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N-Heterocyclic Carbene Mediated Organocatalysis Reactions

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Abstract

Arduengo et al., isolated the first ‘bottleable’ carbene, the first N-heterocyclic carbene (NHC) 1,3-di(adamantyl)imidazol-2-ylidene resulted to an explosion of experimental and theoretical studies of novel NHCs being synthesized and analyzed have huge practical significance. These compounds emerged as successful ligands for coordinating transition metals, the complexes with NHC show diverse applications in the field of catalysis and organic transformation, NHC as ligand to main group elements and their properties and applications. Here this chapter provides the concise overview of N-heterocycle carbene as an organocatalyst that provides different organic transformation on to a carbonyl group. The majority of the NHC catalyzed reactions are employed in the phenomenon of reversing the electrophilic character of carbonyl carbon to nucleophilic carbon (umpolung activity) on coordination suggests benzoin, Stetter and hydroacylation reactions. Also, non-umpolung activity of bis-electrophile α,β -unsaturated acylazoliums reaction with suitable bis-nucleophiles in the organic synthesis have been studied.

Keywords: NHC carbene, Breslow intermediate, benzoin reaction, Stetter reaction, hydroacylation reaction, annulation reaction, acylazoliums, α,β -unsaturated acylazolium

1. Introduction

The first isolable carbene stabilized with adjacent phosphorous and silicon are reported by Bertrand et al. [1]. Soon after in 1991 Arduengo et al., isolated a bottleable carbene in N-heterocyclic scaffold, said to be N-heterocyclic carbene (NHC) [2]. Substituted bulky groups in NHCs adjacent to the carbene carbon provide kinetically stabilized and sterically avoids the dimerization to corresponding olefins. Remarkable stability and simple synthetic protocols revealed enormous applications of NHCs on transition metal, main group elements and as organo catalysts highlights new area of research. From the last two decades NHC organo catalysis has shepherded to extensive applications in the carbon–carbon and carbon–heteroatom bond formation. NHCs as organocatalyst involving umpolung activity of the functional group with carbonyl carbon (majority reaction employ aldehydes as substrate) acts as a transient nucleophile rather than an electrophile. The obtained nucleophile acyl anion is commonly called as “Breslow intermediate” [3]. The purpose of this

chapter, to explore the NHC catalyzed transformations in organic chemistry involving in the benzoin reaction, Stetter reaction, α - β -unsaturated aldehydes in construction of heterocycles, β -functionalization of enals, hydroacylation of double bonds and triple bonds. NHCs are also known as non-umpolung mode transformations catalysis. Specially, the mode of reactivity in the generation of α - β -unsaturated acylazolium intermediates and are intercepted with various bis-nucleophiles for the enantioselective construction of various heterocyclic compounds [4–8].

2. Benzoin reaction

In 1958, Breslow proposed a mechanism in which the reaction precedes *via* an enaminol intermediate popularly known as Breslow intermediate, using thiazonium zwitterion nothing but the resonance structure of an NHC. Deprotonation of thiazonium salt (A) using base generates a nucleophilic thiazolidine on addition to aromatic aldehyde furnish the tetrahedral intermediate (C) followed by proton transfer in order to obtain enaminol (D). In case of benzoin condensation, nucleophilic attack of intermediate on to another equivalent of aldehyde leads to formation of 2-hydroxy ketone (E) with subsequent elimination of the thiazolidine (B) (NHC). Transformation of carbonyl compound as transient nucleophile with NHC example of umpolung reaction and Breslow intermediate can be thought of as acyl anion equivalent (Figure 1) [9].

2.1 Homo benzoin reaction

Homo benzoin reactions are less challenging due to chemoselectivity issue and oxidation of aldehyde to corresponding carboxylic acid that could be avoided by coupling exclusion of oxygen. An efficient benzoin reaction catalyzed by

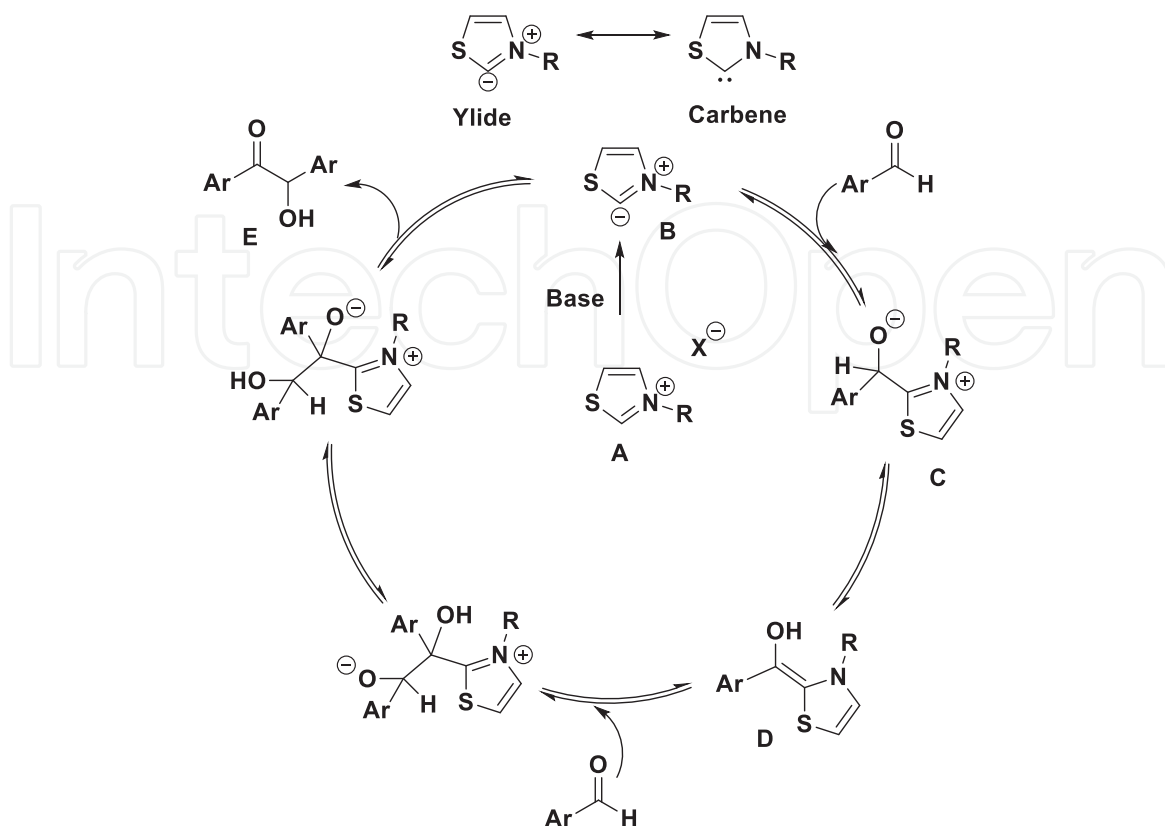


Figure 1.
Proposed mechanism of benzoin reaction.

imidazonium carbene was shown by Xu and Xia in 2005 [10] (**Figure 2**). Iwamoto et al. shows NHC catalyzed benzoin reaction in aqueous media [11, 12]. Enantioselective benzoin reaction employing NHC catalyst have many illustrations by various groups [13] (**Figure 3**). The most efficient enantioselective benzoin reaction was reported by Connon et al. with >99% ee (**Figure 4**) [14].

2.2 Cross benzoin reaction

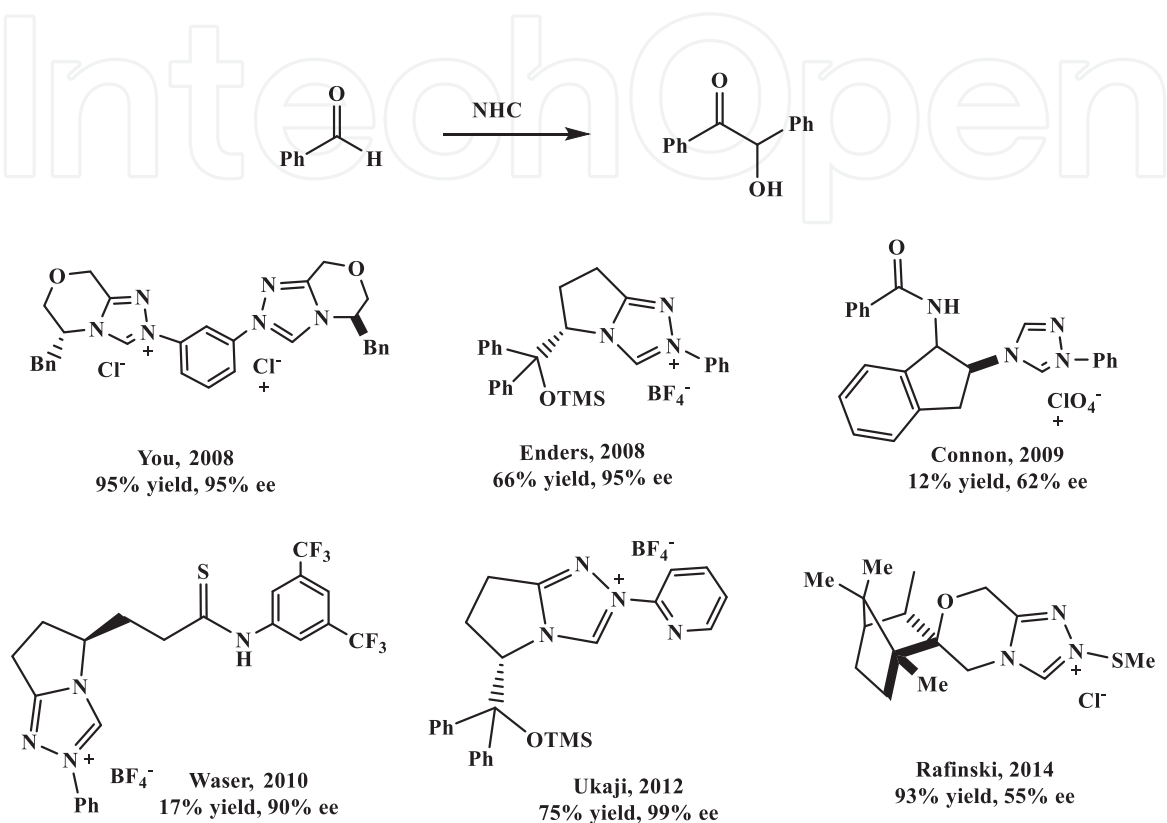


Figure 2.
 Efficient enantioselective homo benzoin reaction.

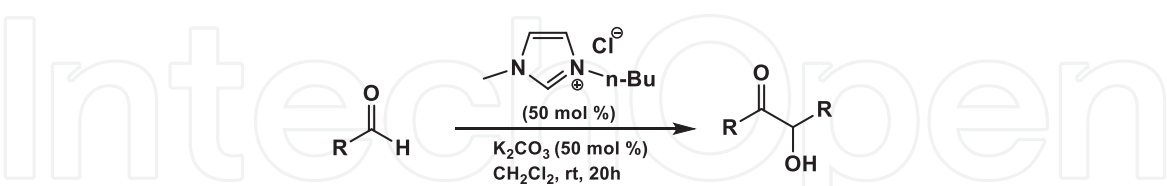


Figure 3.
 An efficient benzoin reaction catalyzed by imidazonium carbene.

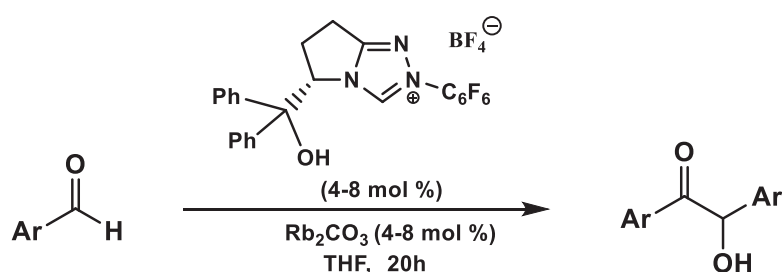


Figure 4.
 The most efficient enantioselective benzoin reaction by Connon et al. with >99%.

In an NHC driven cross benzoin reaction, total four products are possible, a pair of homo benzoin and cross benzoin adducts each. Electronic or steric reasons one of the aldehydes may be significantly less reactive. Connon et al. found that cross benzoin reaction could be biased by synthetically useful amount for the synthesis of desirable cross coupling products (**Figure 5**) [15].

Glorious et al., demonstrated a highly selective cross benzoin reaction with broad substrate scope [16]. Young et al. showed reactivity controlled by the carbene catalyst. An intermolecular cross coupling of aromatic aldehyde for the formation of Breslow intermediate is followed by coupling with acetaldehyde using thiazonium carbene catalyst. In constant acyl anion generation from acetaldehyde preferred by triazolium carbene is followed by coupling with aromatic aldehyde (**Figure 6**) [17].

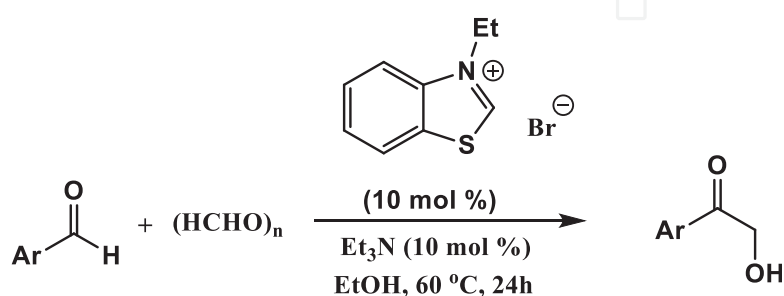


Figure 5.
Cross benzoin reaction by Connon et al.

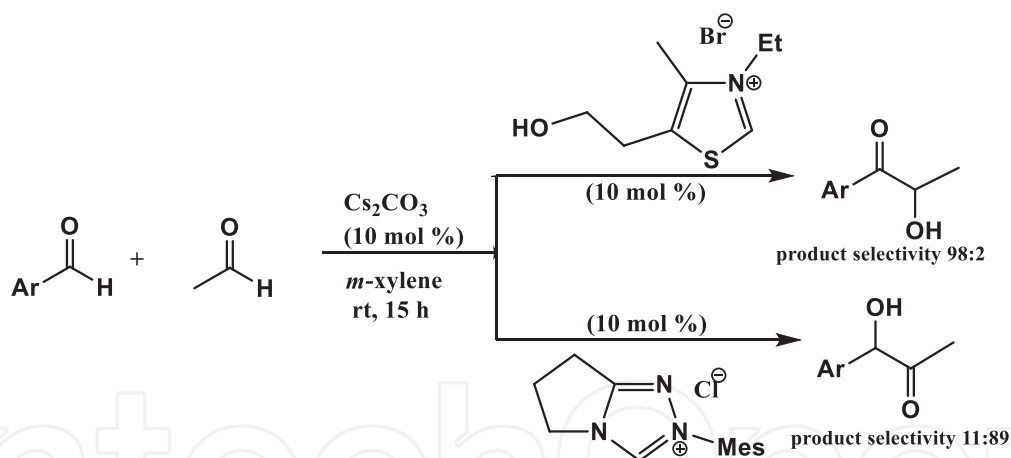


Figure 6.
Reactivity controlled reaction by using different carbene catalyst.

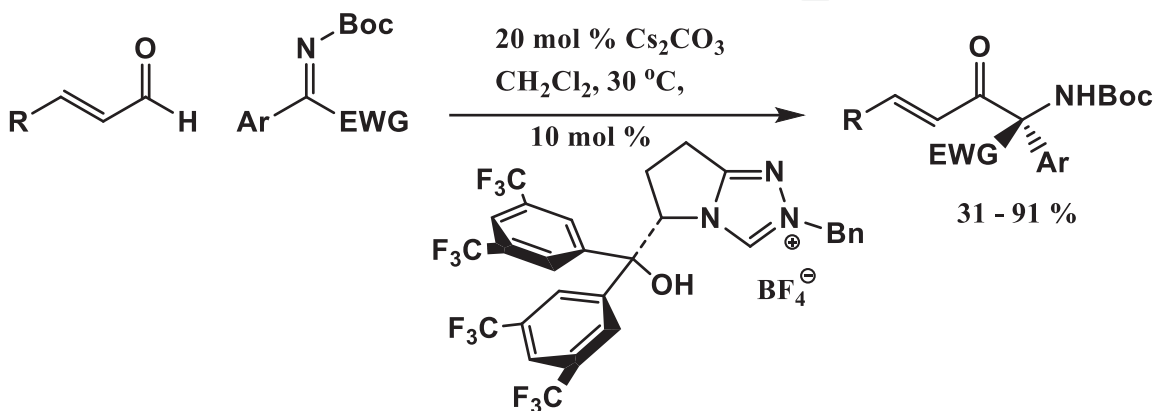


Figure 7.
The first aza benzoin reaction by Enders et al.

2.3 Aza benzoin reaction

The coupling of Breslow intermediate to imines was reported by Murry et al. for the first time [18]. NHC addition to highly electrophilic N-BOC imines leads to the formation of corresponding aza-Breslow intermediate, but this can be reversible under suitable reaction condition to obtain a pure 2-amino ketone [19]. Enders et al., reported the first aza benzoin reaction with trifluoromethyl ketimines using achiral thiazolium precatalyst [20]. Where enals reacts with trifluoromethyl ketone, obtained excellent enantioselectivity using chiral triazolium catalyst, which also furnishes electronic diminished groups tolerance (**Figure 7**) [21].

3. The Stetter reaction

In 1976, Stetter developed the thiazolium catalyzed highly selective conjugate addition reaction of aromatic/aliphatic aldehydes with an array of Michael acceptors and in most cases these reactions proceed in an intermolecular fashion [22, 23]. The Stetter reaction can be catalyzed by broad range of thiazolium, triazolium and imidazolium carbene, mostly α,β -unsaturated ketones are used as Michael acceptor. The formation of 1,4-diketone, γ -ketonitriles and γ -ketoesters resulting from NHC catalyzed Stetter reaction which is not easy by conventional method [24–27]. A mechanism of benzoin reaction of similar fashion is observed in the Stetter reaction, the in-situ generated free carbene (**B**) of azolium salt (**A**) when treated with base reacts with aldehyde, generating the nucleophilic Breslow intermediate (**D**). This intermediate undergoes irreversible addition to the Michael acceptor generating intermediate (**F**), which on proton transfer and subsequent release of free carbene affords the desired Stetter product (**G**) (**Figure 8**) [28].

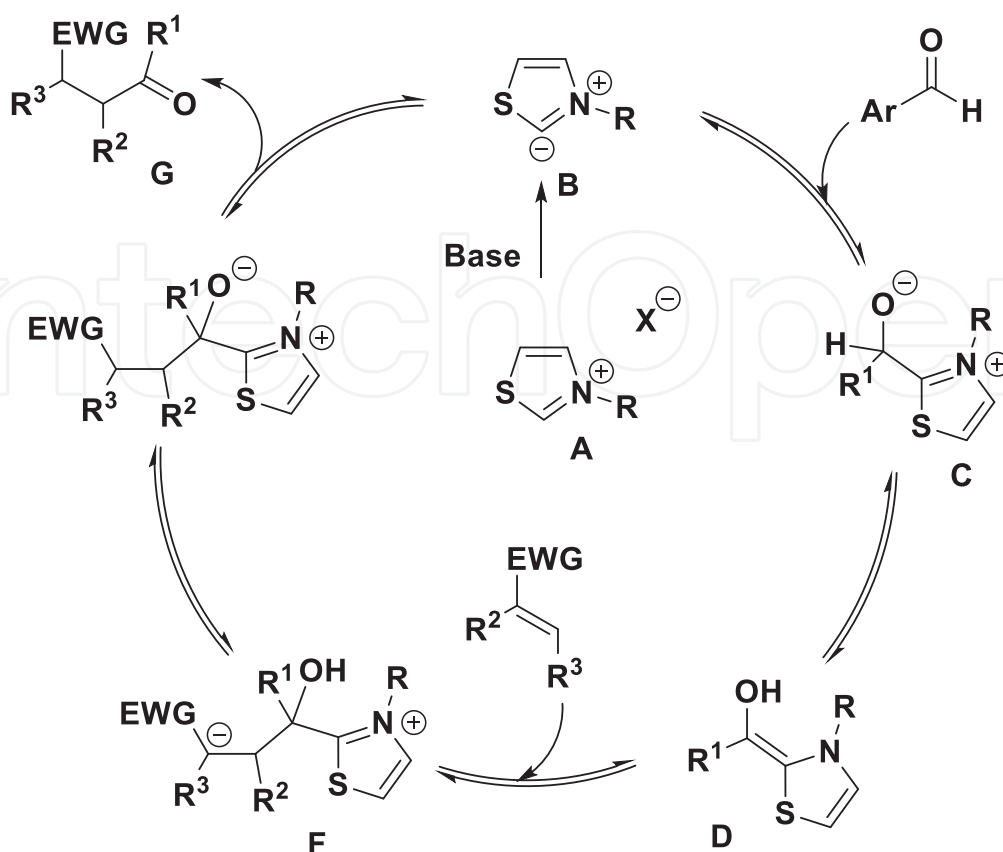


Figure 8.
 Proposed mechanism of Stetter reaction.

3.1 Intramolecular Stetter reaction

The first general intra molecular Stetter reaction was reported by Ciganek in 1995. By the next year, Enders et al. explains the first enantioselective intramolecular Stetter reaction. Later, the implementation of chiral NHC's resulted in asymmetric transformation leading to synthesis of enantioselective 1,4-bifunctional compounds. The amino indanol derived chiral triazolium salt and pentafluoroamyl-substituted were developed by Rovis et al. in 2002 for the most efficient catalyst for the enantioselective intramolecular reaction (**Figure 9**) [29–33].

3.2 Intermolecular Stetter reaction

The initial intermolecular reaction established by Endres et al. with chiral thiazolium catalyzed reaction of *n*-butanal with chalcones resulted in Stetter product with 40% ee [34, 35] (**Figure 10**).

Rovis et al. contributed in the asymmetric intermolecular Stetter reaction of glyoxamide derivatives as aldehyde component and alkylidene molecule as Michael acceptors [36, 37]. DiRocco and Rovis expanded the reaction of intermolecular

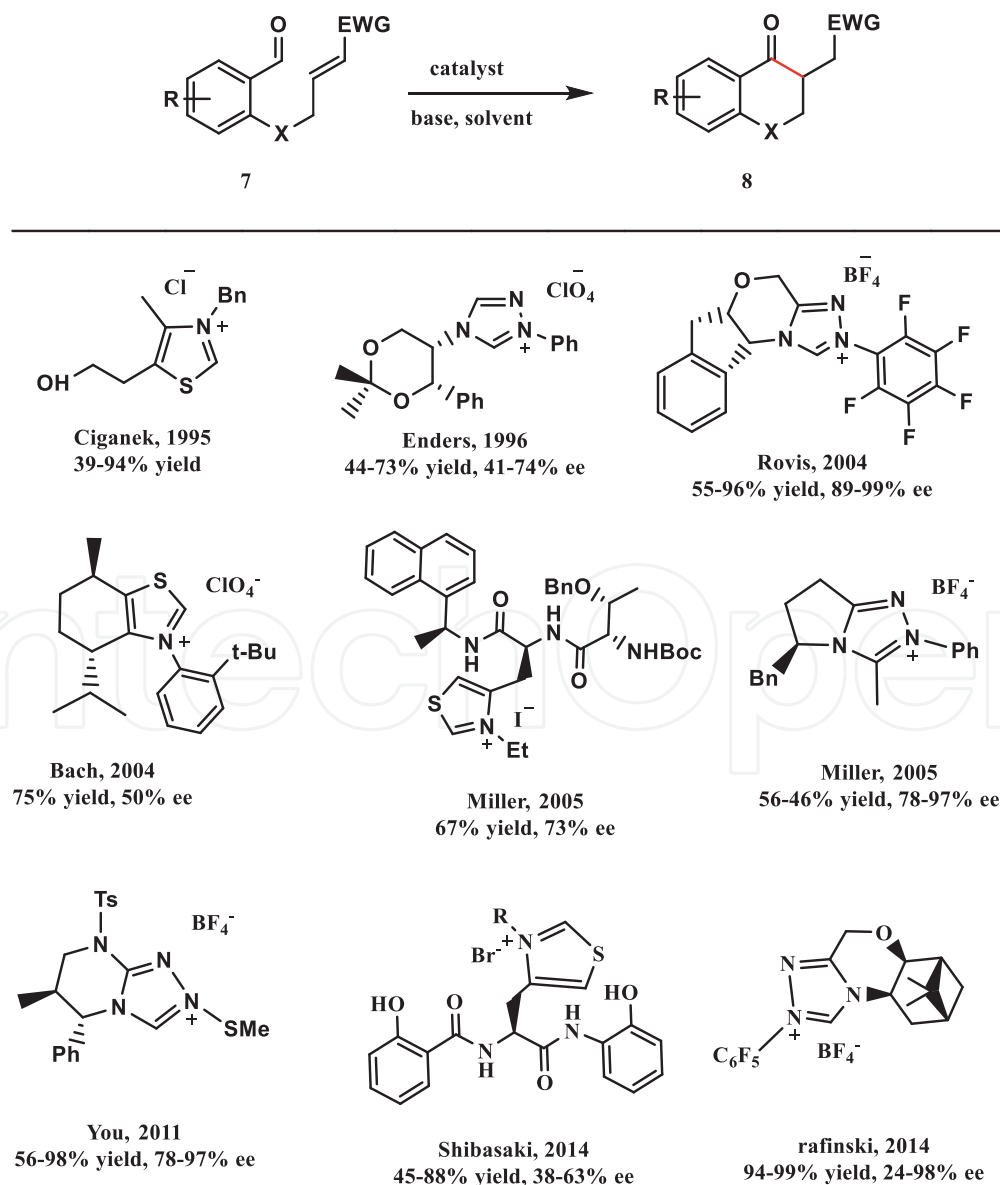


Figure 9.
Some examples of intramolecular Stetter reaction.

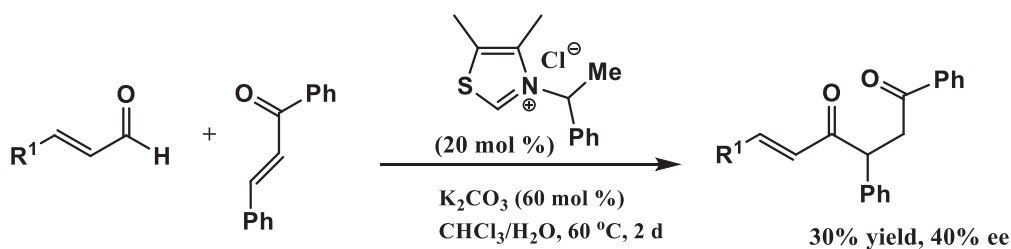


Figure 10.
 The first intermolecular Stetter reaction by Enders et al.

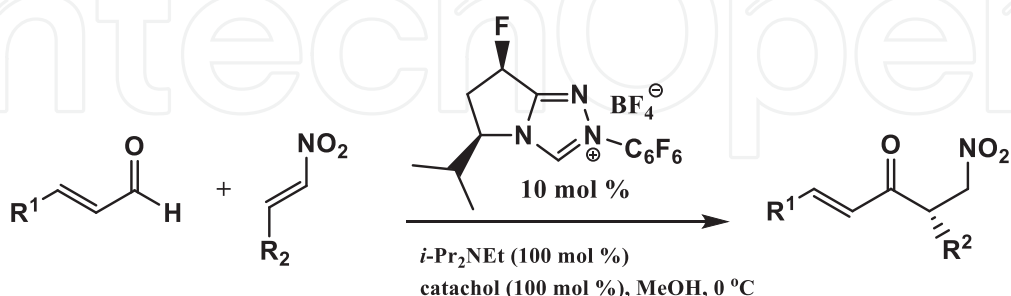


Figure 11.
 Intermolecular Stetter reaction with α,β -unsaturated aldehyde and β -nitrostyrenes.

Stetter reaction with α,β -unsaturated aldehyde as aldehyde component and β -nitrostyrenes using fluorinated triazolium salt (**Figure 11**) [38].

The synthesis of enantiomeric α -amino acid derivative was developed by Glorius et al. using *N*-allylamidoarylate as Michael accepter [39]. Biju co-workers reported the efficient enantioselective NHC catalyzed intermolecular Stetter reaction of aldehydes with α,β -unsaturated sulfones and vinyl phosphonates [40, 41].

3.3 Hydroacylation of enol ethers of double bonds and triple bonds

Acyl anion reaction has been extended followed by the addition to electron neutral as carbon–carbon multiple bonds. She and Pan explained for the first time using alkyl tosylates (**Figure 12**) and found the selectivity changes when the native substrate with a phenyl group [42]. The reaction resulted in the formation of benzofuranone and the mechanism involving the addition of the Breslow intermediate to the C–C double bond of the enol ether [43].

A very important reaction for the synthesis of chromanones from the intermolecular cyclization of 2-allyloxy benzaldehydes using thiazolium NHC-catalyst by Glorius et al. for the first time [44] (**Figure 13**). Biju et al. showed the coupling of cyclopropenes using achiral triazolium with aryl aldehyde coupling partners (**Figure 14**) [45].

3.4 Annulation reaction

The extended Breslow intermediate has explored very well especially for the synthesis of heterocyclic compounds. Bode and Glorius reported NHC catalyzed homoenolate reactivity leading to synthesis of useful molecule from simple enal cascade. The reaction involved in the formation of extended Breslow intermediate from enal with carbene followed by 1,2-addition to aryl aldehyde which was then cyclized to deliver the γ -lactone product (**Figure 15**).

Several groups explored NHC catalyzed to synthesize enantioselective γ -lactone [46–48], spirocyclic γ -lactones [49, 50]. [3 + 4] Annulation reaction between enals

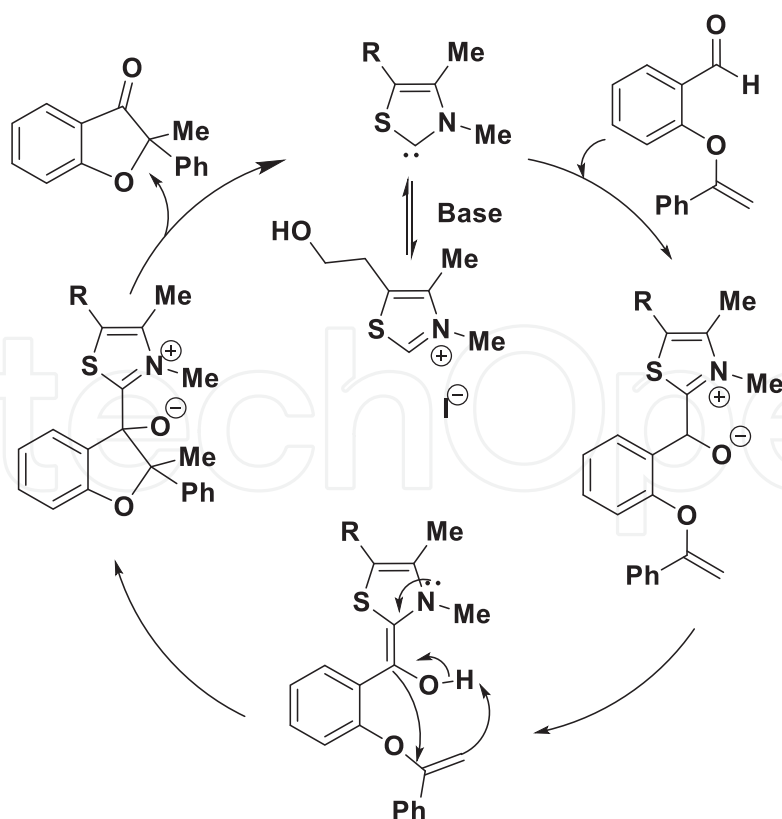
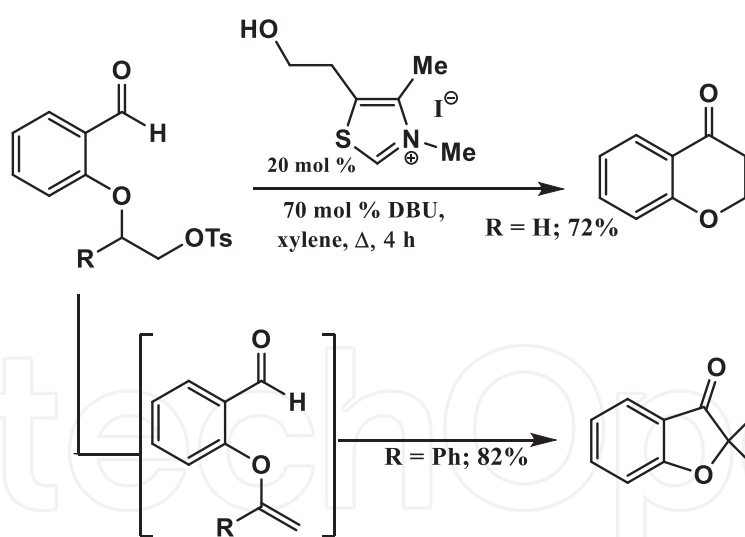


Figure 12.
Proposed mechanism of hydroacylation reaction of enol ether.



Scheme 13

Figure 13.
The intermolecular cyclization of 2-allyloxy benzaldehydes using thiazolium NHC-catalyst.

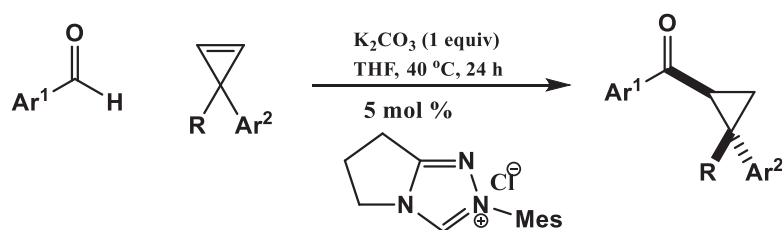


Figure 14.
The coupling of cyclopropenes using achiral triazolium with aryl aldehyde.

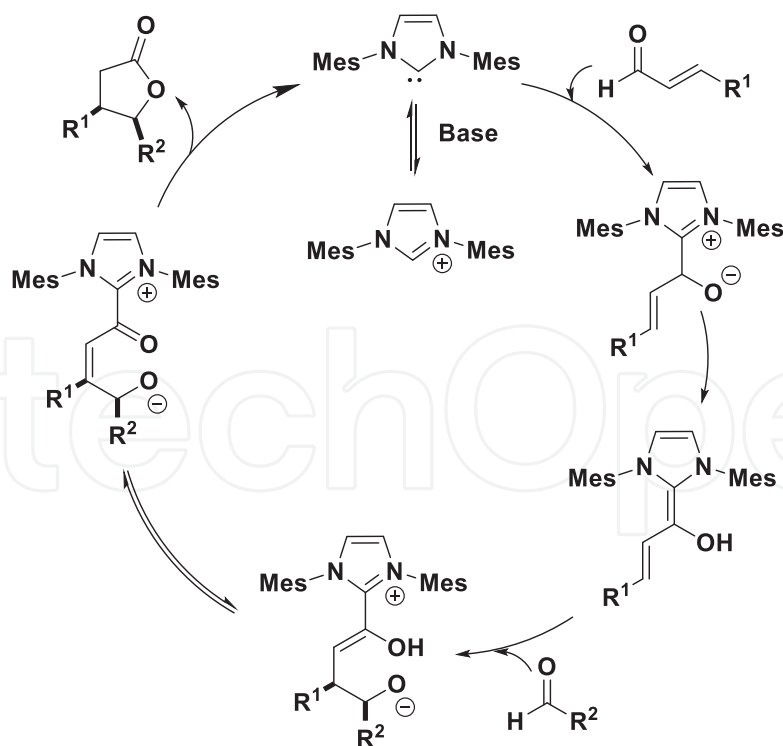


Figure 15.
Mechanism of homoenolate reactivity for the formation of γ -lactone product.

and o-quinonemethides (**Figure 16**) was reported by Ye et al. in 2013 to obtain dioxolane fused-quinone methides [51].

The [8 + 3] annulation of enals and tropone *via* conjugate addition followed by cyclization afforded a lactone (**Figure 17**), reported by Nair et al. [52].

A number of nitrogen-containing heterocycles generated by homoenolate has explored largely. Synthesis of enantioselective cyclic sulfonyl ketamine annulation [53], β -lactam formation [54], synthesis of pyrazolidinones [55], isoxazolidinone formation [56] and mainly nitroso coupling reactions [57] and others have many

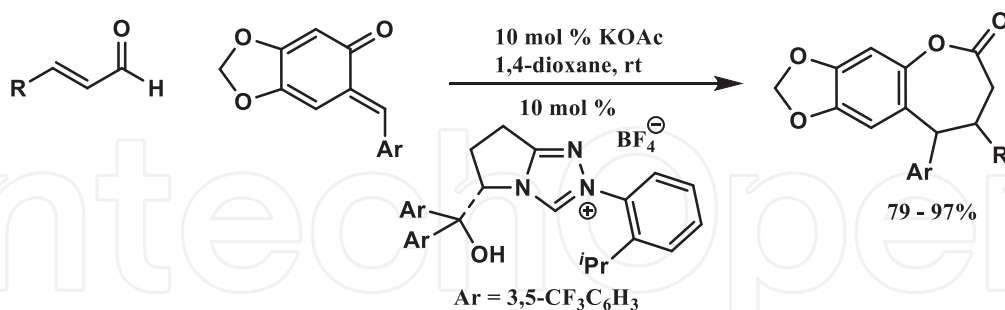


Figure 16.
[3 + 4] Annulation reaction between enals and o-quinonemethides.

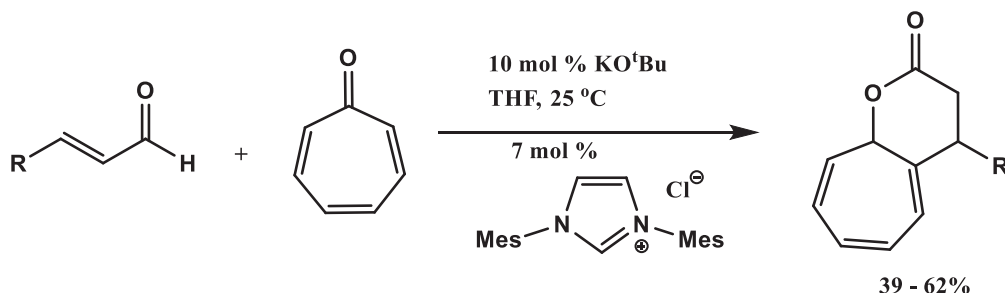
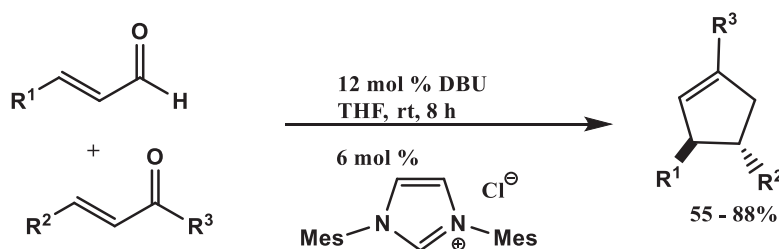


Figure 17.
[8 + 3] Annulation of enals and tropone.

**Figure 18.**

The first NHC generated homoenolate in the formation of cyclopentenones.

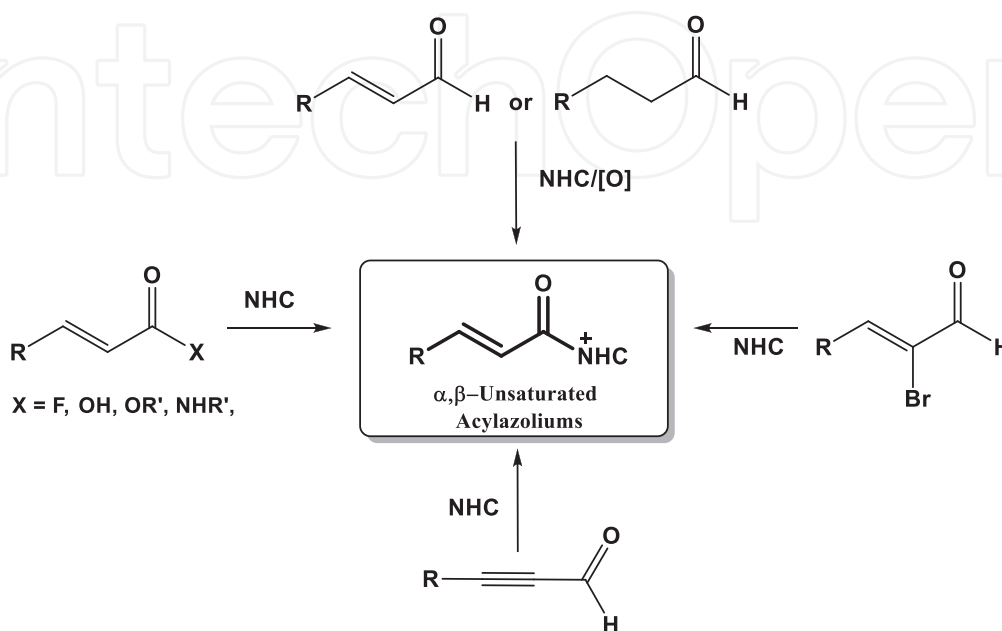
synthetic applications. The first NHC generated homoenolate further utilized in the formation of cyclopentenones was introduced by Nair et al. in 2006 [58, 59]. The homoenolate intermediate reacts with chalcones generates allyloxy, further cyclized 4-membered β -lactone which decarboxylate to provide cyclopentene (Figure 18).

4. α,β -Unsaturated acylazolium intermediate

An important strategy of non-umpolung transformation reaction proceeds through the α,β -unsaturated acylazolium conjugation addition of various bis-nucleophile, a wide variety of carbo cycles and heterocycles are synthesized. 1,2-addition followed by cyclization [4, 5, 60]. α,β -unsaturated acylazoliums can be generated from α,β -unsaturated aldehyde with external oxidants [61–66], ynals, 2-bromo enals [67–69], α,β -unsaturated esters [70] or acyl fluorides [71, 72], etc. (Figure 19).

The main application of acylazolium intermediate found in the biosynthesis of clavulanic acid (potent β -lactamase inhibitor) from conjugation addition of L-arginine to the α,β -unsaturated acylazolium, demonstrated by Merski and Townsend (Figure 20) [73, 74].

Lupton reported the Claisen type reaction of α,β -unsaturated enol esters to the corresponding acylazolium/enolate pair followed by rearranged to 2,3-dihydropyrazones (Figure 21) [71, 72].

**Figure 19.**

Generation of α,β -unsaturated acylazoliums.

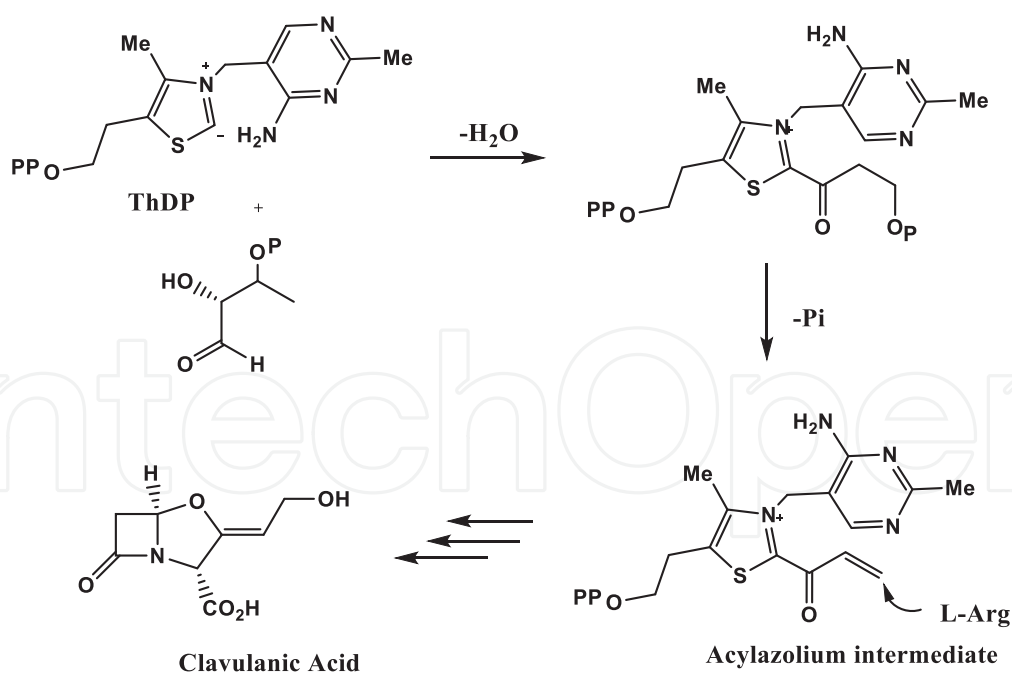


Figure 20.
Acylazolium intermediate found in the biosynthesis of clavulanic acid.

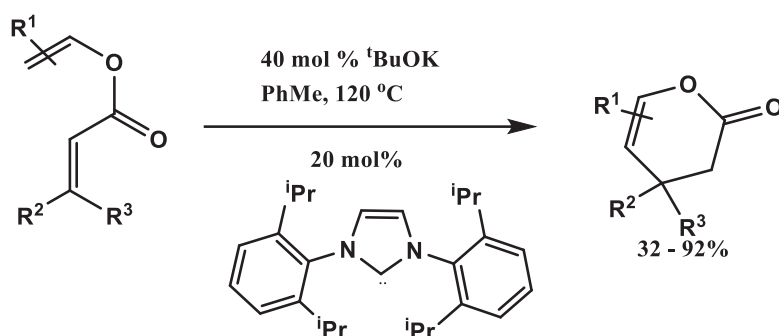


Figure 21.
Claisen type reaction of α,β -unsaturated enol esters to 2,3-dihydropyranones.

The generated electrophilic acylazolium intermediates involved in various annulation and cycloaddition reaction with bis-nucleophiles. α,β -unsaturated acylazolium with various cyclic and acyclic bis-nucleophiles for the synthesis of dihydropyranones and dihydropyridines in a formal $[3 + 3]$ annulation reaction (**Figure 22**), demonstrated by Biju et al. [68].

Cycloaddition reaction of α -bromo enals with 1,3-diketones by using different achiral NHC catalyst obtained the product with the same absolute configuration but different stereodirecting substituents (**Figure 23**) [67].

5. Conclusion

N-heterocyclic carbenes have had a broad scope in the field of organic chemistry, often tolerating the construction of complex molecules from simple starting materials. The various modes of NHC catalysis such as the generation of Breslow intermediates, homoenolates, α,β -unsaturated acylazoliums, NHC enolates can be engaged in the synthesis of various heterocycles and carbocycles. The use of enantiomerically pure carbene catalyst can result in asymmetric synthesis of the

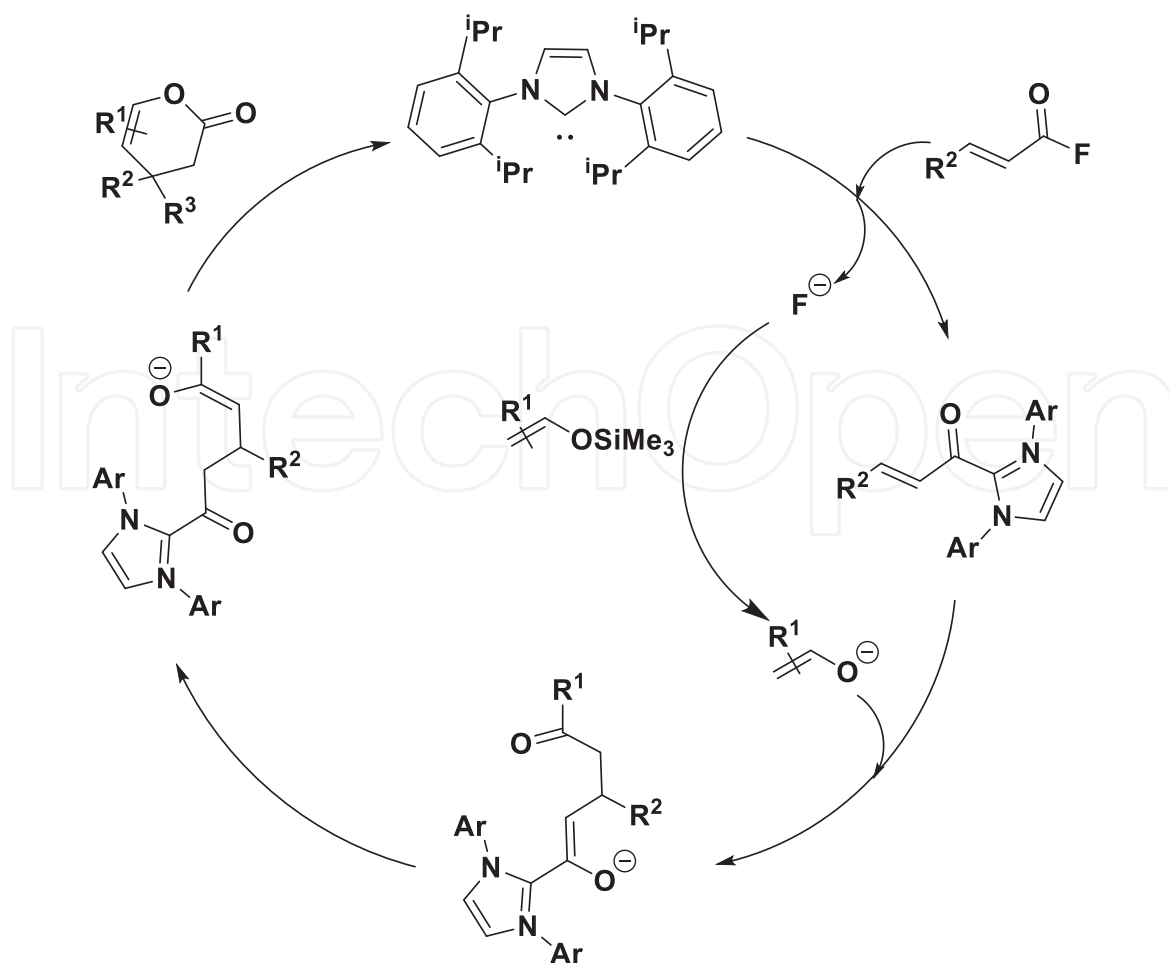


Figure 22.
The synthesis of dihydropyranones in a formal $[3 + 3]$ annulation reaction.

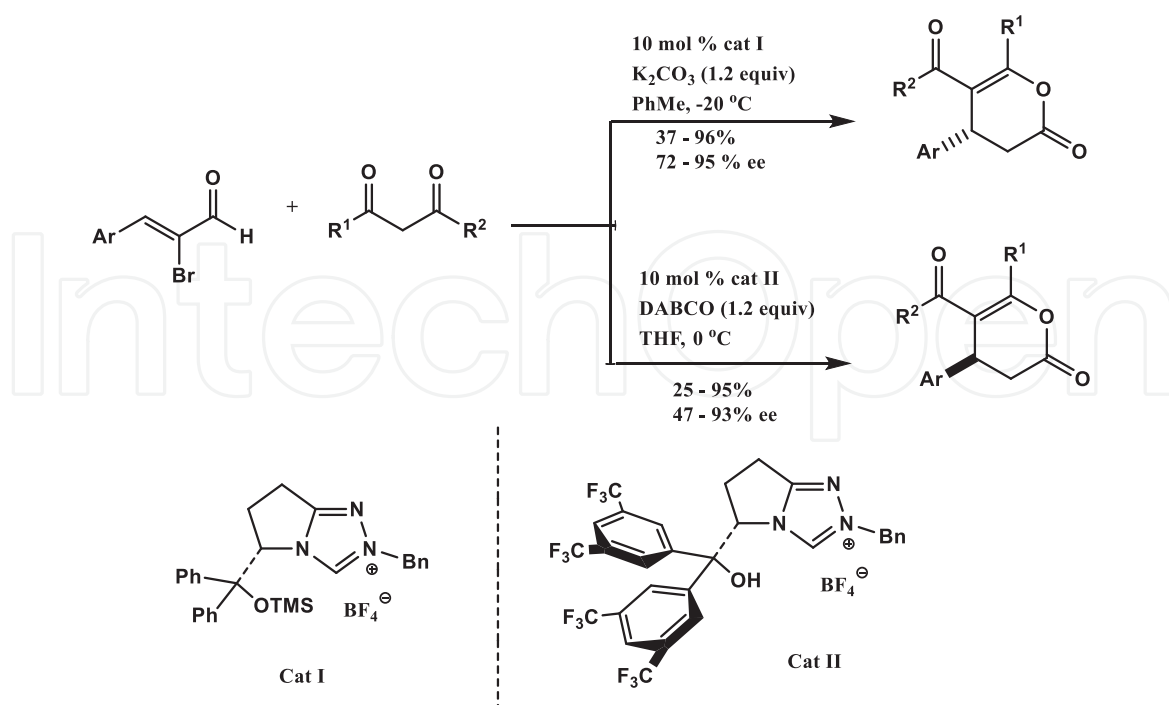


Figure 23.
Cycloaddition reaction of α -bromoaldehydes with 1,3-diketones.

target molecules. This chapter has focused on the reactivity pathways which expand the variety reactions with suitable reaction companions beyond the old-fashioned aldehydes with enhanced catalytic conventions.

Conflict of interest

The authors declare no conflict of interest.

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