# Chapter 1

## *An Introduction to N-Heterocyclic Carbene (NHC) Catalysis*

### 1.1 Introduction

Carbenes are usually short-lived reactive species containing no formal charge on carbon with a valence of two and have two nonbonding electrons. They are considered as fleeting intermediates in molecular chemistry because they do not follow "octet rule".[1] However, apart from electrophilic nature of these traditional carbenes, there are carbenes known to be nucleophilic in nature, where the divalent carbonic centre is flanked by at least one nitrogen atom within the heterocycle are called *N*-heterocyclic carbenes (NHCs). NHCs have not only become versatile ligands for transition metals, but in last two decades these species encompasses an enormous array to a new set of reactions through polarity reversal (umpolung) reactivity and emerged as powerful organic catalysts in molecular chemistry.[2] This NHC-catalyzed umpolung of the functional group, with the carbonyl carbon atom acting as a transient nucleophile introduced a set of elementary steps that operate via distinct reactive species, including acyl anion, homoenolate and enolate. The benzoin condensation, the coupling of two aldehydes and Stetter reaction, addition of aldehydes to Michael acceptors are most prominent conversions. These transformations utilize acyl anion as the main intermediate. In continuation, NHCs has led to a broad range of annulated or acyclic products through homoenolate and enolate as a reactive intermediate. Furthermore, oxidative NHC catalysis i.e. non umpolung mode of reactivity can be conducted by using inorganic, organic and oxygen as sole oxidants. Additionally, the NHC-catalyzed

radical reaction inspired by the enzymatic catalysis have been developed.[3] Herein, we demonstrate the various important action modes of NHCs (Figure 1.1).

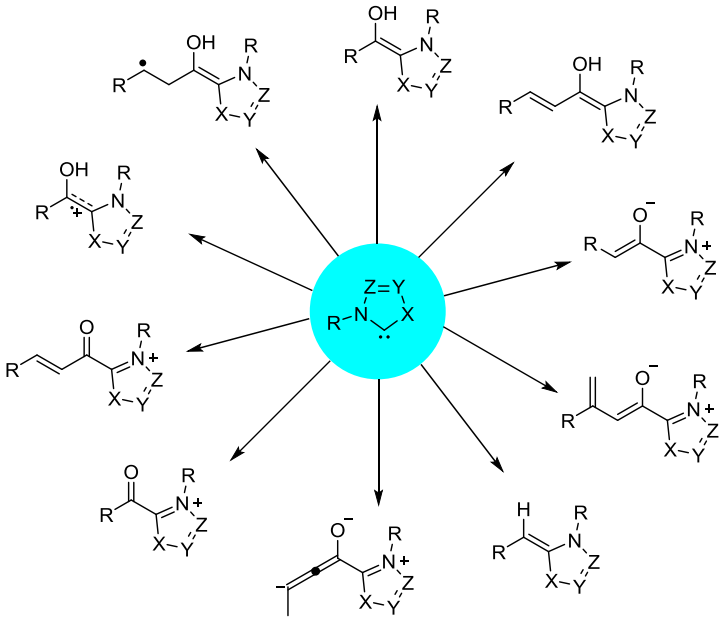
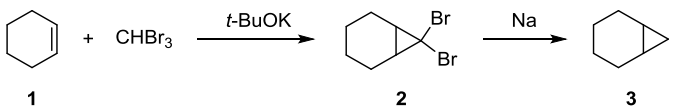


**Figure 1.1** Various important action modes of NHCs

## 1.2 Historical Background of Carbenes

In 1862, A. Geuther made the first statement that dichlorocarbene is a reaction intermediate with a divalent carbon for alkaline hydrolysis of chloroform.[4a] In the year 1897, J. Nef also proposed that Reimer-Tiemann reaction proceeds through dichlorocarbene as the reaction intermediate.[4b] As there was no experimental evidence so carbene moieties were considered as diradicals until 1930s. But in 1954, W. Doering gave the proof of the presence of a dibromomethylene intermediate for the first cyclopropane synthesis (Scheme 1.1).[4c]




**Scheme 1.1** Olefin cyclopropranation *via* methylene intermediate

After this various organic synthesis have been developed which proceed via the methlyene intermediate. These significant developments in this area attracted the chemists to look more closely at this carbene intermediate. First time, carbenes were introduced into the organometallic chemistry by Fisher with a resurgence of interest in 1964.[4d] A carbene is a short lived, highly reactive and neutral species that has a divalent carbon atom with six valence electrons. Although four electrons participate in σ-bonds and two remain at carbene carbon. Since they do not follow "octet rule", carbenes played an important role as transient intermediate in molecular chemistry. Based on the electronic spin they possess, it is necessary to consider both singlet and triplet carbenes (Figure 1.2).[5] In the case of singlet carbene two non bonding electrons at the carbene carbon are paired in highest occupied molecular orbital (HOMO) σ, whereas $p_\pi$ orbital remains vacant. As a result, they are amphiphilic and thus can react as either nucleophilic or electrophilic species. But in the case of triplet carbene two non bonding electrons are in different degenerated $p_x$ and $p_y$ orbital with parallel spins. So they are generally regarded as diradicals due to which triplet carbenes are highly reactive and difficult to isolate. As the total spin of triplet carbene is one so they are paramagnetic in nature and can be observed by electron spin resonance spectroscopy if they persevere long enough.

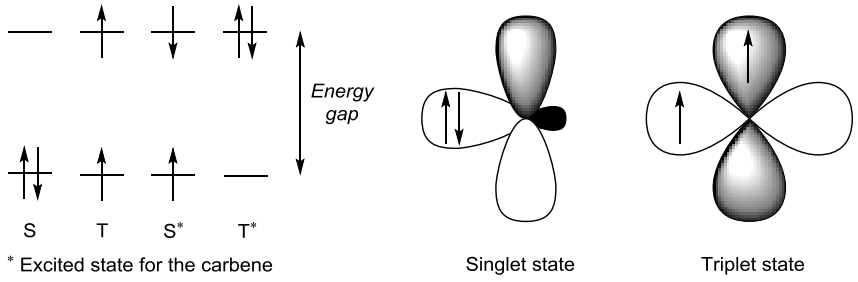



**Figure 1.2** Illustration of different electronic states of carbene

## 1.3 Organometallic Carbene Chemistry

Carbenes have been used to form metal-carbon bond which constitutes the central event in organometallic chemistry. In the 1960s, E. O. Fisher and K. Ölefe have started working on transition metal carbene complexes. In 1964, Fisher discovered the first metal carbene complex.[4d] The dominant bonding in metal carbon bond constituted by Fisher carbenes and transition metal arises from carbene metal σ-donation and metal carbene π-back donation. Fisher carbene complex are electrophilic as π-electrons are usually polarized toward metal resulting an insufficient π-donation from the metal and the adjacent alkoxy substituent. Fisher carbene are associated with low-valent metals and substituents which possess π-donation ability.

On the other hand, Schrock carbenes are poorly stabilized carbenes because they have a minor difference between their singlet and triplet ground state. Therefore they form a covalent metal-carbon bond which typically due to the interaction of triplet state of both carbene and metal center. The metal-carbon bond is known to be a real double bond because π-electrons are almost evenly distributed (Figure 1.3).[1] Consequently, Schrock carbenes are nucleophilic in nature. These carbenes are normally alkyl substituted and interact exclusively with high oxidation state metals.

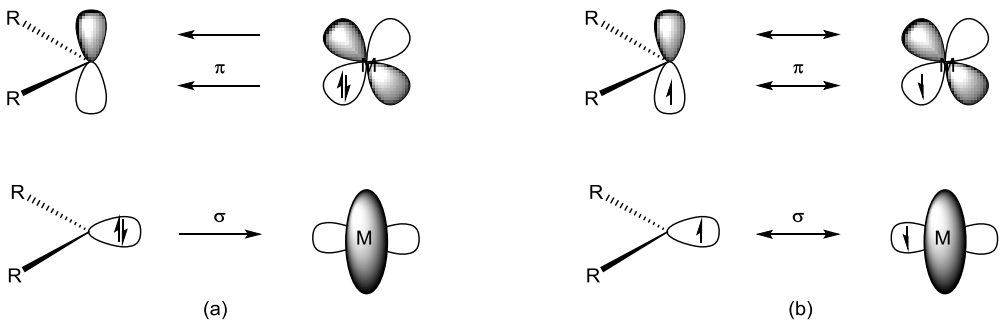


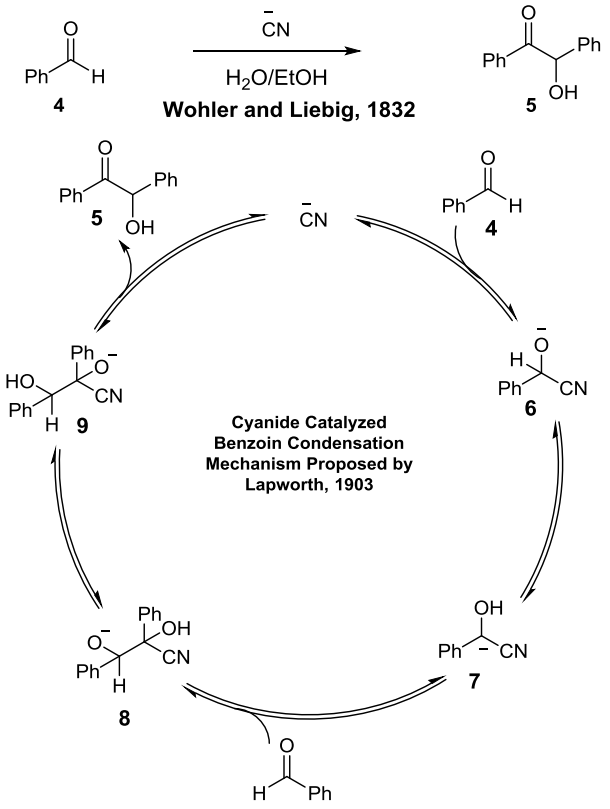

**Figure 1.3** Illustration of the Metal-carbon bonding between (a) Fischer carbenes and (b) Schrock carbenes

## 1.4 Development of NHC-Organocatalysis

In terms of effective chemical transformations like the formation of carbon-carbon bond, organic catalysts are extremely efficient in modern synthetic chemistry. In 1929, Langenback used the word "Organiche Katalysatoren" or organic catalyst.[6a] The term "Organocatalysis" was later described by MacMillan in which a small organic molecule catalyzes a reaction.[6b] Among the plethora of methods developed, Organocatalysis is an effective tool for organic reactions as of low toxicity and atom economy over the transition metal based catalysis which possess some genetic limitations like high cost and toxicity of metal catalyst. Organocatalysis represents a facile reaction course, selectivity, environmentally friendly and offers conversions unprecedented in metal catalysis. The transformations especially the inversion of polarity i.e. umpolung intoduces a new synthetic route by using of NHC Organocatalysis. Catalysis using NHC has appeared as an rewarding research field in organic chemistry. As typical structural features, *N*-heterocyclic carbene also called Arduengo carbenes are highly reactive, neutral species and possess a bivalent carbon atom with an electron sextet.[6c] NHCs are amphiphilic in nature and can behave as both electrophilic and nucleophilic species. As a result they belong to the category of singlet carbene.

The Benzoin condensation catalyzed by NHC has been the focus of intense investigation. In 1832, the initial investigation was carried out from the group of Wöhler and Liebig. They demonstrated cyanide catalyzed self condensation of aromatic aldehyde to provide the corresponding benzoin product.[7a] Hereafter in 1903, Lapworth postulated a mechanism for this condensation reaction (Scheme 1.2).[7b] A key step in

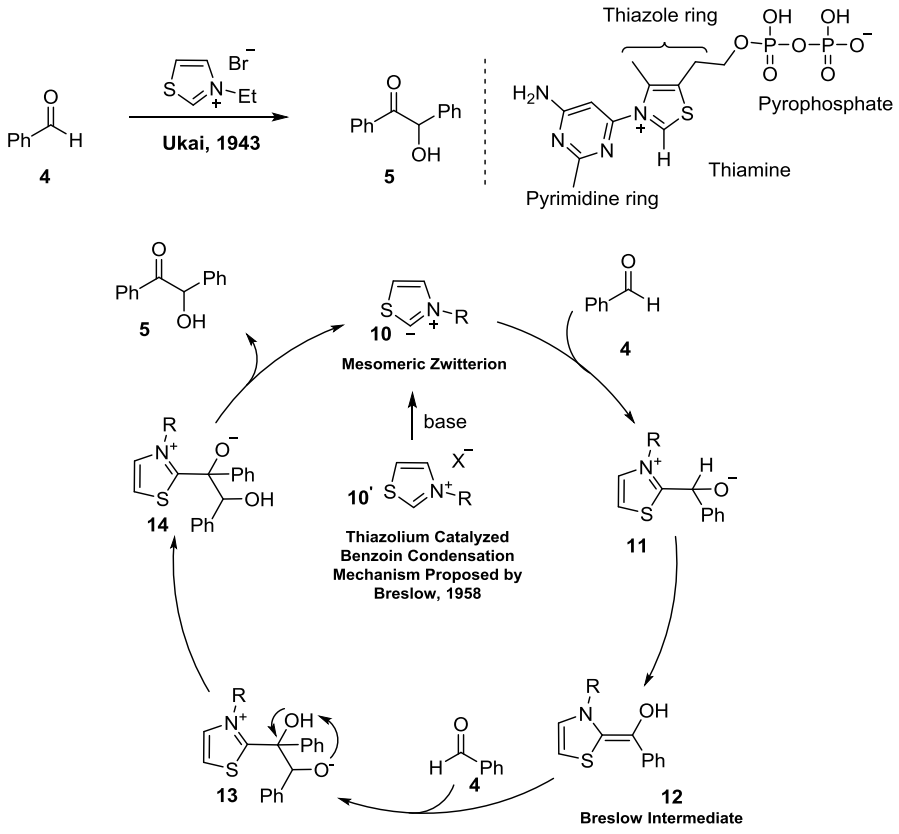
this transformation is the umpolung of aldehyde that is achieved via the formation of carbanion intermediate **7** by addition of cyanide to benzaldehyde followed by protonation through the tetrahedral intermediate **6**. Then, the generated acyl anion intermediate **7** react with another molecule of aldehyde and finally furnish the desired benzoin product **5**.




**Scheme 1.2** Cyanide catalyzed Benzoin condensation

Following on in 1943, Ukai et al. suggested that thiazolium salt could be used as catalyst in benzoin reaction.[8a] Thereafter in 1958, while working on the role of so called coenzyme thiamine (Vitamin B1) Ronald Breslow proposed a mechanistic explanation that implies active part of thiamine could be made of a carbene which could also catalyze the benzoin reaction (Scheme 1.3).[3c] Breslow assumed that *in situ* carbene can

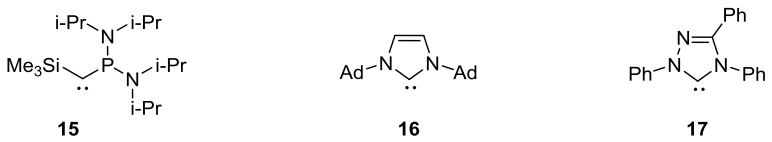
be generated when thiazolium salt is deprotonated at its most acidic position. The key step in the proposed mechanism involves *in situ* generation and addition of carbene **10** to an aldehyde resulting to tetrahedral intermediate **11** followed by proton transfer to give resonance stabilized enaminol type-Breslow intermediate **12**. This nucleophilic acylation reagent **12** reacts with another molecule of aldehyde to deliver the α-hydroxy ketone **5** as the final product and the original carbene catalyst **10** is regenerated.




**Scheme 1.3** Thiamine catalyzed Benzoin condensation

However, from a historical perspective during 1960s first attempt was made to isolate carbene by deprotonation of imidazolium salt with a strong base with the studies of Wanzlick.[8b] But this remained unsuccessful, although carbene could be trapped in the presence of metal fragment whereas in absence of trapping agent only carbene dimers

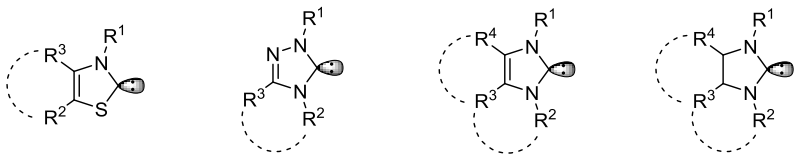
were isolated. The existence of stable carbene was actually reported with the synthesis of phosphinosilylcarbene **15** (Fig. 1.4) by Bertrand and co-workers in 1988.[9a] Furthermore, isolation and characterization of the first crystalline cyclic diaminocarbene **16**, so called NHC was reported by Arduengo et al. in 1991 (Fig. 1.4).[6c] Inspired by this success, Enders et al. studied the triazole heterocycle as an alternative carbene structure with the group of Teles. In 1995, Enders and co-workers reported the synthesis of triazolin-5-ylidene **17** (Fig. 1.4).[9b] Triphenyl triazol-5-ylidene **17** was the first carbene to be commercially available.




**15** **16** **17**

**Figure 1.4** Early *N*-heterocyclic carbenes (Ad = adamantyl)

The area of nucleophilic catalysis comprises a huge range of reactions, with the most popular employing *N*-heterocyclic carbene catalysis. The area of NHCs initially expanded slowly and has been widely utilized as versatile ligands in organometallic chemistry. Since the isolation of stable nucleophilic carbene by Arduengo[6c], Bertrand[9a] and Enders[9b], the NHCs have attracted wide attention from chemical community as they offer an elegant access to a broad range of organic transformations. In general, for these transformations four forms of NHCs are used (Figure 1.5).




**A** **B** **C** **D**

**Figure 1.5** Basic skeleton of *N*-heterocyclic carbenes

Importantly, the stability of NHCs is dependent upon both the electronic and steric factors. Herein, electronic factors include inductive and mesomeric effects and both these contribute to maintain the electro-neutrality of the carbene centre. In terms of inductive effects σ-electron withdrawing substituents favor the singlet state over the triplet state whereas σ-electron donating substituents induce a smaller σ-$p_\pi$ gap which favor a triplet state. Additionally, in the case of mesomeric effect both nitrogen lone pairs interact strongly with the $p_\pi$ orbital of the carbene centre which highlights the different mesomeric forms of NHCs (Figure 1.6). This strong interaction leads to a massive destabilization of the $p_\pi$ orbital resulting in a large σ–$p_\pi$ gap.[1] All these facts conclude that NHCs are not electrophilic but behave like strong nucleophilic species.

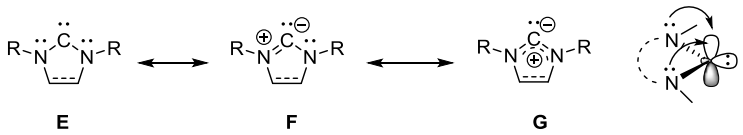



**Figure 1.6** Mesomeric structures of NHCs and stabilization of the singlet ground state

## 1.5 Important Action Modes of NHC

Catalysis of *N*-heterocyclic carbene (NHC) has been shown to provide a number of results which are classified according to the reaction mode and the intermediates produced during the reaction (Figure 1.7). The various reactions through nucleophilic Breslow intermediate (i) with unconventional reaction partners offer transformations unparalleled in metal catalysis. The reaction of Benzoin and Stetter are the two most prominent transformations in the category of traditional umpolung reactions. In the

former transformation addition of *in situ* generated carbene to aldehyde provides acyl anion intermediate, which further combines with another aldehyde molecule to afford α-hydroxy ketones (benzoins). In 1973, Stetter reported for the first time the attachment of acyl anion with Michael acceptor offering efficient access for the synthesis of 1,4-dicarbonyl compounds.[10] On the other hand, a reactive homoenolate intermediate (ii) which possess nucleophilic carbon at β position and can be generated from α,β-unsaturated aldehydes by virtue of NHC catalysis. Additionally, a nucleophilic enolate intermediate (iii) is a result of β-protonation of the homoenolate intermediate. This is a two carbon synthon which typically gives [3+2] and [4+2] annulation reactions and has also been generated from α-halo- or α-aryloxy aldehydes and stable ketenes under NHC catalysis. Furthermore, NHC-bound dienolate intermediate (iv) can be originated from β,β'-disubstituted enals having γ-hydrogen respectively under oxidative NHC-catalysis. Interestingly, enals with leaving group and cyclobutenones also generate dienolate intermediate which participate in formal [4+2] cycloaddition reaction. Notably, an NHC-bound allenoate intermediate (v) induced by the umpolung of ynals bearing a γ-leaving group through NHC-catalyzed internal redox reaction. Basically this allenoate intermediate is a three carbon synthon and commonly deliver [3+2] annulation reactions. The attachment of nucleophillic carbene to Michael acceptors provides the Deoxy-Breslow intermediate (vi), which converts electrophilic β-carbon to nucleophilic carbon. Moreover, the Breslow intermediate can be oxidized to acyl azolium intermediate (vii) by employing external oxidants such as inorganic, $O_2$ and organic oxidants. Likewise, α,β-unsaturated acyl azolium (viii), and α,β-γ,δ-unsaturated acyl

azolium (ix) generated from corresponding enals. Newly, the NHC-catalyzed reaction through radical process (intermediate x and xi) has emerged as a powerful method for various important transformations. Experimental and computational studies also demonstrate that selective formation of each reactive intermediate can be done by controlling the reaction conditions, coupling partner and NHC catalyst.

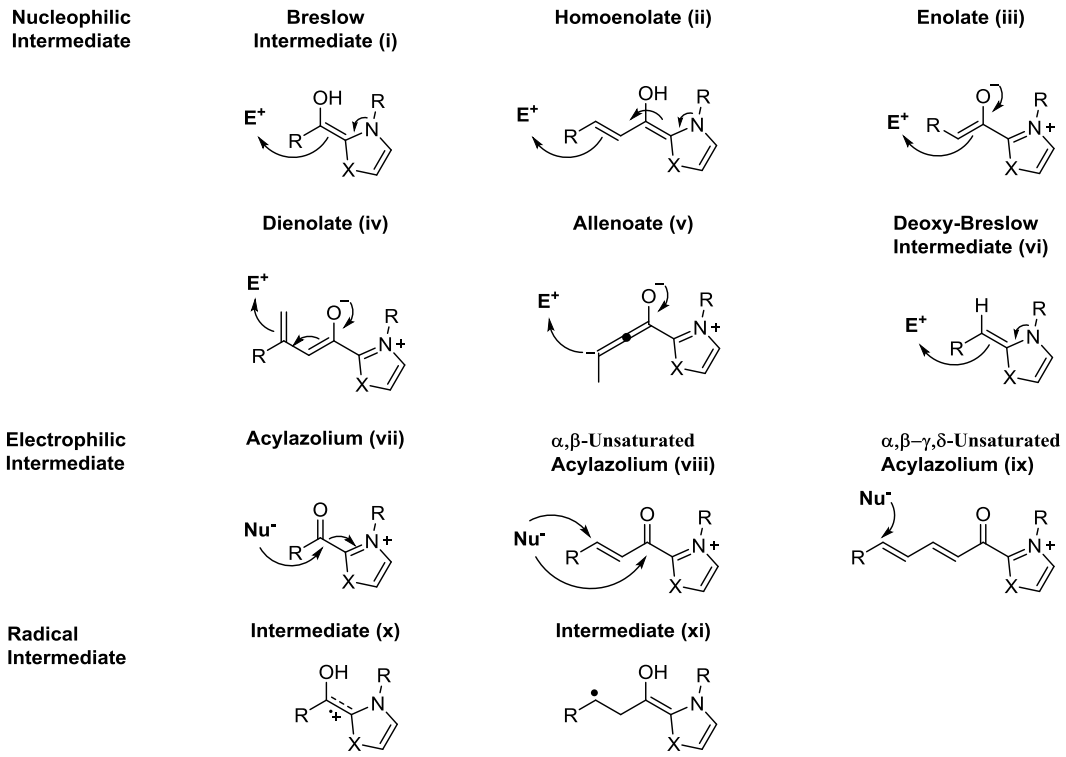



**Figure 1.7** Important action modes of NHC.

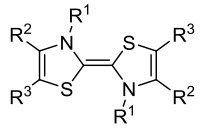
### 1.5.1 Reactions involving NHC-Bound Breslow Intermediate

The NHC-catalyzed polarity inversion of aldehydes through the formation of nucleophilic Breslow intermediate (i), is one of the most studied mode of action in the field of NHC. The transformations such as benzoin condensation (Inter- & Intra-molecular) and Stetter reaction (Intra- & Inter-molecular) are the most marked reactions under the area of NHC-

catalysis. In addition, the hydroacylation reaction of unactivated double and triple bonds catalyzed by NHC through umpolung of aldehydes are well studied.

### (A) Benzoin Condensation

The benzoin condensation catalyzed by NHCs has received substantial attention for several decades because of its employment in the formation of new C-C bonds to access α-functionalized products. In 1832, Wöhler and Liebig reported the self condensation of aromatic aldehyde to produce benzoin by using cyanide as the catalyst (Scheme 1.2).[7a] Later in 1943, Ukai et al. demonstrated self condensation of two same aldehyde so called homo-benzoin condensation employing thiazolium catalyst in existence of base.[8a] Furthermore, Breslow in 1958 suggested a mechanistic explanation for benzoin condensation catalyzed by thiazolium salt (Scheme 1.3).[3c] While an alternative mechanistic model based on the facile formation of carbene dimer (Figure 1.8) was postulated by Lemal and co-workers[11] but finally this could not be stand up to the Breslow mechanistic model.



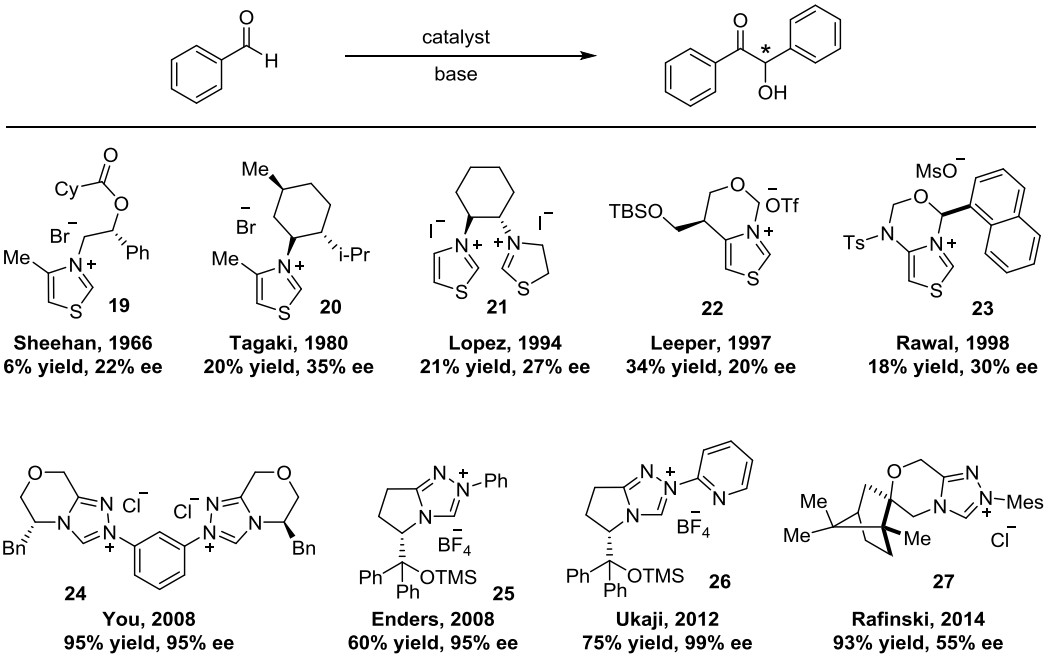

18

**Figure 1.8** Thiazolin-2-ylidene dimer

### (a) Intermolecular Benzoin Condensation

In 1976, Stetter and co-workers were the first to use commercially available thiazolium salt as catalyst for acyloin (aliphatic aldehydes) or benzoin (aromatic aldehydes) condensation on a synthetically useful scale.[12a] Consequently, several chemists have tried best to develop a highly asymmetric version of homo-benzoin reaction that leads to evolution of several chiral NHC precursors. In this context, Sheehan and Hunneman in 1966 reported the first

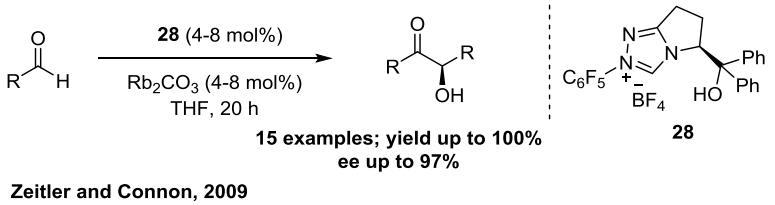
result of asymmetric benzoin condensation employing chiral thiazolium salt **19** as precatalyst and obtained the benzoin in very low yield (6%) and 22% enantiomeric excess (ee).[12b] After this initial report, the effort to increase the efficiency of the homo-benzoin reaction led to the development of a wide variety of various chiral thiazolium and triazolium salt as precatalyst. A assorted series of chiral NHC catalysts, which were employed in asymmetric benzoin condensation is described (Scheme 1.4). The yields and asymmetric induction for benzoin reactions were modest with thiazolium derived NHC-salts (**19-23**) whereas catalyst generated from triazolium based NHC-salts (**24-27**) provided the desired product with increased yields and enantioselectivity.[13] Furthermore, the superiority of triazolium derived NHCs over thiazolium derived counterparts in benzoin condensation was also supported by computational studies.




**Scheme 1.4** Variation of chiral-NHCs for asymmetric homobenzoin condensation

More recently, Connon and Zeitler developed asymmetric benzoin condensation using a triazolium precatalyst **28** which incorporate a hydrogen bond donor providing

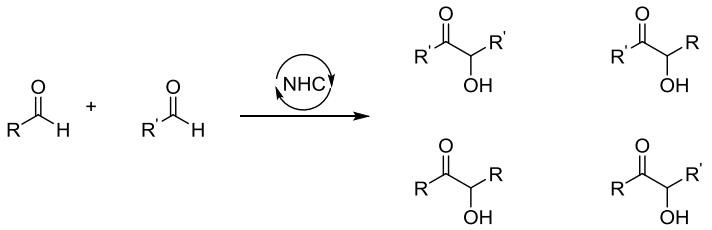
stabilization of secondary interactions in transition state concludes to reach practically fine enantioselectivity.[14]




**Scheme 1.5** Co-operative hydrogen bond assisted enantioselective benzoin condensation

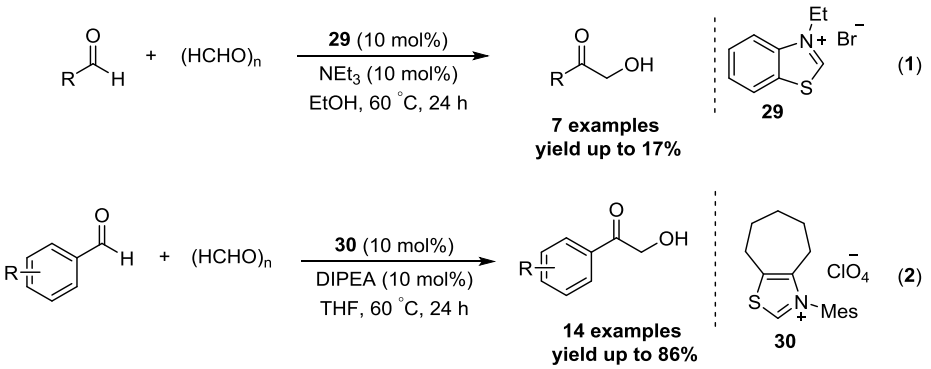
### (b) Intermolecular Cross-Benzoin Reaction

The cross-benzoin reaction is preparation of non-symmetrical products by the cross-coupling of two different aldehydes, wherein one molecule of aldehyde acts as acyl anion equivalent. In this process, a pair of homo-benzoin and cross-benzoin each can be formed providing a mixture with up to eight distinct products including four pair of enantiomers (Scheme 1.6). Notably, a general approach to chemoselective NHC mediated cross-benzoin transformation of electronically and sterically similar aldehydes is still challenging.



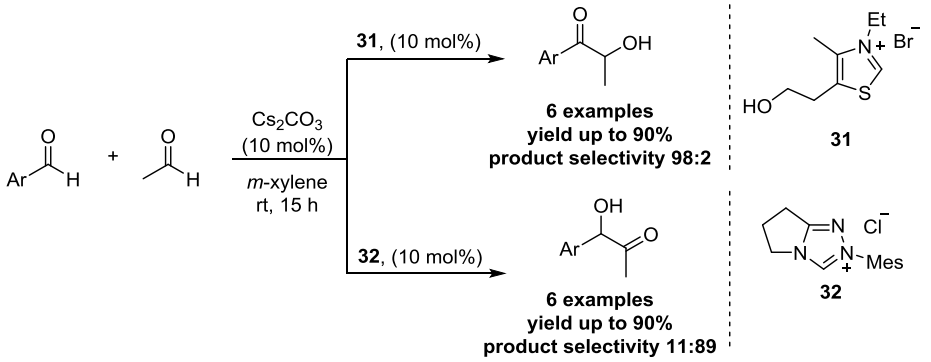

**Scheme 1.6** General intermolecular cross-benzoin reaction

In 1985, Inoue et al. disclosed the NHC mediated cross-benzoin selective transformations of aliphatic and aromatic aldehydes with paraformaldehyde allowing to access α-hydroxy ketones in very low yields (Scheme 1.7, Eq. 1).[15a] Furthermore, Kuhl and Glorius developed thiazolium based catalyst **30** which were used to furnished hydroxy ketone in good to moderate yields (Scheme 1.7, Eq. 2).[15b]




**Scheme 1.7** Cross-benzoin selective reaction

Moreover, Yang and colleagues demonstrated an intermolecular cross-coupling reaction between aromatic aldehydes and acetaldehyde which displayed an exciting variation in reactivity between thiazolium **31** and triazolium **32** derived precursors. The thiazolium-based carbene favored the generation of Breslow equivalent with aromatic aldehydes and successive coupling with aliphatic aldehydes. However, triazolium-based carbene preferentially generate acyl anion intermediate with aliphatic aldehydes followed by addition to aromatic aldehydes (Scheme 1.8).[15c]

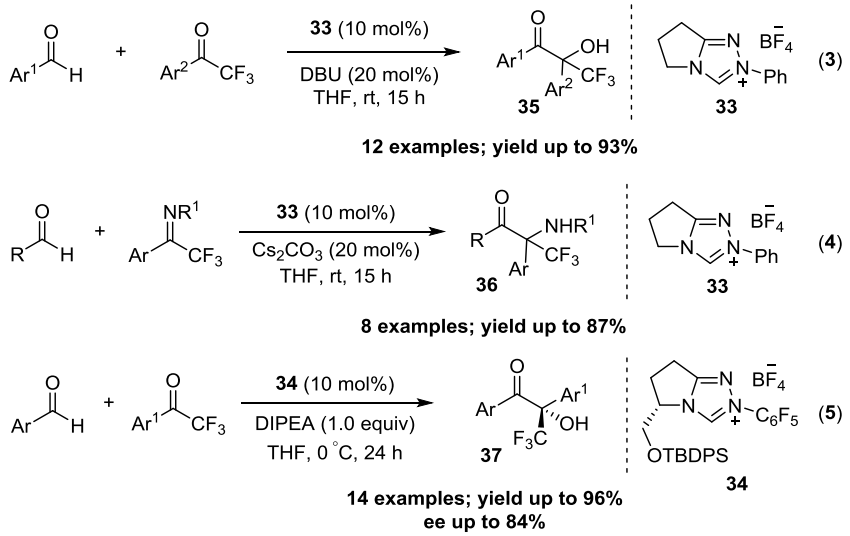



**Scheme 1.8** Catalyst-controlled divergence in cross-benzoin reactions

### (c) Intermolecular Asymmetric Cross-Benzoin Reactions

The expansion of asymmetric cross-benzoin reaction is very challenging because a single catalyst must regulate both chemoselectivity and stereoselectivity. Impressively,

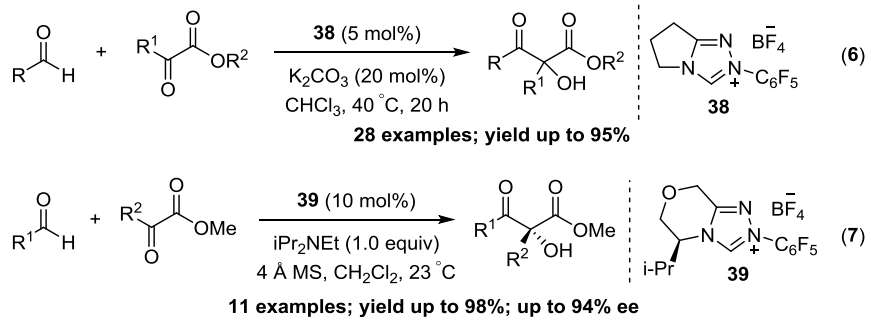
Enders and Henseler disclosed an NHC-catalyzed cross coupling reaction of aryl aldehydes and aryl trifluoromethyl ketones to furnish final product, α-hydroxy-α-trifluoromethyl ketones **35** with high yields and chemoselectivity (Scheme 1.9, Eq. 3).[16a] Herein, the reversibility of the homo-benzoin reactions provides excellent selectivity for the observed cross-benzoin product which has a quaternary stereocentre. Thereafter, they noticed that trifluoromethyl ketimines can also used as electrophiles to broaden the substrate scope (Scheme 1.9, Eq. 4).[16b] Although initial attempts of asymmetric transformation by using a chiral triazolium were not fruitful but latter they were able to overcome this issue by using heteroaromatic aldehyde (acyl donor) in the presence of chiral NHC generated from **34** with aryl trifluoromethyl ketones to furnished the desired trifluoromethylated hydroxy ketones **37** in good yields and enantioselectivity (Scheme 1.9, Eq. 5).[16c]




**Scheme 1.9** Cross-benzoin reaction of aldehydes and trifluoromethyl ketones

Additionally, Connon and Zeitler et al. investigated that α-ketoesters could also be used as electrophilic coupling partner for various aliphatic and aromatic aldehydes which

served as acyl donor for intermolecular cross-benzoin transformation. Remarkably, the authors presented one illustration of an enantioselective product in 48% yield and 76% ee employing chiral NHC-catalyst (Scheme 1.10, Eq. 6).[17a] Furthermore, Gravel and colleagues were successful in broadening the scope of chemoselective and enantioselective version of intermolecular cross-benzoin transformation with aliphatic aldehyde and α-ketoesters. Noticeably, aliphatic α-ketoesters were not compatible under the reaction conditions. The reaction provides the product in good yields and high enantioselectivity by using an electron deficient valine-derived triazolium salt precatalyst **39** (Scheme 1.10, Eq. 7).[17b]

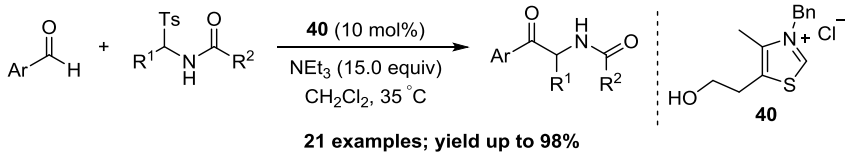



**Scheme 1.10** Cross-benzoin reaction of aldehydes and α-ketoesters

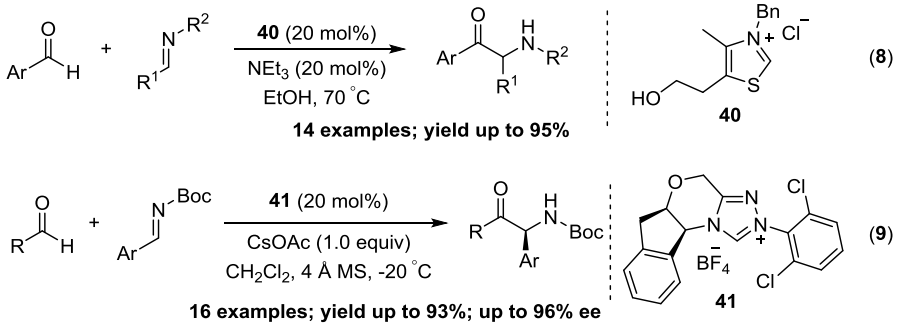
### (d) Intermolecular Cross Aza-Benzoin Reactions

In 2001, Murry and Frantz were first to demonstrate the coupling of acyl anion generated from aldehydes to an imines. They exposed that efficient coupling of Breslow intermediate generated from aldehyde using thiazolium salt **40** as precatalyst and *in situ* formed reactive acylimines by the action of base on the sulfonylamide derivative deliver the desired α-amidoketones in excellent yields (Scheme 1.11).[18a] Subsequently, You and co-workers reported cross-aza benzoin transformation of aryl and hetero-aryl aldehydes with non-activated imines to furnish α-amino ketone products in excellent

yields employing thiazolium precatalyst **40** (Scheme 1.12, Eq. 8).[18b] Notably, the control experiment employing corresponding benzoin (instead of aldehyde) with imines works well which specify that it involves reversible formation of aldehyde homo-benzoin adduct. Later, DiRocco and Rovis disclosed enantioselective cross aza-benzoin reaction of aliphatic aldehyde with N-Boc imines using chiral triazolium salt **41** (Scheme 1.12, Eq. 9).[18c] In this transformation aldehydes acts as acyl donor whereas imines function as receptors. Furthermore, it was observed that addition of NHC to the highly electrophilic N-Boc imines leads to the formation of reversible aza-Breslow intermediates under the reaction conditions and thus cancel out the requirement for a slow addition of highly reactive imines as substrates.

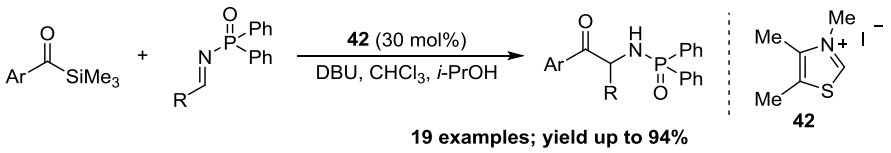



**Scheme 1.11** Cross aza-benzoin reaction of aldehydes and acylimines



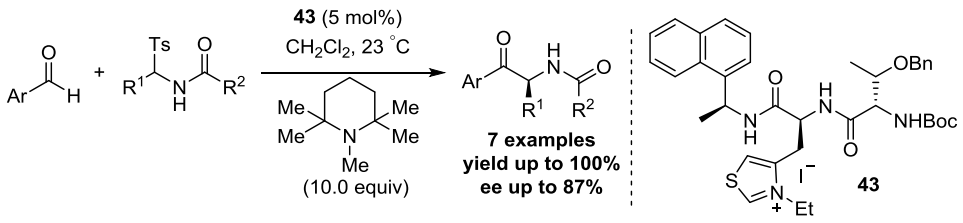

**Scheme 1.12** Cross aza-benzoin reaction of aldehydes and imines

Furthermore, Mattson and Co-workers reported a catalytic cross aza-benzoin transformation using acylsilanes and imines to furnish aminoketones (Scheme 1.13).[19a] Notably, the generated free carbene selectively couples with acyl silanes to generate Breslow intermediate, which then reacts with imines to furnish desired product.




**Scheme 1.13** Cross aza-benzoin reaction of acylsilanes and imines

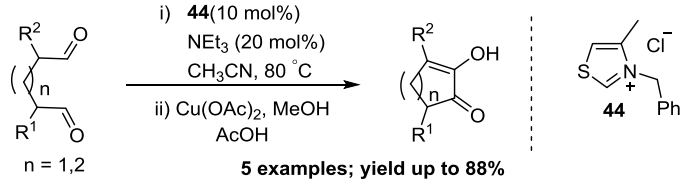
Moreover, Miller et al. in 2005 employed thiazolium-derived chiral salt **43** to expose enantioselective cross aza-benzoin protocol (Scheme 1.14).[19b] The reaction proceeded with generation of Breslow intermediate, which added to masked imines to afford the desired α-amino ketones in excellent yields and good enantioselectivity. This transformation suffers a racemisation of the products resulting a decrease in stereoselectivity under the reaction conditions. This problem was successfully overcome by using a hindered base, pentamethyl piperidine which was inert towards the products and gives the maximum enantioselectivity.




**Scheme 1.14** Enantioselective cross aza-benzoin reaction

### (e) Intramolecular Benzoin Reaction

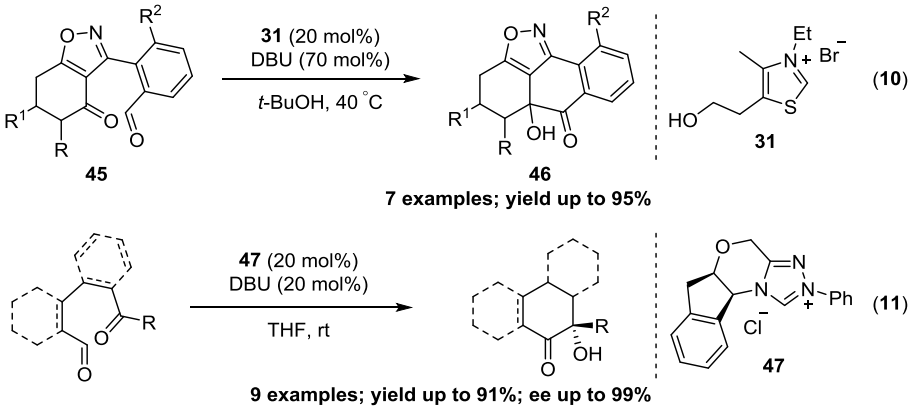
Cookson and Lane demonstrated first intramolecular cross-benzoin condensation in 1976. This report disclosed the formation of 2-hydroxycyclopentanone by the treatment of anhydrous glutaraldehyde with thiazolium salt **44** as precatalyst. The above also endured further oxidation by treatment with Copper (II) acetate affords 2-hydroxycyclopent-2-en-1-one (Scheme 1.15).[20]




**Scheme 1.15** Intramolecular benzoin condensatation

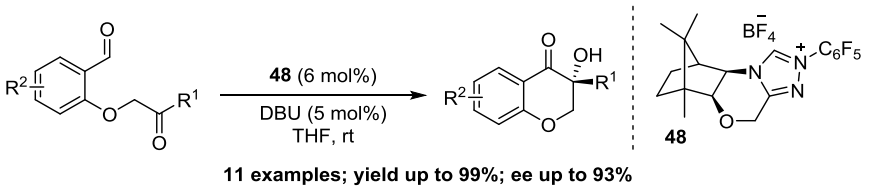
### (f) Intramolecular Cross-Benzoin Reaction

Suzuki and co-workers demonstrated the first intramolecular cross-benzoin condensation of aldehyde and ketone in 2003 (Scheme 1.16, Eq. 10).[21a] This transformation represents the first report on the use of functional group like ketone as an electrophile in non-enzymatic benzoin reaction. Herein, the highly rigid isoxazole-fused cyclohexanone **45** graced with an aryl aldehyde endure a flatten cross-benzoin cyclisation using thiazolium salt **31** as precatalyst to afford a very high stereo- and regioselective polycyclic preanthraquinones analogues **46** in high yields. This efficient protocol authorized the synthesis of orthogonally protected polycyclic quinones using easily accessible starting reagents. Subsequently, they in 2006 advanced enantioselective variant of the same transformation employing an aminoindanol based triazolium catalyst **47** with high yields and excellent enantioselectivity (Scheme 1.16, Eq. 11).[21b]



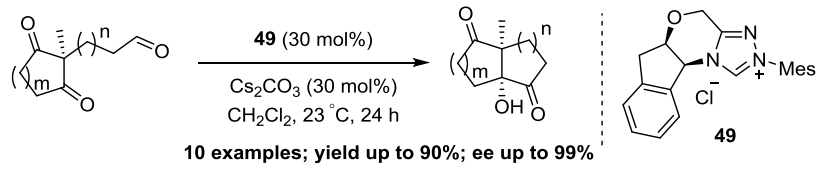

**Scheme 1.16** Intramolecular cross-benzoin condensatation of aldehyde and ketone

Furthermore, You and co-workers developed enantioselective intramolecular heterocoupling between aldehyde and ketone using a camphor-derived triazolium precatalyst **48** for the synthesis of chromanone derivatives possessing a quaternary stereocentre in excellent yields and enantioselectivity (Scheme 1.17).[22a]




**Scheme 1.17** Intramolecular cross-benzoin reaction for chromanone synthesis

In addition, Ema and co-workers developed the synthesis of bicyclic tertiary alcohols possessing a stereogenic centre at both bridgehead carbon *via* an intramolecular crossed benzoin reaction by using the NHC derived from **49** (Scheme 1.18).[22b] Notably, a relatively high loading (30 mol%) of catalyst was crucial for excellent enantioselectivity.

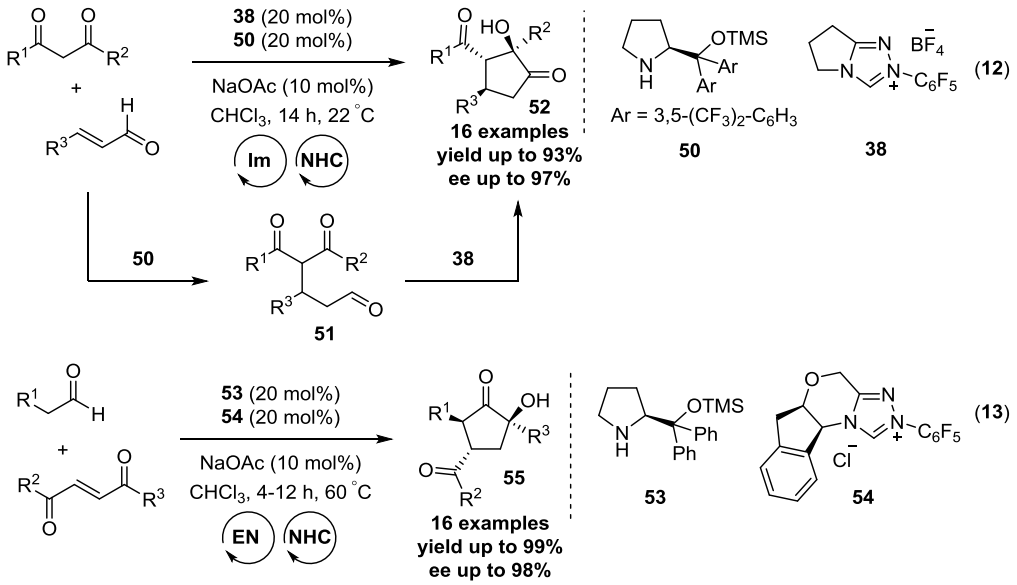



**Scheme 1.18** Intramolecular cross-benzoin reaction to access bicyclic tertiary alcohols

In 2009, Rovis et al. developed a multicatalytic Michael addition-intramolecular benzoin cascade protocol, which leads to the formation of highly functionalized cyclopentanones with excellent enantioselectivity (Scheme 1.19, Eq. 12).[23a] The reaction was initiated with generation of α,β-unsaturated iminium by the reaction of enal and secondary amine catalyst **50**, followed by conjugate nucleophilic addition of diketone, protonation and hydrolysis provides a δ-ketoaldehyde system **51** with release

of **50**. Subsequently, the NHC generated from **38** catalyzes the intramolecular cross-benzoin transformation to furnish desired product **52**. As the NHC precatalyst **38** is achiral so the absolute configuration of reaction is only regulated by secondary amine catalyst **50**. The controlled experiments conclude that Michael addition is reversible but carbene catalyze the intramolecular cross-benzoin process very quickly to furnish final product and thus restrict the destruction of enantioselectivity.

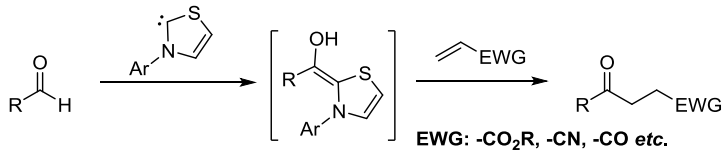
Later, in 2011 they developed a dual enamine-NHC catalytic, conceptually comparable Michael-benzoin cascade reaction (Scheme 1.19, Eq. 13).[23b] The reaction was initiated by the coupling of enolizable aldehyde and secondary amine catalyst **53** to generate enamine, which further combines to an activated Michael acceptor and subsequent hydrolysis gives a δ-ketoaldehyde, which then undergoes intramolecular cross-benzoin condensation employing chiral NHC precatalyst **54** to form the desired highly functionalized cyclopentanol products with excellent enantioselectivity.




**Scheme 1.19** Secondary amine-NHC dual-catalytic, Michael-benzoin cascade reaction

**(B) Stetter Reaction**

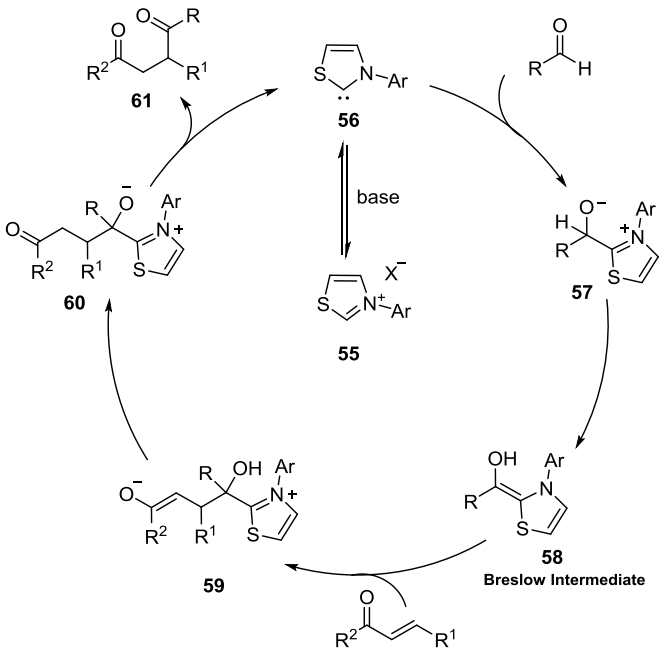
The benzoin condensation was extended to Michael acceptors and thereby significantly increasing the versatility of NHC-catalyzed transformations. In the early of 1970s, Stetter and colleagues reported for the first time the addition of aldehyde to Michael acceptors catalyzed by NHC, giving access to valuable 1,4-bifunctional compounds (Scheme 1.20).[10] In addition, this protocol is precious as it provides abnormal functional group separation and that is not easy to compose by traditional protocols. They succeeded to develop selective conjugate addition reaction using thiazolium-catalyst to cross-couple various aliphatic as well as aromatic aldehydes with different Michael acceptors like α,β-unsaturated esters, ketones, nitriles or sulfones in an intermolecular process. However, the presence of an NHC has been confirmed by the Wanzlick experiments.




**Scheme 1.20** Stetter reaction

Moreover, Arduengo et al. in 1991 isolate and characterize the first stable crystalline NHC to prove that these reactions are catalyzed by NHCs.[6c] A crucial step in the proposed mechanism of Stetter reaction (Scheme 1.21), is nucleophilic addition of *in situ* formed free carbene **56** from azolium precursor **55** to aldehyde, resulting the generation of tetrahedral intermediate **57**, which further transfer proton to the nucleophilic enaminol intermediate commonly known as the Breslow intermediate **58** in a reversible process. This acyl anion intermediate **58** undergoes nucleophilic addition

in irreversible fashion to Michael acceptor to give alkoxide **59** followed by proton transfer to deliver **60** which finally furnished desired 1,4-bifunctional product **61** with regeneration of free carbene**.** In this transformation, the use of chiral NHCs leads to access enantioenriched 1,4-bifunctional compounds. Moreover, Rovis et al. proposed a stepwise mechanistic model for coupling of Breslow intermediate and Michael acceptors.[24a] In addition, they also considered the possibility of a concerted pathway for the same. However, Hawkes and Yates exposed a two-step process for attachment of Breslow intermediate with Michael acceptor, based on DFT calculations.[24b]

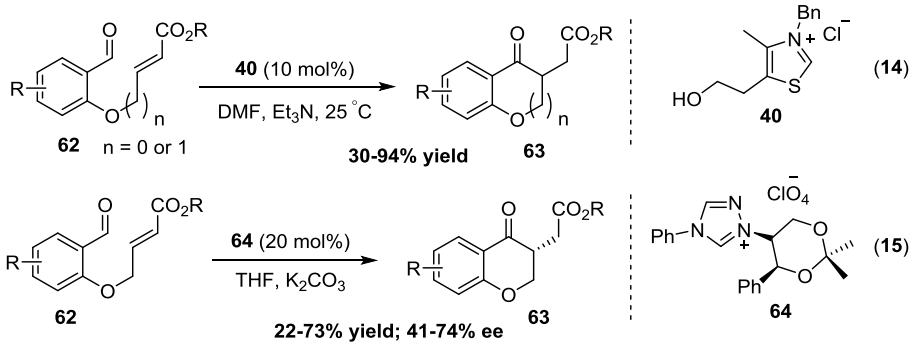



**Scheme 1.21** Catalytic cycle of Stetter reaction

**(a) Intramolecular Stetter Reaction**

In 1995, Ciganek research group reported first general intramolecular Stetter reaction catalyzed by NHC. The intramolecular cyclisation of 2-formyl aryloxy crotonates **62** employing *in situ* produced free carbene from thiazolium salt **40** provides benzo-annulated pyranones **63** (Scheme 1.22, Eq. 14, n = 1).[25a] The reaction of 2-formyl

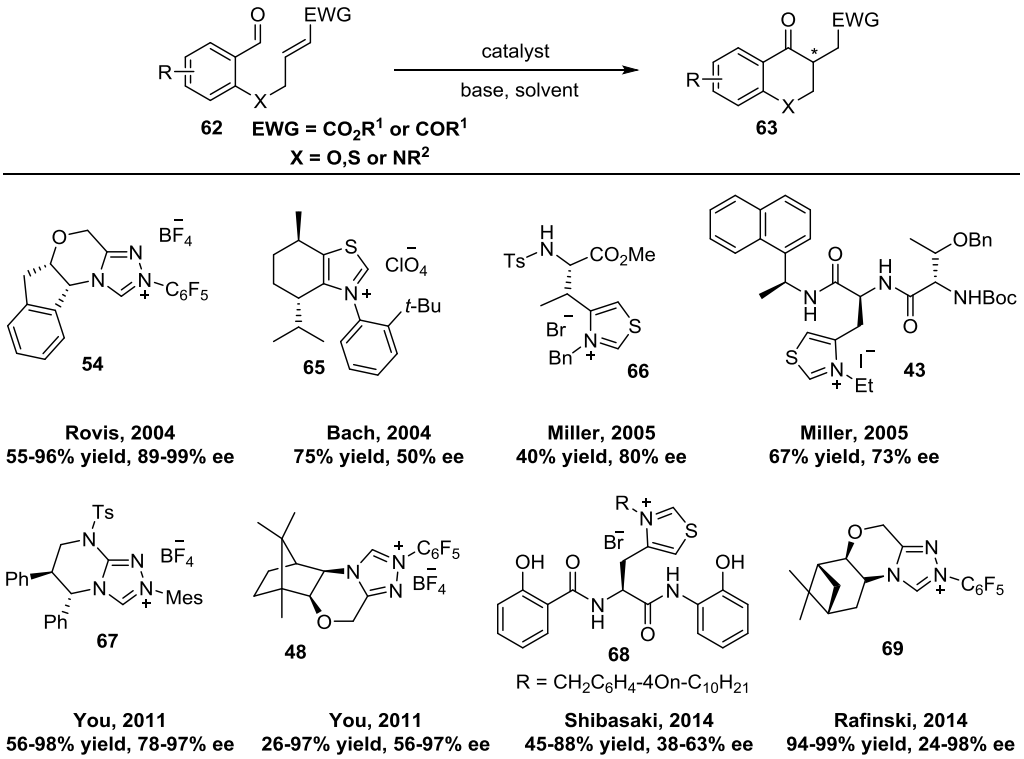
aryloxyacrylates (n = 0) occurred in the absence of base under reflux conditions to afford the furanone derivatives in good yields. The successful formation of **63** from **62** under NHC-catalysis produced a key interest to design various novel chiral NHC precursors that made it possible to establish enantioselective Stetter reaction. In this context, Ender and colleagues in 1996 reported the first enantioselective version of intramolecular Stetter reaction using chiral triazolium salt **64** (Scheme 1.22, Eq. 15).[25b] The various 2-formylaryloxy crotonates **62** endure NHC-catalyzed cyclisation reaction to afford the desired chromanones in average yield and enantioselectivity.



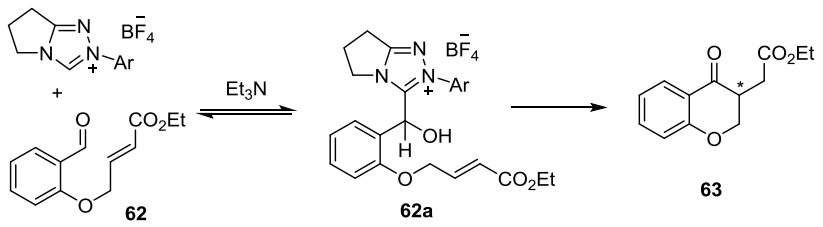

**Scheme 1.22** Seminal intramolecular Stetter reaction

Since the fruitful reports of enantioselective intramolecular Stetter reaction, there has been a significant advancement in this area with a primary focus on the development of new NHC precatalysts. Furthermore, in this context the Rovis, Bach, Miller, You, Shibasaki and Rafinski groups have made great contribution in this arena through developing novel chiral NHC catalysts (Scheme 1.23).[26] The cyclisation of substrate **62** drived from salicylaldehyde furnished chromanone **63** has chosen a typical reaction for comparing the catalytic efficiency. Importantly, Smith and colleagues examine the importance of N-aryl moiety attributed to triazolium based precatalyst in benzoin condensation and Stetter transformation. A variety of tetrahedral intermediates

generated by nucleophilic addition of free carbene on aldehyde **62** were extracted and analyzed. It was determined that formation of **62a** was a reversible process, whereas generation of Stetter product **63** from **62a** was a slow and irreversible process under the reaction condition (Scheme 1.24).[27a] In addition, the best results of intramolecular Stetter reaction was observed by using pentafluoroaryl substituted triazolium precatalyst and triethylamine as a base.

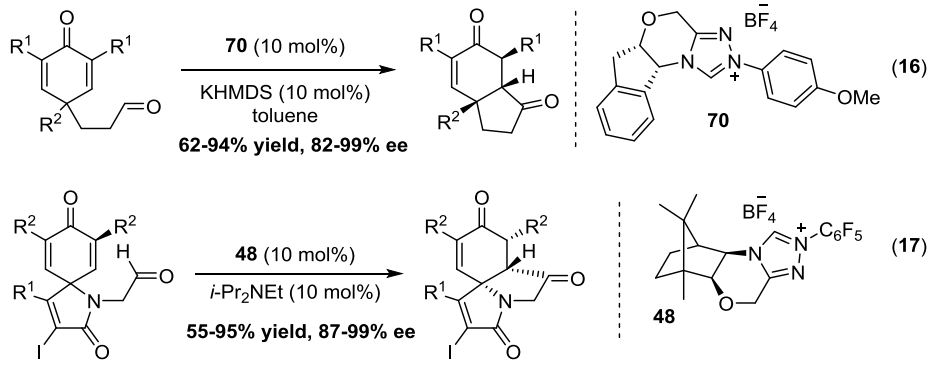



**Scheme 1.23** Variation of chiral-NHCs for asymmetric intramolecular Stetter reaction



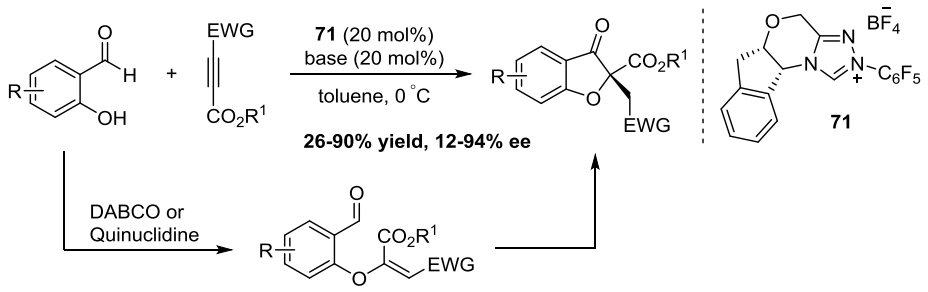

**Scheme 1.24** Aldehyde-NHC adducts isolation for intramolecular Stetter transformation

In 2006, Rovis and Liu reported the carbene catalyzed desymmetrization of cyclohexadienones to furnish hydrobenzofurans by virtue of intramolecular Stetter reaction in good enantioselectivity and diastereoselectivity (Scheme 1.25, Eq. 16).[27b] The carbene generated from the aminoindanol based 4-methoxyaryl-substituted chiral triazolium salt **70** showed the superior reactivity for this intramolecular Stetter reaction. Furthermore, You and colleagues exposed a similar strategy for desymmetrization of cyclohexadienone analogues employing camphor-based triazolium catalyst **48** to access tricyclic carbocycles bearing three contiguous stereocenters with good yields and enantioselectivity (Scheme 1.25, Eq. 17).[27c]



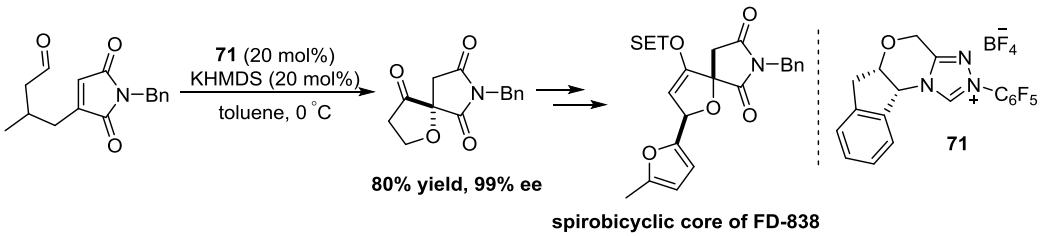

**Scheme 1.25** Desymmetrization of cyclohexadienone derivatives through intramolecular Stetter reaction

In 2010, Rovis et al. reported a sequential one-pot multicatalytic enantioselective reaction of salicylaldehydes with electrophilic alkynes, which proceeds through Michael-intramolecular stetter pathways and furnished benzofuranone derivatives in positive yields and great enantioselectivity. Herein, a base catalyzed the Michael reaction followed by intramolecular stetter reaction catalyzed by chiral NHCs (Scheme 1.26).[28a] In terms of stereoselectivity, the Michael-Stetter one pot technique was found to be preferred over two-step methods.



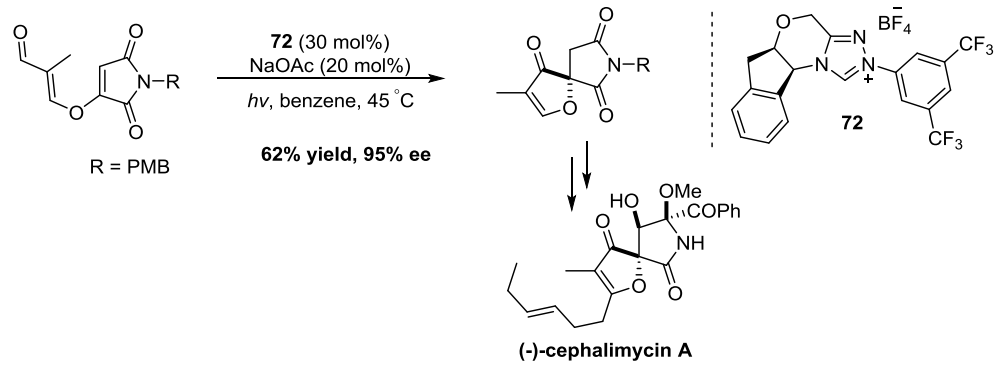

**Scheme 1.26** A cascade oxa-Michael intramolecular Stetter reaction

Recently, Orellana and Rovis developed the enantioselective Stetter transformation for aldehyde bearing an N-benzyl protected maleimide using aminoindanol based chiral NHC **71** to furnish the spirofuranone in 80% yield and 99% ee (Scheme 1.27).[28b] Importantly, this methodology was also elongated for construction of spirocyclic core present in antibiotic FD-838.




**Scheme 1.27** Access to spirobicyclic frame of FD-838 through intramolecular Stetter transformation

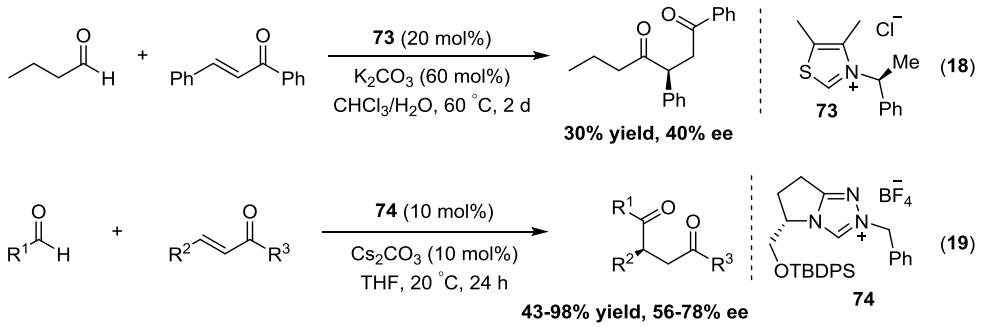
Furthermore, Lathrop and Rovis developed a tandem process involving UV irradiation followed by intramolecular Stetter reaction using chiral triazolium salt **72** of aldehyde derivative to furnish the spirocyclic furanone in moderate yield and exemplary enantioselectivity (Scheme 1.28).[28c] Moreover, this methodology was enforced for the total synthesis of (–)-cephalimycin A.




**Scheme 1.28** A cascade photoisomerization-Stetter reaction

### (b) Intermolecular Stetter Reaction

Even after Stetter's pioneering work in 1970s, a number of new coupling partners in Stetter reaction have been extensively studied.[10] At first, the catalyst designing and reaction procedures have been developed for the enantioselective intramolecular transformations because they diminish reactivity and selectivity issue compared to the intermolecular methodology. Consequently, the advancement on intermolecular Stetter reaction compared to intramolecular Stetter is less due to lower reactivity of β-substituted Michael acceptors in the intermolecular process. However, the recent evolutions on intermolecular Stetter reaction are mainly focused on its enantioselective variant. In 1993, Enders et al. developed the first enantioselective intermolecular Stetter transformation between n-butanal and chalcone using chiral thiazolium catalyst **73** to furnish 1,4-diketone in poor enantioselectivity and yield (Scheme 1.29, Eq. 18).[29a] Recently, they have reported enantioselective intermolecular Stetter methodology of aryl aldehydes and chalcone employing a new carbene drived from triazolium precursor **74** to afford desired products in moderate yields and enantioselectivity (Scheme 1.29, Eq. 19).[29b] Interestingly, the enhancement of enantioselectivity up to 99% ee in product through recrystallization was feasible.



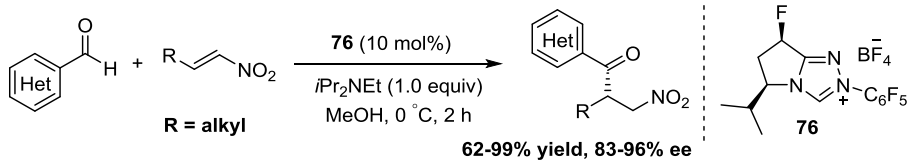

**Scheme 1.29** Asymmetric intermolecular Stetter transformation of aldehyde and chalcone

Independent scrutiny by Rovis and colleagues have made significant progress in the asymmetric intermolecular Stetter reaction. They have disclosed the coupling of glyoxamide analogues derived from morpholine as aldehyde ingredient and alkylidene malonate as Michael acceptor using the phenylalanine based triazolium salt **75** to furnish the desired Stetter product in valuable yield with excellent enantiomeric excess (Scheme 1.30).[30a]


**Scheme 1.30** Asymmetric intermolecular Stetter reaction using alkylidene malonate

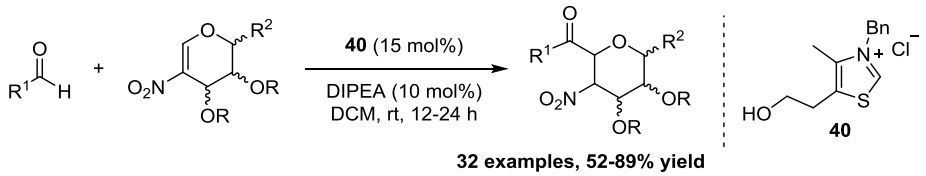
Moreover, Rovis and colleagues developed a general asymmetric intermolecular Stetter method with broad scope by employing hetero-aromatic aldehydes and nitroalkenes as a suitable Michael acceptors in existence of unfamiliar chiral NHC salt **76** (Scheme 1.31).[30b] Importantly, the fluoro and isopropyl substituents in **76** increased the stereoselectivity of the Stetter product. The fluorine effect was further supported by DFT calculations, which showed that fluorine enhanced the electrostatic interaction between acyl anion intermediate and the nitroalkene. The

use of hetero-aromatic aldehyde was necessary to obtain excellent level of reactivity and selectivity.




**Scheme 1.31** Asymmetric intermolecular Stetter reaction using nitroalkene

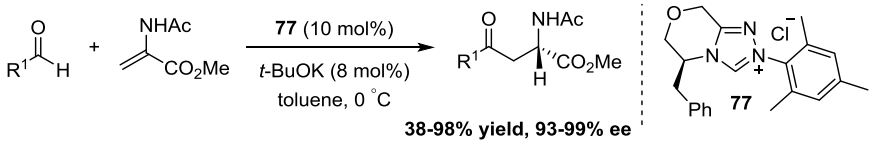
Additionally, Liu and colleagues demonstrated a intermolecular Stetter approach for the reaction of aldehydes with 2-nitroglucal using thiazolium salt **40** to furnish β-selective C-glycoside in moderate yields (Scheme 1.32).[31a] Several (hetero)aromatic aldehydes as well as aliphatic aldehydes afforded the desired Stetter product under the optimized reaction conditions but the nitro-eliminated C-glycosides were accessed when the reaction was carried out in presence of cesium carbonate as the base.




**Scheme 1.32** Intermolecular Stetter reaction using 2-nitroglucal

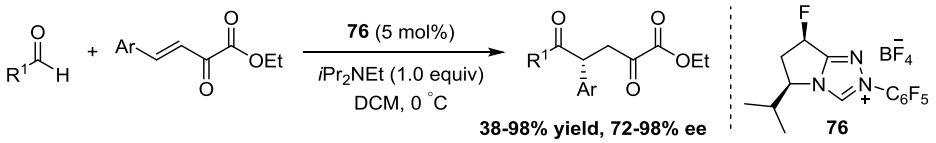
In 2011, Glorius et al. reported an enantioselective variant of intermolecular Stetter transformation by employing aldehyde with *N*-acylamido acrylate as the Michael acceptor in presence of triazolium salt **77** to furnish α-amino acid derivatives in excellent yield and enantioselectivity (Scheme 1.33).[31b] Notably, in this transformation enantioinduction occurred due to enantioselective protonation of enolate intermediate, which was generated by conjugated attachment of the acyl anion with Michael acceptor. In this reaction, the free carbene produced by triazolium salt **77** derived from

L-phenylalaninol delivers best result and low amount of base correlated to the NHC precursor was the secret to successful enantioselectivity.



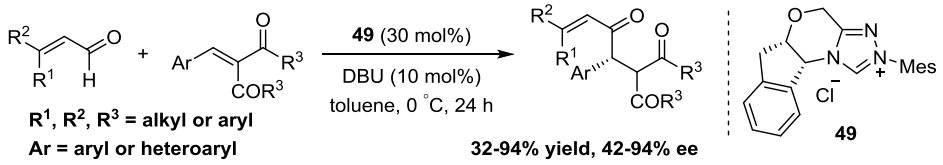

**Scheme 1.33** Asymmetric intermolecular Stetter transformation using *N*-acylamido acrylate

Furthermore, Gravel and co-workers expanded the usage of fluorinated triazolium salt **76** in synthetic chemistry, which was initially matured by Rovis research group.[30b] They employed β,γ-unsaturated α-ketoesters as Michael acceptors to provide enantioselective 1,2,5-tricarbonyl compounds through intermolecular Stetter pathway (Scheme 1.34).[32a] The reaction afforded the desired product in excellent yields and enantioselectivity which were susceptible for a variety of synthetic manipulations.



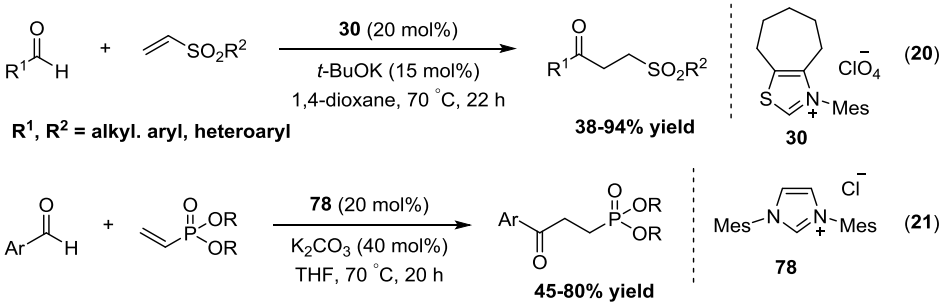

**Scheme 1.34** Asymmetric Stetter reaction employing β,γ-unsaturated α-ketoesters

Moreover, Chi and colleagues developed carbene catalyzed enantioselective intermolecular Stetter transformation between α,β-unsaturated aldehydes and α-acyl chalcones using aminoindanol-derived triazolium salt **49** to furnish desired triketones in reasonable yields with high enantioselectivity (Scheme 1.35).[32b] A wide variety of β-alkyl, β-aryl, and β,β-disubstituted enals worked well and provide corresponding desired product under the reaction condition.




**Scheme 1.35** Asymmetric Stetter reaction of α-acyl chalcones

Furthermore, the NHC-catalyzed highly selective coupling of aldehydes and α,β-unsaturated sulfones through intermolecular Stetter approach was recently reported by Biju research group. The free carbene produced from thiazolium salt **30** catalyzed the reaction to afford γ-keto sulfones in high yields (Scheme 1.36, Eq. 20).[33a] Subsequently, they reported intermolecular Stetter transformation catalyzed by NHC between aldehydes and vinylphosphonates to furnish γ-ketophosphonates in good yields (Scheme 1.36, Eq. 21).[33b] Notably, the imidazolium salt **78** was found to be best catalyst for this transformation.

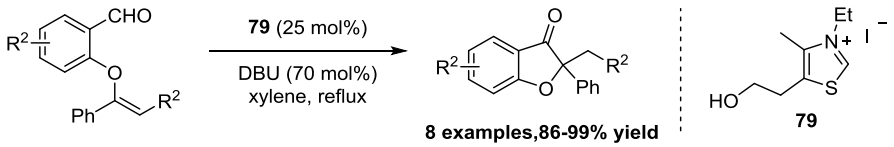



**Scheme 1.36** Intermolecular Stetter reaction using vinylsulfones or vinylphosphonates

### (C) Hydroacylation Reaction of Double and Triple Bonds

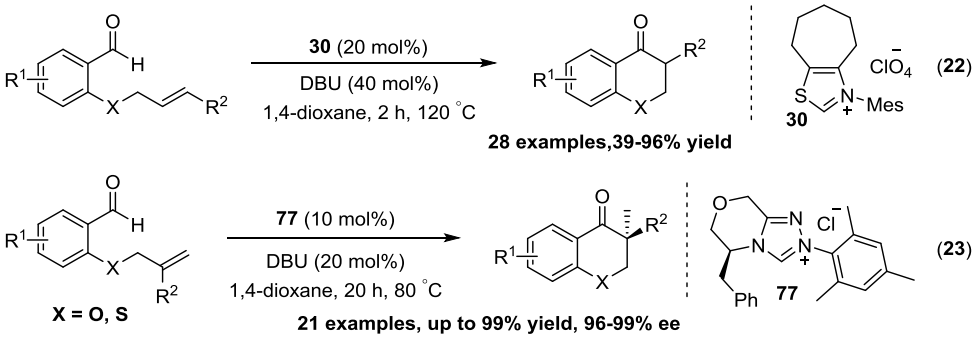
Stetter reaction involves umpolung of aldehydes and subsequent addition of *in situ* formed nucleophilic Breslow intermediate to activated (electron-poor) carbon-carbon multiple bonds. Moreover, the NHC-catalyzed hydroacylation reactions involve umpolung of aldehydes and subsequent addition to unconventional electrophiles for example unactivated

C-C multiple bonds were reported recently. In 2008, She and co-workers demonstrated the NHC-catalyzed intramolecular transformation, which involve nucleophilic addition of Breslow intermediate to enol ethers employing readily available thiazolium salt **79** to furnish benzofuranones in excellent yields (Scheme 1.37).[34a] The proposed mechanism of this transformation involves the intramolecular addition of acyl anion equivalent to C-C double bond of enol ether. Importantly, this was not clear that nucleophilic addition proceeds through concerted or stepwise pathway involving an oxonium species.




**Scheme 1.37** NHC-catalyzed hydroacylation of enol ethers

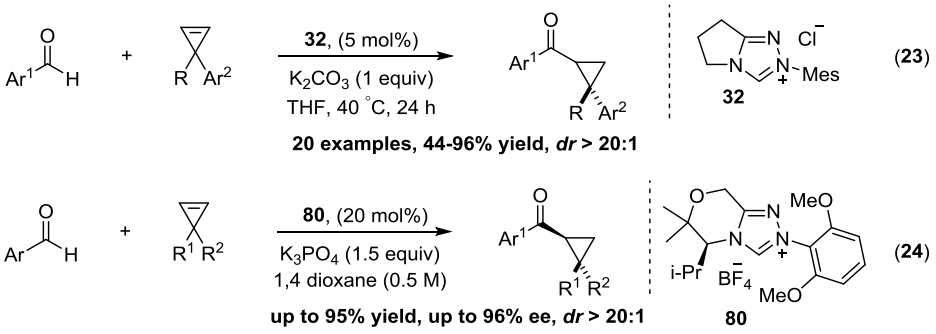
Subsequently, Glorius research group in 2009 developed NHC-mediated intramolecular hydroacylation transformation of unactivated alkenes. In this, the intramolecular cyclization of 2-allyloxy benzaldehydes catalyzed by thiazolium salt **30** furnished desired chromanones in good yields (Scheme 1.38, Eq. 22).[34b] This unique strategy represents the first NHC-organocatalyzed transition-metal-free intramolecular hydroacylation transformation and was also applied to a wide variety of substrates. Furthermore, they uses this approach to synthsize enantioselective chromanones containing all-carbon quaternary centers using chiral triazolium catalyst **77** to access desired product in excellent enantioselectivity (Scheme 1.38, Eq. 23).[34c] Various electronically different 2-allyloxy benzaldehyde derivatives were well tolerated in this reaction.



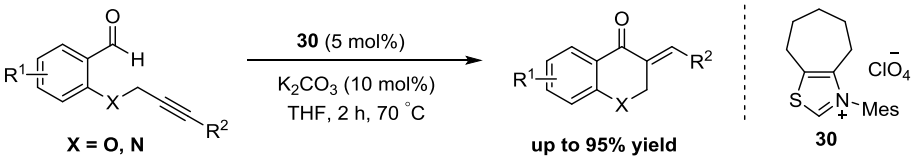

**Scheme 1.38** Hydroacylation reaction of unactivated double bonds catalyzed by NHC

Moreover, Glorius et al. disclosed the first intermolecular hydroacylation transformation of unactivated double bonds. The reaction of aromatic aldehydes and cyclopropenes employing triazolium catalyst **32** furnished the acyl cyclopropanes in moderate yields with high diastereoselectivity under mild conditions (Scheme 1.39, Eq. 23).[35a] Importantly, mechanistic experiments conclude that reaction proceeds through a concerted syn hydroacylation mechanism. Subsequently, they demonstrated the enantioselective intermolecular hydroacylation of cyclopropenes employing electron-affluent chiral triazolium salts **80** possessing substitution at *ortho, ortho'*-postion to deliver the desired acyl cyclopropanes in good yields and enantioselectivity (Scheme 1.39, Eq. 24).[35b]

In 2010, the Glorius group disclosed the intramolecular hydroacylation reaction of unactivated triple bonds. The carbene formed by thiazolium salt **30** catalyzed the reaction of unactivated internal alkynes to afford benzylidene chromanones as a single isomer, which possess synthetically relevant exocyclic olefin group (Scheme 1.40).[36a] Various substrates with electron-donating and-departing groups on both aryl bands were appropriate, providing good yields and also this methodology was further applied to access quinolin-4-ones.

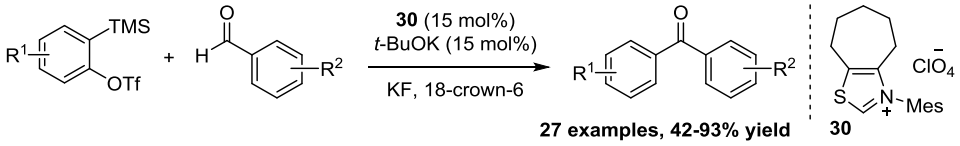



**Scheme 1.39** Hydroacylation of cyclopropenes catalyzed by NHC




**Scheme 1.40** NHC-catalyzed hydroacylation of unactivated internal alkynes

Recently, Biju and Glorius reported a transition-metal-free methodology catalyzed by NHC for intermolecular hydroacylation of arynes. This reaction confess the unusual resistance of nucleophilic carbenes with highly electrophilic arynes. The treatment of various aldehydes with *in situ* generated aryne from 2-trimethylsilylaryl triflate in presence of carbene formed by deprotonation of thiazolium salt **30** using potassium *tert*-butoxide provided numerous aryl ketones in valuable yields (Scheme 1.41).[36b]




**Scheme 1.41** NHC-mediated hydroacylation of arynes

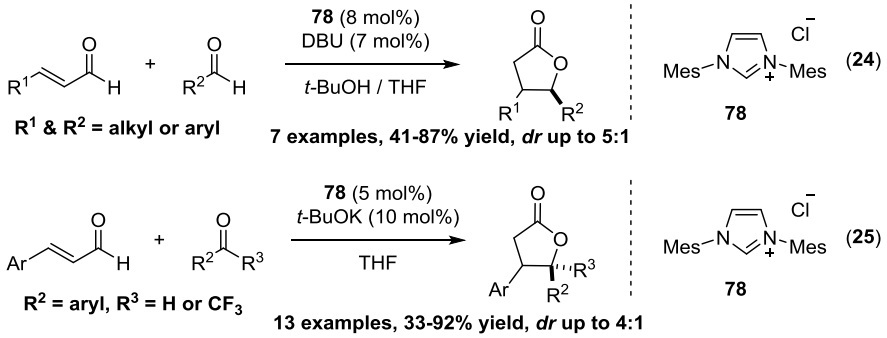
### 1.5.2 Reaction involving NHC-Bound Homoenolate Intermediate

The areas of NHC-organocatalysis remain limited with the Breslow intermediate based reactivity for a very long duration (1943-2004). However, this development has started

to attract more attention of researchers to investigate the various other modes of reactivity by developing new catalyst. Accordingly, the extended Breslow intermediate known as homoenolate intermediate can be generated by employing the α,β-unsaturated aldehydes. Herein, we will focus on the NHC-Bound homoenolate intermediate which considered as a $d^3$-nucleophile and thus constitutes an $a^3$-$d^3$ coupling.

**(a) Functionalization of Enals via Annulative Process**

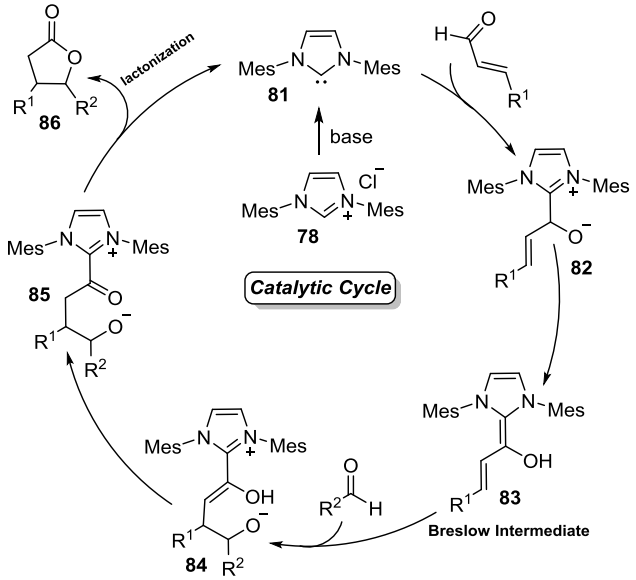
In 2004, the Glorius and the Bode research group independently demonstrated the generation of homoenolate equivalents from α,β-unsaturated aldehydes employing bismesityl imidazolium precatalyst **78**, which further couple with aldehyde leading to the formation of γ-butyrolactones in good yields and diastereoselectivity (Scheme 1.42).[37] Moreover, Glorius research group reported an asymmetric transformation employing trifluoromethyl ketones in place of aldehyde as electrophile.




**Scheme 1.42** Annulation of enals with aldehydes/activated ketones catalyzed by NHC

A plausible mechanistic pathway for this category of conversion is presented in Scheme 1.43. Firstly, the coupling of free carbene and enal in 1,2-fashion generates tetrahedral

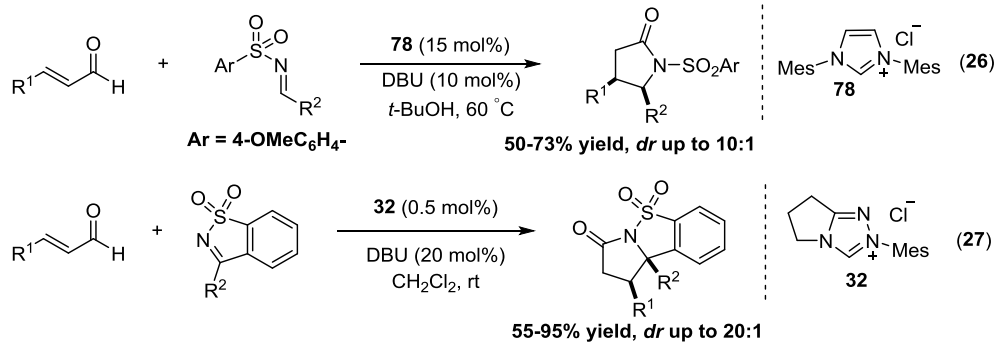
intermediate **82** followed by proton transfer provides conjugated enaminol **83**, usually assigned as homoenolate equivalent. The present $d^3$-nucleophile **83** adds to an electrophile to form the intermediate **84**, which can then tautomerize to give alkoxide intermediate **85** and subsequent intramolecular cyclization provided γ-butyrolactone **86** with regeneration of NHC catalyst.




**Scheme 1.43** Plausible mechanism for γ-butyrolactone synthesis

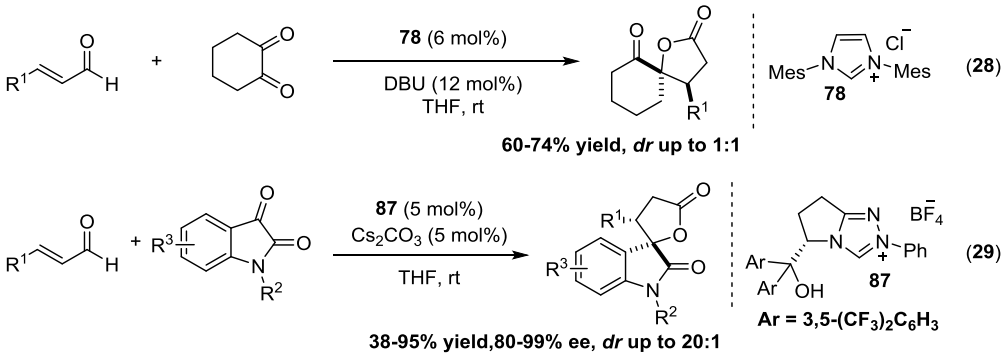
In 2005, Bode and He developed the annulation of enals and N-sulfonyl imines using bismesityl imidazolium precatalyst **78** for the synthesis of γ-lactams in good yields and modest diastereoselectivity (Scheme 1.44, Eq. 26).[38a] A wide range of aromatic enals were tolerated under the reaction condition. However, the variation of imines has limited scope because in several cases the imines underwent irreversible addition to the nucleophilic carbene which leads in cut off the catalytic cycle. Subsequently, they reported the annulation of enals with cyclic sulfonylketimines using catalyst **32** to furnish cis-isomers in quantitative yield with excellent diastereoselectivity (Scheme 1.44, Eq. 27).[38b] The issue associated with irreversible binding of acyclic N-sulfonyl

imines-catalyst was overcome using this cyclic variant. Notably, a wide variety of enals as well as saccharin-derived ketimines were tolerated under the reaction condition.



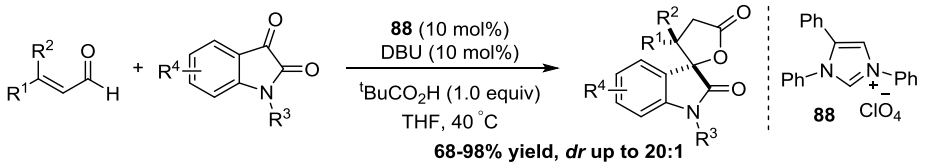

**Scheme 1.44** NHC-catalyzed annulation of enals with imines

In 2006, the Nair research group demonstrated the coupling of homoenolate equivalent generated from enals and 1,2-dicarbonyl to produce spiro γ-lactones in the presence of 1,3-dimesitylimidazol-2-ylidene precatalyst **78**. Notably, 1,2-cyclohexanedione furnished the spirocyclohexanone products in moderate yields with low diastereoselectivity (1:1) (Scheme 1.45, Eq. 28).[39a] In related context, Ye research group developed enantioselective annulation transformation between enals and isatins to afford enantioriched spirooxindole γ-lactone using chiral triazolium precatalyst **87**. The key for excellent diastereo and enantio-selectivity in most cases is the hydrogen-bonding interaction of NHC with the isatins (Scheme 1.45, Eq. 29).[39b]



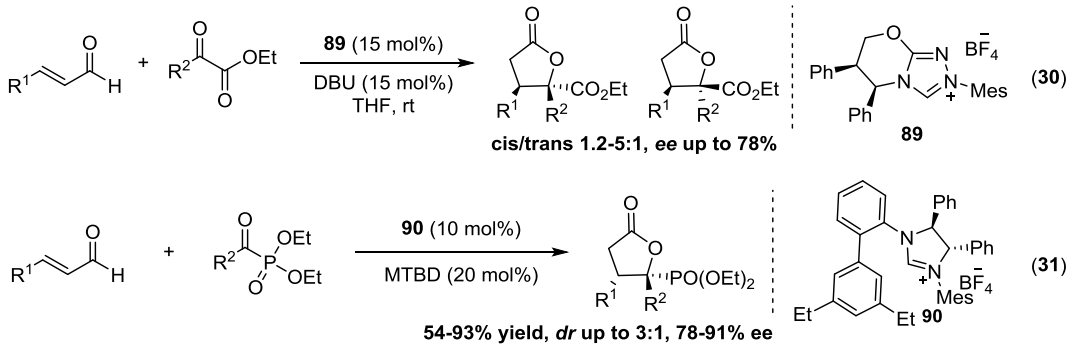

**Scheme 1.45** Annulation of enals with activated ketones catalyzed by NHC

Recently, the Glorius research group developed a dual NHC/ Brønstead acid catalyzed annulation reaction between β,β-disubstituted enals and isatins to produce spirocyclic lactones (Scheme 1.46).[39c] A wide range of aryl and aliphatic substituted enals along with different substitution patterns on isatin moiety were tolerated under the reaction condition. Gratifyingly, the use of Brønstead acid in this transformation increase yield as well as diastereoselectivity.



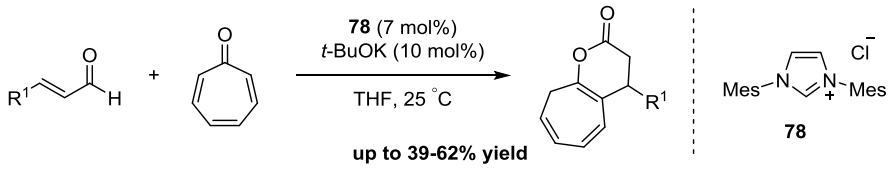

**Scheme 1.46** NHC-catalyzed transformation of β,β-disubstituted enals and isatins

In 2008, You and co-workers exposed that ethyl glyoxalate derivatives with *in situ* generated homoenolate equivalent undergoes annulation transformation using chiral triazolium precatalyst **89** to furnish the γ-lactones in good enantioselectivity for the trans isomer (Scheme 1.47, Eq. 30).[40a] Moreover, Scheidt and colleagues developed an enantioselective homoenolate annulation between enals and acyl phosphonates using chiral imidazolidinium precatalyst **90** to generate γ-lactone in good yields and enantioselectivity (Scheme 1.47, Eq. 31).[40b]




**Scheme 1.47** NHC-catalyzed annulation of β,β-disubstituted enals with isatins

Moreover, Nair and co-workers reported [8+3] annulation between enals and tropone catalyzed by NHC to furnished fused δ-lactone in good yields (Scheme 1.48).[41a] Mechanistically, the transformation advanced by conjugate addition of generated homoenolate equivalent from enals to tropone at more electrophilic position resulting the generation of alkoxide which then undergoes cyclization to furnish the desired product.

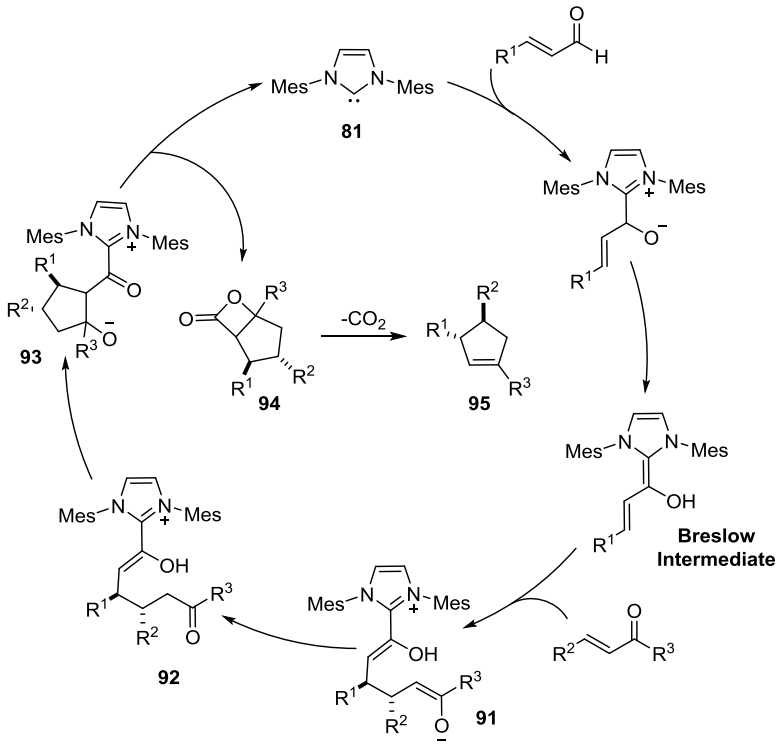



**Scheme 1.48** NHC-mediated transformation of enals with tropone

Apart from heterocycle synthesis, the carbocycles were also synthesized using homoenolate equivalent formed by NHC. In this context, Nair and colleagues in 2006 reported the annulation of enals and chalcones to provide 1,3,4-trisubstituted cyclopentenes (Scheme 1.49).[41b] The transformation concludes in the successful synthesis of cyclopentenes rather than desired cyclopentanones.

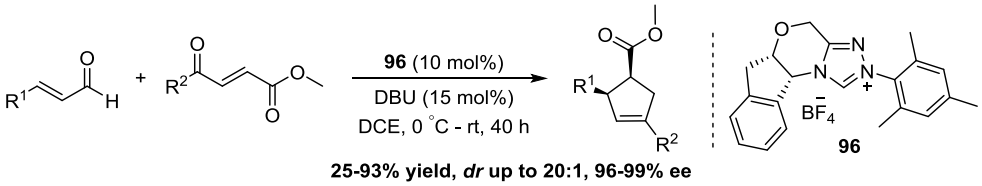
A plausible mechanism suggested that reaction initiates with 1,2-addition of NHC to *trans*-cinnamaldehyde gives rise to the extended Breslow intermediate and subsequent 1,4-addition to chalcone provides the enolate intermediate **91**, which further tautomerize to give ketone **92**. This **92** inttermediate underwent an intramolecular aldol reaction by enol-azolium to produce alkoxide **93**, followed by cyclization of **93** with release of catalyst to give β-lactone **94**, which further decarboxylates to produce the desired cyclopentene product **95** (Scheme 1.50).


**Scheme 1.49** NHC-catalyzed annulation of enals with chalcones



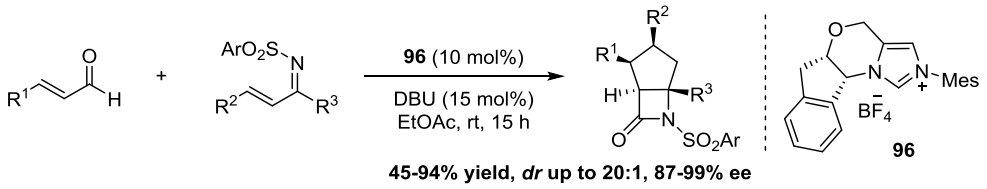

**Scheme 1.50** Plausible mechanism for cyclopentene production

Subsequently, Bode research group developed the enantioselective synthesis of cyclopentenes from enals and 4-oxoenoates using the chiral aminoindanol based triazolium precatalyst **96** (Scheme 1.51).[42a] The transformation furnished the desired product in excellent enantio- and diastereo-selectivity. Importantly, this approach provides cis-isomer in contrast with Nair's approach, which give trans-isomer.



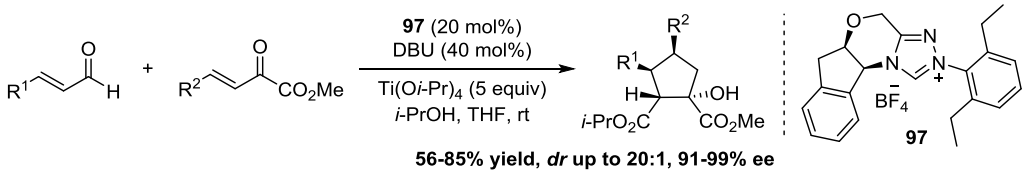

**Scheme 1.51** Annulation of enals and 4-oxoenoates catalyzed by NHC

In 2008, He and Bode demonstrated the conjugate addition of homoenolate to α,β-unsaturated ketimines to access cyclopentane merged β-lactam in high yields and enantioselectivity, and good to excellent diastereoselectivity (Scheme 1.52).[42b] This transformation is noteworthy as it favours the strained β-lactam evolution, in contrast to the chalcone system (Scheme 1.49), which generate the cyclopentenes by decarboxylation. Importantly, a wide variety of enals as well as imines were tolerated under the reaction condition.




**Scheme 1.52** NHC-mediated annulation of enals and ketimines

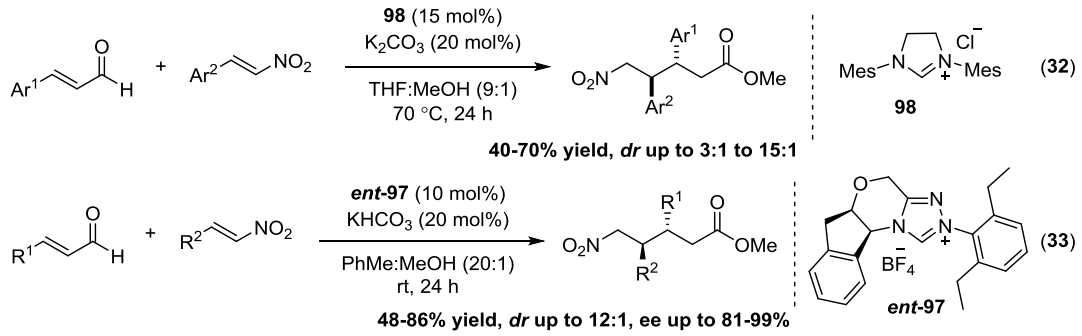
Scheidt et al. in 2011 developed a NHC/Lewis acid catalyzed transformation between enals and α-keto β,γ-unsaturated esters to form highly enantio- and diastereo-selective cyclopentane derivatives in good yields (Scheme 1.53).[42c] In this process linear ester was not formed. Importantly, the enals with alkyl and aryl substitution were well tolerated under the reaction condition but requires the use of aryl esters.




**Scheme 1.53** Annulation of enals and α-keto β,γ-unsaturated esters catalyzed by NHC

**(b) Functionalization of Enals via Non-Annulative Process**

In 2009, Nair and colleagues developed the NHC-mediated homoenolate addition to nitroalkenes to give δ-nitro esters in good yields with moderate diastereoselectivity (Scheme 1.54, Eq. 32).[43a] A wide range of aryl enals as well as nitrostyrene derivatives were well tolerated in the reaction. Moreover, Liu and co-worker exposed the enantioselective homoenolate attachment of enals with nitroalkene using chiral NHC precatalyst ***ent*-97** to furnished desired δ-nitro ester in reasonable yields and enantioselectivity, with moderate to good diastereoselectivity (Scheme 1.54, Eq. 33).[43b] A wide spectrum of aliphatic and aryl enals along with various nitrostyrene analogues, including nitro dienes and nitro enynes worked well in this reaction.

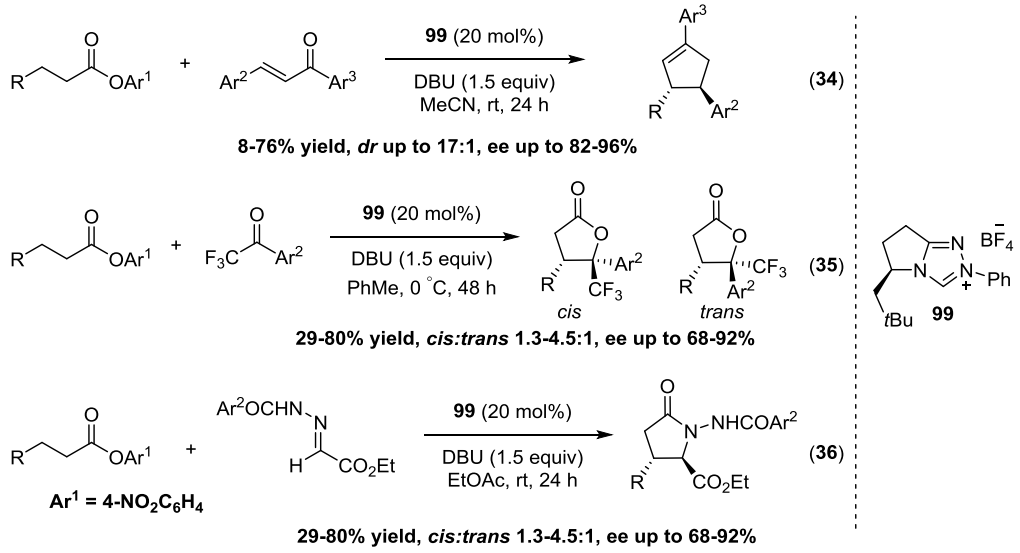



**Scheme 1.54** NHC-catalyzed access to δ-nitro esters

**(c) Alternate Access to Homoenolate Intermediate**

Chi and colleagues in 2013 disclosed that NHC-bound homoenolate intermediate can be generated form substrates other than enals, by employing an efficient bench-stable saturated esters via deprotonation at the $sp^3$ β-carbon (Scheme 1.55, Eq. 34).[44] This reaction affords the desired cyclopentene product in favorable yields and diastereoselectivity, with superb enantioselectivity. As homoenolate precursor, various aryl and aliphatic esters were used and bis-aryl enones were employed as Michael

acceptor. In addition, this homoenolate intermediate has been shown to annulate more electrophiles like trifluoromethyl ketones and hydrazones to furnished enantioenriched γ-lactones and γ-lactams respectively in valuable yields and diastereoselectivity (Scheme 1.55, Eq. 35 and 36).[44] This breakthrough is marked as it functionalizes a typically unreactive β-carbon of saturated ester and thus broadens the scope of NHC-mediated transformations to a field that is commonly associated with metal-mediated C-H activation.




**Scheme 1.55** NHC-catalyzed β-activation of saturated esters

### 1.5.3 Reaction involving NHC-Bound Enolate Intermediate

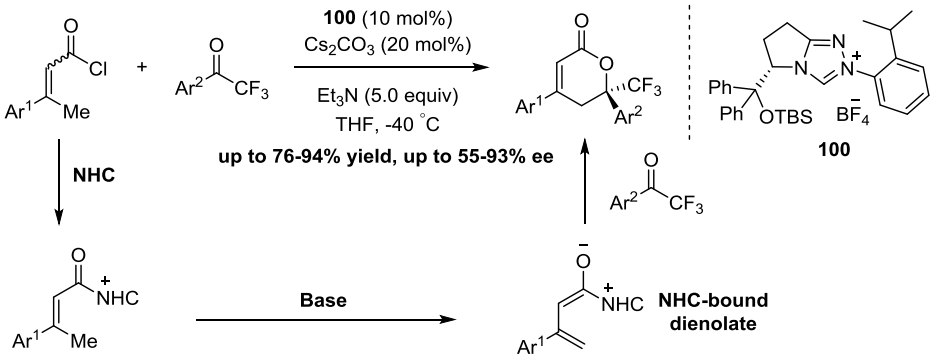
NHC-catalyzed generation and related chemistry of enolate intermediate is disclosed in details in Chapter 2.

### 1.5.4 Reactions involving NHC under Oxidative Conditions

NHC-catalyzed generation of reactive intermediates under oxidative condition and their subsequent reactivity is demonstrated in details in Chapter 3.

### 1.5.5 Reactions involving NHC-Bound Azolium Dienolates

A recent breakthrough in NHC-organocatalysis is the NHC-bound dienolates, which engage in systematic [4+2] cycloaddition transformation by the activation of remote C($sp^3$)-H bond to access six membered heterocycles and carbocycles. In 2011, the Ye research group demonstrated the initial access to catalytically produced NHC-bound dienolates from α,β-unsaturated acyl chlorides, followed by interception with trifluoromethyl ketones to furnish the enantioenriched trifluoromethyl substituted δ-lactones in good yields with excellent enantioselectivity (Scheme 1.56).[45a]

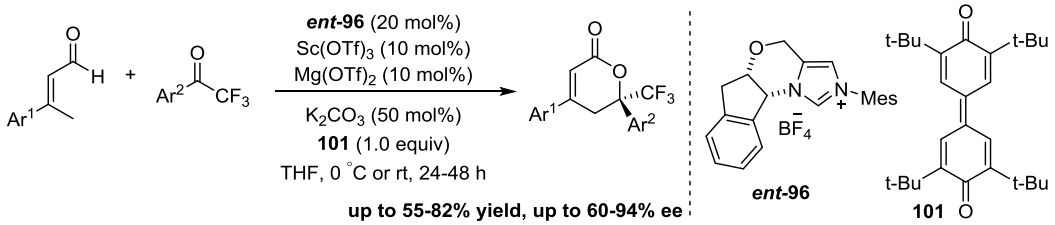



**Scheme 1.56** Generation of NHC-bound dienolate from unsaturated acylchlorides

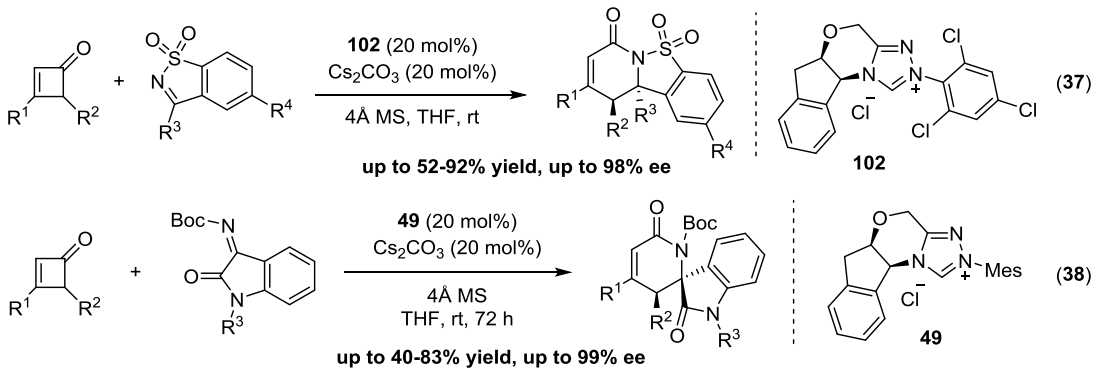
The reaction provide best results with carbene generated from bicyclic triazolium precatalyst **100**, cocatalytic amounts of $Cs_2CO_3$ in excess $Et_3N$. In addition, the other activated ketones such as isatins were also found to be suitable under the optimized condition for the enantioselective synthesis of spirocyclic oxindole-δ-lactones.

In 2012, Chi and co-workers developed the NHC-mediated [4+2] cycloaddition reaction between β,β′-disubstituted enals and trifluoromethyl ketones through NHC-bound dienolate intermediate employing external oxidant **101** (Scheme 1.57).[45b] Importantly, the generally observed homoenolate reactivity in typical NHC-mediated enal reactions

was squashed by inclusion of an additional group at β-carbon of enal. The variation of both the enals and trifluoromethyl ketones worked well under the optimized condition to furnish corresponding desired lactones in positive yields with excellent enantioselectivity. In addition, very high enantioselectivity was obtained with the carbene generated from the chiral triazolium salt ***ent*-96** in combination with Sc/Mg-derived Lewis acid co-catalyst.




**Scheme 1.57** Generation of NHC-bound dienolate from unsaturated aldehyde



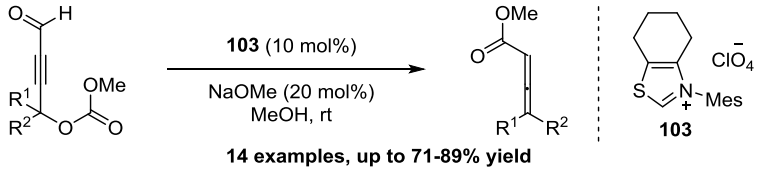

**Scheme 1.58** Generation of NHC-bound dienolate from cyclobutenones

In 2015, the same research group extended the scope to generate NHC-bound dienolate by the use of cyclobutenones (Scheme 1.58).[46] The addition of free carbene generated from the triazolium precatalyst **102/49** to cyclobutenones leads to the formation of NHC-bound dienolate intermediate through a C-C single bond cleavage. This dienolate intermediate further intercept with sulfonyl imines to furnish cyclic lactams in good yields and enantioselectivity (Eq. 37). In addition, the other imines such as isatin imines

were also favorable under the same optimized condition to afford spirolactams in satisfactory yields with superb enantioselectivity (Eq. 38).

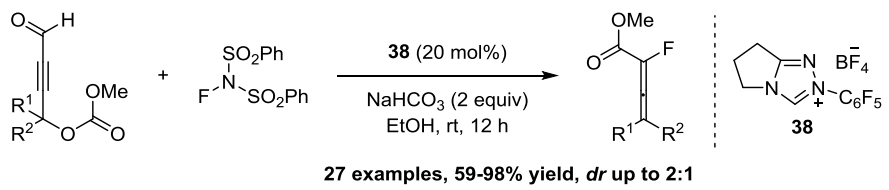
### 1.5.6 Reactions involving NHC-Bound Allenoate Intermediate

In 2012, Sun and colleagues exposed a breakthrough by NHC-mediated internal redox reaction with the isomerization of ynals to allenoates (Scheme 1.59).[47a] Alkynyl aldehydes possessing methyl carbonate at γ-position as a leaving substituent are used as the substrates in the presence of mesityl-substituted thiazolium salt **103** for excellent reactivity. Notably, the variation of alkyl and aryl substituents at the position of $R^1$ and $R^2$ worked well under the optimized condition and provided corresponding allenoates in acceptable yields.



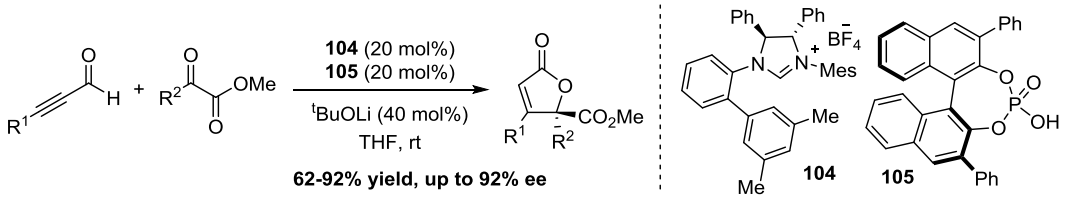

**Scheme 1.59** Generation of NHC-bound allenoates from ynals

Recently, Wang and colleagues developed the NHC-catalyzed synthesis of α-fluoroallenoate by using alkynyl aldehydes as the substrates in the presence of NFSI as a fluorinating source (Scheme 1.60).[47b] The authors proposed that reaction proceeds through a similar cumulenol intermediate, which instead of tautomerization endure nucleophilic addition to NFSI and provides product in pleasant yields with tremendous chemoselectivity.




**Scheme 1.60** NHC-catalyzed α-fluorination of alkynyl aldehydes

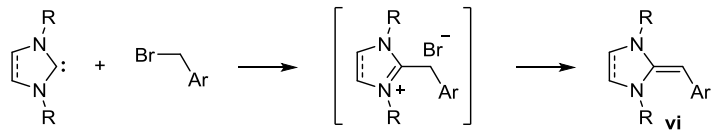
In 2014, Scheidt and co-workers demonstrated a cooperative NHC/Lewis acid mediated enantioselective [3+2] annulation between ynals and α-keto esters to afford γ-butenolides in good to high yields with excellent enantioselectivity (Scheme 1.61).[47c] The reaction afforded best enantioselectivity in the combination of C1-symmetric imidazolidinium precatalyst **104** with C2-symmetric Brønsted acid **105**. A variety of electron-deficient as well as electron-rich aromatic ynals and α-keto esters were tolerated under the reaction condition.




**Scheme 1.61** Synthesis of γ-butenolides catalyzed by cooperative NHC/Chiral Phosphate

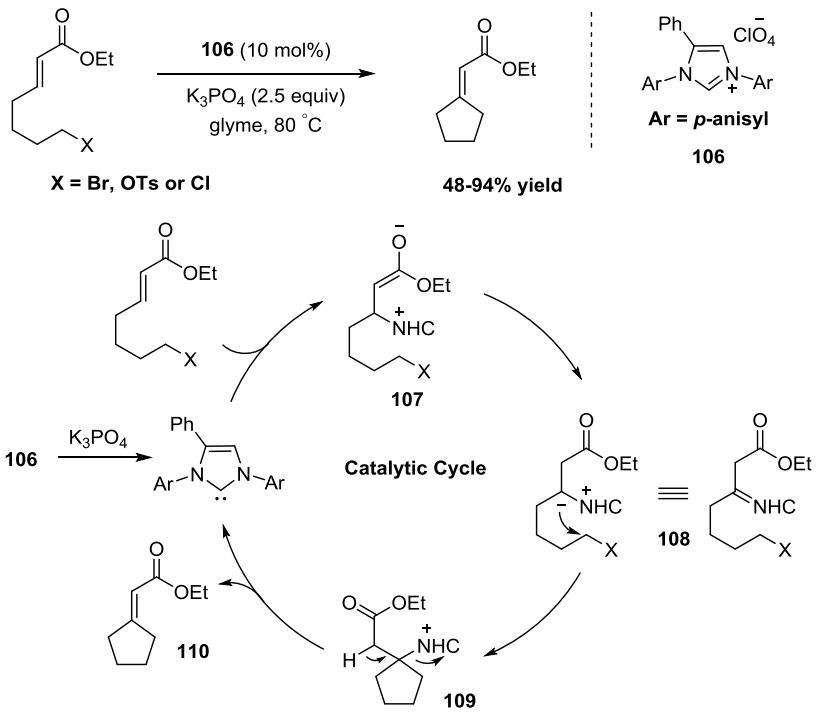
### 1.5.7 Reactions involving NHC-Bound *Deoxy*-Breslow Intermediate

The *umpolung* driven by NHCs is mostly restricted to aldehydes, and the use of other electrophiles has been given minimal attention. In this context, the group of Jacobi von Wangelin reported the isolation of *Deoxy*-Breslow intermediate **vi** through the umpolung of alkyl halides (Scheme 1.62).[48a] Furthermore, Mayr and colleagues performed kinetic measurements to investigate the nucleophilic reactivities of these *deoxy*-Breslow intermediates[48b].




**Scheme 1.62** Generation of *deoxy*-Breslow intermediate by *umpolung* of alkyl halides

In 2006, Fu et al. developed the *umpolung* of Michael acceptors employing NHCs for the intramolecular β-alkylation of α,β-unsaturated esters to afford cyclopentenes (Scheme 1.63).[49a]

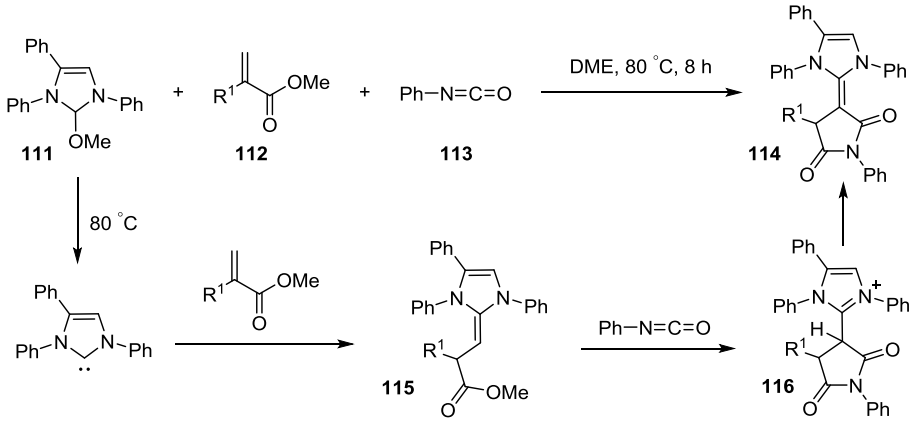



**Scheme 1.63** β-alkylation of α,β-unsaturated esters by *umpolung* of Michael acceptors

It was proposed that transformation advanced with the formation of formal *deoxy*-Breslow intermediate **108** from enolate **107**, which converts the electrophilic β-carbon to nucleophilic and subsequent cyclisation furnished the desired product. This transformation can be regarded as a NHC-catalyzed intramolecular Heck reaction. A variety of Michael acceptors like α,β-unsaturated esters, amides and nitriles worked well in the reaction condition.

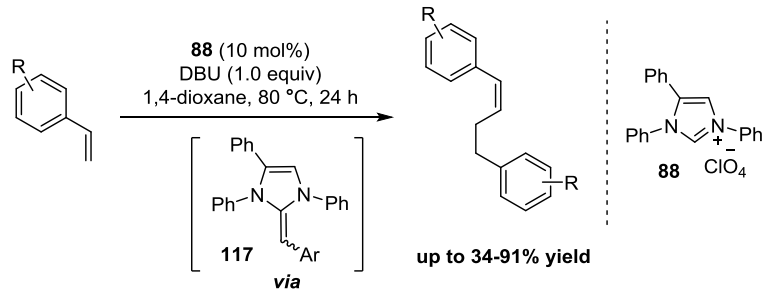
In 2012, Matsuoka et al. reported a tandem one pot three component reaction. The reaction was proceeded with the generation of *deoxy*-Breslow intermediate **115**, by the

addition of NHC to methacrylates **112**, which then undergo annulation with isocyanates **113** to afford urea derivatives **114** in good yields (Scheme 1.64).[49b]




**Scheme 1.64** Multicomponent reaction by *umpolung*/Cyclization cascade

In 2014, the Glorius research group reported the NHC-mediated tail to tail dimerization of activated styrenes in selective manner (Scheme 1.65).[49c]

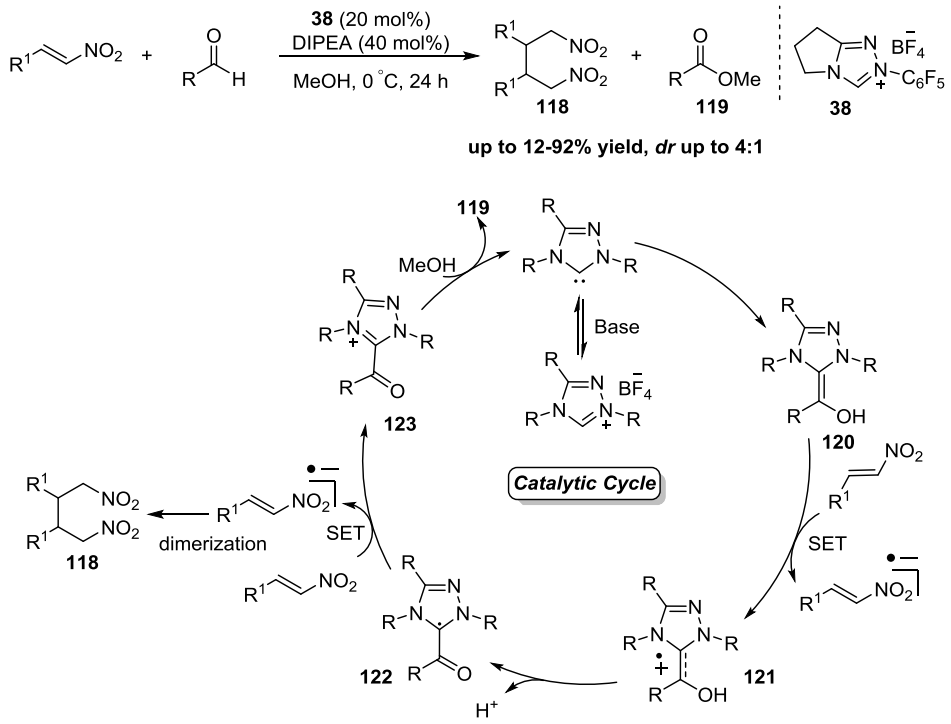



**Scheme 1.65** NHC-catalyzed *umpolung* of styrenes

It was proposed that this protocol proceeds via *deoxy*-Breslow intermediate **117**, which was isolated and characterized successfully. Styrenes bearing electron withdrawing substituent at the *para*-position of the aromatic ring and vinyl pyridines were tolerated under the optimized condition to afford the desired product.

### 1.5.8 Reactions involving Single Electron Transfer Pathways

In 2014, Chi and colleagues reported a NHC-mediated single electron methodology for dimerization of nitroalkenes (Scheme 1.66).[50a]

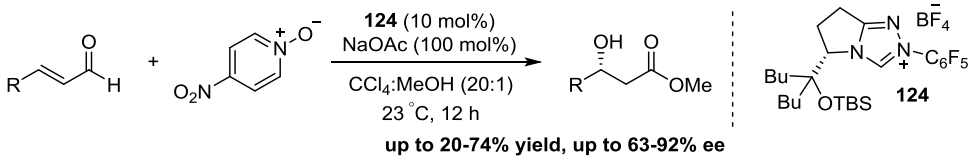



**Scheme 1.66** NHC-catalyzed dimerization of nitroalkenes by single electron transfer pathway

In this reaction the nitroalkene serves as single-electron oxidant and produce radical anion with the Breslow centered radical cation **121**, which then undergoes a deprotonation to give radical acylazolium intermediate **122**, and subsequent release of another single electron in the presence of nitro olefin to generate the acyl azolium intermediate **123**. The radical anion derived from nitroalkene couples with previously formed similar another radical anion and furnished the desired product **118**. The nucleophilic addition of methoxide ion to acylazolium provides ester product **119** with the release of carbene catalyst. Importantly, this proposed pathway is assisted by nitroalkene based radical anion EPR study. A variety of aryl or aliphatic nitroalkenes

with electronically different substitution were well tolerated under optimized condition to afford the dimerized product in moderate to good yields and diastereoselectivity. Interestingly, β,β-disubstituted nitroalkenes were also suitable in this protocol. The aromatic aldehydes were needed as an electron donor in this transformation.

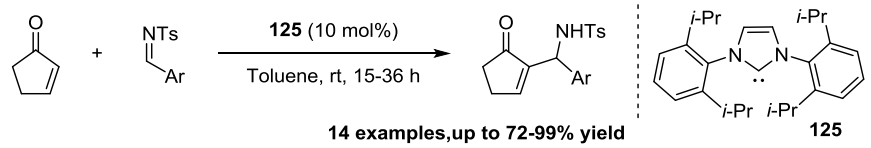
Moreover, White et al. reported β-hydroxylation of enals by single-electron oxidation of Breslow intermediate with the existence of electron deficient nitroarene as the oxidant (Scheme 1.67).[50b] It was found that aromatic and aliphatic enals were suitable to furnish β-hydroxylated products in valuable yields with good enantioselectivity.




**Scheme 1.67** NHC-catalyzed single electron transfer reaction for β-hydroxylation of enals

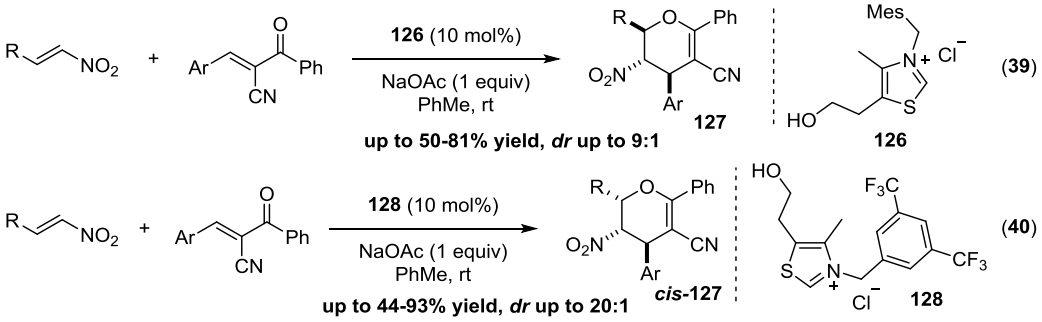
### 1.5.9 Miscellaneous Reactions

In 2007, Ye and colleagues exposed the use of NHCs as a Lewis base to develop the Morita-Baylis-Hillman (MBH) type reaction (Scheme 1.68).[51a] They reported the intermolecular coupling of cyclic enones and N-tosyl aromatic imines using NHC **125** to give the corresponding MBH adduct in good to high yields. In addition, the enantioselective variant was also disclosed, which involve the coupling of cyclopent-2-enone and N-tosylphenylmethanimine to furnish the desired MBH adduct in up to 44% enantioselectivity[51b].



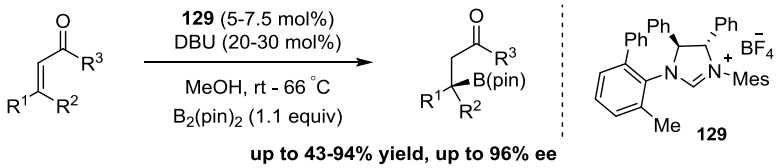

**Scheme 1.68** Morita-Baylis-Hillman transformation catalyzed by NHC

Furthermore, Ye research group in 2013 developed a [4+2] annulation between nitroalkenes and α,β-unsaturated ketone (Scheme 1.69).[52] Mechanistically, the reaction was proceeded through Rauhut-Currier type mechanism, which involve 1,4-addition of nitroalkene-carbene adduct to enone, and subsequent rearrangement of the alkyl azolium by oxygen of the enolate intermediate deliver the desired product. Notably, the use of DABCO or $PPh_3$ instead of catalyst **126** produced only the trace amount of the desired product. In addition, the switch in diastereoselectivity was observed by changing N-substituent of thiazolium salt. The formation of 2,3-trans product **127** is favored in the presence of 2,4,6-trimethylphenyl precatalyst **126** (Eq. 39), whereas electron-deficient 3,5-bis(trifluoromethyl)-phenylthiazolium **128** gives 2,3-cis product selectively (Eq. 40).



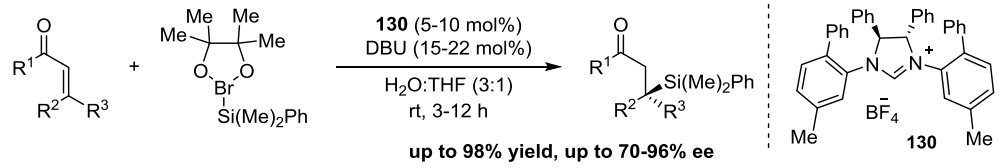

**Scheme 1.69** NHC-mediated [4+2] transformation of nitroalkenes and oxodienes

In 2009, the Hoveyda research group developed the NHC-mediated conjugate addition of boranes to enones to give the β-boronsubstituted ketones[53a]. Numerous Michael acceptors such as enones, enals, enolates and α,β-unsaturated amides were endured in this transformation. Later, they in 2012 developed enantioselective variant of NHC-mediated conjugate borylation using chiral imidazolium precatalyst **129**. This protocol furnished the desire product in admirable yields and enantioselectivity (Scheme 1.70).[53b]




**Scheme 1.70** NHC-mediated conjugate coupling of boranes and enones

In 2011, O'Brien and Hoveyda reported the NHC-catalyzed enantioselective conjugate coupling of silicon and Michael acceptor in a similar fashion to NHC-mediated boron addition. It was believed that the reaction proceeds through the activation of dimethylphenylsilylpinacolatoboron by an NHC catalyst due to high Lewis acidity of boron and thus silicon transfer selectively at β-position of a Michael acceptor (Scheme 1.71).[54] A wide diversity of cyclic enones, acyclic α,β-substituted ketones, lactones, esters and aldehydes worked well as reactants in this protocol to produce β-silylated products in high yields and enantioselectivity. Importantly, the tolerance of enals in this transformation indicates that NHC-catalyst binds exclusively to the complex of silicon-boron instead of aldehyde, resulting to provide products emerging from sense of Breslow intermediate.




**Scheme 1.71** NHC-mediated conjugate attachment of silicones to enones

## 1.6 Conclusion and Central Theme of the Present Work

This chapter has illustrated the various important action modes of NHCs and their reactivity in carbon-carbon and carbon-heteroatom bond forming protocols. From the foregoing discussion, it is clear that the NHC-catalyzed umpolung, non-umpolung and

radical reactivity are attributed to proper selection of the NHC catalyst, coupling partners and reaction conditions. The central theme of this thesis is to utilize NHC-catalysis for the development of new synthetic methods, which can result in the construction of various carbocyclic and heterocyclic derivatives.

NHC-mediated formal [4+2] transformation of α-chloroaldehydes and γ-keto sulfones to access 3,6-disubstituted α-pyrones has been described in the second chapter. The NHC-catalyzed generation of enolate intermediate and their reaction with γ-keto sulfones derivatives affords the desired α-pyrone products. Importantly, the newly formed α-pyrone can be readily converted into a series of value-added molecules via Diels-Alder reaction with a variety of aryne precursors.

Moreover, the compatibility for aerobic oxidation to a diverse family of difficult aldehydes for instance aromatic aldehydes with *ortho*-substitution, terribly electron-affluent aromatic aldehydes and indole-3-carboxaldehydes is one of the challenging task under NHC-organnocatalysis. In view of this, a extremely adequate NHC-mediated protocol for oxidation of aldehydes beneath aerobic condition to furnish analogous carboxylic acids has been discussed in the last chapter of the thesis.

## 1.7 References

(1) For selected reviews on carbenes, see: (a) *Carbene Chemistry*, (Ed.: Bertrand, G.), Marcel Dekker, New York, **2002**. (b) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.*, **2000**, *100*, 39. (c) Moss, R. A.; Jones, M. *Carbenes*, Vol. I, Wiley, New York, **1973**, Vol. II **1975**. (d) Kirmse, W. *Carbene Chemistry*, 2nd ed., Academic Press, New York, **1971**.

(2) For selected reviews on NHC-organocatalysis, see: (a) Zhang, C.-H.; Hooper J. F.; Lupton, D. W. *ACS Catal.* **2017**, *7*, 2583. (b) Wang M. H.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2016**, 55, 14912. (c) Flanigan, D. M.; Romano-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307. (d) Menon, R.; Biju, A. T.; Nair, V. *Chem. Soc. Rev.* **2015**, *44*, 5040. (e) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485. (f) Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res.* **2014**, *47*, 696. (g) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906. (h) De Sarkar, S.; Biswas, A.; Samanta, R. C.; Studer, A. *Chem. Eur. J.* **2013**, *19*, 4664. (i) Knappke, C. E. I.; Imami, A.; vonWangelin, A. J. *ChemCatChem* **2012**, *4*, 937. (j) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 351. (k) Nair, V.; Menon, R.S.; Biju, A. T.; Sinu, C. R.; Paul, R.R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336. (l) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

(3) (a) Ragsdale, S. W. *Chem. Rev.*, **2003**, **103**, 2333. (b) Chabriere, E.; Vernede, X.; Guigliarelli, B.; Charon, M. H.; Hatchikian, E. C.; Fontecilla-Camps, J. C. *Science*, **2001**, *294*, 2559. (c) Breslow, R. *J. Am. Chem. Soc.*, **1958**, *80*, 3719.

(4) (a) Geuther, A.; Hermann, M. *Ann.* **1855**, *95*, 211. (b) Nef, J. U. *Ann.* **1897**, *298*, 202. (c) Doering, W. v E.; Hoffmann, A. K. *J. Am. Chem. Soc.*, **1954**, *76*, 6162. (d) Fischer, E. O.; Maasböl, A. *Angew. Chem., Int. Ed.* **1964**, *3*, 580.

(5) (a) Hoffmann, R. *J. Am. Chem. Soc*. **1968**, *90*, 1475. (b) Hoffmann, R.; Zeiss, G. D.; Van Dine, G. W. *J. Am. Chem. Soc*. **1968**, *90*, 1485. (c) Hoffmann, R.; Gleiter, R. *J. Am. Chem. Soc*. **1968**, *90*, 5457**.**

(6) (a) Langenbeck, W. *Liebigs Ann.* **1929**, *16*, 469. (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (c) Arduengo, III, A. J.; Harlow R. L.; Kline, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 361.

(7) (a) Wohler, F.; Liebig. J. *Ann. Pharm.* **1832,** *3*, 249. (b) Lapworth, A. *J. Chem. Soc.* **1903**, *83*, 995.

(8) (a) Ukai, T.; Tanaka, S.; Dokawa, S.; *Yakugaku Zasshi*. **1943**, *63*, 296. (b) Wanzlick, H. W.; Fjedor, E.; Jerg, K. H. *Chem. Ber*. **1963**, *96*, 1208.

(9) (a) Igau, A.; Grutzmacher, H.; Baceiredo A.; Berand, G. J. *J. Am. Chem. Soc.* **1988,** *110*, 6463. (b) Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J.-P.; Ebel, K.; Brode, S. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1021.

(10) Stetter, H.; Schreckenberg, M. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 81.

(11) Lemal, D. M.; Lovald, R. A.; Kawano, K. I. *J. Am. Chem. Soc.* **1964**, *86*, 2518.

(12) (a) Stetter, H.; Raemsch, R. Y.; Kuhkmann, H. *Synthesis* **1976**, 733. (b) Sheehan, J.; Hunneman, D. H.; *J. Am. Chem. Soc.* **1966**, *88*, 3666.

(13) (a) Ma, Y.; Wei, S.; Wu, J.; Yang, F.; Liu, B.; Lan, J.; Yang, S.; You, J. *Adv. Synth. Catal*. **2008**, *350*, 2645. (b) Enders, D.; Han, J. *Tetrahedron Asymmetry* **2008**, *19*, 1367. (c) Brand, J. P.; Siles, J. I. O.; Waser, J. *Synlett* **2010**, 881. (d) Soeta, T.; Tabatake, Y.; Inomata, K.; Ukaji, Y. *Tetrahedron* **2012**, *68*, 894.

(14) Baragwanath, L.; Rose. C. A.; Zeitler, K.; Connon, S. J. *J. Org. Chem*. **2009**, *74*, 9214.

(15) (a) Matsumoto, T.; Ohishi, M.; Inoue, S. *J. Org. Chem*. **1985**, *50*, 603. (b) Kuhl, N.; Glorius, F. *Chem. Commun.,* **2011**, *47*, 573. (c) Jin, M. Y.; Kim, S. M.; Han, H.; Ryu, D. H.; Yang, J. W. *Org. Lett.* **2011,** *13*, 880.

(16) (a) Enders, D.; Henseler, A. *Adv. Synth. Catal.* **2009**, *351*, 1749. (b) Enders, D.; Henseler, A.; Lowins, S. *Synthesis* **2009**, *24*, 4125. (c) Enders, D.; Grossmann, A.; Fronert, J. Raabe, G. *Chem. Commun.* **2010**, *46*, 6282.

(17) (a) Rose, C. A.; Gundala, S.; Fagan, C.-L.; Franz, J. F.; Connon, S. J.; Zeitler, K. *Chem. Sci.* **2012,** *3,* 735. (b) Thai, K.; Langdon, S. M.; Bilodeau, F.; Gravel, M. *Org. Lett.* **2013,** *15,* 2214.

(18) Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001,** *123,* 9696. (b) Li, G.-Q.; Dai, L.-X.; You, S.-L. *Chem. Commun.* **2007,** 852. (c) DiRocco, D. A.; Rovis, T. *Angew. Chem., Int. Ed.* **2012,** *51,* 5904.

(19) (a) Mattson, A. E.; Scheidt, K. A. *Org. Lett.* **2004,** *6,* 4363. (b) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc.* **2005**, *127,* 1654.

(20) Cookson, R. C.; Lane, R. M. *J. Chem. Soc., Chem. Commun.* **1976,** 804.

(21) (a) Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc.* **2003**, *125,* 8432. (b) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem. Int. Ed.* **2006**, *45,* 3492.

(22) (a) Li, Y.; Feng, Z.; You, S.-L. *Chem. Commun.* **2008,** 2263. (b) Ema, T.; Oue, Y.; Akihara, K.; Miyazaki, Y.; Sakai, T. *Org. Lett.* **2009**, *11,* 4866.

(23) (a) Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131,* 13628. (b) Ozboya, K. E.; Rovis, T. *Chem. Sci.* **2011**, *2*, 1835.

(24) (a) Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284. (b) Hawkes, K. J.; Yates, B. F. *Eur. J. Org. Chem.* **2008**, 5563.

(25) (a) Ciganek, E. *Synthesis* **1995**, 1311. (b) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899.

(26) (a) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876. (b) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* **2004**, 2025. (c) Mennen, S. M.; Blank, J. T.; Tran-Dubé, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195. (d) Jia, M.-Q.; Li, Y.; Rong, Z.-Q.; You, S.-L. *Org. Biomol. Chem.* **2011**, *9*, 2072. (e) Bao, Y.; Kumagai, N.; Shibasaki, M. *Tetrahedron: Asymmetry* **2014**, *25*, 1401 (f) Rafiński, Z.; Kozakiewicz, A.; Rafinska, K. *ACS Catal.* **2014**, *4*, 1404.

(27) (a) Collett, C. J.; Massey, R. S.; Maguire, O. R.; Batsanov, A. S.; O'Donoghue, A. C.; Smith, A. D. *Chem. Sci.* **2013**, *4*, 1514. (b) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552. (c) Jia, M.-Q.; You, S.-L. *Chem. Commun.* **2012**, *48*, 6363.

(28) Filloux, C. M.; Lathrop, S. P.; Rovis, T. *Proc. Natl. Acad. Sci.* **2010**, *107*, 20666. (b) Orellana, A.; Rovis, T. *Chem. Commun.* **2008**, 730. (c) Lathrop, S.; Rovis, T. *Chem. Sci.* **2013**, *4*, 1668.

(29) (a) Enders, D. In *Stereoselective Synthesis*; Springer-Verlag: Heidelberg, **1993**, 63. (b) Enders, D.; Han, J.; Henseler, A. *Chem. Commun.* **2008**, 3989.

(30) (a) Liu, Q.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066. (b) DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10872.

(31) (a) Vedachalam, S.; Tan, S. M.; Teo, H. P.; Cai, S.; Liu, X.-W. *Org. Lett.* **2012**, *14*, 174. (b) Jousseaume, T.; Wurz, N. E.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1410.

(32) (a) Sánchez-Larios, E.; Thai, K.; Bilodeau, F.; Gravel, M. *Org. Lett.* **2011**, *13*, 4942. (b) Fang, X.; Chen, X.; Lv, H.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 11782.

(33) (a) Bhunia, A.; Yetra, S. R.; Bhojgude, S. S.; Biju, A. T. *Org. Lett.* **2012**, *14*, 2830. (b) Patra, A.; Bhunia, A.; Biju, A. T. *Org. Lett.* **2014**, *16*, 4798.

(34) (a) He, J.; Tang, S.; Liu, J.; Su, Y.; Pan, X.; She, X. *Tetrahedron* **2008**, *64*, 8797. (b) Hirano, K.; Biju, A. T.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 14190. (c) Piel, I.; Steinmetz, M.; Hirano, K.; Fröhlich, R.; Grimme, S.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 4983.

(35) (a) Bugaut, X.; Liu, F.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 8130 (b) Liu, F.; Bugaut, X.; Schedler, M.; Fröhlich, R.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 12626.

(36) (a) Biju, A. T.; Wurz, N. E.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 5970. (b) Biju, A. T.; Glorius, F. *Angew. Chem. Int. Ed.* **2010**, *49*, 9761.

(37) (a) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. (b) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc*. **2004**, *126*, 14370.

(38) (a) He, M.; Bode, J. W. *Org. Lett*. **2005**, *7*, 3131. (b) Rommel, M.; Fukuzumi, T.; Bode, J. W. *J. Am. Chem. Soc*. **2008**, *130*, 17266.

(39) (a) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett*. **2006**, *8*, 507. (b) Sun, L-H.; Shen, L.-Y.; Ye, S. *Chem. Commun*. **2011**, *47*, 10136. (c) Li, J.-L.; Sahoo, B.; Daniliuc, C.-G.; Glorius, F. *Angew. Chem., Int. Ed*. **2014**, *53*, 10515.

(40) (a) Li, Y.; Zhao, Z.-A.; He, H.; You, S.-L. *Adv. Synth. Catal*. **2008**, *350*, 1885. (b) Jang, K. P.; Hutson, G. E.; Johnston, R. C.; McCusker, E. O.; Cheong, P. H. Y.; Scheidt, K. A. *J. Am. Chem. Soc*. **2014**, *136*, 76.

(41) (a) Nair, V.; Poonoth, M.; Vellalath, S.; Suresh, E.; Thirumalai, R. *J. Org. Chem*. **2006**, *71*, 8964. (b) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc*. **2006**, *128*, 8736.

(42) (a) Chiang, P.-C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc*. **2007**, *129*, 3520. (b) He, M.; Bode, J. W. *J. Am. Chem. Soc*. **2008**, *130*, 418. (c) Cohen, D. T.; Cardinal-David, B.; Scheidt, K. A. *Angew. Chem., Int. Ed*. **2011**, *50*, 1678.

(43) (a) Nair, V.; Sinu, C. R.; Babu, B. P.; Varghese, V.; Jose, A.; Suresh, E. *Org. Lett.* **2009**, *11*, 5570. (b) Maji, B.; Ji, L.; Wang, S.; Vedachalam, S.; Ganguly, R.; Liu, X.-W. *Angew. Chem., Int. Ed*. **2012**, *51*, 8276.

(44) Fu, Z.; Xu, J.; Zhu, T.; Leong, W. W. Y.; Chi, Y. R. *Nat. Chem*. **2013**, *5*, 835.

(45) (a) Shen, L.-T.; Shao, P.-L.; Ye, S. *Adv. Synth. Catal*. **2011**, *353*, 1943. (b) Mo, J.; Shen, L.; Chi, Y. R. *J. Am. Chem. Soc.* **2012**, *134*, 8810.

(46) Li, B.-S.; Wang, Y.; Jin, Z.; Zheng, P.; Ganguly, R.; Chi, Y. R. *Nat. Commun.* **2015,** *6*, 6207.

(47) (a) Zhao, Y.-M.; Tam, Y.; Wang, Y.-J.; Li, Z.; Sun, J. *Org. Lett*. **2012**, *14*, 1398. (b) Wang, X.; Wu, Z.; Wang, J. *Org. Lett*. **2016**, *18*, 576. (c) Lee, A.; Scheidt, K. A. *Angew. Chem., Int. Ed*. **2014**, *53*, 7594.

(48) (a) Knappke, C. E. I.; Neudörfl, J.-M.; Jacobi von Wangelin, A. *Org, Biomol. Chem*. **2010**, *8*, 1695. (b) Maji, B.; Horn, M.; Mayr, H. *Angew. Chem., Int. Ed*. **2012**, *51*, 6231.

(49) (a) Fischer, C.; Smith, S. W.; Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc*. **2006**, *128*, 1472. (b) Matsuoka, S.-I.; Tochigi, Y.; Takagi, K.; Suzuki, M. *Tetrahedron* **2012**, *68*, 9836. (c) Schedler, M.; Wurz, N. E.; Daniliuc, C. G.; Glorius, F. *Org. Lett*. **2014**, *16*, 3134.

(50) (a) Du, Y.; Wang, Y.; Li, X.; Shao, G.; Webster, R. D.; Chi, Y. R. *Org. Lett*. **2014**, *16*, 5678. (b) White, N. A.; Rovis, T. *J. Am. Chem. Soc*. **2014**, *136*, 14674.

(51) (a) He, L.; Jian, T.-Y.; Ye, S. *J. Org. Chem*. **2007**, *72*, 7466. (b) He, L.; Zhang, Y.-R.; Huang, X.-L.; Ye, S. *Synthesis* **2008**, 2825.

(52) Chen, X.-Y.; Sun, L.-H.; Ye, S. *Chem.-Eur. J*. **2013**, *19*, 4441.

(53) (a) Lee, K.-S.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2009**, *131*, 7253. (b) Wu, H.; Radomkit, S.; O'Brien, J. M.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2012**, *134*, 8277.

(54) O'Brien, J. M.; Hoveyda, A. M. *J. Am. Chem. Soc*. **2011**, *133*, 7712.