CHAPTER 1

Chemistry of \( N \)-Heterocyclic Carbenes and Homoenolates:
An Introduction

1.1. Introduction

Carbenes are neutral divalent carbon species with six valence electrons. Investigations carried out by Staudinger on the decomposition of diazo compounds can be considered as the preliminary work in the field of methylenes (original name for carbenes).\(^1\) The development in carbene chemistry began when Doering introduced carbenes to organic chemistry in 1950s.\(^2\) Since then, these fascinating species have played a crucial role in many important synthetic organic reactions. Depending on the spin multiplicity, carbenes are classified into singlet and triplet states. Singlet carbenes feature a filled and a vacant orbital, thereby showing ambiphilic character while triplet carbenes have two singly occupied orbitals and are generally regarded as diradicals (Figure 1.1).

![Figure 1.1. Spin multiplicity of carbenes](image)

Nucleophilic carbenes are characterized by the presence of heteroatoms such as oxygen, nitrogen and sulfur. These heteroatoms are capable of donating their lone pair electrons to the vacant p-orbitals of carbene carbon. This lone pair electron donation brings nucleophilicity to the carbene species and strongly stabilizes the singlet state and imparts dipolar character (Scheme 1.1).

![Scheme 1.1](image)

Among various nucleophilic carbenes, \( N \)-heterocyclic carbenes (NHCs) are the most widely studied ones. Due to their steric and electronic properties, NHCs are a rapidly growing area of research in transition metal chemistry\(^3\) and in synthetic organic
chemistry. Due to the excellent σ-donating properties and their close resemblance to trialkyl phosphines, NHCs are well exploited as ligands for transition metals. The stability of the transition metal complexes of N-heterocyclic carbenes is often cited as one of the key advances of these ligands versus their phosphine counterparts. NHC-incorporated organometallic catalysts are found to be much more effective than conventional catalysts in many reactions, including Heck reaction, olefin metathesis, and a number of coupling reactions. This allows the constitution of organometallic catalysts of enormous utility in organic synthesis. Recently, chemists are more interested in exploring the utility of NHCs as nucleophilic reagents and organocatalysts. Presently NHCs occupy a distinguished position both as a reagent and catalyst in organic synthesis. The focal theme of the present thesis is exploration of novel reactions catalyzed by NHCs. Therefore, in this introductory chapter, after a brief history of N-heterocyclic carbenes, an overview of NHC catalysis is presented.

1.2. History of N-Heterocyclic Carbenes (NHCs)

The origin of NHC catalysis can be traced to the preliminary experiments of Ugai as well as Mizuhara. Ugai found that, instead of cyanide ions thiazolium salts can be used for the benzoin condensation. From his studies Mizuhara identified that, catalytic property of natural thiamine is based on the thiazolium unit present. In 1958, Breslow presented a mechanism for the thiamine action in benzoin condensation. In his proposal he demonstrated that a thiazol-2-ylidene, a carbene is the catalytically active species. This thiazol-2-ylidene belongs to the class of N-heterocyclic carbene. Subsequently, several attempts were made to isolate stable carbenes. In the 1960s Wanzlick et al. made a deliberate attempt to isolate stable carbenes. Although Wanzlick was unsuccessful in his objective, his recognition that a carbene center at the 2-position of the imidazole ring will be stable due to the electron donating effects of adjacent nitrogen atoms provided the conceptual framework for the development of the chemistry of these species. The first stable carbenes coordinated to metal atoms were synthesized by Wanzlick and co-workers. The isolation of a stable liquid dicarbene was reported in 1989 by Bertrand et al. In 1991, Arduengo and co-workers isolated a stable, crystalline, N-adamantyl substituted carbene (Scheme 1.2).
Chapter 1

The first organocatalytic reaction.

The classical Knoevenagel condensation reported way back in 1894 can be considered as sufficient momentum to research in this area and the term “Organic Catalysts” was coined by Langenbeck. The catalysts are usually robust, inexpensive and readily available small organic molecules. Work in early 1970s signaled the onset of another era of intensive research activity called asymmetric organocatalysis. The elegant work of List, MacMillan, Jacobsen and many other researchers in the 1990s and early 2000s, revisited asymmetric organocatalysis as a powerful strategy for the diastereoselective/enantioselective construction of complex molecular skeletons. In this scenario, the role of NHCs as organocatalyst received great attention.

1.3. NHC as an Organocatalyst

Organocatalysis can be defined as the acceleration of chemical reactions by the addition of a substoichiometric quantity of an organic compound which does not contain an inorganic element. Because of their lower cost and benign environmental impact; organocatalyzed reactions serve an attractive alternative to metal-catalyzed processes. The classical Knoevenagel condensation reported way back in 1894 can be considered as the first organocatalytic reaction. Investigations by Langenbeck in the 1920s provided sufficient momentum to research in this area and the term “Organic Catalysts” (“Organische Katalysatoren”) was coined by Langenbeck. The catalysts are usually robust, inexpensive and readily available small organic molecules. Work in early 1970s signaled the onset of another era of intensive research activity called asymmetric organocatalysis. The elegant work of List, MacMillan, Jacobsen and many other researchers in the 1990s and early 2000s, revisited asymmetric organocatalysis as a powerful strategy for the diastereoselective/enantioselective construction of complex molecular skeletons. In this scenario, the role of NHCs as organocatalyst received great attention.

1.3.1. Benzoin Reaction

Benzoin reaction is the cyanide mediated coupling reaction of aldehydes that leads to the formation of \( \alpha \)-hydroxy ketones. This reaction was first reported by Wöhler and Leibig. An acceptable mechanism for this reaction was proposed by Lapworth in.
1903; in which an intermediate aldehyde-cyanohydrin was deprotonated to generate an acyl anion equivalent with inverted reactivity (umpolung) at the carbonyl carbon. In 1943, Ugai et al. reported that the combination of thiazolium salt and a base could also effectively catalyze the benzoin condensation. This work along with studies of reactions catalyzed by thiamine dependent enzymes indicated that, acyl anion equivalents are also likely intermediates in these thiazolium/base catalyzed processes. It was Breslow who proposed the pathbreaking mechanism for this transformation. In 1958, from his model studies he suggested that the catalytically active species is a thiazolin-2-ylidene C2, a carbene compound, which is formed in situ by the deprotonation of thiazolium salt C1. The catalytic process is demonstrated in scheme (Scheme 1.3).

In this mechanism it is assumed that the thiazolium salt C1 is deprotonated at its most acidic position (C2-carbon) to form the thiazolium-2-ylidene C2, originally drawn as a mesomeric zwitterion. Nucleophilic addition of ylidene C2 to the carbonyl group of an aldehyde 3 generates a thiazolium salt adduct 4. Deprotonation at C-position and reprotonation at O leads to the active aldehyde in the form of the resonance-stabilized enamino intermediate 5 (presently known as the Breslow intermediate). This nucleophilic acyloin reagent reacts again with an electrophilic substrate such as the carbonyl group of...
a second aldehyde molecule. The subsequent elimination of benzoin 7 regenerates the original carbene catalyst. NHCs derived from a number of azolium species viz., thiazolium, imidazolium and triazolium salts have been shown to catalyze the benzoin condensation analogous to the thiamine reaction under biochemical conditions.

In 1966, Sheehan and Hunneman reported the first asymmetric benzoin reaction using chiral thiazolium precatalyst C3. However, the observed enantiomeric excess of the benzoin was only 22% (Scheme 1.4). Several groups have attempted to improve the enantioselectivity of thiazolium catalyzed benzoin reaction.

![Scheme 1.4](image)

A breakthrough in the asymmetric benzoin reaction was achieved in 1996 when Enders and co-workers introduced chiral triazolylidene carbene instead of thiazolylidene carbene (Scheme 1.5). They have utilized a variety of triazolium salts, which provided increased yield and enantioselectivities.

![Scheme 1.5](image)

In 1997 Leeper and co-workers developed a series of rigid bicyclic thiazolium salts for asymmetric benzoin condensation. Rawal and Dvorak synthesized a bicyclic thiazolium salt and utilized it to increase the enantioselectivity of the benzoin reaction. Later, Leeper and co-workers observed increased enantioselectivities up to 80% when they exchanged the thiazole frame-work of the carbene to more reactive triazole system. In 2002, Enders and co-workers took the advantage of the bicyclic restriction introduced by Leeper and Rawal to develop catalyst C5. Use of this catalyst provided a number of benzoin derivatives with enantioselectivities up to 95% (Scheme 1.6).
Coupling of several aldehydes with paraformaldehyde directly provided the corresponding valuable hydroxymethyl ketones.\(^{36}\) In continuation of NHC-catalyzed addition of aldehydes to formaldehyde towards an efficient synthesis of hydroxymethyl ketones,\(^{35}\) recently Khul and Glorius reported a mechanistic study of this \(N\)-heterocyclic carbene-catalyzed hydroxymethylation (Scheme 1.7).\(^{36}\) Coupling of several aldehydes with paraformaldehyde directly provided the corresponding valuable hydroxymethyl ketones.

**Scheme 1.6**

In continuation of NHC-catalyzed addition of aldehydes to formaldehyde towards an efficient synthesis of hydroxymethyl ketones,\(^{35}\) recently Khul and Glorius reported a mechanistic study of this \(N\)-heterocyclic carbene-catalyzed hydroxymethylation (Scheme 1.7).\(^{36}\) Coupling of several aldehydes with paraformaldehyde directly provided the corresponding valuable hydroxymethyl ketones.

**Scheme 1.7**

### 1.3.2. Cross-Benzoin Reaction

The benzoin reaction is typically a homocoupling of two aldehydes, which results in the formation of dimeric compounds; consequently, it limits the scope of this method. Recent developments in the benzoin condensation are the synthesis of non-symmetrical benzoins by cross coupling of two different aldehydes. This can provide four products viz., two homocoupled and two cross-benzoin products. To ensure the success, Breslow intermediate has to be formed predominantly on one aldehyde and it should add selectively to the second aldehyde. Several strategies have been employed to develop this method, including the use of donor acceptor aldehydes, acyl silanes and aryl imines; intramolecular reactions have also been exploited.

Müller and co-workers reported the first example of an enantioselective cross-benzoin reaction that takes the advantage of donor acceptor concept (Scheme 1.8).\(^{37,38}\) The ortho-substitution on the aldehyde hinders the formation of Breslow intermediate and thereby facilitates selectivity.
imines, the authors used α-amido sulfones. This method is suitable for aryl aldehydes with electron-rich and electron-deficient aryl substituents. Reaction with acetaldehyde afforded the corresponding amido ketone in 62% yield.

In 2001, Murry et al. extended the scope of benzoin condensation to the in situ formed acyl imines (Scheme 1.9). Due to the stability and ease of formation of acyl imines, the authors used α-amido sulfones. This method is suitable for aryl aldehydes with electron-rich and electron-deficient aryl substituents. Reaction with acetaldehyde afforded the corresponding amido ketone in 62% yield.

Scheidt and co-workers utilized the acyl silanes and N-diphenylphosphinoylimines to form α-amino ketones (Scheme 1.10). The asymmetric version of the aldehyde-imine cross-coupling was reported with thiazolylalanine-derived catalysts by Miller and co-workers.

Extension of NHC catalyzed cross-benzoin condensation to ketones offered only limited success; a few intramolecular examples can be found in the literature. In 2009, a direct intermolecular cross-benzoin type condensation catalyzed by an N-heterocyclic carbene was developed. The cross-coupling of commercially available aromatic aldehydes and trifluoromethyl ketones results in α-hydroxy-α-trifluoromethyl ketones bearing a quaternary stereocenter with excellent chemoselectivity and good to excellent yields (Scheme 1.11).
Chapter 1

Connon and Zeitler; they utilized α-ketoesters as the cross-coupling partner (Scheme 1.12). Use of relatively electron deficient triazolium pre-catalysts avoided the undesired hydroacylation pathways already reported with related substrates.

Very recently, Thai et al. showed that an electron-deficient, valine-derived triazolium salt catalyzed, highly chemo- and enantioselective cross-benzoin reaction between aliphatic aldehydes and α-ketoesters (Scheme 1.13).

1.3.3. Stetter Reaction

In the 1970s Stetter reported the direct addition of aromatic aldehyde to α,β-unsaturated nitriles and ketones in the presence catalytic amount of sodium cyanide. Later this method was successfully applied to aliphatic aldehydes by the use of catalytic amount of thiazolium salts in presence of bases. Several azolium salts such as imidazolium, thiazolium and triazolium salts are found to be effective as catalysts for this transformation. When α,β-unsaturated ketones are employed, the reaction is often called Michael-Stetter reaction; a representative reaction involving an imidazolium salt, an α,β-unsaturated ketone and an aldehyde is shown in Scheme 1.14.
The first asymmetric version of the Michael-Stetter reaction employing a chiral azolium salt for the synthesis of the benzopyran derivative 28 was reported by Enders and co-workers (Scheme 1.15). Independently, Rovis and co-workers have shown that the use of a fused chiral triazolium salt leads to the product in higher yield and enantioselectivity.

In 2008, Enders et al. reported the first general NHC-catalyzed enantioselective intermolecular addition of aldehydes to chalcones (Scheme 1.16).

An asymmetric intermolecular Stetter reaction of enals with nitroalkenes catalyzed by chiral \(N\)-heterocyclic carbenes was developed Rovis and DiRocco (Scheme 1.17). The presence of catechol profoundly impacted the reaction rate and efficiency. The reaction proceeded with high selectivities and afforded good yield of the Stetter product. Internal redox products were not observed despite the protic conditions.

Chi and co-workers reported an \(N\)-heterocyclic carbene catalyzed enantioselective Stetter reactions of enals and modified chalcones (Scheme 1.18). The selective
capturing of the enal acyl anion intermediates was realized by an alteration of the reaction partners and the proper choice of the NHC catalyst.

\[
\text{Me} - \text{C} = \text{O} + \text{Ph} - \text{C} = \text{O} \quad \text{C15 (30 mol %)} \quad \text{DBU (20 mol %)} \\
\text{Me} - \text{C} = \text{O} \quad \text{36, 90\%, ee 94\%}
\]

**Scheme 1.18**

Recently, the authors disclosed a catalytic activation of carbohydrates as formaldehyde equivalents to generate acyl anions as one-carbon nucleophilic units for a Stetter reaction (Scheme 1.19).\(^{54}\) This activation involves N-heterocyclic carbene-catalyzed carbon–carbon bond cleavage of carbohydrates via a retro-benzoin-type process to generate the acyl anion intermediates.

\[
\text{HO} - \text{C} - \text{O} - \text{C} - \text{O} \quad \text{C8 (20 mol %)} \\
\text{HO} - \text{C} - \text{O} - \text{C} - \text{O} \quad \text{38, 81\%}
\]

**Scheme 1.19**

### 1.3.4. Transesterification Reactions

Stable NHCs have been found to be very efficient catalysts for transesterification and acylation reactions. The first example of an NHC catalyzed transesterification type reaction was reported by Hedrick et al. in 2002 (Scheme 1.20).\(^{55}\)

\[
\text{Me} - \text{C} - \text{O} \quad \text{C16 (3 mol %)} \\
\text{Me} - \text{C} - \text{O} \quad \text{BnCl (10 mol %)} \\
\text{40, 99\% conv.}
\]

**Scheme 1.20**

Following these reports, the groups of Nolan, Hedrick and Waymouth independently reported the NHC catalyzed transesterification of a wide range of esters (Scheme 1.21).\(^{56,57}\)

\[
\text{Me} - \text{C} - \text{O} - \text{C} - \text{O} + \text{Ph} - \text{OH} \quad \text{C16} \\
\text{Me} - \text{C} - \text{O} - \text{C} - \text{O} + \text{Me} - \text{C} = \text{O}
\]

**Scheme 1.21**
An NHC catalyzed amidation of unactivated esters with amino alcohols was reported by Movassaghi and Schmidt (Scheme 1.22). In addition to the synthetic utility, these studies have thrown light on the mechanism of NHC catalyzed transesterifications.

\[
\begin{align*}
\text{Ph} & \quad \text{O} & \quad \text{OMe} & \quad + & \quad \text{H}_2\text{N} & \quad \text{H} & \quad \text{OH} \\
45 & & & & & & 46 \quad \xrightarrow{C16 (5 \text{ mol} \%) \text{ THF, 23 } \text{°C}} \quad \text{Ph} & \quad \text{N} & \quad \text{OH} \\
& & & & & & 47, 100% \\
\end{align*}
\]

Scheme 1.22

1.3.5. Internal Redox Reaction

Internal redox esterification reaction is another emerging area of research in NHC catalysis. The diastereoselective synthesis of β-hydroxy esters from 2,3-epoxyaldehydes by Chow et al. is an excellent illustration of this protocol (Scheme 1.23). The proposed reaction mechanism involves NHC mediated epoxide ring opening.

\[
\begin{align*}
\text{Ph} & \quad \text{O} & \quad \text{H} & \quad + & \quad \text{OH} & \quad \xrightarrow{C17 (10 \text{ mol} \%) \text{ i-Pr}_2\text{NEt} (8 \text{ mol} \%) \text{ CH}_2\text{Cl}_2, \text{rt, 15 h}} & \quad \text{Ph} & \quad \text{OH} \\
48 & & & & & & 49, (10:1) 89\% & & 42 \\
\end{align*}
\]

Scheme 1.23

In conjunction with the efforts to extend the utility of the umpolung reactivity, Rovis reported the conversion of α-haloaldehyde into an acylating agent catalyzed by NHCs. In this process an activated carboxylate has been generated at the expense of a β-leaving group (Scheme 1.24).

\[
\begin{align*}
\text{Ph} & \quad \text{O} & \quad \text{H} & \quad + & \quad \text{OH} & \quad \xrightarrow{C18 (20 \text{ mol} \%) \text{ Et}_3\text{N} (1 \text{ equiv}) \text{ PhMe, rt, 24 h}} & \quad \text{CO} & \quad \text{OBn} \\
50 & & & & & & 51 & & 42 \\
\end{align*}
\]

Scheme 1.24

Bode et al. have shown an efficient catalytic method for the redox esterification of formylcyclopropanes, which involves the ring opening of cyclopropane via carbon-carbon bond cleavage (Scheme 1.25).

\[
\begin{align*}
\text{Ph} & \quad \text{O} & \quad \text{H} & \quad + & \quad \text{OMe} & \quad \xrightarrow{C19 (5 \text{ mol} \%) \text{ MeOH DBU (20 \text{ mol} \%) \text{ THF, rt, 15 h}}} & \quad \text{Ph} & \quad \text{O} & \quad \text{Ph} & \quad \text{O} & \quad \text{OMe} \\
52 & & & & & & 53, 90\%, \text{ ee 89}\% & & & & & & 52 \\
\end{align*}
\]

Scheme 1.25
Recently, Enders and co-workers developed a new NHC-catalyzed one-pot reaction. Hydroxamic esters were formed by the reaction of nitroso benzenes, aldehydes and enals in a one-pot, two step reaction (Scheme 1.26).\(^{62}\) Initially, an aza-benzoin-type condensation reaction between nitroso benzenes and aldehydes catalyzed by NHC took place. The resulting \(N\)-arylhydroxamic acids subsequently reacted with enals through an NHC catalyzed redox esterification reaction.

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
54 & \quad 3
\end{align*}
\]

Scheme 1.26

1.4. Homoenolates

Carbon–carbon bond formation constitutes the central event in organic synthesis. The vast majority of carbon–carbon and carbon-heteroatom bond forming reactions occurring in Nature and in the laboratory are at the carbon adjoining the carbonyl group of ketones and aldehydes. Among the plethora of methods developed over the years, a large number of them take advantage of the activation of methyl/methylene, imparted by the electron withdrawing effect of an adjacent carbonyl group, and proceed via the intermediacy of enol/enolate or enamine. Enolate anion is a versatile reactive intermediate, and it is usually generated in the laboratory by the removal of the \(\alpha\)-proton of a carbonyl compound, often with the aid of alkali metal reagents. Addition of a secondary amine to the carbonyl compound followed by the elimination of water affords enamines. Just as a carbonyl would facilitate the reaction of an electrophile at the \(\alpha\)-carbon via enol/enolate, the reaction at the \(\beta\) carbon via a potentially reactive intermediate, a homoenolate is conceptually feasible. By analogy to enolate, homoenolate\(^{63}\) is a species containing anionic carbon \(\beta\) to a carbonyl group or a moiety that can be transformed to a carbonyl group (Scheme 1.27).

\[
\begin{align*}
\text{Me} & \quad \text{M} \\
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{O}
\end{align*}
\]

Scheme 1.27

In 1962 Nickon introduced the concept of homoenolates to organic chemistry community,\(^{64}\) and he proved the existence of such a species by demonstrating the
racemization of (+)-camphenilone 56 by alkaline treatment and its deuterium exchange to produce 57 and 58, consistent with the symmetrical intermediate 59. The racemization is attributed to the deprotonation of C6-H to form a non-classical anion, termed homoenolate anion whose charge is stabilized by delocalization to the carbonyl group (Scheme 1.28).

Scheme 1.28

1.4.1. Metal Homoenolates

The application of homoenolates in organic synthesis was limited, presumably due to the difficulty in directly generating homoenolates. The use of homoenol silyl ether, in the form of cyclopropanone ketal 61, was the simplest solution offered to this problem. It was Nakamura and Kuwajima who first described the potential utility of this homoenolate equivalent in carbon–carbon bond-formation (Scheme 1.29).\(^b\) In their report, the addition of 61 to a carbonyl compound in the presence of TiCl\(_4\) delivers \(\gamma\)-lactones in high yield. Presumably this is the first example of a homoaldol reaction.

Scheme 1.29

An important innovation to circumvent the problem of chlorinated side-products associated with trichlorotitanium homoenolates was introduced by Helquist.\(^a\) The acetal-embedded Grignard reagent 63 was used as homoenolate equivalent (Scheme 1.30). Copper catalyzed conjugate addition of 63 to cyclohexenone, followed by deprotection and subsequent intramolecular aldol condensation afforded bicyclic cyclopentene derivative 66 in good yield.
Another important event in the area of homoenolate occurred when Nakamura et al. developed a method for the catalytic generation of homoenolate. They showed that zinc homoenolate can be generated by the reaction of siloxycyclopropane with catalytic amount of zinc chloride; synthetic utility of was demonstrated by its participation in homoaldol reaction (Scheme 1.31).

Induction of chirality in homoenolate reaction was the main challenge to accomplish stereocontrolled homoaldol reactions. First example of a chiral homoenolate equivalent and its application in asymmetric reactions was reported by Albrecht and Enders. The most advanced and synthetically useful chiral homoenolate equivalents are the 2-alkenyl-1-metallocarbamates introduced by Hoppe. In his elegant work, Hoppe has shown that these species react with aldehydes and ketones with virtually complete 1,3-transfer of chirality to form optically active homoaldol products. An illustrative example is given in Scheme 1.32. Analogous work was subsequently reported by Whisler and Beak also.

---

**Scheme 1.30**

**Scheme 1.31**

**Scheme 1.32**
Fry et al. synthesized the first metal free homoenolate by the reaction of β-trimethylsilyl propionate with tetrabutylammonium triphenyldifluorosilicate (TBAT). It was found to be reactive enough to add to imines, aldehydes and ketones (Scheme 1.33).71

![Scheme 1.33](image)

1.4.2. N-Heterocyclic Carbene (NHC) Derived Homoenolates

Based on the mechanistic pathways available to the “Breslow intermediate” two research groups led by Glorius72 and Bode73 independently and simultaneously reported a conceptually new approach to generate homoenolate from enal using N-heterocyclic carbene. They surmised that, just as the addition of NHC to aldehyde would generate an enol/enaminol (Breslow intermediate), the addition of NHC to α,β-unsaturated aldehyde can, in principle, generate a conjugated acyl anion, more appropriately called homoenolate (Scheme 1.34).

![Scheme 1.34](image)

The homoenolate intermediate II formed by NHC catalysis on reaction with an aldehyde culminated in the synthesis of γ-butyrolactones. The formation of γ-butyrolactones can be depicted as the addition of homoenolate to aldehyde to generate an alkoxide intermediate 80, which undergoes an intramolecular lactonization with the activated carboxylate surrogate (Scheme 1.35). In the absence of other electrophiles, enal undergoes homodimerization.
Subsequent work by Bode has shown that this homoenolate annulation can be extended to the synthesis of \( \gamma \)-lactams (Scheme 1.36).\(^{74}\)

In his original work, Glorius has reported that, with the exception of \( \alpha,\alpha,\alpha \)-trifluoroacetophenone, ketones failed to undergo homoenolate annulations. Work from our laboratory has shown that homoenolate reactions proceed well with activated carbonyl compounds viz., 1, 2-diones, yielding spiro \( \gamma \)-butyrolactones in high yields and excellent diastereoselectivities (Scheme 1.37).\(^ {75}\) It was found that the spiroannulation strategy could be extended to isatins also, which afforded a diastereomeric mixture (1:1) of spiro \( \gamma \)-butyrolactone oxindole derivative. Spirooxindole derivatives are known to be important structural units of biologically active natural products such as the mycotoxin triptoquivaline.
Further investigations in our laboratory have shown that acyclic 1,2-diones also undergo this NHC catalyzed homoenolate annulation to yield \( \gamma \)-butyrolactones in high yields (Scheme 1.38).\(^{76}\)

![Scheme 1.38](image)

In a related study, the reaction of homoenolate from 90 underwent an uncommon [8+3] annulation with tropone to afford bicyclic \( \delta \)-lactone derivative 92 (Scheme 1.39). Interestingly, aliphatic enals could also be converted to the corresponding \( \delta \)-lactones by this method.\(^{77}\)

![Scheme 1.39](image)

Inspired by the homoenolate annulation to an activated carbonyl to afford a lactone, we were intrigued by the possibility of homoenolate annulation with an activated carbon–carbon double bond such as that of a chalcone. An attempted synthesis of cyclopentanone from chalcone and enal resulted in the serendipitous synthesis of 3,4-trans-disubstituted-1-aryl cyclopentene (Scheme 1.40).\(^{78}\)

![Scheme 1.40](image)

Mechanistic rationale for the cyclopentene formation can considered as occurring via the initial Michael addition of homoenolate to the enone. Subsequent intramolecular aldol reaction set the stage for the formation of a \( \beta \)-lactone. This \( \beta \)-lactone is unstable and it undergoes a retro [2+2] process to yield the cyclopentenes.

Subsequently, an asymmetric version of cyclopentene annulation using \( N \)-mesityl-substituted chiral triazole carbene was reported by Bode and coworkers (Scheme 1.41).\(^{79}\)
They attributed the cis-cyclopentene formation to an NHC-catalyzed oxy-Cope rearrangement.

![Scheme 1.41](image)

Interestingly, β-lactone intermediate invoked in our cyclopentannulation has accrued additional support from the work of Scheidt; who isolated a bicyclic β-lactone from an intramolecular variant of this reaction. The enantioselective formation of α,α-disubstituted cyclopentene 99 was interpreted by invoking the intramolecular aldol reaction of achiral tricarbonyl compound 97 catalyzed by chiral N-heterocyclic carbene (Scheme 1.42).

![Scheme 1.42](image)

When the annulation reaction of homoenolates and chalcones was conducted in a protic solvent, a new facet of homoenolate reactivity was revealed. The annulation of homoenolates with chalcones catalyzed by imidazolium salt C12 in methanol proceeded to afford β-hydroxycyclopentane carboxylate 101 as the major product along with acyclic δ-ketoester 102 as minor product. It is noteworthy that the cyclopentane product 101 possesses four contiguous stereocenters including a quaternary one (Scheme 1.43).

![Scheme 1.43](image)

Recent work in our group on the reactions of homoenolates with different kinds of cross-conjugated dienones demonstrated that subtle changes in the structure of the
reactants would lead to reactive intermediates that may differ considerably in stability and thus alter the outcome of the reaction completely (Scheme 1.44). For example, stereoselective formation of spirocyclopentanone products was observed when dibenzylidene cyclopentanones 103 were employed as dienone components. However, homoenoenate annulation of acyclic dienones resulted in the formation of separable mixtures of cyclopentenes 106 and cyclopentanones 107.\(^8\) On the other hand, under similar reaction conditions dibenzylidene cyclohexanones 108 afforded cyclopentene derivatives 110 as the only product with exclusive diastereoselectivity.\(^8\) A facile Diels–Alder reaction of 110 with dimethylacetylene dicarboxylate (DMAD) and subsequent oxidation of the Diels–Alder adduct delivered a hexasubstituted benzene derivative 111. NHC mediated annulation of enals to 2,4-dien-1-ones led to efficient diastereoselective synthesis of 1,3-diaryl-4-styrenyl cyclopentenes.\(^8\)

\[\text{Scheme 1.44}\]

In an extension of their previous work, Bode and co-workers synthesized bicyclic \(\beta\)-lactams from enals and unsaturated \(N\)-sulfonyl ketimines.\(^8\) They invoked a tandem, or possibly concerted, crossed-benzoin/oxy-Cope reaction to explain the cis-relative configuration of the cyclopentane substituents. The high preference for this process was due to the slow \(\beta\)-protonation of unactivated enals to generate the corresponding enolate (Scheme 1.45).
1,3-dipoles such as azomethine imines and nitrones take part in formal [3+3] cycloaddition reactions with NHC-homoenolate. Synthesis of pyridazinones\textsuperscript{86} and γ-amino esters\textsuperscript{87} by the addition of azomethine imines and nitrones respectively to enals catalyzed by NHC was reported (Scheme 1.46).

A direct electrophilic amination of homoenolates catalyzed by N-heterocyclic carbenes was developed by Scheidt and co-workers.\textsuperscript{88} The addition of a carbene derived from triazolium salt C\textsubscript{23} to an α,β-unsaturated aldehyde generates a homoenolate intermediate which undergoes a formal [3+2] cycloaddition with an 1-acyl-2-aryldiazene to afford pyrazolidinone as a single regioisomer (Scheme 1.47).

In 2012 Jiao et al. demonstrated that N-aryl isatin imines can be used as stable and useful electrophiles in the NHC-catalyzed addition of enals to imines.\textsuperscript{89} They have developed an efficient one-pot protocol for the synthesis of spirocyclic γ-lactam oxindoles by a synthetically challenging addition of homoenolate equivalents to N-aryl isatin imines and subsequent acid hydrolysis (Scheme 1.48).
Recently, Cheng’s group and our group reported an $N$-heterocyclic carbene catalyzed direct dithiolation of enals with organic disulfides (Scheme 1.49).\(^{90}\) In this catalytic method thioesterification take place in a one-pot operation.

Recently, Cheng’s group and our group reported an $N$-heterocyclic carbene catalyzed spirobislactone synthesis by the annulation of benzofuran-2,3-diones and enals via homoenolate intermediate (Scheme 1.50).\(^{91}\) The ketone-carbonyl group annulated products and the ester-carbonyl group annulated products can be obtained as major products with good yields by convenient catalyst regulation. Furthermore, commercially available thiazolium salt can also catalyze this reaction with modest yield.

**1.4.3. Dual Activation in $N$-Heterocyclic Carbene Organocatalysis**

Recently, NHC-involving dual catalytic approaches have received much attention. In such cases, typically, combination of $N$-heterocyclic carbene with a second catalyst that may be another organocatalyst, or a metal-based catalyst or another NHC is used. The appropriate combination of catalysts allows two compatible yet independent catalytic systems in one-pot to undergo tandem processes. Furthermore, simultaneous action of two activators in a bond-forming event enables new reactivity, which often cannot be achieved by mono catalytic approaches.
Hamada and co-workers effectively utilized this strategy for the first time in the synthesis of dihydroquinolinones by a one-pot sequential Pd-catalyzed allylic amination and thiazolylidene-catalyzed Stetter reaction (Scheme 1.51).\(^9^2\)

\[
\begin{align*}
\text{129} + \text{130} & \xrightarrow{\text{C7 (20 mol%), Pd(OAc)}_2 (5 \text{ mol%)} \atop \text{PPh}_3 (12 \text{ mol%), i-Pr}_2\text{NEt (5 equiv)} \atop \text{t-BuOH, 50 °C}}} \text{131, 98%}
\end{align*}
\]

Scheme 1.51

In the area of NHC catalysis, Scheidt group has made a number of important contributions, demonstrating the simultaneous catalytic activation of two reaction partners in the same step using NHC and metal catalyst. These include the cooperative catalysis\(^9^3\) by carbenes and Lewis acids in a highly stereoselective route to γ-lactams from acyl hydrazones and enals (Scheme 1.52).\(^9^4\) In this reaction NHC activates the enal and co-catalyst [Mg(OT-Bu)\(_2\)] activates the acyl hydrazine.

\[
\begin{align*}
\text{31} + \text{132} & \xrightarrow{\text{C24 (5 mol%), Mg(OT-Bu)\(_2\) (5 mol%) \atop \text{TBD (5 mol%), THF, 60 °C}}} \text{133, 78%, ee 97%, dr 9:1}
\end{align*}
\]

Scheme 1.52

The continuous quest for new types of NHC-catalyzed processes has found some important synergetic actions of NHC-and other organocatalysts. Vora and Rovis reported an orthogonal amide formation by NHC- and 1-hydroxy-7-azabenzotriazole (HOAt) relay catalysis.\(^9^5\) Lathrop and Rovis reported an NHC-catalysis in combination with iminium catalysis, culminating in the enantioselective synthesis of functionalized cyclopentanols (Scheme 1.53).\(^9^6\)
1.5. Definition of the Problem

Introduction of NHC mediated generation of homoenolate, a three carbon synthon directly from enals has made it possible to explore the synthetic utility of this unique reactive intermediate. Work from different research groups including our own has revealed the versatility and usefulness of NHC-bound homoenolate annulation with a wide range of electrophiles leading to various carbocycles and heterocycles. Homoenolates have also been shown to add efficiently to sulfonimines leading to precursors of novel γ-aminobutyric acid (GABA) derivatives. However, NHC-catalysis is an emerging area and it will be very interesting to explore the potentiality of homoenolates in the construction of novel carbon–carbon and carbon-heteroatom bonds, ultimately leading to viable routes for carbo- and heterocycles.

In the initial phase of our study we undertook a systematic investigation of the reactivity of homoenolate, generated from enals by NHC catalysis, towards various β-nitrostyrenes, powerful Michael acceptors. These results comprise the subject matter of second chapter. Third chapter deals with an NHC-catalyzed transformation leading to the synthesis of 3-alkyl coumarins. The next chapter describes an efficient intramolecular homoenolate reaction of 2-O-alkenoate appended cinnamaldehydes. In the fifth and final chapter, transformation of cinnamils to vinylfulvenes and o-terphenyls is described.

1.6. References


27. Wöhler; Liebig Ann. Pharm. 1832, 3, 249.


   
   (b) Seetha Lakshmi, K. C; Paul, R. R; Suresh, E.; Nair, V. *Synlett* **2014**, *25*, 853.


