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Complete List of Authors:	Nair, Vijay; Regional Research Laboratory (CSIR), Organic Chemistry Section Menon, Rajeev; Indian Institute of Chemical Technology, Natural Products Chemistry Biju, Akkattu; National Chemical Laboratory (CSIR), Organic Chemistry Division

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ARTICLE TYPE

Recent advances in employing homoenolates generated by N-heterocyclic carbene (NHC) catalysis in carbon-carbon bond-forming reactions

Rajeev S. Menon,[a] Akkattu T. Biju,[b] and Vijay Nair*[c]

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The use of NHCs for generating homoenolate species has gained widespread popularity in the recent years. A number of highly stereoselective processes of NHC-homoenolates have emerged. Homoenolate reactions have also been employed as key steps in total synthesis of a number of natural products. The use of compatible co-catalysts, improved NHC-catalyst design and use of novel precursors for homoenolate generation are among the major developments of this area that were disclosed recently. This *tutorial review* organises and presents the advancements in this rapidly growing area of catalysis and in the process updates a previous account published in 2011 in this journal.

Key Learning points

- The conceptual framework of NHC-catalysed homoenolate chemistry for beginners.
- The variety of reactions that such homoenolates can partake in.
- A consolidated picture of various reaction pathways available to NHC-homoenolates
- Major recent advances in asymmetric synthesis using NHC-homoenolate chemistry
- The use of unconventional precursors for NHC-mediated homoenolate generation

1. Introduction

Carbon-carbon bond forming reactions of enolates and their synthetic equivalents constitute the bedrock of organic synthesis. *Nature's* way of making carbon-carbon bonds almost always involves an enol/enolate/enamine type nucleophile and it is *natural* that man emulates this. Removal of a α-hydrogen of a carbonyl compound by a suitable base is the standard method to generate an enolate intermediate. Availability of methods for the generation enolates of defined regio-and stereochemistry and their use in stereoselective aldol reactions has enabled the modern chemist to undertake the synthesis of numerous complex natural products with confidence. Modern organocatalysis pivots around enamine activation of carbonyl compounds which can be dated back to the pioneering work of Stork[1] on the synthesis and use of enamines as enolate equivalents.

Carbon-carbon bond formation at the α-position of carbonyl compounds mostly rely on aldol-type processes, whereas bond formation at the β-position is usually achieved by another classical reaction, the Michael addition. The latter reaction exploits the electrophilic nature of the β-carbon of an α,β-unsaturated carbonyl compound. A rather counter-intuitive consideration of negatively polarised β-carbon opens up many interesting synthetic possibilities. Such a reactive intermediate that is homologous to an enolate would constitute a 'homoenolate'. By definition it must exhibit nucleophilic character at the carbon β-to a carbonyl group or a moiety that can be transformed into a carbonyl group (Fig. 1).[2]

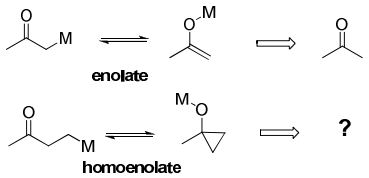
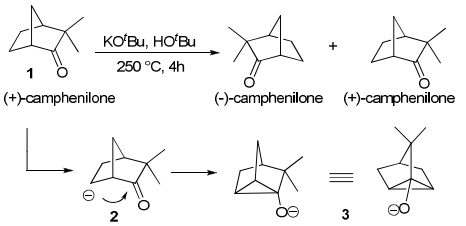


Figure 1: Comparison of enolate and homoenolate

As the carbonyl group is incapable of stabilizing a β-negative charge, indirect methods are required for the generation of homoenolates. Historically, the 1962 report of base-catalysed racemisation of (+)-camphenilone **1** by Nickon and Lambert may be considered as the first description of a homoenolate generation (Scheme 1).[3] The racemisation of **1** was explained by invoking homoenolate **2** that is formed by base-mediated deprotonation at the β-carbon (note that α-deprotonation would lead to a bridge-head double bond-bearing enolate). The non-classical anion **2** interacts with the ketone functionality leading to the symmetric cyclopropanolate **3** and subsequent C-protonation leads to racemisation. The involvement of **3** was established by deuterium labeling studies.

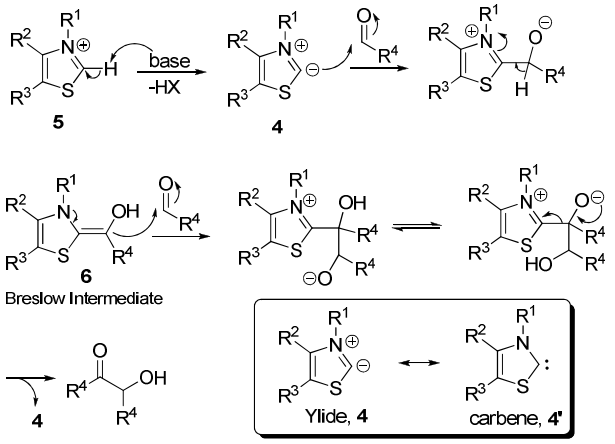


Scheme 1: Homoenolate involvement in the racemisation of camphenilone

Although the concept was demonstrated as early as in 1962, the use of homoenolates was seldom explored as a strategy in organic synthesis, mainly due to the lack of mild and convenient methods for generating them. In 2004, NHC-catalysed generation of homoenolates from enals was discovered and this triggered a flurry of activity in the area of homoenolate chemistry. A detailed discussion of the recent developments in this area are provided in the following sections.

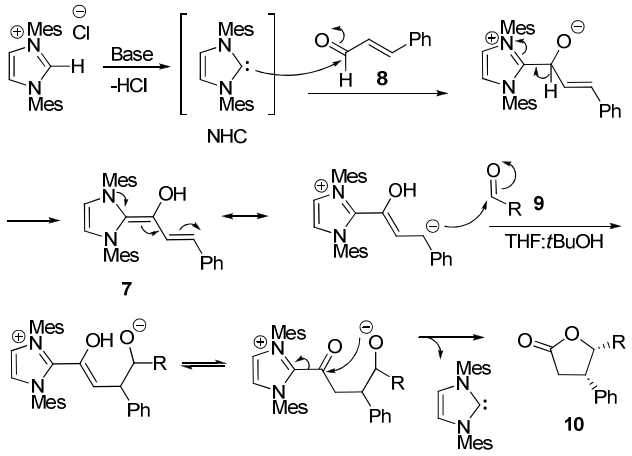
2. N-Heterocyclic carbenes (NHCs) and homoenolates

The ideal starting point for any discourse on NHCs is the seminal report[4] by Breslow on the generation of thiazolylidene species **4** by deprotonation of the corresponding thiazolium species **5**. The latter is a key structural fragment of the co-enzyme thiamine which is known to mediate a number of biotransformations such as pyruvic acid decarboxylation and acetoin condensation. Breslow postulated that the thiazolydine species **4** functions as a nucleophilic catalyst that is responsible for the biotransformations mediated by the co-enzyme. He also demonstrated that a similar thiazolylidene intermediate can catalyse benzoin condensation of aldehydes. The key intermediate **6** in Breslow's postulate is commonly referred to as the 'Breslow intermediate' (Scheme 2).[5] The mechanistic insight provided by Breslow's work facilitated various subsequent explorations. It was later recognised that the thiazolylidene **4** may also be represented as its resonance form **4'** (Scheme 2) which is a nucleophilic heterocyclic carbene (NHC). Presently, the utility of NHCs as organocatalysts, ligands, reagents and stable, isolable carbenes stands well-established.



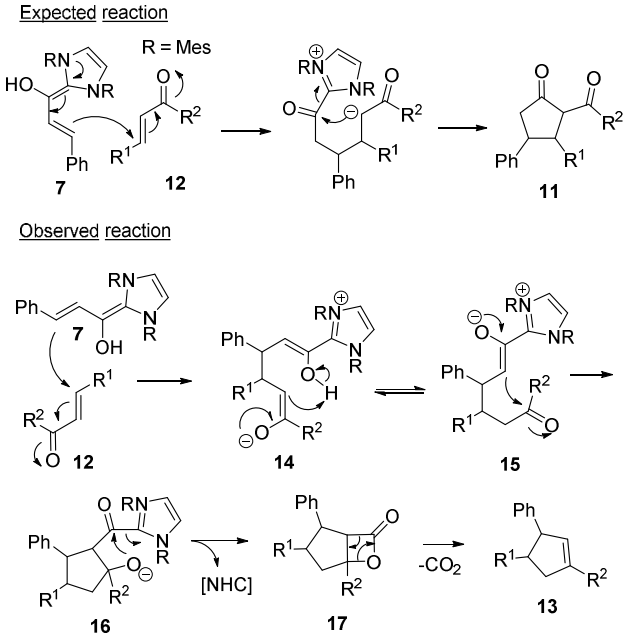
Scheme 2: NHC-catalysed benzoin reaction: Breslow's postulate

Aldehydes function as acyl anion equivalents under conditions of NHC catalysis. Analogous reactive intermediates generated from α,β-unsaturated aldehydes can exhibit nucleophilic character at the β-carbon by virtue of conjugation. In 2004, Glorius[6] and Bode[7] independently reported that extended Breslow intermediates such as **7** are indeed generated from enals **8** and they could be intercepted with aldehydes **9** leading to the formation of γ-lactones **10** (Scheme 3). The formation of **10** clearly involves a homoenolate species. In the absence of an intercepting agent, homo-dimerisation of the enal leading to the formation of corresponding γ-lactone was observed.[7]



Scheme 3: NHC-catalysed generation of homoenolates from enals

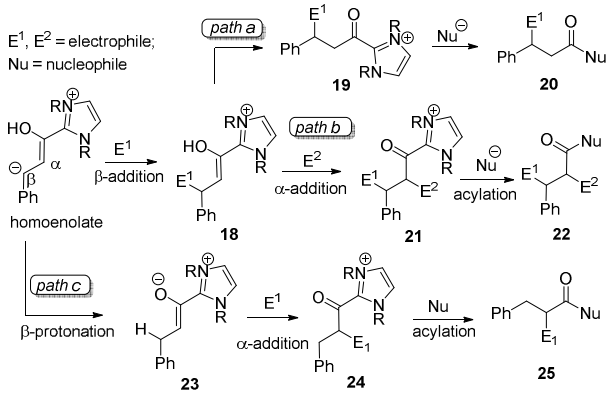
Investigation of the reactions of NHC-homoenolates with Michael acceptors in our group unraveled another intriguing reaction pathway in 2006.[8] A [3+2]-annulation analogous to the one depicted in Scheme 3 would have led to an acyl cylopentanone **11**; however, the reaction of **7** with enone **12** afforded a trisubstituted cyclopentene **13** (Scheme 4). The mechanistic events that culminate in the formation of **13** are also depicted in Scheme 4. The initial Michael addition of homoenolate **7** to the enone produces an enolate **14** which does not engage in an intramolecular *C*-acylation to produce the expected acyl cyclopentanone. Instead, **14** exists in a dynamic equilibrium with the isomeric enolate **15** which undergoes an intramolecular aldol reaction with the ketone functionality. The alkoxide **16** thus generated ejects the NHC catalyst to form a β-lactone intermediate **17**. The cyclopentene product **13** is then formed via a retro-[2+2] decarboxylation reaction.



Scheme 4: Cyclopentene synthesis from homoenolates and enones

The above-mentioned reports heralded a new era in the area of homoenolate chemistry and NHC catalysis and a variety of novel and stereoselective transformations involving homoenolates derived from enals were reported in the following years. We have attempted to put the developments in this rapidly growing area of research into perspective in two earlier tutorial reviews.[9,10] In the last three years developments such as new reactivity modes of NHC-enal homoenolates, co-catalysis involving NHCs, new precursors for homoenolate generation and improved chiral NHC design were reported. This tutorial review aims to bring these discoveries together and thereby provide a better understanding of the reactions of NHC-homoenolates. Selected articles published in this area since 2011 are covered in addition to some important pre-2011 reports which are relevant for the discussion. The discussion is limited to carbon-carbon bond-forming reactions involving NHC-homoenolates. Other modes of NHC-catalysis have been covered in a few recent reviews.[11-12]

A thematic representation of the various reactivity/regioselectivity modes available for the extended Breslow intermediate **7** is depicted in Scheme 5. Acyl anion type reactivity (benzoin and Stetter reactions) are rarely observed with enals presumably due to steric bulk of the NHC moiety. Addition of an electrophile E^1 most commonly takes place at the β-carbon. The resulting enol **18** may tautomerise to form the acyl azolium **19** which can react with a nucleophilic species (embedded in E^1 or external) to form the final product **20** (path a). Alternatively, enol **18** may react with a second electrophile E^2 (embedded in E^1 or external) at the α-carbon forming the more functionalised acyl azolium **21**. Acylation of the latter with a nucleophile furnishes the product **22** in which all the carbon atoms of the original enal are functionalised (path b). When the reaction conditions favor protonation at the β-carbon (or an internal proton shift of the homoenolate), the enolate **23** is generated which reacts at the α-carbon with the electrophile E^1. Acylation of the α-functionalised acyl azolium **24** then affords the final product **25** (path c).



Scheme 5: Reactivity/regioselectivity modes of NHC-homoenolates

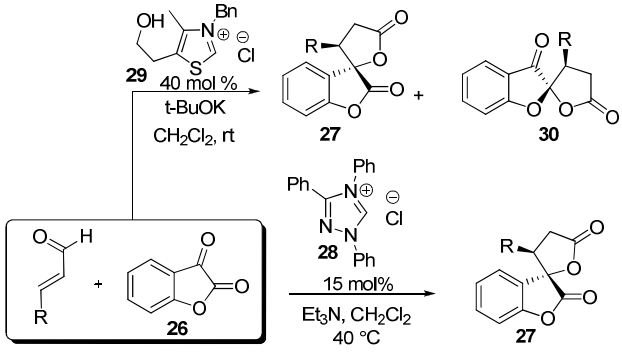
It is important to note that aspects of stereoselection (relative and absolute) also need to be considered for each of the bond-forming steps depicted in Scheme 5, while developing NHC-catalysed transformations.

In the following sections, different types of NHC-homoenolate reactions are discussed in detail. The classification is loosely based on the type of electrophile as well as the mechanistic pathways involved.

3. Reaction of homoenolates with carbonyl electrophiles

The seminal reports by Glorius[6] and Bode[7] in fact represent the first example of [3+2] annulation of an NHC-homoenolate with a carbonyl group (Scheme 3). Aldehydes and *N*-sulfonyl imines[13] react readily with homoenolates to afford γ-lactones and γ-lactams respectively. Ordinary ketones do not react with homoenolates; however, keto functionalities of 1,2-diones and isatins annulate homoenolates to afford the corresponding lactones.[14]

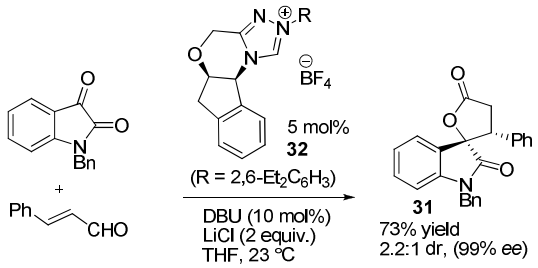
Nair[15] and Cheng[16] independently reported NHC-catalysed spiroannulation of benzofuran-2,3-dione **26** by enals leading to the stereoselective formation of bis-spirofuranone **27** (Scheme 6). The NHC derived from the triazolium salt **28** afforded the spirocyclic products **27** whereas the use of NHC generated from thiazolium salt **29** resulted in the formation of two spirocyclic products **27** and **30**.



Scheme 6: NHC-catalysed spiroannulation of benzofurandiones and enals

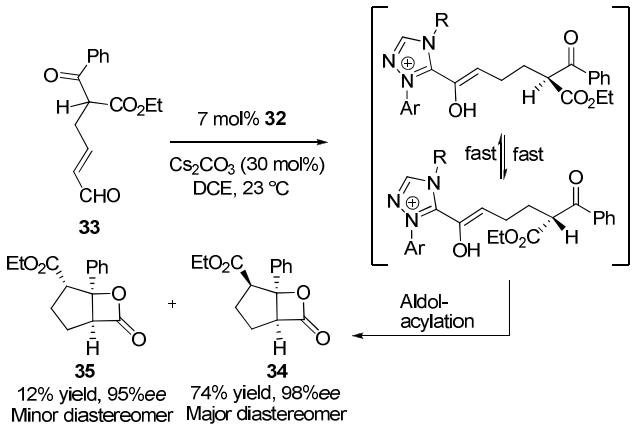
An enantioselective homoenolate annulation of enals with isatins has been reported to afford spirocyclic lactones **31** under

conditions of cooperative catalysis by chiral triazolium NHC **32** and the Lewis acid, lithium chloride (Scheme 7).[17] Intriguingly, the use of LiCl was detrimental for the enals bearing β-alkyl substituents. This method has found application in the asymmetric total synthesis of the anticancer marine natural product maremycin B. Notably, Ye reported the related enantioselective annulation reaction where the key for asymmetric induction is the hydrogen-bonding interaction of NHC with the isatins.[18]



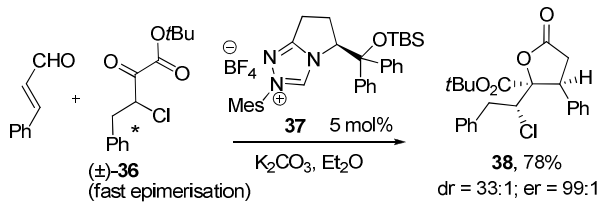
Scheme 7: Asymmetric spirolactone synthesis via NHC-LiCl cooperative catalysis

An azolium NHC-catalysed dynamic kinetic resolution (DKR) of β-keto esters **33** endowed with an enal moiety afforded highly substituted β-lactones **34-35** with excellent levels of stereoselectivity. Here, the homoenolate generated from the enal **33** undergoes protonation and the resulting diastereomeric pair of NHC enols undergoes fast epimerisation under the basic conditions required for NHC generation (Cs_2CO_3). An intramolecular aldol reaction followed by acylation affords the cylopentane fused β-lactones **34-35** (Scheme 8). Notably, one out of the four potential diastereomeric products is formed preferentially. The reaction proceeds via a 6-membered cyclic transition state formed by a favorable hydrogen-bonding interaction between the NHC-enol and ketone oxygen. A destabilizing gauche interaction of the ethyl ester and the aryl group is responsible for the observed diastereoselectivity.[19a] Recently, Scheidt applied the NHC-catalyzed DKR/ decarboxylation strategy for the enantioselective formal synthesis of the benzopyran estrogen receptor β-agonist.[19b]



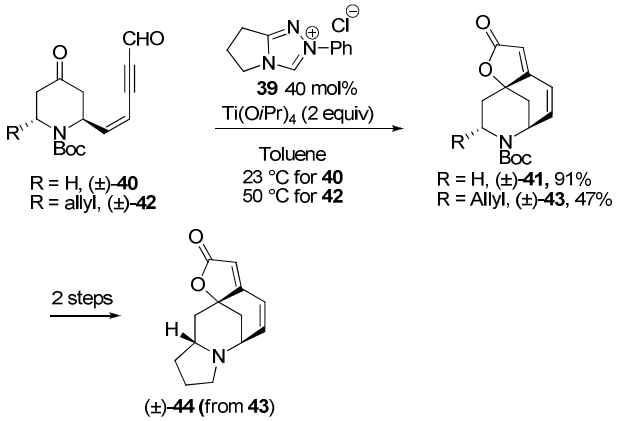
Scheme 8: NHC-catalysed dynamic kinetic resolution of β-keto esters

Johnson reported an intermolecular asymmetric NHC-homoenolate annulation reaction which involves the dynamic kinetic resolution of racemic β-chloro α-keto esters **36**. The chiral NHC **37** promotes homoenolate annulation of the highly electrophilic keto group in **36** leading to the formation of the γ-lactone product **38** in excellent diastereo- and enantioselectivity (Scheme 9). Rapid epimerisation of the halogen bearing chiral center is operating under the enantiomer-distinguishing conditions of homoenolate annulation and this results in the selective formation of a single enantiomer of the final product **38**. This intermolecular DKR process selectively installs three contiguous stereocenters in a highly functionalised product.[20]



Scheme 9: NHC-catalysed intermolecular dynamic kinetic resolution via homoenolate annulation

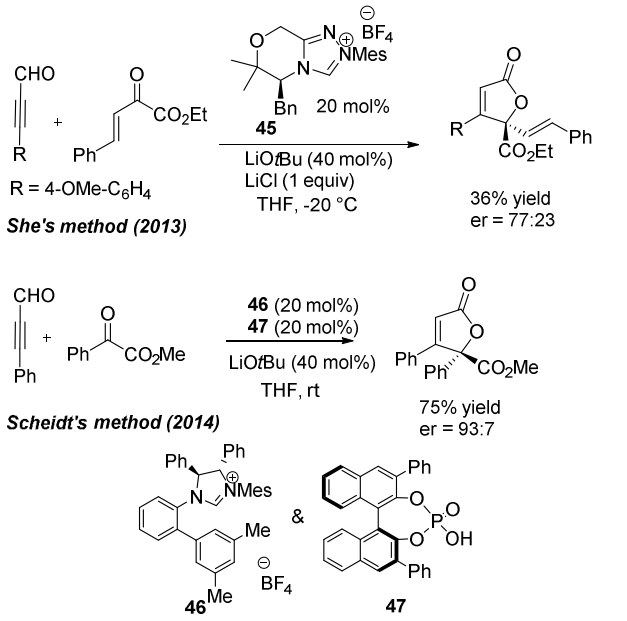
NHC-compatible co-catalysts have been successfully employed for activating the otherwise inert ketones towards homoenolate annulation. An elegant application of NHC-Lewis acid co-operative catalysis for the synthesis of securinega alkaloids was reported by Snyder. The combination of the triazolium precatalyst **39** and titanium isopropoxide promoted the spirocyclisation in toluene. The sparingly soluble nature of the catalyst **39** in toluene ensures that the concentration of the reactive species is reduced and thus the competing decomposition routes for the rather labile ynal **40** are blocked. The model system **40** afforded an excellent yield of the tricyclic product **41**, whereas the allyl derivative **42** afforded a lower yield of the desired product **43** under slightly different reaction conditions. The butenolide **43** was then transformed into the natural product 3-deshydroxy-secu'amamine A **44** in just two steps (Scheme 10).[21]



Scheme 10: NHC-Lewis acid cooperative catalysis in alkaloid synthesis

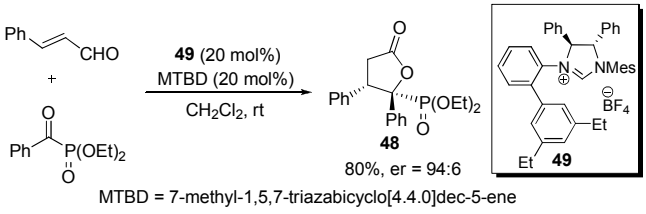
Asymmetric, intermolecular variants of the above-described butenolide synthesis from ynals and 1,2-dioness were developed by She[22a] and Scheidt.[22b] She's method involves the triazolium catalyst **45** and LiCl as the Lewis acid to achieve very good yields and moderate enantioselectivity for the products. Scheidt's protocol relies on the combination of a C_1-symmetric

imidazolium catalyst **46** and a chiral Brønsted acid **47** to furnish the corresponding butenolides in high yields and enantioselectivities (Scheme 11).



Scheme 11: Ynal-ketone intermolecular annulation via NHC-Lewis acid cooperative catalysis

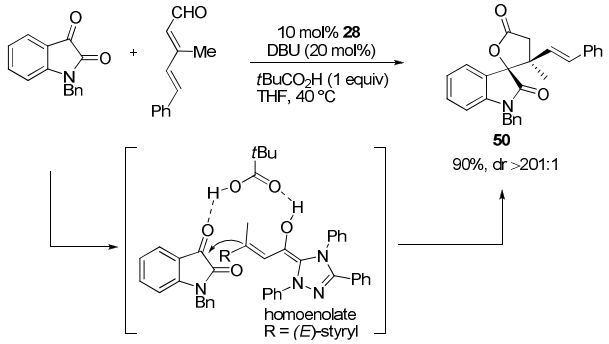
A [3+2] annulation of homoenolates and acylphosphonates leading to the formation of enantioenriched γ-lactones **48** was reported recently. Computational modeling of transition states allowed the rational design of a chiral NHC generated from the imidazolium salt **49** which provided excellent levels of enantioselectivity for the lactone products (Scheme 12).[23]



MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene

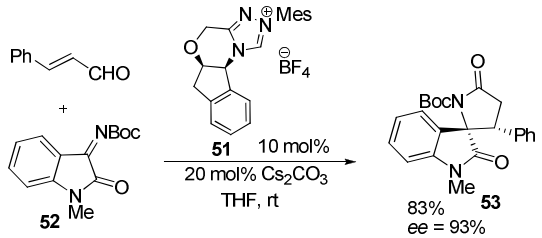
Scheme 12: [3+2] annulation of homoenolates and acylphosphonates

Reactions of homoenolates generated from sterically demanding β-disubstituted enals has also been reported. The stereoselective annulation of such disubstituted homoenolates with isatins proceeded smoothly in the presence of an additional Brønsted acid co-catalyst leading to the formation of spirocyclic oxindoles **50** bearing two highly congested contiguous quaternary carbon centers (Scheme 13).[24] The acid co-catalyst activates and connects the reaction partners through hydrogen bonding. A catalytic enantioselective version of the process was also developed albeit with somewhat reduced diastereoselectivity.



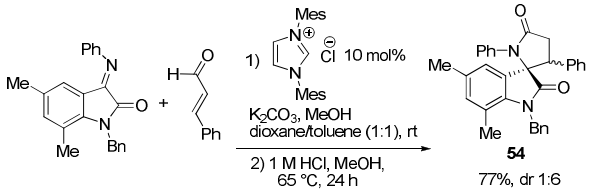
Scheme 13: NHC- Brønsted acid dual catalysis for spirolactone synthesis

Chiral triazolium catalyst **51** promotes a highly enantioselective spiroannulation of isatin-derived *N*-Boc ketimines **52** and enals to afford spirocylic oxindole γ-lactams **53** (Scheme 14).[25]



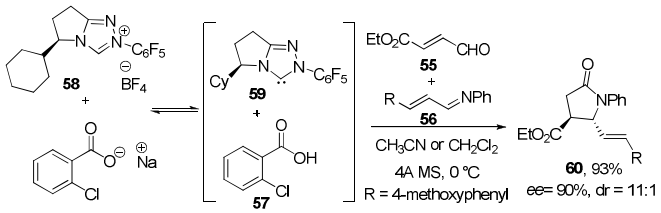
Scheme 14: NHC-catalysed spiroannulation of isatin-ketimines

Jiao reported the one-pot synthesis of similar γ-lactam oxindoles **54** by NHC-catalysed reactions of enals with *N*-aryl isatin-imines via homoenolate intermediate. The diastereoselectivity of the reactions was moderate (Scheme 15).[26]



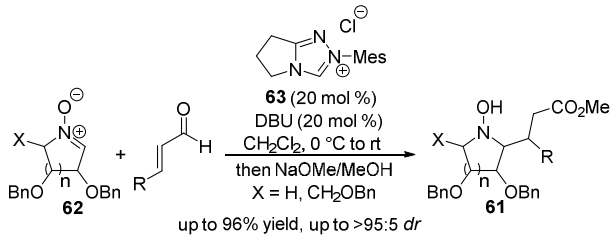
Scheme 15: NHC-catalysed reactions of enals with *N*-aryl isatin-imines

Rovis demonstrated that strongly electrophilic and commercially available ethyl *trans*-4-oxo-2-butenoate **55** and unactivated α,β-unsaturated imines **56** can be annulated in a highly enantio- and diastereoselective manner by homoenolates under conditions of NHC-Brønsted acid cooperative catalysis. The conjugate acid **57** of the 2-chlorobenzoate base used for deprotonation of precatalyst **58**, serves as the Brønsted acid in the reaction. The pentafluorophenyl bearing NHC **59** is less electron-rich and is not affected by the weak Brønsted acid **57**. The Brønsted acid brings the reagents together via hydrogen bonding interactions with the nitrogen of imine **56** and the OH group of Breslow intermediate. The functionalised *trans*-γ-lactam products **60** are obtained in excellent yields (Scheme 16).[27]



Scheme 16: Asymmetric lactam synthesis via NHC- Brønsted acid cooperative catalysis

Yu reported the formation of γ-hydroxy amino esters **61** by NHC-catalysed addition of enals to sugar derived cyclic nitrones **62** (Scheme 17). The products **62** were then employed in the synthesis of a variety of polyhydroxylated pyrrolizidines and indolizidines.[28]

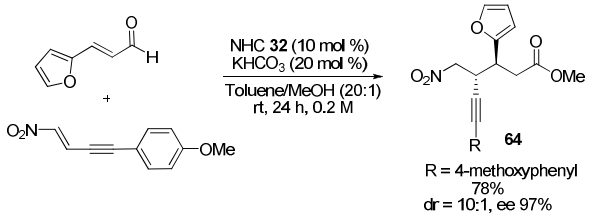


Scheme 17: NHC-catalysed addition of enals to sugar derived cyclic nitrones

4. Reaction of homoenolates with Michael acceptors

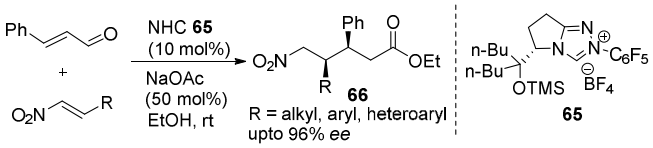
NHC-homoenolates generally react with Michael acceptors to afford cyclopentene-type products as described in Scheme 5. Non-annulative Michael additions in which an external nucleophile reacts with the acyl azolium species is also well-known (see path a, Scheme 5). Yet another reaction sequence that involves β-protonation and a carbon-carbon bond forming event at the α-carbon (path c, Scheme 5) is also not uncommon (Only limited examples of the latter reaction pathway is provided in this review, since the key bond formation involves an enolate rather than a homoenolates). Recent developments in the addition of NHC-homoenolates to Michael acceptors are summarised in the following section via selected examples.

A stereoselective Michael addition of homoenolates to nitrostyrenes to afford acyclic γ-nitrocarboxylates of *anti*-configuration was reported by us in 2009.[29] Recently, Liu reported the asymmetric variant of this transformation which is catalysed by the chiral NHC derived from **32**. The formation of corresponding *anti* δ-nitro esters **64** proceeded with high enantioselectivity. Different types of nitrodienes and nitroenynes were also successfully employed as the Michel acceptors in this transformation (Scheme 18).[30]



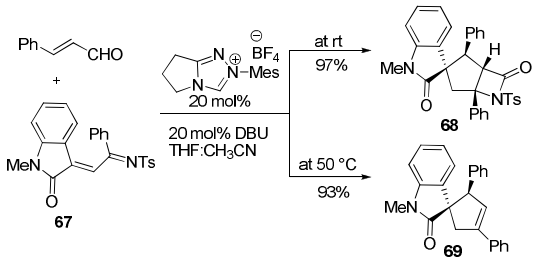
Scheme 18: NHC-catalysed homoenolate addition to nitroalkenes

The above-mentioned protocol by Liu as well as our earlier work leads to the selective formation of *anti* diastereomers of the nitroesters. Interestingly, a similar asymmetric homoenolate-nitroolefin Michael addition that preferentially produces the *syn* isomers was reported by Rovis (Scheme 19).[31] The key to the success of this method was the development of the chiral NHC precatalyst **65** that minimises the undesired acyl anion reactivity by virtue of its steric bulk. Rovis's method is also compatible with previously unreported aliphatic nitroolefins. It may be noted that the δ-nitro esters **66** generated by any of these methods may be readily converted into the corresponding δ-lactams by reductive lactamisation.



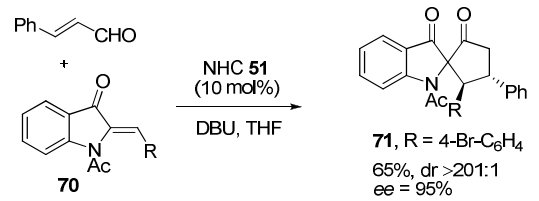
Scheme 19: *Syn*-selective NHC-catalysed homoenolate addition to nitroalkenes

Oxindole-derived α,β-unsaturated imines **67** react with NHC-homoenolates to afford β-lactam fused spirocyclic oxindoles **68** or spirocyclopentene oxindoles **69**. It may be noted that the β,β-disubstituted imines **67** are sterically demanding reaction partners and the resulting products bear an all-carbon spirocenter. High yields of the β-lactam derivatives **68** are obtained at room temperature. Cyclopentene products **69**, on the other hand, may be selectively obtained by conducting the reaction at 50 °C (Scheme 20).[32]



Scheme 20: NHC-catalysed spiro-oxindole synthesis

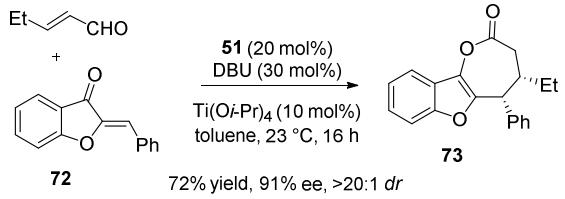
Enantioselective homoenolate [3+2]-annulation of azaaurones **70** was reported by Glorius.[33] The spirocyclic products **71** were obtained in good yields and excellent enantioselectivities in presence of the aminoindanol-triazolium precatalyst **51** (Scheme 21).



Scheme 21: Asymmetric homoenolate [3+2]-spiroannulation of azaaurones

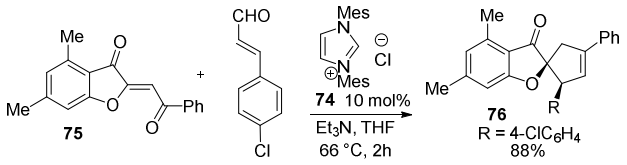
Independent investigation by Zhao demonstrated the

diastereoselective and enantioselective [3+4] annulation of enals with aurones **72** leading to the efficient synthesis of ε-lactones **73** (Scheme 22).[34] The use of Ti(O*i*-Pr)$_4$ as the Lewis acid improved the reactivity and minimized the formation of spiroannulated product. They have also developed a protocol using a different NHC for the selective formation of the spirocyclic compounds.



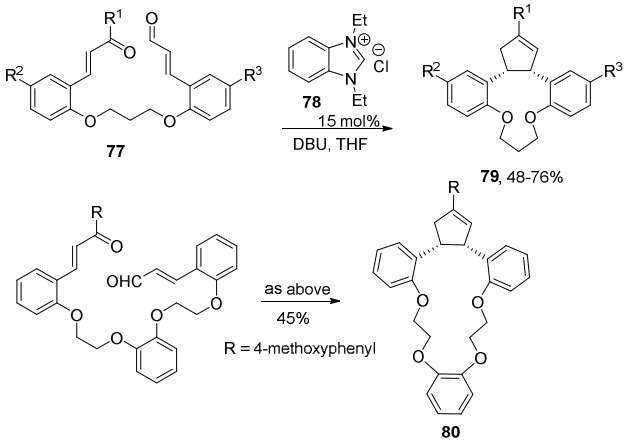
Scheme 22: Enantioselective homoenolate [3+4]-annulation of aurones

Imidazolium NHC **74** catalyses the homoenolate annulation of enals with 2-aroylidene benzofuran-3-ones **75** (aurone analogues) leading to the synthesis of cyclopentene-fused spirobenzofuran-3-ones **76** (Scheme 23).[35] Here, the initial homoenolate addition happens at the more substituted endocyclic carbon of the aurone derivative **75**.



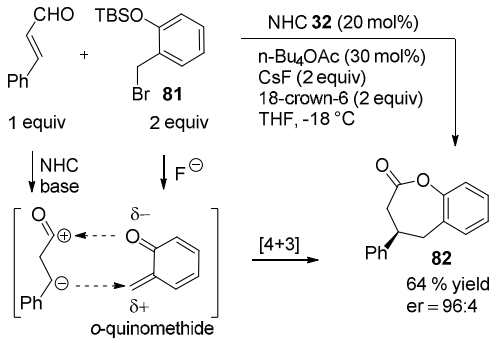
Scheme 23: Homoenolate annulation of aurone analogues

Cyclopentene fused macrocyclic ethers were synthesised *via* intramolecular homoenolate cyclopentannulation of enones. Various chalcone appended enals **77**, on treatment with the benzimidazole-derived NHC **78**, afforded good yields of the macrocyclic cyclopentenes **79**. Ring sizes ranging from 10-13 could be efficiently constructed by varying the methylene tether length. The designer "semicrown" cyclopentene **80** was also synthesised by employing this method (Scheme 24).[36] The mechanistic pathway is presumably analogous to that of the intermolecular cyclopentannulation of enones and chalcones (see Scheme 4).



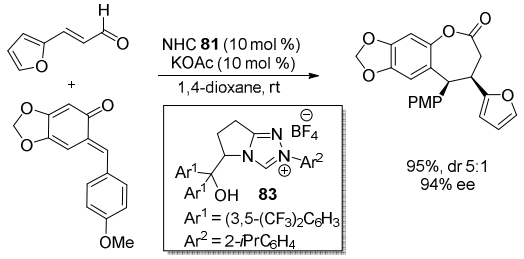
Scheme 24: Homoenolate cyclopentannulation leading to macrocycles

The use of an additional catalyst to generate a transient electrophile that can interact with NHC-derived homoenolates constitutes an attractive strategy for extending the scope of NHC catalysis beyond the conventional C-C and C-X π systems. The realisation of this concept faces serious challenges such as the compatibility of catalysts, generating viable equilibrium concentrations of the transient nucleophile (homoenolate) and the transient electrophile, potential reaction of the NHC catalyst with the transient electrophile, *etc*. A successful demonstration of this idea was provided by Scheidt in a double Lewis base mediated asymmetric formal [4+3] annulation reaction between homoenolates and *o*-quinomethides. The latter species is generated from stable silyl protected phenolic precursors **81** by the action of fluoride anion, while the NHC-derived homoenolate is simultaneously produced from enals by the triazolium catalyst **32** and base. After extensive experimentation, conditions were developed for the selective annulation of the highly reactive *o*-quinomethide with the NHC-homoenolate leading to the formation of seven-membered lactones (2-benzoxepinones, **82**) in good yields and excellent enantioselectivity (Scheme 25).[37]



Scheme 25: Dual Lewis-base strategy for homoenolate annulation with *o*-quinomethides.

Ye's group independently reported the NHC-catalysed enantioselective annulations of enals with stable preformed *o*-quinomethides using NHC generated from the triazolium salt **83** (Scheme 26).[38]



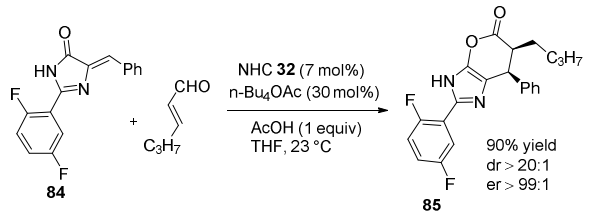
Scheme 26: Homoenolate annulation with stable *o*-quinomethides

5. Reactions that involve β-protonation of homoenolates

Addition of the simplest electrophile, H^+, to an enal-derived NHC-homoenolate generates an enol intermediate. This can in turn react with another electrophile leading to a carbon-carbon bond formation at the α-carbon of the enal (path c, Scheme 5). Two selected examples of this category are presented below to demonstrate the utility of this pathway.

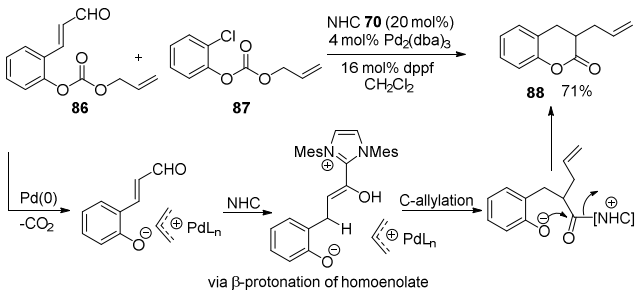
NHC-catalysed addition of α,β-unsaturated aldehydes to alkylidene imidazolidinones **84** afforded enantioenriched bicyclic

lactones **85** through a formal [4+2] annulation. The competing pathway of homoenolate [3+2] annulation to produce γ-lactones was suppressed by introducing an equimolar quantity of a protic acid additive (acetic acid) to the combination of triazolium precatalyst **32** and an acetate base in the reaction. Under these conditions, β-protonation of the homoenolate is faster and the resultant enol reacts with alkylidene imidazolidinones **84** at the α-carbon of the enal leading to the formation of the δ-lactones **85** (Scheme 27).[39]



Scheme 27: NHC-catalysed formal [4+2] annulation of alkylidene imidazolidinones

A proof of concept process that proceeds *via* cooperative catalysis involving NHC and a palladium catalyst was developed by Scheidt in 2014.[40] The combined use of NHCs and late transition metals poses a serious challenge as the former display a high propensity to bind to the latter. NHC is more likely to end up as ligand on the metal than being available for promoting the desired carbene-mediated catalytic pathway. The conditions for promoting a C-C bond-forming event between an NHC-bound enal and π-allyl palladium complex was developed after considerable screening experiments. The precursor for π-allyl palladium complex was incorporated into the enal scaffold **86**; yet an external allyl source **87** was also necessary to achieve good conversions. Mechanistically, the reaction proceeds via β-protonation of the homoenolate, followed by allylation at the α-position by the π-allyl palladium complex, and intramolecular acylation of the phenoxide to afford the allyl dihydrocoumarin **88** (Scheme 28).[40]

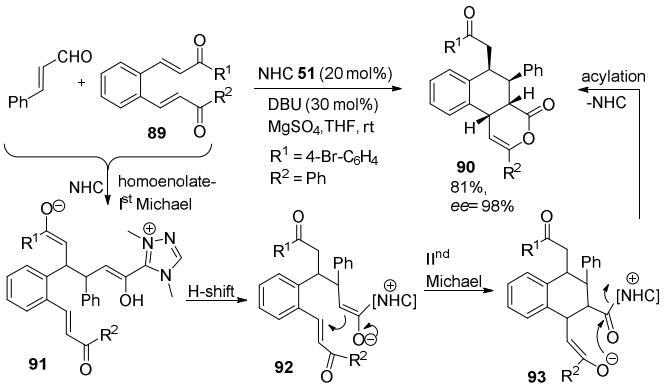


Scheme 28: NHC-palladium cooperative catalysis

6. Cascade reactions of homoenolates

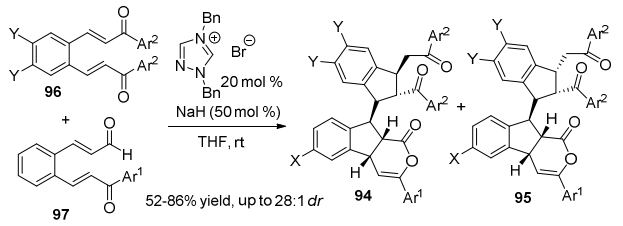
A variety of cascade processes of homoenolates can be set in motion by incorporating two or more reactive functionalities in the reaction partner. A number of recent reports describe NHC-catalysed cascade processes of carefully designed substrates involving the formation of a number of new bonds in a selective manner. Some of them are discussed in the following passages.

An NHC-mediated cascade annulation of enals with benzodi(enones) **89** leading to the formation of benzotricyclic products **90** with exceptional levels of regio- and stereoselectivities was reported by Chi in 2011. New bonds are formed at all the three reactive carbons of the enal component and four contiguous steroecenters are installed in the process. The aminoindanol triazolium catalyst **51** provided very high levels of enantioselectivity. Mechanistically, the homoenolate equivalent undergoes a Michael addition with the more electron deficient of the enones to generate the enolate **91**. Of the numerous reaction pathways that are available to **91**, a protonation-tautomerisation sequence leading to the enolate **92** is preferred. A stereoselective intramolecular Michael addition to the remaining enone moiety ensues and the enolate **93** is acylated at the oxygen end by the NHC bound carbonyl (Scheme 29).[41] The observed selectivity of this cascade reaction, despite the presence of multiple electrophilic sites for reactions, is a testament to the high levels of control that NHC catalyst are capable of exerting.



Scheme 29: Cascade annulation of enals with (di)enones

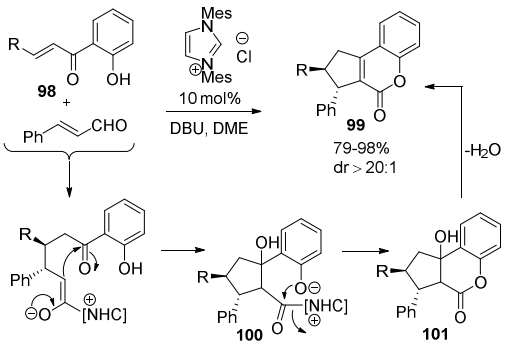
Cheng reported the synthesis of 9-indanylindeno (2,1-c) pyran-1-ones **94-95** via a related NHC-catalysed cascade reaction of 2-aroylvinylchalcones **96** with 2-aroylvinylcinnamaldehydes **97** (Scheme 30).[42a] Recently, the same group also reported the NHC-catalyzed diastereoselective and enantioselective annulation of 2-aroylvinylcinnamaldehydes with α,β-unsaturated imines.[42b] Depending on the N-substituent on NHC, either indeno[2,1-c]pyran-1-one derivatives or indenocyclopentan-1-ones were isolated in high yield and enantioselectivity.



Scheme 30: NHC-catalysed cascade reactions of 2-aroylvinylchalcones and 2-aroylvinylcinnamaldehydes

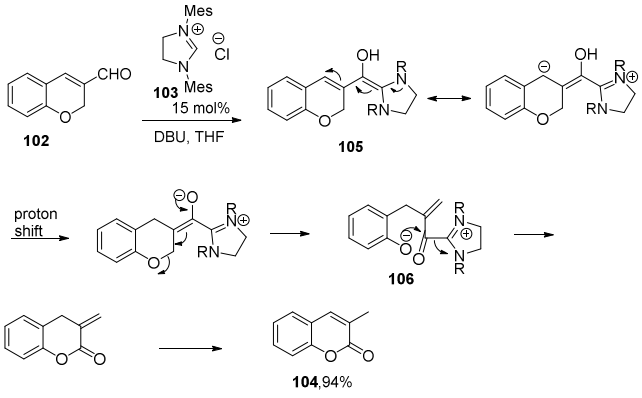
Annulation of NHC-homoenolates with 2'-hydroxy chalcones **98** led to a highly diastereoselective synthesis of cyclopentane fused coumarins **99**. Mechanistically, this transformation follows a route similar to that of the homoenolate-enone cyclopentannulation up to the intramolecular aldol reaction stage. The acyl azolium **100** does not engage in a β-lactone formation as

in the cyclopentannulation. Instead, a 6-membered lactone **101** is formed by the acylation of the phenolic oxygen by the acyl azolium species. Finally, coumarin **99** is formed from **101** via dehydration (Scheme 31).[43]



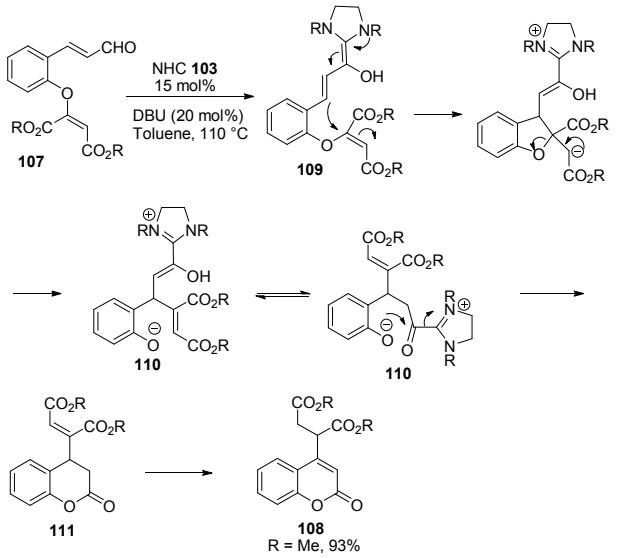
Scheme 31: NHC-catalysed cascade coumarin synthesis

A mechanistically intriguing transformation of the endocyclic homoenolate derived from 2*H*-chromene-3-carboxaldehyde **102** was reported by our group. Exposure of **102** to the imidazolinium NHC catalyst **103** triggered an unexpected bond reorganisation to afford the coumarin derivative **104**. Mechanistically, this rearrangement presumably involves the β-protonation of the Breslow intermediate **105** followed by an enolate-assisted C-O bond cleavage and subsequent intramolecular acylation of the phenoxide **106** (Scheme 32).[44] The key bond-breaking event of this transformation is reminiscent of the classical Grob fragmentation, but here a C-O bond is ruptured whereas the latter involves a C-C bond fission.



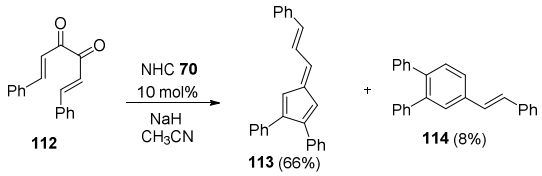
Scheme 32: NHC-catalysed rearrangement of chroemene-3-carboxaldehyde

An NHC-catalysed cascade reaction of cinnamaldehyde **107** appended with a 2-*O*-alkenoate substituent furnished substituted coumarin derivatives **108**. The homoenolate **109** resulting from **107** is well placed to engage in an intramolecular conjugate addition-elimination with the *O*-alkenoate handle to generate the phenoxide **110**. Addition of the latter to the acyl azolium moiety produces the dihydrocoumarin derivative **111** which isomerises to the final product **108** (Scheme 33).[45]



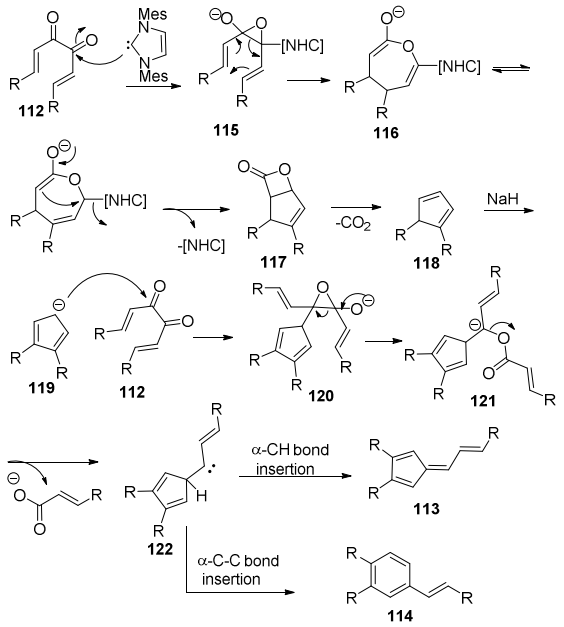
Scheme 33: NHC-catalysed coumarin synthesis via a cascade process

Exposure of 1,6-diphenylhexa-1,5-diene-3,4-dione (cinnamil, **112**) to the NHC catalyst **70** led to an unexpected cascade transformation leading to the formation of 2,3,7-triaryl vinylfulvenes **113** along with *o*-terphenyl derivatives **114**. Improved yields of *o*-terphenyl derivatives **114** may be obtained by conducting the reaction in toluene in the presence of potassium carbonate (Scheme 34).[46]



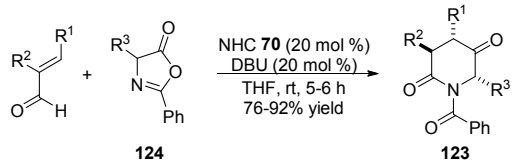
Scheme 34: NHC-catalysed formation of vinylfulvenes and *o*-terphenyls from cinnamil

A tentative mechanistic rationalisation of this intriguing transformation is provided in Scheme 35. The addition of NHC **70** to cinnamil **112** may be followed by the formation of an epoxy intermediate **115**. An anion assisted oxy-Cope rearrangement then generates the oxepine derivative **116**. Isomerisation of **116**, followed by internal displacement of the NHC moiety affords the transient bicyclic β-lactone **117**. A retro-[2+2] fragmentation of **117** produces the cyclopentadiene **118**. As the reaction conditions are basic, deprotonation of **118** and addition of the cyclopentadienyl anion **119** to another molecule of cinnamil may then occur. Subsequent formation of transient epoxide **120** culminates in the cleavage of the carbon-carbon bond that connected the two carbonyl groups of **112**. The allylic carbanion **121** thus generated may eject the cinnamate fragment to form a carbene **122**. The vinyl fulvene **113** is then produced via the insertion of the carbene to the adjacent C-H bond. Alternatively, insertion of the carbene to the endocyclic carbon-carbon bond furnishes the *o*-terphenyl derivative **114**. It may be noted that the mechanistic rationalisation presented here is largely speculative and the involvement of a non-carbene pathway[46] in the conversion of **121** into the final products **113-114** cannot be ruled out at this stage.



Scheme 35: Mechanistic rationalisation for the NHC-catalysed cascade reaction of cinnamils

Yadav reported diastereoselective synthesis of multifunctionalised piperidines **123** by NHC-catalysed cascade reactions of enals with azalactones **124**. The final product results from a formal [3+3] annulation of the homoenolates with an α-amino acid equivalent (Scheme 36).[47]

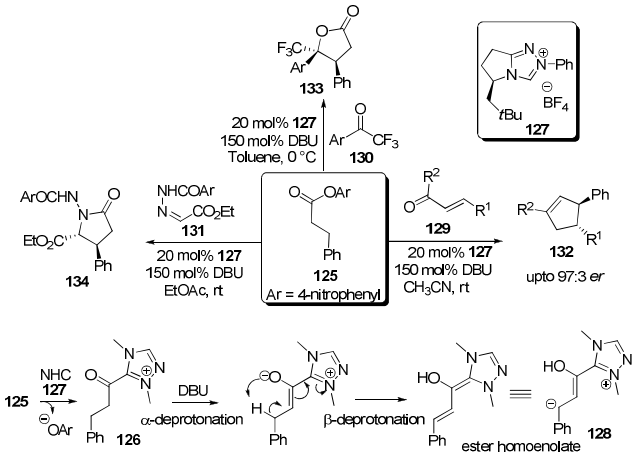


Scheme 36: NHC-mediated annulation of enals and azalactones

7. New precursors for homoenolates

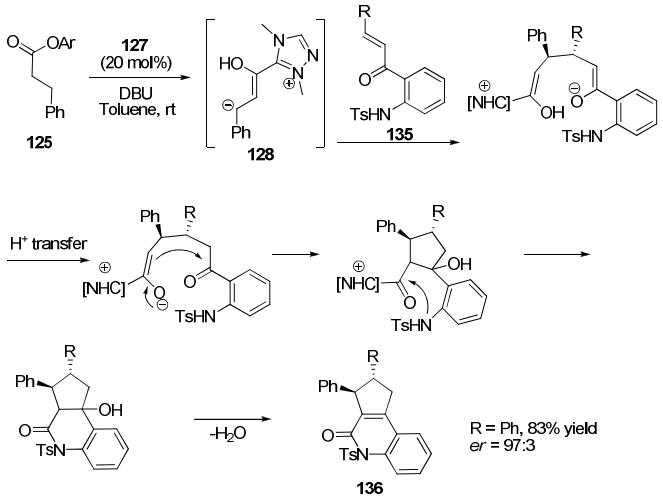
The demonstration by Chi that NHC-bound homoenolates may be generated from substrates other than enals is one of the most intriguing discoveries that was made in this area in recent years. This breakthrough has greatly expanded the scope of NHC-mediated transformations to a territory that is traditionally associated with metal-mediated C-H-activation. A brief discussion on the key aspects of these reports is presented below.

NHC-catalysed generation of homoenolates from saturated carboxylic esters **125** via deprotonation at the sp^3 β-carbon was reported by Chi in 2013. The adduct **126** formed from the ester **125** and the chiral triazolium NHC **127** is converted into the homoenolate **128** presumably via successive deprotonations as depicted in Scheme 37. The homoenolate **128** has been shown to annulate electrophiles such as enones **129**, trifluoromethyl ketones **130** and hydrazones **131** leading to the formation of enantioenriched cyclopentenes **132**, γ-lactones **133** and γ-lactams **134** respectively (Scheme 37).[48] This fundamentally important discovery complements the classical α-deprotonation chemistry of esters (and other carbonyl compounds) and opens up new possibilities in organic synthesis in general and NHC catalysis in particular.



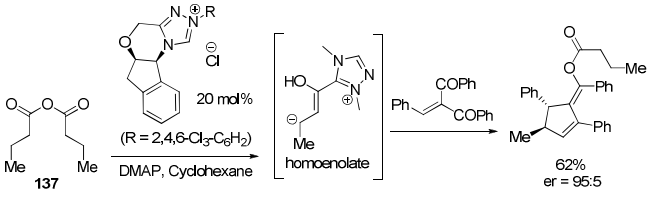
Scheme 37: NHC-catalysed β-sp^3-CH activation of carboxylic esters

An interesting cascade reaction involving the saturated ester-derived homoenolate **128** and amino enones **135** leading to the enantioselective formation of polycyclic quinolinones **136** illustrates the power of this new mode of NHC-activation. The initial C-C bond event takes place between the otherwise inert β-carbon of the ester **125** and the electrophilic β-carbon of enone **135**. The amino appendage engages in the final acylation of the NHC bound carbonyl (originally ester) to afford the quinolinone products **136** (Scheme 38).[49]



Scheme 38: NHC-catalysed cascade involving β-sp^3-CH activation of carboxylic esters

Chi also demonstrated that carboxylic anhydrides **137** can also furnish reactive homoenolate equivalents under NHC-catalysis. Annulation reactions of such homoenolates with alkylidene diketones, chalcones and isatins proceed with excellent efficiency and stereoselectivity (Scheme 39).[50]



Scheme 39: β-CH activation of anhydrides and annulation of alkylidene diketones

8. Conclusions and Future prospects

The chemistry of NHC-derived homoenolates has made tremendous progress in the last four years. Some of the significant developments include, *inter alia*, the generation of homoenolates by activation of non-conventional precursors such as esters and anhydrides, dynamic kinetic resolution processes of challenging substrates, cascade processes that generate molecular complexity in a single operation from relatively simple substrates and selective reaction of homoenolates with other transient reactive intermediates such *o*-quinomethides. The catalyst toolbox of chiral NHCs has also been upgraded significantly paving way for the development of highly stereoselective processes. The simultaneous use of NHCs along with compatible Lewis acids or bases to activate otherwise inert electrophiles has also gained popularity. NHC-homoenolates have featured in key bond-forming events in the syntheses of a number of natural products. As more and more reactions of NHCs emerge, inherent reactivity mode preferences of various types of NHC-catalysts will be revealed. Collectively, this information will bestow an improved predictive power upon the chemist thereby minimising arduous catalyst screening. In the near future, 'standard' reaction conditions may become available to choose a desired route from the divergent pathways that exist for a given combination of substrates in NHC-catalysis.

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Notes and references

[a] *Medicinal Chemistry and Pharmacology Division, CSIR-Indian Institute of Chemical Technology, Hyderabad-500 007, India.*

[b] *Organic Chemistry Division, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune – 411008, India*

[c] *Organic Chemistry Section, CSIR-National Institute for Interdisciplinary Science and Technology, Trivandrum 695 019, Fax: 91 471 2491712; Tel: 91 471 2490406; E-mail: vijaynair_2001@yahoo.com*

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