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Exploring Molecular Complexity by N-Heterocyclic Carbene Organocatalysis: New Activation and Reaction Diversity

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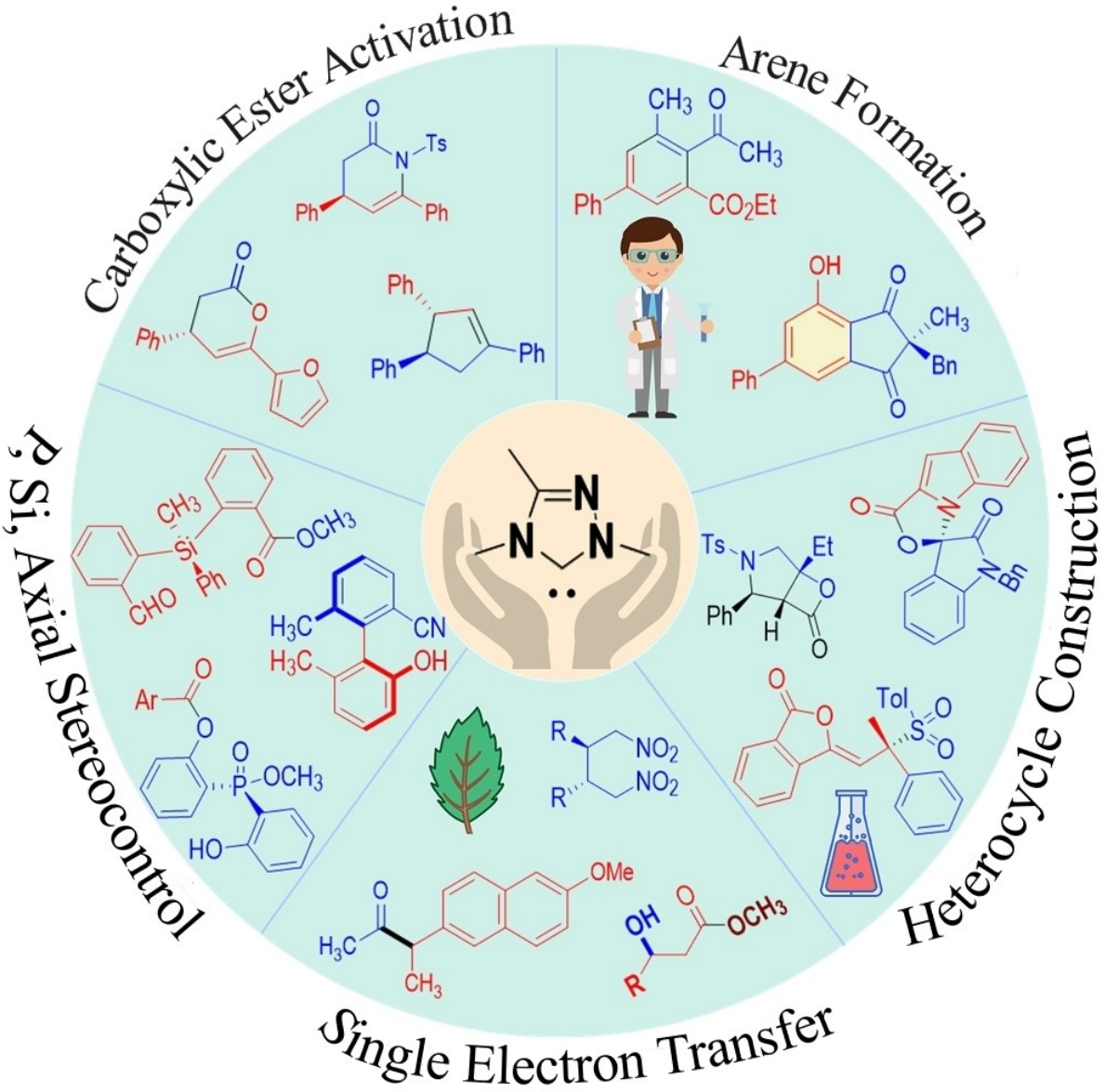

Abstract: The development of catalytic synthetic approaches towards molecular complexity from simple materials continues to be an ultimate goal in synthetic chemistry. Over the past decades, N-heterocyclic carbene (NHC) organocatalysis has been extensively investigated to provide opportunities for a vast number of novel chemical transformations. Various activation modes and reactive intermediates enabled by NHC small-molecule catalysts, such as Breslow intermediates, (homo)enolates, acyl azoliums and their derived unsaturated azoliums exhibit great potential in the construction of complicated skeletons. This personal account will summarize our group's recent work in the exploration of new activation modes of NHC catalysis towards molecular complexity with a focus on the development and applications of NHC to achieve diversity and enantioselectivity in the preparation of functional molecules.

Keywords: N-Heterocyclic Carbene, Organocatalysis, Asymmetric catalysis, NHC-bound intermediates, Molecular complexity

1. Introduction

Since the first report of Ukai *et al.* that thiazolium salts could serve as the catalyst precursor in Benzoin condensations in 1943,[1] N-heterocyclic carbene (NHC) has been explored as efficient small-molecule catalyst to stimulate umpolung reactivity of various aldehydes. Particularly, after Breslow proposed the reaction mechanism of the NHC-catalyzed Benzoin reaction in 1958[2] and independent identification of stable carbene structure by Bertrand[3] and Arduengo,[4] NHC catalysis has received considerable interest and extensive investigations from chemists. To date, NHC represents one of the most widely developed organocatalysts along with chiral amine,[5] Brønsted acid[6] and other small-molecule catalysts.[7] A striking number of novel chemical transformations have been achieved by NHC catalysis through various activation modes and reactive NHC-bound intermediates.[8]

Herein, this account overviews the recent progress of our exploration in new activation modes of NHC catalysis that enables rapid access of a diverse set of functional molecules. Briefly, our long-standing interest and engagement in this area since 2010 focuses in five main topics: (1) activation of carboxylic esters for stereoselective synthesis; (2) arene-forming constructions; (3) chiral heterocycle synthesis via N/S addition or heteroatom activations; (4) construction of stereogenic P-, Si- and axial/planar molecules; (5) functionalizations involving single-electron-transfer (SET) processes, that are achieved under the NHC catalyst control and will be discussed in the following sections of this account.

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2. NHC-catalyzed Activation of Carboxylic Esters for Stereoselective Synthesis

N-heterocyclic carbenes are widely explored in the activation of various aldehydes and their derived enals. A large number of methods have been developed for the efficient preparation of esters or amides through several key intermediates such as enolates, azoliums and others (Scheme 1a). Intrigued by the "inverted" strategy starting from the carboxylic acid derivatives, we identified stable esters with a good leaving group could be efficiently activated by NHCs to form various reactive intermediates that could be harvested for enantioselective construction of various functional heterocycles.

NHC-bound enolates are efficient reaction intermediates that can be generated from acyl azoliums under basic conditions.[8a–c,e,f] Initially, stable esters **1** featuring a 4-$NO_2C_6H_4O$ group were tested to generate an acyl azolium intermediate **I** (Scheme 1b). A deprotonation process smoothly occurred due to the increased acidity of the α-carbon, offering enolate **II** as a key intermediate to react with suitable electrophiles.[9] Formal [2 + 4] cycloaddition reactions were achieved with this catalytic strategy when α,β-unsaturated imine substrates **2** were used. Notably, aliphatic substituted carboxylic esters worked in the cycloaddition as well, yielding the lactam products in good yields and diastereo- and enantioselectivities in the presence of Mesityl-substituted triazolium **B** as the NHC pre-catalyst and a strong base DBU with THF as the solvent, while Ph-substituted catalyst **C** gave the product in a poor yield of 16% (Scheme 2).[10]

We later disclosed the generation of the smallest enolate intermediate with this strategy from simple acetic ester substrate **6**, which was stable, readily prepared and inexpensive (Scheme 3). The in-situ afforded triazolium enoalte **II**, serving as a two-carbon synthon, underwent highly enantioselective

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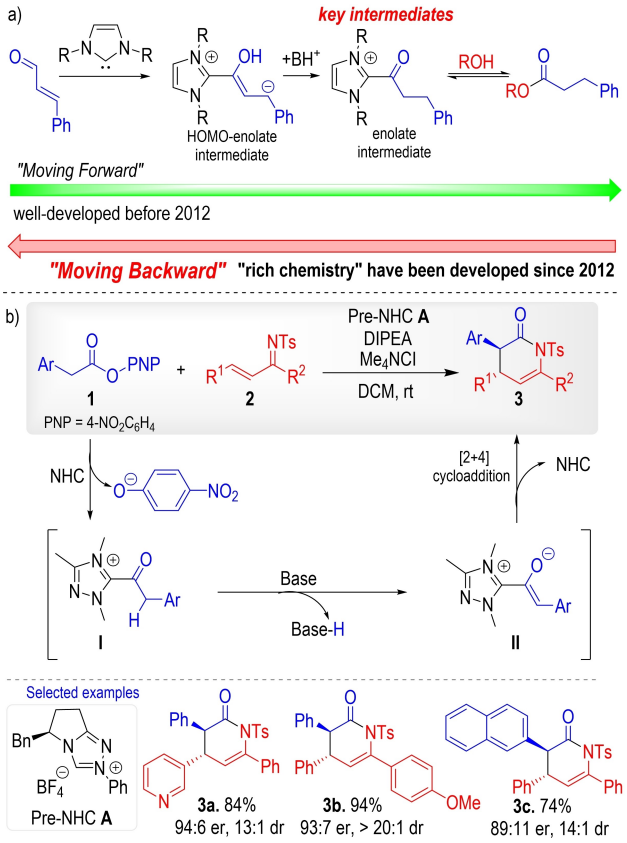
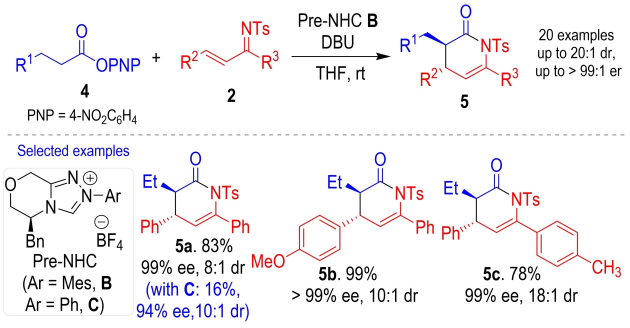
Yanyan Wang graduated with a bachelor's degree in applied chemistry from Guizhou Education University in 2020. She then joined the Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University in 2021 to pursue her Master degree. Currently, Yanyan investigates on the organic asymmetric catalysis and development of agrochemicals under the guidance of Prof. Yonggui Robin Chi and Prof. Xingxing Wu.

Prof. Xingxing Wu received his BS and master degree from East China Normal University (ECNU) during 2006–2013 under the supervision of Prof. Junliang Zhang. He then joined the group of Prof. Yonggui Robin Chi at Nanyang Technological University, Singapore to pursue his PhD. Xingxing subsequently moved to University of Basel (Switzerland) since 2018, working with Prof. Christof Sparr as a postdoctoral researcher. He started his independent research at Guizhou University (China) in 2022, focusing on catalyst-controlled stereoselective synthesis and preparation of chiral functional molecules for green pesticide development. Xingxing is a recipient of the Marie-Curie Individual Fellowship (ERC), National Natural Science Fund for Excellent Young Scientists Fund Program (Overseas) and the Chinese Government Award for outstanding Self-financed Students Abroad.

Prof. Robin Chi received his undergraduate training from Tsinghua University and Hong Kong Baptist University during 1998–2002. He obtained PhD in Chemistry from the University of Wisconsin-Madison under the guidance of Prof. Sam Gellman in 2007. After a two-year postdoctoral stay at the University of California-Berkeley with Prof. Jean Frechet, he started his independent career at Nanyang Technological University and was quickly promoted to full professor and chair professor. His current research, supported by students and researchers from Nanyang Technological University and Guizhou University, concerns both fundamental and user-inspired challenges in the areas of chemical synthesis, green pesticides, and medicinal molecules. Recent focuses include the development of new basic activation modes and reactions mediated by NHC organic catalysts; complex chemo-selectivity challenges; rapid construction or modification of sophisticated molecules that include biomacromolecules; green reactions and processes for industrial applications, and development of new pesticides and medicinal molecules.



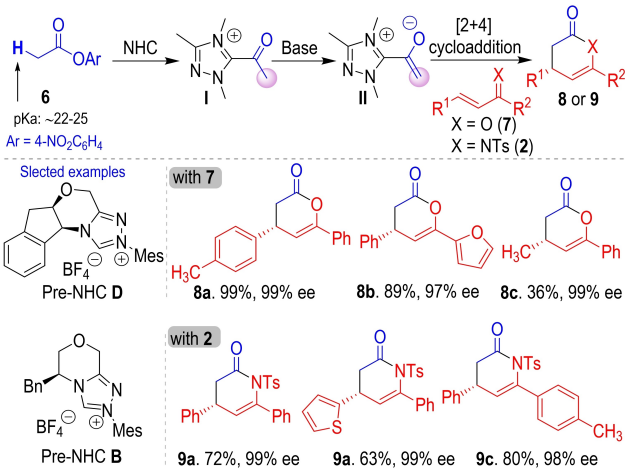
Scheme 1. NHC-catalyzed generation of enolate intermediate from carboxylic esters.



Scheme 2. NHC-catalyzed α-activation of saturated aliphatic esters.

annulations with α,β-unsaturated ketones **7** and imines **2** under the carbene catalyst control, providing a rapid access to α-unsubstituted δ-lactones **8** and lactams **9** that were difficult to prepare using other methods.[11]

In addition to the α-carbon activation with saturated esters, we further realized LUMO activation of α,β-unsaturated esters **10** with an electrophilic β-carbon for highly enantioselective formal [3+3] reactions with enamides **11**. Mechanistically,

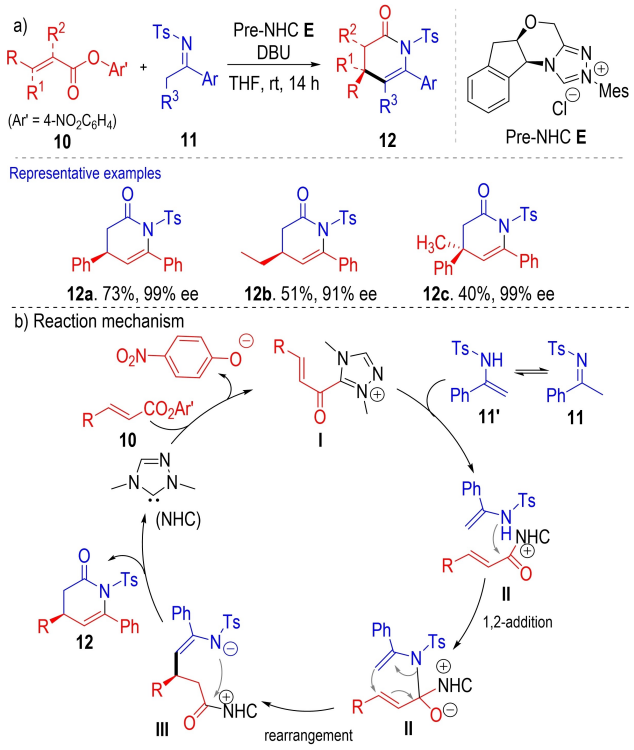


Scheme 3. NHC-catalyzed activation of acetic esters.

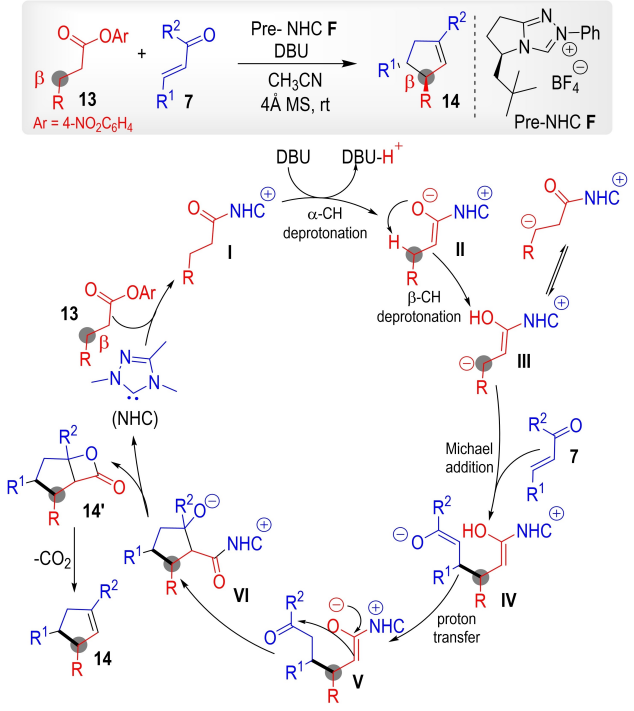
addition of the NHC catalyst to the ester substrate **10** would produce an α,β-unsaturated acyl azolium intermediate **I**, which could be trapped by the 1,2-addition of enamide **11′**, formed through the isomerization of imine substrate **11** under basic conditions.[12a] Subsequent Claisen rearrangement, tautomerization and lactam formation process would give the final lactam products **12** and regenerate the NHC catalyst to complete the catalytic cycle.[12b–d,8f] It is noteworthy that an alternative mechanism involving a 1,4-addition pathway by the nucleophilic addition of enamide **11′** to α,β-unsaturated acyl azolium **I** can not be ruled out from the observed results.[8e,j] Notably, the use of sterically demanding β,β-disubstituted esters were compatible in this approach, leading to optically enriched lactam products (eg. **12c**) containing a quaternary stereogenic center (Scheme 4). Later, the formation of vinyl enolate intermediates was reported when γ-carbon substituted unsaturated ester substrates were used, achieving highly efficient additions to hydrazones to provide δ-lactam products in high enantioselectivity.[13]

Compared to the previously discussed classical nucleophilic α-carbon activation of saturated carboxylic esters to form enolate equivalents or LUMO activation of α,β-unsaturated esters, direct use of the β-carbons of saturated carbonyl compounds such as alkyl esters as nucleophiles through catalyst activation strategy remains illusive.

In 2013, we successfully realized the nucleophilic β-carbon activation of saturated carboxylic esters **13** through the NHC-catalyzed ester activation approach (Scheme 5).[14] A postulated pathway for this reaction was depicted in Scheme 5. An enolate intermediate **II** was initially formed through the addition of NHC catalyst **F** to ester substrate **13** and a subsequent deprotonation of the acidic α-CH of intermediate **I**. The ester β-CH proton of intermediate **II** would become acidic arisen from the electron-withdrawing property of the



Scheme 4. NHC-catalyzed β-activation of α,β-unsaturated esters.

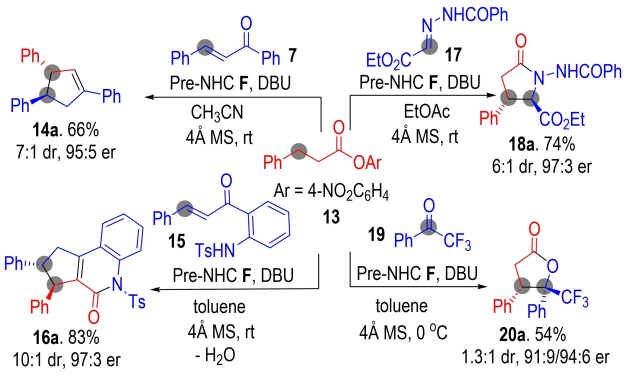


Scheme 5. NHC-catalyzed β-sp^3-CH activation of saturated ester.

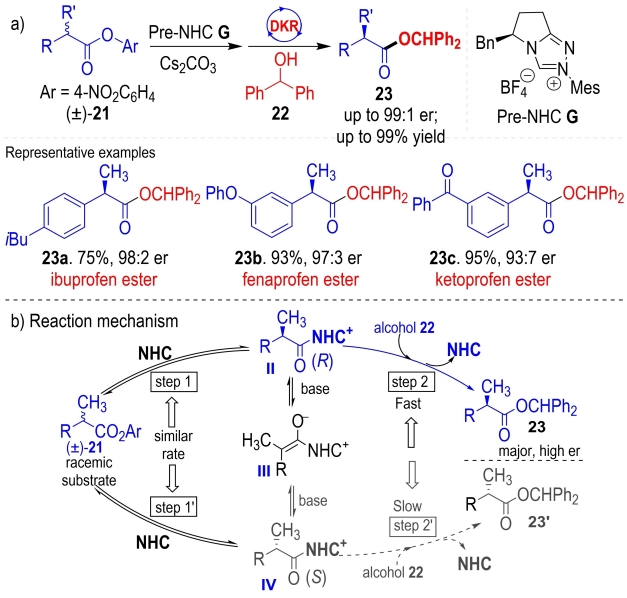
triazolium moiety and the conjugated nature of the triazolium-bounded enolate **II**. Intermediate **III** would thereby be generated through the deprotonation of the β-CH of enolate **II**, featuring a β-carbon as a nucleophilic center. Intermediate **III** could undergo nucleophilic addition to various electrophiles such as enones **7**, with a mechanism similar to the previous reported NHC-catalyzed homoenolate activation of α,β-unsaturated aldehydes.

The generality of this approach was demonstrated by the diverse synthesis of various enantioenriched heterocycles. For instance, chiral cyclopentene products **14a** and **16a** could be afforded from reactions with simple enones **7** and *ortho*-amino substituted α,β-unsaturated ketones **15** through cascade annulation processes. On the other side, lactam **18a** and lactone **20a** products were obtained through [3+2] cycloaddition reactions between the saturated carboxylic ester **13** and corresponding imine **17** and activated ketone **19** (Scheme 6).[15]

Propionic acid scaffold bearing a stereogenic α-carbon is widely present in bioactive molecules and non-steroidal anti-inflammatory drugs such as ibuprofen and ketoprofen. The carboxylic esters activation approach for stereoselective synthesis provides an excellent platform to prepare this type of functional molecules. In 2016, the group of us reported the dynamic kinetic resolution of α,α-disubstituted carboxylic esters with up to 99:1 er and 99% yield enabled by NHC catalysis (Scheme 7).[16] The DKR started with the addition of chiral carbene catalyst **G** to the racemic ester substrate (±)-**21** to give a mixture of two diastereomeric acyl azolium intermediates (**II** and **IV**). The chiral resolution occurred due to different reactivities of intermediates **II** and **IV** upon the addition of alcohol substrate **22**. Moreover, the carbene catalyst also played a significant role in promoting the in-situ racemization of the ester substrate (±)-**21** via the acyl azolium **IV** and enolate intermediate **III** and thus to achieve the overall highly enantioselective DKR process.



Scheme 6. Various electrophiles used in NHC-catalyzed β-sp^3-CH activation of saturated esters.

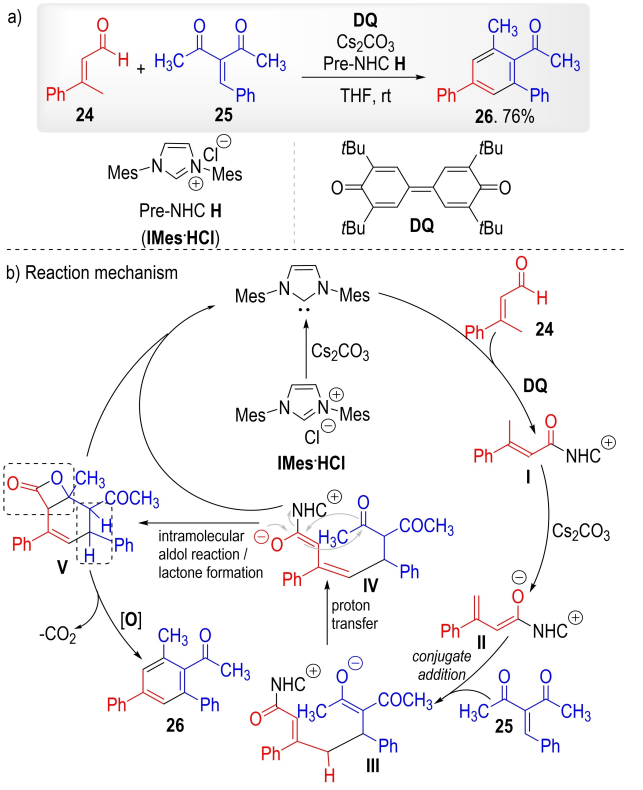


Scheme 7. NHC-catalyzed DKR via α-activation of ester.

3. NHC-catalyzed Arene-forming Reactions

Aromatic scaffolds are widely present in feedstock chemicals, pharmacological and biological active molecules as well as natural products and materials.[17] A striking number of methods have been developed to prepare multisubstituted arenes, which can be divided by two typical strategies: one is the direct functionalization of arene core structures such as electrophilic substitution or halogenation and successive transition metal-catalyzed cross couplings or direct C–H activations; the other is the direct construction of the arene cores by various approaches with pre-functionalized building blocks.[18]

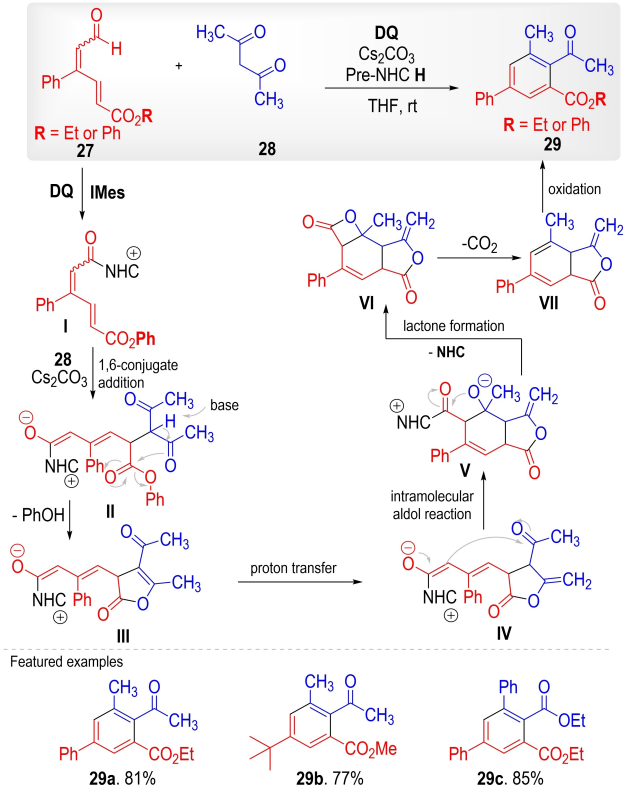
By consideration of the organocatalytic strategy to efficient access to multisubstituted benzene structures, in 2014, we reported an NHC-catalyzed formal [3+3] cycloaddition of β-methyl enal **24** and α,β-unsaturated ketone **25** to provide aromatic product **26** for the first time (Scheme 8).[19] The use of **IMes** catalyst (Pre-NHC **H**)and stoichiometric amount of **DQ** oxidant in THF efficiently promote the benzene-forming reaction and gave the desired product in 76% yield. A postulated reaction pathway is depicted in Scheme 8. Briefly, a vinyl enolate intermediate **II** was generated after deprotonation of the initially formed α,β-unsaturated acyl azolium **I** from the oxidation of Breslow intermediate. Michael addition to enone **25** gave intermediate **III**, followed by intramolecular proton transfer led to intermediate **IV**. Subsequent aldol reaction–lactone formation and spontaneous decarboxylation and oxidation afforded the desired multi-substituted benzene products **26** in high efficiency.



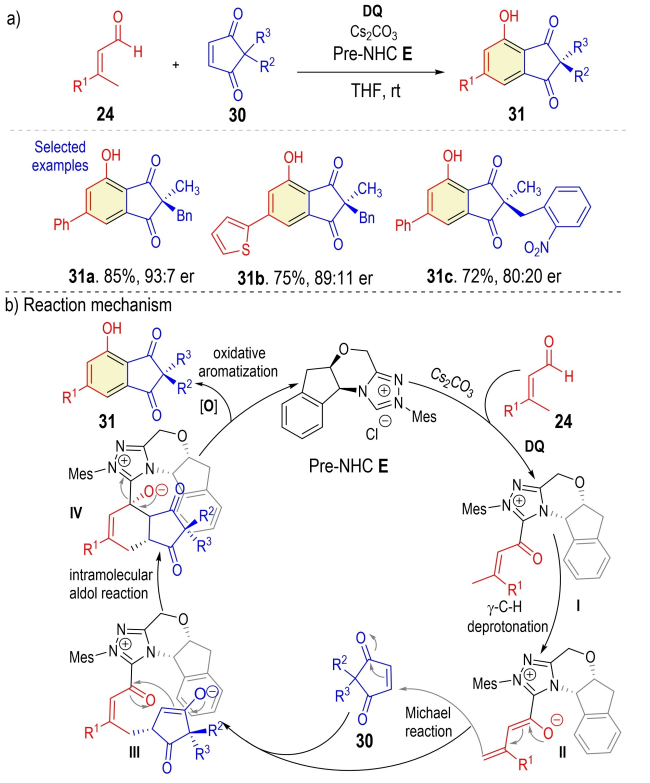
Scheme 8. NHC-catalylzed [3+3] cycloaddition reaction for benzene synthesis.

By exploration of the NHC-catalyzed δ-LUMO carbon activation of α,β-γ,δ-diunsaturated enals **27**, a formal [4+2] reaction for construction of multisubstituted benzene frameworks was developed by us in 2015 (Scheme 9). With ester substituted dienal **27**, the δ-carbon was readily activated to be electrophilic species under the condition of Pre-NHC **H** and **DQ** oxidant that can react with 1,3-dicarbonyl **28** to give the aromatic product **29** in high yield. The plausible reaction pathway involves the key 1,6-conjugate addition of the nucleophile **28** to unsaturated acyl azolium **I**. Subsequent intramolecular aldol-lactonization and decarboxylation process deliver the benzene products in good yields.[20]

Multi-substituted arenes attached with all-carbon quaternary centers are unique core structures in functional molecules and various natural products.[21] To solve the key challenge of the enantioselective installation of the quaternary carbon centers during the preparation of such molecules, in 2019, we disclosed a [4+2] cycloaddition reactions by intercepting the desymmetrization strategy to construct chiral arenes featuring all-carbon quaternary carbon centers. The phenol products **31** were produced in high yields and enantioselectivities under the optimal conditions. A mechanism accounting for the [4+2] cycloaddition was proposed and illustrated in Scheme 10.



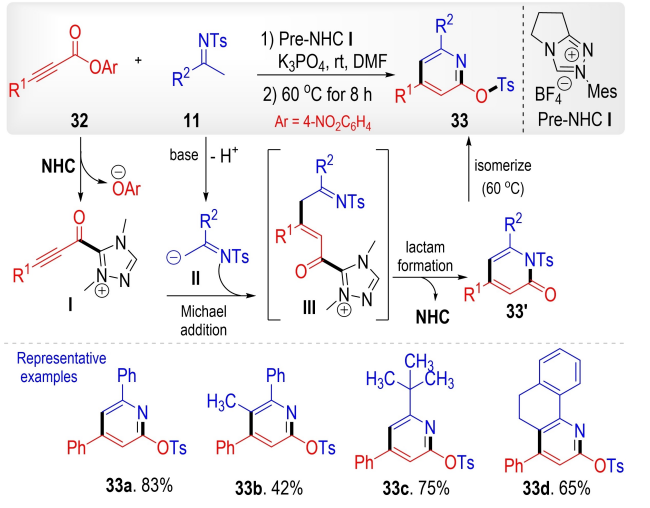
Scheme 9. NHC-catalylzed δ-LUMO activation for aromatic synthesis.



Scheme 10. NHC-catalyzed chiral arene formations via [4 + 2] cycloaddition reactions.

Initially, a nucleophilic vinyl enolate **II** was generated under the oxidative NHC conditions, which underwent a stepwise Michael addition and intramolecular adol reaction processes. The highly enantioselective desymmetrization is controlled by the chiral indane moiety of NHC inducing the more steric bulky R^2 moiety on the top face (Scheme 10, **II to III**), provding a general route for the stereoselective synthesis of fused benzene derivatives (Scheme 10).[22]

The synthesis of heteroarenes, such as pyridines have also been achieved by the NHC-catalyzed arene-forming strategy. For example, in 2017, we reported an effective [3 + 3] cycloadditions of alkyne esters **32** with enamides **11** by NHC-catalyzed LUMO activation of alkyne esters. The multi-functionalized pyridines **33** were prepared in good yields (Scheme 11).[23]



Scheme 11. NHC-catalyzed alkyne activation and pyridine synthesis.

4. NHC-catalyzed Chiral Heterocycle Synthesis via N/S Addition or Heteroatom Activations

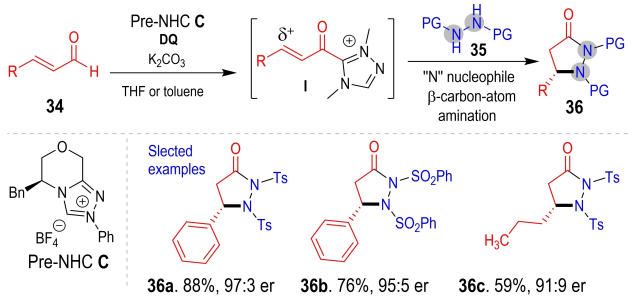
N-, S-, or O-containing heterocycles are ubiquitous in natural products, medicinal and agrochemical compounds, as well as other functional molecules.[24] Stereoselective construction of carbon-heteroatom (C–X) bonds thereby continues to be a substantial objective in synthetic chemistry. Numerous efforts have been devoted in the development of carbene organo-catalyst-controlled strategy for the efficient asymmetric C–X bond formations. In the past decade, we have engaged in this program by consideration of two approaches, one of which is

to activate β-carbon atoms of unsaturated carbonyl compounds through NHC-bound (unsaturated) acyl azolium intermediates that could react with nucleophilic heteroatoms. The other alternative method is the direct NHC-catalyzed covalent bond activation of heteroatoms by forming reactive intermediates that could significantly increase the nucleophilicity of the N–, O– or other heteroatoms.

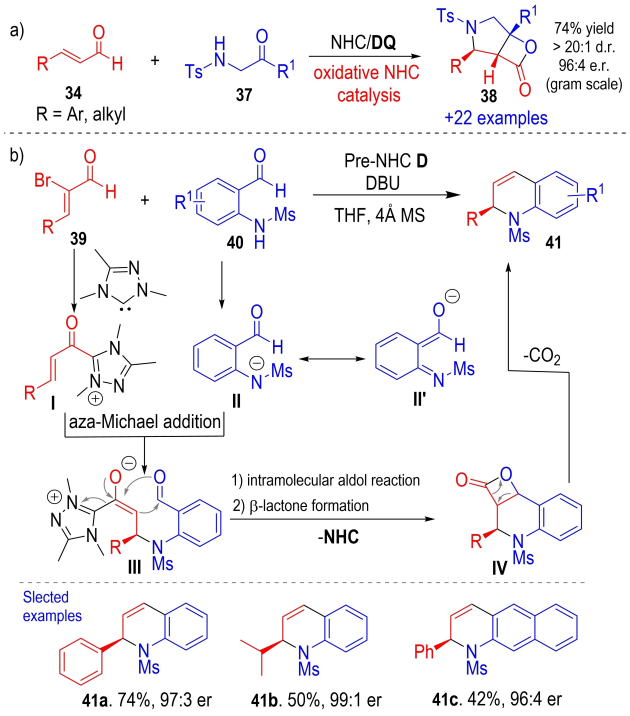
4.1. Heterocycle Synthesis Involving NHC Catalyst-controlled Heteroatom Additions

In 2016, we realized a highly enantioselective β-carbon amination protocol of unsaturated aldehydes **34** by NHC-catalyzed formal [3+2] cycloadditions (Scheme 12).[25] The results of investigation suggested that the sulfonyl group on the N atom of hydrazides **35** was crucial to the key addition of the nitrogen atom of hydrazide to the catalytically generated α,β-unsaturated acyl azolium intermediate by forming a "N" anion under basic conditions (NH pKa around 17.1 in DMSO from Bordwell pKa table). Various aromatic and alkyl substituted enals were transformed smoothly to the desired pyrazolidinone products **36** in good to excellent yields and enantioselectivities.

The success on the direct carbon–nitrogen bond construction prompted us to apply this strategy for diverse preparations of N-containing heterocycles. By using α-amino ketone **37** as the nucleophilic "N" source, multisubstitued pyrrolidine fused β-lactones **38** were obtained in good yields, excellent diastereoselectivity and enantioselectivity through an aza-Michael addition initiated highly selective cascade process (Scheme 13a).[26] Quinolines, as a frequent scaffold in a wide array of bioactive compounds, could be afforded by the NHC-catalyzed annulation between 2-aminoaldehydes **40** and α-bromoenals **39** (Scheme 13b). The key steps include the chemo-selective activation of enal substrates to give the electrophilic unsaturated acyl azoliums **I**, followed by the aza-Michael addition and subsequent intramolecular aldol, lactonization and decarboxylation processes, leading to the chiral dihydroquinolines **41** in high enantioselectivity.

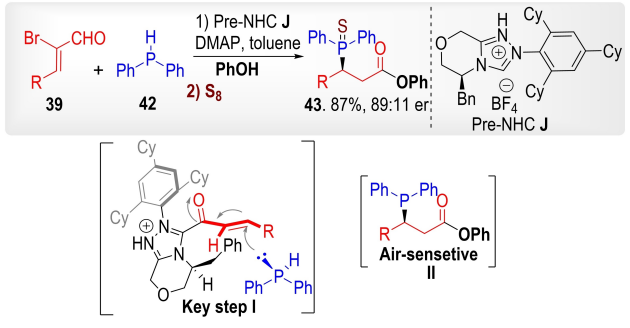


Scheme 12. NHC-catalyzed nucleophilic β-carbon amination of enals.

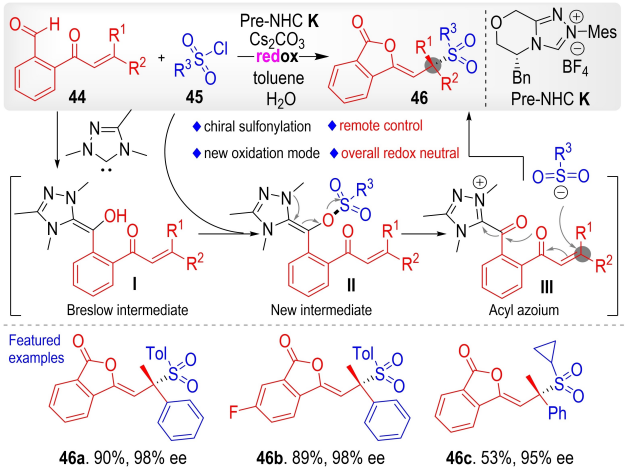


Scheme 13. NHC-catalyzed nucleophilic amination functionalizations.

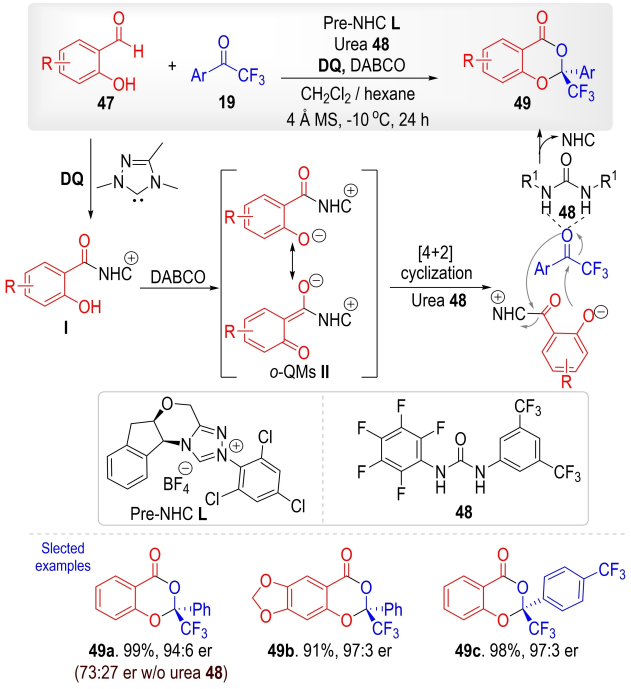
Phosphines and sulfinate are also capable to undergo nucleophilic attack to the NHC-derived α,β-unsaturated acyl azolium intermediates. In 2021, we achieved a highly enantioselective C–P bond construction by NHC catalysis to prepare β-phosphine carbonyl compounds **43**, which could be easily derivatized to chiral phosphine ligands or catalysts (Scheme 14).[27] Very recently, we disclosed a quick access of sulfone-containing bicyclic lactones **46** by carbene-catalyzed reaction between enone derived aldehydes **44** and sulfonyl chlorides **45** (Scheme 15).[28] Under the conditions of Pre-NHC **K**, Cs_2CO_3 and H_2O in toluene, the chiral sulfones **46**



Scheme 14. NHC-catalyzed nucleophilic addition of secondary hydrophosphine.



Scheme 15. Chiral sulfonylation via new redox NHC catalysis.



Scheme 16. NHC-catalyzed salicylaldehyde activation and O–H bond functionalization.

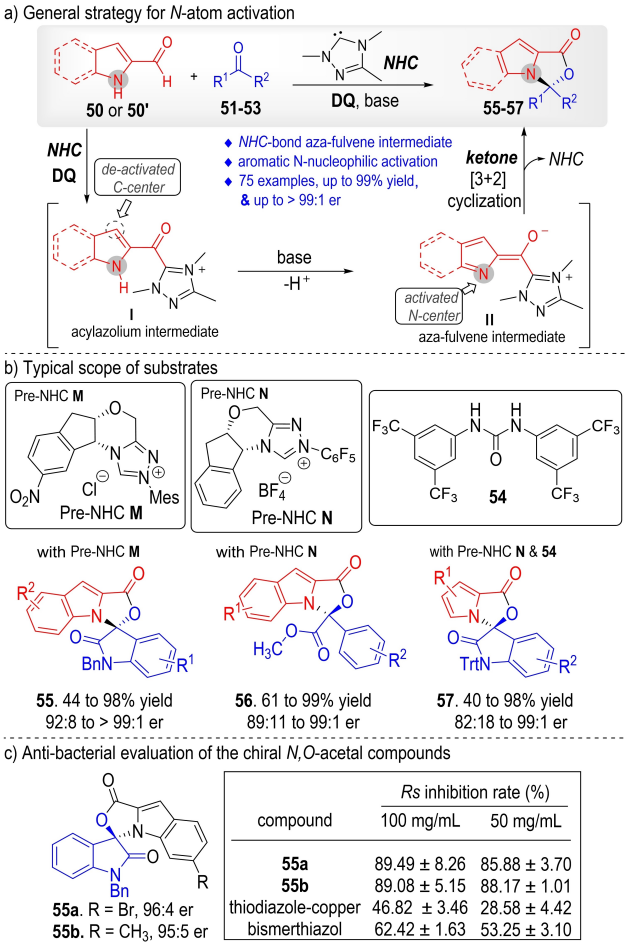
were afforded in excellent yields and optical purity (up to 98% ee). The sulfonyl chloride plays two roles in the catalytic cycle: as an oxidant of the Breslow intermediate and a nucleophilic substrate via its reduced sulfinate anion form. Notably, the presence of water in the reaction is highly important by modulating the deactivation and reactivation pathways of the carbene catalyst.

4.2. Heterocycle Synthesis Involving NHC-catalyzed Heteroatom Activations

An alternative strategy we developed for the synthesis of heterocycles is to activate heteroatoms through addition of NHC catalysts to certain substrates for enantioselective C–X (X=N, O *etc.*) bond constructions. In 2017, we found that carbene catalyst could activate 2-hydroxyl benzaldehydes **47** that enabled highly efficient phenol OH functionalizations. The reaction steps involve the formation of acyl azolium intermediate **I** under oxidative conditions. Facile dearomatization would occur due to the electron-deficient azoliums and electron-donating OH group, leading to the key azolium-derived *ortho*-quinone methide intermediates **II** (***o*-QMs**). After reactions with ketones **19**, a diverse set of ketal-like 1,3-dioxin-4-one products **49** were provided in high yields with modest enantioselectivities. The incorporation of urea **48** as the hydrogen-bond donating co-catalyst was found to be crucial to enhance the stereoselectivity dramatically (from 73:27 er to 94:6 er for **49a**) (Scheme 16).[29]

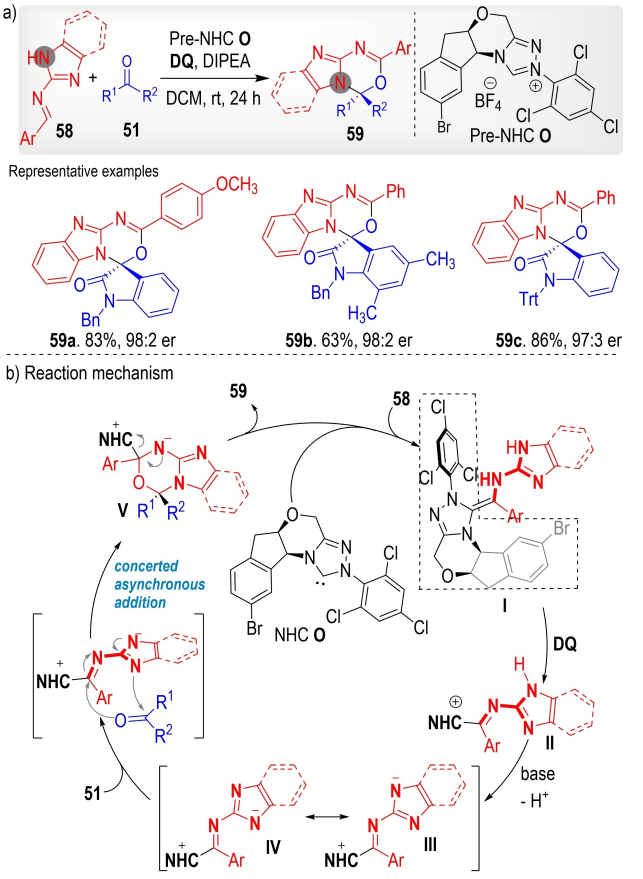
Encouraged by the highly efficient *O*-atom functionalization, we further turned our effort to explore the activation of nitrogen atoms for heterocycle synthesis. Enabled by NHC catalysis under oxidative conditions, the nitrogen atom in the aromatic π-system of indole-2-carbaldehydes **50** and pyrrole-2-aldehyde **50′** was readily activated to undergo formal [3+2] cycloaddition with ketone substrates **51–53** via aza-fulvenetype acyl azolium intermediates. N,O-acetal products **55–57** were prepared in excellent yields and er values. Notably, several particular compounds exhibit promising antibacterial activity against Ralstonia solanacearum (*Rs*) that may find applications in agrochemical development (Scheme 17c).[30] With the concept of NHC-catalyzed nitrogen activation, we also achieved the quick synthesis of multicyclic products by the reaction of indole-7-carbaldehydes with activated ketone or imine electrophiles that furnish heterocyclic compounds bearing pyrroloquinazoline or oxazinoindole scaffolds.[31]

Another carbene-catalyzed heteroatom activation mode involves the formation of triaza-diene intermediate for enantioselective synthesis of heterocycles. The reaction of (benz)imidazolederived aldimine **58** with electron-deficient ketone **51** such as isatin provided novel spiro-bicyclic products **59** in high yields and excellent enantioselectivities (Scheme 18).[32] Briefly, the reaction occurred through the initial addition of the NHC catalyst to the imine **58**, followed by the generation of aza-Breslow intermediate **I** after proton transfer process. In the presence of the **DQ** oxidant, the aza-Breslow species could be oxidized to the electron-deficient intermediate **II** that enhances the acidity of the remote NH. Deprotonation under basic conditions would lead to the key triaza-diene intermediate **III** that participates in the subsequent transformations with ketone electrophiles **51**.



compound	Rs inhibition rate (%) 100 mg/mL	50 mg/mL
55a	89.49 ± 8.26	85.88 ± 3.70
55b	89.08 ± 5.15	88.17 ± 1.01
thiodiazole-copper	46.82 ± 3.46	28.58 ± 4.42
bismerthiazol	62.42 ± 1.63	53.25 ± 3.10

Scheme 17. Examples of chiral N,O-acetal compounds and anti-bacterial evaluation.



Scheme 18. NHC-catalyzed activation and asymmetric reaction of heteroatoms.

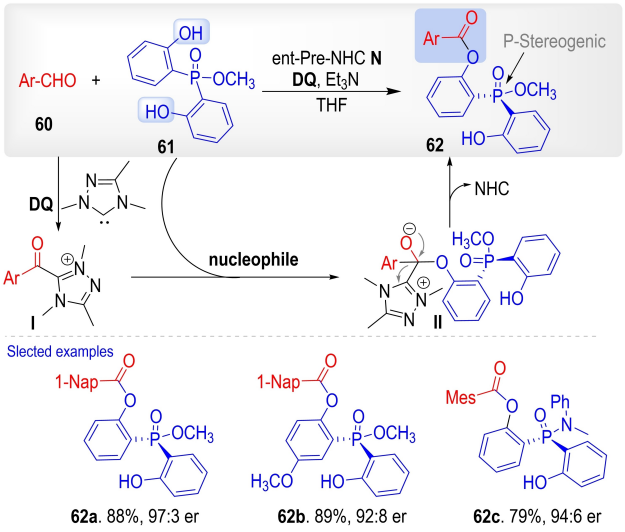
5. NHC-catalyzed Enantioselective Control Over stereogenic-phosphorus, Silicon or Atropoisomeric Molecules

In previous sections, we have discussed various catalytic strategies for highly enantioselective preparation of functional molecules that bears one or multiple stereocenters. Stereoselective synthesis of other chiral compounds without the presence of stereogenic carbons, that include chiral phosphorus, silicon and configurationally stable atropoisomeric molecules remains a challenging topic despite the significant development of modern asymmetric catalysis. We engage our effort by applying NHC organocatalysis to prepare these chiral structures.

5.1. Enantioselective Preparation of P- and Si-stereogenic Compounds

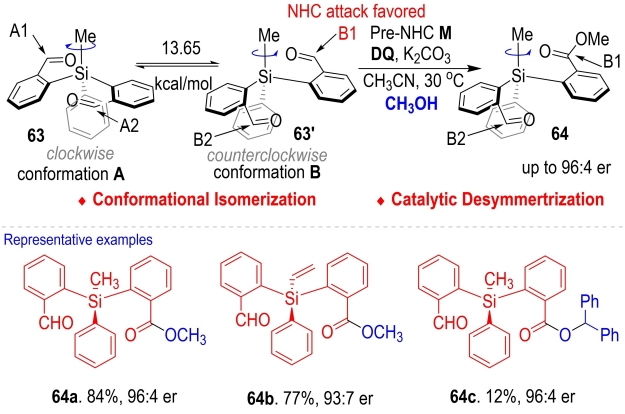
The development of catalytic method for highly stereoselective preparation of enantiomerically enriched phosphorus compounds bearing P-stereogenic centers has received extensive attention because these chiral scaffolds are widely explored in pharmaceutical development and design of ligands and organocatalysts in synthetic chemistry.[33] In 2016, we achieved a highly selective protocol to prepare P-stereogenic phosphinates **62** by NHC-catalyzed desymmetrization of bis(hydroxyphenyl) phosphinates **61** (Scheme 19).[34] Various phosphinate and phosphinamides in high optical purity (up to 99:1 er) were readily prepared under the conditions of *ent*-NHC **N** and **DQ** oxidant. Notably, the reactions could be carried out with a relative low catalyst loading by using as less as 1 mol% of NHC in gram scale synthesis, revealing the high efficiency of the NHC catalyst control.

Enantioselective construction of tetrasubstituted silane with a Si-stereogenic center can also be achieved by the NHC-



Scheme 19. Access to P-stereogenic compounds *via* NHC-catalyzed desymmetrization.

catalyzed desymmetrization approach. The synthesis of silicon-containing compounds is of high importance since they are widely utilized in material science and catalysis development.[35] The overall reaction process selectively oxidizes one of the two formyl groups of the Si-containing dialdehyde substrate **63** to a carboxylic ester group under oxidative NHC conditions (Scheme 20), leading to chiral tetrasubstituted silanes **64** with high enantioselectivities and good tolerance of functional groups. Intriguingly, the DFT calculations reveals the presence of two conformations of the substrate (conformation **A** and **B**) that can readily isomerize under the reaction conditions, and the highly selective desymmetrization is achieved in the oxidation step to form the acyl azoliums.[36]

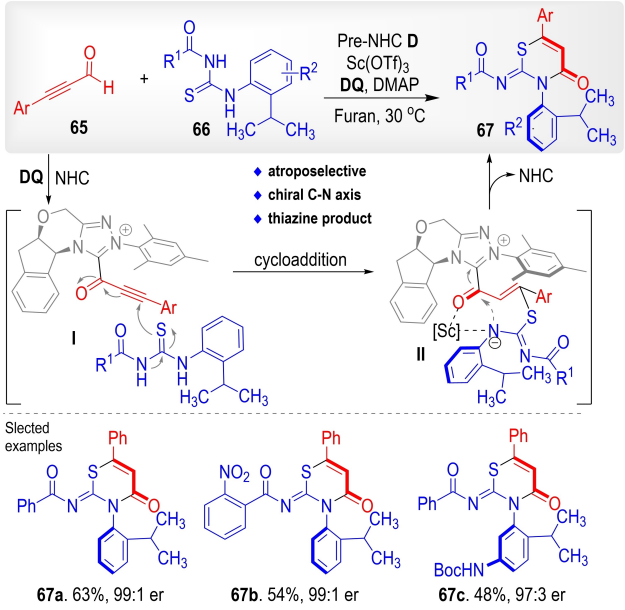


Scheme 20. Construction of chiral Si center *via* NHC-catalyzed desymmetrization.

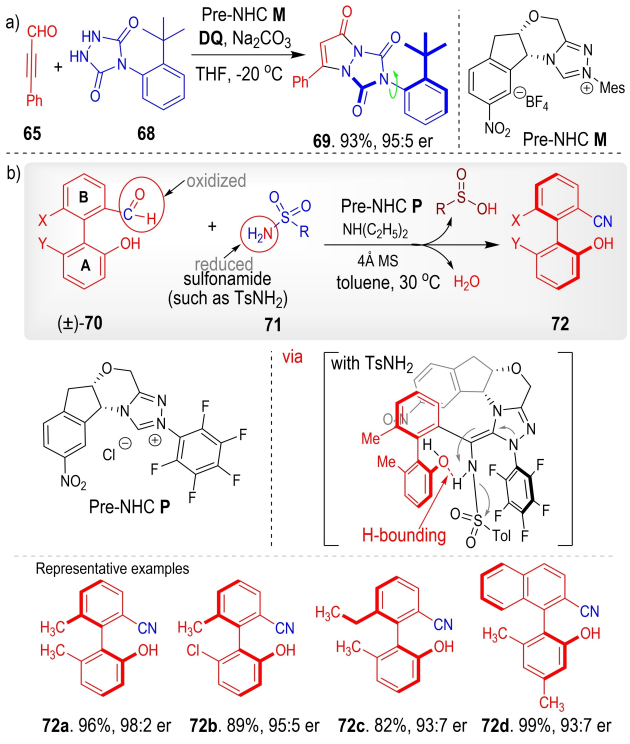
5.2. Catalyst Control Over Axially or Planar Chiral Molecules

The wide applications of axially chiral compounds in natural products, biologically active molecules and organic synthesis prompted us to search for efficient synthetic approaches to prepare such functional scaffolds in a highly stereoselective manner.[37] In 2021, we disclosed an atroposelective annulation of pre-functionalized ynals **65** and thioureas **66**, leading to thiazine derivatives **67** featuring a C–N axis in high optical purity (Scheme 21).[38] The reaction was promoted by NHC-**D** as the pre-catalyst and **DQ** as the oxidant via the acetylenic acyl azolium **I** reactive intermediate. The use of furan solvent and $Sc(OTf)_3$ as an additive were found to be beneficial to enhance the product yields. Mechanistically, the transformation proceeded through the initial formation of NHC/ynal-derived acetylenic acylazolium intermediate **I**. Sulfur-Michael addition to form intermediate **II** and subsequent atroposelective lactam formation under the NHC catalyst control gave the thiazine products **67** in high optical purity.

The power of carbene organocatalysis in atroposelective synthesis was further utilized in the preparation of various axially chiral bi(hetero)aryl frameworks. For instance, a [3 + 2] annulation was developed that allows for the access of axially chiral urazole derivatives via a desymmetrization strategy (Scheme 22a).[39] Chiral biaryl benzonitrile derivatives **72** could be prepared by an NHC-catalyzed DKR process of CN formation from racemic mixtures of 2-arylbenzaldehydes **70** with a dynamic interconverting axis and sulfonamide sub-



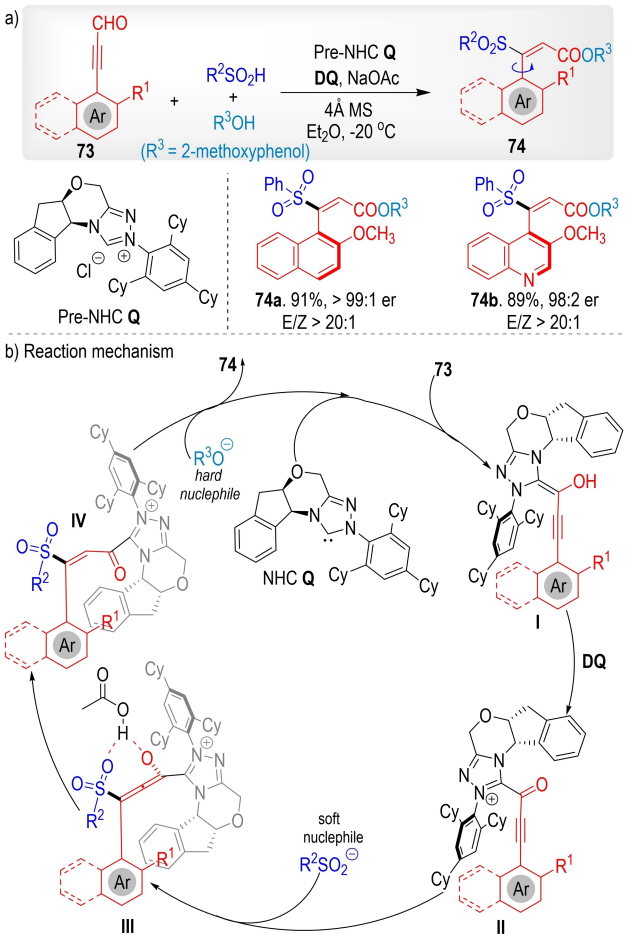
Scheme 21. NHC-catalyzed atroposelective heteroatom cycloaddition reaction.



Scheme 22. Atroposelective synthesis of benzonitriles *via* catalytic C–N formation.

strates **71** (Scheme 22b).[40] Furthermore, we have disclosed the NHC catalyzed atroposelective preparation of the challenging axially chiral styrenes. The indanol-derived NHC catalyst **Q** bearing bulkyl 2,4-6-tricyclohexyl phenyl on the triazolium core promoted the reaction of ynals **73**, sulfinic acids and phenol substrates to furnish a broad scope of acyclic chiral styrene products **74** with moderate to high yields (up to 99%) and excellent optical purities (up to >99:1 e.r.) (Scheme 23).[41]

The NHC-catalyzed atroposelective synthesis further motivated us to explore the catalytic strategy for establishment of stereogenic planar compounds. Chiral ferrocene derivatives with a stereogenic plane are broadly explored in organic synthesis and medicinal research.[42] Very recently, we achieved the carbene-controlled rapid preparation of chiral multifunctional ferrocenes **78** or **79** by highly enantioselective desymmetrization of pro-chiral ferrocene-derived dicarbaldehydes **75** (Scheme 24).[43] The enantio-determing step involves the highly selective oxidation of Breslow intermediate **II** resulting from steric repulsions between the intermediate and oxidant. The final enantioenriched planar chiral ester is formed after esterification with 2-nitrophenol **76**. Interestingly, the obtained chiral ferrocene products exhibit promissing bioactivities for novel pesticide development in crop protections.

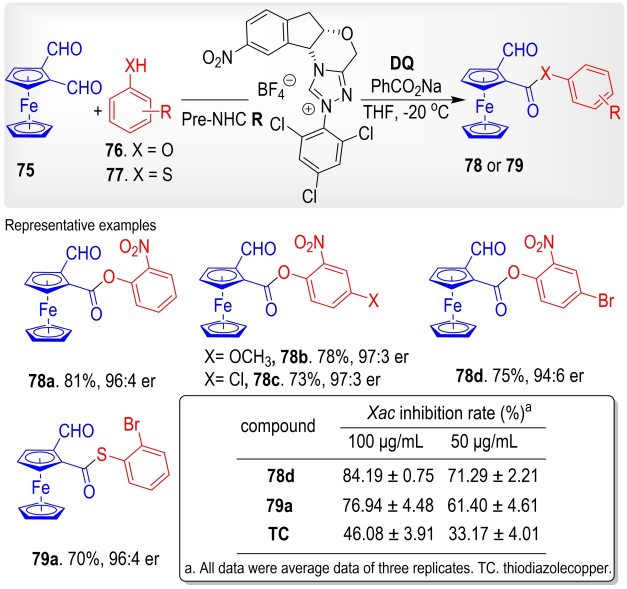


Scheme 23. NHC-catalyzed atroposelective synthesis of axially chiral styrenes.

6. NHC-catalyzed Single-Electron-Transfer (SET) Reactions

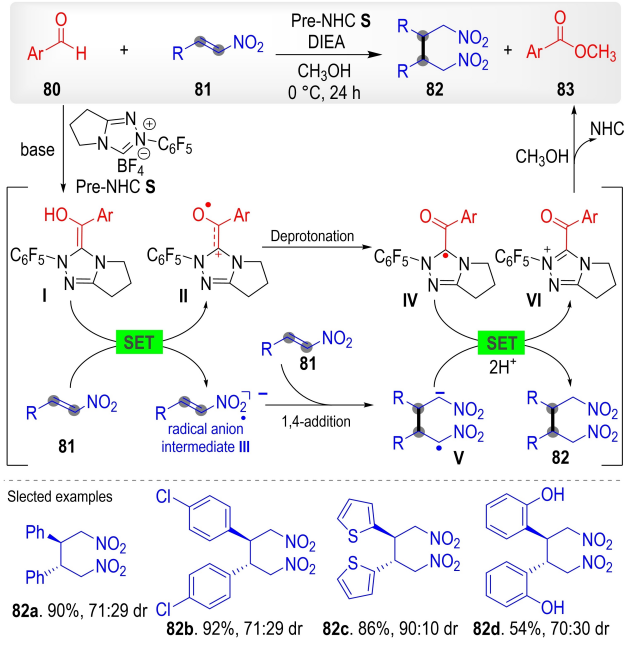
N-heterocyclic carbenes (NHCs) have been extensively explored as organocatalysts to realize a large number of synthetic transformations. Most of these reactions, however, proceed through electron-pair transfer steps. In sharp contrast, NHC catalysis involving single-eletron-transfer (SET) process remained elusive for long time. Nevertheless, new reaction developments based on radical activation process would significantly expand the scope of NHC organocatalysis and encourage more possibilities in chemical bond connections for functional molecule synthesis.

In living systems, thiamine pyrophosphate (abbreviated as TPP, a precursor of NHC) mediated oxidative decarboxylation of pyruvate to eventually form acetyl-CoA proceeds through the key acyl azolium ion via two steps of SET processes from the Breslow intermediate. Numerous efforts have been devoted to mimic this radical process in Nature. Our enthusiasm in this field started from 2014 when we observed an unprece-



Scheme 24. NHC-catalyzed desymmetrization of Ferrocene dicarbaldehydes and anti-bacterial evaluation.

dented reductive β,β-carbon coupling product of α,β-nitroalkenes **81** in the presence of NHC **S** and aldehydes **80** (Scheme 25). A reaction pathway to account for the generated coupling product is illustrated in Scheme 25.[44] Initially, a radical anion **III** was formed by a SET oxidation of Breslow



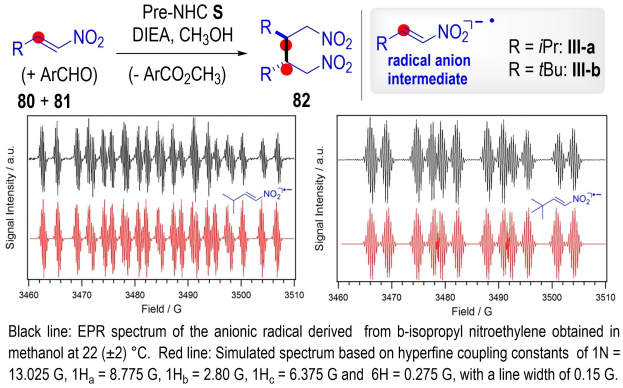
Scheme 25. Reductive β,β-coupling reaction of nitroalkene.

intermediate **I** produced from NHC catalyst **S** and aldehyde substrates **80**. A subsequent 1,4-addition to nitrostyrenes **81** would give intermediate **V**, which could undergo another SET oxidation with NHC-bound radical intermediate **IV** to furnish the final the coupling product **82** upon protonations. On the other side, the acyl azolium intermediate **VI** was trapped by nucleophilic MeOH to regenerate the free carbene catalyst for the next catalytic cycle. This hypothesis was strongly supported by the signal of anionic radical illustrating from EPR spectroscopy (Scheme 26).

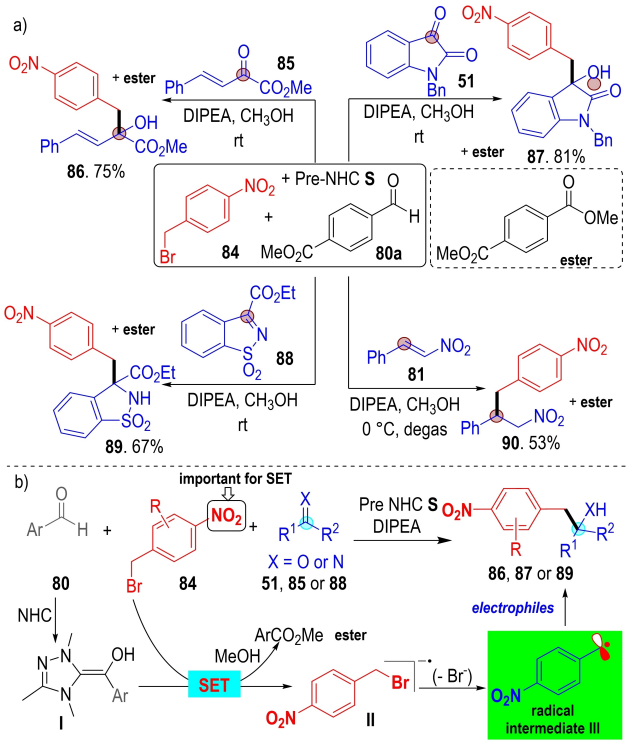
4-Nitrobenzyl halides are another type of organo-oxidants that could serve as efficient electron acceptors to selectively oxidize Breslow intermediates through SET process.[45] In 2016, we developed a variety of reductive coupling approaches by harvesting the generated radical intermediates from nitrobenzyl bromides **84** under NHC catalysis with typical electrophiles such as activated ketones, imines or nitroalkenes. For instance, α-ketoesters **85**, isatins **51**, sulfonyl imines **88** or nitroalkenes **81** were readily transformed to the corresponding 1,2- or 1,4-addition products **86**, **87**, **89** and **90** in modest to high yields under the conditions of aldehyde, NHC in the presence of DIPEA as the base and MeOH as the solvent (Scheme 27a).[46]

A general reaction pathway was postulated for these reactions and depicted in Scheme 27b. The Breslow intermediate **I** furnished from NHC and aldehyde **80** was oxidized by nitrobenzyl bromide **84** to form a radical cation intermediate. In the meantime, the nitrobenzyl radical **III** was afforded after releasing the bromide anion (Br^-) from anion intermediate **II**, which could readily undergo addition to ketones (or other electrophiles) to form radical intermediate. Further reduction by Breslow intermediate-derived radical cation and protonation would deliver the corresponding coupling product **86**, **87** or **89**.

In the previous example, the aldehyde substrate was oxidized efficiently to carboxylic ester under mild conditions



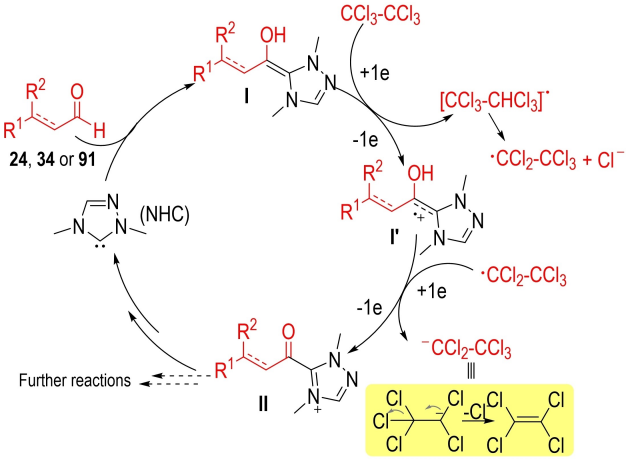
Scheme 26. EPR experiments for evidence of radical intermediates **III**.



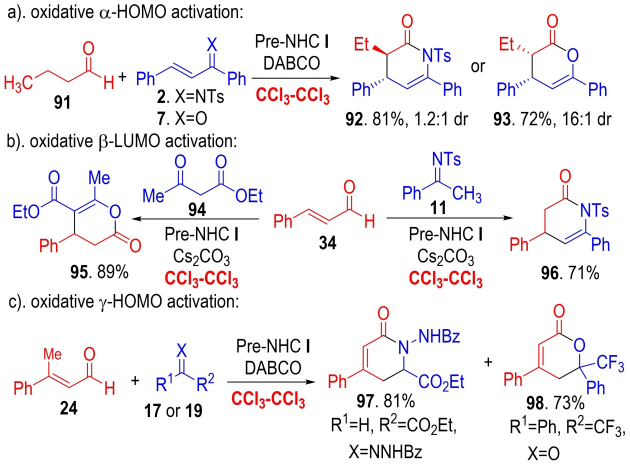
Scheme 27. NHC-catalyzed benzylation of electrophiles.

by nitro-benzyl bromide through two times of SET processes. This study motivated us to investigate structurally simple and inexpensive polyhalides as oxidants for oxidative NHC catalysis. The readily available C_2Cl_6 are evaluated to form acyl azoliums **II** from oxidiation of the aldehyde-derived Breslow intermediate **I** (Scheme 28).[47] Mechanistically, the oxidation went through two SET processes involving several radical intermediates, yielding $CCl_2{=}CCl_2$ as the reductant which is hydroponic volatile and hence could be easily removed under reduced pressure. Effective functionalizations of α,β and γ-carbon atoms of aldehydes and enals were realized to afford various six-membered lactams or lactones in excellent yields under the oxidative conditions with polyhalide oxidants (Scheme 29). Highly enantioselective transformations are readily achieved when chiral NHCs were used under the optimal conditions.

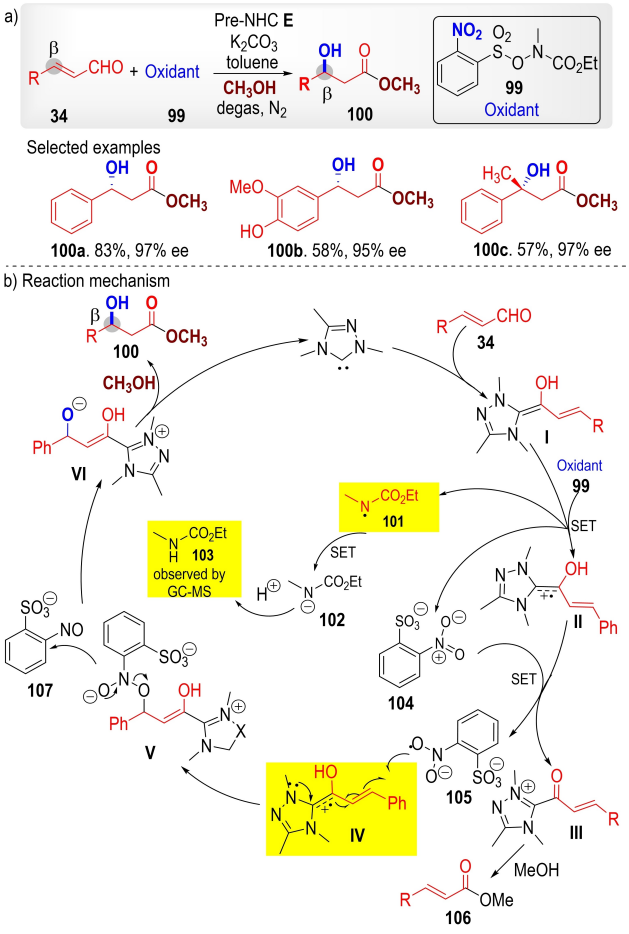
Chiral β-hydroxyl esters and their derivatives are important scaffolds and ubiquitous core structures widely present in bioactive compounds and natural products.[48] In 2015, the group of Rovis[49] and us both independently reported a NHC-catalyzed radical reactions for highly enantioselective β-hydroxylation of unsaturated aldehydes (Scheme 30).[50] Under the mild conditions with NHC **E** and nitroarene derivatives **99** as the SET oxidants, desired β-hydroxyl esters **100** were provided in high yields and excellent enantioselectivities. The proposed reaction mechanism involved an oxidative SET process between Breslow intermediate **I** and nitroarene oxidant **99** to generate three radical intermediates: **101**, **105** and NHC-bound radical cation **II**. The radical cation **II** was further oxidized by nitro compounds **104** to provide a nitro radical anion **105** and acyl azolium intermediate **III** which was trapped by MeOH to furnish the ester as the major side product **106**. In the other pathway, the N-centered radical **103** abstract one electron from another equivalent of Breslow intermediate **I** to form anther NHC-bound radical cation **IV** and a carbamate anion **102** that was confirmed by GC-MS of the protonated carbamate **113**. Radical coupling between radical intermediates **IV** and **102** afforded adduct **V** with a new C–O bond formation on the enal β-carbon. Subsequent bond dissociation and esterification would deliver the desired product **100**. By using a new class of nitroarene oxidants with



Scheme 28. Simple polyhalides as oxidant by a two-steps SET process.



Scheme 29. Scope of the SET oxidative process with C_2Cl_6.

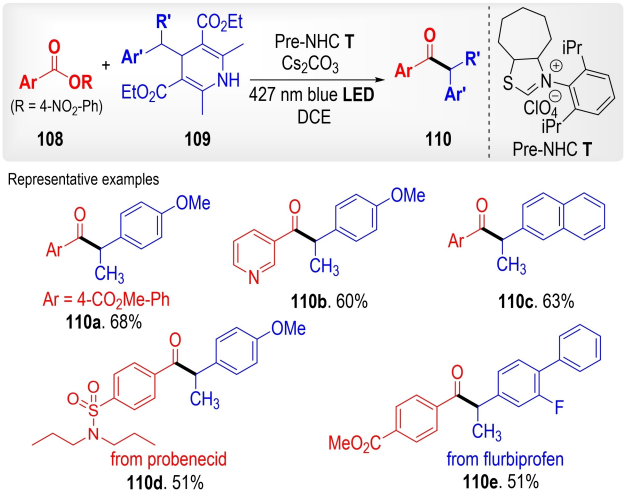


Scheme 30. NHC-catalyzed β-hydroxylation of α,β-unsaturated aldehydes.

a chiral moiety, later in 2019, we developed another enantioselective β-hydroxylation approach of enals with an achiral carbene catalyst.[51]

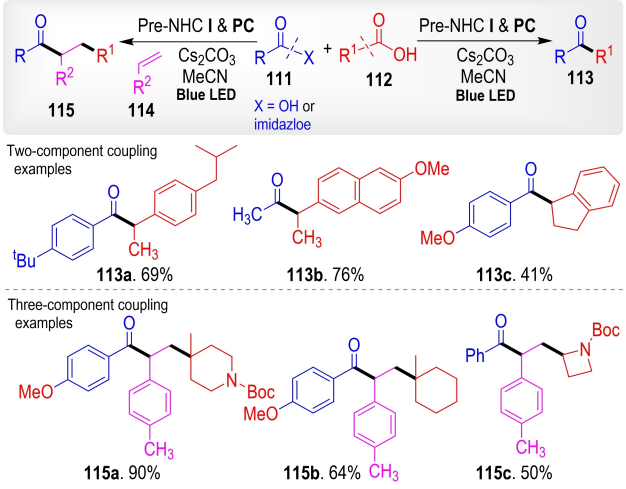
The key SET processes of the discussed examples above involve a single-electron oxidation of the reductive Breslow intermediate. Generation of radical intermediates from single-electron reduction of azolium ester intermediates provides an alternative strategy for reaction design as pioneered by Scheidt,[52] Studer[53] and their co-workers.[54]

Ketones are fundamental subunits in natural and synthetic molecules with wide applications in medicines, agrochemicals, and materials.[55] The exploration of new synthetic strategies for their efficient preparations remain an active topic. In 2021, we developed a direct photoexcitation of acyl azoliums for ketone (**110**) synthesis by coupling with Hantzsch esters **109**. The reaction proceeded smoothly under mild conditions with a good tolerance of various functional groups. Moreover, products with one or two medicinal fragments can be simply achieved (Scheme 31).[56]



Scheme 31. NHC-catalyzed $1e^-$ reduction via direct photoexcitation of acyl azolium.

Carboxylic acids and related derivatives are feedstock building blocks and ubiquitous structures in organic synthesis.[57] With the concept of cooperative carbene and photocatalysis, very recently, we disclosed an operationally simple ketone synthetic approach by coupling acyl imidazoles **111** and carboxylic acids **112** (Scheme 32).[58] The reaction shows a broad substrate scope with a wide array of ketones **113** or **115** were prepared in good yields, including multiple drug molecules and bioactive fragments were modified or direct coupled together with the developed method. Notably, the catalytic process was also compatible by the addition of another alkene **114** as a third component, leading to multi-



Scheme 32. NHC-catalyzed radical coupling of two/three-components for ketone synthesis

substituted ketone products **115** in high yield and complete regioselectivity.

7. Conclusion and Outlook

In conclusion, we have summarized our recent studies in the development of new activation modes of NHC catalysis. Various strategies were developed in the rapid synthesis of a vast number of chiral or achiral functional molecules that greatly expand the scope of classical NHC catalysis. (1) Stable carboxylic esters with a good leaving group could be efficiently activated by NHCs to form various reactive intermediates, such as NHC-derived acyl azolium, (vinyl) enolate, homoenolate and other unsaturated acyl azolium, that could be harvested for preparation of various chiral heterocycles in high stereoselectivity. (2) The arene-forming reactions by NHCs proved to be a highly efficient organocatalytic approach for rapid access to multisubstituted benzene structures which requires tedious manipulation by other methods. Formal [3 + 3], [4 + 2] and other cycloadditions were developed utilizing various NHC-bound reactive intermediates to achieve the aromatic synthesis. (3) Two approaches involving β-carbon LUMO activation of NHC-bound (unsaturated) acyl azolium intermediates and covalent activation of heteroatoms by forming reactive NHC-derived intermediates respectively were achieved for highly enantioselective heterocycle synthesis. (4) Furthermore, the power of NHC catalysis was demonstrated in the enantioselective control over stereogenic-phosphorus, silicon and axial/planar molecules which is a relative challenging task for the chirality control by other methods. (5) In addition to the vast majority of NHC organocatalysis involving electron-pair transfer steps, we have also focused on new reaction developments through single electron transfer (SET) processes and made some achievements in the coupling and oxidation reactions.

In future, the development of a more efficient activation strategy for highly enantioselective construction of biologically active functional molecules by NHC catalysis is still in continuous demand, particularly the fascinating transformations involving asymmetric synthesis through SET processes. Furthermore, these structurally diverse carbo- and heterocyclic compounds have showed significant bioactivities against plant diseases and would inspire more investigations with the aim of discovery of novel lead compounds for agrochemical or medicine discoveries. We anticipate the development of new NHC catalyst structures with improved stabilities and reactivities may open avenues for application of NHC-catalyzed enantioselective transformations in industrial chemical process for practical preparations of functional molecules by lowering down the catalyst loadings (ideally less than 0.1 mol%) with broad substrate scope. The other trend that could expect is to address the challenge in enantioselective construction of novel stereogenic P-, Si- and axial/planar molecules by NHC organocatalysis.

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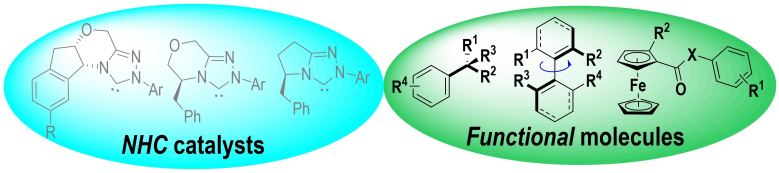
REVIEW



Over the past decades, N-heterocyclic carbene (NHC) organocatalysis has received considerable interest to provide numerous opportunities for a vast number of novel chemical transformations. This account overviews our group's recent work in the exploration of new activation modes of NHC catalysis towards molecular complexity with a focus on the development and applications of NHC to achieve reaction diversity and enantioselectivity in the preparation of functional molecules.

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