catalysts have been prepared and utilized for this transformation. Progresses in this area have been summarized in previous reviews.[17] The results of some excellent examples in homo-benzoin reactions are listed in Scheme 8. It has been shown that the development of NHC catalysts bearing novel chiral scaffolds is critical to the enantioselectivities of the homo-benzoin reactions.[18]

The cross-benzoin reaction involves two different aldehydes or aldehydes with electrophilic carbonyl substrates. One of the seminal intermolecular cross-benzoin reactions of two aldehydes was carried out by Cookson and Lane in 1976[19] and was followed by Stetter and Dämbkes.[20] Even though four different products were afforded in this intermolecular reaction, it was shown that the chemoselectivity is viable in this catalytic system. After that, many research groups have investigated the cross-benzoin reactions of different aldehydes, notably by Inoue, Connon, Glorius, Yang and Gravel *et al*.[21] One of the interesting results has been reported by Yang and coworkers, with an intermolecular cross benzoin of aromatic aldehyde with aliphatic aldehyde described in their work.[22] The chemoselectivities in the Yang's report could be effectively controlled by the different NHC catalysts (Scheme 9).

Scheme 8 NHCs used for asymmetric benzoin reaction

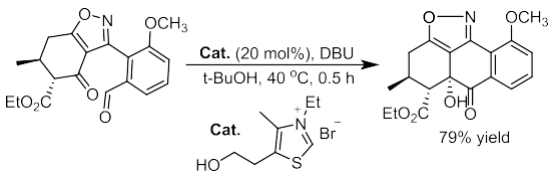


Scheme 9 Cross benzoin reaction reported by Yang



The first intramolecular cross-benzoin reaction was reported by Suzuki and coworkers in 2003.[23] The use of ketones as the cross-benzoin reaction partner has inspired scientists to further investigate the stereoselective cross-benzoin reactions (Scheme 10).

Scheme 10 The first intramolecular crossed benzoin condensation between aldehyde and ketone reported by Suzuki

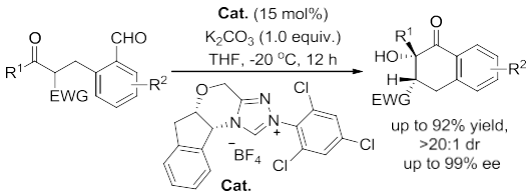


Subsequently, the groups of Enders, Suzuki and You independently reported the asymmetric intramolecular cross-benzoin

reactions in good to excellent yields and ee values.[24]

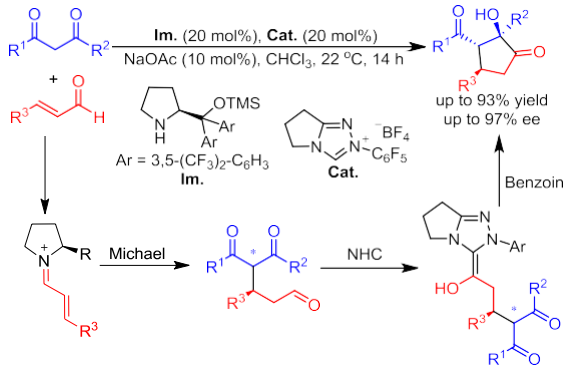
In 2009, Ema and coworkers reported the first asymmetric desymmetrization of cyclic 1,3-diketones affording bicyclic tertiary alcohols through an intramolecular cross-benzoin reaction.[25] In 2014, Johnson's group disclosed an intermolecular benzoin transformation through the dynamic kinetic resolution (DKR) of β-stereogenic α-keto esters with two stereocenters formed.[26] Meanwhile, the first intramolecular cross-benzoin reaction through DKR process enabled by NHC was reported in 2016 by the Fang's group (Scheme 11).[27] A variety of tetralone derivatives bearing two contiguous stereocenters and multiple functionalities were afforded in moderate to excellent yields with high levels of stereoselectivities.

Scheme 11 Intramolecular cross-benzoin reaction enabled by dynamic kinetic resolution



A cooperative catalytic Michael addition-intramolecular benzoin cascade reaction of functionalized cyclopentanones was developed in 2009 by Rovis and coworkers (Scheme 12).[28] The chiral secondary amine catalyzed Michael addition of aliphatic aldehydes generated the intramolecular benzoin substrate. Then the carbene catalyst could promote the diastereoselective intramolecular cross-benzoin reaction to give the desired products. Noteworthy, the azolium salt is an achiral molecular in this cascade sequence and this cascade reaction constitutes a fine example of symbiotic dual-catalysis. Noteworthy, the enamine and NHC dual-catalytic reactions were also independently reported by Enders, Melchiorre and Chen *et al*.[29]

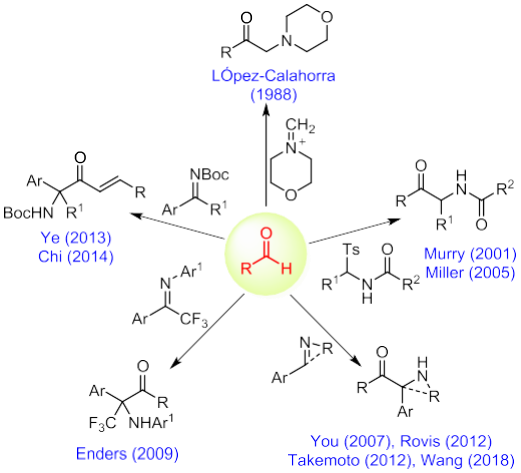
Scheme 12 Secondary amine and NHCs catalyzed cascade reaction reported by Rovis



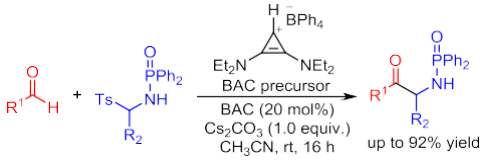
Aza-benzoin reactions have been achieved through the coupling of aldehydes and aza-electrophiles. Imines possessing electron-withdrawing N-substituents constitute the most commonly used aza-electrophile. The aza-benzoin reaction was first reported by López-Calahorra in 1988. The progress in this field is summarized in Scheme 13.[30]

In 2014, Gravel and coworkers reported the aza-benzoin reaction of aldehydes and phosphinoylimines, with a new bis(amino)-cyclopropenylidene (BAC) used as the NHC catalyst (Scheme 14).[31] The carbene catalyst used in this work is different from the conventional thiazolium and triazolium salt derived NHC catalysts. However, the attempts to the enantioselective version of this reaction using chiral BAC carbenes were unsuccessful.

Scheme 13 Aza-benzoin reactions to access α-amino ketones

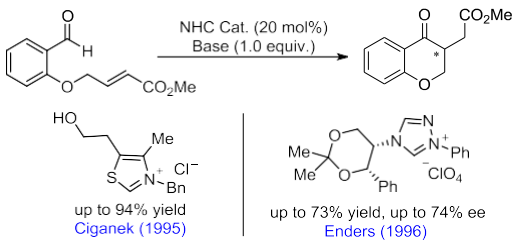


Scheme 14 Aza-benzoin reaction catalyzed by BAC-carbene



In the early 1970s, Stetter and coworkers discovered the conjugate additions of aldehydes to Michael acceptors employing thiazolium salts as the catalysts.[32] Since then, the catalytic 1,4-additions of aldehydes to acceptors bearing activated double bonds were named as Stetter reactions. Ciganek reported the intramolecular Stetter reaction in 1995.[33] In the next year, Enders and coworkers disclosed the first enantioselective intramolecular Stetter reaction using chiral triazolium salt-derived NHC catalysts (Scheme 15), with the corresponding products afforded in moderate yields with up to 74% ee values.[34]

Scheme 15 Intramolecular Stetter reaction

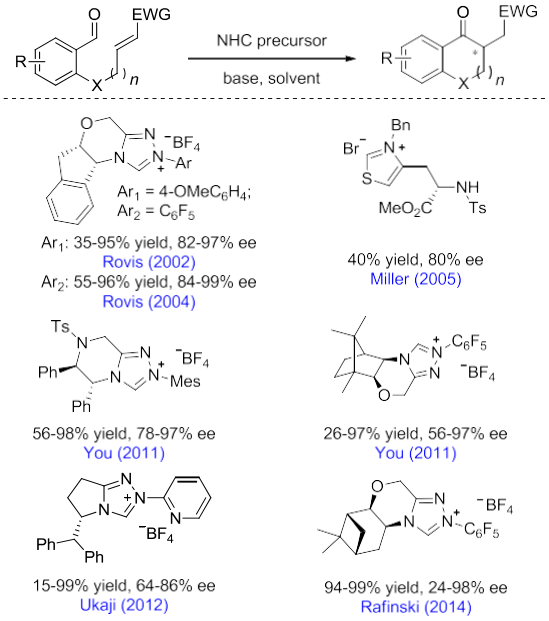


Following these pioneering reports, several research groups investigated more efficient and selective catalysts for this transformation. The progresses in the area of NHC-catalyzed Stetter reactions have been summarized in previous reviews. Some examples of the highly enantioselective intramolecular Stetter reactions were presented below (Scheme 16).[35]

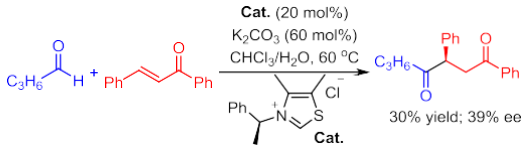
The intermolecular Stetter reactions have been powerful strategies in the synthesis of complex molecules. Since the first report by Stetter in the 1970s, new coupling partners have been extensively explored. The first asymmetric intermolecular Stetter reaction was studied by Enders and coworkers in 1990s describing the reaction of *n*-butanal with chalcone catalyzed by the chiral thiazolium salt (Scheme 17).[36]

In 2008, an enantioselective intermolecular Stetter reaction was demonstrated by Enders and coworkers (Scheme 18).[37] The reaction was catalyzed by the triazolium salt and afforded the

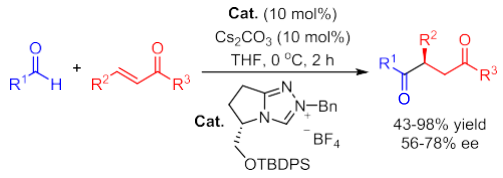
Scheme 16 Highly enantioselective intramolecular Stetter reaction



Scheme 17 The first asymmetric intermolecular Stetter reaction



Scheme 18 Asymmetric intermolecular Stetter reaction



desired products in good to excellent yields and moderate enantioselectivities.

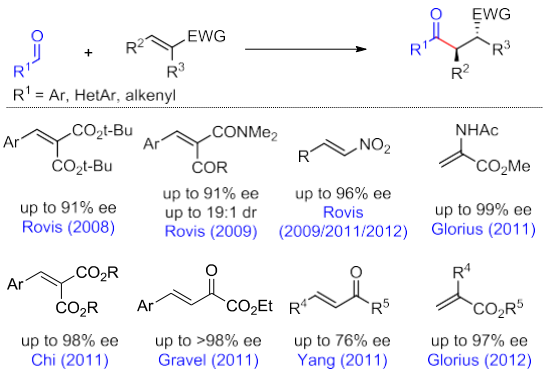
Meanwhile, scientists have expanded the scope of the Michael acceptors to arylsulfonyl-indoles, vinyl sulfones, vinylphosphonates, nitroalkenes and so on. Some examples of highly enantioselective intermolecular Stetter reaction with different Michael acceptors were listed below (Scheme 19).[38]

A one-pot cascade multi-catalytic process was developed by Hamada and coworkers in 2006, describing a Pd-catalyzed allylic amination and thiazolium salt catalyzed Stetter reaction cascade.[39] Functionalized dihydroquinolines were afforded as the final products in this protocol. This work inspired the future research in the carbene catalyzed complicated Stetter reactions associated with another catalyst.

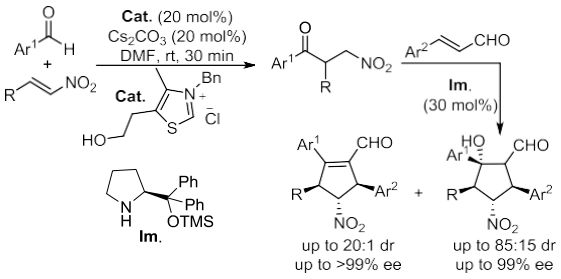
The intermolecular Stetter reaction was disclosed by Hong *et al.* in 2010. Substituted arylaldehydes were coupled with Michael acceptors and then went through intramolecular aldol reactions to generate complex products from simple starting materials. NHC and secondary amine were used as the co-operative catalysts in this cascade process (Scheme 20).[40]

In 2010, Rovis' group reported a dual catalytic one-pot asymmetric Michael/Stetter reaction (Scheme 21). The cascade process constituted an amine-mediated Michael addition and a carbene

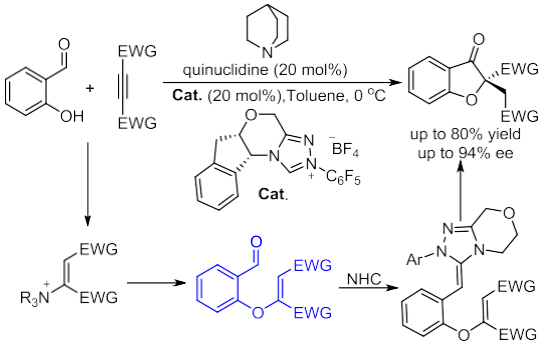
Scheme 19 Enantioselective intermolecular Stetter reaction with various Michael acceptors



Scheme 20 Stetter-Michael addition cascade reaction



Scheme 21 Enantioselective synthesis of benzofuranones



promoted intramolecular Stetter reaction.[41] Five years later, Sunoj and coworkers studied the reaction mechanism and gave explanations on the origin of the chirality induction through DFT calculations.[42]

A Stetter reaction promoted by co-operative NHC and thiourea catalysts was disclosed by Liu in 2016. They described the direct intermolecular Stetter reaction of aromatic aldehydes with nitroolefines (Scheme 22a).[43]

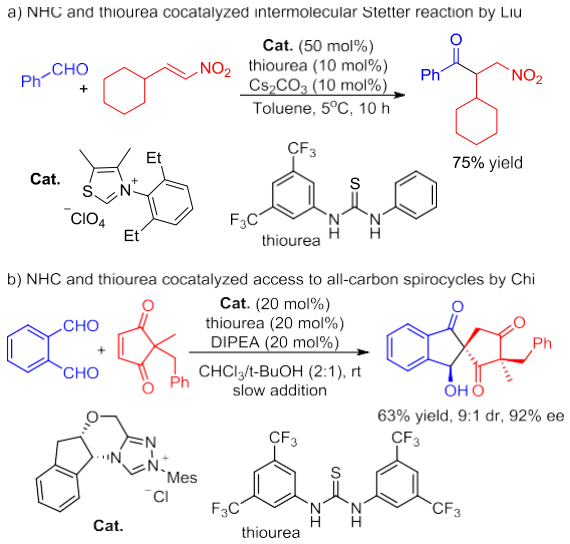
Recently, an NHC catalytic approach for rapid asymmetric access to spirocyclic molecules was disclosed by Chi and coworkers (Scheme 22b).[44] The cascade reaction involves an intermolecular Stetter reaction catalyzed by NHC and followed by an intramolecular aldol reaction. The Stetter reaction is also a desymmetrization process, through which the configuration of remote carbon stereocenter is controlled by the chiral NHC catalyst. Interestingly, both NHC and thiourea cocatalyst are essential in this catalytic reaction, and no product was formed without the presence of the thiourea cocatalyst.

2.3. Hydroacylation of alkenes and alkynes

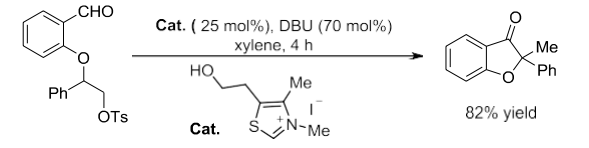
Breslow intermediate can also react with electron neutral alkenes and alkynes. In 2006, She, Pan and coworkers first reported

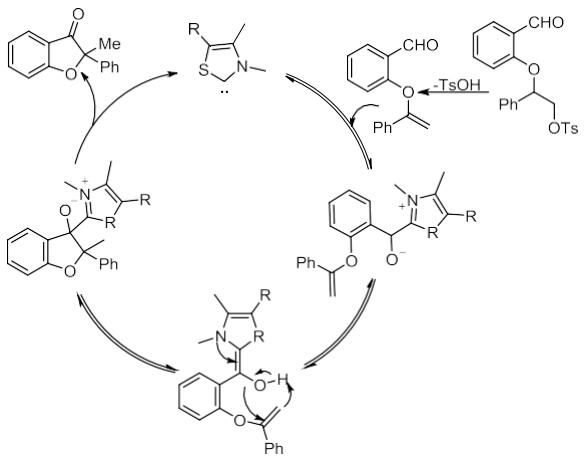
the NHC-catalyzed intramolecular hydroacylation reaction of alkyl tosylates. Enol ethers were generated *in situ* with elimination of the tosyl group under basic conditions (Scheme 23).[45] After an intramolecular Stetter reaction, the cyclized pyranone product could be afforded in a good yield in excellent regio-selective fashion.

Scheme 22 NHC and thiourea cooperative catalysis



Scheme 23 NHC-catalyzed intramolecular hydroacylation reaction

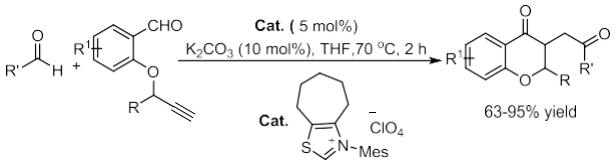




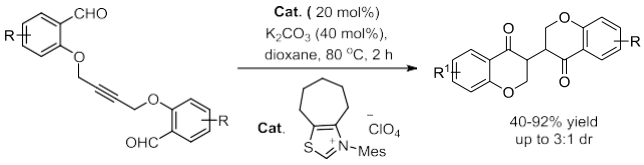
In 2010, Glorius and co-workers reported an NHC-catalyzed hydroacylation–Stetter cascade reaction. The intramolecular hydroacylation reaction of the aldehydes and the terminal alkynes gave the cyclized chromanone intermediates bearing terminal alkene groups. Then, the chromanone intermediates underwent intermolecular Stetter reactions with aromatic aldehydes to give the final products in good to excellent yields (Scheme 24).[46]

Recently, Liu and coworkers developed an intramolecular hydroacylation–Stetter cascade reaction for the synthesis of bisbenzopyrones (Scheme 25).[47] The reaction proceeds through the intramolecular hydroacylation of one aldehyde with alkyne

Scheme 24 NHC-catalyzed hydroacylation–Stetter cascade reaction



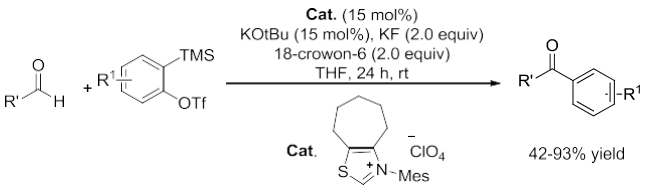
Scheme 25 Intramolecular hydroacylation–Stetter reaction



followed by intramolecular Stetter reaction to obtain the desired product. Symmetrical and unsymmetrical substitutions on the alkynyl bisbenzaldehyde were well tolerated.

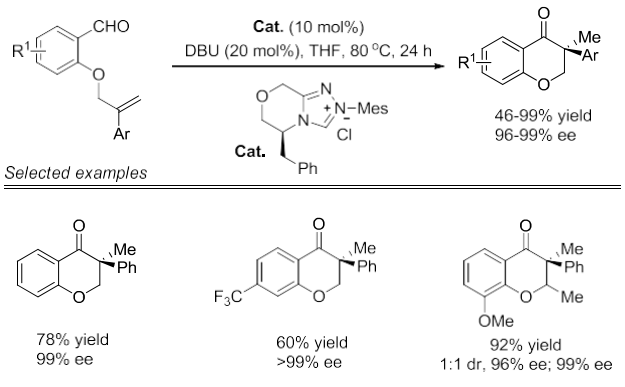
Arynes are active electrophilic species that can react with Breslow intermediates. In 2010, Glorius and coworkers reported the NHC-catalyzed intermolecular hydroacylation reaction of arynes (Scheme 26).[48] The arynes were generated from 2-trimethylsilyaryl triflate in the presence 2.0 equiv each of KF and 18-crown-6. A broad scope of aldehydes and aryne precursors worked well in this process and the desired products were afforded in good to excellent yields.

Scheme 26 Hydroacylation of arynes



In 2009, Glorius and coworkers described the NHC-catalyzed intramolecular hydroacylation reaction of unactivated C–C double bonds.[49a] Two years later, the same group disclosed the asymmetric hydroacylation of unactivated alkenes with NHC catalysis (Scheme 27).[49b] A broad scope of chromanone derived products bearing quaternary stereocenters were obtained in excellent yields and enantioselectivities. DFT studies of the reaction mechanism suggested that the C—C and C—H bond formations took place in a concerted reaction pathway.

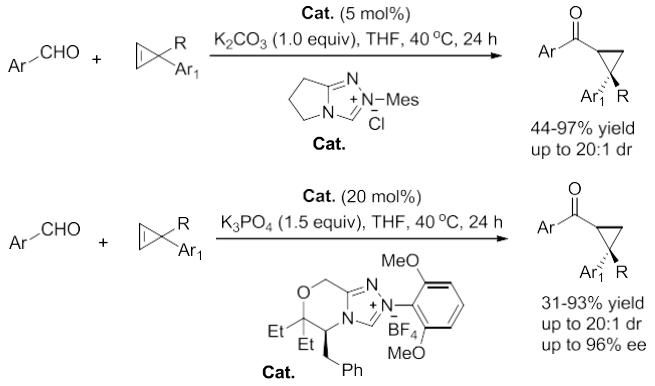
Scheme 27 Enantioselective hydroacylation of alkenes



In 2011, Glorius and coworkers reported the NHC-catalyzed

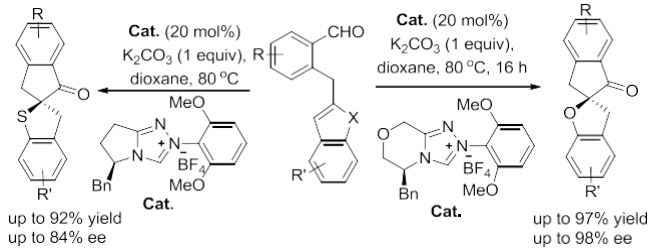
intermolecular hydroacylation of aldehydes and cyclopropenes.[50a] Subsequently, the enantio- and diastereoselective intermolecular hydroacylation of cyclopropenes with arylaldehydes was reported by the same group. An electron-rich chiral triazolium salt was found to be an effective chiral catalyst for this transformation (Scheme 28).[50b]

Scheme 28 NHC-catalyzed hydroacylation of cyclopropenes



In 2016, Glorius and coworkers reported the organocatalyzed enantioselective dearomatization of benzofurans and benzothiophenes via direct hydroacylation of unactivated C-C double bond. DFT calculations and experimental studies both suggested that the mechanisms of the hydroacylation of benzofurans and benzothiophenes are different. Benzofurans reacted in a concerted, highly enantioselective pathway and benzothiophenes reacted through a stepwise reaction mechanism (Scheme 29).[51]

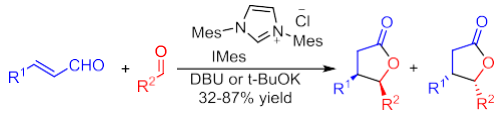
Scheme 29 Hydroacylation of benzofurans and benzothiophenes



2.4. Annulation reactions of homoenolate intermediates

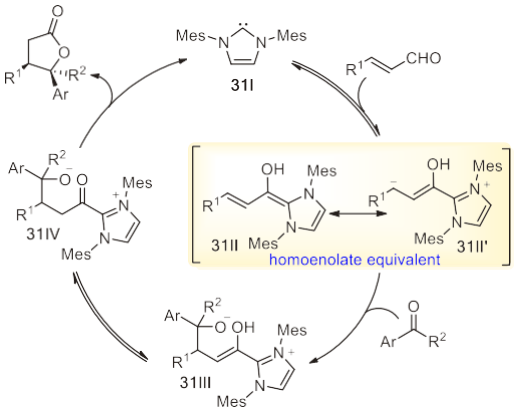
The groups of Glorius and Bode independently reported that the enals could react as homoenolate precursors in the presence of NHC catalysts in 2004. In both cases, the commercially available IMes salt and strong bases (DBU or tBuOK) were used and the a^3-d^3 umpolung was realized through crossing the conjugated α,β-unsaturated Breslow intermediate (Scheme 30). The disubstituted γ-butyrolactones were generated in moderate to good yields.[52]

Scheme 30 First homoenolate activation reported by glorius and bode



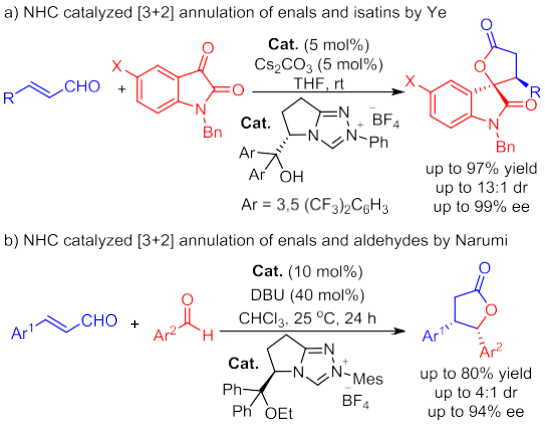
In the postulated reaction mechanism (Scheme 31), the α,β-unsaturated aldehyde is attacked by the *in situ* formed car- bene **31I**. The Breslow intermediate **31II** then tautomerizes to the conjugated homoenolate **31II'**, and then attacks the other aldehyde or ketone as a d^3-nuclephile to form the alcoholate **31III**. The tautomerization of **31III** gives the acylimidazolium intermediate **31IV**, which goes through an intramolecular cycloaddition to afford the desired γ-butyrolactone product and release the catalyst.

Scheme 31 Proposed mechanism for homoenolate activation



Highly reactive ketones such as trifluoromethyl ketones, α-ketoesters, 1,2-diketones, isatins and tropone were also suitable electrophiles in this type of reaction. But only limited examples of the enantioselective formation of lactones have been reported.[53] An excellent example has been reported by Ye and coworkers when they used a hydroxyl-containing NHC as the catalyst in the synthesis of isatin derived chiral lactones in highly diastereo- and enantioselective fashion (Scheme 32a).[54] Recently, an asymmetric homoenolate cross-annulation of enals and aldehydes with high enantioselectivity was disclosed (Scheme 32b).[55] The reaction proceeds in a highly chemoselective manner. The conjugated Breslow intermediates were preferably generated from enals rather than simple aldehydes, enabling the homoenolate addition of enals in preference to competing acyl anion-mediated reactions.

Scheme 32 Highly diastereo- and enantioselective NHC-catalyzed [3+2] annulation of enals

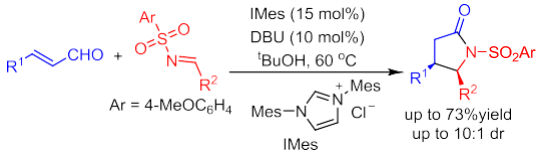


The diastereoselective synthesis of γ-lactams from *N*-sulfonyl aldimines and ketimines was also reported. He and Bode first reported this transformation in 2005 through the homoenolate addition of enals to imines (Scheme 33). The reaction tolerates a broad scope of aromatic enals and aryl imines to generate γ-lactams in good yields and moderate to good diastereoselectivities.[56]

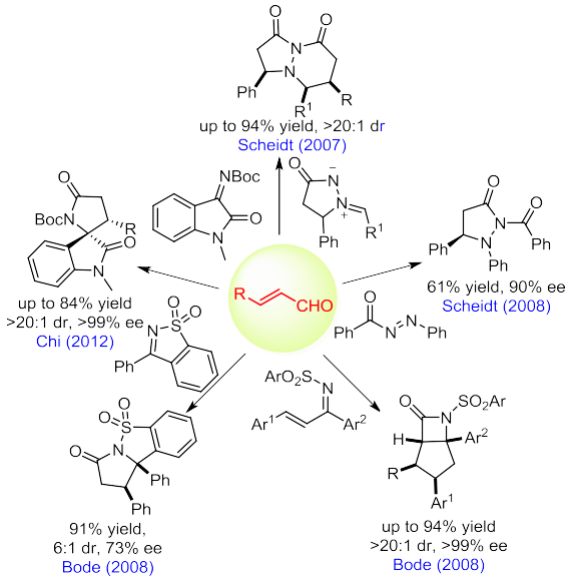
Scheidt and coworkers reported that azomethine ylides are capable coupling partners for the NHC-catalyzed homoenolate activation process. A formal [3+3] reaction was disclosed to pre-

pare pyridazinones as the final products. In 2008, the same group showed that diazenes are competent electrophiles for NHC-catalyzed homoenolate reactions to afford pyrazolidinones. Bode *et al*. subsequently disclosed a highly diastereo- and enantioselective reaction for the synthesis of β-lactam products via 1,4-addition to α,β-unsaturated *N*-sulfonyl ketimines. In the same year, Bode's group successfully used cylic sulfonylketimines to react with aryl or aliphatic enals in this reaction. In 2012, NHC-catalyzed annulation reaction of isatin *N*-Boc ketimines and enals was developed by Chi and coworkers (Scheme 34).[57]

Scheme 33 Cycloaddition of homoenolate and sulfonylimines

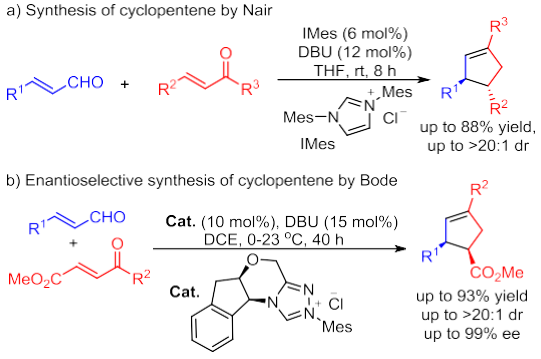


Scheme 34 Nitrogen heterocycles formation via homoenolate annulation



In addition to heterocycle synthesis, the NHC-generated homoenolate intermediates have also been used in the synthesis of five-membered carbocycles. Nair and coworkers first disclosed this transformation in 2006, with enals and chalcones used as the reaction partners.[58] Shortly after this seminal report, Bode's group disclosed an enantioselective cyclopentene formation reaction (Scheme 35).[59] After that, Scheidt, Glorius and coworkers also contribute to the development of this transformation with various catalytic approaches.[60]

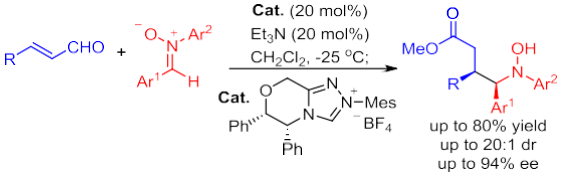
Scheme 35 Synthesis of cyclopentenes



2.5. Non-annulation reactions of homoenolate intermediates

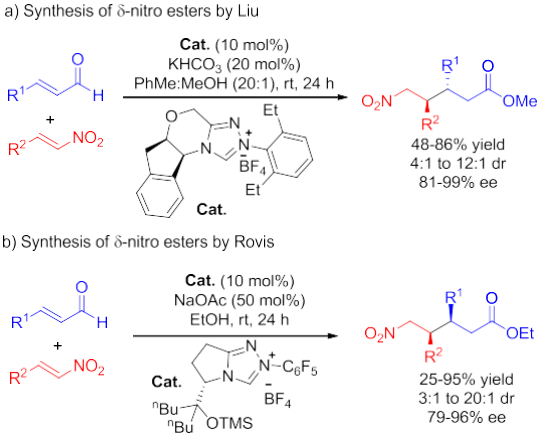
NHC-catalyzed homoenolate reactions are not limited to annulation reactions. Scheidt and Bode first reported the non-annulative processes independently in 2005.[61] In 2008, Scheidt and colleagues demonstrated that the nucleophilic addition of N-Mes triazolium-derived homoenolates to nitrones could be performed with high enantioselectivity. The unstable heterocyclic-hydroxyamino ester products were easy to be broken with sodium methoxide (Scheme 36). In this reaction, aliphatic and aryl enals were tolerated, but the nitrone moiety only tolerated aryl substituents at the carbon and nitrogen atoms.[62]

Scheme 36 Synthesis of γ-hydroxyamino esters via homoenolate by Scheidt



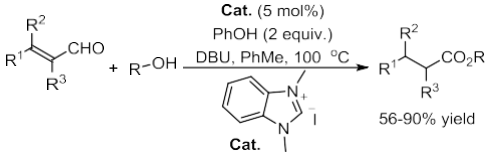
In 2009, Nair's group reported the NHC-promoted homoenolate addition to nitroalkenes to obtained δ-nitro esters.[63] A short time later, the groups of Liu and Rovis reported the enantioselective synthesis of δ-nitro esters in 2012 and 2013, respectively (Scheme 37). In this type of reactions, a variety of nitrostyrene derivatives were coupled with aryl and aliphatic enals.[64]

Scheme 37 Synthesis of enantioselective δ-nitro esters via homoenolate



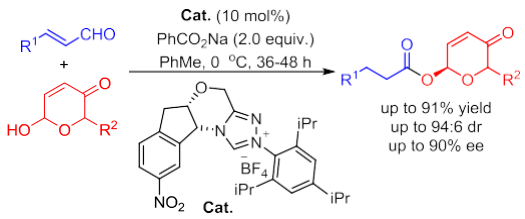
In early 2005, Scheidt and coworkers first disclosed the protonation of the NHC-bounded homoenolate intermediate in the presence of phenol and alcohol to form the corresponding saturated ester (Scheme 38).[65]

Scheme 38 Protonation of homoenolate by Scheidt.



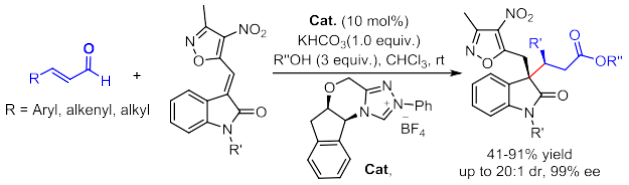
In the field of DKR reactions, Wang and coworkers have reported the asymmetric o-acylation of 6-hydroxypyranones through β-protonated esterification with enals catalyzed by a chiral NHC (Scheme 39).[66]

Scheme 39 NHC-catalyzed DKR of 6-hydroxypyranones via homoenolate



In 2019, Ye and coworkers reported the NHC-catalyzed β-addition reactions of enals with oxindole-derived 5-alkenylisoxazoles. 3,3-Disubstituted oxindole products bearing contiguous all-carbon quaternary and tertiary stereocenters were obtained in good yields with moderate to excellent diastereoselectivities and excellent enantioselectivities (Scheme 40).[67]

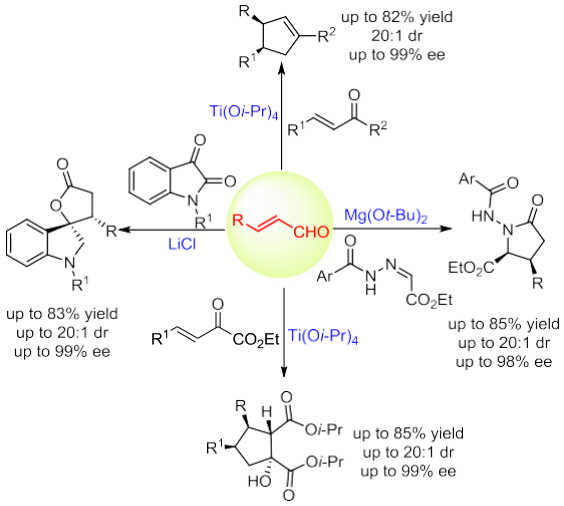
Scheme 40 NHC-catalyzed β-addition of enal to alkylenyloxindoles



2.6. Cooperative catalysis with NHC-bounded homoenolate intermediates

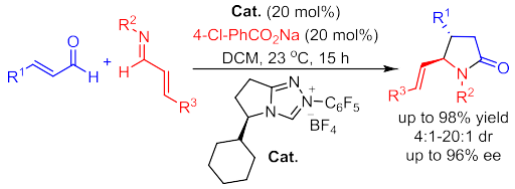
Cooperative catalysis using NHCs with other catalysts has become a widespread and powerful strategy for improving the reaction yields and selectivities. In 2010, Scheidt and coworkers disclosed the first NHC and Lewis acid cooperative catalysis for access to substituted cyclopentanes.[68] Shortly after that, the same group disclosed a number of NHC/Lewis acid cooperative catalytic systems for the addition of homoenolate to electrophiles using the same *N*-substituent triazolium salt pre-catalyst (Scheme 41).[69]

Scheme 41 NHC/Lewis cooperative catalysis via homoenolate by Scheidt and colleagues



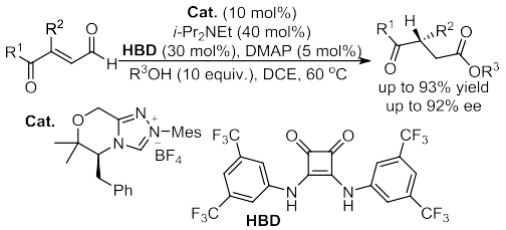
Brønsted acids can be particularly useful in carbonyl activation. Rovis' group reported that by using a weak benzoate salt as the base to deprotonate the azolium salt, the conjugate acid could in turn activate the imine electrophile for homoenolate addition (Scheme 42).[70]

Scheme 42 NHC/Brønsted acid cooperative catalysis



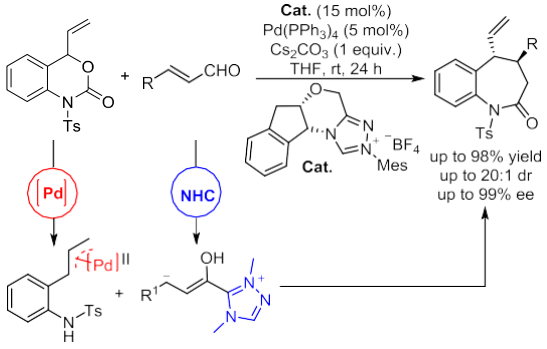
In 2015, Scheidt and coworkers disclosed the cooperative NHC/H-bond donor (HBD) activation for an enantioselective β-protonation reaction of α,β-unsaturated aldehydes (Scheme 43). This cooperative catalytic system could improve both of the reaction yield and stereoselectivity when compared with the single NHC-catalyzed processes.[71]

Scheme 43 Enantioselective β-protonation via NHC/HBD cooperative catalysis strategy



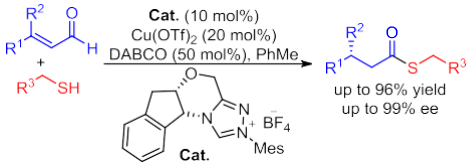
Glorius has demonstrated in 2016 that transition-metal catalysis can be combined with NHC organocatalysis in cooperative fashion (Scheme 44). Asymmetric induction can be realized through the cooperative activation by a chiral NHC with palladium co-catalyst.[72]

Scheme 44 NHC/palladium cooperative catalysis



In 2017, Huang reported a highly enantioselective β-protonation of enals with mercaptans via synergistic NHC/amine/copper catalysis. The close correlationship between the product stereoselectivity and the sulfurphilcity of the metals has inspired an organocatalytic proton-shuttling approach for the highly stereoselective protonation of homoenolate intermediates (Scheme 45).[73]

Scheme 45 Enantioselective β-protonation via a proton shuttling strategy



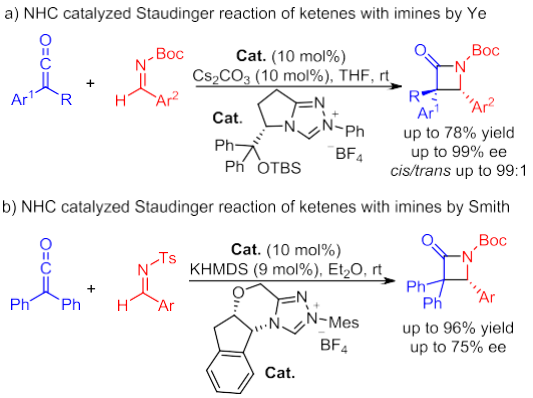
3. Activation of Ketenes and Aldehydes for Access to Enolate, Dienolate, and α,β-Unsaturated Acylazolium Intermediates

Ketenes are compounds with adjacent carbon-carbon and carbon-oxygen double bonds. They are also suitable reactive substrates that could be activated by NHC organic catalysts.

3.1. Activation of ketenes for access to enolate intermediates

Ye, Smith and coworkers have pioneered the NHC-catalyzed cycloaddition reactions of ketenes with various electrophiles. Ye's group demonstrated that NHCs could catalyze the reaction of pheny(ethyl)ketene with N-Boc imine to give the corresponding β-lactam in good yield. Meanwhile, they successfully showed that chiral NHCs derived from *L*-pyroglutamic acid could promote the reactions of various ketenes with *N*-substituted imines with good enantioselectivities (Scheme 46a).[74] Almost at the same time, Smith's group also independently reported the NHC-catalyzed [2+2] cycloaddition of *N*-tosylimines and disubstituted ketenes (Scheme 46b).[75]

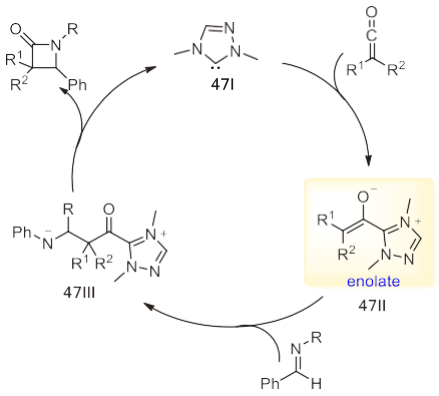
Scheme 46 Chiral NHC-catalyzed Staudinger reaction of ketenes with imines



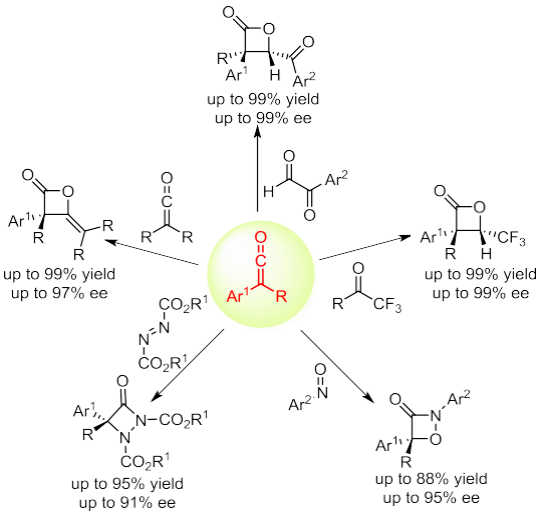
In the postulated mechanism (Scheme 47), the free NHC **47I** attacks the ketene to give a reactive zwitterion intermediate **47II**. This intermediate has a structure bearing an enolate and an azolium cation as a potential leaving group. The addition of enolate **47I** to the imine gives adduct **47III**. Cyclization of intermediate **47III** affords the desired product of β-lactam and regenerates the NHC catalyst.

Shortly after the seminal reports, Ye and coworkers successfully developed the asymmetric [2+2] cycloaddition of ketenes. Some examples are shown in Scheme 48.[76]

Scheme 47 Proposed mechanism for chiral NHC-catalyzed Staudinger reaction of ketens and imines

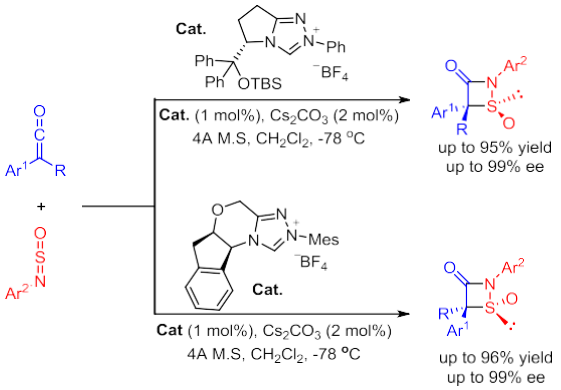


Scheme 48 [2+2] cycloaddition of ketenes reported by Ye



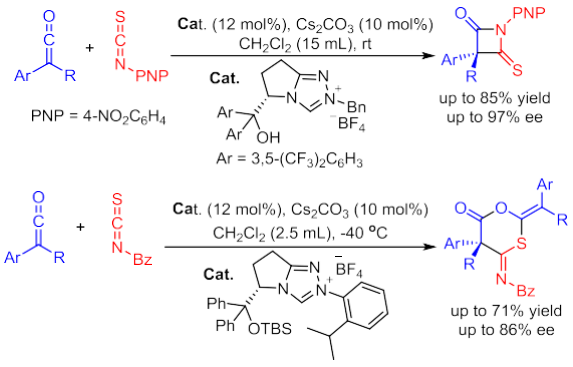
In 2011, Ye and coworkers reported the NHC-catalyzed [2+2] cycloaddition of ketenes with *N*-sulfinylanilines. Cycloadducts were afforded in good yields with excellent enantioselectivities. It is noteworthy that both enantiomers of the products have been obtained by choosing different NHC catalysts (Scheme 49).[77]

Scheme 49 Enantioselective formal [2+2] cycloaddition of ketenes and *N*-sulfinylanilines via NHCs catalysis.



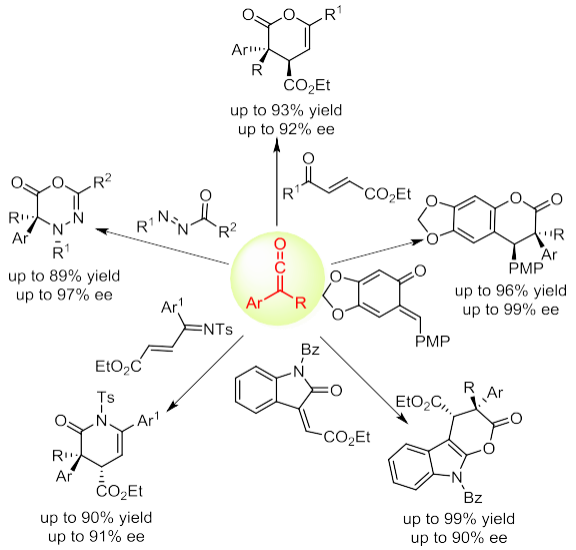
The enantioselective [2+2] cycloaddition of ketenes to 4-nitrophenyl isothiocyanate promoted by NHC catalysts was also reported. It is interesting to note that the [2+2+2] cycloadduct was obtained when benzoyl isothiocyanate was used to react with the ketene substrate (Scheme 50).[78]

Scheme 50 [2+2] and [2+2+2] cycloaddition of ketenes



The [4+2] cycloaddition reactions of ketenes are efficient approaches for the synthesis of six-membered heterocycles. In 2008, Ye and coworkers found that the NHC-catalyzed [4+2] cycloaddition reaction of disubstituted ketenes with enones gave the corresponding δ-lactones. After this report, Ye and coworkers further developed the NHC-catalyzed [4+2] cycloaddition reaction (Scheme 51).[79]

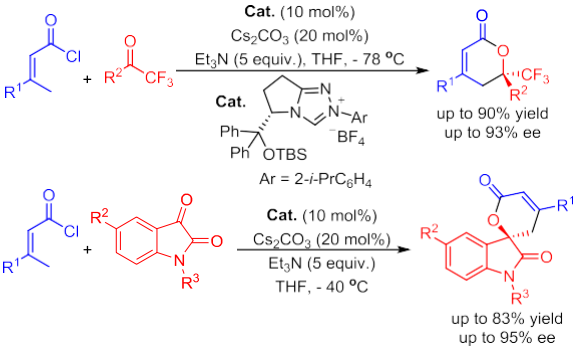
Scheme 51 [4+2] cycloaddition of ketenes



3.2. Activation of ketenes for access to dienolate intermediates

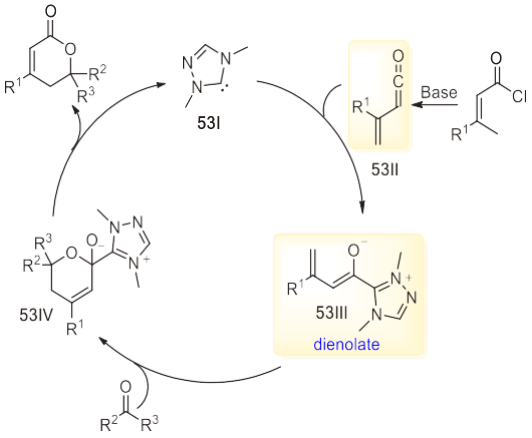
Ye and coworkers also proved that dienolates could be generated when vinylketenes were employed in the NHC-catalyzed reactions instead of alkyl- or aryl-substituted ketenes. Vinylketenes are not stable, but can be generated *in situ* from α,β-unsaturated acyl chlorides in the presence of bases. In 2011, Ye and coworkers successfully disclosed the NHC-catalyzed [4+2] annulation of unsaturated acyl chlorides with trifluoromethyl ketones. In this work, isatins could also be used as electrophiles for the reaction and gave the spirocyclic oxindole-δ-lactones in moderate yields and excellent enantioselectivities (Scheme 52).[80]

Scheme 52 NHC-catalyzed cyclization of unsaturated acyl chlorides and ketones



In the postulated mechanism (Scheme 53), the catalytic cycle of this NHC-catalyzed reaction was initiated by the addition of the free NHC **53I** to the *in situ* generated vinyl ketene **53II**. The dienolate intermediate **53III** was afforded and reacted with ketones in a hetero-Diels-Alder reaction pathway and afforded a cyclized intermediate **53IV**, which could lead to the dihydropyranone product after elimination of the NHC catalyst.

Scheme 53 Possible catalytic cycle



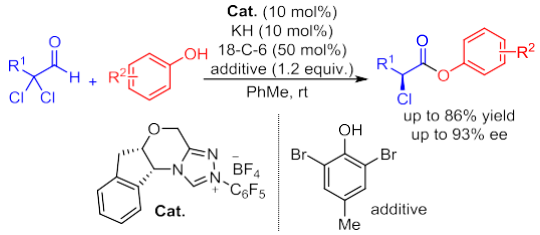
The NHCs were also found to be efficient catalysts for the [4+2] annulation of α,β-unsaturated acyl chlorides with azodicarboxylates or 3-alkylideneoxindoles. However, low enantioselectivities were observed in these cases. Therefore, cinchona alkaloids were used in order to achieve good enantioselectivities in these reactions.[81]

3.3. Activation of aldehydes for access to enolate intermediates

Ketenes, enals, α-functionalized aldehydes and activated esters are the most commonly used azolium enolate precursors. This section focuses on the generation of azolium enolates by using aldehydes as the reaction substrates.

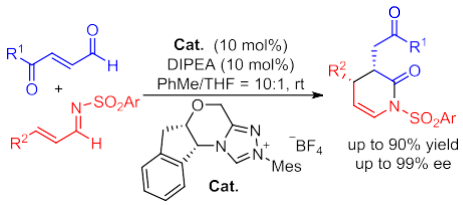
In 2005, Rovis and coworkers reported a highly enantioselective esterification reaction involving NHC-bound azolium enolate intermediates. The redox esterification of α,α-dichloro aldehydes catalyzed chiral NHCs gave the corresponding α-halo esters in moderate to good yields and high ee values (Scheme 54).[82] Vora and Rovis subsequently extended this chemistry to the enantioselective hydrogenation of halo aldehydes. In 2010, they reported the synthesis of α-chloro and α-fluoro carboxylic acids through a mild biphasic redox process.[83]

Scheme 54 Enantioselective synthesis of α-chloro esters



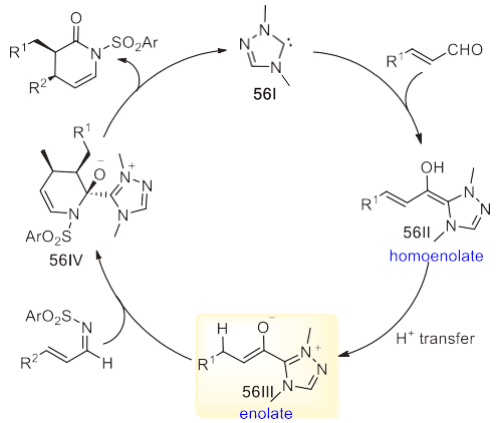
In 2006, Bode and coworkers reported the first example of the NHC-catalyzed generation of a highly reactive dienophile that participated in $LUMO_{diene}$-controlled Diels-Alder cyclization with α,β-unsaturated imines under mild conditions (Scheme 55).[84]

Scheme 55 NHC-catalyzed highly enantioselective Diels-Alder reactions between azadienes and enolates



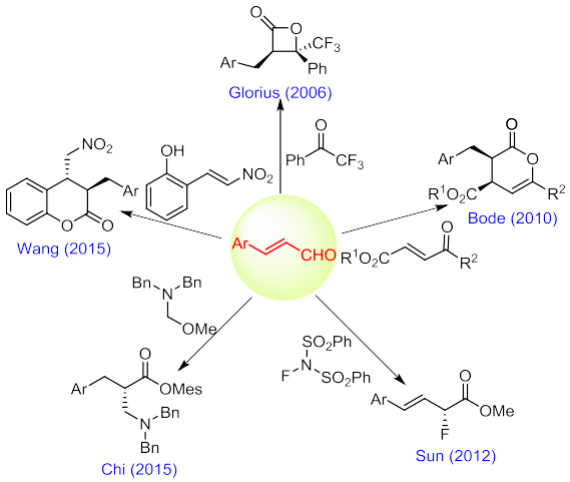
In the postulated mechanism (Scheme 56), the α,β-unsaturated aldehyde was attacked by the *in situ* formed carbene **56I**. The Breslow intermediate **56II** then tautomerized to the conjugated homoenolate **56II'**, which then underwent a proton transfer process to generate the enolate intermediate **56III**. The enolate **56III** could then react with the α,β-unsaturated imine substrate through a formal [4 + 2] reaction to afford the intermediate **56IV**, which could afford the desired product after elimination of the NHC catalyst.

Scheme 56 Proposed mechanism for NHC-mediated enolate generation



The catalytic generation of the chiral enolate equivalent from α,β-unsaturated aldehydes with chiral NHC catalysts can make the highly enantioselective hetero-Diels-Alder reactions possible. The reactions proceeded under mild conditions with both aliphatic and aromatic substituted enals used as substrates. Synthetically valuable products could be afforded in excellent yields with outstanding stereoselectivities (Scheme 57).[85]

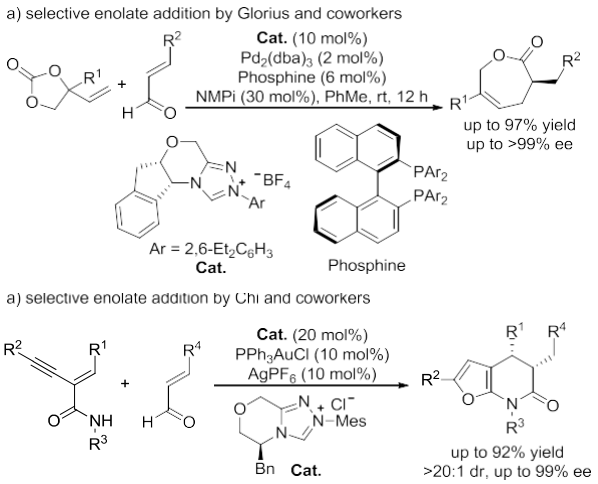
Scheme 57 Enolates generated from α,β-unsaturated aldehydes



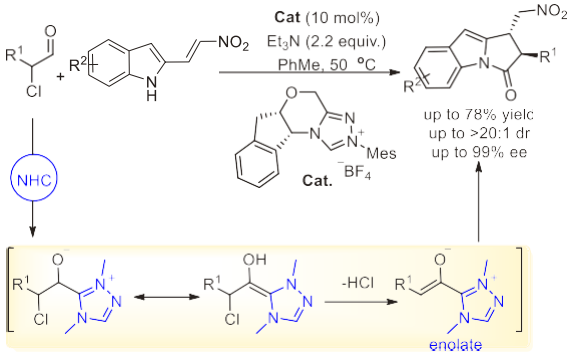
The highly enantioselective [5+2] annulation of enals with vinylethylene carbonates through a cooperative NHC/Pd catalytic process was reported by Glorius in 2018. Recently, our group disclosed that the ynamide substrate could be activated by a gold catalyst to form unsaturated ketimine intermediate. The unsaturated ketimine intermediate could subsequently react with enals (via azolium enolate intermediate generated with NHC) effectively to form bicyclic lactam products with excellent diastereo-and enantio-selectivities (Scheme 58).[86]

The generation of the chiral enolate intermediates via NHC-catalyzed intramolecular redox reactions of α-haloaldehydes was disclosed by Bode's group in 2006.[87] In 2013, Enders and colleagues demonstrated an interesting formal [3+2] cycloaddition of NHC-bound azolium enolates with 2-nitrovinylindoles. Chiral azolium enolates were generated *in situ* from α-chloro aldehydes and chiral NHC precursors (Scheme 59).[88]

Scheme 58 Highly enantioselective annulation of enolate intermediate

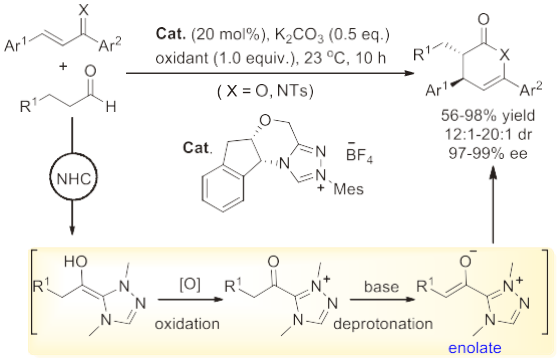


Scheme 59 Formal [3+2] annulation of α-chloroaldehydes with nitrovinylindoles



In 2012, Rovis and coworkers reported that simple aliphatic aldehydes could serve as enolate precursors for the highly enantioselective synthesis of lactones and lactams through oxidative NHC organocatalytic reactions. Reaction of the aliphatic aldehyde with an NHC catalyst gave the Breslow intermediate, which could be oxidized and deprotonated to give the enolate intermediate. Finally, [4+2] cycloaddition would afford a six-membered ring product (Scheme 60). After this seminal report, Chi, Wang, Ren and coworkers further developed this method with a variety of functional molecules used as the reaction substrates.[89]

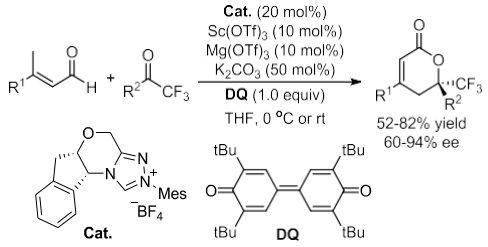
Scheme 60 Hetero-Diels-Alder reactions through oxidative enolate formation



3.4. Activation of aldehydes for access to dienolate intermediates

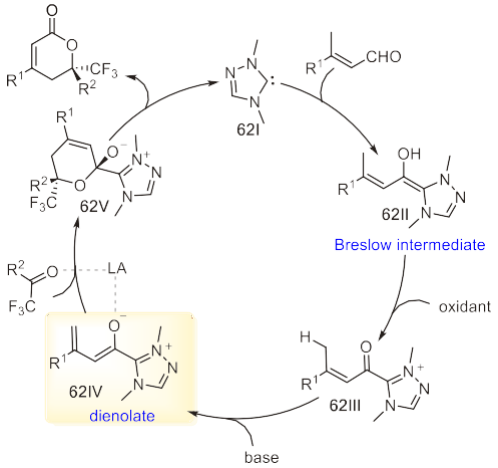
Recently, the azolium dienolate intermediates generated by NHCs have been employed in asymmetric synthesis. α,β-Unsaturated aldehydes can be utilized to generate the azolium dienolate intermediate with NHC catalysts. In 2012, our group reported the NHC-catalyzed azolium dienolates activation reaction of enals in the presence of quinone oxidant (**DQ**; Scheme 61).[90]

Scheme 61 NHC-catalyzed oxidative [4+2] cycloaddition of enals and trifluoromethyl ketones



In the postulated mechanism (Scheme 62), we employed β-methyl enals as precursors of azolium dienolates to react with ketones. The addition of the NHC catalyst **62I** to the enal substrate gave the Breslow intermediate **62II**, which was then oxidized by **DQ** to afford the α,β-unsaturated acyl azolium intermediate **62III**. The latter then delivers **62IV** by the γ-deprotonation of **62III** in the presence of a base. To achieve high enantioselectivities of the corresponding lactones, the Lewis acid cocatalysts, $Sc(OTf)_3$ and $Mg(OTf)_2$, were used. It was proposed that the Lewis acid played an important role in connecting the trifluoromethyl ketones with the dienolate intermediates.

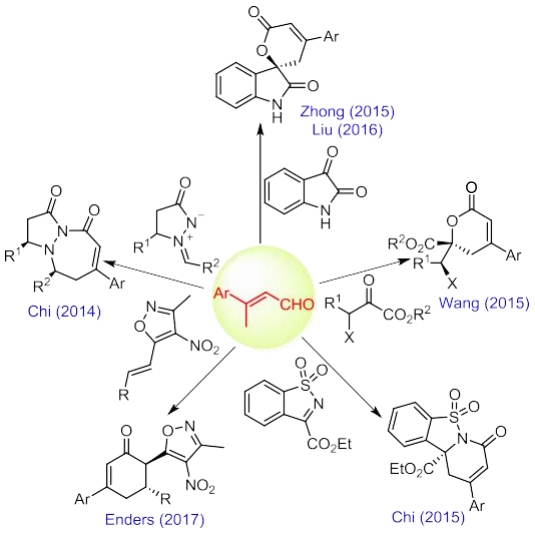
Scheme 62 NHC-catalyzed oxidative [4+2] cycloaddition via dienolate intermediate



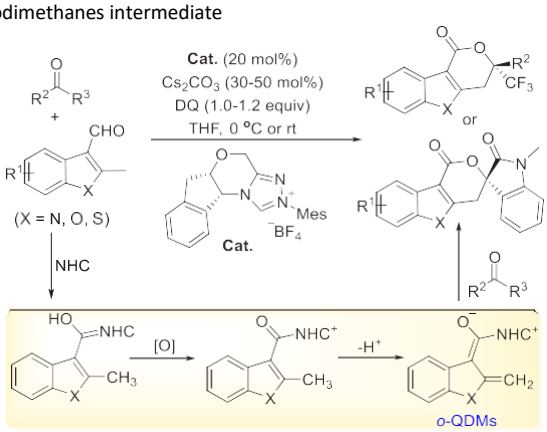
The NHC-catalyzed oxidative azolium dienolate activation strategy could be applied in a variety of cycloaddition reactions. Typical examples involving NHC-catalyzed azolium dienolates by employing the oxidative γ-functionalization of enals are shown in Scheme 63.[91]

In 2013, Chi and coworkers reported that the heteroaryl aldehydes containing an indole, benzofuran or benzothiophene moiety also worked well in this process (Scheme 64). NHC-catalyzed oxidative activation of 2-methylindole-3-carboxaldehyde generated NHC-bound *o*-QDM azolium dienolates as a key intermediate. This intermediate then underwent a formal [4+2] cycloaddition

Scheme 63 NHC-catalyzed oxidative cycloaddition of enals via dienolate intermediate



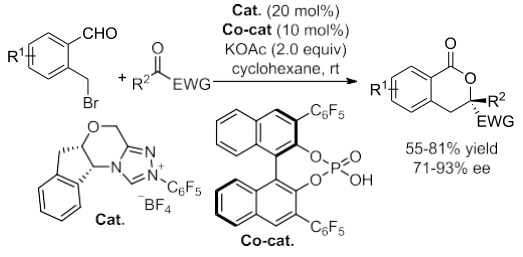
Scheme 64 NHC-catalyzed oxidative [4+2] cycloaddition via *ortho*-quinodimethanes intermediate



with a trifluoromethyl ketone or isatin to form a polycyclic lactone, which contains a quaternary spirocyclic chiral carbon center. The α-branched aryl aldehydes were employed as suitable substrates and gave the corresponding products in moderate to good yields and high enantioselectivities.[92]

Glorius and Rovis independently demonstrated that a leaving group at the *ortho*-benzylic position of aromatic aldehydes facilitated the formation the *o*-QDM intermediates, which acted as a diene for a [4+2] cycloaddition with activated ketones. Moreover, Rovis and coworkers successfully developed a highly enantioselective version of this transformation by using a cooperative NHC and Brønsted acid catalytic strategy (Scheme 65).[93]

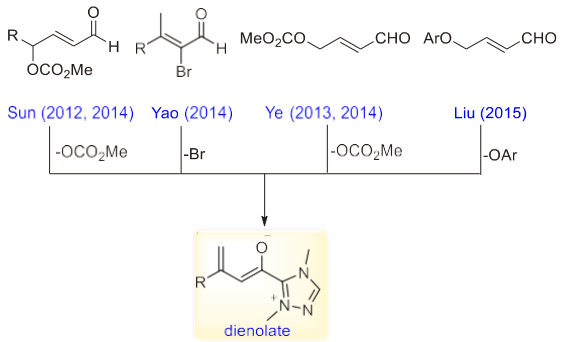
Scheme 65 Enantioselective [4+2] cycloaddition of 2-(bromomethyl)-benzaldehyde with ketones



The generation of the acyl azolium dienolate by introducing

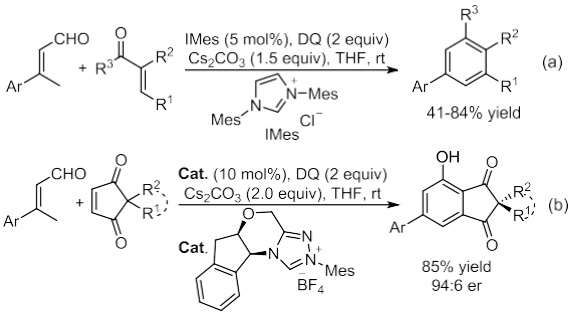
various leaving groups has also been developed. Typical examples are listed below (Scheme 66).[94]

Scheme 66 NHC-bounded dienolate generated from precursors of aldehydes introducing a leaving group



Our group has utilized the NHC-mediated azolium dienolate intermediates to construct multisubstituted benzene derivatives (Scheme 67). We construct the benzene core through a car- bene-catalyzed formal [3+3] reaction.[95]

Scheme 67 Synthesis of multi-substituted benzenes



3.5. Activation of aldehydes for access to α,β-unsaturated acyl azolium intermediates

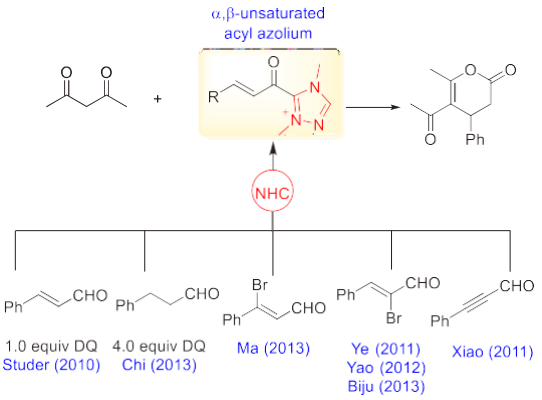
In 2006, Zeitler reported the first redox isomerization of alkynyl aldehydes to the α,β-unsaturated acyl azolium intermediate.[96] In the past decade, the α,β-unsaturated acyl azolium has been extensively reported. In 2007, Scheidt and coworkers reported the use of MnO_2 as the external oxidant for the conversation of α,β-unsaturated aldehydes to the α,β-unsaturated acyl azolium.[97] The organic oxidants of azobenzene and diphenoquinone oxidant (**DQ**) were developed by Connon and Studer, respectively.[98]

Lupton and coworkers reported the first annulation of the α,β-unsaturated acyl azolium in 2009.[99] Subsequently, numerous annulations via α,β-unsaturated acyl azolium were reported. The cycloaddition reactions of the α,β-unsaturated acyl azoliums with the enolates of 1,3-dicarbonyls have been extensively developed. Efforts have been devoted into the development of new methods for acyl azolium generation from various starting materials (Scheme 68).[100]

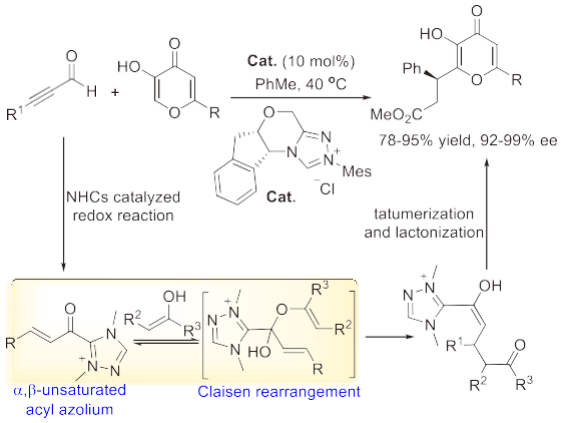
In 2010, Bode and coworkers reported the enantioselective synthesis of pyranones through the reaction of kojic acid derivatives with the α,β-unsaturated acyl azolium intermediate generated from the redox isomerization of ynals (Scheme 69).[101]

You and coworkers have shown that naphthols and electron-rich phenols could also be used as the bis-nucleophiles for the enantioselective synthesis of dihydropyranones. A novel chiral NHC precatalyst has been developed in this report (Scheme 70).[102]

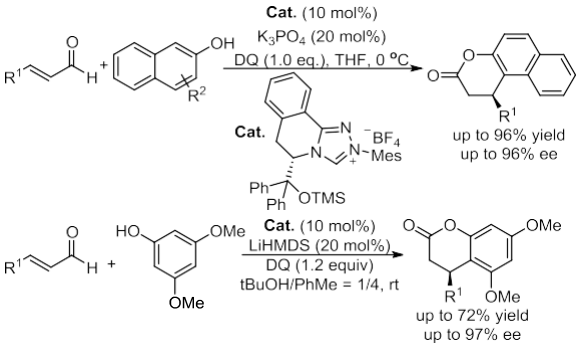
Scheme 68 [3+3] annulations via α,β-unsaturated acyl azolium



Scheme 69 Enantioselective claisenrearrangement catalyzed by NHCs



Scheme 70 Enantioselective [3+3] annulations reported by You

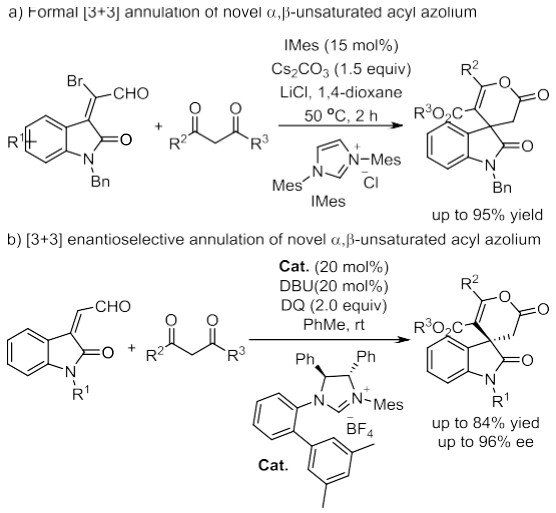


Lu, Xu and coworkers have disclosed that the istain-derived 2-bromoenals could also be used as the α,β-unsaturated acyl azolium precursors. Specifically, Xu's group have reported that isatin-derived enals could give the desired products bearing quaternary chiral carbon centers in excellent enantioselectivities under oxidative conditions (Scheme 71).[103]

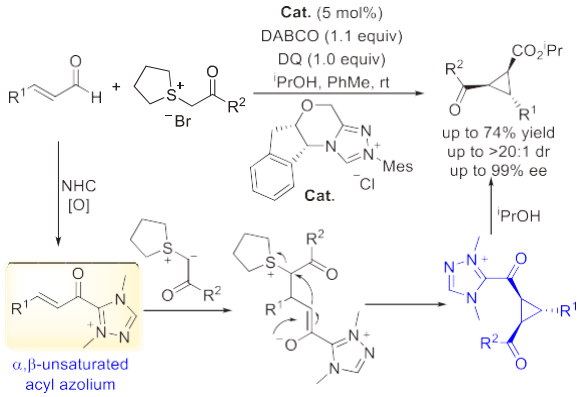
In 2012, Studer and coworkers reported the NHC-catalyzed synthesis of cyclopropyl carboxylic acid esters from enals, sulfur ylides and alcohols (Scheme 72).[104]

The annulation of the α,β-unsaturated acyl azolium with enamines was reported by Bode and coworkers. Dihydropyridinones were afforded as the final products in this process (Scheme 73).[105]

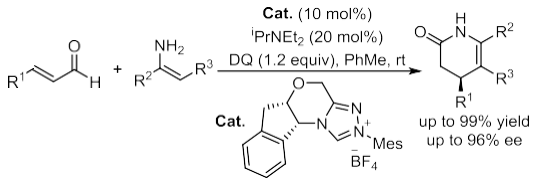
Scheme 71 Formal [3+3] annulation of isatin-derived enals with dicarbonyl compounds



Scheme 72 Studer's *2+1+ annulation with sulfur ylides

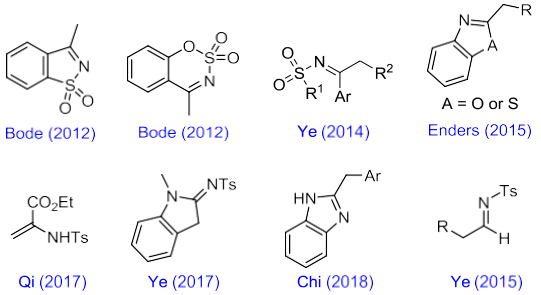


Scheme 73 Bode's *3+3+ annulation with enamines



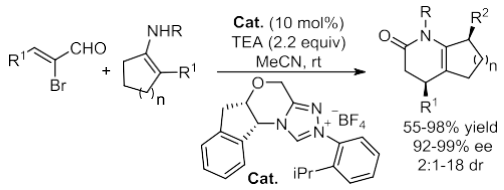
After this seminal report, various enamine substrates were subsequently explored as the reactants in the [3+3] annulation reactions. Typical examples are shown in Scheme 74.[106]

Scheme 74 [3+3] annulation of α,β-unsaturated acyl azolium and enamine substrates



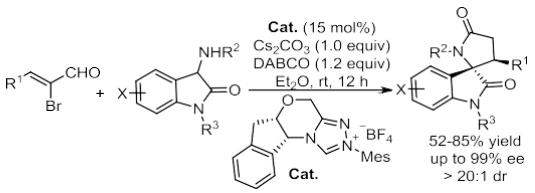
Recently, Ye and coworkers reported an NHC-catalyzed DKR reaction of enamines through a [3+3] annulation with bromoenals. Meanwhile, a kinetic resolution of α,α-disubstituted imines was also developed for the enantioselective construction of dihydropyridone products (Scheme 75).[107]

Scheme 75 [3+3] annulation of enamines and enals via dynamic kinetic resolution



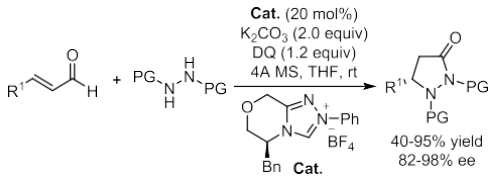
In addition to the *3+3+ annulation of α,β-unsaturated acyl azolium intermediates, the [3+2] annulation was also widely studied. In 2014, Ye and coworkers demonstrated that the α,β-unsaturated acyl azolium could react with *N*-sulfonyl-α-aminoketones to afford lactams.[108] A related strategy was reported via α-bromoenals by the same group in 2016 (Scheme 76).[109]

Scheme 76 Ye's *3+2+ annulations with aminoketones



In 2016, Chi and coworkers reported the addition of nucleophilic nitrogen atoms of hydrazide to the catalytically generated α,β-unsaturated acyl azolium intermediates (Scheme 77). The reaction installed a nitrogen atom at the β-carbon atom of an enal and afforded a pyrazolidinone adduct with a good yield and excellent enantioselectivity.[110]

Scheme 77 Enantioselective nucleophilic β-carbon amiation of enals by carbene catalyzed formal [3+2] reactions

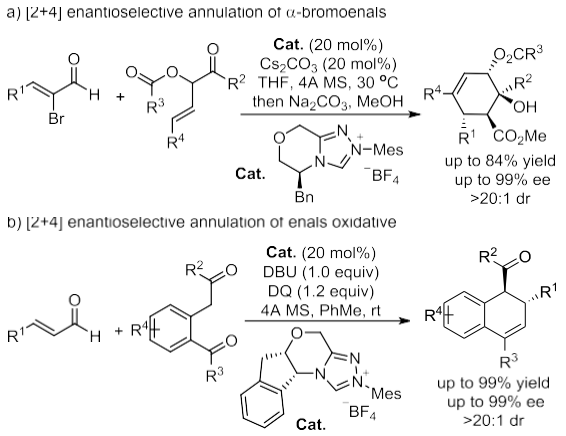


Fang and coworkers reported an all-carbon annulation reaction of α,β-unsaturated acyl azolium and dienolate. α-Bromoenals and α-benzoyloxy ketones were used as the reaction substrates (Scheme 78a).[111] Subsequently, the same group reported that 1,5-diketones could also work well in this intermolecular [2+4] annulation (Scheme 78b).[112]

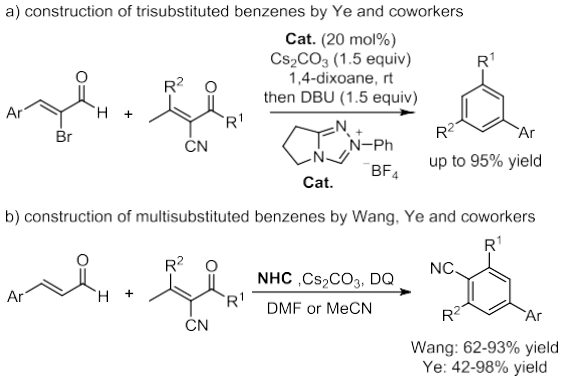
The group of Ye[113] and Wang[114] independently reported the NHC-catalyzed synthesis of polysubstituted benzenes from the reaction of α-cyanoenones and the α,β-unsaturated acyl azolium (Scheme 79).

Recently, our group have developed a chemo- and enantioselective strategy for access to dihydroquinoline molecules. α-Bromoenals are selectively activated by NHC catalysts through [2+4] annulations in the presence of 2-aminobenzaldehydes (Scheme 80).[115]

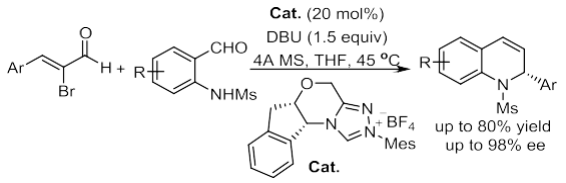
Scheme 78 Fang's enantioselective [2+4] annulation reactions



Scheme 79 [2+4] annulations to prepare substituted benzenes



Scheme 80 NHC-catalyzed chemoselective reactions of enals and α-aminobenzaldehydes for access to chiral dihydroquinolines



An NHC-catalyzed domino sequence via α,β-unsaturated acyl azolium intermediates has been developed. Several newly developed Michael/aldol domino reactions for the asymmetric synthesis of functional molecules are summarized in Scheme 81.[116]

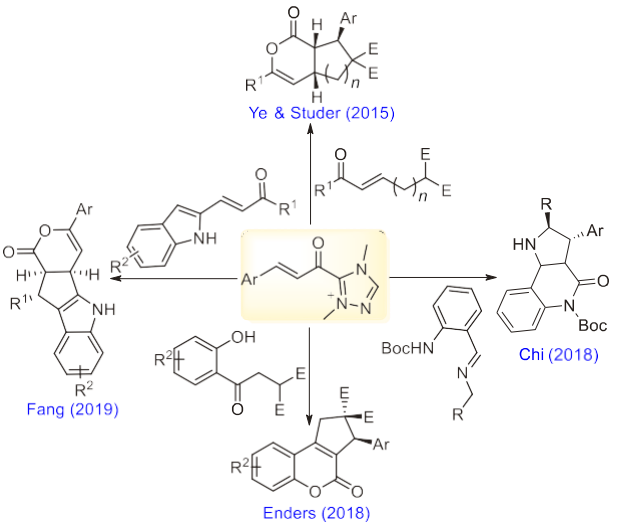
4. Activation of Carboxylic Esters for Access to Homoenolate, Enolate, Dienolate, and α,β-Unsaturated Acylazolium Intermediates

Compared to aldehyde and ketene substrates, carboxylic acids and their derivatives such as esters are readily available and easy to synthesize. NHC-bounded enolate, homoenolate, dienolate and α,β-unsaturated azolium intermediates can be generated from NHC and carboxylic ester substrates.

4.1. Activation of esters for access to enolate intermediates

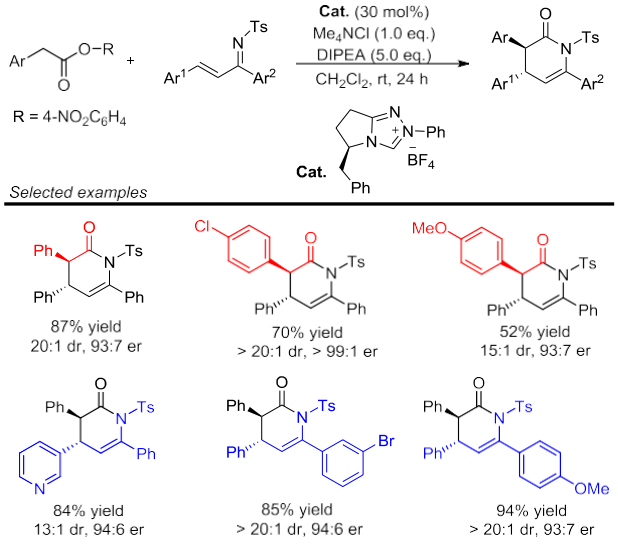
In 2012, Chi and coworkers developed the first NHC-catalyzed generation of enolate intermediates from stable α-aryl carboxylic esters, which could undergo enantioselective reactions with α,β-unsaturated imines to produce cyclic δ-lactams in good to

Scheme 81 Domino reactions involving α,β-unsaturated acyl azolium intermediates



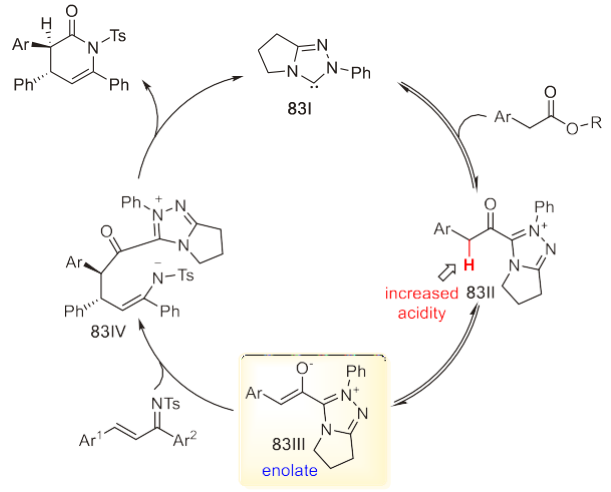
high yields and excellent stereoselectivities (Scheme 82).[117] In this transformation the α-carbon of the carboxylic ester was activated as a nucleophilic reactive site. As illustrated in Scheme 83, the catalytic reaction goes through the nucleophilic addition of NHC to the ester substrate directly rather than an *in-situ* formation of ketene intermediates. First, carboxylic ester with a good leaving group (OAr, Ar = 4-$NO_2C_6H_4$) is attacked by the NHC catalyst and an azolium intermediate (**II**) was formed with an increased acidic α-C-H bond. Then the α-carbon was deprotonated by an additional base to form the enolate intermediate (**III**). The enolate intermediate then reacts with the α,β-unsaturated imine via a Michael addition and cyclization process to produce the lactam product.

Scheme 82 NHC-catalyzed α-aryl carboxylic ester activation

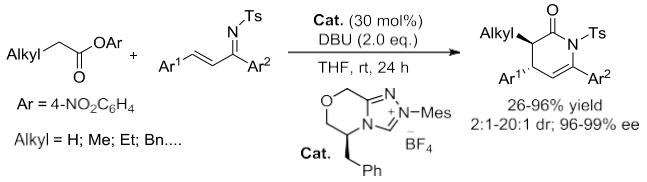


In addition to α-aryl substituted carboxylic esters, α-alkyl substituted carboxylic esters could also generate enolate intermediates under strong basic conditions. In 2013, Chi and coworkers described an NHC-catalyzed [2+4] cycloaddition of α-alkyl substituted carboxylic esters with α,β-unsaturated imine substrates (Scheme 84).[118] The amino alcohol derived triazolium salt was used as the NHC pre-catalysts with DBU used as the base in this

Scheme 83 Enolate intermediate generated from carboxylic ester



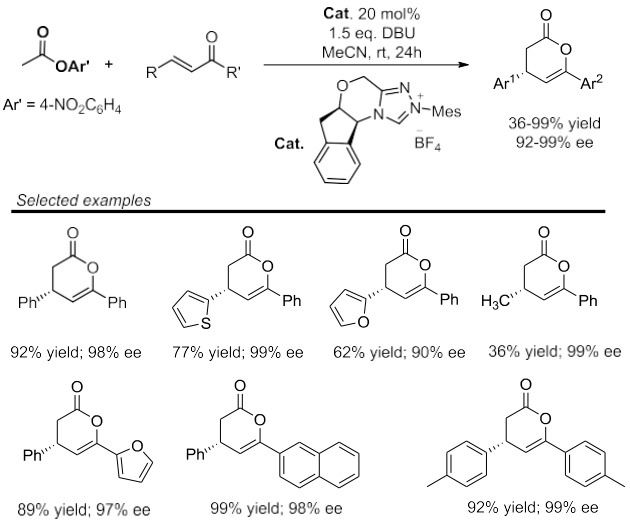
Scheme 84 NHC-catalyzed α-alkyl carboxylic ester activation



reaction. The lactam products could be obtained in good yields with excellent diastereo- and enantio-selectivities (> 96% ee).

In 2013, Chi and coworkers reported the NHC-catalyzed generation of enolate intermediate from the simple acetic acid ester.[119] The smallest enolate intermediate readily underwent highly enantioselective reactions with unsaturated ketones or imines under strong basic conditions. α-Unsubstituted δ-lactone or lactam products that are difficult to make from other methods were smoothly synthesized with very high enantioselectivities (Scheme 85).

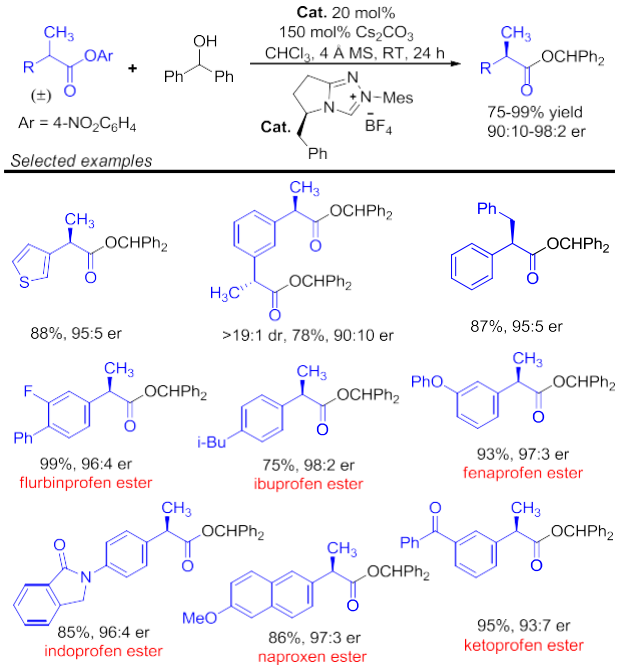
Scheme 85 NHC-catalyzed acetic ester activation



In 2016, Chi and co-authors reported a carbene-catalyzed dynamic kinetic resolution of α,α-disubstituted carboxylic esters via enolate activation process. A broad range of chiral disubstituted propionic acid esters were prepared in excellent yields and enantioselectivities (up to 99% yield and 99 : 1 er) (Scheme 86).[120]

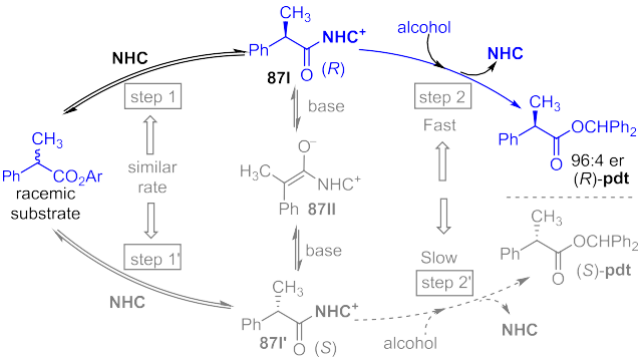
Derivatives of propionic acids bearing stereogenic α-carbon centers are widely used as non-steroidal anti-inflammatory drugs (NSAIDs), such as *i*buprofen and naproxen. This method provides efficient approaches to make this kind of bioactive molecules, especially in enantiomerically pure forms.

Scheme 86 NHC-catalyzed DKR via enolate intermediate



There are two possible reaction pathways for this transformation. Control experiments and DFT calculations have been carried out to get insights into the reaction mechanism. A plausible reaction mechanism is shown in Scheme 87. Initially, the chiral carbene catalyst reacts with the ester substrate (in racemic form) to give a mixture of two diastereomeric acyl azolium intermediates (**87I** and **87I'**). These two intermediates exhibit different reactivities with alcohol substrates. In this transformation, the acyl azolium **87I** isomerized to the acyl azolium **87II** through enolization enabled by carbene catalysts. Then the acyl azolium **87I'** could react with the alcohol substrates and realized the dynamic kinetic resolution of the ester substrates.

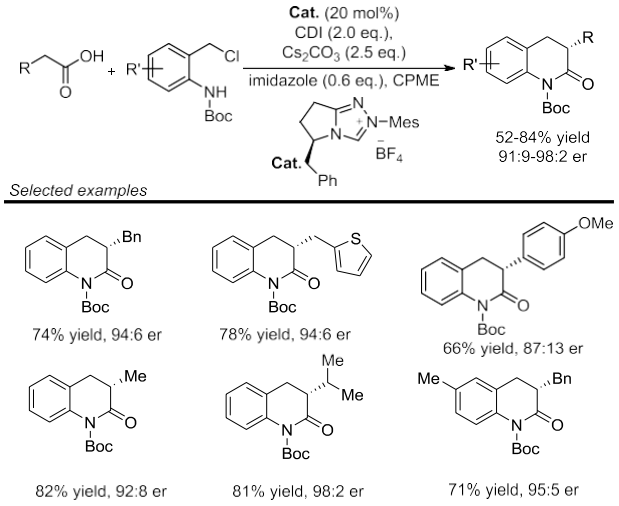
Scheme 87 Proposed dynamic kinetic resolution (DKR) pathway



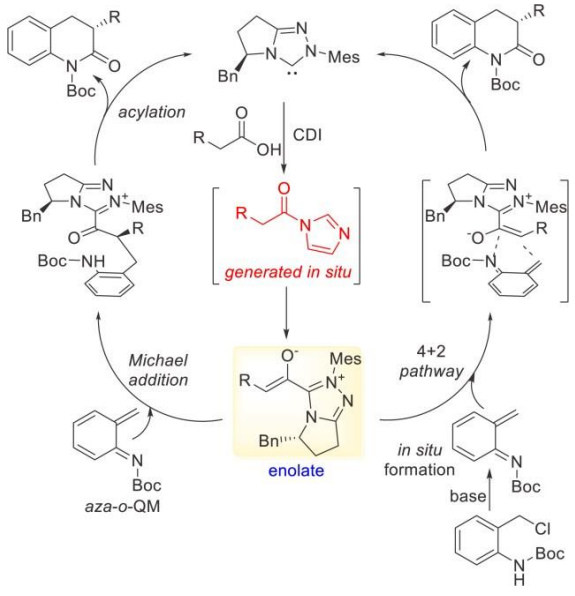
Most of the carboxylic acids are stable and readily available. Carboxylic acids are critical synthetic starting materials for esters preparation. Therefore, the direct use of carboxylic acids as starting materials via *in-situ* activation strategies in NHC-catalyzed reactions is very interesting and attractive. In 2014, Scheidt and

coworkers developed the first NHC catalytic generation of enolate intermediates directly from the carboxylic acids (Scheme 88).[121] In this reaction, CDI was used as an acid activating reagent and the carboxylic acid could be efficiently converted to an activated amide intermediate. Chiral NHC catalyst reacts with the active amide to form the enolate intermediate in the presence of excess amount of strong bases. Then chiral enolate intermediate reacts with the electrophilic aza-*o*-quinone methide *in situ* formed from aminobenzyl chloride. Finally, the chiral dihydroquinolone product could be obtained with a good yield and er value (Scheme 89).

Scheme 88 NHC-catalyzed α-activation of carboxylic acid



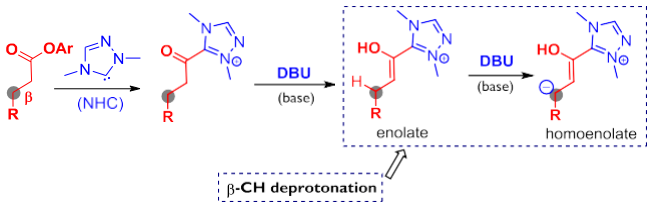
Scheme 89 Proposed mechanism for NHC-catalyzed α-activation of carboxylic acid



4.2. Activation of esters for access to homoenolate intermediates

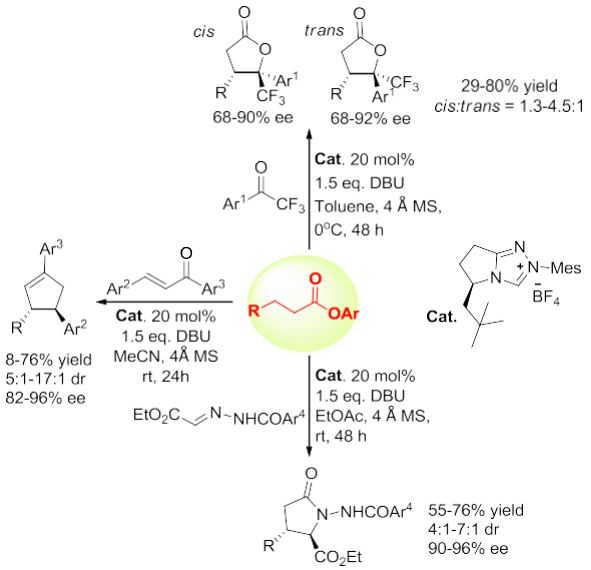
In 2013, Chi and coworkers reported the first catalytic activation of the β-carbons of saturated esters as nucleophiles through NHC organocatalysis.[122] Under basic conditions, the β-C-H of the NHC-bounded enolate intermediate could be further deprotonated to form the homoenolate intermediate (Scheme 90). This catalytic activation mode of the β-carbons of saturated esters has inspired the development of new and useful reactions and synthetic strategies.

Scheme 90 Postulated pathway for ester β-carbon activation



The catalytically generated nucleophilic β-carbons could participate in enantioselective reactions with various electrophilic substrates. For example, enantioenriched lactams/lactones could be obtained via [3+2] cycloaddition reactions between the saturated carboxylic esters and corresponding hydrazines/trifluoroketones. Chiral cyclopentanes could be afforded from reactions with α,β-unsaturated ketones through cascade process (Scheme 91).[122]

Scheme 91 NHC-catalyzed esters β-carbon activation

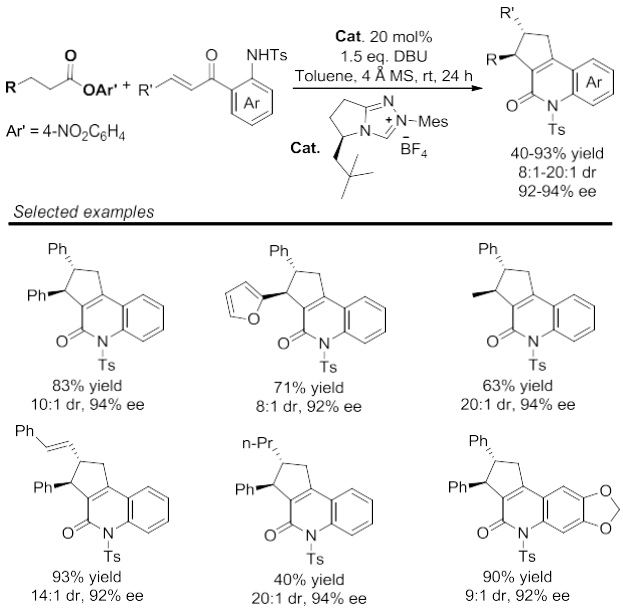


One year later, Chi and coworkers reported another transformation through NHC-catalyzed β-carbon activation of ester substrates. Multicyclic oxoquinoline-type heterocyclic products could be obtained through a cascade reaction between saturated esters and amino enones in good yields and high ee values (Scheme 92).[123]

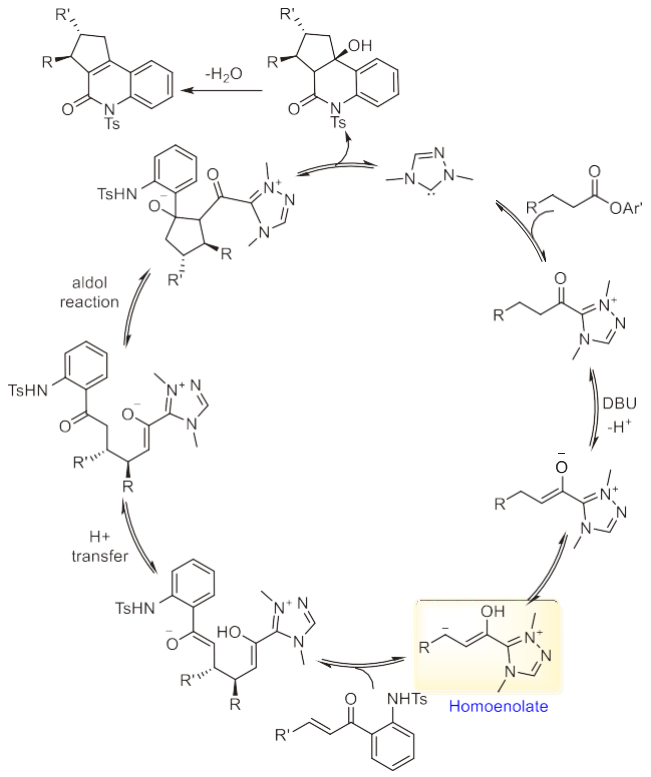
The postulated reaction mechanism was shown in Scheme 93. First, chiral NHC catalyst reacts with saturated carboxylic esters to form acyl azolium intermediate. Then, homoenolate intermediate could be generated from the enolate intermediate via deprotonation under basic condition. Finally, the target products could be formed from reaction of the homoenolate intermediate and enones via Michael addition/isomerization/aldol reaction/dehydration cascade processes (Scheme 93).

In 2016, Xu and coworkers described a formal [3+2] annulation reaction of saturated carboxylic esters with isatins by using a chiral NHC catalyst and HOBT (1-hydroxybenzotriazole) co-catalyst.[124] In this reaction, the spirooxindole lactone products bearing two vicinal stereogenic centers were obtained in good yields (up to 92% yield) and excellent diastereoselectivities (>20 : 1 dr) and enantioselectivities (up to 98% ee) (Scheme 94). Without HOBT, both the diastereo- and enantioselectivities decreased. The

Scheme 92 Cascade reaction in NHC-catalyzed esters carbon activation



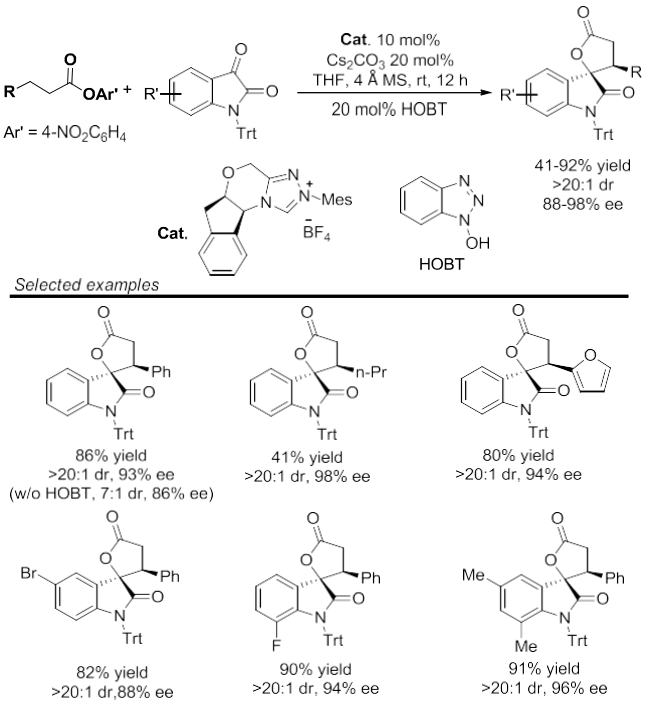
Scheme 93 Mechanism for NHC-catalyzed esters β-carbon activation



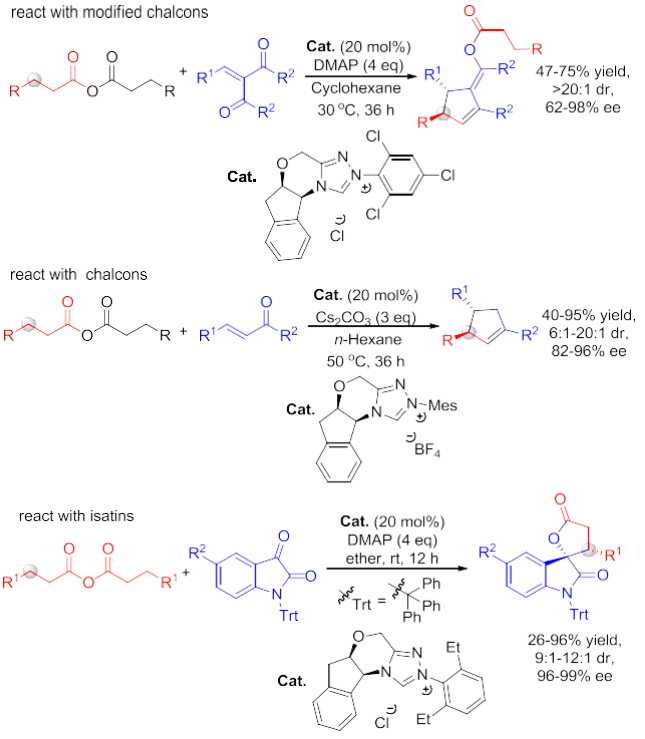
author proposed that HOBt could help to enhance both of the diastereo- and enantioselectivities via hydrogen bonding interactions.

In these two reports, aryl substituents are generally required at the β-positions of the saturated ester substrates. In 2014, Chi and coworkers developed the first NHC-catalyzed β-carbon functionalization of carboxylic anhydrides.[125] The aliphatic carboxylic anhydrides are used for the NHC-catalyzed β-activation of the alkyl substituted β-carbons. A variety of electrophiles (such as chalcons, isatins, *etc*.) could be used as substrates to react with the β-carbons of aliphatic anhydrides and afforded the corresponding products in good yields and er values (Scheme 95).

Scheme 94 NHC-catalyzed β-carbon functionalization of esters and isatins



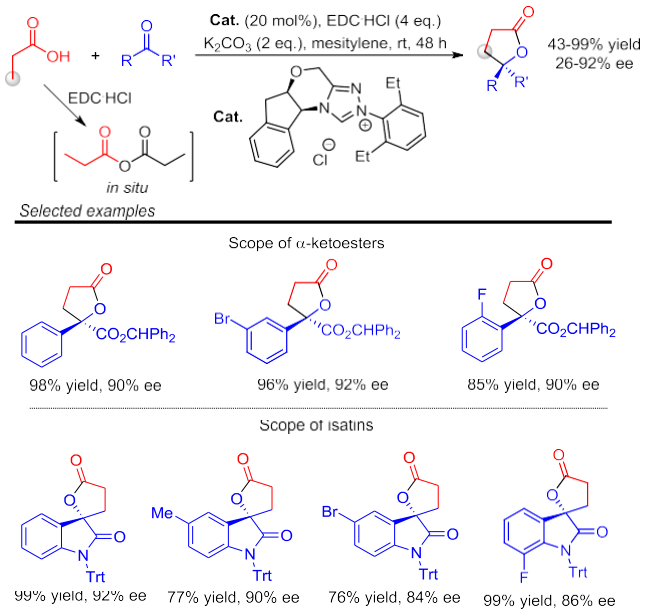
Scheme 95 NHC-catalyzed β-activation of aliphatic anhydrides



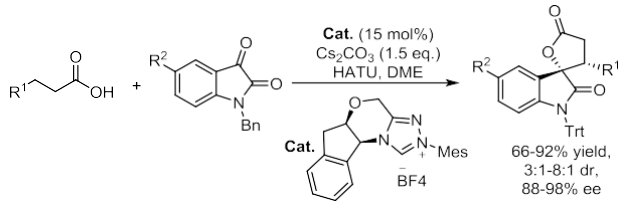
In addition to the β-carbon activation of carboxylic esters and anhydrides, NHC-catalyzed nucleophilic β-carbon activation of carboxylic acids is also developed. In 2015, Chi and coworkers reported a nucleophilic β-carbon activation of propionic acid by using EDCI as the dehydrating reagent.[126] Nucleophilic β-carbon of the *in situ* generated propionic anhydride reacts with electron-deficient ketones to obtain corresponding lactone products in good yields and enantioselectivities (Scheme 96). Almost at the same time, Yao and coworkers described the β-activation of car-

boxylic acids bearing β-aryl or alkyl substituents by using HATU (1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate) as the acid activating reagent and produced the spirocyclic oxindole products in very good yields and stereoselectivities (Scheme 97).[127]

Scheme 96 NHC-catalyzed β-carbon functionalization of propionic acid



Scheme 97 NHC-catalyzed β-carbon activation of saturated acid



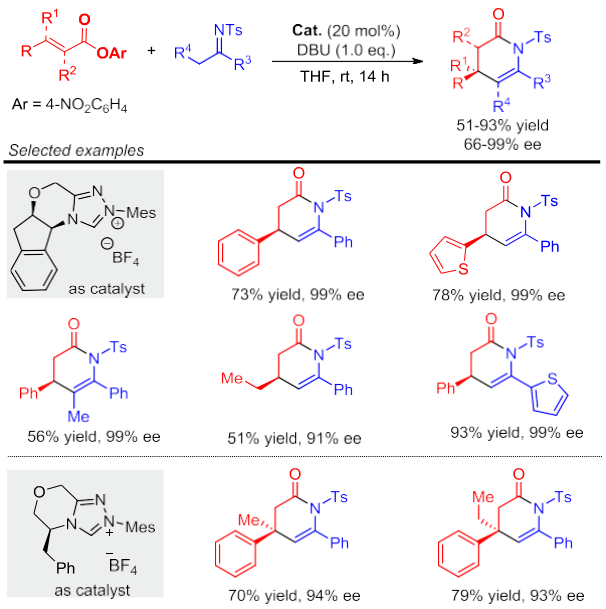
4.3. Activation of esters for access to α,β-unsaturated acyl azolium intermediates

α,β-Unsaturated carboxylic ester is another precursor for the generation of α,β-unsaturated acyl azolium. In 2013, Chi and coworkers reported the first carbene catalyzed formal [3+3] annulation reactions of α,β-unsaturated carboxylic esters with ketimines (Scheme 98).[128] The reaction showed very good tolerance to various substituents on both of the ester and imine substrates. The steric hindered substrates of β,β-disubstituted α,β-unsaturated carboxylic esters also worked well in this transformation. The desired chiral lactam products were smoothly afforded in good to excellent yields and excellent enantioselectivities (up to 93% yield and 99% ee).

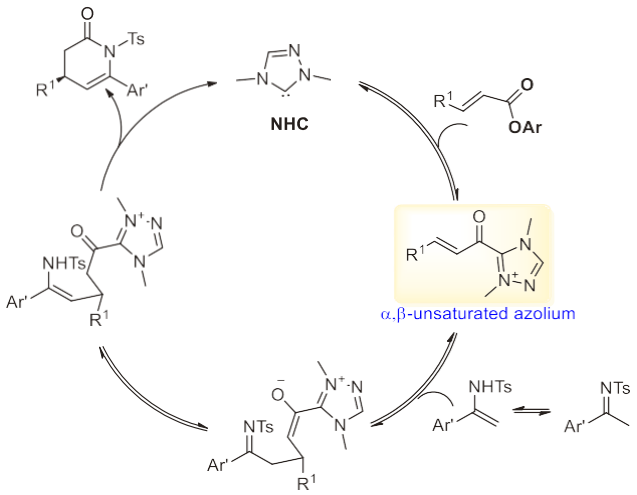
The proposed reaction mechanism is shown in Scheme 99. Free NHC catalyst reacts with α,β-unsaturated carboxylic esters to form α,β-unsaturated acyl azolium as the key intermediate. Then 1,4-addition happens between this intermediate and nucleophilic enamide that isomerized from ketimine. Finally, the nucleophilic N atom of enamide attacks the acyl azolium to form the productand releases the NHC catalyst.

The NHC-catalyzed β-LUMO activation of α,β-unsaturated carboxylic esters could also be used in the preparation of various multi-cyclic lactone molecules (Scheme 100).[129] Under the optimal condition, this reaction could afford the desired multi-cyclic lactone products via a one-pot cascade approach. The functional group tolerance of both of the esters and the enones was good

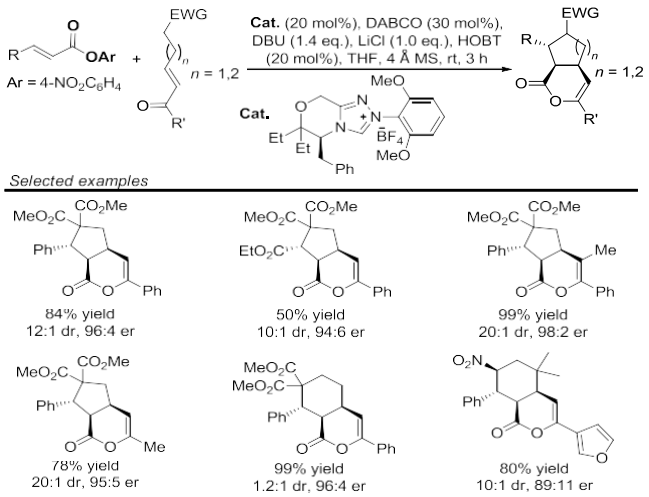
Scheme 98 NHC-catalyzed β-LUMO activation of carboxylic ester



Scheme 99 Proposed mechanism for NHC-catalyzed β-LUMO activation



Scheme 100 NHC-catalyzed cascade reaction via β-LUMO activation

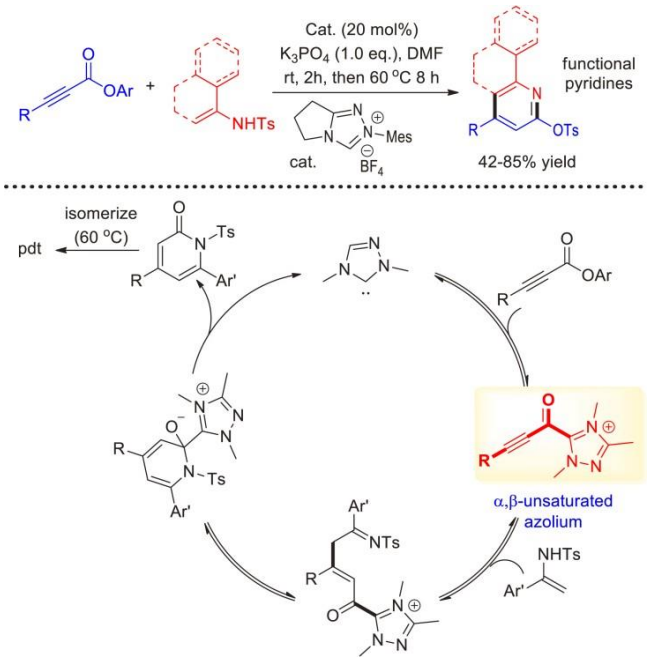


and the chiral cyclic lactone products were generally afforded in

moderate to good yields and enantioselectivities (up to 99% yield, 99 : 1 er).

In 2017, Chi and coworkers reported the first NHC-catalyzed LUMO activation of α,β-unsaturated alkyne esters for access to functional pyridines.[130] The pyridine derivatives could be effectively synthesized in moderate to good yields. In this reaction, a new unsaturated acyl azolium intermediate bearing a carbon-carbon triple bond was involved (Scheme 101).

Scheme 101 NHC-catalyzed LUMO activation of α,β-unsaturated alkyne esters



It has been shown that the NHC-bounded enolate and homoenolate intermediates could be generated from saturated carboxylic esters. The α,β-unsaturated acyl azolium intermediates can also be generated from saturated carboxylic esters under oxidative conditions. In 2017, Chi and coworkers developed the formal [3+3] annulation reaction of saturated carboxylic esters and ketimines or 1,3-diketones via oxidative NHC catalysis (Scheme 102).[131] In this report, the direct electrophilic β-sp^3 carbon activation of saturated esters has been realized under oxidative conditions.

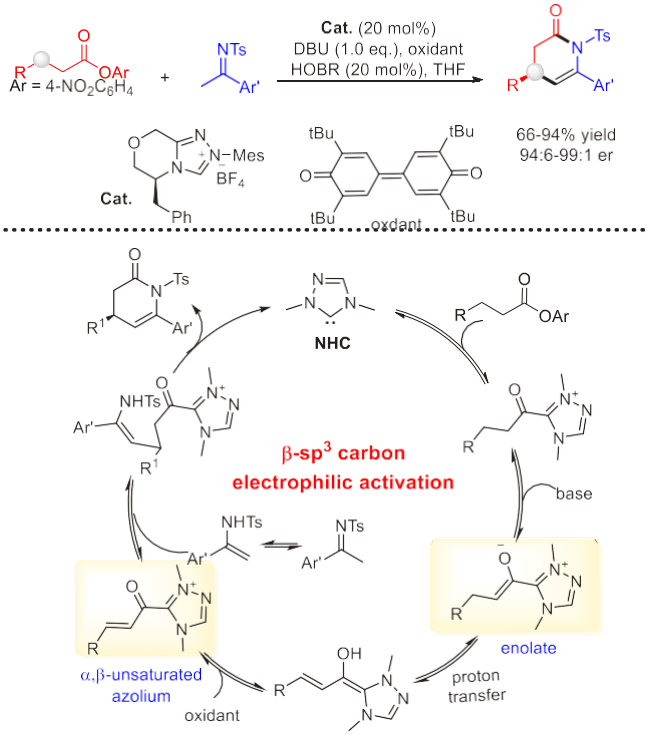
In 2015, Zhong, Yang and coworkers reported an NHC-catalyzed enantioselective [3+3] annulation reaction of 3,3-disubstituted α,β-unsaturated NHPI esters and N-Ts ketimines (Scheme 103).[132] The desired dihydropyridinone products bearing all carbon quaternary stereogenic centers could be obtained in good yields and excellent enantioselectivities (most >99% ee). This methodology demonstrated that NHPI esters are promising reactants in NHC organocatalysis.

In addition, the α,β-unsaturated acyl azolium intermediates can also be generated from stable carboxylic acids. In 2014, Ye and coworkers described several cycloaddition reactions between α,β-unsaturated carboxylic acids and various nucleophilic substrates.[133] In this transformation, PivCl was first used as activating reagent to form mixed anhydride *in situ*. Then the mixed anhydride could be activated by NHC catalyst to form the electrophilic α,β-unsaturated acyl azolium intermediates (Scheme 104).

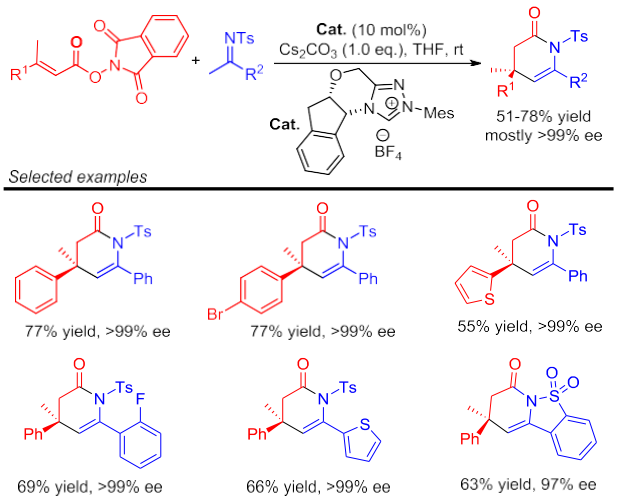
4.4. Activation of esters for access to dienolate intermediates

The γ-carbon activations of α,β-unsaturated esters by NHC catalysts are also well developed. In 2013, Chi and coworkers

Scheme 102 NHC-catalyzed β-LUMO activation of saturated esters



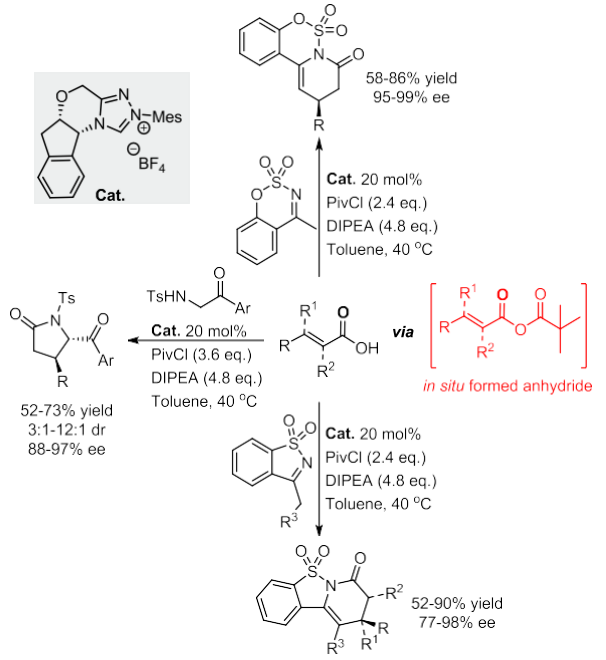
Scheme 103 NHC-catalyzed β-LUMO activation of NHPI esters



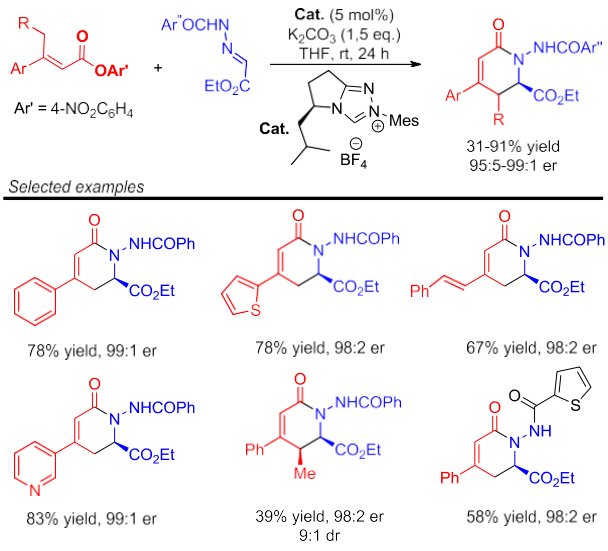
developed the first NHC-catalyzed γ-carbon activation of α,β-unsaturated esters.[134] Addition of the NHC catalyst to the α,β-unsaturated carboxylic ester gives acyl azolium intermediate. Deprotonation of the α,β-unsaturated acyl azolium intermediate leads to the dienolate intermediate (vinylogous enolate intermediate). This dienolate intermediate reacts with electrophilic hydrazone to afford δ-lactam products in good yields and enantioselectivities (Scheme 105). These lactam products can be easily transformed to optically enriched pipecolic acid derivatives.

In 2016, Xu and coworkers reported an NHC-catalyzed formal [4+2] annulation reaction of 2-methyl-heteroarene-3-carboxylic esters with isatinderived ketimines.[135] Optical heteroarene-fused δ-lactams bearing quaternary stereogenic centers could be afforded in moderate to good yields and excellent enantioselectivities through this method (Scheme 106). A postulated catalytic cycle is depicted in Scheme 107. Free NHC catalyst reacts with

Scheme 104 NHC-catalyzed β-LUMO activation of carboxylic acids



Scheme 105 NHC-catalyzed γ-carbon activation of unsaturated esters



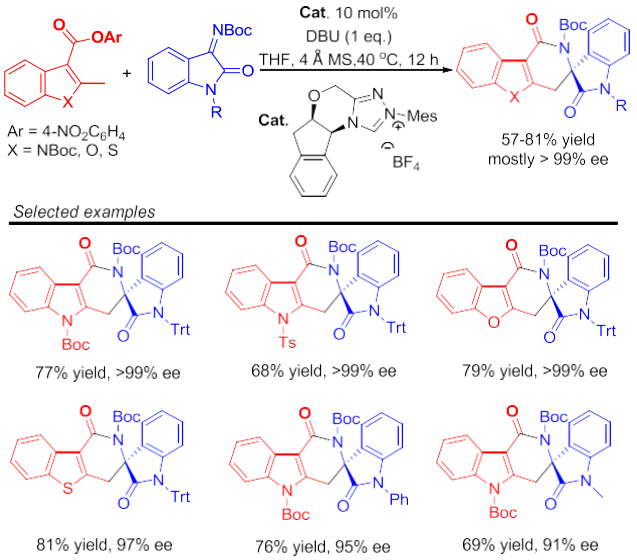
N-Boc-2-methyl-indole-3-carboxylic ester to form acyl azolium intermediate. Then deprotonation of the indole benzylic sp^3-carbon with DBU affords indole-2,3-quinodimethane intermediate. This key intermediate behaves as a 1,4-dipolarophile, which undergoes a Mannich-type addition with isatin-derived ketimine followed by lactamization to furnish the δ-lactam product and regenerate the NHC catalyst.

In 2015, Yao and coworkers described an NHC-catalyzed highly enantioselective formal *4+2+ annulation reaction of α,β-unsaturated esters of *N*-hydroxybenzotriazole (HOBt) bearing γ-H with isatin derivatives.[136] This protocol could give spirocyclic oxindole-dihydropyranones in good yields with high enantioselectivities (Scheme 108). The use of HOBt esters as substrates has dramatically extended the scope of ester substrates in NHC catalysis.

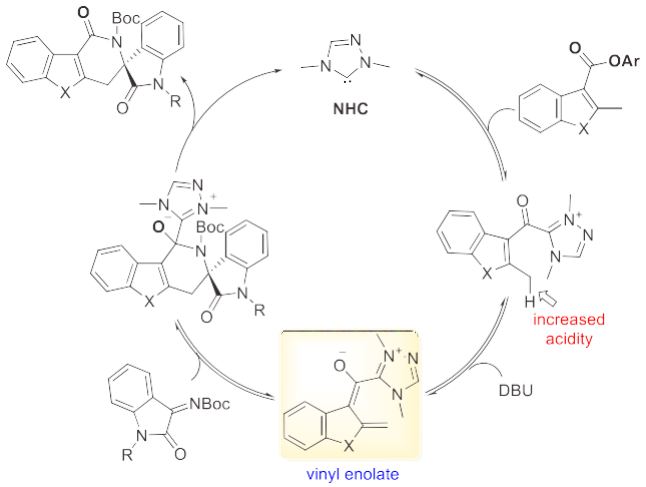
NHC-bounded dienolate intermediate can also be generated from α,β-unsaturated carboxylic acid through activation of *in situ* formed anhydride. For example, in 2016 Ye and coworkers reported an NHC-catalyzed *4+2+ annulation reaction of α,β-unsaturated carboxylic acid with active imines such as hydrazones and isatin-derived ketimines.[137] Dihydropyridinone and spirocyclic oxindolodihydropyridinone products were obtained in moderate to good yields and excellent enantioselectivities (up to 91% yield, up to 99 : 1 er). In this reaction, the dienolate key intermediate is generated from α,β-unsaturated carboxylic acids via *in situ* formed mixed anhydrides (Scheme 109).

In 2019, Lu, Du and coworkers described an NHC-catalyzed *in situ* activation of 3-arylbut-2-enoic acids for the enantioselective γ-addition to 2-aryl-3H-indol-3-ones via dienolate pathway.[138] In this reaction, peptide coupling reagent pyBOP was used as a new activation reagent. This protocol offers a rapid and efficient pathway for the synthesis of tricyclic indolin-3-ones bearing quater-

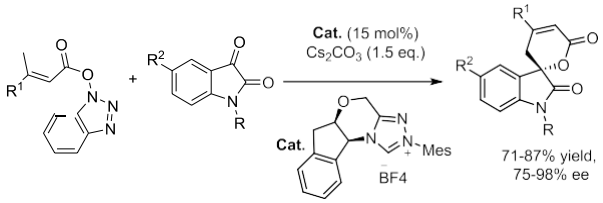
Scheme 106 NHC-catalyzed benzylic carbon activation



Scheme 107 Proposed mechanism for NHC-catalyzed benzylic carbon activation

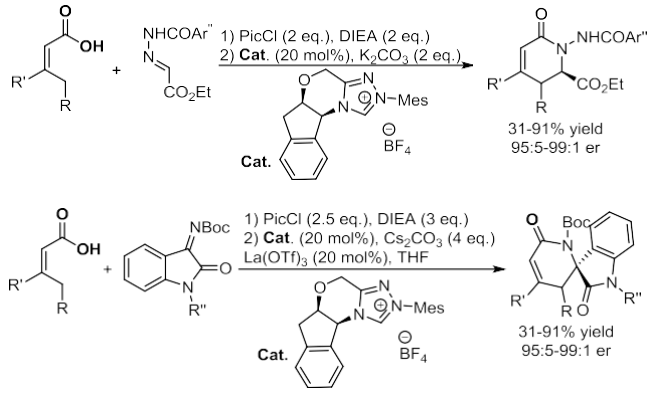


Scheme 108 NHC-catalyzed γ-carbon activation of HOBt esters

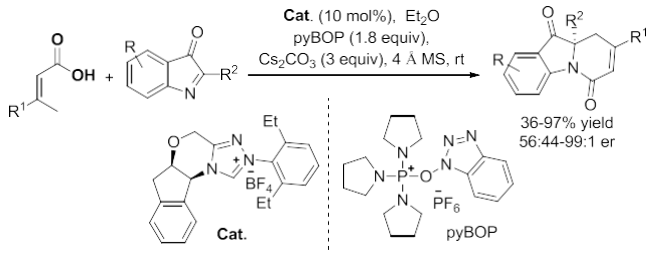


nary carbon centers (Scheme 110).

Scheme 109 NHC-catalyzed γ-carbon activation of unsaturated acids



Scheme 110 NHC-catalyzed γ-carbon activation of unsaturated acids



In 2015, Yao and coworkers reported the first NHC-catalyzed γ-carbon activation of saturated carboxylic acid under oxidative conditions.[139] Using HATU as an activation reagent, the anhydride of saturated carboxylic acid was first generated *in situ*. Then car- bene catalyst reacts with anhydride to form α,β-unsaturated acyl azolium intermediate in the present of an oxidant. Further depro- tonation of the α,β-unsaturated acyl azolium intermediate gave the dienolate intermediate for the following cycloaddition reac- tions. A plausible reaction pathway is illustrated in Scheme 111.

5. Single-Electron-Transfer Activations and Radical Intermediates

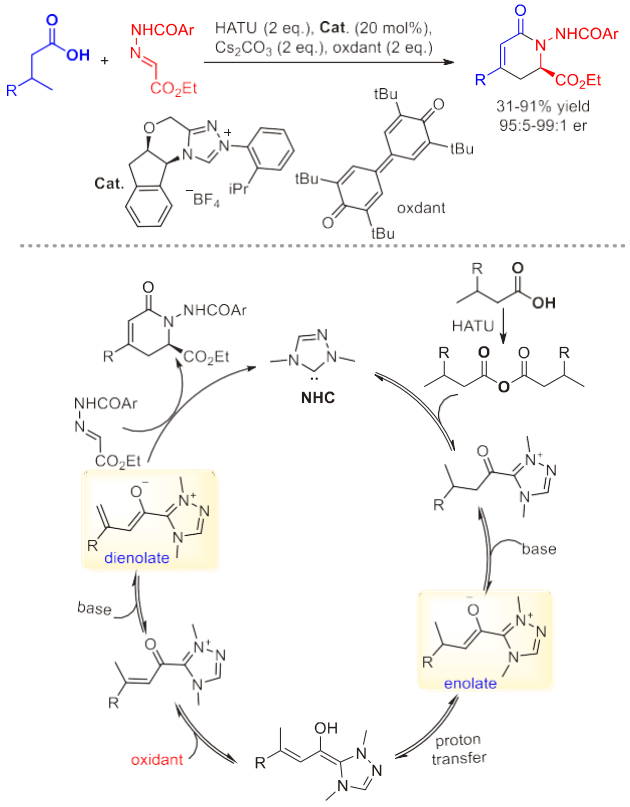
Single-electron-transfer radical reactions have attracted much attention in the current organic chemistry. They have also played significant roles in the NHC organocatalytic reactions. Recently, NHC-catalyzed radical reactions have exhibited powerful capacities in the preparation of new functional molecules.

5.1. Inspiration from bioorganic chemistry

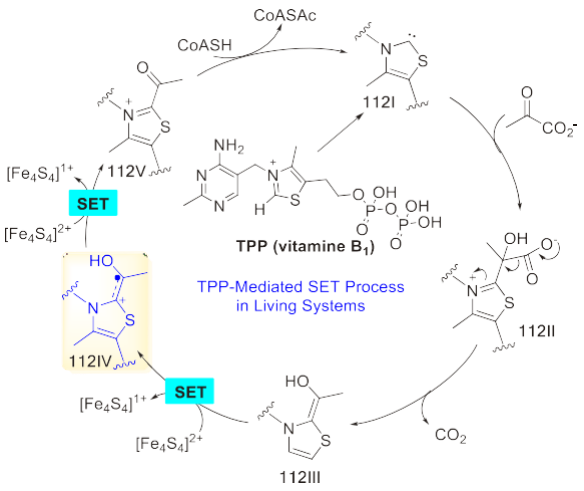
In bioorganic chemistry, one of the basic chemical reactions in living systems is the catalytic acylation of CoASH. Thiamine pyrophosphate (vitamin B1, abbreviated as TPP) is the critical coenzyme that catalyzes the oxidative decarboxylation reaction of pyruvate anion and transforms it to the acylation reagent to react with CoASH.[140] In 2001, Fontecilla-Camps and coworkers reported the crystal structure of the free radical intermediate of pyruvate ferredoxin oxidoreductase (abbreviated as $[Fe_4S_4]^{2+}$ or PFOR) and demonstrated that the CoAS-Ac synthesis by PFOR proceeded via SET processes (Scheme 112).[141]

The catalytic reactivity of the TPP molecule is provided by the thiazolium motif in its chemical structure. The thiazolium motif could be deprotonated to generate the free carbene catalyst **112I**, which could react with pyruvate to form intermediate **112II**. Decarboxylation of intermediate **112II** affords the Breslow

Scheme 111 NHC-catalyzed β-carbon functionalization of esters and isatins



Scheme 112 Acylation of CoASH catalyzed by TPP and PFOR



intermediate **112III**, which could then be oxidized by $[Fe_4S_4]^{2+}$ through two SET procedures (via radical intermediate **112IV**) to afford the acyl azolium intermediate **112V**. Intermediate **112V** could be used as the efficient acylation reagent and reacts with CoASH to give CoAS-Ac, and releases the carbene catalyst for additional chemical and biological transformations.

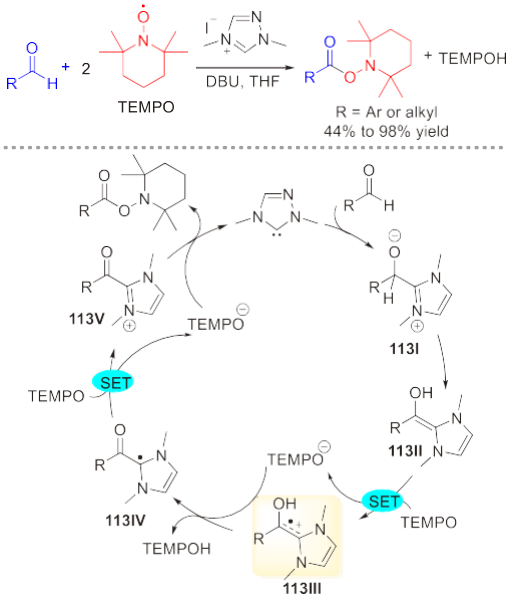
The detailed reaction mechanisms of the NHC-catalyzed SET transformations have been extensively studied. Rehbein and coworkers have re-evaluated the benzoin reactions and the formal hydroacylation reactions of alkynes and found that radical intermediates are involved in these NHC catalytic reactions.[142] In 2019, Bertrand and Martin demonstrated the fate of several NHC-cata- lyzed transformation in the presence of mild oxidants, and it had been assumed that Breslow intermediates could undergo a single

electron transfer below –1.0 V versus Fc/Fc^+. Moreover, the relevant electrochemical surrogates of these paramagnetic species have been experimentally isolated.[143]

5.2. Pioneering SET reactions in NHC organocatalysis

Inspired by the natural oxidative decarboxylation process, the biomimetic oxidation of the Breslow intermediates through radical pathways was then intensively studied using various oxidants. In 2008, Studer and coworkers described an NHC-catalyzed oxidative esterification of aldehydes using TEMPO as the single electron oxidant to mimic the PFOR in living systems.[144] As illustrated in Scheme 113, the Breslow intermediate **113II** could be oxidized by TEMPO to afford the radical cation **113III** and the anion of $TEMPO^-$. Deprotonation of the radical cation **113III** by $TEMPO^-$ generated the electro-neutral radical intermediate **113IV** and TEMPOH. Then intermediate **113IV** could be further oxidized by the TEMPO radical to form the acyl azolium intermediate **113V** and $TEMPO^-$. Finally, $TEMPO^-$ could attack the acyl azolium **113V** to generate the acylation product and releases the NHC catalyst for further catalytic cycles. Both aromatic and aliphatic aldehydes worked well in this transformation (Scheme 113).

Scheme 113 Biomimetic oxidants of aldehydes

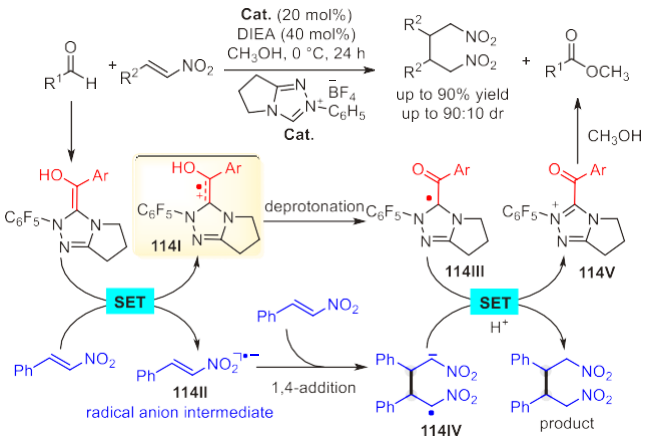


5.3. SET reactions with oxidants in NHC organocatalysis

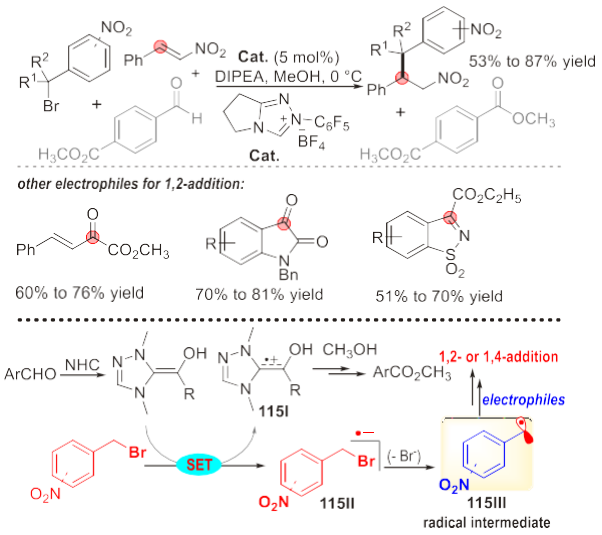
In 2014, Chi and coworkers developed the NHC-catalyzed reductive β,β-coupling reaction of nitroalkenes through SET radical pathways.[145] In this process, nitroalkenes have proven to be effective oxidants. Nitroalkenes could oxidize the Breslow intermediates to generate the corresponding radical cation **114I** and radical anion **114II**. Radical anion **114II** could react with another nitroalkene to form the radical anion **114IV**, which was then reduced by radical intermediate **114III** to afford the β,β-coupling product. The acylation product generated from intermediate **114V** and methanol is the major side product (Scheme 114).

4-Nitrobenzyl compounds could serve as efficient electron acceptors to selectively oxidize nucleophiles and generate radical intermediates. Electron-rich Breslow intermediates could be oxidized by 4-nitrobenzyl compounds via SET process. In 2016, Chi and coworkers reported the NHC-catalyzed benzylation reaction of electrophiles with 4-nitrobenzyl bromide via SET process.[146] Various electrophiles such as ketoesters, isatins and cyclic imines worked well in this transformation and afforded the desired products in good yields. One year later, nitroalkenes were also found as effective electrophiles in this SET process.[147] In these reactions, the nitro group on the benzyl bromide is crucial for the SET reaction processes (Scheme 115).

Scheme 114 Reductive β,β-coupling reaction of nitroalkenes

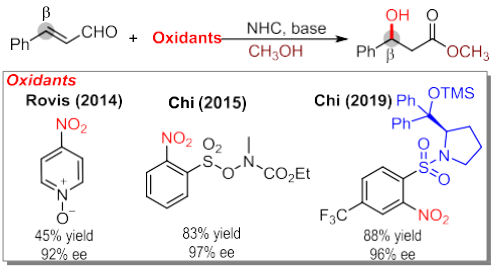


Scheme 115 NHC-catalyzed benzylation of electrophiles



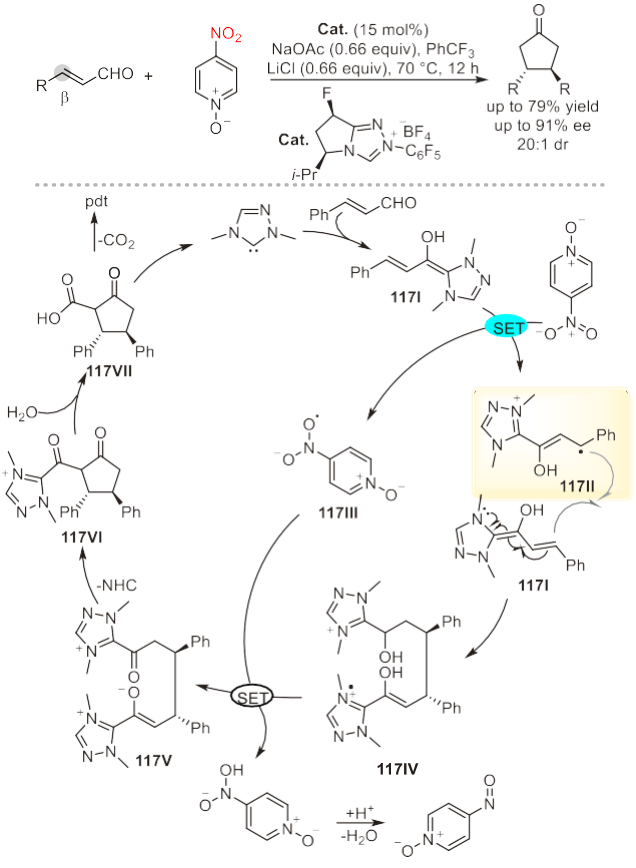
In addition to aromatic aldehyde, Breslow intermediates derived from α,β-unsaturated aldehydes have also played critical roles in the NHC-catalyzed SET reactions. In 2014, Rovis'[148] and Chi's[149] groups independently reported the NHC-catalyzed asymmetric β-hydroxylation reaction of α,β-unsaturated aldehydes using nitroarene derivatives as the key oxidants via SET processes. In 2019, Chi and coworkers further developed a new class of chiral oxidants for this process. With these chiral oxidants, highly enantioselective β-hydroxylation products of enals are realized by using a simple achiral NHC catalyst (Scheme 116).[150]

Scheme 116 NHC-catalyzed β-hydroxylation of α,β-unsaturated aldehydes



In 2015, Rovis and coworkers disclosed another example of NHC-catalyzed SET reactions.[151] 3,4-Diary substituted cyclopentanones could be obtained from enals in high enantioselectivities through NHC catalytic radical processes. As illustrated in Scheme 117, radical intermediate **117II** could be generated through oxidation of the Breslow intermediate **117I** by 4-nitropyridine N-oxide. Then the intermediate **117II** could attack another Bres- low intermediate **117I** to form a new radical cation **117IV**. Radical cation **117IV** could undergo an SET process to form acyl azolium **117V**. The cyclopentanone intermediate **117VI** was then afforded through the intramolecular attack by the enolate azolium. Cyclopentanone intermediate **117VI** was then hydrolyzed by water to give the β-ketoacid **117VII**. Finally, decarboxylation of the unstable β-ketoacid led to the formation of the 3,4-diphenylcyclopentanone as the final product (Scheme 117).

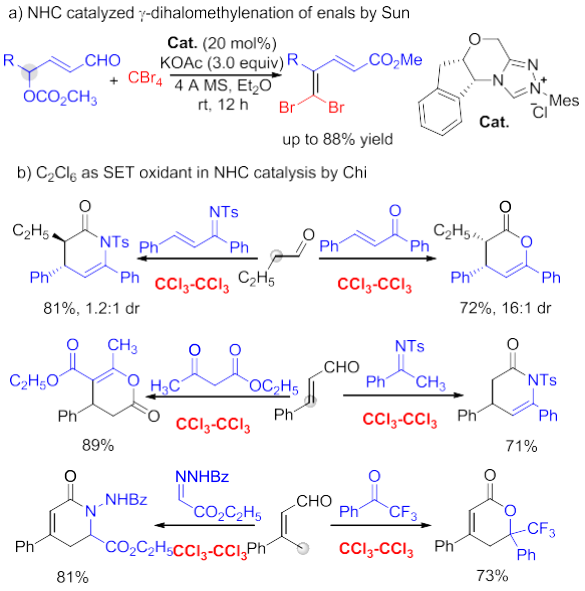
Scheme 117 Synthesis of 3,4-diaryl cyclopentanones through nhc-catalyzed SET reaction



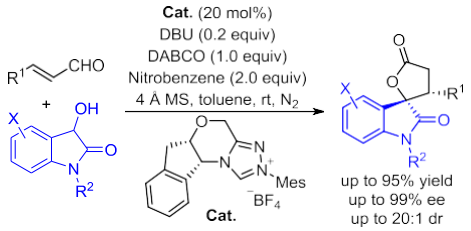
For NHC-catalyzed SET reactions, the identification of a suitable oxidant that can selectively oxidize the Breslow intermediates is critical. Structurally simple and inexpensive oxidants are always welcome for this kind of transformations. Polyhalides have been found as suitable oxidants that can be used in a variety of NHC-catalyzed SET reactions. In 2016, Sun and coworkers dis- closed an NHC-catalyzed γ-dihalomethylenation reaction of enals through an intermolecular C—C bond formation with CBr_4 used as the sole oxidant (Scheme 118a).[152] In 2017, Chi and coworkers reported several NHC-catalyzed annulation reactions of aldehydes using hexachloroethane (C_2Cl_6) as the oxidant. Hexachloroethane is readily available, inexpensive and efficient oxidant for a variety of synthetic transformations in NHC catalysis. These reactions are believed to go through two steps of SET procedures (Scheme 118b).[153]

In 2017, Ye and coworkers developed an NHC-catalyzed oxidative [3+2] annulation of dioxindoles and enals for access to oxindole-γ-lactones in good yields with excellent diastereo- and enantioselectivities.[154] The reaction proceeds via a radical cross coupling process. Nitrobenzene is an SET oxidant that can oxidize Breslow intermediate and enolate intermediate to free radical. Both radicals from enolate and homoenolate intermediates were observed by EPR spectra (Scheme 119)

Scheme 118 Polyhalides as new SET oxidants in NHC organocatalysis



Scheme 119 NHC-catalyzed cross coupling of homoenolate and enolate



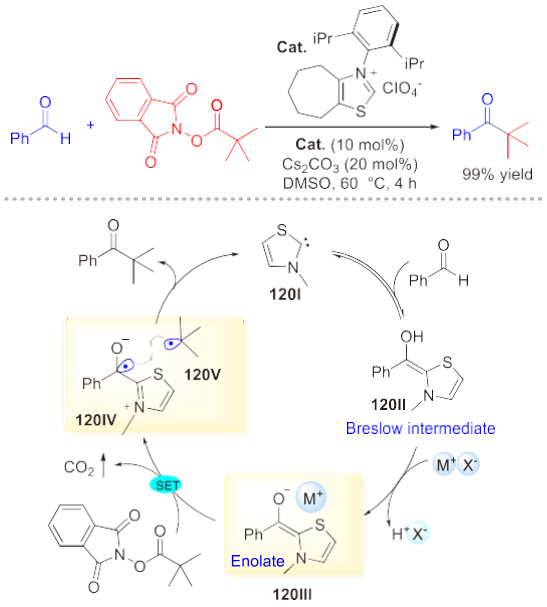
5.4. NHC-catalyzed decarboxylative alkylation of aldehydes

In 2019, Ohmiya, Nagao and coworkers have made significant contributions in the area of NHC mediated radical reactions. They demonstrated that NHCs could promote the decarboxylative coupling reaction of aryl aldehydes and tertiary or secondary alkyl carboxylic acid-derived redox-active esters and gave aryl alkyl ketones as the final products.[155] The postulated reaction mechanism is depicted in Scheme 120. The NHC catalyst could react with aldehyde to generate the Breslow intermediate **120II**. Deprotonation of the enol OH of the Breslow intermediate by a base generates a highly reductive enolate ion pair **120III**. With the assistance of the counterion (M^+), the single electron transfer between the enolate **120III** and the redox-active ester provides a ketyl radical **120IV** and an alkyl radical **120V**. Finally, the radical-radical coupling between these two intermediates afforded the desired ketone product and regenerate the NHC catalyst.

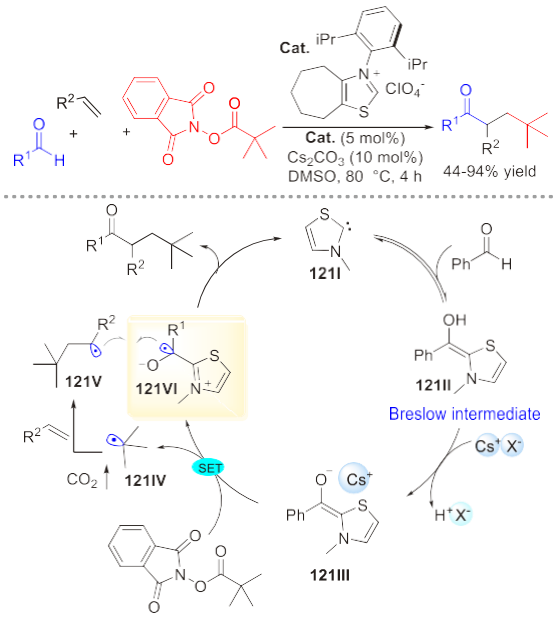
Several months later, Ohmiya, Nagao and coworkers reported that NHCs could also catalyze the vicinal alkylacylation of styrenes, acylates and acrylonitrile. Simple aldehydes and tertiary alkyl carboxylic acid derived redox-active esters were used as the reactants to produce the functionalized ketone compounds. The reaction proceeds via a radical addition and radical-radical coupling relay process.[156] The author proposed that the reaction involves

radical formations that were similar to their previous report (Scheme 121).

Scheme 120 NHC-catalyzed decarboxylative alkylation of aldehydes



Scheme 121 NHC-catalyzed radical relay enabling vicinal alkylacylation of alkenes

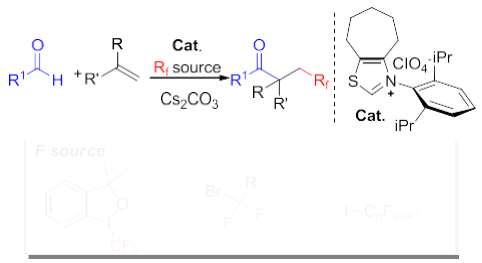


Very recently, two groups simultaneously reported the NHC-catalyzed multicomponent acylfluoromethylation reactions of alkenes in the presence of aldehydes and electrophilic fluoroalkyl reagents through SET processes.[157] These protocols allow the rapid access to functionalized fluoroketones from readily available starting materials under mild conditions. Fluorine reagents such as Togni reagent, difluoroalkyl bromides or iodides have served as the radical initiators (Scheme 122).

5.5. SET reactions through cooperative NHC/photoredox catalysis

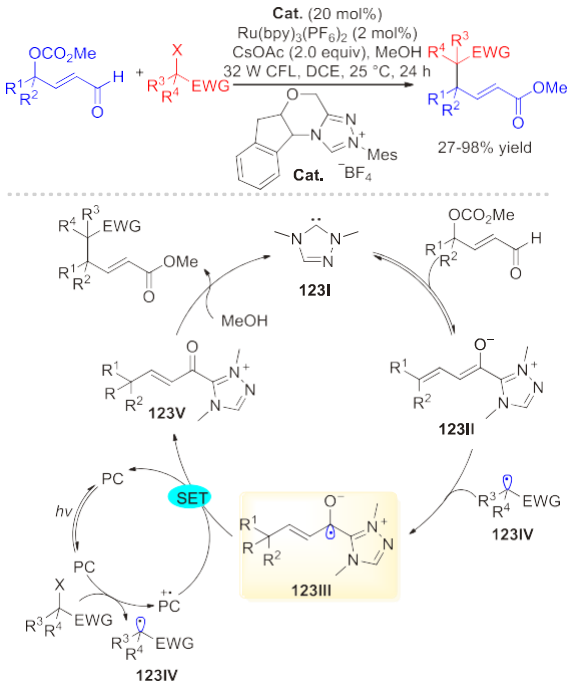
Photo-induced organic radical reactions are one class of the most significant synthetic approaches in the modern organic synthesis. In 2012, Rovis and coworkers reported the first example

Scheme 122 NHC-catalyzed radical acylfluoroalkylation of alkenes



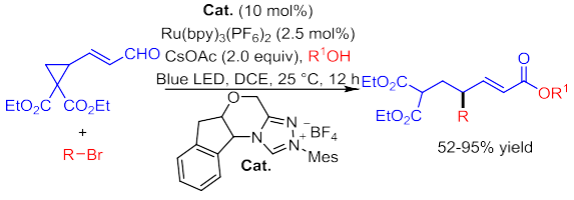
of NHC/photo-cocatalyzed umpolung addition of aldehydes to the *in situ* generated iminiums. In this protocol, NHC-mediated radical intermediate was not involved.[158] In 2019, Ye and coworkers described the first γ- and ε-alkylation of enals through SET radical processes under the dual catalysis of a photoredox catalyst and NHC.[159] The proposed reaction mechanism is shown in Scheme 123. The alkyl radical **123IV** is generated from alkyl halide through photocatalytic processes and could react with the dienolate intermediate **123II**. The homoenolate radical intermediate **123III** could be afforded through the radical addition reaction between **123II** and **123IV**. SET oxidation of the intermediate **123III** by the oxidized photocatalyst led to intermediate **123V**, which could then react with MeOH to generate the desired product and release the NHC catalyst.

Scheme 123 Visible-light-driven NHC-catalyzed alkylation



In early 2020, Ye and coworkers established the photo/NHC cocatalyzed ring-opening carbon-carbon bond cleavage of cyclopropyl enal (Scheme 124). The γ-carbons of the enal substrates

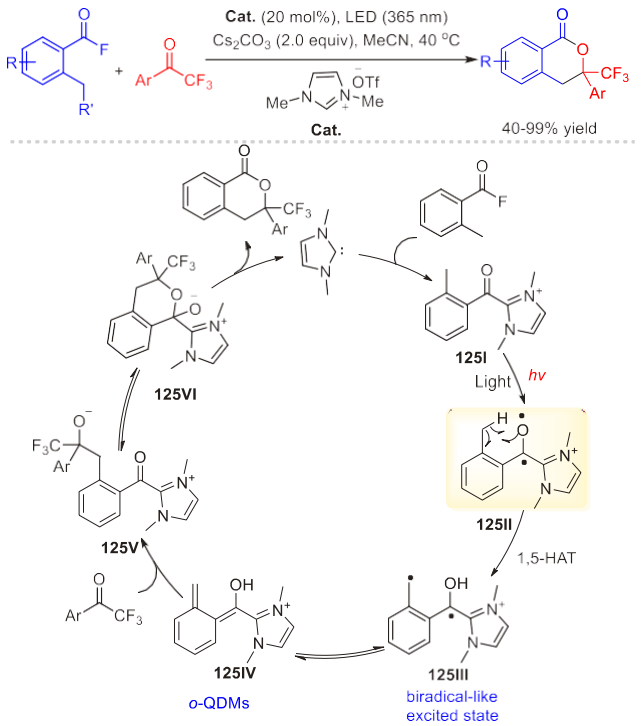
Scheme 124 Photo/NHC co-catalyzed ring opening



could be alkylated by alkyl halides via an SET pathway.[160] The reaction mechanism is similar to their previous report depicted in Scheme 123.

Recently, Hopkinson and coworkers developed a NHC-catalyzed photoenolization/Diels-Alder reaction of acid fluorides and trifluoroacetophenones. Based on control experiments and TD-DFT calculations, the authors proposed the reaction mecha- nism as shown in Scheme 125.[161] The free carbene catalyst could react with the acyl fluoride to generate the o-toluoyl azolium intermediate **125I**. This intermediate is then activated by UVA irradiation to afford the triplet excited state **125II**. A swift 1,5-HAT from the *o*-benzylic position to the carbonyl oxygen atom gave rise to the triplet dienol bi-radical **125III**, which was in resonance with the *o*-QDM **125IV**. The *o*-QDM **125IV** could react with the trifluoroacetophenones through a concerted Diels-Alder reaction or a stepwise addition process to afford the final lactone product.

Scheme 125 Visible-light-driven NHC-catalyzed Diels-Alder reaction



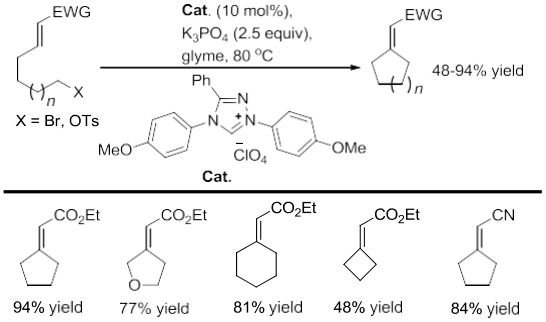
6. Activation of Michael Acceptors, Styrenes and Imines

Besides carbonyl compounds, electron-deficient Michael acceptors, styrenens and imines could also be activated by NHC organic catalysts. In 2006, Fu and coworkers first disclosed the conjugate addition of the NHCs to Michael acceptors. NHC catalysts first reacted with Michael acceptors to generate formal deoxy-Breslow intermediates, which transform the normally electrophilic β-carbons to nucleophiles for additional intramoleculer cyclization reactions (Scheme 126).[162]

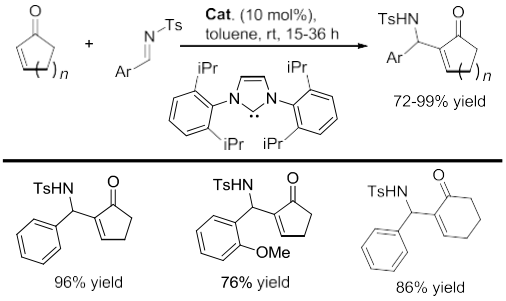
In 2007, Ye and coworkers reported an NHC-catalyzed Morita–Baylis–Hillman (MBH) reaction. Both of the five and six-membered enones worked well in this transformation and gave the desired products in good yields (Scheme 127).[163] In 2013, Ye group disclosed another MBH reaction of nitrostyrenes with azo dicarboxylates. The reaction tolerates a broad scope of arylnitrostyrenes to generate the desired products in good yields (Scheme 128).[164]

In 2011, Scheidt and coworkers demonstrated an NHC-catalyzed umpolung of vinyl sulfones. Rearrangement took place after the addition reaction of the NHC catalyst and the vinyl disulfone substrates. Then the activated disulfone intermediates could undergo a cycloaddition reaction with nitrones to give isoxazolines as the final products in excellent yields as single diastereomers (Scheme 129).[165]

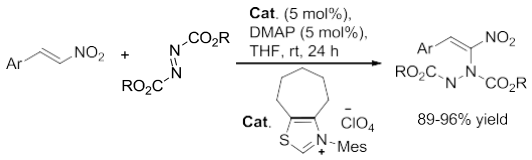
Scheme 126 Umpolung of Michael acceptors



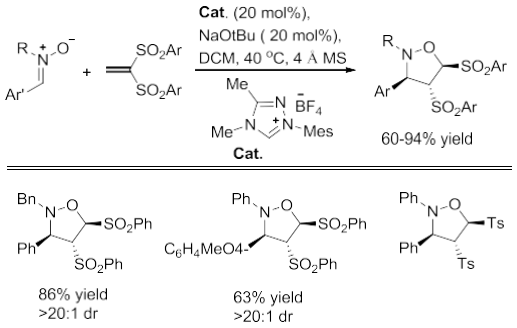
Scheme 127 NHC-catalyzed Morita–Baylis–Hillman reaction



Scheme 128 MBH reaction of nitrostyrenes and diazo dicarboxylates



Scheme 129 NHC-catalyzed umpolung of vinyl sulfones



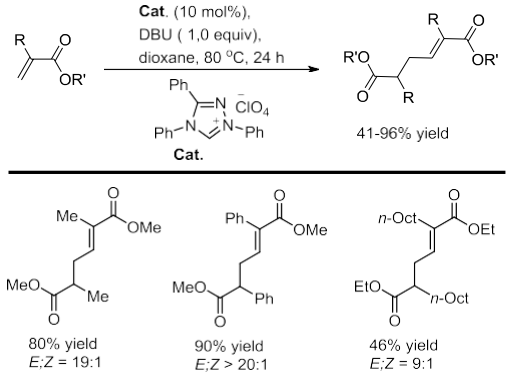
In 2011, the groups of Matsuoka and Glorius independently developed the tail-to-tail dimerization of acrylates with NHC organocatalysis (Scheme 130).[166]

In 2017, Biju and coworkers developed an NHC-catalyzed umpolung of imines via aza-Breslow intermediates. The aza-Breslow intermediate underwent an intramolecular aza-Stetter reaction to generate the indole derivatives in excellent yields (Scheme 131).[167]

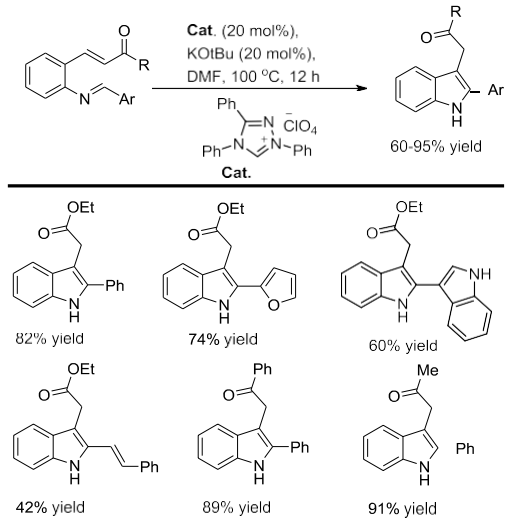
Very recently, Biju and coworkers reported the NHC-catalyzed

umpolung of diimines for the enantioselective synthesis of dihydroquinoxalines (Scheme 132).[168] The reaction proceeded via aza-Breslow intermediates, with the OH groups existed in the substrates stabilizing the reactive intermediates via intermolecular hydrogen bonding interactions.

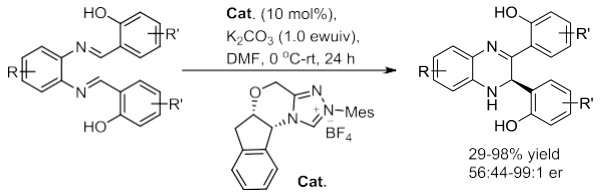
Scheme 130 NHC-catalyzed dimerization of acrylates



Scheme 131 NHC-catalyzed umpolung of imines



Scheme 132 NHC-catalyzed asymmetric umpolung of imines



7. Conclusions and Perspectives

The past 20 years have witnessed prosperous development in NHC organocatalysis. Classical activation modes with NHC catalysts have been well established and widely used in the modern organic synthesis. Numerous functional molecules, with both significant bio-active and synthetic utilities, have been efficiently prepared through NHC catalytic reactions in both racemic and enantioselective fashion. Compared with the classical activation modes including the umpolung of aldehydes and the electron pair transformations of enals, the activation of carboxylic esters and the radical reactions with NHC catalysts have been relatively less developed. Challenges still exist within these activation strategies. For example, the umpolung of the carboxylic acid carbonyl carbons has yet been realized. Asymmetric radical reactions with NHC organocatalysis are still rare. Therefore, new catalytic strategies are needed to seek for solutions to various challenges within this field. Cooperative catalytic reactions and new NHC catalyst development might be promising approaches in future investigations.

Acknowledgement

We acknowledge financial support by the National Natural Science Foundation of China (No. 21772029), the National Key Technologies R&D Program (No. 2014BAD23B01), The 10 Talent Plan (Shicengci) of Guizhou Province ([2016]5649), the Natural Science Foundation of Guizhou Province ([2018]2802), the Guizhou Province First-Class Disciplines Project (GNYL(2017)008), Jinan University (Guangzhou), Guizhou University of Traditional Chinese Medicine (China) and Guizhou University (China)

References

[1] (a) Igau, A.; Grutzmacher, H.; Baceiredo, A.; Bertrand, G. Analogous α,α'-bis-Carbenoid Triply Bonded Species: Synthesis of a Stable λ3-Phosphinocarbene-λ5-Phosphaacetylene. *J. Am. Chem. Soc*. **1988**, *110*, 6463-6466; (b) Igau, A.; Baceiredo, A.; Trinquier, G.; Bertrand, G. [Bis(diisopropylamino)phosphino]trimethylsilylcarbene: A Stable Nucleophilic Carbene. *Angew. Chem. Int. Ed.* **1989**, *28*, 621–622.

[2] Arduengo, A. J.; Harlow, R.; Kline, M. A Stable Crystalline Carbene. *J. Am. Chem. Soc.* **1991**, *113*, 361–363.

[3] For reviews of NHC in transition metal catalysis, see: (a) Doddi, A.; Peters, M.; Tamm, M. *N*-Heterocyclic Carbene Adducts of Main Group Elements and Their Use as Ligands in Transition Metal Chemistry. *Chem. Rev.* **2019**, *119*, 6994–7112; (b) Peris, E. Smart *N*-Heterocyclic Carbene Ligands in Catalysis. *Chem. Rev.* **2018**, *118*, 9988–10031; (c) Gan, M.-M.; Liu, J.-Q.; Zhang, L.; Wang, Y.-Y.; Hahn, F. E.; Han, Y.-F. Preparation and Post-Assembly Modification of Metallosupramolecular Assemblies from Poly(*N*-Heterocyclic Carbene) Ligands. *Chem. Rev*. **2018**, *118*, 9587–9641.

[4] (a) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. Stable Carbenes. *Chem. Rev*. **2000**, *100*, 39–92; (b) Frémonta, P.; Marionb, N.; Nolan, S. P. Carbenes: Synthesis, Properties, and Organometallic Chemistry. *Coord. Chem. Rev*. **2009**, *253*, 862–892.

[5] (a) Benhamou, L.; Chardon, E.; Lavigne, G.; Stéphane, B.-L.; César, V. Synthetic Routes to *N*-Heterocyclic Carbene Precursors. *Chem. Rev*. **2011**, *111*, 2705–2733; (b) Flanigan, D. M.; Fedor, R.-M.; White, N. A.; Rovis, T. Organocatalytic Reactions Enabled by *N*-Heterocyclic Carbenes. *Chem. Rev*. **2015**, *115*, 9307–9387.

[6] Reviews on the carbene history: (a) Arduengo III, A. J.; Krafczyk, R. Auf der Suchenach Stabilen Carbenen. *Chem. Unserer Zeit*. **1998**, *32*, 6–14; (b) Garrison, J. C.; Youngs, W. J. Ag(I) *N*-Heterocyclic Carbene Complexes: Synthesis, Structure, and Application. *Chem. Rev*. **2005**, *105*, 3978–4008; (c) Nolan, S. P. *N-Heterocyclic Carbenes in Synthesis*, Wiley-VCH, Weinheim, Germany, **2006**, pp. 1–304.

[7] Enders, D.; Breuer, K.; Raabe, J.; Runsink, Teles, J. H.; Melder, J. P.; Ebel, K.; Brode, S. Preparation, Structure, and Reactivity of 1,3,4-Triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ylidene, a New Sta- ble Carbene. *Angew. Chem. Int. Ed.* **1995**, *34*, 1021–1023.

[8] Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An Overview of *N*-Heterocyclic Carbenes. *Nature* **2014**, *510*, 485–496.

[9] Ukai, T.; Tanaka, S.; Dokawa, S. A New Catalyst for Acyloin Condensation. *J. Pharm. Soc. Jpn*. **1943**, *63*, 296–304.

[10] Breslow, R. On the Mechanism of Thiamine Action. IV[1] Evidence from Studies on Model Systems. *J. Am. Chem. Soc*. **1958**, *80*, 3719–3726.

[11] Sheehan, J. C.; Hunneman, D. H. Homogeneous Asymmetric Catalysis. *J. Am. Chem. Soc*. **1966**, *88*, 3666–3667.

[12] Bugaut, X.; Glorius, F. Organocatalytic Umpolung: *N*-Heterocyclic Carbenes and Beyond. *Chem. Soc. Rev*. **2012**, *41*, 3511–3522.

[13] Seebach, D. Methods of Reactivity Umpolung. *Angew. Chem. Int. Ed.* **1979**, *18*, 239–258.

[14] (a) Jordan, F.; Kudzin, Z. H.; Rios, C. B. Generation and Physical Properties of Enamines Related to the Key Intermediate in Thiamin Diphosphate-Dependent Enzymic Pathways. *J. Am. Chem. Soc*. **1987**, *109*, 4415–4416; (b) Simonovic, S.; Frison, J.-C.; Koyuncu, H.; Whitwood, A. C.; Douthwaite, R. E. Addition of *N*-Heterocyclic Carbenes to Imines: Phenoxide Assisted Deprotonation of an Imidazolium Moiety and Generation of Breslow Intermediates Derived from Imines. *Org. Lett*. **2009**, *11*, 245–247; (c) Lai, W.; Li, C.; Chen, H.; Shaik, S. Hydrogen-Abstraction Reactivity Patterns from A to Y: The Valence Bond Way. *Angew. Chem. Int. Ed.* **2012**, *51*, 5563–5570; (d) Berkessel, A.; Elfert, S.; Yatham, V. R.; Neudörfl, J.-M.; Schlörer, N. E.; Teles, J. H. Umpolung by *N*-Heterocyclic Carbenes: Generation and Reactivity of the Elusive 2,2-Diamino Enols (Breslow Intermediates). *Angew. Chem. Int. Ed.* **2012**, *51*, 12370–12374.

[15] DiRocco, D. A.; Oberg, K. M.; Rovis, T. Isolable Analogues of the Breslow Intermediate Derived from Chiral Triazolylidene Carbenes. *J. Am. Chem. Soc*. **2012**, *134*, 6143–6145.

[16] Thai, K.; Sánchez-Larios, E.; Gravel, M. Carbene Catalysts. In *Comprehensive Enantioselective Organocatalysis*: *Catalysts*, *Reactions*, *and Applications*, Ed.: Prter, I. D., Wiley-VCH Verlag GmbH & Co. KGaA, **2013**, pp. 495–522.

[17] For NHC as organocatalysis reviews, see: (a) Enders, D.; Niemeier, O.; Henseler, A. Organocatalysis by *N*-Heterocyclic Carbenes. *Chem. Rev.* **2007**, *107*, 5606–5655; (b) Bugaut, X. Benzoin and Aza-Benzoin. In *Comprehensive Organic Synthesis*, 2nd ed., Oxford, UK, **2014**, pp. 424–470; and reference *5+.

[18] (a) Enders, D.; Breuer, K.; Teles, J. H. A Novel Asymmetric Benzoin Reaction Catalyzed by a Chiral Triazolium Salt. Preliminary communication. *Helv. Chim. Acta* **1996**, *79*, 1217–1221; (b) Knight, R. L.; Leeper, F. J. Comparison of Chiral Thiazolium and Triazolium Salts as Asymmetric Catalysts for the Benzoin Condensation. *J. Chem. Soc., Perkin Trans.* **1998**, *29*, 1891–1894; (c) Enders, D.; Kallfass, U. An Efficient Nucleophilic Carbene Catalyst for the Asymmetric Benzoin Condensation. *Angew. Chem. Int. Ed.* **2002**, *41*, 1743–1745; (d) Ma, Y.; Wei, S.; Wu, J.; Yang, F.; Liu, B.; Lan, J.; Yang, S.; You, J. From Mono-Triazolium Salt to Bis-Triazolium Salt: Improvement of the Asymmetric Intermolecular Benzoin Condensation. *Adv. Synth. Catal*. **2008**, *350*, 2645–2651; (e) Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. Highly Enantioselective Benzoin Condensation Reactions Involving a Bifunctional Protic Pentafluorophenyl-Substituted Triazolium Precatalyst. *J. Org. Chem.* **2009**, *74*, 9214–9217; (f) Rafioski, Z.; Kozakiewicz, A.; Rafioska, K. Highly Efficient Synthesis of Spirocyclic (1R)-Camphor-Derived Triazolium Salts: Application in the Catalytic Asymmetric Benzoin Condensation. *Tetrahedron* **2014**, *70*, 5739–5745.

[19] Cookson, R. C.; Lane, R. M. Conversion of Dialdehydes into Cyclic α-Ketols by Thiazolium Salts: Synthesis of Cyclic 2-Hydroxy-2-Enones. *J. Chem. Soc.*, *Chem. Commun*. **1976**, 804–805.

[20] Stetter, H.; Daembkes, G. Über die präparative Nutzung der Thiazoliumsalz-katalysierten Acyloin-und Benzoin-Bildung; ∏ [1]. Herstellung Unsymmetrischer Acyloine und α-Diketone. *Synthesis* **1977**, 403–404.

[21] (a) Matsumoto, T.; Ohishi, M.; Inoue, S. Selective Cross-Acyloin Condensation Catalyzed by Thiazolium salt. Formation of 1-Hydroxy 2-one from Formaldehyde and Other Aldehydes. *J. Org. Chem*. **1985**, *50*, 603–606; (b) Rose, A. C.; Gundala, S.; Connon, S. J.; Zeitler, K. Chemoselective Crossed Acyloin Condensations: Catalyst and Substrate Control. *Synthesis* **2011**, 190–198; (c) Piel, I.; Pawelczyk, M. D.; Hirano, K.; Fröhlich, R.; Glorius, F. A Family of Thiazolium Salt Derived *N*-Heterocyclic Carbenes (NHCs) for Organocatalysis: Synthesis, Investigation and Application in Cross-Benzoin Condensation. *Eur. J. Org. Chem*. **2011**, *2011*, 5475–5484; (d) Kuhl, N.; Glorius, F. Direct and Efficient *N*-Heterocyclic Carbene-Catalyzed Hydroxymethylation of Aldehydes. *Chem. Commun*. **2011**, *47*, 573–575; (e) Langdon, S. M.; Wilde, M. M. D.; Thai, K.; Gravel, M. Chemoselective *N*-Heterocyclic Carbene-Catalyzed Cross-Benzoin Reactions: Importance of the Fused Ring in Triazolium Salts. *J. Am. Chem. Soc*. **2014**, *136*, 7539–7542.

[22] (a) Jin, M. Y.; Kim, S. M.; Han, H.; Ryu, D. H.; Yang, J. W. Switching Regioselectivity in Crossed Acyloin Condensations between Aromatic Aldehydes and Acetaldehyde by Altering *N*-Heterocyclic Carbene Catalysts. *Org. Lett*. **2011**, *13*, 880–883; (b) Liu, R.; Yu, C.; Xiao, Z.; Li, T.; Wang, X.; Xie, Y.; Yao, C. NHC-Catalyzed Oxidative γ-Addition of α,β-Unsaturated Aldehydes to Isatins: a High-Effi- ciency Synthesis of Spirocyclic Oxindole-Dihydropyranones. *Org. Biomol. Chem*. **2014**, *12*, 1547–1550.

[23] Hachisu, Y.; Bode, J. W.; Suzuki, K. Catalytic Intramolecular Crossed Aldehyde-Ketone Benzoin Reactions: A Novel Synthesis of Functionalized Preanthraquinones. *J. Am. Chem. Soc*. **2003**, *125*, 8432–8433.

[24] (a) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. Catalytic Enantioselective Crossed Aldehyde-Ketone Benzoin Cyclization *Angew. Chem. Int. Ed*. **2006**, *45*, 3492–3494; (b) Enders, D.; Niemeier, O.; Balensiefer, T. Asymmetric Intramolecular Crossed-Benzoin Reactions by *N*-Heterocyclic Carbene Catalysis. *Angew. Chem. Int. Ed.* **2006**, *45*, 1463–1467; (c) Li, Y.; Feng, Z.; You, S.-L. D-Camphor-Derived Triazolium Salts for Catalytic Intramolecular Crossed Aldehyde–Ketone Benzoin Reactions. *Chem. Commun*. **2008**, *39*, 2263–2265.

[25] Ema, T.; Oue, Y.; Akihara, K.; Miyazaki, Y.; Sakai, T. Stereoselective Synthesis of Bicyclic Tertiary Alcohols with Quaternary Stereocenters via Intramolecular Crossed Benzoin Reactions Catalyzed by *N*-Heterocyclic Carbenes. *Org. Lett*. **2009**, *11*, 4866–4869.

[26] Goodman, C. G.; Johnson, J. S. Dynamic Kinetic Asymmetric Cross-Benzoin Additions of β-Stereogenic α-Keto Esters. *J. Am. Chem. Soc*. **2014**, *136*, 14698–14701.

[27] Zhang, G.; Yang, S.; Zhang, X.; Lin, Q.; Das, D. K.; Liu, J.; Fang, X. Dynamic Kinetic Resolution Enabled by Intramolecular Benzoin Reaction: Synthetic Applications and Mechanistic Insights. *J. Am. Chem. Soc*. **2016**, *138*, 7932–7938.

[28] (a) Lathrop, S. P.; Rovis, T. Asymmetric Synthesis of Functionalized Cyclopentanones via a Multicatalytic Secondary Amine/*N*-Heterocyclic Carbene Catalyzed Cascade Sequence. *J. Am. Chem. Soc*. **2009**, *131*, 13628–13630; (b) Ozboya, K. E.; Rovis, T. Enamine/Carbene Cascade Catalysis in the Diastereo- and Enantioselective Synthesis of Functionalized Cyclopentanones. *Chem. Sci*. **2011**, *2*, 1835–1838

[29] (a) Enders, D.; Grossmann, A.; Huang, H.; Raabe, G. Dual Secondary Amine/*N*-Heterocyclic Carbene Catalysis in the Asymmetric Michael/Cross-Benzoin Cascade Reaction of β-Oxo Sulfones with Enals *Eur. J. Org. Chem*. **2011**, *2011*, 4298–4301; (b) Liu, Y.; Nappi, M.; Eduardo, C. E.-A.; Melchiorre, P. Multicatalytic Asymmetric Synthesis of Complex Tetrahydrocarbazoles via a Diels–Alder/Benzoin Reaction Sequence. *Org. Lett*. **2012**, *14*, 1310–1313; (c) Ma, C.; Gu, J.; Teng, B.; Zhou, Q.-Q.; Li, R.; Chen, Y.-C. 1-Azadienes as Regio- and Chemoselective Dienophiles in Aminocatalytic Asymmetric Diels–Alder Reaction. *Org. Lett*. **2013**, *15*, 6206–6209.

[30] (a) Castells, J.; López-Calahorra, F.; Bassedas, M.; Urrios, P. A New Thiazolium Salt-Catalyzed Synthesis of α-Aminoketones from Aldehydes and Iminium Salts. *Synthesis* **1988**, 314–315; (b) Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. Synthesis of α-Amido Ketones via Organic Catalysis: Thiazolium-Catalyzed Cross-Coupling of Aldehydes with Acylimines. *J. Am. Chem. Soc*. **2001**, *123*, 9696–9697; (c) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. Thiazolylalanine-Derived Catalysts for Enantioselective Intermolecular Aldehyde–Imine Cross-Couplings. *J. Am. Chem. Soc*. **2005**, *127*, 1654–1655; (d) Li, G.-Q.; Dai, L.-X.; You, S.-L. Thiazolium-Derived *N*-Heterocyclic Carbene-Catalyzed Cross-Coupling of Aldehydes with Unactivated Imines. *Chem. Commun*. **2007**, *8*, 852–854; (e) DiRocco, D. A.; Rovis, T. Catalytic Asymmetric Cross-Aza-Benzoin Reactions of Aliphatic Aldehydes with N-Boc-Protected Imines. *Angew. Chem. Int. Ed*. **2012**, *51*, 5904–5906; (f) Uno, T.; Kobayashi, Y.; Takemoto, Y. *N*-Heterocyclic Carbene-Catalyzed Di-

rect Cross-Aza-Benzoin Reaction: Efficient Synthesis of α-Amino-β-Keto Esters. *Beilstein J. Org. Chem.* **2012**, *8*, 1499–1504; (g) Enders, D.; Henseler, A.; Lowins, S. *N*-Heterocyclic Carbene Catalyzed Nucleophilic Acylation of Trifluoromethyl Ketimines. *Synthesis* **2009**, *41*, 4125–4128; (h) Sun, L.-H.; Liang, Z.-Q.; Jia, W.-Q.; Ye, S. Enantioselective *N*-Heterocyclic Carbene Catalyzed Aza-Benzoin Reaction of Enals with Activated Ketimines. *Angew. Chem. Int. Ed*. **2013**, *52*, 5803–5806; (i) Xu, J.; Mou, C.; Zhu, T.; Song, B.-A.; Chi, Y. R. *N*-Heterocyclic Carbene-Catalyzed Chemoselective Cross-Aza-Benzoin Reaction of Enals with Isatin-Derived Ketimines: Access to Chiral Quaternary Aminooxindoles. *Org. Lett*. **2014**, *16*, 3272–3275.

[31] Wilde, M. M. D.; Gravel, M. Bis(amino)cyclopropenylidene (BAC) Catalyzed Aza-Benzoin Reaction. *Org. Lett*. **2014**, *16*, 5308–5311.

[32] (a) Stetter, H.; Schreckenberg, M. A New Method for Addition of Aldehydes to Activated Double Bonds. *Angew. Chem. Int. Ed*. **1973**, *12*, 81–81; (b) Stetter, H.; Kuhlmann, H. Addition of Aliphatic Aldehydes to Activated Double Bonds. *Angew. Chem. Int. Ed*. **1974**, *13*, 539–539; (c) Stetter, H.; Kuhlmann, H. Addition Aliphatischer, Heterocyclischer und Aromatischer Aldehyde an Butenon. *Chem. Ber*. **1976**, *109*, 3426–3431; (d) Stetter, H. Catalyzed Addition of Aldehydes to Activated Double Bonds-A New Synthetic Approach. *Angew. Chem. Int. Ed*. **1976**, *15*, 639–647.

[33] Ciganek, E. Esters of 2,3-Dihydro-3-oxobenzofuran-2-acetic Acid and 3,4-Dihydro-4-oxo-2H-1-benzopyran-3-acetic Acid by Intramolecular Stetter Reactions. *Synthesis* **1995**, 1311–1314.

[34] Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. The First Asymmetric Intramolecular Stetter Reaction. Preliminary Communication. *Helv. Chim. Acta* **1996**, *79*, 1899–1902.

[35] (a) Kerr, M. S.; Alaniz, J. R.; Rovis, T. A Highly Enantioselective Catalytic Intramolecular Stetter Reaction. *J. Am. Chem. Soc*. **2002**, *124*, 10298–10299; (b) Kerr, M. S.; Rovis, T. Enantioselective Synthesis of Quaternary Stereocenters via a Catalytic Asymmetric Stetter Reaction. *J. Am. Chem. Soc*. **2004**, *126*, 8876–8877; (c) Steven, M. M.; Jarred, T. B.; Michelle, B. T. D.; Jason, E. I.; Miller, S. J. A Peptide-Catalyzed Asymmetric Stetter Reaction. *Chem. Commun*. **2005**, *2*, 195–197; (d) Jia, M.-Q.; Li, Y.; Rong, Z.-Q.; You, S.-L. Synthesis of (1R,2R)-DPEN-Derived Triazolium Salts and Their Application in Asymmetric Intramolecular Stetter Reactions. *Org. Biomol. Chem*. **2011**, *9*, 2072–2074; (e) Rong, Z.-Q.; Li, Y.; Yang, G.-Q.; You, S.-L. δ-Camphor-Derived Triazolium Salts for Enantioselective Intramolecular Stetter Reactions. *Synlett* **2011**, 1033–1037; (f) Soeta, T.; Tabatake, Y.; Ukaji, Y. An Asymmetric Intramolecular Stetter Reaction Catalyzed by a Chiral Triazolium Precatalyst Bearing a Pyridine Moiety. *Tetrahedron* **2012**, *68*, 10188–10193; (g) Rafioski, Z.; Kozakiewicz, A.; Rafioska, K. (−)-β-Pinene-Derived *N*-Heterocyclic Carbenes: Application to Highly Enantioselective Intramolecular Stetter Reaction. *ACS Catal*. **2014**, *4*, 1404–1408.

[36] Dalko, P. I. *Comprehensive Enantioselective Organocatalysis*: *Catalysts*, *Reactions*, *and Applications*, 1st ed., Wiley-VCH Verlag GmbH & Co. KGaA, **2013**, pp. 495–522.

[37] Enders, D.; Han, J.; Henseler, A. Asymmetric Intermolecular Stetter Reactions Catalyzed by a Novel Triazolium Derived *N*-Heterocyclic Carbene. *Chem. Commun*. **2008**, 3989–3991.

[38] (a) Liu, Q.; Perreault, S.; Rovis, T. Catalytic Asymmetric Intermolecular Stetter Reaction of Glyoxamides with Alkylidenemalonates. *J. Am. Chem. Soc*. **2008**, *130*, 14066–14067; (b) Liu, T.; Rovis, T. Enantio- and Diastereoselective Intermolecular Stetter Reaction of Glyoxamide and Alkylidene Ketoamides. *Org. Lett*. **2009**, *11*, 2856–2859; (c) DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. Catalytic Asymmetric Intermolecular Stetter Reaction of Heterocyclic Aldehydes with Nitroalkenes: Backbone Fluorination Improves Selectivity. *J. Am. Chem. Soc*. **2009**, *131*, 10872–10874; (d) DiRocco, D. A.; Rovis, T. Catalytic Asymmetric Intermolecular Stetter Reaction of Enals with Nitroalkenes: Enhancement of Catalytic Efficiency through Bifunctional Additives. *J. Am. Chem. Soc*. **2011**, *133*, 10402–10405; (e) DiRocco, D. A.; Noey, E. L.; Houk, K. N.; Rovis, T. Catalytic Asymmetric Intermolecular Stetter Reactions of Enolizable Aldehydes with Nitrostyrenes: Computational Study Provides Insight into the Success of the Catalyst. *Angew. Chem. Int. Ed*. **2012**, *51*, 2391–2394; (f) Jousseaume, T.; Wurz, N. E.; Glorius, F. Highly Enantioselective Synthesis of α-Amino Acid Derivatives by an NHC-Catalyzed Intermolecular Stetter Reaction. *Angew. Chem. Int. Ed*. **2011**, *50*, 1410–1414; (g) Fang, X.; Chen, X.; Lv, H.; Chi, Y. R. Enantioselective Stetter Reactions of Enals and Modified Chalcones Catalyzed by *N*-Heterocyclic Carbenes. *Angew. Chem. Int. Ed*. **2011**, *50*, 11782–11785; (h) Eduardo, S.-L.; Thai, K.; Bilodeau, F.; Gravel, M. Highly Enantioselective Intermolecular Stetter Reactions of β-Aryl Acceptors: α-Ketoester Moiety as Handle for Activation and Synthetic Manipulations. *Org. Lett*. **2011**, *13*, 4942–4945; (i) Kim, S. M.; Jin, M. Y.; Kim, M. J.; Cui, Y.; Kim, Y. S.; Zhang, L.; Song, C. E.; Ryu, D. H.; Yang, J. W. *N*-Heterocyclic Carbene-Catalysed Intermolecular Stetter Reactions of Acetaldehyde. *Org. Biomol. Chem*. **2011**, *9*, 2069–2071; (g) Wurz, N. E.; Daniliuc, C. G.; Glorius, F. Highly Enantioselective Intermolecular Stetter Reaction of Simple Acrylates: Synthesis of α-Chiral γ-Ketoesters. *Chem. Eur. J*. **2012**, *18*, 16297–16301.

[39] Nemoto, T.; Fukuda, T.; Hamada, Y. Efficient Synthesis of 3-Substituted 2,3-Dihydroquinolin-4-ones Using a One-Pot Sequential Multi-Catalytic Process: Pd-Catalyzed Allylic Amination-Thiazolium Salt-Catalyzed Stetter Reaction Cascade. *Tetrahedron Lett*. **2006**, *47*, 4365–4368

[40] (a) Hong, B.-C.; Dange, N. S.; Hsu, C.-S.; Liao, J.-H. Sequential Organocatalytic Stetter and Michael-Aldol Condensation Reaction: Asymmetric Synthesis of Fully Substituted Cyclopentenes via a [1 + 2 + 2] Annulation Strategy. *Org. Lett*. **2010**, *12*, 4812–4815; (b) Hong, B.-C.; Dange, N. S.; Hsu, C.-S.; Liao, J.-H.; Lee, G.-H. Dynamic Kinetic Asymmetric Synthesis of Five Contiguous Stereogenic Centers by Sequential Organocatalytic Stetter and Michael-Aldol Reaction: Enantioselective Synthesis of Fully Substituted Cyclopentanols Bearing a Quaternary Stereocenter. *Org. Lett*. **2011**, *13*, 1338–1341.

[41] Filloux, C. M.; Lathrop, S. P.; Rovis, T. Multicatalytic, Asymmetric Michael/Stetter Reaction of Salicylaldehydes and Activated Alkynes. *Proc. Natl. Acad. Sci*. **2010**, *107*, 20666–20671.

[42] Reddi, Y.; Sunoj, R. B. Asymmetric Dual-Catalytic Cascade by Chiral *N*-Heterocyclic Carbene and Quinuclidine: Mechanism and Origin of Enantioselectivity in Benzofuranone Formation. *ACS Catal*. **2015**, *5*, 1596–1603.

[43] Cheng, Q.-F.; Wang, J.-W.; Wang, Q.-F.; Liu, Z. Intermolecular Stetter Reaction of Aromatic Aldehydes with (E)-(2-Nitrovinyl)cyclohexane Induced by *N*-Heterocyclic Carbene and Thiourea. *Chin. Chem. Lett.* **2016**, *27*, 1032–1035

[44] Zhuo, S.; Zhu, T.; Zhou, L.; Mou, C.; Chai, H.; Lu, Y.; Pan, L.; Jin, Z.; Chi, Y. R. Access to All-Carbon Spirocycles through a Carbene and Thiourea Cocatalytic Desymmetrization Cascade Reaction. *Angew. Chem. Int. Ed*. **2019**, *131*, 1798–1802

[45] (a) He, J.; Zheng, J.; Liu, X.; She, X.; Pan, X. *N*-Heterocyclic Carbene Catalyzed Nucleophilic Substitution Reaction for Construction of Benzopyrones and Benzofuranones. *Org. Lett.* **2006**, *8*, 4637−4640; (b) He, J.; Tang, S.; Liu, J.; Su, Y.; Pan, X.; She, X. *N*-Heterocyclic Carbene Catalyzed Intramolecular Nucleophilic Addition of Carbonyl Anion Equivalents to Enol Ethers. *Tetrahedron* **2008**, *64*, 8797–8800.

[46] Biju, A. T.; Wurz, N. E.; Glorius, F. *N*-Heterocyclic Carbene-Catalyzed Cascade Reaction Involving the Hydroacylation of Unactivated Alkynes. *J. Am. Chem. Soc*. **2010**, *132*, 5970−5971.

[47] Zhao, M.; Liu, J.-L.; Liu, H.-F.; Chen, J.; Zhou, L. Construction of Bisbenzopyrone via *N*-Heterocyclic Carbene Catalyzed Intramolecular Hydroacylation–Stetter Reaction Cascade. *Org. Lett*. **2018**, *20*, 2676–2679.

[48] Biju, A. T., Glorius, F. Intermolecular *N*-Heterocyclic Carbene Catalyzed Hydroacylation of Arynes. *Angew. Chem. Int. Ed*. **2010**, *49*, 9761–9764.

[49] (a) Piel, I.; Steinmetz, M.; Hirano, K.; Fr hlich, R.; Grimme, S.; Glorius, F. Highly Asymmetric NHC-Catalyzed Hydroacylation of

Unactivated Alkenes. *Angew. Chem. Int. Ed*. **2011**, *50*, 4983−4987; (b) Hirano, K.; Biju, A. T.; Piel, I.; Glorius, F. *N*-Heterocyclic Carbene-Catalyzed Hydroacylation of Unactivated Double Bonds. *J. Am. Chem. Soc.* **2009**, *131*, 14190−14191.

[50] (a) Bugaut, X.; Liu, F.; Glorius, F. *N*-Heterocyclic Carbene (NHC)-Catalyzed Intermolecular Hydroacylation of Cyclopropenes. *J. Am. Chem. Soc*. **2011**, *133*, 8130−8133; (b) Liu, F.; Bugaut, X.; Schedler, M.; Fr hlich, R.; Glorius, F. Designing *N*-Heterocyclic Car- benes: Simultaneous Enhancement of Reactivity and Enantioselec- tivity in the Asymmetric Hydroacylation of Cyclopropenes. *Angew. Chem. Int. Ed*. **2011**, *50*, 12626−12630.

[51] Janssen-M ller, D.; Fleige, M.; Schl ns, D.; Wollenburg, M.; Daniliuc, C. G.; Neugebauer, J.; Glorius, F. NHC-Catalyzed Enantioselective Dearomatizing Hydroacylation of Benzofurans and Benzothiophenes for the Synthesis of Spirocycles. *ACS Catal*. **2016**, *6*, 5735−5739.

[52] (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *N*-Heterocyclic Carbene-Catalyzed Generation of Homoenolates: γ-Butyrolactones by Direct Annulations of Enals and Aldehydes. *J. Am. Chem. Soc*. **2004**, *126*, 14370–14371; (b) Burstein, C.; Glorius, F.; Organocatalyzed Conjugate Umpolung of α,β-Unsaturated Aldehydes for the Synthesis of γ-Butyrolactones. *Angew. Chem. Int. Ed*. **2004**, *43*, 6205–6208.

[53] Burstein, C.; Serena, T.; Xie, X.; Glorius, F. *N*-Heterocyclic Carbene-Catalyzed Conjugate Umpolung for the Synthesis of γ-Butyrolactones. *Synthesis* **2006**, 2418–2439; (b) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *N*-Heterocyclic Carbene Catalyzed Reaction of Enals and 1,2-Dicarbonyl Compounds: Stereoselective Synthesis of Spiro γ-Butyrolactones. *Org. Lett*. **2006**, *8*, 507–509; (c) Nair, V.; Poonoth, M.; Vellalath, S.; Suresh, E.; Thirumalai, R. An *N*-Heterocyclic Carbene-Catalyzed [8 + 3] Annulation of Tropone and Enals via Homoenolate. *J. Org. Chem*. **2006**, *71*, 8964–8965; (d) Li, Y.; Zhao, Z.-A.; He, H.; You, S.-L. Stereoselective Synthesis of γ-Butyrolactones via Organocatalytic Annulations of Enals and Keto Esters. *Adv. Synth. Catal*. **2008**, *350*, 1885–1890; (e) Struble, J. R.; Bode, J. W. Formal Synthesis of Salinosporamide A via NHC-Catalyzed Intramolecular Lactonization. *Tetrahedron* **2009**, *65*, 4957–4967.

[54] Sun, L.-H.; Shen, L.-T.; Ye, S. Highly Diastereo- and Enantioselective NHC-Catalyzed [3+2] Annulation of Enals and Isatins. *Chem. Commun*. **2011**, *47*, 10136–10138.

[55] Ide, R.; Kyan, R.; Le, T. P.; Kitagawa, Y.; Sato, K.; Mase, N.; Narumi, T. Chemoselective Umpolung of Enals for Asymmetric Homoenolate Cross-Annulation of Enals and Aldehydes Catalyzed by *N*-Heterocyclic Carbene. *Org. Lett*. **2019**, *21*, 9119–9123.

[56] He, M.; Bode, J. W. Catalytic Synthesis of γ-Lactams via Direct Annulations of Enals and N-Sulfonylimines. *Org. Lett*. **2005**, *7*, 3131–3134.

[57] (a) Chan, A.; Scheidt, K. A. Highly Stereoselective Formal [3 + 3] Cycloaddition of Enals and Azomethine Imines Catalyzed by *N*-Heterocyclic Carbenes. *J. Am. Chem. Soc*. **2007**, *129*, 5334–5335; (b) Chan, A.; Scheidt, K. A. Direct Amination of Homoenolates Catalyzed by *N*-Heterocyclic Carbenes. *J. Am. Chem. Soc*. **2008**, *130*, 2740–2741; (c) He, M.; Bode, J. W. Enantioselective, NHC-Catalyzed Bicyclo-β-Lactam Formation via Direct Annulations of Enals and Unsaturated N-Sulfonyl Ketimines. *J. Am. Chem. Soc*. **2008**, *130*, 418–419; (d) Rommel, M.; Fukuzumi, T.; Bode, J. W. Cyclic Ketimines as Superior Electrophiles for NHC-Catalyzed Homoenolate Additions with Broad Scope and Low Catalyst Loadings. *J. Am. Chem. Soc*. **2008**, *130*, 17266–17267; (e) Lv, H.; Tiwari, B.; Mo, J.; Xing, C.; Chi, Y. R. Highly Enantioselective Addition of Enals to Isatin-Derived Ketimines Catalyzed by *N*-Heterocyclic Carbenes: Synthesis of Spirocyclic γ-Lactams. *Org. Lett*. **2012**, *14*, 5412–5415.

[58] Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *N*-Heterocyclic Carbene-Catalyzed Reaction of Chalcones and Enals via Homoenolate: An Efficient Synthesis of 1,3,4-Trisubstituted Cyclopentenes. *J. Am. Chem. Soc*. **2006**, *128*, 8736–8737.

[59] Chiang, P.-C.; Kaeobamrung, J.; Bode, J. W. Enantioselective, Cyclopentene-Forming Annulations via NHC-Catalyzed Benzoin-Oxy-Cope Reactions. *J. Am. Chem. Soc*. **2007**, *129*, 3520–3521.

[60] (a) Cohen, D. T.; Cardinal-David, B.; Scheidt, K. A. Lewis Acid Activated Synthesis of Highly Substituted Cyclopentanes by the *N*-Heterocyclic Carbene Catalyzed Addition of Homoenolate Equivalents to Unsaturated Ketoesters. *Angew. Chem. Int. Ed.* **2011**, *50*, 1678–1682; (b) Guo, C.; Schedler, M.; Daniliuc, C. G.; Glorius, F. *N*-Heterocyclic Carbene Catalyzed Formal [3+2] Annulation Reaction of Enals: An Efficient Enantioselective Access to Spiro-Heterocycles. *Angew. Chem. Int. Ed.* **2014**, *53*, 10232–10236.

[61] (a) Chan, A.; Scheidt, K. A. Conversion of α,β-Unsaturated Aldehydes into Saturated Esters: An Umpolung Reaction Catalyzed by Nucleophilic Carbenes. *Org. Lett*. **2005**, *7*, 905–908; (b) Sohn, S. S.; Bode, J. W. Catalytic Generation of Activated Carboxylates from Enals: A Product-Determining Role for the Base. *Org. Lett*. **2005**, *7*, 3873–3876.

[62] Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. Highly Diastereo- and Enantioselective Additions of Homoenolates to Nitrones Catalyzed by *N*-Heterocyclic Carbenes. *J. Am. Chem. Soc*. **2008**, *130*, 2416–2417.

[63] Nair, V.; Sinu, C. R.; Babu, B. P.; Varghese, V.; Jose, A.; Suresh, E. Novel Nucleophilic Heterocyclic Carbene Mediated Stereoselective Conjugate Addition of Enals to Nitrostyrenes via Homoenolate. *Org. Lett*. **2009**, *11*, 5570–5573.

[64] (a) Maji, B.; Ji, L.; Wang, S.; Vedachalam, S.; Ganguly, R.; Liu, X.-W. *N*-Heterocyclic Carbene Catalyzed Homoenolate-Addition Reaction of Enals and Nitroalkenes: Asymmetric Synthesis of 5-Carbon-Synthon δ-Nitroesters. *Angew. Chem. Int. Ed.* **2012**, *124*, 8401–8405; (b) White, N. A.; DiRocco, D. A.; Rovis, T. Asymmetric *N*-Heterocyclic Carbene Catalyzed Addition of Enals to Nitroalkenes: Controlling Stereochemistry via the Homoenolate Reactivity Pathway to Access δ-Lactams. *J. Am. Chem. Soc*. **2013**, *135*, 8504–8507.

[65] Chan, A.; Scheidt, K. A. Conversion of α,β-Unsaturated Aldehydes into Saturated Esters: An Umpolung Reaction Catalyzed by Nucleophilic Carbenes. *Org. Lett*. **2005**, *7*, 905–908.

[66] Zhao, C.; Li, F.; Wang, J. *N*-Heterocyclic Carbene Catalyzed Dynamic Kinetic Resolution of Pyranones. *Angew. Chem. Int. Ed*. **2016**, *55*, 1820–1824.

[67] Zhang, C.-L.; Han, Y.-F.; Ye, S. *N*-Heterocyclic Carbene-Catalyzed β-Addition of Enals to 3-Alkylenyloxindoles: Synthesis of Oxindoles with All-Carbon Quaternary Stereocenters. *Chem. Commun*. **2019**, *55*, 7966–7969.

[68] Benoit, C.-D.; Raup, D. E. A.; Scheidt, K. A. Cooperative *N*-Heterocyclic Carbene/Lewis Acid Catalysis for Highly Stereoselective Annulation Reactions with Homoenolates. *J. Am. Chem. Soc*. **2010**, *132*, 5345–5347.

[69] (a) Raup, D. E. A.; Benoit, C.-D.; Holte, D.; Scheidt, K. A. Cooperative Catalysis by Carbenes and Lewis Acids in a Highly Stereoselective Route to γ-Lactams. *Nat. Chem.* **2010**, *2*, 766–771; (b) Cohen, D. T.; Benoit, C.-D.; Scheidt, K. A. Lewis Acid Activated Synthesis of Highly Substituted Cyclopentanes by the *N*-Heterocyclic Carbene Catalyzed Addition of Homoenolate Equivalents to Unsaturated Ketoesters. *Angew. Chem. Int. Ed.* **2011**, *50*, 1678–1682; (c) Julien, D.-T.; O'Bryan, E. A.; Schroeder, T. B. H.; Cohen, D. T.; Scheidt, K. A. An *N*-Heterocyclic Carbene/Lewis Acid Strategy for the Stereoselective Synthesis of Spirooxindole Lactones. *Angew. Chem. Int. Ed.* **2012**, *124*, 5047–5051.

[70] Zhao, X.; DiRocco, D. A.; Rovis, T. *N*-Heterocyclic Carbene and Brønsted Acid Cooperative Catalysis: Asymmetric Synthesis of trans-γ-Lactams. *J. Am. Chem. Soc.* **2011**, *133*, 12466–12469.

[71] (a) Wang, M. H.; Cohen, D. T.; Schwamb, C. B.; Mishra, R. K.; Scheidt, K. A. Enantioselective β-Protonation by a Cooperative Catalysis Strategy. *J. Am. Chem. Soc*. **2015**, *137*, 5891–5894; (b) Wang, M. H.; Barsoum, D.; Schwamb, C. B.; Cohen, D. T.; Goess, B. C.; Riedrich, M.; Chan, A.; Maki, B. E.; Mishra, R. K.; Scheidt, K. A. Catalytic, Enantioselective β-Protonation through a Cooperative Activation Strategy. *J. Org. Chem.* **2017**, *82*, 4689–4702.

[72] Guo, C.; Fleige, M.; Janssen-Müller, D.; Daniliuc, C. G.; Glorius, F. Cooperative *N*-Heterocyclic Carbene/Palladium-Catalyzed Enantioselective Umpolung Annulations. *J. Am. Chem. Soc*. **2016**, *138*, 7840–7843.

[73] Chen, J.; Yuan, P.; Wang, L.; Huang, Y. Enantioselective β-Protonation of Enals via a Shuttling Strategy. *J. Am. Chem. Soc*. **2017**, *139*, 7045–7051.

[74] Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. Chiral *N*-Heterocyclic Carbene Catalyzed Staudinger Reaction of Ketenes with Imines: Highly Enantioselective Synthesis of N-Boc β-Lactams. *Org. Lett.* **2008**, *10*, 277–280.

[75] Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *N*-Heterocyclic Carbene Catalysed β-Lactam Synthesis. *Org. Biomol. Chem.* **2008**, *6*, 1108–1113.

[76] (a) He, L.; Lv, H.; Zhang, Y.-R.; Ye, S. Formal Cycloaddition of Disubstituted Ketenes with 2-Oxoaldehydes Catalyzed by Chiral *N*-Heterocyclic Carbenes. *J. Org. Chem.* **2008**, *73*, 8101–8103; (b) Wang, X.-N.; Shao, P-L.; Lv, H.; Ye, S. Enantioselective Synthesis of β-Trifluoromethyl-β-Lactones via NHC-Catalyzed Ketene−Ketone Cycloaddition Reactions. *Org. Lett.* **2009**, *11*, 4029–4031; (c) Wang, T.; Huang, X.-L.; Ye, S. Enantioselective Formal [2+2] Cycloaddition of Ketenes with Nitroso Compounds Catalyzed by *N*-Heterocyclic Carbenes. *Org. Biomol. Chem*. **2010**, *8*, 5007–5011; (d) Huang, X.-L.; Chen, X.-Y.; Ye, S. Enantioselective Synthesis of Aza-β-lactams via NHC-Catalyzed [2 + 2] Cycloaddition of Ketenes with Diazenedicarboxylates. *J. Org. Chem.* **2009**, *74*, 7585–7587; (e) Lv, H.; Zhang, Y.-R.; Huang, X.-L.; Ye, S. Asymmetric Dimerization of Disubstituted Ketenes Catalyzed by *N*-Heterocyclic Carbenes. *Adv. Synth. Catal.* **2008**, *350*, 2715–2718.

[77] Jian, T.-Y.; He, L.; Tang, C.; Ye, S. *N*-Heterocyclic Carbene Catalysis: Enantioselective Formal [2+2] Cycloaddition of Ketenes and N-Sulfinylanilines. *Angew. Chem. Int. Ed.* **2011**, *50*, 9104–9107.

[78] Wang, X.-N.; Shen, L.-T.; Ye, S. NHC-Catalyzed Enantioselective [2 + 2] and [2 + 2 + 2] Cycloadditions of Ketenes with Isothiocyanates. *Org. Lett.* **2011**, *13*, 6382–6385.

[79] (a) Zhang, Y.-R.; Lv, H.; Zhou, D.; Ye, S.; Chiral *N*-Heterocyclic Carbene-Catalyzed Formal [4+2] Cycloaddition of Ketenes with Enones: Highly Enantioselective Synthesis of trans- and cis-δ-Lactones. *Chem. Eur. J.* **2008**, *14*, 8473–8476; (b) Lv, H.; You, L.; Ye, S. Enantioselective Synthesis of Dihydrocoumarins via *N*-Heterocyclic Carbene-Catalyzed Cycloaddition of Ketenes and *o*-Quinone Methides. *Adv. Synth. Catal.* **2009**, *351*, 2822–2826; (c) Lv, H.; Chen, X.-Y.; Sun, L.-H.; Ye, S. Enantioselective Synthesis of Indole-Fused Dihydropyranones via Catalytic Cycloaddition of Ketenes and 3-Alkylenyloxindoles. *J. Org. Chem.* **2010**, *75*, 6973–6976; (d) Jian, T.-Y.; Chen, X.-Y.; Sun, L.-H.; Ye, S. *N*-Heterocyclic Carbene-Catalyzed [4 + 2] Cycloaddition of Ketenes and 3-Aroylcoumarins: Highly Enantioselective Synthesis of Dihydrocoumarin-Fused Dihydropyranones. *Org. Biomol. Chem.* **2013**, *11*, 158–163; (e) Jian, T.-Y.; Shao, P.-L.; Ye, S. Enantioselective [4+2] Cycloaddition of Ketenes and 1-Azadienes Catalyzed by *N*-Heterocyclic Carbenes. *Chem. Comm.* **2011**, *47*, 2381–2383; (f) Huang, X.-L.; He, L.; Shao, P.-L.; Ye, S. [4+2] Cycloaddition of Ketenes with N-Benzoyldiazenes Catalyzed by *N*-Heterocyclic Carbenes. *Angew. Chem. Int. Ed.* **2009**, *48*, 192–195.

[80] Shen, L.-T.; Shao, P.-L.; Ye, S. *N*-Heterocyclic Carbene-Catalyzed Cyclization of Unsaturated Acyl Chlorides and Ketones. *Adv. Synth. Catal*. **2011**, *353*, 1943–1948.

[81] (a) Shen, L.-T.; Sun, L.-H.; Ye, S. Highly Enantioselective γ-Amination of α,β-Unsaturated Acyl Chlorides with Azodicarboxylates: Efficient Synthesis of Chiral γ-Amino Acid Derivatives. *J. Am. Chem. Soc.* **2011**, *133*, 15894–15897; (b) Shen, L.-T.; Jia, W.-Q.; Ye, S. Catalytic [4+2] Cyclization of α,β-Unsaturated Acyl Chlorides with 3-Alkylenyloxindoles: Highly Diastereo-and Enantioselective Synthesis of Spirocarbocyclic Oxindoles. *Angew. Chem. Int. Ed.* **2013**, *52*, 585–588.

[82] Reynolds, N. T.; Rovis, T. Enantioselective Protonation of Catalytically Generated Chiral Enolates as an Approach to the Synthesis of α-Chloroesters. *J. Am. Chem. Soc.* **2005**, *127*, 16406–16407.

[83] Vora, H. U.; Rovis, T. *N*-Heterocyclic Carbene Catalyzed Asymmetric Hydration: Direct Synthesis of α-Protio and α-Deuterio α-Chloro and α-Fluoro Carboxylic Acids. *J. Am. Chem. Soc.* **2010**, *132*, 2860–2861.

[84] He, M.; Struble, J. R.; Bode, J. W. Highly Enantioselective Azadiene Diels−Alder Reactions Catalyzed by Chiral *N*-Heterocyclic Carbenes. *J. Am. Chem. Soc.* **2006**, *128*, 8418–8420.

[85] (a) Burstein, C.; Tschan, S.; Xie, X.; Glorius, F. *N*-Heterocyclic Carbene-Catalyzed Conjugate Umpolung for the Synthesis of γ-Butyrolactones. *Synthesis* **2006**, *14*, 2418–2439; (b) Kaeobamrung, J.; Kozlowski, M. C.; Bode, J. W. Chiral *N*-Heterocyclic Carbene-Catalyzed Generation of Ester Enolate Equivalents from α,β-Unsaturatedaldehydes for Enantioselective Diels–Alder Reactions. *Proc. Natl. Acad. Sci.* **2010**, *107*, 20661–20665; (c) Zhao, Y.-M.; Cheung, M. S.; Lin, Z.; Sun, J. Enantioselective Synthesis of β,γ-Unsaturated α-Fluoroesters Catalyzed by *N*-Heterocyclic Carbenes. *Angew. Chem. Int. Ed.* **2012**, *51*, 10359–10363; (d) Xu, J.; Chen, X.; Wang, M.; Zheng, P.; Song, B.-A.; Chi, Y. R. Aminomethylation of Enals through Carbene and Acid Cooperative Catalysis: Concise Access to β^2-Amino Acids. *Angew. Chem. Int. Ed.* **2015**, *54*, 5161–5165; (e) Wu, Z.; Wang, X.; Li, F.; Wu, J.; Wang, J. Chemoselective *N*-Heterocyclic Carbene-Catalyzed Cascade of Enals with Nitroalkenes. *Org. Lett*. **2015**, *17*, 3588–3591.

[86] (a) Singha, S.; Patea, T.; Daniliuc, C. G.; Glorius, F. Highly Enantioselective [5 + 2] Annulations through Cooperative *N*-Heterocyclic Carbene (NHC) Organocatalysis and Palladium Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 3551–3554; (b) Zhou, L.; Wu, X.; Yang, X.; Mou, C.; Song, R.; Yu, S.; Chai, H.; Pan, L.; Jin, Z.; Chi, Y. R. Gold and Carbene Relay Catalytic Enantioselective Cycloisomerization/Cyclization Reactions of Ynamides and Enals. *Angew. Chem. Int. Ed.* **2020**, *59*, 1557–1561.

[87] He, M.; Uc, G. J.; Bode, J. W. Chiral *N*-Heterocyclic Carbene Catalyzed, Enantioselective Oxodiene Diels-Alder Reactions with Low Catalyst Loadings. *J. Am. Chem. Soc.* **2006**, *128*, 15088–15089.

[88] Ni, Q.; Zhang, H.; Grossmann, A.; Loh, C. C. J.; Merkens, C.; Enders, D. Asymmetric Synthesis of Pyrroloindolones by *N*-Heterocyclic Carbene Catalyzed *2+3+ Annulation of α-Chloroaldehydes with Nitrovinylindoles. *Angew. Chem. Int. Ed.* **2013**, *52*, 13562–13566.

[89] (a) Zhao, D.; Ruhl, K. E.; Rovis, T. *N*-Heterocyclic-Carbene-Catalyzed Asymmetric Oxidative Hetero-Diels-Alder Reactions with Simple Aliphatic Aldehydes. *Angew. Chem. Int. Ed.* **2012**, *51*, 12330–12333; (b) Mo, J.; Yang, R.; Chen, X.; Tiwari, B.; Chi, Y. R. Direct α-Functionalization of Simple Aldehydes via Oxidative *N*-Heterocyclic Carbene Catalysis. *Org. Lett.* **2013**, *15*, 50–53; (c) Lin, L.; Yang, Y.; Wang, M.; Lai, L.; Guo, Y.; Wang, R. Oxidative *N*-Heterocyclic Carbene Catalyzed Stereoselective Annulation of Simple Aldehydes and 5-Alkenyl Thiazolones. *Chem. Commun*, **2015**, *51*, 8134–8137; (d) Xu, J.; Yuan, S.; Peng, J.; Miao, M.; Chen, Z.; Ren, H. Enantioselective [2+2] Annulation of Simple Aldehydes with Isatin-Derived Ketimines via Oxidative *N*-Heterocyclic Carbene Catalysis. *Chem. Commun*. **2017**, *53*, 3430–3433; (e) Yuan, S.; Luo, Y.; Peng, J.; Miao, M.; Xu, J.; Ren, H. Oxidative Asymmetric [2 + 3] Annulation of Aldehydes with Azomethine Imines Enabled by *N*-Heterocyclic Carbene Catalysis. *Org. Lett.* **2017**, *19*, 6100–6103.

[90] Mo, J.; Chen, X.; Chi, Y. R. Oxidative γ-Addition of Enals to Trifluoromethyl Ketones: Enantioselectivity Control via Lewis Acid/*N*-Heterocyclic Carbene Cooperative Catalysis. *J. Am. Chem. Soc.* **2012**, *134*, 8810–8813

[91] (a) Lin, Y.; Yang, L.; Deng, Y.; Zhong, G. Cooperative Catalysis of *N*-Heterocyclic Carbene and Brønsted Acid for a Highly Enantioselective Route to Unprotected Spiro-Indoline-Pyrans. *Chem. Commun*. **2015**, *51*, 8330–8333; (b) Rong, X.; Yao, H.; Xia, W.; Du, Y.; Zhou, Y.; Liu, H. Enantioselective Assembly of Spirolactones through NHC-Catalyzed Remote γ-Carbon Addition of Enals with Isatins. *ACS Comb. Sci*. **2016**, *18*, 220–224; (c) Wu, Z.; Li, F.; Wang, J. Intermolecular Dynamic Kinetic Resolution Cooperatively Catalyzed by an *N*-Heterocyclic Carbene and a Lewis Acid. *Angew. Chem. Int. Ed.*

2015, *54*, 1629–1633; (d) Zheng, P.-C.; Cheng, J.; Su, S.; Jin, Z.; Wang, Y.-H.; Yong, S.; Jin, L.-H.; Song, B.-A.; Chi, Y. R. Oxidative *N*-Heterocyclic Carbene-Catalyzed γ-Carbon Addition of Enals to Imines: Mechanistic Studies and Access to Antimicrobial Compounds. *Chem. Eur. J.* **2015**, *21*, 9984–9987; (e) Chen, X.-Y.; Liu, Q.; Chanhan, P.; Peuronoe, A.; Rissanen, K.; Jafari, E.; Enders, D. *N*-Heterocyclic Carbene Catalyzed [4+2] Annulation of Enals via a Double Vinylogous Michael Addition: Asymmetric Synthesis of 3,5-Diaryl Cyclohexenones. *Angew. Chem. Int. Ed.* **2017**, *56*, 6241–6245; (f) Wang, M.; Huang, Z.; Xu, J.; Chi, Y. R. *N*-Heterocyclic Carbene-Catalyzed [3+4] Cycloaddition and Kinetic Resolution of Azomethine Imines. *J. Am. Chem. Soc.* **2014**, *136*, 1214–1217.

[92] Chen, X.; Yang, S.; Song, B.-A.; Chi, Y. R. Functionalization of Benzylic C(sp^3) H Bonds of Heteroaryl Aldehydes through *N*-Heterocyclic Carbene Organocatalysis. *Angew. Chem. Int. Ed.* **2013**, *52*, 11134–11137.

[93] (a) Janssen-Müller, D.; Singha, S.; Olyschläger, T.; Daniliuc, C. G.; Glorius, F. Annulation of *o*-Quinodimethanes through *N*-Heterocyclic Carbene Catalysis for the Synthesis of 1-Isochromanones. *Org. Lett.* **2016**, *18*, 4444–4447; (b) Chen, D.-F.; Rovis, T. *N*-Heterocyclic Carbene and Chiral Brønsted Acid Cooperative Catalysis for a Highly Enantioselective [4+2] Annulation. *Synthesis* **2016**, *49*, 293–298.

[94] (a) Zhao, Y.-M.; Cheung, M. S.; Lin, Z.; Sun, J. Enantioselective Synthesis of β,γ-Unsaturated α-Fluoroesters Catalyzed by *N*-Heterocyclic Carbenes. *Angew. Chem. Int. Ed.* **2012**, *51*, 10359–10363; (b) Chen, X.-Y.; Xia, F.; Cheng, J.-T.; Ye, S. Highly Enantioselective γ-Amination by *N*-Heterocyclic Carbene Catalyzed [4+2] Annulation of Oxidized Enals and Azodicarboxylates. *Angew. Chem. Int. Ed.* **2013**, *125*, 10838–10841; (c) Xiao, Z.; Yu, C.; Li, T.; Wang, X.-S.; Yao, C. *N*-Heterocyclic Carbene/Lewis Acid Strategy for the Stereoselective Synthesis of Spirocyclic Oxindole-Dihydropyranones. *Org. Lett.* **2014**, *16*, 3632–3635; (d) Dong, X.; Sun, J. Catalytic Asymmetric α-Aldol Reaction of Vinylogous N-Heterocyclic Carbene Enolates: Formation of Quaternary and Labile Tertiary Stereocenters. *Org. Lett.* **2014**, *16*, 2450–2453; (e) Cheng, J.-T.; Chen, X.-Y.; Gao, Z.-H.; Ye, S. *N*-Heterocyclic Carbene Catalyzed Generation and [4+2] Annulation of Unsubstituted Dienolate - Enantioselective Synthesis of Spirocyclic Oxindolodihydropyranones. *Eur. J. Org. Chem*. **2015**, 1047–1053; (f) Xiao, Y.; Wang, J.; Xia, W.; Shu, S.; Jiao, S.; Zhou, Y.; Liu, H. γ-Carbon Activation through *N*-Heterocyclic Carbene/ Brønsted Acids Cooperative Catalysis: A Highly Enantioselective Route to δ-Lactams. *Org. Lett.* **2015**, *17*, 3850–3853.

[95] Zhu, T.; Zheng, P.; Mou, C.; Yang, S.; Chi, Y. R. Benzene Construction via Organocatalytic Formal [3+3] Cycloaddition Reaction. *Nat. Commun*. **2014**, *5*, 5027–5033.

[96] Zeitler, K. Stereoselective Synthesis of (E)-α,β-Unsaturated Esters via Carbene-Catalyzed Redox Esterification. *Org. Lett.* **2006**, *8*, 637–640.

[97] Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. Tandem Oxidation of Allylic and Benzylic Alcohols to Esters Catalyzed by *N*-Heterocyclic Carbenes. *Org. Lett.* **2007**, *9*, 371–374.

[98] Sarkar, S. D.; Grimme, S.; Studer, A. NHC Catalyzed Oxidations of Aldehydes to Esters: Chemoselective Acylation of Alcohols in Presence of Amines. *J. Am. Chem. Soc.* **2010**, *132*, 1190−1191.

[99] Ryan, S. J.; Candish, L.; Lupton, D. W. *N*-Heterocyclic Carbene-Catalyzed Generation of α,β-Unsaturated Acyl Imidazoliums: Synthesis of Dihydropyranones by their Reaction with Enolates. *J. Am. Chem. Soc.* **2009**, *131*, 14176–14177.

[100] (a) Smrkar, S. D.; Studer, A. NHC-Catalyzed Michael Addition to α,β-Unsaturated Aldehydes by Redox Activation. *Angew. Chem. Int. Ed.* **2010**, *49*, 9266–9269; (b) Mo, J.; Shen, L.; Chi, Y. R. Direct β-Activation of Saturated Aldehydes to Formal Michael Acceptors through Oxidative NHC Catalysis. *Angew. Chem. Int. Ed.* **2013**, *52*, 8588–8591; (c) Wang, G.; Chen, X.; Miao, G.; Yao, W.; Ma, C. Divergent NHC-Catalyzed Oxidative Transformations of 3-Bromoenal: Selective Synthesis of 2H-Pyran-2-ones and Chiral Dihydropyranones. *J. Org. Chem.* **2013**, *78*, 6223–6232; (d) Sun, F.-G.; Sun, L.-H.; Ye, S. *N*-Heterocyclic Carbene-Catalyzed Enantioselective Annulation of Bromoenal and 1,3-Dicarbonyl Compounds. *Adv. Synth. Catal*. **2011**, *353*, 3134–3138; (e) Yao, C.; Wang, D.; Lu, J.; Li, T.; Jiao, W.; Yu, C. *N*-Heterocyclic Carbene Catalyzed Reactions of α-Bromo-α,β-unsaturated Aldehydes/α,β-Dibromoaldehydes with 1,3-Dinucleophilic Reagents. *Chem. Eur. J*. **2012**, *18*, 1914–1917; (f) Yetra, S. R.; Bhunia, A.; Patra, A.; Mane, M. V.; Vanka, K.; Biju, A. T. Enantioselective *N*-Heterocyclic Carbene-Catalyzed Annulations of 2-Bromoenals with 1,3-Dicarbonyl Compounds and Enamines via Chiral α,β-Unsaturated Acylazoliums. *Adv. Synth. Catal*. **2013**, *355*, 1089–1097; (g) Zhu, Z.-Q.; Zheng, X.-L.; Jiang, N.-F.; Wan, X.; Xiao, J.-C. Chiral *N*-Heterocyclic Carbene Catalyzed Annulation of α,β-Unsaturated Aldehydes with 1,3-Dicarbonyls. *Chem. Commun*. **2011**, *47*, 8670–8672.

[101] Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. An Enantioselective Claisen Rearrangement Catalyzed by *N*-Heterocyclic Carbenes. *J. Am. Chem. Soc.* **2010**, *132*, 8810–8812.

[102] Li, G.-T.; Gu, Q.; You, S.-L. Enantioselective Annulation of Enals with 2-Naphthols by Triazolium Salts Derived from L-phenylalanine. *Chem. Sci.* **2015**, *6*, 4273–4278.

[103] (a) Xu, J.; Zhang, W.; Liu, Y.; Zhu, S.; Liu, M.; Hua, X.; Chen, S.; Lu, T.; Du, D. Formal [3 + 3] Annulation of Isatin-Derived 2-Bromoenals with 1,3-Dicarbonyl Compounds Enabled by Lewis Acid/*N*-Heterocyclic Carbene Cooperative Catalysis. *RSC Adv.* **2016**, *6*, 18601–18606; (b) Lin, J.-B.; Cheng, X.-N.; Tian, X.-D.; Xu, G.-Q.; Luo, Y.-C.; Xu, P.-F. A C1-Symmetric *N*-Heterocyclic Carbene Catalysed Oxidative Spiroannulation of Isatin-Derived Enals: Highly Enantioselective Synthesis of Spirooxindole δ-Lactones. *RSC Adv*. **2018**, *8*, 15444–15447.

[104] Biswas, A.; Sarkar, S. D.; Tebben, L.; Studer, A. Enantioselective Cyclopropanation of Enals by Oxidative *N*-Heterocyclic Carbene Catalysis. *Chem. Commun*. **2012**, *48*, 5190–5192.

[105] Wanner, B.; Mahatthananchai, J.; Bode, J. W. Enantioselective Synthesis of Dihydropyridinones via NHC-Catalyzed Aza-Claisen Reaction. *Org. Lett.* **2011**, *13*, 5378–5381.

[106] (a) Kravina, A. G.; Mahatthananchai, J.; Bode, J. W. Enantioselective, NHC-Catalyzed Annulations of Trisubstituted Enals and Cyclic N-Sulfonylimines via α,β-Unsaturated Acyl Azoliums. *Angew. Chem. Int. Ed.* **2012**, *51*, 9433–9436; (b) Zhang, H.-M.; Jia, W.-Q.; Liang, Z.-Q.; Ye, S. *N*-Heterocyclic Carbene-Catalyzed [3+3] Cyclocondensation of Bromoenals and Ketimines: Highly Enantioselective Synthesis of Dihydropyridinones. *J. Org. Chem.* **2014**, *3*, 462–465; (c) Enders, D.; Ni, Q.; Xiong, J.; Song, X.; Raabe, G. *N*-Heterocyclic Carbene Catalyzed Enantioselective Annulation of Benzothiazolyl Ethyl Acetates with 2-Bromoenals. *Synlett* **2015**, *26*, 1465–1469; (d) Zhao, L.-L.; Li, X.-S.; Cao, L.-L.; Zhang, R.; Shi, X.-Q.; Qi, J. Access to Dihydropyridinones and Spirooxindoles: Application of *N*-Heterocyclic Carbene-Catalyzed [3+3] Annulation of Enals and Oxindole-Derived Enals with 2-Aminoacrylates. *Chem. Commun*. **2017**, *53*, 5985–5988; (e) Chen, Q.; Zhu, T.; Majhi, P. K.; Mou, C.; Chai, H.; Zhang, J.; Zhuo, S.; Chi, Y. R. Carbene-Catalyzed Enantioselective Oxidative Coupling of Enals and Di(hetero)arylmethanes. *Chem. Sci.* **2018**, *9*, 8711–8715; (f) Gao, Z.-H.; Chen, X.-Y.; Zhang, H.-M.; Ye, S. *N*-Heterocyclic Carbene-Catalyzed [3+3] Cyclocondensation of Bromoenals with Aldimines: Highly Enantioselective Synthesis of Dihydropyridinones. *Chem. Commun*. **2015**, *51*, 12040–12043.

[107] Chen, K.-Q.; Gao, Z.-H.; Ye, S. (Dynamic) Kinetic Resolution of Enamines/Imines: Enantioselective *N*-Heterocyclic Carbene Catalyzed [3+3] Annulation of Bromoenals and Enamines/Imines. *Angew. Chem. Int. Ed.* **2019**, *58*, 1183–1187.

[108] Chen, K.-Q.; Gao, Z.-H.; Song, C.-Y.; Zhang, C.-L.; Wang, Z.-X.; Ye, S. *N*-Heterocyclic Carbene Catalyzed Cyclocondensation of α,β-Unsaturated Carboxylic Acids: Enantioselective Synthesis of Pyrrolidinone and Dihydropyridinone Derivative. *Angew. Chem. Int. Ed.* **2014**, *53*, 11611–11615.

[109] Chen, K.-Q.; Li, Y.; Zhang, C.-L.; Sun, D.-Q.; Ye, S. *N*-Heterocyclic Carbene-Catalyzed [3 + 2] Annulation of Bromoenals with 3-Amino-

oxindoles: Highly Enantioselective Synthesis of Spirocyclic Oxindolo-γ-lactams. *Org. Biomol. Chem*. **2016**, *14*, 2007–2014.

[110] Wu, X.; Liu, B.; Zhang, Y.; Jeret, M.; Wang, H.; Zheng, P.; Yang, S.; Song, B-A.; Chi, Y. R. Enantioselective Nucleophilic β-Carbon-Atom Amination of Enals: Carbene-Catalyzed Formal [3+2] Reactions. *Angew. Chem. Int. Ed.* **2016**, *55*, 12280–12284.

[111] Zhang, G.; Xu, W.; Liu, J.; Das, D. K.; Yang, S.; Perveen, S.; Zhang, H.; Li, X.; Fang, X. Enantioselective Intermolecular All-Carbon [4+2] Annulation via *N*-Heterocyclic Carbene Organocatalysis. *Chem. Commun*. **2017**, *53*, 13336–13339.

[112] Perveen, S.; Zhao, Z.; Zhang, G.; Liu, J.; Anwar, M.; Fang, X. Enantioselective Synthesis of 1,2-Dihydronaphthalenes via Oxidative *N*-Heterocyclic Carbene Catalysis. *Org. Lett.* **2017**, *19*, 2470–2473.

[113] Zhang, C.-L.; Ye, S. *N*-Heterocyclic Carbene-Catalyzed Construction of 1,3,5-Trisubstituted Benzenes from Bromoenals and α-Cyano-β-methylenones. *Org. Lett.* **2016**, *18*, 6408–6411.

[114] Jia, Q.; Wang, J. *N*-Heterocyclic Carbene-Catalyzed Convenient Benzonitrile Assembly. *Org. Lett.* **2016**, *18*, 2212–2215.

[115] Wu, S.; Liu, C.; Luo, G.; Jin, Z.; Zheng, P.; Chi, Y. R. NHC-Catalyzed Chemoselective Reactions of Enals and Aminobenzaldehydes for Access to Chiral Dihydroquinolines. *Angew. Chem. Int. Ed.* **2019**, *131*, 18581–18584.

[116] (a) Liang, Z.-Q.; Wang, D.-L.; Zhang, H.-M.; Ye, S. Enantioselective Synthesis of Bicyclic δ-Lactones via *N*-Heterocyclic Carbene-Catalyzed Cascade Reaction. *Org. Lett*. **2015**, *17*, 5140−5143; (b) Bera, S.; Daniliuc, C. D.; Studer, A. Enantioselective Synthesis of Substituted δ-Lactones by Cooperative Oxidative *N*-Heterocyclic Carbene and Lewis Acid Catalysis. *Org. Lett.* **2015**, *17*, 4940–4943; (c) Wang, J.; Li, Y.; Wang, H.; Jin, Z.; Chi, Y. R. Carbene-Catalyzed Enantioselective Addition of Benzylic Carbon to Unsaturated Acyl Azolium for Rapid Synthesis of Pyrrolo[3,2-c]quinolones. *ACS Catal.* **2018**, *8*, 9859–9864; (d) Liu, Q.; Chen, X.-Y.; Puttreddy, R.; Rissanen, K.; Enders, D. *N*-Heterocyclic Carbene Catalyzed Quadruple Domino Reactions: Asymmetric Synthesis of Cyclopenta[c]chromenones. *Angew. Chem. Int. Ed.* **2018**, *130*, 17346–17349; (e) Anwar, M.; Yang, S.; Xu, W.; Liu, J.; Perveen, S.; Kong, X.; Zehra, S. T.; Fang, X. Carbene-Catalyzed Asymmetric Friedel–Crafts Alkylation-Annulation Sequence and Rapid Synthesis of Indole-Fused Polycyclic Alkaloids. *Commun. Chem.* **2019**, *2*, 85.

[117] Hao, L.; Du, Y.; Lv, H.; Chen, X.; Jiang, H.; Shao, Y.; Chi, Y. R. Enantioselective Activation of Stable Carboxylate Esters as Enolate Equivalents via *N*-Heterocyclic Carbene Catalysts. *Org. Lett.* **2012**, *14*, 2154–2157.

[118] Hao, L.; Chen, S.; Xu, J.; Tiwari, B.; Fu, Z.; Li, T.; Lim, J.; Chi, Y. R. Organocatalytic Activation of Alkylacetic Esters as Enolate Precursors to React with α,β-Unsaturated Imines. *Org. Lett.* **2013**, *15*, 4956–4959.

[119] Chen, S.; Hao, L.; Zhang, Y.; Chi, Y. R. Asymmetric Access to the Smallest Enolate Intermediate via Organocatalytic Activation of Acetic Ester. *Org. Lett.* **2013**, *15*, 5822–5825.

[120] Chen, X.; Fong, J. Z. M.; Xu, J.; Mou, C.; Song, Y.; Chi, Y. R. Carbene-Catalyzed Dynamic Kinetic Resolution of Carboxylic Esters. *J. Am. Chem. Soc.* **2016**, *138*, 7212–7215.

[121] Lee, A.; Younai, A.; Price, C. K.; Izquierdo, J.; Mishra, R. K.; Scheidt, K. A. Enantioselective Annulations for Dihydroquinolones by in situ Generation of Azolium Enolates. *J. Am. Chem. Soc.* **2014**, *136*, 10589–10592.

[122] Fu, Z.; Xu, J.; Zhu, T.; Leong, W. W. Y.; Chi, Y. R. β-Carbon Activation of Saturated Carboxylic Esters Through *N*-Heterocyclic Carbene Organocatalysis. *Nat. Chem.* **2013**, *5*, 835–839.

[123] Fu, Z.; Jiang, K.; Zhu, T.; Torres, J.; Chi, Y. R. Access to Oxoquinoline Heterocycles via *N*-Heterocyclic Carbene-Catalyzed Ester Activation and Selective Domino Reaction. *Angew. Chem. Int. Ed.* **2014**, *53*, 6506–6510.

[124] Xu, J.; Yuan, S.; Miao, M.; Chen, Z. 1-Hydroxybenzotriazole-Assisted, *N*-Heterocyclic Carbene Catalyzed β-Functionalization of Saturated Carboxylic Esters: Access to Spirooxindole Lactones. *J. Org. Chem*. **2016**, *81*, 11454–11460.

[125] Jin, Z.; Chen, S.; Wang, Y.; Zheng, P.; Yang, S.; Chi, Y. R. β-Functionalization of Carboxylic Anhydrides with β-Alkyl Substituents through Carbene Organocatalysis. *Angew. Chem. Int. Ed.* **2014**, *53*, 13506–13509.

[126] Jin, Z.; Fu, Z.; Jiang, K.; Torres, J.; Zheng, P.; Yang, S.; Song, B.-A.; Chi, Y. R. Nucleophilic β-Carbon Activation of Propionic Acid as a 3-Carbon Synthon by Carbene Organocatalysis. *Chem. Eur. J.* **2015**, *21*, 9360–9363.

[127] Xie, Y.; Yu, C.; Li, T.; Tu, S.; Yao, C. An NHC-Catalyzed in Situ Activation Strategy to β-Functionalize Saturated Carboxylic Acid: An Enantioselective Formal [3+2] Annulation for Spirocyclic Oxindolo-λ-butyrolactones. *Chem. Eur. J*. **2015**, *21*, 5355–5359.

[128] Chen, J.; Huang, Z.; Chi, Y. R. NHC Organocatalytic LUMO Activation of α,β-Unsaturated Esters to React with Enamides. *Angew. Chem. Int. Ed.* **2013**, *52*, 8592–8596.

[129] Fu, Z.; Wu, X.; Chi, Y. R. Rapid Access to Bicyclic δ-Lactones via Carbene-Catalyzed Activation and Cascade Reaction of Unsaturated Carboxylic Esters. *Org. Chem. Front.* **2016**, *3*, 145–149.

[130] Mou, C.; Wu, J.; Huang, Z.; Sun, J.; Jin, Z.; Chi, Y. R. Carbene-Catalyzed LUMO Activation of Alkyne Esters for Access to Functional Pyridines. *Chem. Commun.* **2017**, *53*, 13359–13362.

[131] Liu, B.; Wang, W.; Huang, R.; Yan, J.; Wu, J.; Xue, W.; Yang, S.; Jin, Z.; Chi, Y. R. Direct Activation of β-sp^3-Carbons of Saturated Carboxylic Esters as Electrophilic Carbons via Oxidative Carbene Catalysis. *Org. Lett.* **2018**, *20*, 260–263.

[132] Zhang, Z.; Zeng, X.; Xie, D.; Chen, D.; Ding, L.; Wang, A.; Yang, L.; Zhong, G. *N*-Heterocyclic Carbene-Catalyzed Activation of Esters of N-Hydroxyphthalimide: A Highly Enantioselective Route to Chiral Dihydropyridinones Bearing an All Carbon Quaternary Stereogenic Center. *Org. Lett*. **2015**, *17*, 5052–5055.

[133] Chen, X.-Y.; Gao, Z.-H.; Song, C.-Y.; Zhang, C.-L.; Wang, Z.-X.; Ye, S. *N*-Heterocyclic Carbene Catalyzed Cyclocondensation of α,β-Unsaturated Carboxylic Acids: Enantioselective Synthesis of Pyrrolidinone and Dihydropyridinone Derivatives. *Angew. Chem. Int. Ed.* **2014**, *53*, 11611–11615.

[134] Xu, J.; Jin, Z.; Chi, Y. R. Organocatalytic Enantioselective γ-Aminoalkylation of Unsaturated Ester: Access to Pipecolic Acid Derivatives. *Org. Lett*. **2013**, *15*, 5028–5031.

[135] Xu, J.; Yuan, S.; Miao, M. *N*‑Heterocyclic Carbene Catalyzed [4 + 2] Annulation Reactions with in situ Generated Heterocyclic ortho-Quinodimethanes. *Org. Lett.* **2016**, *18*, 3822–3825.

[136] Que, Y.; Li, T.; Yu, C.; Wang, X.-S.; Yao, C. Enantioselective Assembly of Spirocyclic Oxindole-dihydropyranones through NHC-Catalyzed Cascade Reaction of Isatins with N-Hydroxybenzotriazole Esters of α,β-Unsaturated Carboxylic Acid. *J. Org. Chem*. **2015**, *80*, 3289–3294.

[137] Jia, W.-Q.; Zhang, H.-M.; Zhang, C.-L.; Gao, Z.-H.; Ye, S. *N*-Heterocyclic Carbene-Catalyzed *4 + 2+ Annulation of α,β-Unsaturated Carboxylic Acids: Enantioselective Synthesis of Dihydropyridinones and Spirocyclic Oxindolodihydropyridinones. *Org. Chem. Front*. **2016**, *3*, 77–81.

[138] Fang, S.; Jin, S. Ma, R.; Lu, T.; Du, D. Asymmetric Synthesis of C2-Quaternary Indolin-3-ones Enabled by *N*-Heterocyclic Carbene Catalysis. *Org. Lett*. **2019**, *21*, 5211–5214.

[139] Que, Y.; Xie, Y.; Li, T.; Yu, C.; Tu, S.; Yao, C. An *N*-Heterocyclic Carbene-Catalyzed Oxidative γ-Aminoalkylation of Saturated Carboxylic Acids through in Situ Activation Strategy: Access to δ-Lactam. *Org. Lett*. **2015**, *17*, 6234–6237.

[140] Mansoorabadi, S. O.; Seravalli, J.; Furdui, C.; Krymov, V.; Gerfen, G. J.; Begley, T. P.; Melnick, J.; Ragsdale, S. W.; Reed, G. H. EPR Spectroscopic and Computational Characterization of the Hydroxyethylidene-Thiamine Pyrophosphate Radical Intermediate of Pyruvate: Ferredoxin Oxidoreductase. *Biochemistry* **2006**, *45*, 7122–7131.

[141] Chabrière, E., Vernède, X., Guigliarelli, B., Charon, M.-H.; Hatchikian, E. C.; Fontecilla-Camps, J. C. Crystal Structure of the Free Radical Intermediate of Pyruvate: Ferredoxin Oxidoreductase. *Science* **2010**,

294, 2559–256.

[142] (a) Rehbein, J.; Ruser, S. M.; Phan, J. NHC-Catalysed Benzoin Condensation-Is It All Down to the Breslow Intermediate? *Chem. Sci.* **2015**, *6*, 6013–6018; (b) Phan, J.; Ruser, S. M.; Zeitler, K.; Rehbein, J. NHC-Stabilized Radicals in the Formal Hydroacylation Reaction of Alkynes. *Eur. J. Org. Chem.* **2019**, 557–561.

[143] Regnier, V.; Romero, E. A.; Molton, F.; Jazzar, R.; Bertrand, G.; Martin , D. What Are the Radical Intermediates in Oxidative *N*-Heterocyclic Carbene Organocatalysis? *J. Am. Chem. Soc.* **2019**, *141*, 1109–1117.

[144] Guin, J.; Sarkar, S. D.; Grimme, S.; Studer, A. Biomimetic Carbene-Catalyzed Oxidations of Aldehydes Using TEMPO. *Angew. Chem. Int. Ed.* **2008**, *47*, 8727–8730.

[145] Du, Y.; Wang, Y.; Li, X.; Shao, Y.; Li, G.; Webster, R. D.; Chi, Y. R. *N*-Heterocyclic Carbene Organocatalytic Reductive β,β-Coupling Reactions of Nitroalkenes via Radical Intermediates. *Org. Lett.* **2014**, *16*, 5678–5681.

[146] Li, B.-S.; Wang, Y.; Proctor, R. S. J.; Zhang, Y.; Webster, R. D.; Yang, S.; Song, B.; Chi, Y. R. Carbene-Catalysed Reductive Coupling of Nitrobenzyl Bromides and Activated Ketones or Imines via Single-Electron-Transfer Process. *Nat. Commun*. **2016**, *7*, 12933.

[147] Wang, Y.; Du, Y.; Huang, X.; Wu, X.; Zhang, Y.; Yang, S.; Chi, Y. R. Carbene-Catalyzed Reductive Coupling of Nitrobenzyl Bromide and Nitroalkene via the Single-Electron-Transfer (SET) Process and Formal 1,4-Addition. *Org. Lett.* **2017**, *19*, 632–635.

[148] White, N. A.; Rovis, T. Enantioselective *N*‑Heterocyclic Carbene-Catalyzed β−Hydroxylation of Enals Using Nitroarenes: An Atom Transfer Reaction That Proceeds via Single Electron Transfer. *J. Am. Chem. Soc.* **2014**, *136*, 14674–14677.

[149] Zhang, Y.; Du, Y.; Huang, Z.; Xu, J.; Wu, X.; Wang, Y.; Wang, M.; Yang, S.; Webster, R. D.; Chi, Y. R. *N*‑Heterocyclic Carbene-Catalyzed Radical Reactions for Highly Enantioselective β‑Hydroxylation of Enals. *J. Am. Chem. Soc.* **2015**, *137*, 2416–2419.

[150] Wang, H.; Wang, Y.; Chen, X.; Mou, C.; Yu, S.; Chai, H.; Jin, Z.; Chi, Y. R. Chiral Nitroarenes as Enantioselective Single-Electron-Transfer Oxidants for Carbene-Catalyzed Radical Reactions. *Org. Lett.* **2019**, *21*, 7440–7444.

[151] White, N. A.; Rovis, T. Oxidatively Initiated NHC-Catalyzed Enantioselective Synthesis of 3,4-Disubstituted Cyclopentanones from Enals. *J. Am. Chem. Soc.* **2015**, *137*, 10112–10115.

[152] Yang, W.; Hu, W.; Dong, X.; Li, X.; Sun, J. *N*-Heterocyclic Carbene Catalyzed ϒ-Dihalomethylenation of Enals by Single-Electron Transfer. *Angew. Chem. Int. Ed.* **2016**, *55*, 15783–15786.

[153] Wu, X.; Zhang, Y.; Wang, Y.; Ke, J.; Jeret, M.; Reddi, R. N.; Yang, S.; Song, B-A.; Chi, Y. R. Polyhalides as Efficient and Mild Oxidants for Oxidative Carbene Organocatalysis by Radical Processes. *Angew. Chem. Int. Ed.* **2017**, *56*, 2942–2946.

[154] Che, X.-Y.; Chen, K.-Q.; Sun, D.-Q.; Ye, S. *N*-Heterocyclic Carbene-Catalyzed Oxidative [3 + 2] Annulation of Dioxindoles and Enals: Cross Coupling of Homoenolate and Enolate. *Chem. Sci.* **2017**, *8*, 1936–1941.

[155] Ishii, T.; Kakeno, Y.; Nagao, K.; Ohmiya, H. *N*‑Heterocyclic Carbene-Catalyzed Decarboxylative Alkylation of Aldehydes. *J. Am. Chem. Soc.* **2019**, *141*, 3854–3858.

[156] Ishii, T.; Ota, K.; Nagao, K.; Ohmiya, H. *N*-Heterocyclic Carbene-Catalyzed Radical Relay Enabling Vicinal Alkylacylation of Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 14073–14077.

[157] (a) Li, J.-L.; Liu, Y.-Q.; Zou, W.-L.; Zeng, R.; Zhang, X.; Liu, Y.; Han, B.; He, Y.; Leng, H.-J.; Li, Q.-Z. Radical Acylfluoroalkylation of Olefins through *N*-Heterocyclic Carbene Organocatalysis. *Angew. Chem. Int. Ed.* **2020**, *59*, 1863–1870; (b) Zhang, B.; Peng, Q.; Guo, D.; Wang, J. NHC-Catalyzed Radical Trifluoromethylation Enabled by Togni Reagent. *Org. Lett.* **2020**, *22*, 443–447.

[158] DiRocco, D. A.; Rovis, T. Catalytic Asymmetric α-Acylation of Tertiary Amines Mediated by a Dual Catalysis Mode: *N*-Heterocyclic Carbene and Photoredox Catalysis. *J. Am. Chem. Soc.* **2012**, *134*, 8094–8097.

[159] Dai, L.; Xia, Z.-H.; Gao, Y.-Y.; Gao, Z.-H.; Ye, S. Visible-Light-Driven *N*-Heterocyclic Carbene Catalyzed ϒ-and ε-Alkylation with Alkyl Radicals. *Angew. Chem. Int. Ed.* **2019**, *58*, 18124–18130.

[160] Dai, L.; Ye, S. Photo/*N*-Heterocyclic Carbene Co-catalyzed Ring Opening and ϒ-Alkylation of Cyclopropane Enal. *Org. Lett.* **2020**, *22*, 986–990.

[161] Mavroskoufis, A.; Rajes, K.; Golz, P.; Agrawal, A.; Ruß, V. T.; Götze, J. P.; Hopkinson, M. N. *N*-Heterocyclic Carbene Catalyzed Photoenolization/Diels-Alder Reaction of Acid Fluorides. *Angew. Chem. Int. Ed.* **2020**, *59*, 3190–3194.

[162] Fischer, C.; Smith, S. W.; Powell, D. A.; Fu, G. C. Umpolung of Michael Acceptors Catalyzed by *N*-Heterocyclic Carbenes. *J. Am. Chem. Soc*. **2006**, *128*, 1472−1473.

[163] He, L.; Jian, T.-Y.; Ye, S. N-Heterocyclic Carbene Catalyzed Aza-Morita−Baylis−Hillman Reaction of Cyclic Enones with NTosylarylimines. *J. Org. Chem*. **2007**, *72*, 7466−7468.

[164] Chen, X.-Y.; Xia, F.; Ye, S. Catalytic MBH Reaction of β-Substituted Nitroalkenes with Azodicarboxylates. *Org. Biomol. Chem*. **2013**, *11*, 5722−5726.

[165] Atienza, R. L.; Roth, H. S.; Scheidt, K. A. *N*-Heterocyclic Carbene-Catalyzed Rearrangements of Vinyl Sulfones. *Chem. Sci*. **2011**, 1772−1776.

[166] (a) Matsuoka, S.-I.; Ota, Y.; Washio, A.; Katada, A.; Ichioka, K.; Takagi, K.; Suzuki, M. Organocatalytic Tail-to-Tail Dimerization of Olefin: Umpolung of Methyl Methacrylate Mediated by NHeterocyclic Carbene. *Org. Lett*. **2011**, *13*, 3722−3725; (b) Biju, A. T.; Padmanaban, M.; Wurz, N. E.; Glorius, F. *N*-Heterocyclic Carbene Catalyzed Umpolung of Michael Acceptors for intermolecular Reactions. *Angew. Chem. Int. Ed*. **2011**, *50*, 8412−8415.

[167] Patra, A.; Mukherjee, S.; Das, T. K.; Jain, S.; Gonnade, R. G.; Biju, A. T. *N*-Heterocyclic-Carbene-Catalyzed Umpolung of Imines. *Angew. Chem. Int. Ed*. **2017**, *56,* 2730 –2734.

[168] Das, T. K.; Ghosh, A.; Balanna, K.; Behera, P.; Gonnade, R. G.; Marelli, U. K.; Das, A. K.; Biju, A. T. *N*-Heterocyclic Carbene-Catalyzed Umpolung of Imines for the Enantioselective Synthesis of Dihydroquinoxalines. *ACS Catal*. **2019**, *9*, 4065−4071.