Recent advances in carbon–carbon bond-forming reactions involving homoenolates generated by NHC catalysis

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Homoenolate, a species containing anionic carbon β to a carbonyl group or a moiety that can be transformed into a carbonyl group, is a potential three carbon synthon. Recent introduction of a protocol for the generation of homoenolate directly from enals by NHC (nucleophilic heterocyclic carbene) catalysis has made it possible to explore the synthetic utility of this unique reactive intermediate. The versatility of NHC-bound homoenolate is illustrated by its annulation with various carbonyl compounds leading to γ-butyrolactones, spiro-γ-butyrolactones, and δ-lactones. Interception of homoenolate with imines afforded γ-lactams and bicyclic β-lactams. Formation of cyclopentenes and spirocyclopentanones respectively by reaction with enones and dienones is also noteworthy. This *tutorial review* focuses on these and other types of reactions which attest to the synthetic potential of NHC-bound homoenolates in organic synthesis.

1. Introduction

Carbon–carbon bond formation constitutes the central event in organic synthesis. Naturally, therefore, the design and development of methodologies for carbon–carbon bond formation has been an area of perennial interest, ever since the dawn of organic chemistry. 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. In other words, reactions occurring at the carbon adjacent to the carbonyl group of aldehyde, ketone, carboxyl surrogates *etc*., proceed *via* the intermediacy of enol/enolate or enamine. In this context, it is noteworthy that the vast majority of carbon–carbon bond-forming reactions occurring in nature also proceed *via* the intermediacy of enol/enolate or enamine.

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The enolate anion is a versatile reactive intermediate, and it is usually generated in the laboratory by the removal of the α-proton of a carbonyl compound, often with the aid of alkali metal reagents. Enamines are conventionally prepared by the addition of a secondary amine to the carbonyl compound followed by the elimination of water. Just as a carbonyl would facilitate the reaction of an electrophile at the α-carbon *via* enol/enolate, the reaction at the β carbon *via* a potentially reactive intermediate, a *homoenolate*, is conceptually feasible. By analogy to enolate, homoenolate[1–3] is a species containing anionic carbon β to a carbonyl group or a moiety that can be transformed into a carbonyl group (Fig. 1).

Indeed, the concept of the homoenolate anion was introduced by Nickon and Lambert[4] in a seminal paper, as early as 1962, and they proved the existence of such a species by demonstrating the racemization of (+)-camphenilone by alkaline treatment and its deuterium exchange to produce **2** and **3**, consistent with the symmetrical intermediate **4**. 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).

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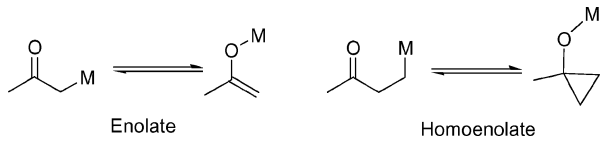
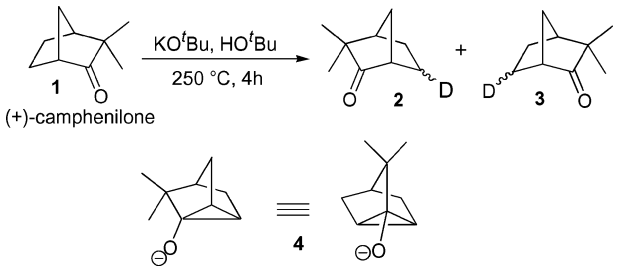


Fig. 1 Concept of homoenolate.

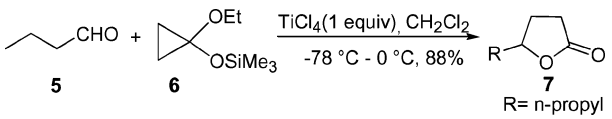


Scheme 1 Racemization of (+)-camphenilone *via* homoenolate.

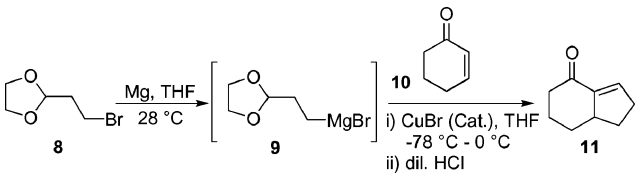
A survey of the literature revealed that although the concept of homoenolate formation was known since the early 1960s (*vide supra*), it did not find any application in organic synthesis for a long time. The situation changed dramatically in recent years and several research groups, including our own, have uncovered a number of synthetic protocols of novelty and value by engaging homoenolates, generated directly from enals. The results obtained so far augur well for the discovery of even more exciting chemistry in the near future. The purpose of this tutorial review is two fold. Primarily, it is aimed at introducing the general community of chemists to this new and exciting field. Secondly, it is aimed at encouraging the practitioners of synthetic organic chemistry to explore this area more broadly and deeply so that elegant and useful reactions may be revealed. The literature coverage is thorough, with some emphasis on the work from the authors' laboratory. Since the focal theme of this review is the chemistry of NHC-bound homoenolates, metal homoenolates and related species are covered only briefly here.

2. Metal homoenolates

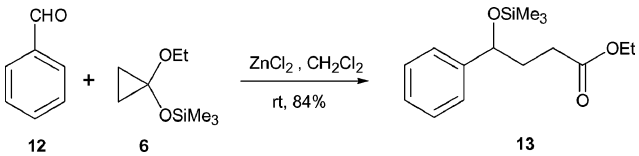
As already mentioned in the introduction, in contrast to the wide-ranging use of enolates, the application of homoenolates in organic synthesis has been limited, presumably due to the difficulty in generating homoenolates directly. The simplest solution offered to this problem was the use of a homoenol silyl ether, in the form of cyclopropanone ketal **6**. The potential utility of this homoenolate equivalent in carbon–carbon bond formation was first described by Nakamura and Kuwajima in their report on the addition of **6** to a carbonyl compound in the presence of $TiCl_4$, delivering γ-lactones in high yield.[5] Presumably this is the first example of a homoaldol reaction (Scheme 2).



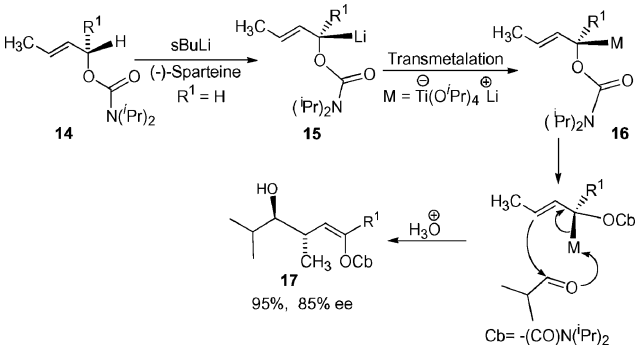
Scheme 2 Cyclopropanone ketal as a homoenolate equivalent.



Scheme 3 Homoenolate from acetal embedded Grignard reagent.



Scheme 4 Catalytic generation of homoenolate using $ZnCl_2$.



Scheme 5 Chiral homoenolate equivalent in the homoaldol reaction.

The major problem with trichlorotitanium homoenolate was its propensity to undergo side reactions, leading to chlorinated byproducts. An important innovation to circumvent this problem was introduced by Helquist *et al*.,[6] who used the acetal-embedded Grignard reagent **9** as a homoenolate equivalent (Scheme 3). Copper catalyzed conjugate addition of **9** to cyclohexenone, deprotection and intramolecular aldol condensation afforded bicyclic cyclopentene derivative **11** in good yield.

A remarkable innovation in the area of homoenolate occurred when Nakamura *et al*. developed a method for the catalytic generation of homoenolate.[7] They showed that zinc homoenolate can be generated by the reaction of siloxycyclopropane **6** with a catalytic amount of zinc chloride; its synthetic utility was demonstrated by its participation in a homoaldol reaction (Scheme 4).

Subsequent efforts to generate homoenolate equivalents include the use of β-propionate anion equivalents[8] and α-heteroatom-substituted allyl anions by a number of investigators.[9–14]

Inducing chirality in a homoenolate reaction is the main challenge to accomplish stereocontrolled homoaldol reactions. The first example of a chiral homoenolate equivalent and its application in asymmetric reactions was reported by Ahlbrecht, Enders *et al*.[15] To date, the most advanced and synthetically useful chiral homoenolate equivalents are the 2-alkenyl-1-metallocarbamates introduced by Hoppe *et al*. In their elegant work, Hoppe *et al*. have shown that these species react with aldehydes and ketones with very efficient transfer of

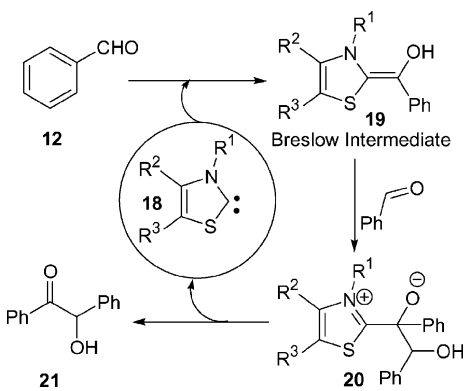
chirality to form optically active homoaldol products.[16,17] An illustrative example is given in Scheme 5. Analogous work was reported by Beak and Whisler also.[18]

3. Nucleophilic heterocyclic carbene (NHC) derived homoenolates

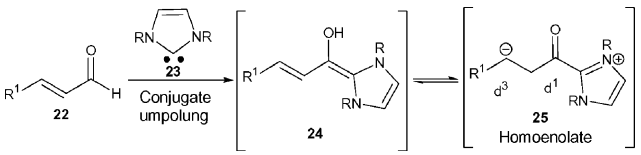
Although the term nucleophilic heterocyclic carbene (NHC)[19] came into usage only recently, the existence of such species was clearly established half a century ago. Historically, it was known that coenzyme thiamine catalyses decarboxylation and a number of other important reactions in biological systems, but no mechanistic guidance was available. In 1958, Breslow postulated that the thiazolium moiety in thiamine is acidic enough to be deprotonated under mildly basic conditions to generate a thiazolylidene species (currently referred to as an NHC), capable of addition to an activated carbonyl group, leading to polarity reversal of the latter (umpolung), and thus sets in motion a sequence of events culminating in decarboxylation of pyruvic acid, acetoin condensation *etc*. Moreover, in this pathbreaking work, Breslow demonstrated his mechanistic model for the thiazolium salt catalyzed benzoin condensation.[20] The thiazolylidene, the actual catalyst, formed *in situ*, couples with an aldehyde to generate a d^1-nucleophile[21] **19**, generally referred to as "Breslow intermediate". Reaction of the latter with another molecule of aldehyde afforded the α-hydroxy ketone product **21** (Scheme 6).

Based on the mechanistic pathways available to the Breslow intermediate, the groups of Bode[22] and Glorius[23] independently introduced a conceptually new approach for the generation of a homoenolate from an enal using an NHC. They surmised that just as the addition of an NHC to an aldehyde would generate an enol/enaminol (Breslow intermediate), the addition of an NHC to an α,β-unsaturated aldehyde can, in principle, generate a conjugated acyl anion, more appropriately called a homoenolate (Scheme 7).

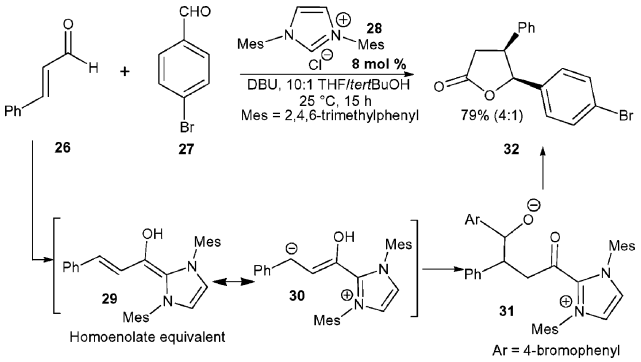
This homoenolate was harnessed to undergo annulation with aldehydes leading to the efficient synthesis of γ-butyrolactones. Mechanistically, the reaction can be viewed as the addition of the homoenolate to an aldehyde to form an alkoxide intermediate **31**, which is trapped intramolecularly by the activated carboxyl surrogate (Scheme 8).[22–23]



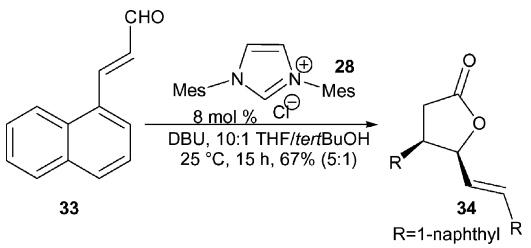
Scheme 6 Breslow's postulate of NHC catalysis in benzoin condensation.



Scheme 7 NHC mediated formation of homoenolate from an α,β-unsaturated aldehyde.



Scheme 8 Enal–aldehyde annulation *via* a homoenolate.

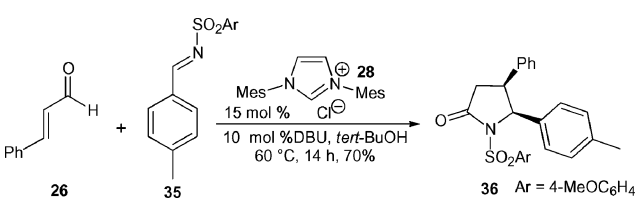


Scheme 9 Homodimerisation of enal.

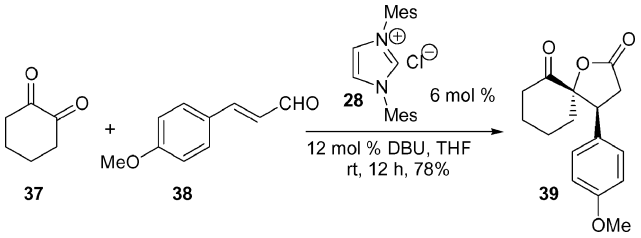
In the absence of other electrophiles, homodimerisation of enal is the only reaction that occurs (Scheme 9).[22]

Subsequent work by Bode and He has shown that this annulation is applicable to the synthesis of γ-lactams (Scheme 10).[24] The scope of this lactam synthesis is limited, and in many cases the imines undergo irreversible addition to the nucleophilic catalyst thereby aborting the catalytic cycle.

Ketones, with the exception of α,α,α-trifluoroacetophenone,[23] failed to undergo this annulation. In the context of our interest in the chemistry of 1,2-diones[25] and multicomponent reactions (MCRs) involving NHCs,[26] it was surmised that homoenolate annulation, although generally unsuccessful with ketones, was likely to succeed with an activated carbonyl compound such as 1,2-dione. Gratifyingly, in the presence of a catalytic amount of 1,3-dimesitylimidazol-2-ylidene (IMes) **28**, reaction of 1,2-cyclohexanedione **37** with a wide array of cinnamaldehydes afforded the spiro-γ-butyrolactones **39** in high yield and



Scheme 10 Annulation of enal and imine *via* homoenolate.



Scheme 11 Interception of homoenolate with cyclic 1,2-diones.

excellent diastereoselectivity. It may be mentioned that this is one of the very few straightforward routes to spiro-γ-butyrolactones (Scheme 11).[27]

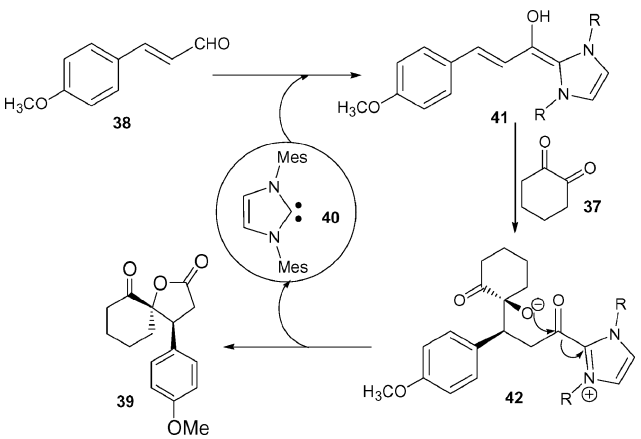
Mechanistically, the spirolactone formation can be interpreted by an adaptation of the catalytic cycle proposed by Bode and Glorius (Scheme 12).

Subsequent to the investigations described, it was found that the spiro-annulation could be extended to another interesting class of 1,2-dicarbonyl compounds, *viz*., isatins. The reaction yielded a separable diastereomeric mixture (1 : 1) of spiro-γ-butyrolactone oxindole derivatives, which is an important structural unit of biologically active natural products such as the mycotoxin tryptoquivaline (Scheme 13).[27]

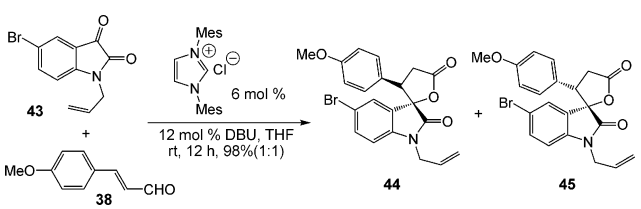
Further investigations have shown that acyclic 1,2-diones also undergo this NHC catalyzed homoenolate annulation to yield γ-butyrolactones in high yields (Scheme 14).[28]

In a related study, the reaction of the homoenolate from **50** with tropone afforded bicyclic δ-lactone derivative **51** (Scheme 15). Interestingly, aliphatic enals such as crotonaldehyde could also be converted to the corresponding δ-lactones by this method.[29]

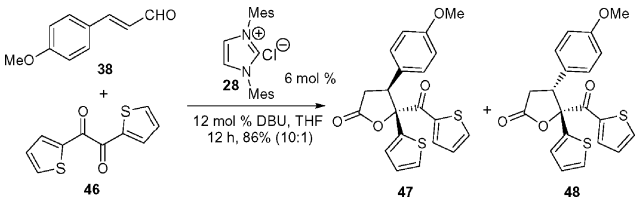
A mechanistic rationale for the reaction may be outlined as follows. The homoenol **24**, formed by the reaction of IMes with the enal, conceivably undergoes conjugate addition to



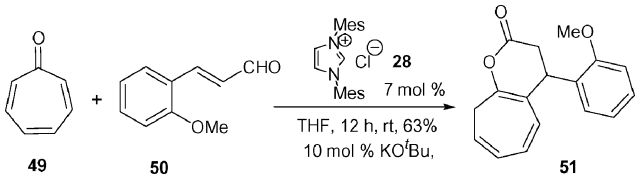
Scheme 12 Mechanistic interpretation of spiro-lactonisation.



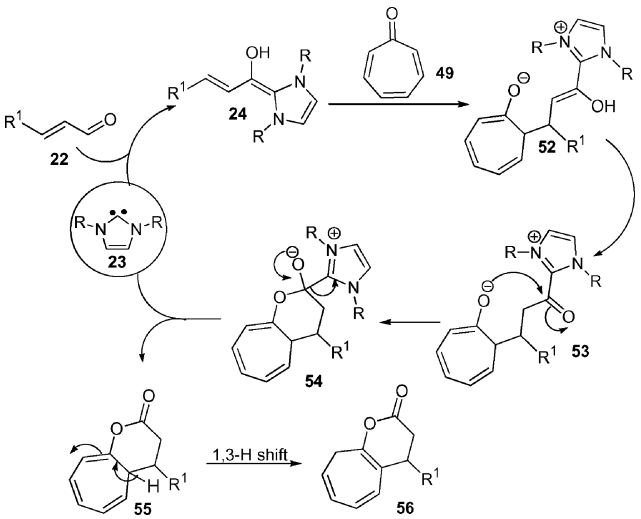
Scheme 13 Annulation of N-alkyl isatin with homoenolate.



Scheme 14 Homoenolate annulation with acyclic 1,2 diones.



Scheme 15 One pot synthesis of bicyclic δ-lactone.

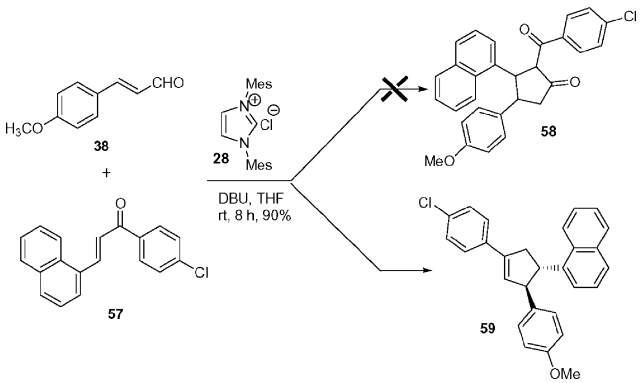


Scheme 16 Plausible mechanism for δ-lactone formation.

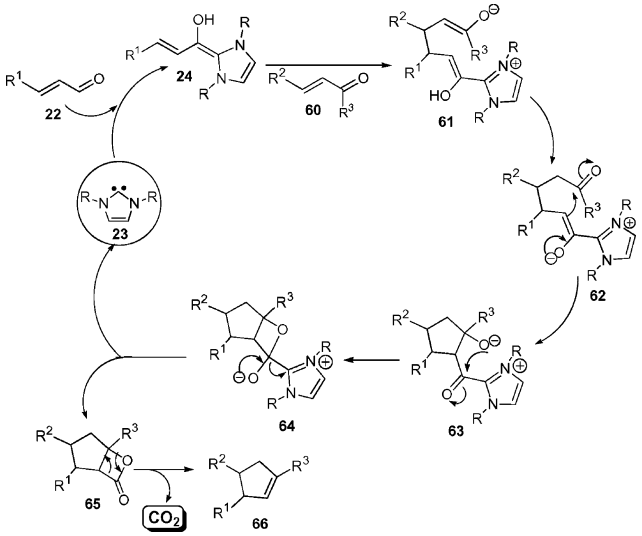
tropone to generate the enolate **52** which then cyclises to afford **55** with the ejection of IMes, thus perpetuating the catalytic cycle. The initially formed lactone **55** presumably undergoes isomerisation to the more stable lactone **56** (Scheme 16).

Inspired by the homoenolate annulation to an activated carbonyl to afford a lactone, we speculated that there is an even chance of annulation occurring at the carbon–carbon double bond of an enone to afford an acyl cyclopentanone. A serendipitous turn of events in this anticipated cyclopentanone synthesis, however, led to a very efficient synthesis of 3,4-*trans*-disubstituted-1-aryl cyclopentene, **59** (Scheme 17).[30]

It is reasonable to assume that the sequence of events begins with the conjugate addition of homoenolate to the chalcone to produce enolate **61**. This enolate, presumably due to steric constraints, does not engage in an intramolecular aldol reaction; instead, it undergoes proton transfer to generate a more stable enolate **62**. The latter then undergoes an intramolecular aldol reaction, followed by β-lactonisation and a retro [2 + 2] process of the β-lactone to yield the cyclopentene with the loss of carbon dioxide (Scheme 18). Spectroscopic evidence obtained for the loss of CO_2 provides unequivocal support



Scheme 17 Stereoselective cyclopentene synthesis *via* the homoenolate reaction.

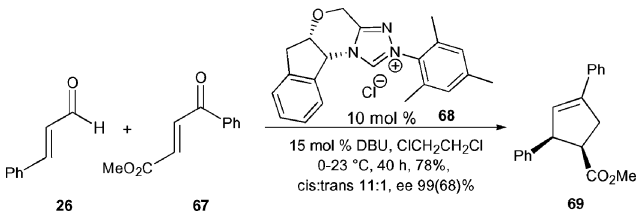


Scheme 18 Postulated catalytic cycle for cyclopentene annulation.

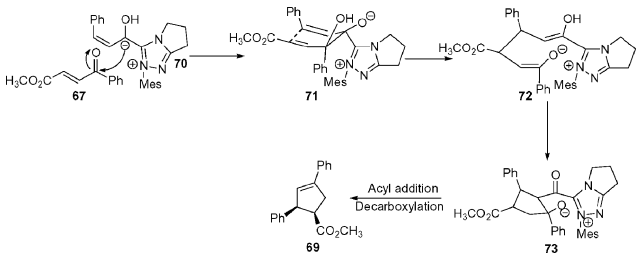
for this mechanistic postulate. The unexpected turn of events may also be attributed to the relative instability of the initially formed enolate and its transformation to **62** by deprotonation of the methylene adjacent to the imidazolium moiety. The relative stability of **62** *vis a vis* **61** is accrued by the inductive and coulombic influence imparted by the imidazolium moiety.

Subsequent to our report on the cyclopentene annulation, an asymmetric version of this reaction, using *N*-mesityl-substituted chiral triazole carbene, was reported by Bode *et al*. (Scheme 19).[31]

In this paper, the authors have invoked an intramolecular aldehyde–ketone crossed-benzoin condensation and an oxy-Cope rearrangement to rationalize the enhanced chiral



Scheme 19 Enantioselective annulation to cyclopentene.



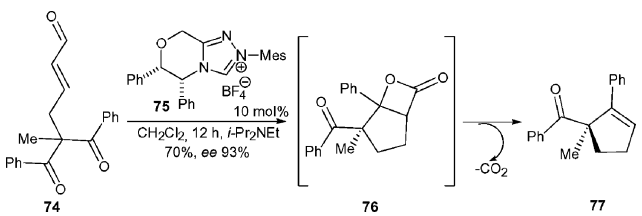
Scheme 20 NHC catalyzed oxy-Cope rearrangement.

induction and the *cis* disposition of the cyclopentene substituents. This mechanistic divergence between imidazolium catalysis and triazolium catalysis remains unexplained (Scheme 20).

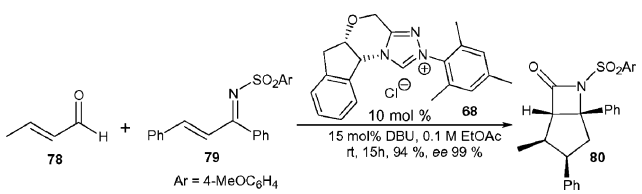
Interestingly, the β-lactone intermediate invoked in our cyclopentannulation (Scheme 17) has accrued additional support from the work of Scheidt *et al*. who isolated a bicyclic β-lactone from an intramolecular variant of this reaction.[32] The enantioselective formation of α,α-disubstituted cyclopentene **77** was interpreted by invoking the intramolecular aldol reaction of achiral tricarbonyl compound **74** catalysed by chiral *N*-heterocyclic carbene **75** (Scheme 21).

In an extension of this reaction, bicyclic β-lactams were synthesized from enals and unsaturated *N*-sulfonyl ketimines. Here also the authors have invoked a tandem, or possibly concerted, crossed-benzoin–oxy-Cope reaction to explain the *cis*-relative configuration of the cyclopentane substituents. The success of the reaction rests on the use of nonactivated enals which are slow to undergo homoenolate tautomerization to the corresponding enolate (Scheme 22).[33]

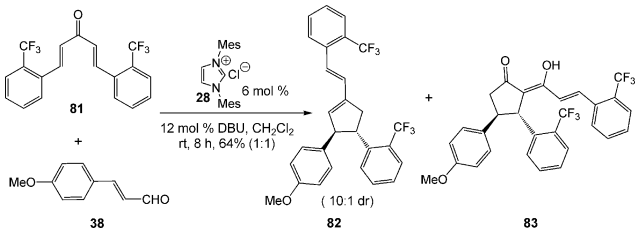
In the context of the cyclopentene annulation observed in the reaction of homoenolate with chalcone, we were curious about the outcome of such a reaction involving cross conjugated dienones instead of chalcone. With the assumption that the primary enolate formed in this case would be more stable than the one derived from chalcone, cyclopentanone formation was considered probable, at least to some extent. In the event, the reaction of the enal with the dienones catalysed by a NHC afforded a separable mixture of 1,3,4-trisubstituted



Scheme 21 Enantioselective formation of α,α-disubstituted cyclopentene.



Scheme 22 Enantioselective β-lactam synthesis.



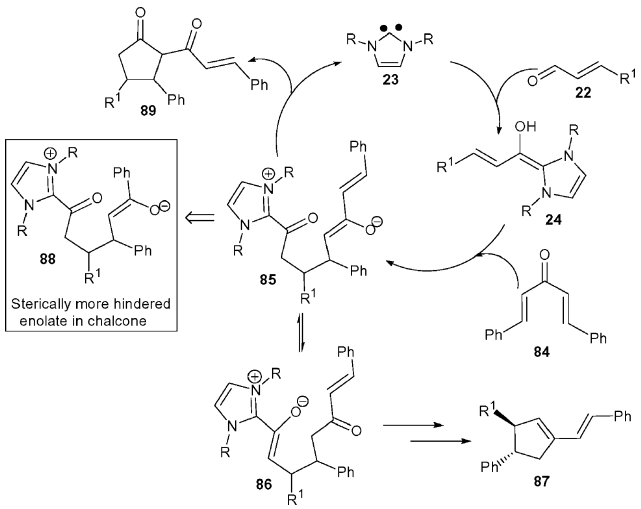
Scheme 23 Reaction of homoenolate with acyclic dienones.

cyclopentene **82** and 2,3,4-trisubstituted cyclopentanone **83** (Scheme 23).[34] It may be recalled that the chalcone reaction yielded only a cyclopentene derivative (*cf*. Scheme 17).

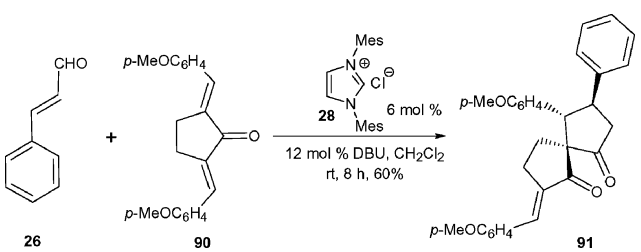
The mechanistic underpinnings of the reaction are far from clear. However, the following interpretation may be offered to explain the formation of the products. The enolate **85**, being sterically less hindered *vis a vis* **88**, undergoes the expected annulation to afford the cyclopentanone **89**. In parallel, **85** also undergoes isomerisation by proton transfer to afford **86**, and the latter follows a course similar to the one outlined in Scheme 18 to deliver the cyclopentene **87** (Scheme 24).

Very recently we examined the homoenolate annulation with dibenzylidene cyclopentanone. In this case exclusive formation of spiro annulated cyclopentanone **91** was observed which complements the cyclopentene synthesis (Scheme 25).[34]

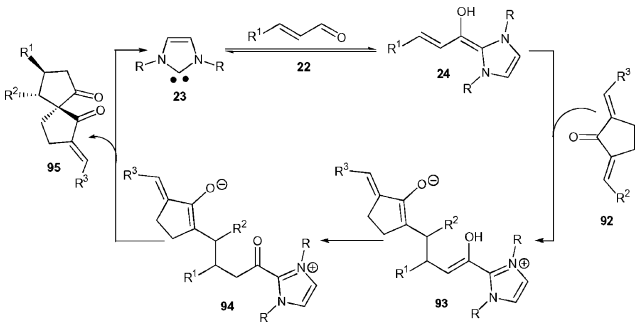
The formation of spirocyclopentanone at the exclusion of the bicyclic cyclopentene may be rationalized by invoking the conjugate addition of homoenolate to **92**, leading to **94**, followed by the aldol cyclisation of the latter with the



Scheme 24 Plausible mechanistic routes for the formation of cyclopentanone and cyclopentene.



Scheme 25 Homoenolate annulation with dibenzylidene cyclopentanone.



Scheme 26 Proposed reaction pathway for spiro-annulation.

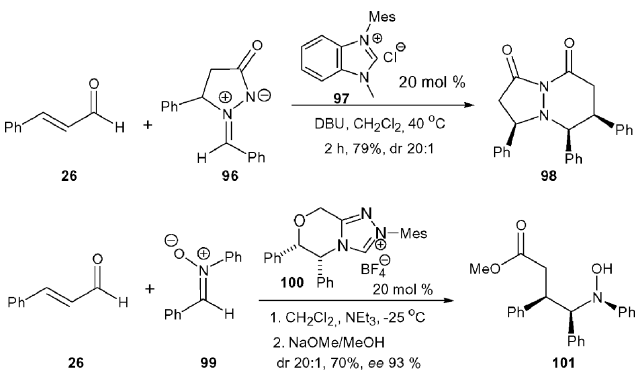
activated carboxyl surrogate. The *trans* disposition of R^1 and R^2 is predicated by the conjugate addition mechanism in imidazolium catalysis (Scheme 26).

4. Carbon–nitrogen bond formation *via* homoenolate

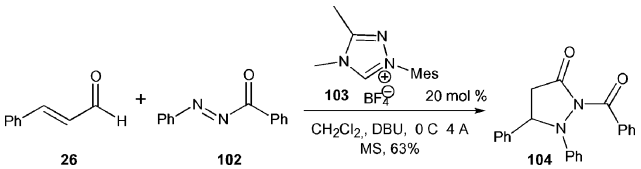
Recently homoenolate mediated C–N bond formation has been reported. Since this is relevant to the focal theme of the review, selected examples are given in this section.

1,3-Dipoles such as azomethine imines and nitrones take part in formal [3 + 3] cycloaddition reactions with NHC–homoenolates. Synthesis of pyridazinones[35] and γ-amino esters[36] by the addition of azomethine imines and nitrones respectively to enals catalysed by NHCs was reported very recently (Scheme 27).

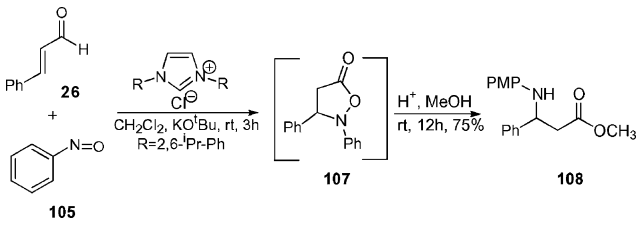
Electrophilic amination of homoenolates catalyzed by *N*-heterocyclic carbenes was realized by Scheidt and co-workers. The reaction involves a formal [3 + 2] cycloaddition of a homoenolate equivalent, generated from cinnamaldehyde, to diazene to afford a pyrazolidinone as a single regioisomer.[37] Among the number of catalysts screened, the triazolium carbenes gave the best results (Scheme 28).



Scheme 27 Homoenolate annulation with 1,3 dipoles.



Scheme 28 Annulation of homoenolate with a diazene.



Scheme 29 NHC catalyzed β-amination of enals.

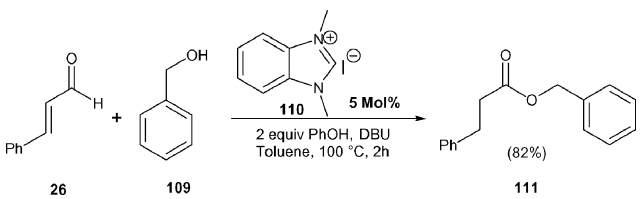
β-Amination reactions of homoenolate with nitrosobenzene catalysed by an NHC was recently reported by Ying and co-workers. The homoenolate upon reaction with nitrosobenzene initially afforded *N*-phenylisoxazolidin-5-one, which subsequently got transformed to *N*-*p*-methoxyphenyl α-phenethylamino acid ester by acid catalysed esterification followed by a Bamberger-type rearrangement (Scheme 29).[38]

5. β-Protonation of homoenolate

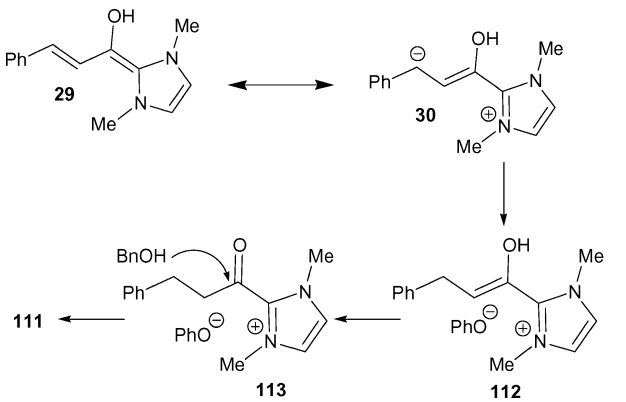
In their effort to further exploit homoenolate reactivity, Scheidt and Chan have shown that enal **26** can be converted to a saturated ester by NHC catalysed addition of an alcohol (Scheme 30).[39]

Evidently, acting as a proton source, phenol protonates the homoenolate to form a new NHC-bound enol **112**. The latter undergoes tautomerisation to an activated carboxyl surrogate **113** which then participates in nucleophilic displacement by the alcohol (Scheme 31).

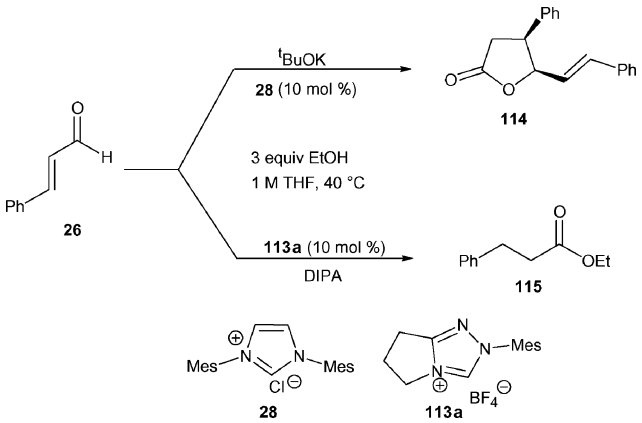
Contemporaneous work by Bode and Sohn showed the product-determining effect of the base. The combination of strong base and strongly nucleophilic carbene displays a clear preference for carbon–carbon bond-formation whereas the less nucleophilic carbene–mild base combination leads to the protonation of the homoenolate and subsequent formation of



Scheme 30 Formation of saturated esters from homoenolate.



Scheme 31 Mechanistic interpretation of the redox reaction of homoenolate.

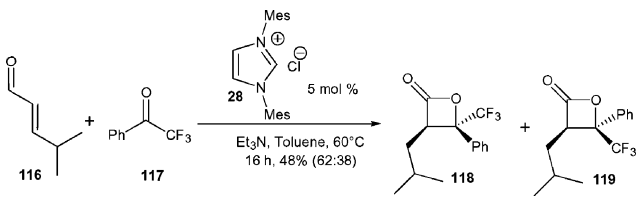


Scheme 32 Effect of catalytic base on the fate of the homoenolate.

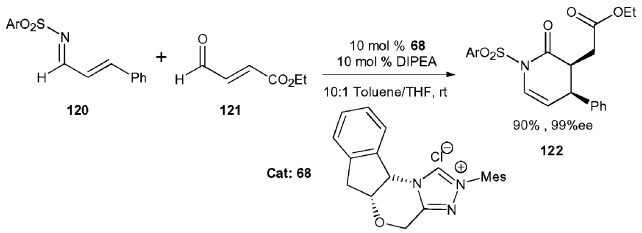
the ester. Here the weak base, acting as a proton shuttle, protonates the homoenolate without an additional proton source (Scheme 32).[40]

Another interesting mode of homoenolate reactivity was observed by Glorius and co-workers when they generated homoenolate in less polar solvents at higher temperatures; under these conditions the homoenolate tautomerised to the enolate, which then underwent β-lactonisation with ketones (Scheme 33).[41]

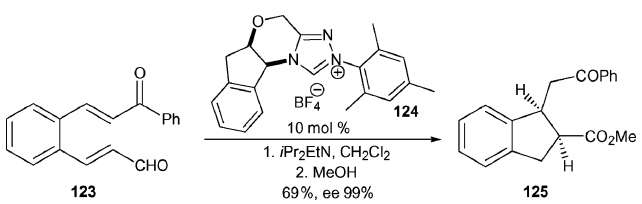
The catalytic protonation of homoenolate should lead to the formation of a catalyst-bound enol or enolate, and Bode and co-workers have elegantly used this enolate in their enantioselective Diels–Alder reaction with α,β-unsaturated imines to afford dihydropyridinones (Scheme 34).[42]



Scheme 33 β-Lactone formation *via* conjugate umpolung.



Scheme 34 Catalytic, enantioselective Diels–Alder reaction.



Scheme 35 Homoenolate in an intramolecular Michael reaction.

Scheidt and co-workers have very recently described the use of this powerful strategy in intramolecular Michael reactions of substrates of the type **123** to afford various 1,5-dicarbonyl compounds after the addition of an alcohol (Scheme 35).[43]

6. Conclusions

From the foregoing account, it is clear that the application of NHC–homoenolate as a powerful three carbon synthon for unconventional C–C bond formation is gaining acceptance. Although most of the work using homoenolates has involved intermolecular reactions, it is reasonable to assume that NHC–homoenolate chemistry will prove its usefulness in the intramolecular arena as well. Evidently, this is an emerging area and a number of groups are currently exploring the potential applications of homoenolates in the construction of carbon–carbon and carbon–heteroatom bonds. *Inter alia*, some of the emerging protocols will undoubtedly find application in the synthesis of a variety of carbo- and heterocycles.

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