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Recent Advances in the N-Heterocyclic Carbene (NHC)-Organocatalyzed Stetter Reaction and Related Chemistry

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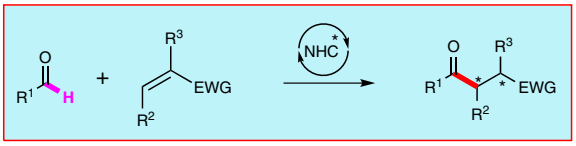

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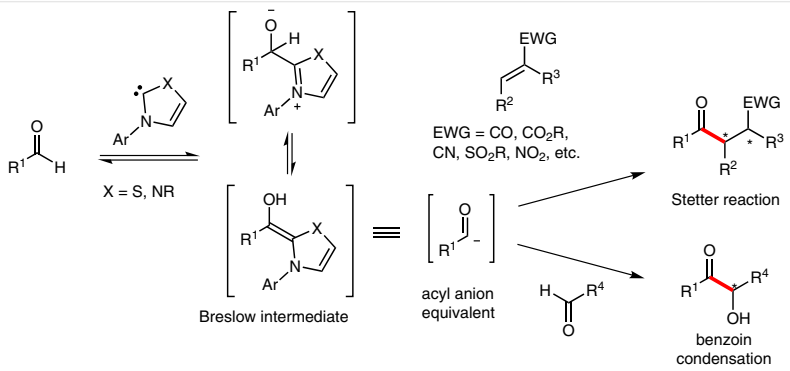
Abstract Recent developments in the N-heterocyclic carbene (NHC)-catalyzed umpolung of aldehydes followed by their interception with activated carbon–carbon double bonds, namely the Stetter reaction, are presented. Advances in the inter- and intramolecular versions of this reaction, enantioselective transformations as well as the use of unactivated olefins in this type of reaction are discussed.

Key words N-heterocyclic carbenes, Stetter reaction, organocatalysis, umpolung, asymmetric catalysis

1 Introduction

The Stetter reaction constitutes the cyanide ion or N-heterocyclic carbene (NHC)-catalyzed umpolung of aldehydes followed by their interception with electrophilic carbon–carbon double bonds (Michael acceptors).[1,2] The reaction results in the formation of 1,4-bifunctional compounds such as γ-diketones, γ-ketonitriles, and γ-keto esters, thus creating an unnatural functional group distance, which is not easy to construct using conventional methods (Scheme 1).[3] Another reaction that takes advantage of the umpolung of aldehydes is the benzoin reaction, where the nucleophilic Breslow intermediate adds to the carbonyl group of aldehydes or ketones in an intermolecular or intramolecular fashion.[2m,4]

The cyanide ion catalyzed reaction between aldehydes and Michael acceptors such as α,β-unsaturated carboxylic esters, ketones, and nitriles proceeding via umpolung strategy was first developed by Stetter and Schreckenberg in 1973.[5] In 1976, Stetter developed the thiazolium-catalyzed, highly selective conjugate addition method to cross-couple



Scheme 1 NHC-catalyzed Stetter reaction and benzoin condensation

a wide variety of (hetero)aromatic and aliphatic aldehydes with an array of Michael acceptors, and in most cases these reactions proceeded in an intermolecular fashion.[1] However, the existence of an NHC was supported by the experiments of Wanzlick,[6a] and the role of an NHC as the catalytically active species was validated by the isolation and characterization of first stable crystalline NHC by Arduengo and co-workers in 1991.[6b] The Stetter reaction proceeds via the generation of a nucleophilic acyl anion equivalent (enaminol intermediate commonly known as the Breslow intermediate),[7a] which on reaction with the Michael acceptor results in the formation of the 1,4-bifunctional compound. It may be noted in this context that the indirect evidence for the existence of the Breslow intermediate was suggested as early as 2003 by Nair and co-workers, who isolated the protected Breslow intermediate,[8a] and direct evidence was provided by Berkessel and co-workers by NMR spectroscopy and X-ray diffraction.[8b,c]

The Stetter reaction can be catalyzed by a broad range of carbenes derived from thiazolium salts and triazolium salts (usually applicable in the enantioselective Stetter reaction). Most often, α,β-unsaturated ketones are used as the Michael acceptors. Notably, the use of prochiral Michael acceptors can furnish two new stereocenters in this reaction. Moreover, the 1,4-diketones are precursors for the synthesis of valuable heterocycles such as furans, pyrroles, and thiophenes, and also synthons for the synthesis of natural products. A recent class of transformations utilizing the umpolung of aldehydes is the hydroacylation reaction, where the acyl anion equivalent undergoes addition to an unactivated carbon–carbon multiple bond.[9]

The purpose of this review is to highlight the recent developments in NHC-catalyzed Stetter reactions and related umpolung processes reported in the last five years. The reactions uncovered before 2009 have already been the subject of excellent reviews, and hence not attempted herein.[3] Since the focus is on Stetter reactions, recent advances in

Biographical Sketches

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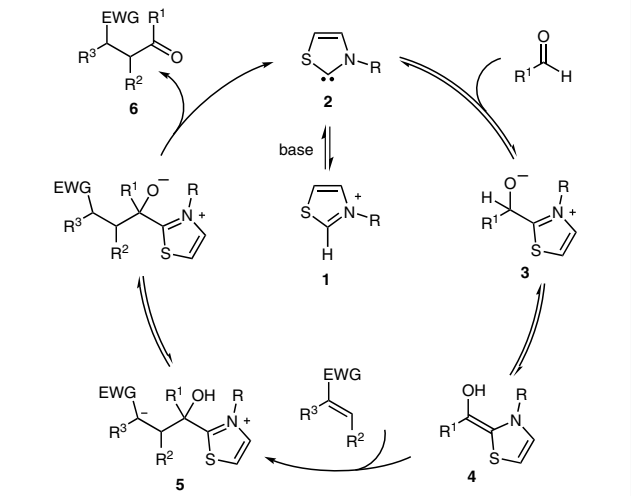
benzoin reactions and reactions proceeding via NHC-bound enolate and homoenolate intermediates are not included in this review.

2 Proposed Mechanism of the Stetter Reaction

Breslow demonstrated the mechanism of the benzoin reaction catalyzed by a thiazolium salt or a cyanide anion, proceeding via the key enaminol intermediate (called the Breslow intermediate).[7] Interestingly, in most cases, the benzoin reaction is found to be reversible. The mechanism of the Stetter reaction is similar to that of the benzoin reaction, the difference being the irreversible nature of the Stetter reaction as well as the addition of Breslow intermediate to Michael acceptors. According to the proposed mechanism for the NHC-catalyzed Stetter reaction (Scheme 2), the free carbene **2** is generated from the azolium precursor **1** upon treatment with base. The carbene **2** adds to the aldehyde, generating the nucleophilic Breslow intermediate **4**, by way of tetrahedral intermediate **3**. Up until the generation of **4**, the steps are considered to be reversible. It should be noted in this context that Rovis and co-workers reported in 2011 that the proton transfer from the tetrahedral intermediate **3** to Breslow intermediate **4** is the first irreversible step in the triazolinylidine carbene catalyzed asymmetric intramolecular Stetter reaction.[10] The Breslow intermediate **4** then undergoes an irreversible addition to the Michael acceptor, generating the intermediate **5**, which on proton transfer and subsequent release of free carbene affords the desired Stetter product **6**. The implementation of chiral NHCs in this process can result in asymmetric transformations leading to the enantioselective synthesis of 1,4-bifunctional compounds.



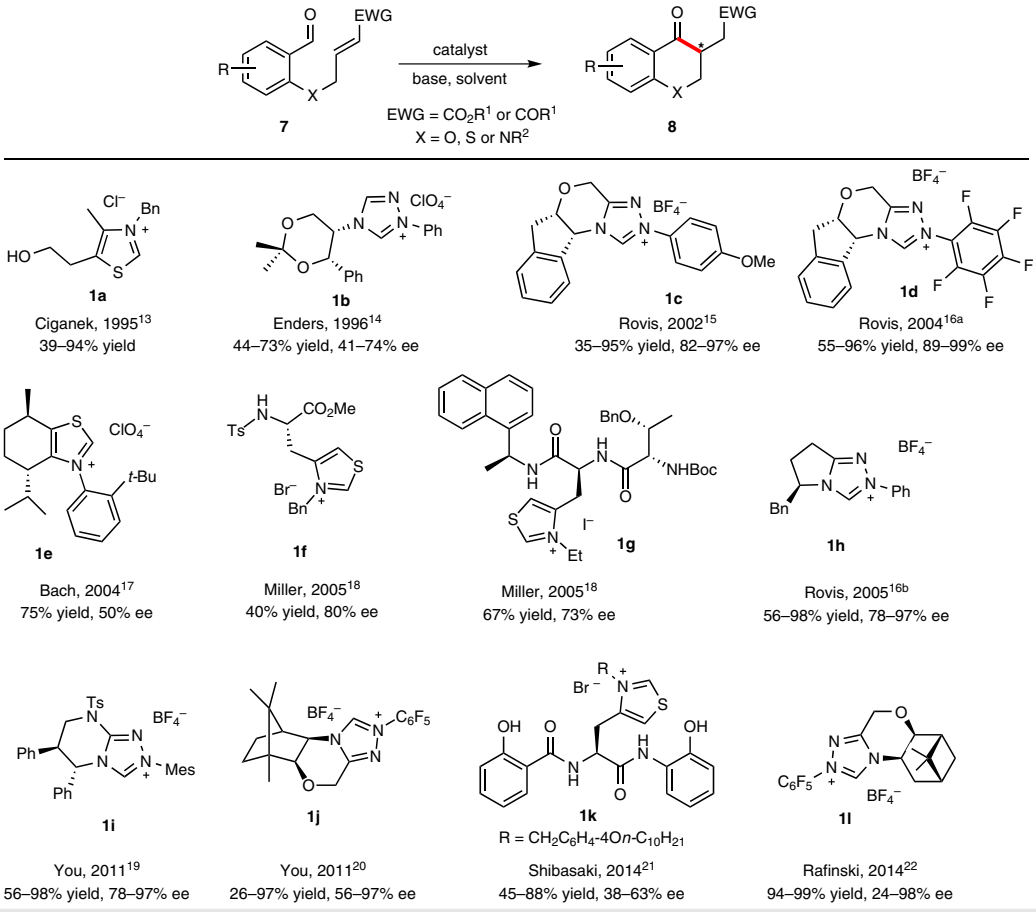
Scheme 2 Proposed mechanism of the Stetter reaction

The Rovis research group studied the mechanism of the intramolecular Stetter reaction in detail.[11] Although a stepwise mechanism for the addition of Breslow intermediate to the Michael acceptor was proposed, they also considered the possibility of Breslow intermediate addition to Michael acceptors in a concerted pathway, analogous to the reverse-Cope elimination. Moreover, based on DFT calculations, Hawkes and Yates demonstrated that the addition of Breslow intermediate to the Michael acceptor is a two-step process in which the carbon–carbon coupling is the rate-determining step, and is followed by the final proton transfer.[12] In addition, the Breslow intermediate was found to play a critical role in controlling the stereochemistry of the product in the asymmetric Stetter reaction.

3 Intramolecular Stetter Reactions

The NHC-catalyzed intramolecular Stetter reaction was developed by Ciganek in 1995.[13] The NHC derived from the thiazolium salt **1a** catalyzed the intramolecular cyclization of 2-formylaryloxy crotonates **7** and 2-formylaryloxy acrylates afforded benzannulated pyranones and furanones, respectively (Scheme 3). The reaction was found to take place in the absence of base, and in *N*,*N*-dimethylformamide under reflux conditions. The successful demonstration of this reaction provided the foundation for the rational design of various chiral NHC precursors, which enabled the development of the enantioselective Stetter reaction. In 1996, Enders and co-workers demonstrated the first asymmetric intramolecular Stetter reaction utilizing the NHC derived from chiral triazolium salt **1b**.[14] Various aromatic aldehydes **7**, which are connected to the Michael acceptor through a tether (usually the oxygen tether) underwent NHC-catalyzed cyclization reactions, affording several 4-chromanones in moderate yield (44–73%) and enantioselectivity (41–74% ee). For the development of new NHC precatalysts and for comparing their catalytic activities, the cyclization of salicylaldehyde-derived substrate **7** to chromanone **8** has become a standard reaction.

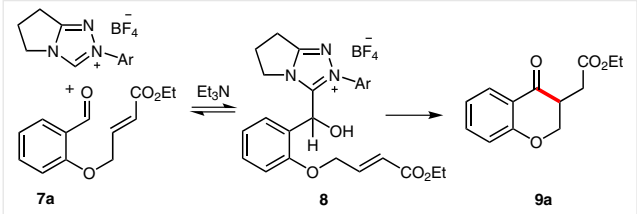
A highly enantioselective intramolecular Stetter reaction of substrates like **7** using the aminoindanol-derived chiral triazolium salt **1c** was developed by Rovis and co-workers in 2002.[15] Subsequently, Rovis and co-workers developed the aminoindanol-derived pentafluoroaryl-substituted chiral triazolium salt **1d** and phenylalanine-derived triazolium salt **1h**.[16] The chiral carbenes derived from **1d** and **1h** are found to be the most efficient catalysts for the intramolecular Stetter reaction, furnishing the target products in reasonable yields and with excellent enantiomeric excess.[11,16] Moreover, Bach and co-workers developed the axially chiral thiazolium salt **1e** with an *N*-aryl substituent, which afforded the Stetter adduct **8** in up to 75% yield and 50% ee.[17] Thiazolium salts **1f** and **1g** based on a peptide backbone were developed by Miller and co-workers for the



Scheme 3 Catalysts developed for the intramolecular Stetter reaction

intramolecular Stetter reaction.[18] You and co-workers reported the chiral triazolium salt **1i**, synthesized from readily available diphenyl ethylenediamine (DPEN), which can furnish the chromanone derivative **8** in excellent yields and up to 97% ee.[19] In addition, they developed the chiral triazolium salt **1j**, derived from the inexpensive D-camphor, for the enantioselective intramolecular Stetter reaction.[20] Very recently, the intramolecular Stetter reaction of salicylaldehyde derivative **7** to chromanone **8** was demonstrated by using the bis(hydroxyaryl)diamide-containing chiral thiazolium salt **1k** (by Shibasaki and co-workers),[21] and using β-pinene-derived chiral triazolium salt **1l** (by Rafińsky and co-workers).[22] It may be noted in this context that C_2-symmetric chiral cyclophane dihydroimidazolium salts for use in the intramolecular Stetter reaction were developed by Zhang and co-workers to afford the chromanones in moderate yields and enantiomeric excess.[23]

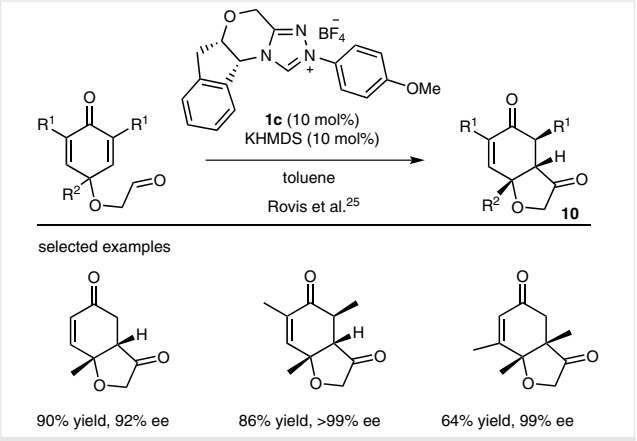
Recently, Smith and co-workers investigated the role of the *N*-aryl substituent of triazolium-derived NHCs in the Stetter reaction and benzoin condensation. A series of tetrahedral intermediates (the hydroxybenzylammonium salts) **8** derived from the addition of NHCs on aldehyde **7a** were isolated, and it was found that the generation of **8** was reversible under the reaction conditions and that the formation of the Stetter adduct **9a** from **8** was a slow process (Scheme 4).[24] Moreover, the pentafluoroaryl-substituted triazolium precatalysts showed superior reactivity in the intramolecular Stetter reaction using triethylamine as the base.



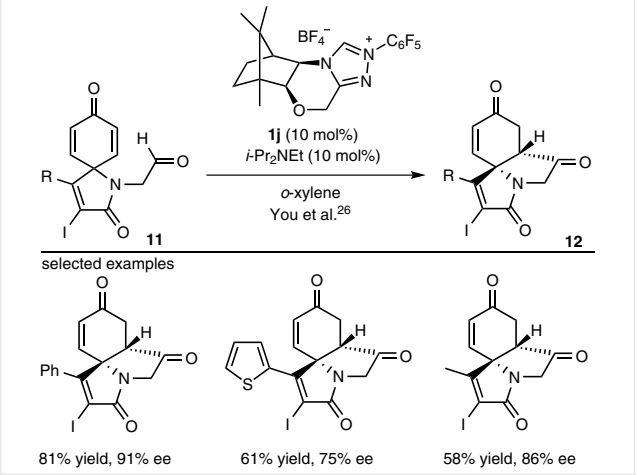
Scheme 4 Isolation of aldehyde–NHC adducts in the Stetter reaction (Smith et al.)

The NHC-catalyzed desymmetrization of cyclohexadienones via the intramolecular Stetter reaction was demonstrated by Liu and Rovis in 2006. A wide variety of tethered cyclohexadienone carboxaldehydes underwent efficient cy-

clization leading to the formation of hydrobenzofurans **10** containing up to three contiguous stereocenters (Scheme 5).[25] The carbene generated from the 4-methoxyaryl-substituted triazolium salt **1c** was found to be the best catalyst for this intramolecular Stetter reaction. The analogous desymmetrization reaction of cyclohexadienone derivatives **11** using the camphor-derived triazolium salt **1j** leading to the formation of the tricyclic compound **12** in moderate to good yield and good enantioselectivity was developed by Jia and You (Scheme 6).[26] In the case of α-substituted cyclohexadienones, the carbene generated from **1d**, the aminoindanol-derived chiral triazolium salt bearing a pentafluorophenyl group, resulted in a diastereoselective and enantioselective intramolecular Stetter reaction leading to the formation of the tricyclic products in excellent yields (up to 96% yield) and enantiomeric excess (up to 99% ee).[26b] They also applied this method for the enantioselective construction of tricyclic carbocycles possessing a quaternary stereocenter by the desymmetrization of cyclohexadienones using the camphor-derived NHC precatalyst **1j**.[27]

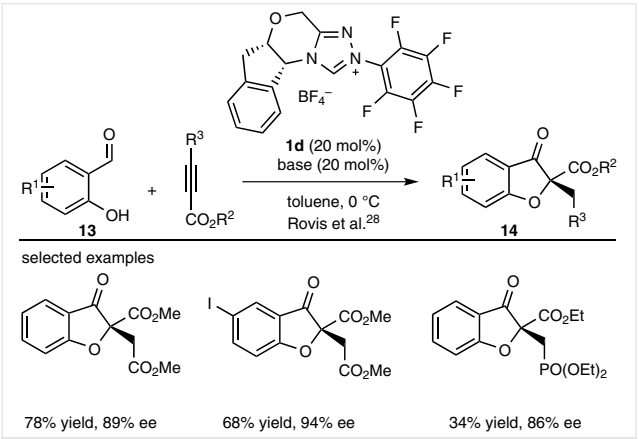


Scheme 5 Desymmetrization of cyclohexadienones via intramolecular Stetter reaction



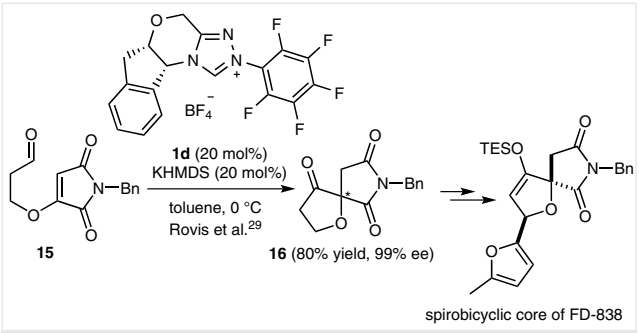
Scheme 6 Desymmetrization of cyclohexadienones via intramolecular Stetter reaction

A one-pot, multicatalytic asymmetric Michael–intramolecular Stetter reaction between salicylaldehydes **13** and electrophilic alkynes was reported by Rovis and co-workers. The Michael reaction was catalyzed by bases such as DABCO or quinuclidine while chiral NHCs catalyzed the Stetter reaction (Scheme 7).[28] Activated internal alkynes and electrophilic allenes were used as the Michael acceptors in this reaction, furnishing benzofuranone products **14** in moderate to good yields and excellent enantiomeric excess. Notably, this one-pot Michael–Stetter strategy was found to be superior to the two-step procedure in terms of enantioselectivity.



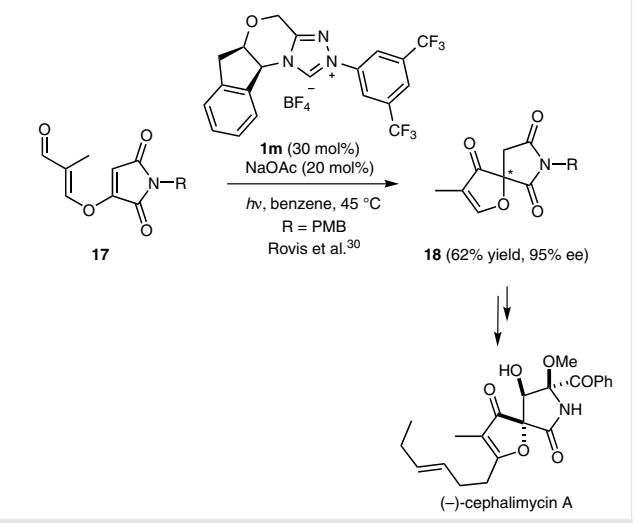
Scheme 7 One-pot Michael–Stetter strategy

The enantioselective intramolecular Stetter reaction of aldehyde **15** possessing an *N*-benzyl-substituted maleimide was recently demonstrated by Orellana and Rovis. The aminoindanol-derived chiral NHC afforded the spirofuranone **16** up to 80% yield and 99% ee.[29] Moreover, this methodology was extended to the synthesis of the spirocyclic core of the antibiotic FD-838 (Scheme 8). Recently, a tandem process involving a photoisomerization followed by intramolecular Stetter reaction was uncovered by Lathrop and Rovis. The UV irradiation of the aldehyde derivative **17** in the presence of the chiral triazolium salt **1m** and sodium acetate resulted in the formation of the spirocyclic furanone



Scheme 8 Application of the intramolecular Stetter reaction to the spirobicyclic core of FD-838

18 in 62% yield and 95% ee (Scheme 9).[30] The UV irradiation enables the isomerization of the olefin to the geometry necessary for the Stetter reaction. In addition, this protocol was applied to the total synthesis of (–)-cephalimycin A.

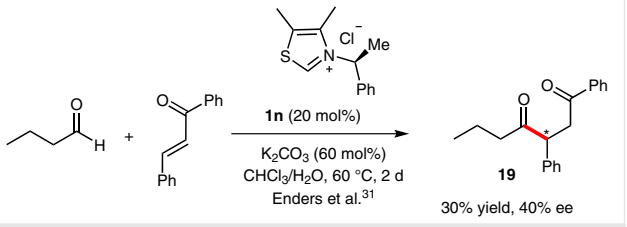


Scheme 9 Photoisomerization–Stetter reaction cascade

4 Intermolecular Stetter Reactions

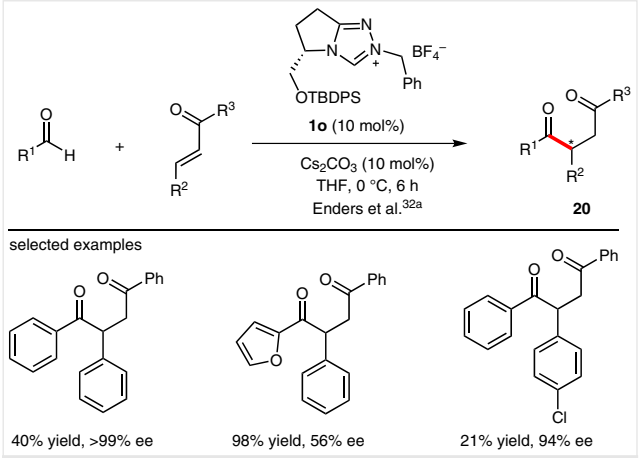
Although the first report on the intermolecular Stetter reaction appeared in 1976, the enantioselective intermolecular Stetter reaction remained as a challenge until recently. The catalyst development as well as reaction procedures for the enantioselective intramolecular Stetter reaction was well established relative to those of the intermolecular reaction. Moreover, the Michael acceptors with a β-substitution usually showed lower reactivity in the intermolecular Stetter reaction.

The first enantioselective intermolecular Stetter reaction was reported by Enders and co-workers. The reaction of *n*-butanal with chalcone was catalyzed by the carbene generated from the chiral thiazolium salt **1n**. The desired 1,4-diketone **19** was isolated in 30% yield and 40% ee (Scheme 10).[31]



Scheme 10 Asymmetric intermolecular Stetter reaction of *n*-butanal with chalcone

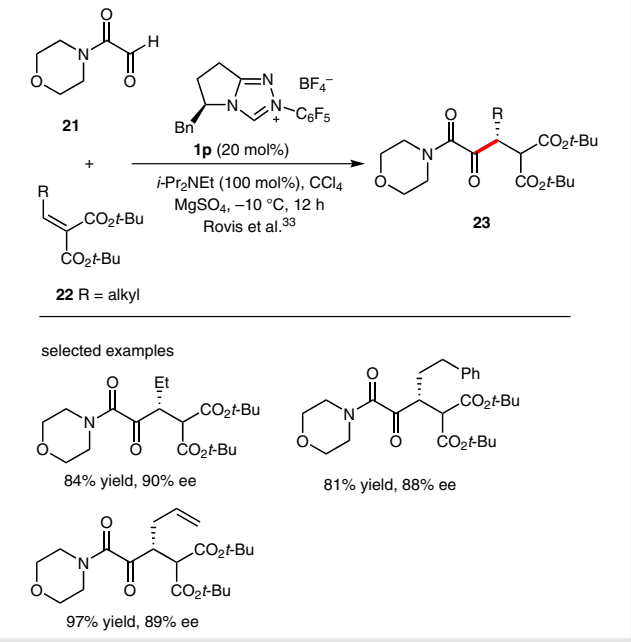
In 2008, Enders and co-workers demonstrated the enantioselective intermolecular Stetter reaction of (hetero)aromatic aldehydes with chalcones, and the reaction was catalyzed by the NHC derived from triazolium salt **1o**. The reaction afforded the 1,4-diketones **20** in moderate to good yields and with moderate to good enantioselectivity values (Scheme 11).[32a] Notably, the enantiomeric excess of the products could be improved up to 99% ee by recrystallization. The key to success for the high levels of selectivity using **1o** was the presence of the *N*-benzyl substituent, which sheds light on the impact of the N-substituent on the activity of triazolium-based NHC precatalysts in the intermolecular Stetter reaction. Subsequently, the Enders research group demonstrated the enantioselective intermolecular Stetter reaction of heteroaromatic aldehydes with β-aryl arylidenemalonates as Michael acceptors using NHC precatalyst **1o**.[32b] The ketomalonate products were obtained in 84–98% yield and up to 87% ee.



Scheme 11 Asymmetric intermolecular Stetter reaction of aldehydes with chalcones

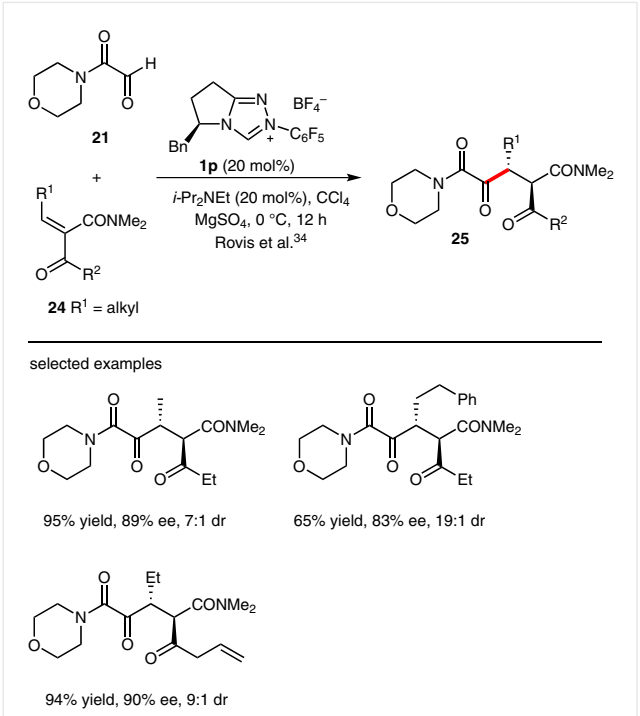
Independent investigations by Rovis and co-workers resulted in the asymmetric intermolecular Stetter reaction between morpholine-derived glyoxamide derivative **21** as the aldehyde component and alkylidenemalonate **22** as the Michael acceptor. Various β-alkyl-substituted alkylidenemalonates were well tolerated under the reaction conditions, affording the desired Stetter products **23** in good yields with high enantioselectivity in the presence of the phenylalanine-derived NHC catalyst **1p** (Scheme 12).[33] Notably, a drawback of this method was that alkylidene malonate with two ester groups (*tert*-butyl ester) reduced the opportunity for further functionalization. In order to overcome the limitation with the Michael acceptor, the Rovis research group subsequently developed the highly enantioselective and diastereoselective intermolecular Stetter reaction of the glyoxamide **21** and β-alkyl alkylidene ketoamides **24** (Scheme 13).[34] In the presence of NHC precatalyst **1p**, the reaction of **21** and **24** afforded the 1,4-di-

carbonyl compounds **25** in good to excellent yields. It is noteworthy that the 1,4-dicarbonyl compounds synthesized using this method are suitable candidates for further functionalization to synthetically valuable compounds in organic synthesis. Later, a related intermolecular Stetter reaction strategy was reported by Johnson and co-workers, who used ethyl glyoxylate as the aldehyde component and benzylidene malonates/enones as the Michael acceptors.[35] In the former case, the Stetter adduct, the β-aryl α-keto ester, was subjected to dynamic kinetic resolution via asymmetric transfer hydrogenation using a ruthenium(II) catalyst to afford trisubstituted γ-butyrolactones.[35a]

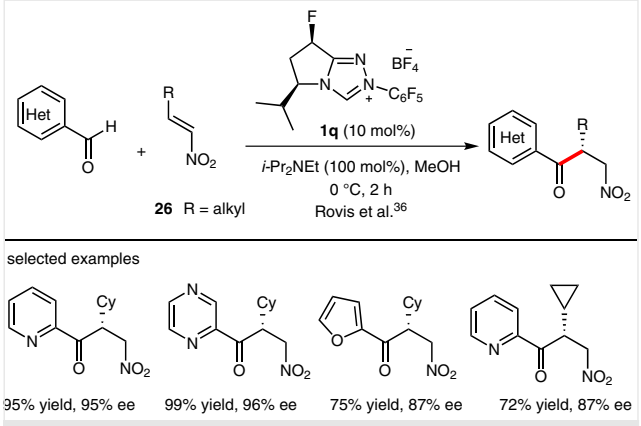


Scheme 12 Asymmetric intermolecular Stetter reaction of glyoxamides with alkylidenemalonates

As part of their efforts to develop a general and broad-scope enantioselective intermolecular Stetter reaction, the Rovis research group used nitroalkenes **26** as feasible Michael acceptors with a new chiral NHC pre-catalyst, **1q**. By exploiting the stereoelectronic as well as steric effects induced by the fluoro and isopropyl substituents in **1q**, a facile and efficient intermolecular enantioselective Stetter reaction of nitroalkenes and heteroaromatic aldehydes was developed (Scheme 14).[36] It is noteworthy, however, that the use of heteroaromatic aldehyde was essential for high levels of selectivity and reactivity. Additionally, Rovis, Houk and co-workers used quantum mechanical investigations to gain insight into the role of the fluorine atom in **1q** on reactivity and selectivity.[37] These studies showed that the preferred conformation of the salt **1q** is controlled by stereoelectronic effects. Furthermore, generation of the acyl anion equivalent from the heteroaromatic aldehyde and **1q** results in the *exo* conformation of the pyrrolidine ring of **1q**, and the favored transition state is stabilized by the interaction between the developing negative charge on the nitro group of **26** and the developed positive charge on **1q**.



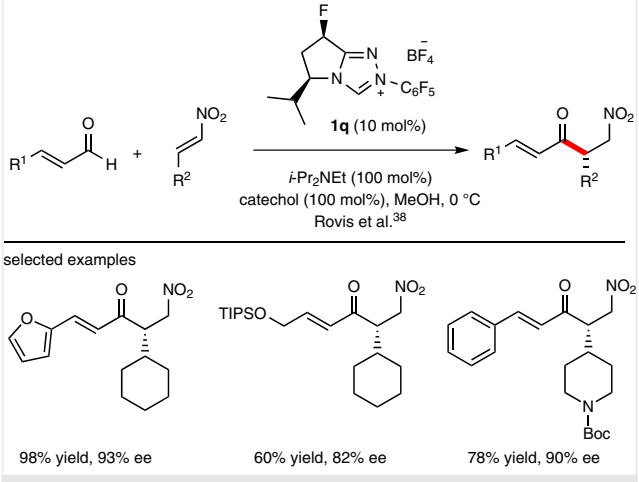
Scheme 13 Asymmetric intermolecular Stetter reaction of glyoxamides with alkylidene ketoamides



Scheme 14 Asymmetric intermolecular Stetter reaction of heteroaromatic aldehydes with nitroalkenes

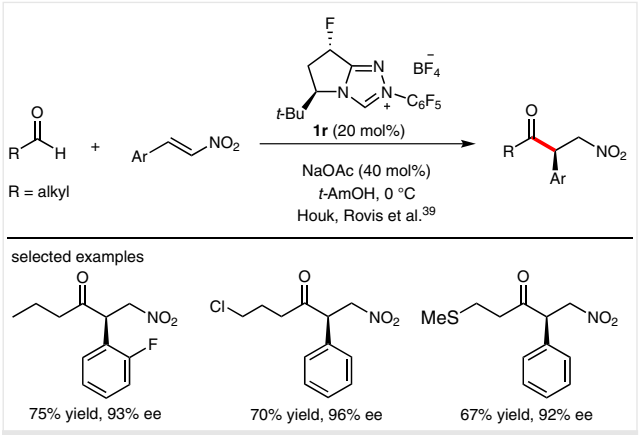
The scope of the asymmetric intermolecular Stetter reaction was further expanded by DiRocco and Rovis by employing α,β-unsaturated aldehydes as aldehyde components. The reaction of enals with β-nitrostyrenes was catalyzed by the fluorinated triazolium salt **1q**, and the

presence of catechol as the bifunctional Brønsted acid was found to be crucial for achieving the reactivity and selectivity (Scheme 15).[38] In addition, the presence of catechol allowed the reaction to be carried out under low catalyst loadings without affecting the reactivity. Under the reaction conditions, products derived from the homoenolate reactivity were not observed.[2i,n] Moreover, Houk, Rovis and co-workers demonstrated the intermolecular Stetter reaction by using enolizable aldehydes as the coupling partner for β-nitrostyrenes.[39] A wide variety of aliphatic aldehydes and β-aryl nitrostyrenes were well tolerated under these reaction conditions using the chiral triazolium salt **1r** as catalyst (Scheme 16). Interestingly, the *trans* fluorinated geometry in the pyrrolidine ring of **1r** was essential for high reactivity and selectivity. Additionally, the NHC-catalyzed acyl anion addition to the anomeric carbon of 2-nitroglucal leading to the formation of β-selective C-glycosides **27** in good yields was reported by Liu and co-workers. The thiazolium salt **1a** was optimal for this reaction (Scheme 17).[40] However, when the reaction was performed using cesium carbonate as the base, the nitro-eliminated C-glycosides were obtained.

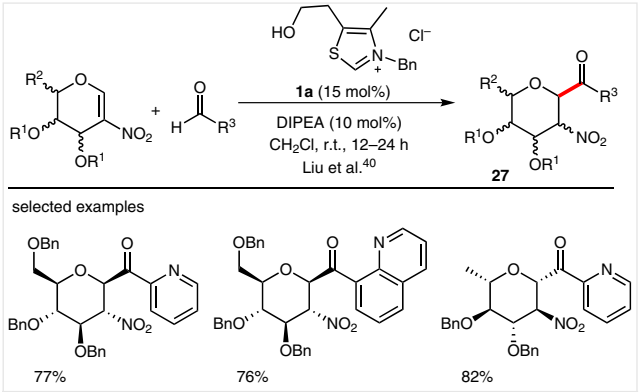


Scheme 15 Asymmetric intermolecular Stetter reaction of α,β-unsaturated aldehydes with β-nitrostyrenes

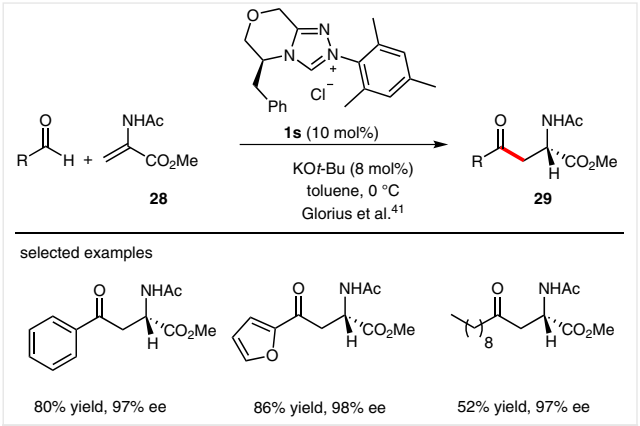
In 2011, Glorius and co-workers developed the synthesis of enantioenriched α-amino acid derivatives by an intermolecular Stetter reaction using *N*-acylamido acrylate **28** as the Michael acceptor. Notably, in this reaction, the two important pathways, the carbon–carbon bond-forming event between the Breslow intermediate and the Michael acceptor as well as enantioselective protonation, were efficiently combined. Several aldehydes reacted with the dehydroamino ester **28** in the presence of the NHC generated from L-phenylalaninol-derived triazolium salt **1s**, affording the α-amino acid derivatives **29** in high yield and enantiomeric excess (Scheme 18).[41]



Scheme 16 Asymmetric intermolecular Stetter reaction of enolizable aldehydes with β-nitrostyrenes



Scheme 17 NHC-catalyzed C-glycosylation using the Stetter reaction



Scheme 18 Asymmetric intermolecular Stetter reaction of *N*-acylamido acrylates

In addition to traditional stepwise addition of the nucleophilic Breslow intermediate to Michael acceptor **28** as shown in intermediate **30** (the approach of the Michael acceptor **28** from the bottom face in an *anti* fashion, which is likely supported by a hydrogen bond between the enol hydrogen and the carbonyl oxygen of the Michael acceptor),

Glorius and co-workers proposed a concerted mechanism proceeding through a cyclic five-membered transition state **31** to shed light on the mode of asymmetric induction (Figure 1). Moreover, Kuniyil and Sunoj recently investigated the origin of stereoselectivity and the role of potassium *tert*-butoxide in this reaction using DFT calculations and suggested that *tert*-butanol played a role in the intermolecular protonation event.[42] In addition, the computed enantiomeric excess values are in agreement with the experimental results.

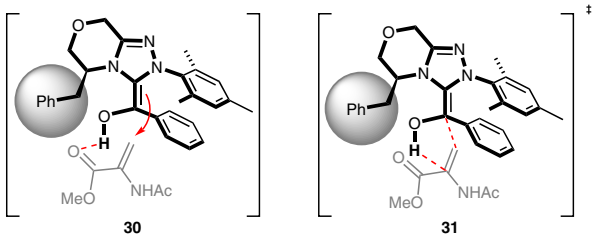
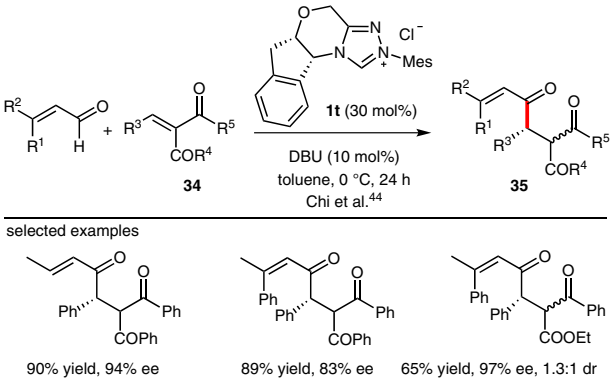


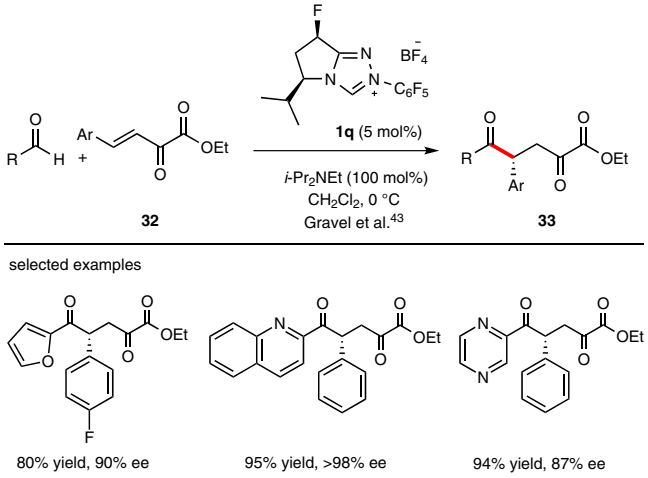
Figure 1 Stepwise and concerted pathways in the enantioselective intermolecular Stetter reaction involving *N*-acylamido acrylate

The synthetic utility of the fluorinated triazolium salt **1q** developed by the Rovis group was further demonstrated by Gravel and co-workers who used β,γ-unsaturated α-keto esters **32** as Michael acceptors in the asymmetric intermolecular Stetter reaction (Scheme 19). The reaction furnished 1,2,5-tricarbonyl compounds **33** in high yields and enantiomeric excess.[43] Various (hetero)aromatic aldehydes underwent smooth Stetter reaction, and the resultant products were amenable to a variety of synthetic manipulations. Moreover, the enantioselective Stetter reaction of α.β-unsaturated aldehydes with α-acyl chalcones **34** was recently uncovered by Chi and co-workers. The carbene generated from the sterically demanding aminoindanol-derived triazolium salt **1t** catalyzed the selective acyl anion addition to modified chalcones to afford the triketones **35** in good yields and excellent enantiomeric excess (Scheme 20).[44] Notably, various β-alkyl, β-aryl, and β,β-disubstituted enals worked well under these reaction conditions. It is important to note that under slightly different reaction conditions, the same reagents and catalyst afforded the Diels–Alder adducts by the [4+2] cycloaddition of the NHC-bound enolate generated from enal and **1t** with the modified chalcones.[45]



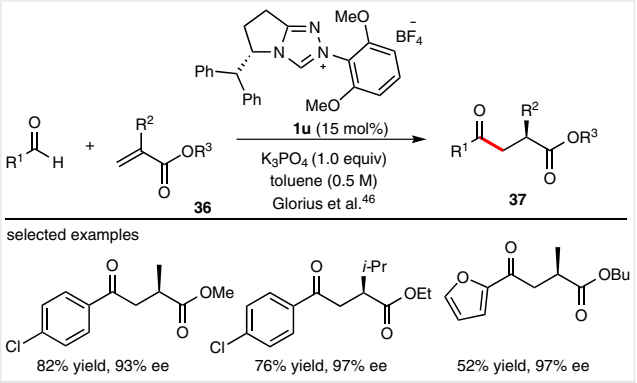
Scheme 20 Asymmetric intermolecular Stetter reaction of α,β-unsaturated aldehydes with modified chalcones

α,β-Unsaturated esters were considered to be moderately poor electrophiles and weak Michael acceptors in NHC catalysis. In 2012, Glorius and co-workers reported the asymmetric intermolecular Stetter reaction using simple acrylates **36** resulting in the formation of α-chiral γ-keto esters **37** (Scheme 21).[46] The carbene generated from the slightly electron-rich 2,6-dimethoxyaryl-substituted triazolium salt **1u** was found to be efficient for catalyzing this transformation. A wide variety of (hetero)aromatic and ali-



Scheme 19 Asymmetric intermolecular Stetter reaction using β,γ-unsaturated α-keto esters as Michael acceptors

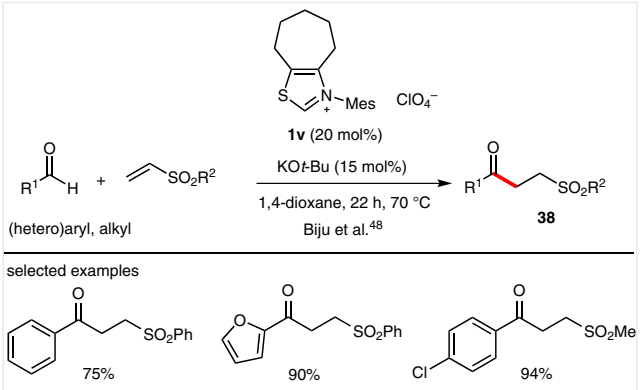
phatic aldehydes, and several acrylates, underwent smooth Stetter reaction under the optimized reaction conditions.



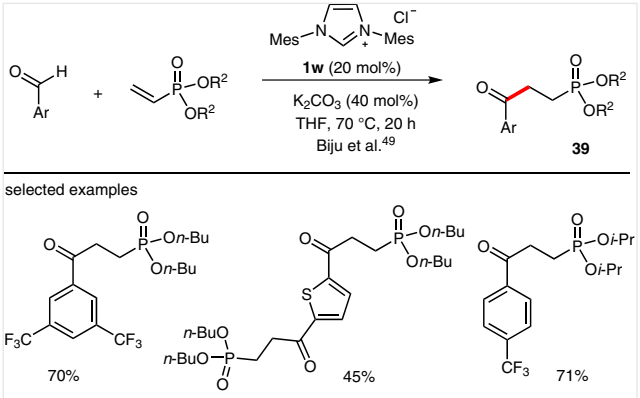
Scheme 21 Asymmetric intermolecular Stetter reaction using α,β-unsaturated esters

The NHC-catalyzed reaction of aldehydes with vinylsulfone as Michael acceptor was known by Stetter as early as 1978. Interestingly, the product was not the expected γ-keto sulfone, but instead a 1:1 mixture of symmetric 1,4-diketone and γ-disulfone.[47] In 2012, Biju and co-workers reported the highly selective and efficient NHC-catalyzed intermolecular Stetter reaction of aldehydes with α,β-unsaturated sulfones for the synthesis of γ-keto sulfones **38** in moderate to excellent yields (Scheme 22).[48] The carbene generated from the thiazolium salt **1v** was efficient in catalyzing this transformation. Mechanistic studies indicated that the reaction proceeds via the generation of benzoin as the intermediate in this reaction, and the nucleophilic Breslow intermediate can add to the vinylsulfone in a stepwise manner or in a concerted pathway. Very recently, Biju and co-workers demonstrated the synthetic utility of vinylphosphonates as Michael acceptors in the intermolecular Stetter reaction. This atom-economic and practical NHC-catalyzed transformation afforded the γ-ketophosphonates **39** in moderate to good yields (Scheme 23).[49] The carbene generated from the imidazolium salt **1w** was efficient for this cross-coupling reaction. This method for the synthesis of γ-ketophosphonates can be considered as an alternative to the well-known method for accessing these compounds via the phospha-Michael reaction. It may be noted in this context that the enantioselective intramolecular Stetter reaction of vinylphosphonates and vinylphosphine oxides has been uncovered by Cullen and Rovis.[16d]

The synthetic utility of acetaldehyde as a biomimetic acyl anion source in the intermolecular Stetter reaction was developed by Ryu, Yang and co-workers. The enantioselective Stetter reaction using acetaldehyde and chalcones catalyzed by the carbene generated from **1d** resulted in the formation of the 1,4-diketone **40** in moderate enantioselectivity (Scheme 24).[50] Moreover, the use of butane-2,3-dione

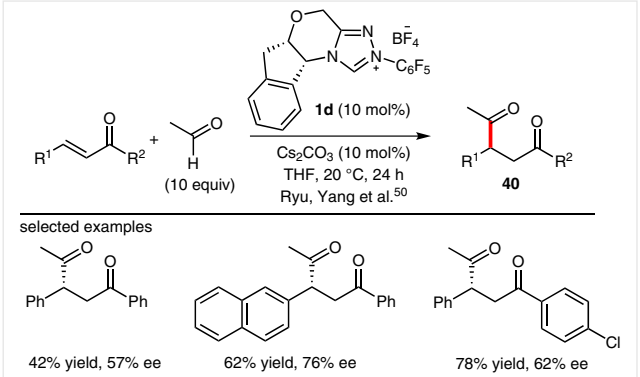


Scheme 22 Intermolecular Stetter reaction using vinylsulfones

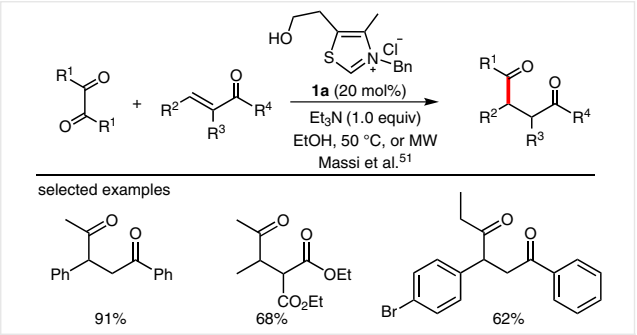


Scheme 23 Intermolecular Stetter reaction using vinylphosphonates

(biacetyl) as an effective, bench-stable, and inexpensive alternative surrogate of acetaldehyde for acyl anion generation was developed by Massi and co-workers. The reaction was catalyzed by the carbene generated from thiazolium salt **1a** and proceeded under classical heating as well as microwave heating (Scheme 25).[51] Several acyclic and cyclic 1,2-diones have been used for acyl anion generation. The Stetter reaction of biacetyl and chalcones using thiazolium salt precatalysts that are immobilized on silica and mono-



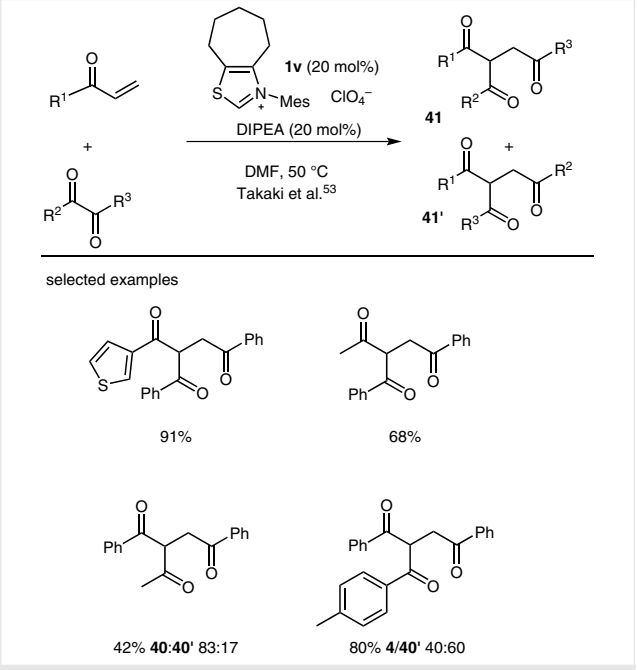
Scheme 24 Synthetic utility of acetaldehyde in the Stetter reaction



Scheme 25 Use of biacetyl for acyl anion generation in the Stetter reaction

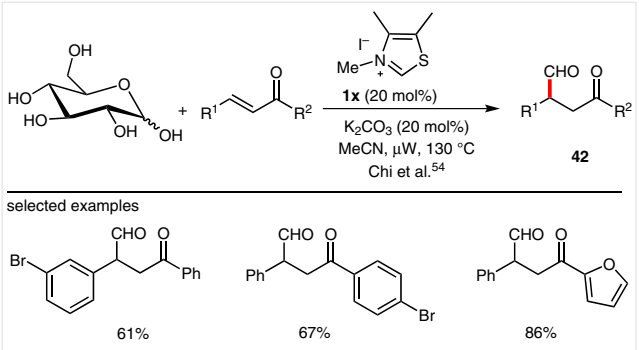
lithic polystyrene was reported by Dambruoso, Massi and co-workers.[52] In a related context, the utility of diaryl 1,2-diones for the generation of benzoyl-protected Breslow intermediate followed by Stetter-type reaction using β-unsubstituted enone as Michael acceptor was elaborates by Takaki and co-workers. The NHC-catalyzed umpolung of benzils were observed for the first time, and the double acylation afforded the triketones **41** in high yields using **1v** as the NHC precatalyst (Scheme 26).[53]

The application of biomass-based carbohydrates as formal formaldehyde equivalents to generate acyl anion intermediates in the Stetter reaction was disclosed by Chi and co-workers. This one-carbon nucleophile generated from the carbene derived from **1x** added to various chalcones and led to the formation of β-formyl ketones **42** in good



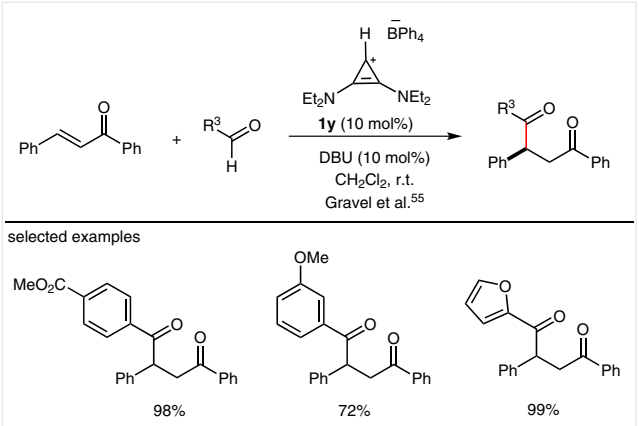
Scheme 26 NHC-catalyzed double acylation of enones with benzils

yields under microwave conditions (Scheme 27).[54] The reaction involves the NHC-catalyzed carbon–carbon bond cleavage of carbohydrates via a retro-benzoin type reaction to generate the acyl anion intermediates. The noteworthy features of this reaction include the renewable nature of carbohydrates, the first application of formaldehyde-derived acyl anions, and the easy access to β-formyl ketones.



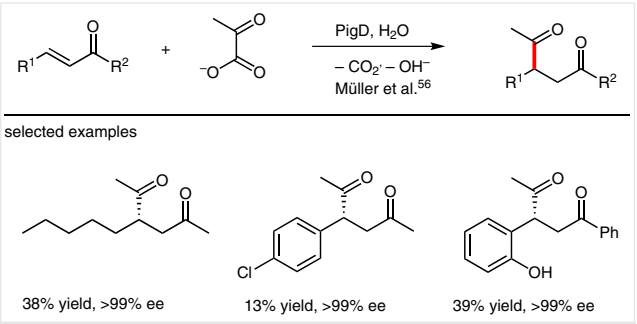
Scheme 27 Use of carbohydrates as formaldehyde equivalents in the Stetter reaction

Recently, the carbene generated from the bis(amino)cyclopropenium salt **1y** was used by Wilde and Gravel in the intermolecular Stetter reaction between aldehydes and chalcones. The relatively unhindered precatalyst **1y** was found to be superior to the commonly used azolium salts in this reaction. One advantage of using **1y** as carbene precursor is that the reaction does not proceed via the intermediacy of benzoin products. Various electronically different aldehydes were well tolerated in this reaction, affording the 1,4-diketones in high yields (Scheme 28).[55] They also used the chiral bis(amino)cyclopropenium salt derived carbenes for the enantioselective Stetter reaction and observed the desired products in up to 36% ee.



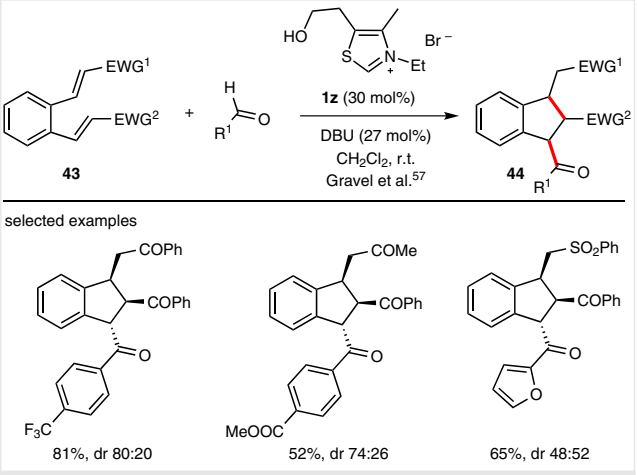
Scheme 28 Diaminocyclopropenylidene-catalyzed intermolecular Stetter reaction

Müller and co-workers recently uncovered an enantioselective enzymatic Stetter reaction. The thiamine diphosphate dependent enzyme PigD catalyzed the intermolecular enantioselective Stetter reaction of pyruvates with various enones (Scheme 29).[56] The PigD decarboxylates the pyruvate and the resulting two-carbon acyl anion equivalent can add to the enone in a Michael fashion to afford the desired product.

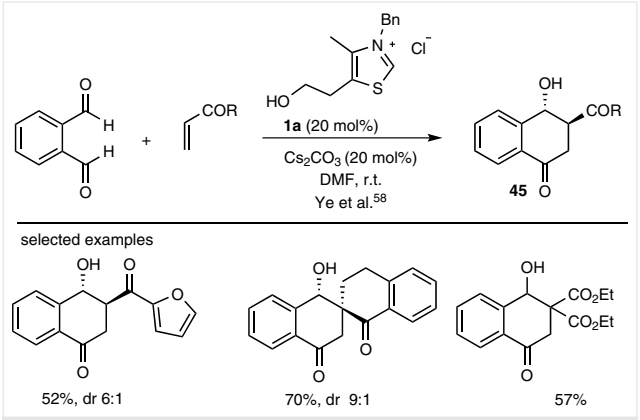


Scheme 29 Enzymatic intermolecular Stetter reaction

The intermolecular Stetter reaction can be combined with other carbon-carbon bond-forming processes in a cascade pathway. In 2009, Sánchez-Larios and Gravel reported the domino Stetter–Michael reaction cascade for the diastereoselective synthesis of indanes. The carbene generated from the thiazolium salt **1z** was responsible for the intermolecular Stetter reaction of the aldehyde and the dienone **43**. The initial Stetter reaction was followed by an intramolecular Michael reaction to form the indane derivative **44** (Scheme 30).[57] Moreover, Ye and co-workers disclosed a cascade reaction comprising a Stetter and aldol sequence for the diastereoselective synthesis of 4-hydroxytetralones. The carbene generated from **1a** catalyzed the reaction of 2-phthalaldehyde and the Michael acceptor, which was followed by an intramolecular aldol reaction to afford the 4-hydroxytetralones **45** in good yields and *trans* selectivity (Scheme 31).[58] Interestingly, with 1,2-diactivated Michael acceptors, the NHC-catalyzed cascade reaction using 2-phthalaldehyde afforded 2,2-disubstituted 3-hydroxyindanones by way of a formal [4+1] annulation.[59]



Scheme 30 NHC-catalyzed domino Stetter–Michael cascade for indane synthesis

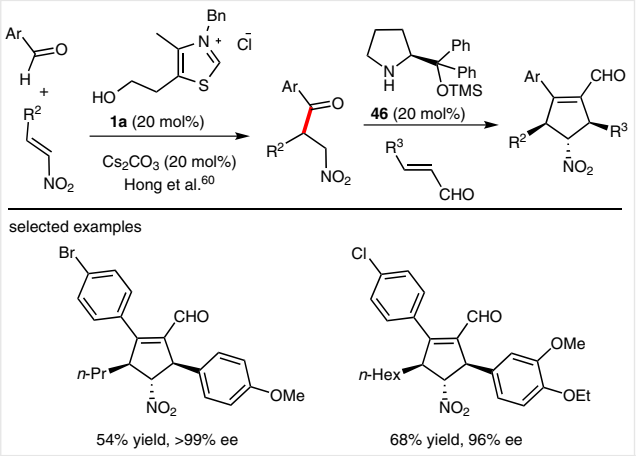


Scheme 31 NHC-catalyzed domino Stetter–aldol cascade for 4-hydroxytetralone synthesis

Hong and co-workers realized the sequential NHC-catalyzed Stetter reaction between aromatic aldehydes and nitroalkenes followed by a chiral secondary amine catalyzed Michael–aldol condensation cascade leading to the synthesis of functionalized cyclopentenes in good yields and excellent enantiomeric excess. The carbene generated from the thiazolium salt **1a** catalyzed the Stetter reaction, and the chiral proline derivative **46** catalyzed the Michael–aldol condensation sequence (Scheme 32).[60] Overall, the protocol represents an organocatalytic formal [1+2+2] annulation reaction for the simple and direct stereoselective construction of fully functionalized cyclopentenes. Interestingly, when the reaction was carried out using heteroaromatic aldehydes such as picolinaldehyde, the reaction followed a sequential Stetter and Michael–aldol reaction leading to the synthesis of fully substituted cyclopentanols.[61]

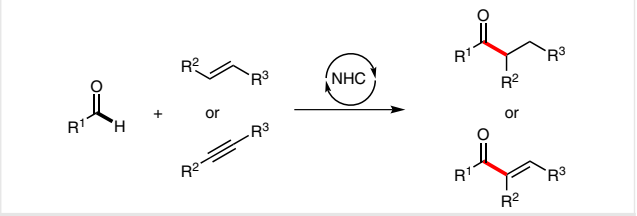
5 Hydroacylation Reactions

By definition, the Stetter reaction represents the umpolung of aldehydes followed by the nucleophilic addition of the generated acyl anion equivalents to activated carbon–carbon multiple bonds (electron-poor). Similar polarity reversal of aldehydes using NHCs, and the interception of the resultant Breslow intermediate to other electrophiles such as aldehydes, ketones (benzoin reaction), and imines (aza-benzoin reaction), has been well demonstrated. Furthermore, in 2011, the umpolung concept of electrophiles was extended to Michael acceptors such as methacrylates.[62] However, the umpolung of aldehydes followed by the addition across unactivated carbon–carbon multiple bonds,



Scheme 32 Sequential Stetter and Michael–aldol condensation cascade

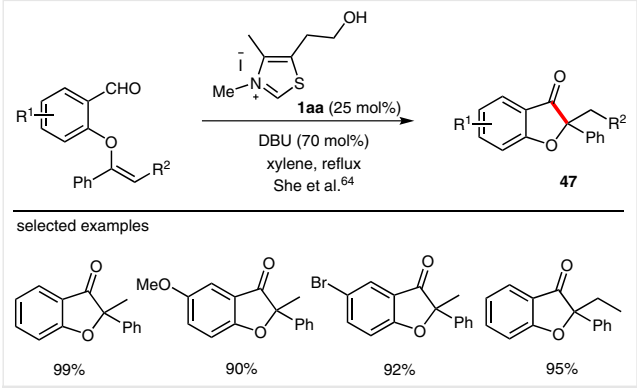
namely the NHC-catalyzed hydroacylation reaction, was underexplored until recently (Scheme 33).[8] On the other hand, transition-metal-catalyzed hydroacylation reactions to unactivated carbon–carbon bonds are well studied.[63]



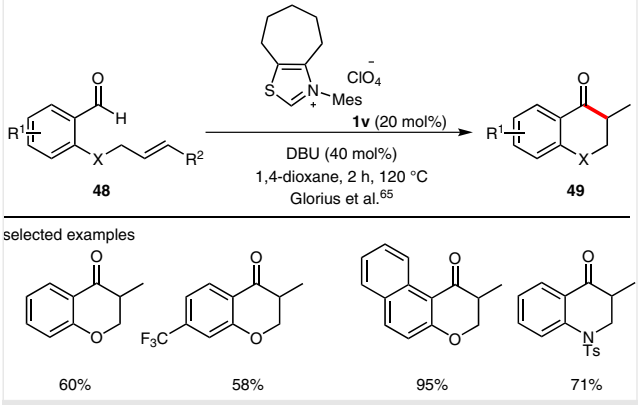
Scheme 33 Hydroacylation of unactivated olefins

The NHC-catalyzed nucleophilic addition reaction of acyl anion equivalents to enol ethers taking place in an intramolecular fashion catalyzed by the carbene generated from commercially available thiazolium salt **1aa** was disclosed by She and co-workers. The reaction resulted in the formation of benzofuranones **47** in high yields (Scheme 34).[64] The authors proposed a mechanism involving the addition of the Breslow intermediate to the carbon–carbon double bond of the enol ether; however, it was unclear whether the addition proceeded via a concerted pathway or involved an oxonium intermediate.

In 2009, Glorius and co-workers demonstrated an unprecedented intramolecular NHC-catalyzed hydroacylation of unactivated alkenes. The carbene generated from thiazolium salt **1v** catalyzed the intramolecular cyclization of 2-allyloxy benzaldehydes **48** to form the corresponding chromanones **49** (Scheme 35).[65] This reaction was the first transition-metal-free NHC-organocatalyzed intramolecular hydroacylation of unactivated carbon–carbon double bonds. This unique hydroacylation strategy was applicable to a broad range of substrates, and in all cases, the desired chromanone was formed in moderate to good yields. Moreover, this methodology was applicable to the synthesis of chromanones containing all-carbon quaternary centers.



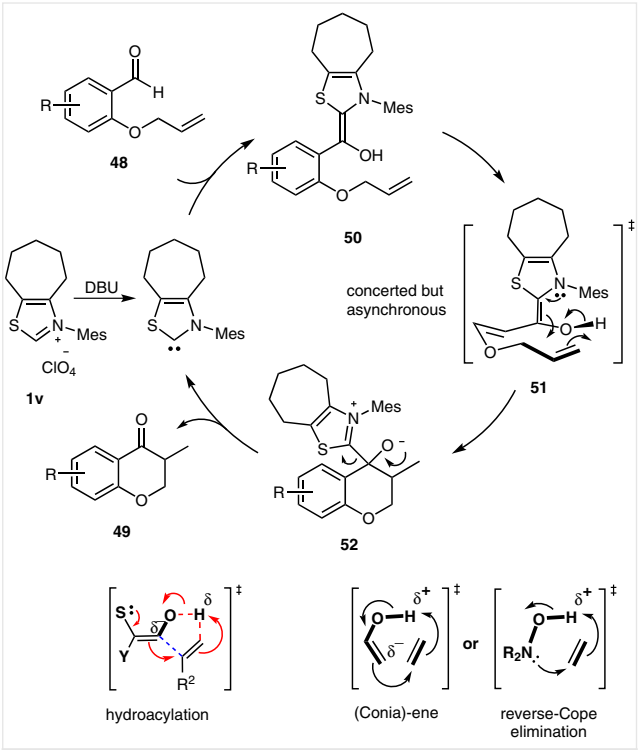
Scheme 34 NHC-catalyzed hydroacylation of enol ethers



Scheme 35 NHC-catalyzed hydroacylation of unactivated double bonds

The proposed mechanism of the NHC-catalyzed hydroacylation reaction is shown in Scheme 36. The addition of the carbene generated from **1v** to aldehyde **48** generates the nucleophilic Breslow intermediate **50**. The acyl anion equivalent **50** could add to the unactivated olefin via a concerted transition state **51** to generate the zwitterionic tetrahedral intermediate **52**. The release of the carbene from intermediate **52** leads to the desired product **49**. Interestingly, the transition state **51** resembles the Conia-ene type transition state with regard to the polarity of the participating olefins, and the reverse-Cope type elimination in terms of the five-membered transition state. Notably, the likelihood of addition of Breslow intermediates to electrophilic carbon–carbon double bonds in the Stetter reaction in a concerted manner similar to the reverse-Cope elimination was previously suggested by Rovis and co-workers.[11] Moreover, DFT calculations were carried out by Grimme, Glorius and co-workers to shed light on the essential step of the reaction (namely, whether the proton migration or the carbon–carbon bond formation occurs first). These studies indicated a concerted but highly asynchronous transition state in

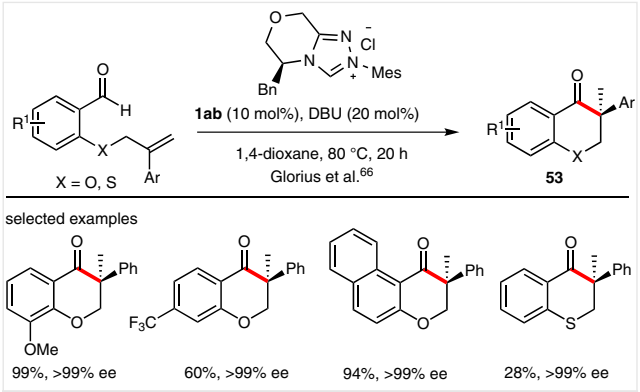
the intramolecular hydroacylation of unactivated olefins.[66] Additionally, the electron localization function (ELF) analysis in carbon–carbon bond formation in NHC-catalyzed hydroacylation reactions was carried out by Domingo and coworkers. These studies showed that the NHC-catalyzed hydroacylation reactions are completely different from the intramolecular Stetter reaction, which is triggered by a polar Michael addition.[67]



Scheme 36 Proposed mechanism for the hydroacylation of unactivated olefins

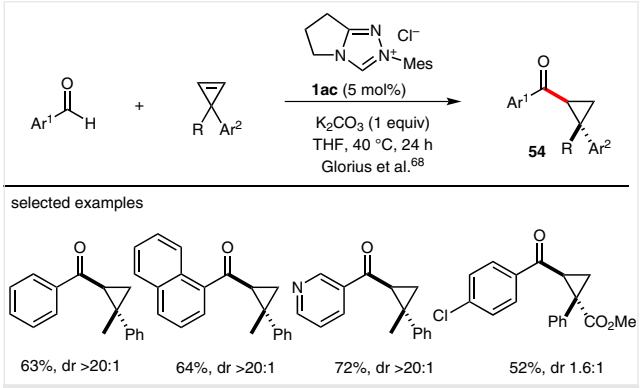
Glorius and co-workers applied this methodology to the enantioselective construction of chromanones possessing all-carbon quaternary stereocenters. The NHC generated from the chiral triazolium salt **1ab** showed high levels of reactivity and selectivity, affording the chiral chromamones **53** in 99% ee in most of the cases (Scheme 37).[66] The observed high enantioselectivity was in accordance with the proposed concerted mechanism. The reaction worked well with a variety of electron-releasing and electron-withdrawing substituents on 2-allyloxy benzaldehyde derivatives.

Subsequently, Glorius and co-workers developed the first intermolecular hydroacylation of cyclopropenes, which are electron-neutral olefins. The reaction of aromatic aldehydes with cyclopropenes under mild conditions using the carbene generated from triazolium salt **1ac** afforded the acyl cyclopropanes **54** in excellent diastereoselectivity and good yields (Scheme 38).[68] Mechanistic experiments demonstrated that the product formation takes place via a



Scheme 37 NHC-catalyzed enantioselective hydroacylation of unactivated double bonds

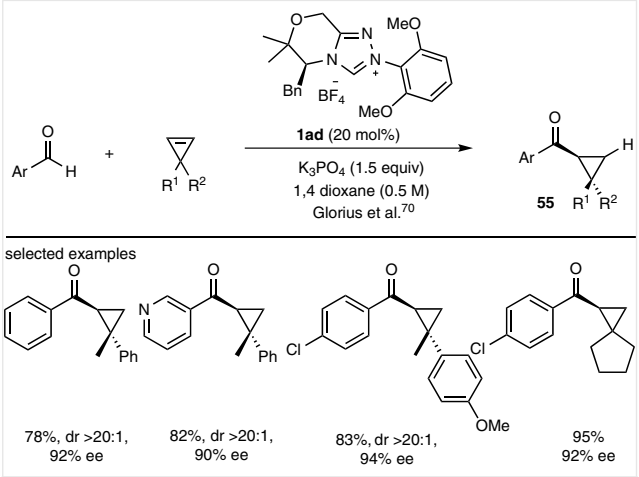
concerted *syn* hydroacylation mechanism. DFT calculations carried out by Ajitha and Suresh on the hydroacylation of cyclopentenes determined the role of base in promoting the proton-transfer step leading to the generation of the Breslow intermediate.[69]



Scheme 38 NHC-catalyzed hydroacylation of cyclopropenes

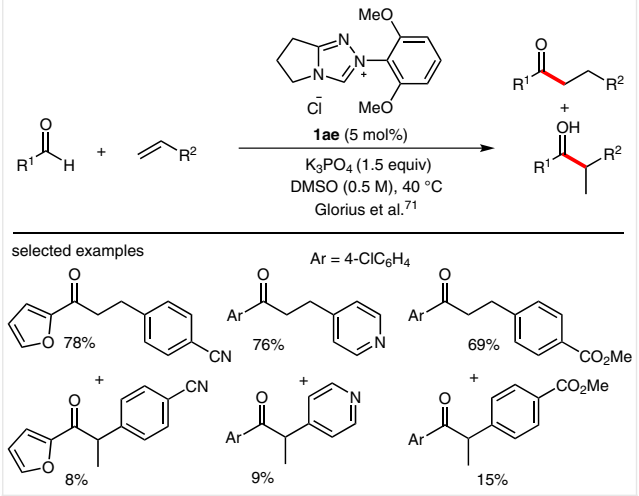
Recently, Glorius and co-workers developed new chiral *ortho*,*ortho'*-disubstituted electron-rich triazolium salts, and demonstrated their utility in enantioselective and diastereoselective hydroacylations of cyclopropenes. The carbene derived from the triazolium salt **1ad** allowed the simultaneous enhancement of reactivity as well as selectivity in the intermolecular addition to electron-neutral olefins.[70] Moreover, **1ad** showed superior reactivity and selectivity compared to other commonly used chiral triazolium salts. The reaction afforded acyl cyclopropanes **55** in moderate to good yields and good enantiomeric excess (Scheme 39).

The intermolecular hydroacylation of electron-neutral olefins is considered to be a long-standing challenge in organocatalysis. More recently, Glorius and co-workers addressed this issue and uncovered the first NHC-catalyzed intermolecular hydroacylation of styrenes, which are among the most important bulk chemicals. The reaction afforded a mixture of linear and branched hydroacylated



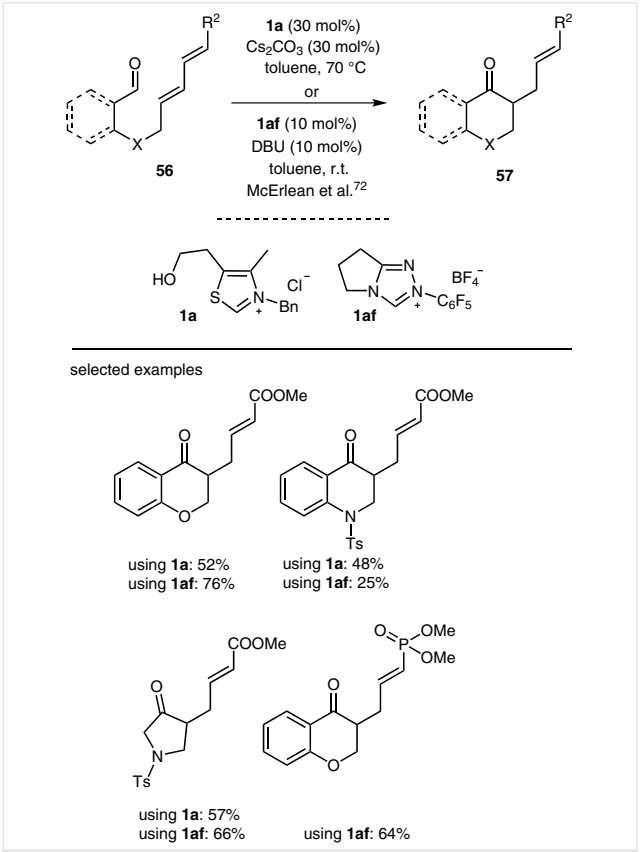
Scheme 39 NHC-catalyzed asymmetric hydroacylation of cyclopropenes

products in good yields (Scheme 40).[71] The carbene generated from the relatively electron-rich triazolium salt **1ae** was the best catalyst for this transformation. The Breslow intermediate generated from aldehydes and NHCs can add to styrenes in three possible ways leading to the formation of the different regioisomeric products.



Scheme 40 NHC-catalyzed intermolecular hydroacylation of styrenes

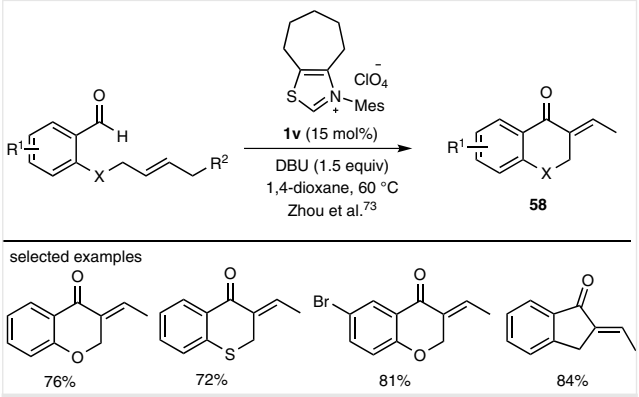
Recently, an intramolecular vinylogous version of the Stetter reaction was reported by Law and McErlean. The NHC-catalyzed intramolecular 1,6-addition of aldehyde **56** bearing an α,β,γ,δ-unsaturated carbonyl moiety afforded diverse chromanones **57** in good yields (Scheme 41).[72] This reaction can also be visualized as an intramolecular hydroacylation reaction. Thiazolium (**1a**)- or triazolium (**1af**)-derived carbenes showed better reactivity than the imidazolium salts. An enantioselective version of this reaction using the NHC derived from **1d** afforded the target products in up to 96% ee.



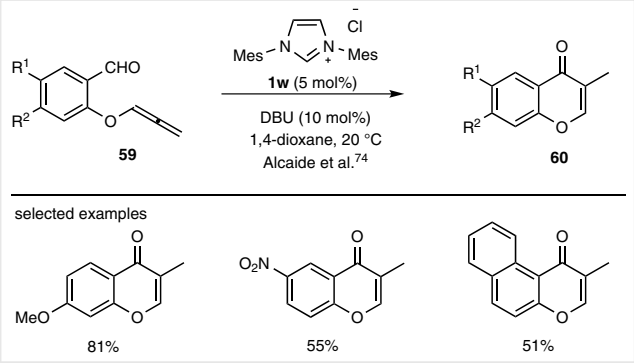
Scheme 41 NHC-catalyzed vinylogous Stetter reaction

Moreover, the NHC-catalyzed intramolecular S_N2' reaction of aldehydes with allylic electrophiles leading to the formation of α,β-unsaturated chromanones **58** was developed by Chen, Zhou and co-workers. Mechanistic studies showed that this reaction does not proceed by way of an addition–elimination mechanism, but proceeds through an S_N2' pathway. The carbene generated from the thiazolium salt **1v** showed good reactivity in this intramolecular cyclization reaction (Scheme 42).[73]

Very recently, the NHC-catalyzed hydroacylation of allenyl aldehydes **59** leading to the synthesis of chromones **60** was disclosed by Alcaide, Almendros and co-workers. The NHC generated from the imidazolium salt **1w** was used under the optimized conditions (Scheme 43).[74] It may be noted in this context that a cascade reaction comprised of a tertiary amine catalyzed N-allylation of indole 2-carboxaldehydes followed by the NHC-catalyzed hydroacylation of the resultant homoallylic amines for the synthesis of pyrroloindolones was reported by Xu and co-workers.[75]



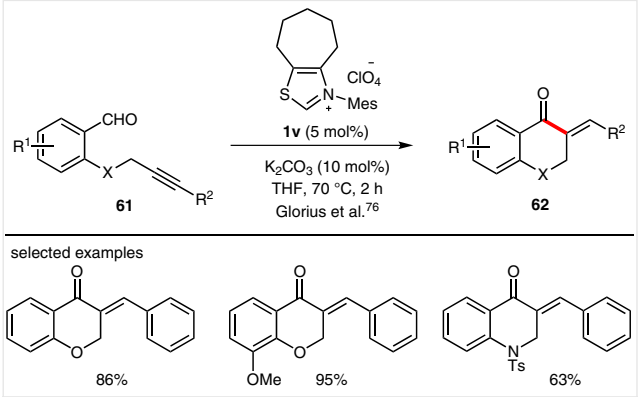
Scheme 42 NHC-catalyzed intramolecular acylation of allyl electrophiles



Scheme 43 NHC-catalyzed hydroacylation of allenyl aldehydes

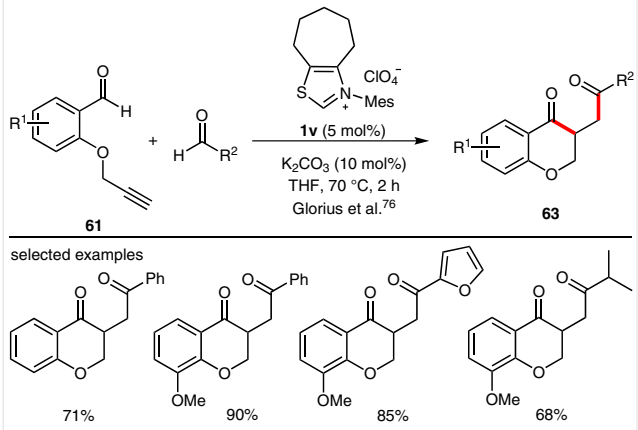
The NHC-catalyzed hydroacylation reactions are not limited to carbon–carbon double bonds. In 2010, Glorius and co-workers developed the intramolecular hydroacylation of unactivated triple bonds. Reaction of the unactivated internal alkynes **61** with the carbene generated from **1v** resulted in the efficient formation of benzylidene chromanones **62**, possessing a synthetically important exocyclic olefin, as a single isomer (Scheme 44).[76] Variations in the electron-releasing and electron-withdrawing groups on both aromatic rings of **61** were well tolerated, and the reaction was also applied for the synthesis of quinolin-4-ones. It may be mentioned in this context that related NHC-catalyzed intramolecular hydroacylation reactions of alkynal phosphonates leading to the synthesis of chromone phosphonates was reported more recently by Shi and co-workers.[77]

In a further development, the NHC-catalyzed hydroacylation reaction of terminal alkynes was combined with a second NHC-catalyzed Stetter reaction in a cascade process. Reaction of the 2-propargyloxy aldehydes **61** with a different coupling aldehyde catalyzed by the carbene generated from **1v** resulted in the synthesis of chromanones **63** with a 1,4-diketone motif in good to excellent yields (Scheme 45).[76] The generation of the carbene using a mild base was a



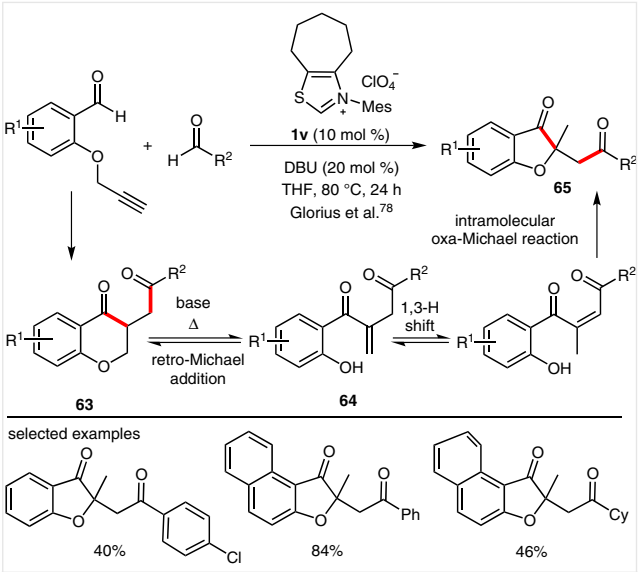
Scheme 44 NHC-catalyzed hydroacylation of unactivated internal alkynes

key factor for this reaction. Notably, these reactions proceeded with a high level of selectivity and required low catalyst loading (5 mol%). In addition, this methodology was applied to the synthesis of a benzopyranopyrrole derivative by a hydroacylation–Stetter cascade followed by reaction with an aniline derivative in a one-pot operation.

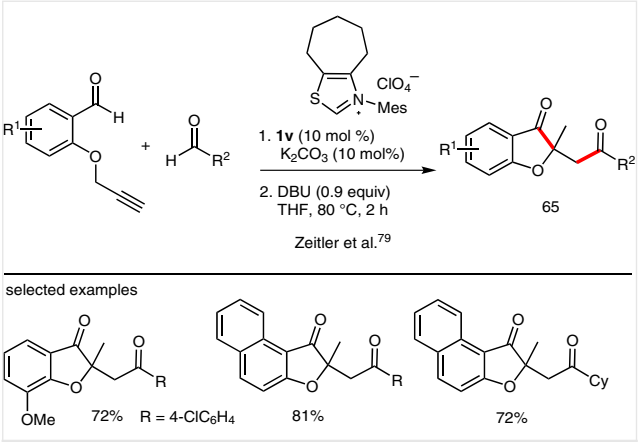


Scheme 45 NHC-catalyzed hydroacylation–Stetter cascade

Subsequently, Glorius and co-workers found that the NHC-catalyzed hydroacylation–Stetter cascade was indeed very sensitive to the base used and the reaction temperature. When the reaction was carried out using DBU as the base at 80 °C, the chromanone product **63** underwent a retro-Michael addition to generate the phenol **64**, which on 1,3-H shift followed by intramolecular oxa-Michael reaction afforded the 2,2-disubstituted benzofuranone derivative **65** (Scheme 46).[78] Overall, the reaction can be considered as an NHC- and base-catalyzed intramolecular hydroacylation–Stetter–rearrangement cascade to the synthesis of benzofuranones. Independently, Zeitler and co-workers demonstrated a closely relatec reaction using the carbene generated from **1v** under analogous reaction conditions. They used a one-pot, two-step protocol for the synthesis of benzofuranones (Scheme 47).[79]

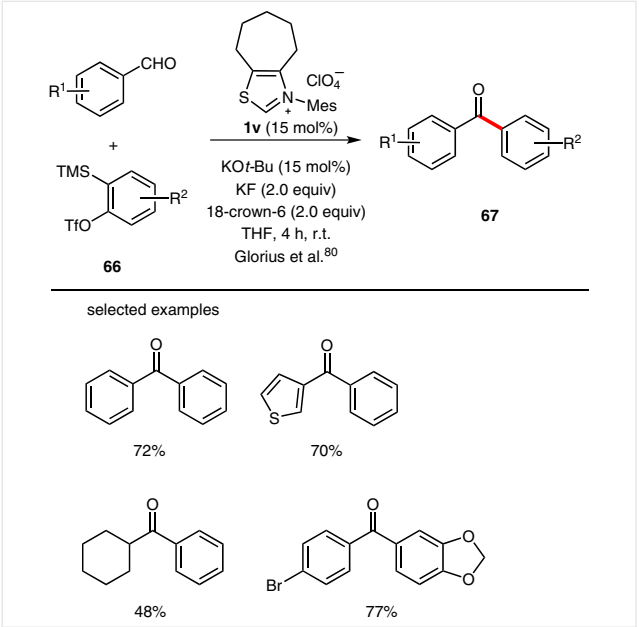


Scheme 46 NHC- and base-catalyzed hydroacylation–Stetter–rearrangement cascade



Scheme 47 One-pot NHC- and base-catalyzed hydroacylation–Stetter–rearrangement cascade

In the context of the intermolecular hydroacylation of triple bonds, Biju and Glorius recently disclosed the NHC-catalyzed hydroacylation of arynes.[80] This reaction represents the NHC-catalyzed formal insertion of arynes into the C_{formyl}–H bond of aldehydes, and reveals the rare tolerance of nucleophilic carbenes toward electrophilic arynes. Notably, arynes are highly electrophilic and reactive intermediates, used for the synthesis of a variety of disubstituted benzene derivatives.[81] The NHC-catalyzed aryne hydroacylation worked well with a wide variety of aldehydes. The aryne was generated in situ from 2-trimethylsilylaryl triflate **66** using two equivalents each of potassium fluoride and 18-crown-6, and the carbene was generated from **1v** by deprotonation using potassium *tert*-butoxide. The reaction furnished several aryl ketones **67** in moderate to excellent yield (Scheme 48).[80] This method can be considered as a transition-metal-free synthetic strategy to access a wide range of aryl ketones, and the chemoselectivity observed in this process is noteworthy.

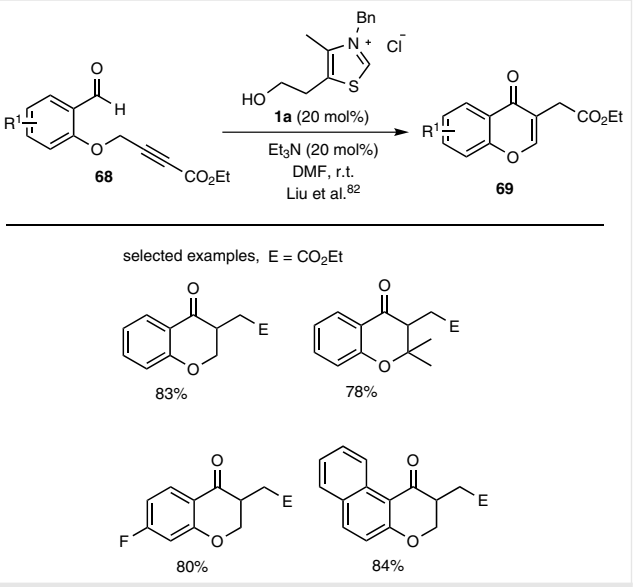


Scheme 48 NHC-catalyzed intermolecular hydroacylation of arynes

The NHC-catalyzed intramolecular hydroacylation of activated carbon–carbon triple bonds was developed by Liu and co-workers. The carbene generated from the thiazolium salt **1a** was efficient for the cyclization of salicylaldehyde-derived alkynes **68** resulting in the synthesis of pharmaceutically important chromone derivatives **69** (Scheme 49).[82] The reaction worked well with various oxygen-tethered salicylaldehyde derivatives. It may be noted in this context that NHC-catalyzed intramolecular cross-coupling reaction of aldehydes with nitriles for the synthesis of 3-aminochromones was developed by the same research group in 2010.[83]

6 Applications in Total Synthesis

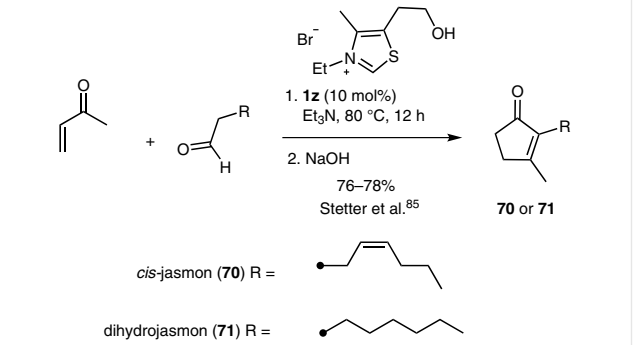
Owing to the versatility and the unique nature of inducing umpolung on aldehydes, NHC-catalyzed reactions have emerged as a powerful technique for the synthesis of complex molecules.[84] This is partly due to the recent developments in NHC-catalyzed Stetter reactions. Until recently, complex molecule syntheses using NHC catalysis were rare, owing to the limited substrate scope of many of the NHC-catalyzed reactions. However, in the last two decades, this field has evolved to become one of the important methods for transition-metal-free construction of carbon–carbon



Scheme 49 NHC-catalyzed intramolecular hydroacylation of activated alkynes

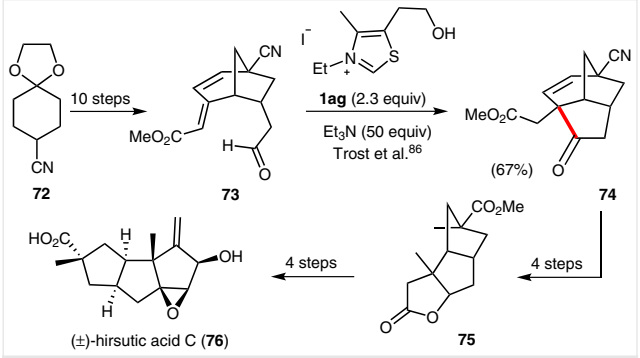
bonds. In this section, recent applications of the Stetter reaction in the construction of natural products and complex molecules are summarized.

In 1975, Stetter and Kuhlmann disclosed the total syntheses of *cis*-jasmon (**70**) and dihydrojasmon (**71**) using NHC catalysis.[85] The carbene generated from the thiazolium salt **1z** was used for the Stetter reaction between methyl vinyl ketone and an aliphatic aldehyde; this was followed by an aldol condensation to afford the natural products **70** and **71** (Scheme 50). This reaction appears to be the first demonstration of the Stetter reaction used in natural product synthesis.



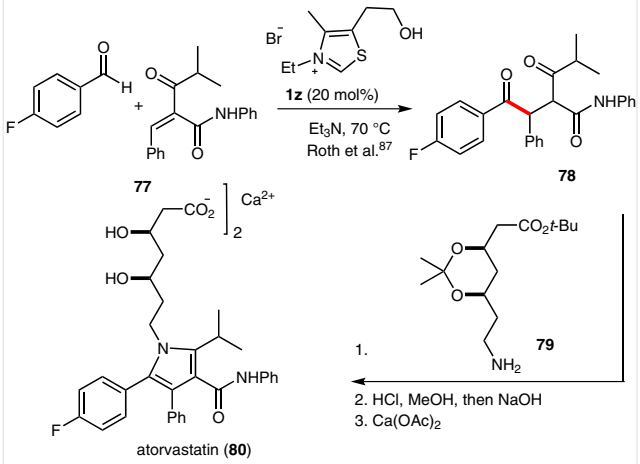
Scheme 50 Total syntheses of *cis*-jasmon and dihydrojasmon

In 1979, Trost and co-workers developed the synthesis of the natural product hirsutic acid C (**76**), which is a tricyclic sesquiterpene having antibiotic and antitumor activity. The key step in the synthesis is an intramolecular Setter reaction. The aldehyde precursor for the Stetter reaction **73** was synthesized in 10 steps starting from cyano compound **72**. Treatment of the aldehyde **73** with an excess of the thiazolium salt **1ag** and triethylamine furnished the tricyclic ketone **74** in 67% yield (Scheme 51).[86] Compound **74** was converted into γ-lactone **75**, in four steps, using the reduction, γ-lactonization, ozonolysis, reduction sequence. Another four-step sequence from **75** afforded hirsutic acid in a total of 19 steps with an overall yield of 3.4%.



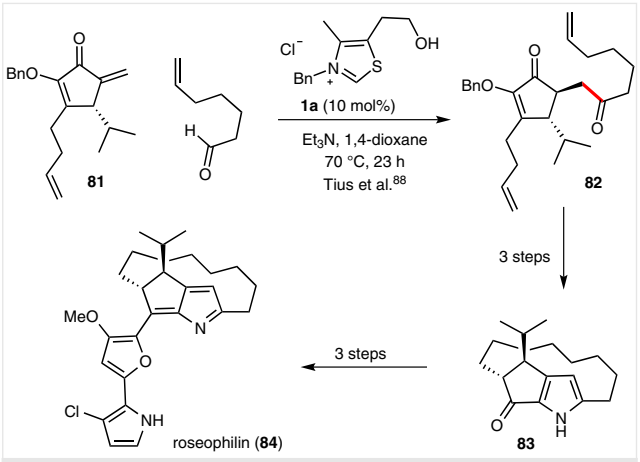
Scheme 51 Total synthesis of hirsutic acid incorporating an intramolecular Stetter reaction

Roth and co-workers disclosed the synthesis of atorvastatin calcium (**80**), which is a drug marketed under the trade name Lupitor. Lupitor is used to control the cholesterol levels in the blood. The key step in its synthesis is the intermolecular Stetter reaction between 4-fluorobenzaldehyde and the Michael acceptor **77**. The reaction worked well in the presence of the carbene generated from thiazolium salt **1z** to afford the 1,4-diketone **78** in 80% yield (Scheme 52).[87] The Paal–Knorr reaction of the 1,4-diketone **78** with heptanoate amine **79** afforded atorvastatin.



Scheme 52 Synthesis of atorvastatin using an intermolecular Stetter reaction

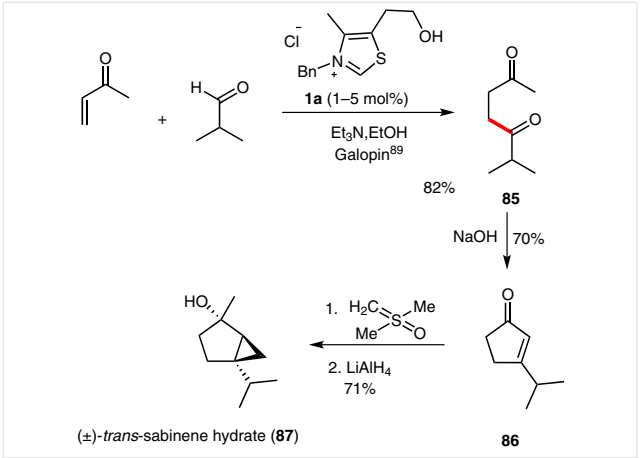
Another natural product synthesis accomplished using NHC catalysis as an important step is that of roseophilin (**84**), which contains an azofulvene moiety that is conjugated to pyrrolylfuran and an ansa macrocycle. A 12-step formal synthesis of roseophilin followed by an enantioselective variant was demonstrated by Harrington and Tius.[88] The key step in the synthesis of **84** is a Nazarov cyclization reaction leading to the cyclopentenone **81**. Reaction of **81** with hept-6-enal using the NHC generated from thiazolium salt **1a** and triethylamine as base furnished the Stetter adduct **82** as a *trans*-isomer (Scheme 53). Ring-opening metathesis of **82**, followed by selective reduction of the olefin and Paal–Knorr cyclization resulted in the formation of the enantiopure roseophilin core **83**. Alkylation of a difuryl compound under basic conditions with **83** completed the synthesis of roseophilin.



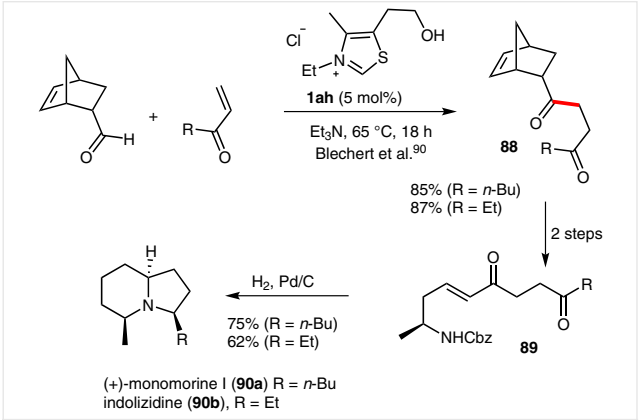
Scheme 53 Synthesis of roseophilin

In 2001, Galopin achieved a short synthesis of (±)-*trans*-sabinene hydrate (**87**), which is an important flavor found in various essential oils from mint and other herbs. The intermolecular Stetter reaction of isovaleraldehyde and methyl vinyl ketone catalyzed by the carbene generated from **1a** afforded the 1,4-diketone **85** in 82% yield (Scheme 54).[89] Aldol cyclization of **85** promoted by base furnished the cyclopentenone **86**. Cyclopropanation under Corey–Chaychovsky conditions followed by reduction afforded the (±)-*trans*-sabinene hydrate in 28% overall yield.

A stereoselective synthesis of two 3,5-dialkyl-substituted indolizidine alkaloids, namely (+)-monomorine I (**90a**), and (3*R*,5*S*,9*S*)-3-ethyl-5-methylindolizidine (**90b**), where the first step was an intermolecular Stetter reaction, was reported by Randl and Blechert. The Stetter reaction between norbornene carboxaldehyde and vinyl ketone afforded the expected 1,4-diketone **88** in excellent yield (Scheme 55).[90] A retro Diels–Alder of **88** followed by intermolecular cross-metathesis with carbobenzyloxy-protected (*S*)-pent-en-2-amine afforded the carbamate **89** in good yield. The



Scheme 54 Synthesis of (±)-*trans*-sabinene hydrate

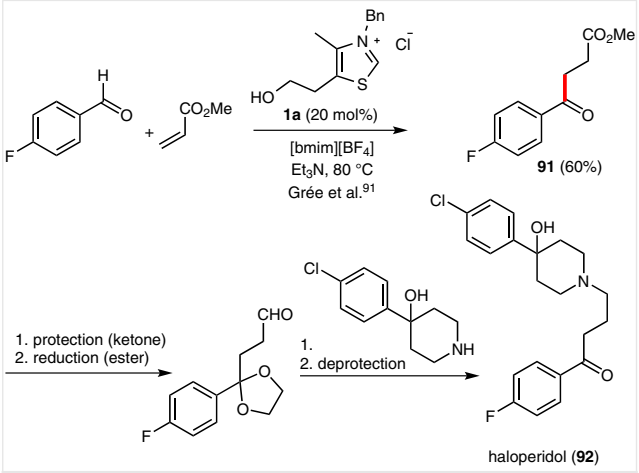


Scheme 55 Synthesis of indolizidine alkaloids

reductive amination of **89** readily furnished the natural products **90a** and **90b** in good yields.

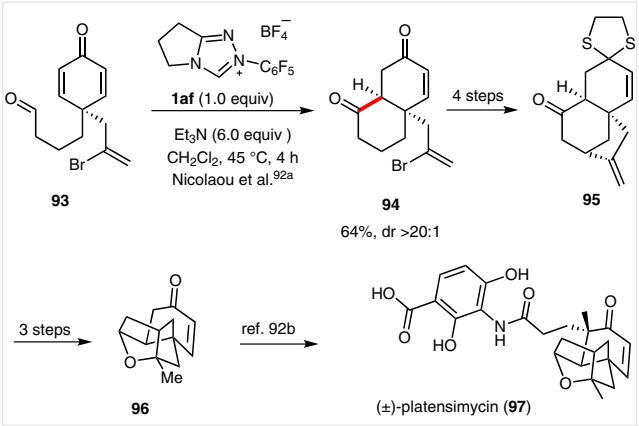
In 2004, Grée and co-workers achieved the synthesis of haloperidol (**92**), which is a widely used antipsychotic drug, using an intermolecular Stetter reaction as the key step. The cross-coupling of 4-fluorobenzaldehyde and methyl acrylate was carried out using the carbene generated from **1a** in the presence of the room-temperature ionic liquid [bmim][BF_4] to afford the 1,4-dicarbonyl compound **91** in 60% yield (Scheme 56).[91] Compound **91** was converted into haloperidol (**92**) in four steps through protection of the ketone, reduction of the ester to an aldehyde (using DIBAL-H), reductive amination using commercially available piperidinol, and finally a deprotection sequence.

Nicolaou and co-workers reported the formal synthesis of (±)-platensimycin (**97**), where the key steps involved an intramolecular Stetter reaction and a tin-promoted radical cyclization. The intramolecular Stetter reaction of the bromide using the carbene generated from triazolium salt **1af** readily afforded the cyclohexanone **94** in 64% yield and excellent diastereoselectivity (Scheme 57).[92a] The tetracyclic



Scheme 56 Synthesis of haloperidol

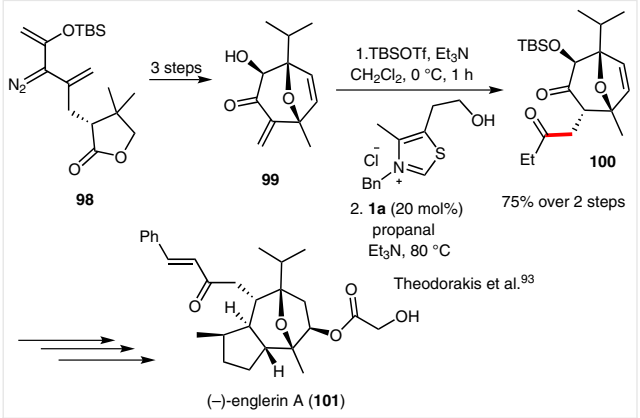
compound **95** was accessible from **94** in four steps following a protection of the carbonyl as its dithiane and oxidation of the free ketone followed by tin-mediated radical cyclization. In three steps, **95** was converted into the core structure **96** of (±)-platensimycin.[92b]



Scheme 57 Formal synthesis (±)-platensimycin

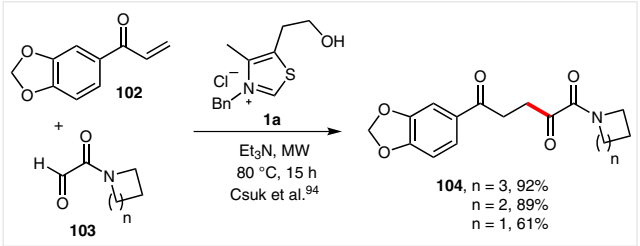
The enantioselective formal synthesis of (–)-englerin A (**101**) was achieved by Theodorakis and co-workers using a rhodium(II)-catalyzed [4+3]-cycloaddition reaction and an intermolecular Stetter reaction as the key steps. The rhodium(II)-catalyzed [4+3]-cycloaddition reaction of diazo ester **98** with 2-isopropyl-5-methylfuran afforded the enone **99** in three steps. Protection of the secondary alcohol in **99** followed by intermolecular Stetter reaction using the carbene generated from **1a** furnished 1,4-diketone **100** in 75% yield for the two steps (Scheme 58).[93] The diketone **100** can be converted into (–)-englerin A following known procedures.

Very recently, the synthesis of piperodione and its analogues was accomplished by Csuk and co-workers, who used an intermolecular Stetter reaction as a key step. The



Scheme 58 Synthesis of (–)-englerin A

reaction of enone **102** with aldehyde **103** was carried out in the presence of thiazolium salt **1a** under microwave conditions to afford piperodione (**104**; n = 3) in 92% yield (Scheme 59).[94] Two piperodione analogues were similarly synthesized.



Scheme 59 Synthesis of piperodione and analogues

7 Conclusion

In the last two decades, NHCs have evolved from being just a laboratory curiosity to being valuable synthetic tools in chemistry in general, and catalysis in particular. One of the most important modes of action of NHCs in organocatalysis is the umpolung of aldehydes. This review summarized the recent advances in NHC-catalyzed Stetter reactions and Stetter-type reactions. Recent developments in intramolecular as well as intermolecular Stetter reactions, various enantioselective reactions, and hydroacylation reactions were discussed. It is expected that the summary of recent advances in this field highlighted herein will inspire the development of a wide range of new applications of NHCs in catalysis, especially those of an asymmetric nature.

The intermolecular Stetter reaction continues to be a challenging reaction. We believe that the future studies in this area will be devoted to the intermolecular Stetter reaction using challenging β,β-disubstituted Michael acceptors for the construction of all-carbon quaternary stereocenters with perfect control of stereochemistry. Moreover, in the area of NHC-catalyzed hydroacylation reactions, the inter-

molecular version is presently limited to styrenes and cyclopropenes. Future studies in this area will undoubtedly be dedicated to developing innovative and general intermolecular hydroacylation reactions of olefins, as well as enantioselective variants. Moreover, future research and focus in this area will result in more and more synthetic strategies for the construction of biologically interesting scaffolds, and will greatly add to the arsenal of NHC-catalysis applications in the total synthesis of complex molecules.

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References

(1) (a) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639. (b) Stetter, H.; Kuhlmann, H. In *Organic Reactions*; Vol. 40; Paquette, L. A., Ed.; Wiley & Sons: New York, **1991**, 407.

(2) For recent reviews on NHC-organocatalysis, see: (a) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485. (b) Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res.* **2014**, *47*, 696. (c) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906. (d) De Sarkar, S.; Biswas, A.; Samanta, R. C.; Studer, A. *Chem. Eur. J.* **2013**, *19*, 4664. (e) Knappke, C. E. I.; Imami, A.; von Wangelin, A. J. *ChemCatChem* **2012**, *4*, 937. (f) Grossmann, A.; Enders, D. *Angew. Chem. Int. Ed.* **2012**, *51*, 314. (g) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 351. (h) Hirano, K.; Piel, I.; Glorius, F. *Chem. Lett.* **2011**, *40*, 786. (i) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336. (j) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 11686. (k) Cohen, D. T.; Scheidt, K. A. *Chem. Sci.* **2012**, *3*, 53. (l) Vora, H. U.; Wheeler, P.; Rovis, T. *Adv. Synth. Catal.* **2012**, *354*, 1617. (m) Chiang, P.-C.; Bode, J. W. In *N-Heterocyclic Carbenes*; The Royal Society of Chemistry: London, **2011**, 399. (n) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691. (o) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

(3) For reviews on the Stetter reaction, see: (a) Read de Alaniz, J.; Rovis, T. *Synlett* **2009**, 1189. (b) Rovis, T. *Chem. Lett.* **2008**, *37*, 2. For a recent highlight, see: (c) Christmann, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 2632. See also: (d) Read de Alaniz, J.; Kerr, M. S.; Moore, J. L.; Rovis, R. *J. Org. Chem.* **2008**, *73*, 2033.

(4) (a) Bugaut, X. In *Comprehensive Organic Synthesis II*; Vol. 1; Molander, G. A.; Knochel, P., Eds.; Elsevier: Oxford, **2014**, 424. (b) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534.

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

(6) (a) Wanzlick, H.-W. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 75. (b) Arduengo, A. J. III.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.

(7) (a) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719. (b) Breslow, R.; Kim, R. *Tetrahedron Lett.* **1994**, *35*, 699. (c) White, M.; Leeper, F. *J. Org. Chem.* **2001**, *66*, 5124.

(8) (a) Nair, V.; Bindu, S.; Sreekumar, V.; Rath, N. P. *Org. Lett.* **2003**, *5*, 665. (b) Berkessel, A.; Elfert, S.; Yatham, V. R.; Neudörfl, J.-M.; Schlörer, N. E.; Teles, J. H. *Angew. Chem. Int. Ed.* **2012**, *51*, 12370. (c) Berkessel, A.; Yatham, V. R.; Elfert, S.; Neudörfl, J.-M. *Angew. Chem. Int. Ed.* **2013**, *52*, 11158.

(9) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182.

(10) Moore, J. L.; Silvestri, A. P.; Read de Alaniz, J.; DiRocco, D. A.; Rovis, T. *Org. Lett.* **2011**, *13*, 1742.

(11) Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284.

(12) Hawkes, K. J.; Yates, B. F. *Eur. J. Org. Chem.* **2008**, 5563.

(13) Ciganek, E. *Synthesis* **1995**, 1311.

(14) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899.

(15) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298.

(16) (a) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876. (b) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725. (c) Moore, J. L.; Kerr, M. S.; Rovis, T. *Tetrahedron* **2006**, *62*, 11477. (d) Cullen, S. C.; Rovis, T. *Org. Lett.* **2008**, *10*, 3141.

(17) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* **2004**, 2025.

(18) Mennen, S. M.; Blank, J. T.; Tran-Dubé, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195.

(19) Jia, M.-Q.; Li, Y.; Rong, Z.-Q.; You, S.-L. *Org. Biomol. Chem.* **2011**, *9*, 2072.

(20) Rong, Z.-Q.; Li, Y.; Yang, G.-Q.; You, S.-L. *Synlett* **2011**, 1033.

(21) Bao, Y.; Kumagai, N.; Shibasaki, M. *Tetrahedron: Asymmetry* **2014**, *25*, 1401.

(22) Rafiński, Z.; Kozakiewicz, A.; Rafinska, K. *ACS Catal.* **2014**, *4*, 1404.

(23) Lu, T.; Gu, L.; Kang, Q.; Zhang, Y. *Tetrahedron Lett.* **2012**, *53*, 6602.

(24) Collett, C. J.; Massey, R. S.; Maguire, O. R.; Batsanov, A. S.; O'Donoghue, A. C.; Smith, A. D. *Chem. Sci.* **2013**, *4*, 1514.

(25) (a) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552. (b) Liu, Q.; Rovis, T. *Org. Process Res. Dev.* **2007**, *11*, 598.

(26) (a) Jia, M.-Q.; You, S.-L. *Chem. Commun.* **2012**, *48*, 6363. (b) Jia, M.-Q.; Liu, C.; You, S.-L. *J. Org. Chem.* **2012**, *77*, 10996.

(27) Jia, M.-Q.; You, S.-L. *Synlett* **2013**, *24*, 1201.

(28) Filloux, C. M.; Lathrop, S. P.; Rovis, T. *Proc. Natl. Acad. Sci.* **2010**, *107*, 20666.

(29) Orellana, A.; Rovis, T. *Chem. Commun.* **2008**, 730.

(30) Lathrop, S.; Rovis, T. *Chem. Sci.* **2013**, *4*, 1668.

(31) (a) Tiebes, J. *Diploma Thesis*; RWTH Aachen: Germany, **1990**. (b) Enders, D. In *Stereoselective Synthesis*; Springer-Verlag: Heidelberg, **1993**, 63. (c) Enders, D.; Bockstiegel, B.; Dyker, H.; Jegelka, U.; Kipphardt, H.; Kownatka, D.; Kuhlmann, H.; Mannes, D.; Tiebes, J.; Papadopoulos, K. In *Dechema-Monographies*; Vol. 129; VCH: Weinheim, **1993**, 209.

(32) (a) Enders, D.; Han, J.; Henseler, A. *Chem. Commun.* **2008**, 3989. (b) Enders, D.; Han, J. *Synthesis* **2008**, 3864.

(33) Liu, Q.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066.

(34) Liu, Q.; Rovis, T. *Org. Lett.* **2009**, *11*, 2856.

(35) (a) Steward, K. M.; Gentry, E. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 7329. (b) Steward, K. M.; Corbett, M. T.; Goodman, C. G.; Johnson, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 20197.

(36) DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10872.

(37) Um, J. M.; Dirocco, D. A.; Noey, E. L.; Rovis, T.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *133*, 11249.

(38) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 10402.

(39) DiRocco, D. A.; Noey, E. L.; Houk, K. N.; Rovis, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 2391.

(40) Vedachalam, S.; Tan, S. M.; Teo, H. P.; Cai, S.; Liu, X.-W. *Org. Lett.* **2012**, *14*, 174.
(41) Jousseaume, T.; Wurz, N. E.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1410.
(42) Kuniyil, R.; Sunoj, R. B. *Org. Lett.* **2013**, *15*, 5040.
(43) Sánchez-Larios, E.; Thai, K.; Bilodeau, F.; Gravel, M. *Org. Lett.* **2011**, *13*, 4942.
(44) Fang, X.; Chen, X.; Lv, H.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 11782.
(45) Fang, X.; Chen, X.; Chi, Y. R. *Org. Lett.* **2011**, *13*, 4708.
(46) Wurz, N. E.; Daniliuc, C. G.; Glorius, F. *Chem. Eur. J.* **2012**, *18*, 16297.
(47) Stetter, H.; Bender, H.-J. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 131.
(48) Bhunia, A.; Yetra, S. R.; Bhojgude, S. S.; Biju, A. T. *Org. Lett.* **2012**, *14*, 2830.
(49) Patra, A.; Bhunia, A.; Biju, A. T. *Org. Lett.* **2014**, *16*, 4798.
(50) Kim, S. M.; Jin, M. Y.; Kim, M. J.; Cui, Y.; Kim, Y. S.; Zhang, L.; Song, C. E.; Ryu, D. H.; Yang, J. W. *Org. Biomol. Chem.* **2011**, *9*, 2069.
(51) Bortolini, O.; Fantin, G.; Fogagnolo, M.; Giovannini, P. P.; Massi, A.; Pacifico, S. *Org. Biomol. Chem.* **2011**, *9*, 8437.
(52) Bortolini, O.; Cavazzini, A.; Dambruoso, P.; Giovannini, P. P.; Caciolli, L.; Massi, A.; Pacificoa, S.; Ragno, D. *Green Chem.* **2013**, *15*, 2981.
(53) Takaki, K.; Ohno, A.; Hino, M.; Shitaoka, T.; Komeyama, K.; Yoshida, H. *Chem. Commun.* **2014**, *50*, 12285.
(54) Zhang, J.; Xing, C.; Tiwari, B.; Chi, Y. R. *J. Am. Chem. Soc.* **2013**, *135*, 8113.
(55) (a) Wilde, M. M. D.; Gravel, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 12651. (b) For a highlight on this work, see: Connon, S. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 1203.
(56) (a) Dresen, C.; Richter, M.; Pohl, M.; Ludeke, S.; Muller, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 6600. (b) Beigia, C.; Waltzera, S.; Zareib, M.; Müller, M. *J. Biotechnol.* **2014**, *191*, 64.
(57) (a) Sanchez-Larios, E.; Gravel, M. *J. Org. Chem.* **2009**, *74*, 7536. (b) For a related NHC-catalyzed Stetter–aldol–Michael and Stetter–aldol–aldol sequence for the synthesis of bis-indanes see: Sanchez-Larios, E.; Holmes, J. M.; Daschner, C. L.; Gravel, M. *Org. Lett.* **2010**, *12*, 5772.
(58) Sun, F.-G.; Huang, X.-L.; Ye, S. *J. Org. Chem.* **2010**, *75*, 273.
(59) Sun, F.-G.; Ye, S. *Synlett* **2011**, 1005.
(60) Hong, B.-C.; Dange, N. S.; Hsu, C.-S.; Liao, J.-H. *Org. Lett.* **2010**, *12*, 4812.
(61) Hong, B. C.; Dange, N. S.; Hsu, C.-S.; Liao, J.-H.; Lee, G.-H. *Org. Lett.* **2011**, *13*, 1338.
(62) For initial reports, see: (a) Katada, A.; Ichioka, K.; Takagi, K.; Suzuki, M. *Org. Lett.* **2011**, *13*, 3722. (b) Biju, A. T.; Padmanaban, M.; Wurz, N. E.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 8412.
(63) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725.
(64) He, J.; Tang, S.; Liu, J.; Su, Y.; Pan, X.; She, X. *Tetrahedron* **2008**, *64*, 8797.
(65) Hirano, K.; Biju, A. T.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 14190.
(66) Piel, I.; Steinmetz, M.; Hirano, K.; Fröhlich, R.; Grimme, S.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 4983.
(67) Domingo, L. R.; Saéz, J. A.; Arnó, M. *RSC Adv.* **2012**, *2*, 7127.
(68) Bugaut, X.; Liu, F.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 8130.
(69) Ajitha, M. J.; Suresh, C. H. *Tetrahedron Lett.* **2013**, *54*, 7144.
(70) (a) Liu, F.; Bugaut, X.; Schedler, M.; Fröhlich, R.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 12626. (b) Schedler, M.; Fröhlich, R.; Daniliuc, C.-G.; Glorius, F. *Eur. J. Org. Chem.* **2012**, 4164.
(71) Schedler, M.; Wang, D. S.; Glorius, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 2585.
(72) (a) Law, K. R.; McErlean, C. S. P. *Chem. Eur. J.* **2013**, *19*, 15852. (b) For a related vinylogous Stetter reaction in a cascade process, see: Dell'Amico, L.; Rassu, G.; Zambrano, V.; Sartori, A.; Curti, C.; Battistini, L.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *J. Am. Chem. Soc.* **2014**, *136*, 11107.
(73) Zhao, M.; Yang, H.; Li, M. M.; Chen, J.; Zhou, L. *Org. Lett.* **2014**, *16*, 2904.
(74) Alcaide, B.; Almendros, P.; Fernández, I.; Martínez del Campo, T.; Naranjo, T. *Chem. Eur. J.* **2015**, *21*, 1533.
(75) Lu, H.; Lin, J.-B.; Liu, J.-B.; Xu, P.-F. *Chem. Eur. J.* **2014**, *20*, 11659.
(76) Biju, A. T.; Wurz, N. E.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 5970.
(77) Wang, Z.; Yu, Z.; Wang, Y.; She, D. *Synthesis* **2012**, 1559.
(78) Padmanaban, M.; Biju, A. T.; Glorius, F. *Org. Lett.* **2011**, *13*, 5624.
(79) Franz, J. F.; Fuchs, P. J. W.; Zeitler, K. *Tetrahedron Lett.* **2011**, *52*, 6952.
(80) Biju, A. T.; Glorius, F. *Angew. Chem. Int. Ed.* **2010**, *49*, 9761.
(81) (a) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191. (b) Wu, C.; Shi, F. *Asian J. Org. Chem.* **2013**, *2*, 116. (c) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (d) Gampe, C. M.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3766. (e) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140. (f) Okuma, K. *Heterocycles* **2012**, *85*, 515.
(82) Vedachalam, S.; Wong, Q.-L.; Maji, B.; Zeng, J.; Ma, J.; Liu, X.-W. *Adv. Synth. Catal.* **2011**, *353*, 219.
(83) Vedachalam, S.; Zeng, J.; Gorityala, B. K.; Antonio, M.; Liu, X.-W. *Org. Lett.* **2010**, *12*, 352.
(84) For a recent review on application of NHC catalysis on natural products synthesis, see reference 2j.
(85) Stetter, H.; Kuhlmann, H. *Synthesis* **1975**, 379.
(86) Trost, B. M.; Shuey, C. D.; Dininno, F.; Mcelvain, S. S. *J. Am. Chem. Soc.* **1979**, *101*, 1284.
(87) Baumann, K. L.; Butler, D. E.; Deering, C. F.; Mennen, K. E.; Millar, A.; Nanninga, T. N.; Palmer, C. W.; Roth, B. D. *Tetrahedron Lett.* **1992**, *33*, 2283.
(88) (a) Harrington, P. E.; Tius, M. A. *Org. Lett.* **1999**, *1*, 649. (b) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509.
(89) Galopin, C. C. *Tetrahedron Lett.* **2001**, *42*, 5589.
(90) Randl, S.; Blechert, S. *J. Org. Chem.* **2003**, *68*, 8879.
(91) Anjaiah, S.; Chandrasekhar, S.; Grée, R. *Adv. Synth. Catal.* **2004**, *346*, 1329.
(92) (a) Nicolaou, K. C.; Tang, Y. F.; Wang, J. H. *Chem. Commun.* **2007**, 1922. (b) Nicolaou, K. C.; Li, A.; Edmonds, D. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 7086.
(93) Xu, J.; Caro-Diaz, E. J. E.; Theodorakis, E. A. *Org. Lett.* **2010**, *12*, 3708.
(94) Sommerwerk, S.; Kern, S.; Heller, L.; Csuk, R. *Tetrahedron Lett.* **2014**, *55*, 6243.