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Extending NHC-Catalysis: Coupling Aldehydes with Unconventional Reaction Partners

AKKATTU T. BIJU, NADINE KUHL, AND FRANK GLORIUS*

Organisch-Chemisches Institut der Westfälische Wilhelms-Universität Münster, Corrensstrasse 40, 48149 Münster, Germany

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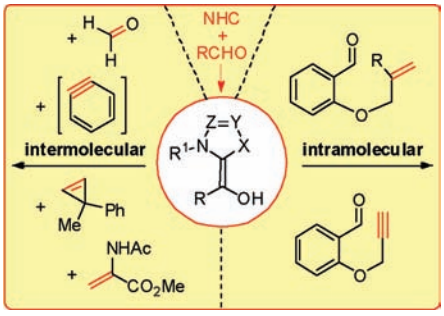

Transition metal catalysis is a powerful means of effecting organic reactions, but it has some inherent drawbacks, such as the cost of the catalyst and the toxicity of the metals. Organocatalysis represents an attractive alternative and, in some cases, offers transformations unparalleled in metal catalysis. Unique transformations are a particular hallmark of N-heterocyclic carbene (NHC) organocatalysis, a versatile method for which a number of modes of action are known. The NHC-catalyzed umpolung (that is, the inversion of polarity) of electrophilic aldehydes, through formation of the nucleophilic Breslow intermediate, is probably the most important mode of action. In this Account, we discuss the reaction of Breslow intermediates with unconventional reaction partners.

In two traditional umpolung reactions, the benzoin condensation and the Stetter reaction, some selectivity issues represent significant challenges, especially in intermolecular variants of these reactions. In intermolecular cross-benzoin reactions, high levels of selectivity were recently obtained, even in the hydroxymethylation of aldehydes with formaldehyde. The key to success was careful choice of the NHC catalyst and reaction conditions. Among asymmetric Stetter reactions, intermolecular versions have posed a long-standing challenge. Recently, the groups of Enders and Rovis reported the first selective and efficient systems. We have contributed to this field by developing an efficient intermolecular Stetter reaction for the formation of α-amino acid derivatives, with broad aldehyde scope and high enantiomeric excess.

Moreover, tailor-made thiazolylidene catalysts allowed the unprecedented use of nonactivated olefins and alkynes as aldehyde coupling partners. The basis for this reactivity is a unique mode of NHC organocatalysis: dual activation. In a concerted but asynchronous transition state, the positively polarized proton of the Breslow intermediate activates the coupling partner (for example, an olefin), while the nucleophilic enamine moiety starts to attack the activated coupling partner. As a consequence of the concerted nature of this mechanism, excellent values for enantiomeric excess were obtained for many substrates in the intramolecular hydroacylation of alkenes. In addition, thiazolylidene catalysts have enabled the coupling of aldehydes with reactive species, for example, with arynes and with activated alkyl bromides.

NHC catalysis should continue to flourish and lead to surprising developments. One remaining challenge is the asymmetric intermolecular hydroacylation of unactivated olefins. In this area, metal-based catalysts have shown promising early results, but they are far from being either general or practical. It will be interesting to see which class of catalyst, whether metal-based or NHC-based, eventually develops into the method of choice.

1. Introduction

In recent years, N-heterocyclic carbenes (NHCs) have developed from being laboratory curiosities to efficient synthetic tools of chemistry. They have found widespread applications as versatile ligands in transition metal catalysis[1] and as organocatalysts in their own right.[2] In organocatalytic

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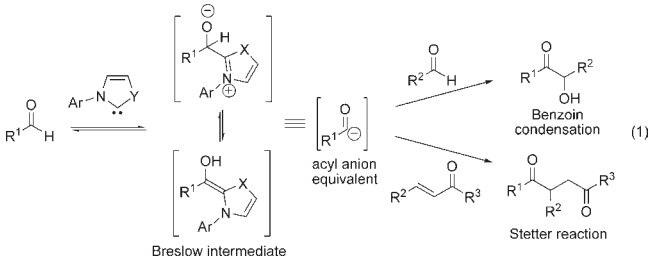
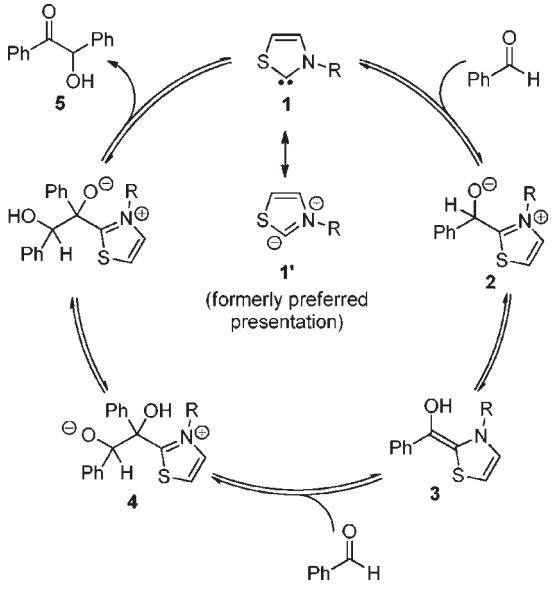
applications, NHCs are mainly used for the umpolung of aldehydes. In these reactions, addition of the NHC to the aldehyde finally results in the generation of an acyl anion equivalent, the Breslow intermediate. The benzoin condensation and Stetter reaction are the two most well-known transformations, which employ the Breslow intermediate as key intermediate (eq 1). Generally, imidazolium, thiazolium, or triazolium salt-derived NHCs have been used successfully for umpolung reactions, and during recent years there has been an increased interest in NHC-catalyzed transformations and many new reactions have been developed. The purpose of the present Account is to provide an update about the recent developments in NHC organocatalysis. Mainly, the Account is focused on NHC-catalyzed reactions of unconventional electrophiles developed in our laboratory, but adequate description of related work carried out by others is also given.



From a historical perspective, a report by Ukai et al. in 1943 demonstrating that thiazolium salts could be used as catalysts in the benzoin reaction constitutes an early example for the involvement of azolium salts in organocatalysis.[3] Breslow proposed a mechanistic explanation for the thiazolium salt-catalyzed benzoin condensation in 1958.[4] In this mechanism, the catalytically active species was represented as a thiazolium zwitterion, the resonance structure of an NHC, and the reaction was postulated to proceed via the enaminol intermediate **3**, the "Breslow intermediate" (Scheme 1). However, the existence of carbenes as catalytically active species in these processes was only realized almost three decades later when the synthesis of stable phosphinocarbene was reported by Bertrand and co-workers in 1988[5] and the isolation and characterization of stable NHC was unequivocally established by Arduengo and co-workers in 1991.[6] Although NHCs were used long before these findings, these seminal discoveries marked a true breakthrough and initiated extensive research in the application of NHCs in catalysis.

Following the proposal of Breslow,[4] a key step in benzoin condensation is the nucleophilic attack of the in situ generated carbene **1** to the aldehyde, leading to the tetrahedral intermediate **2**, which undergoes proton transfer to the nucleophilic enaminol intermediate **3**. This acyl anion equivalent **3**

SCHEME 1. Proposed Mechanism of Benzoin Condensation



reacts as a nucleophile with another molecule of aldehyde to furnish the final product, the α-hydroxy ketone **5**, and the original NHC catalyst **1** is regenerated (Scheme 1).

The phenomenal success of NHCs in organocatalysis can be attributed primarily to their electronic properties leading to different modes of action in catalysis (Figure 1). The pronounced nucleophilicity of NHCs allows the addition to electrophiles such as aldehydes leading to the formation of the tetrahedral intermediate (A). The azolium moiety is strongly electron-withdrawing, acidifying the α-position (E). Alternatively, the same tetrahedral intermediate can undergo hydride transfer in the presence of easily reducible substrates such as activated carbonyl compounds resulting in an acyl azolium species and a reduced reaction partner (H). The enaminol moiety (Breslow intermediate) prepared in mode (E) is highly nucleophilic and acts as an acylating agent in a variety of NHC-catalyzed transformations (B, then F). Furthermore, the addition of an NHC to α,β-unsaturated aldehydes can lead to a dienaminol intermediate, rendering the β-carbon atom nucleophilic (C).[7] Additionally, the enaminol can trigger an elimination, if there is a leaving group at the α-position of the aldehyde (D). In this process, a nucleophilic enol(ate) can form, in which the attached azolium species acts as a bystander (I).[8] Moreover, the catalyst can increase the electrophilicity in acyl azolium species and act as a good leaving group, re-entering the catalytic cycle (G). A variety of NHC-catalyzed redox processes lead to the formation of acyl azolium species using an oxidant.[9] Finally, the Breslow intermediate can also act in a dual push–pull

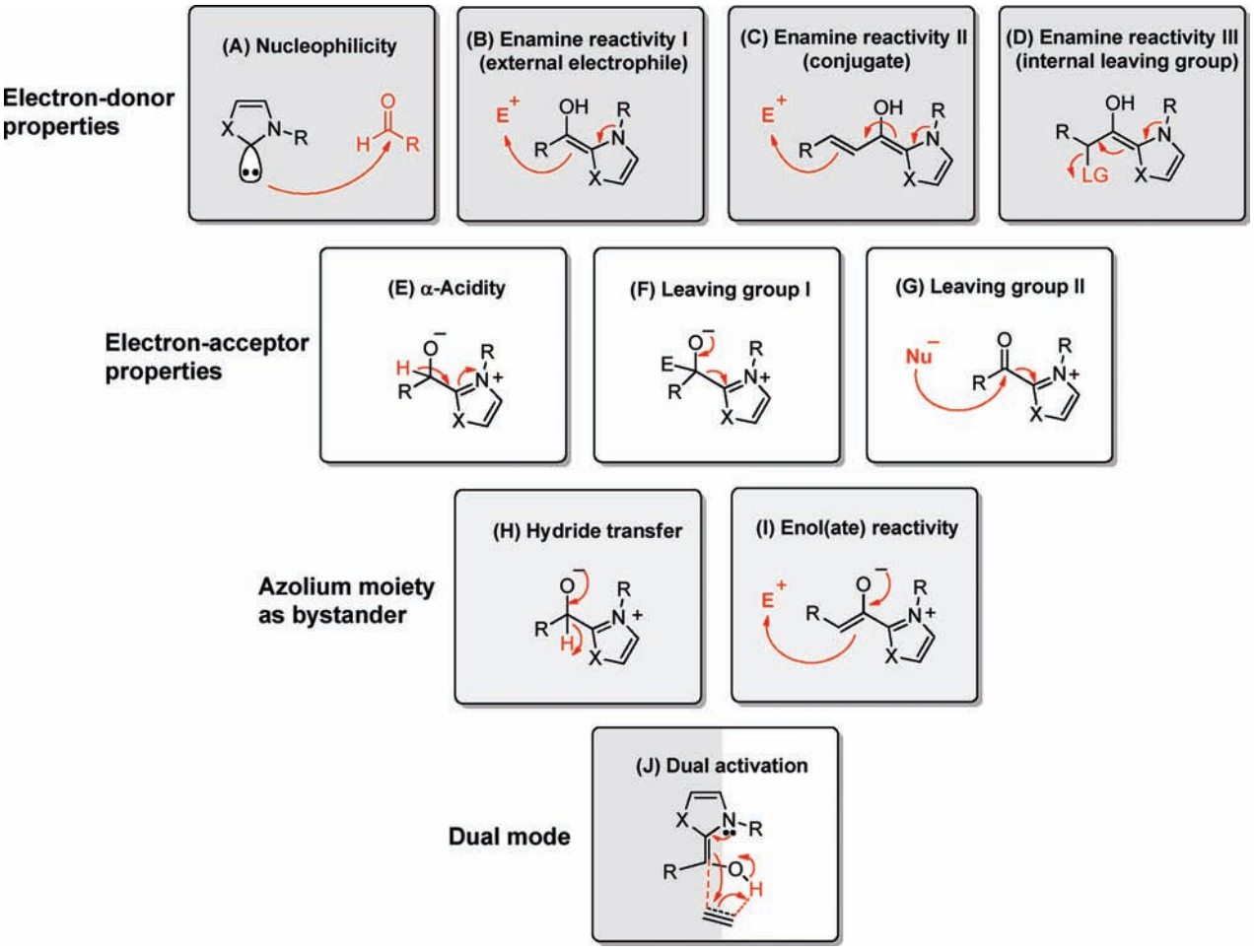
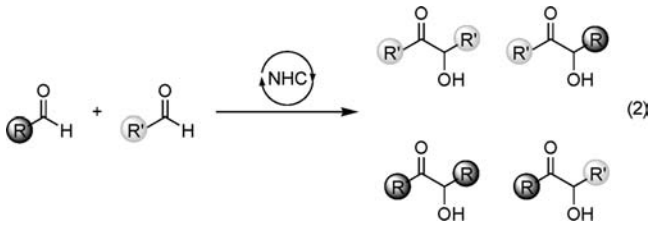


FIGURE 1. Most Prominent Modes of Action in NHC-Organocatalysis.

fashion (see chapter 4): the positively polarized proton of the enaminol can interact with the reaction partner and withdraw electron-density from it, activating it for the attack of the enamine part of the Breslow intermediate (J). The electronic and steric properties of NHCs can be tuned over a wide range by choosing different nitrogen heterocycles as well as by the proper choice of substituents on nitrogen and the backbone. Slight structural differences can have a dramatic effect on catalytic activity and selectivity of carbenes.

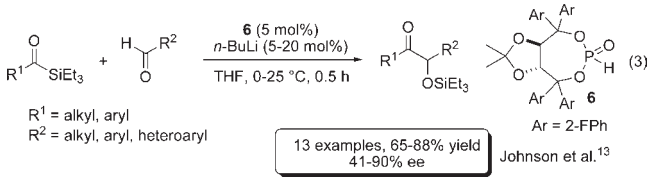
2. Recent Advances in Benzoin Reaction

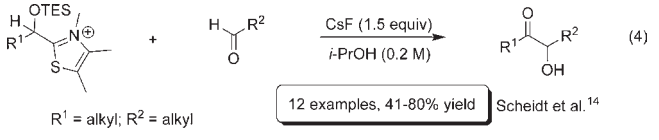
The benzoin reaction, the coupling of two aldehydes, is one of the first transformations found to be catalyzed by NHCs.[3] Since the benzoin reaction is a valuable strategy to form new C–C bonds leading to the formation of α-functionalized carbonyl compounds, this unique process and its mechanism have been intensively studied.[10a] Moreover, the effort to develop a highly asymmetric homobenzoin reaction led to the development of numerous chiral NHC precursors. However, the asymmetric benzoin reaction and the intramolecular cross-benzoin reaction have received a lot of attention recently, and a recent review on NHC-organocatalysis covers the literature on this subject.[2f,10] Thus, in the following, we will focus on recent developments in the field of intermolecular cross-benzoin reactions. In this process, a mixture with up to eight different products (four pairs of enantiomers) can be anticipated (eq 2), which renders the intermolecular cross-benzoin reaction especially challenging in terms of chemoselectivity. Indeed, a general solution for a chemoselective NHC-catalyzed cross-benzoin reaction is still elusive.[11]

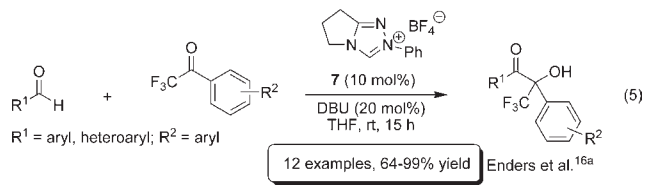


One strategy for selective cross-benzoin reactions is the modification of one aldehyde component to control the chemoselectivity. Johnson and co-workers demonstrated

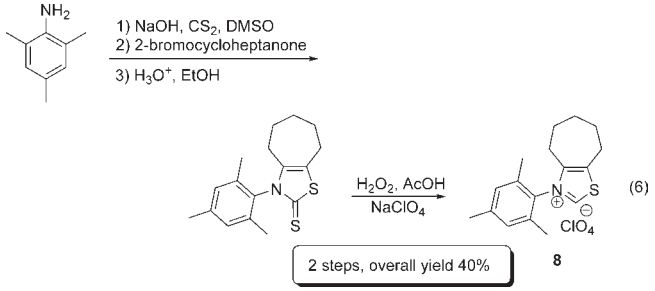
this approach by utilizing acylsilanes as coupling partners for aldehydes in a highly regiospecific cyanide-catalyzed cross silyl benzoin reaction.[12] The noteworthy features of this transformation include the in situ protection of the secondary hydroxyl group as a silyl ether and the inhibition of the homobenzoin formation. Subsequently, the Johnson group reported the enantioselective cross silyl benzoin reaction using (*R*,*R*)-TADDOL-derived metallophosphite (eq 3).[13] Recently, Scheidt and co-workers reported the use of *O*-silyl thiazolium carbinol as acyl anion precursor by its reaction with aldehyde in the presence of CsF (eq 4).[14] As basic conditions can be avoided by liberating the acyl anion equivalent with a fluoride source, this method is superior for synthesizing even difficult cross-acyloin products (coupling of one or two aliphatic aldehydes). Another approach of masking one component to avoid its reaction with the NHC has already been demonstrated in aza-benzoin reactions.[15] Additionally, Enders and Henseler reported the use of trifluoromethyl ketone as an electrophile in a cross-benzoin reaction using the carbene precursor **7**.[16a] The excellent selectivity for the α-hydroxy-α-trifluoromethyl ketones is a result of the reversibility of the homobenzoin reaction. Therefore, products of a broad range of aromatic and heterocyclic aldehydes could be converted into the corresponding products in excellent yield (eq 5). By introducing a new chiral triazolium catalyst, this cross-benzoin reaction using heteroaromatic aldehydes succeeded in an asymmetric fashion in good to excellent yields and moderate to good enantioselectivities, which could be improved by crystallization.[16b]







In an earlier report, Inoue and co-workers[17] demonstrated the use of paraformaldehyde as a reaction partner in benzoin and acyloin reactions allowing the selective formation of α-hydroxyketones although in low yield and with a narrow substrate scope. The common methods to synthesize this important class of compounds are often non-C−C bond forming hydrolyses or oxidations. Therefore, their synthesis via an NHC-catalyzed formation of a new C−C bond would represent an attractive alternative. Along our research in the field of dual NHC-metal-catalysis, we have recently developed a new thiazolium salt **8** with a seven-membered ring in the backbone and a sterically demanding mesityl substituent on nitrogen.[18] The synthesis of **8** was accomplished in two steps following a modified procedure of Bach and co-workers (eq 6).[19]



During our investigation, we found that thiazolium salt **8** gave the best results for the hydroxymethylation of a broad range of aromatic and aliphatic aldehydes with formaldehyde (Table 1).[20] Our mechanistic experiments revealed that, besides other effects, the nucleophilic attack of the Breslow intermediate onto formaldehyde is fast, leading to the selective formation of the observed product **10**.

Inspired by an early work of Stetter and Dämbkes,[21] Zeitler, Connon and co-workers[22] recently studied the cross-acyloin reaction between aromatic and aliphatic aldehydes (eq 7). The formation of only one cross-acyloin product was achieved using bulky triazolium-derived catalyst **11** (catalyst control) in combination with an aromatic aldehyde possessing a *directing* substituent in the *ortho*-position (substrate control). For the latter, bromine proved to be beneficial as it features the proper steric demand as well as the right electronic characteristics. Interestingly, the same chemoselectivity using triazolium catalyst **11** has very recently been observed by Yang and co-workers for the acyloin reaction of simple aromatic aldehydes with acetaldehyde.[23]

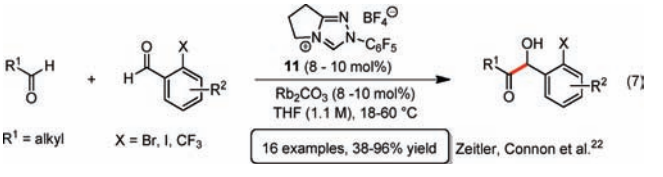
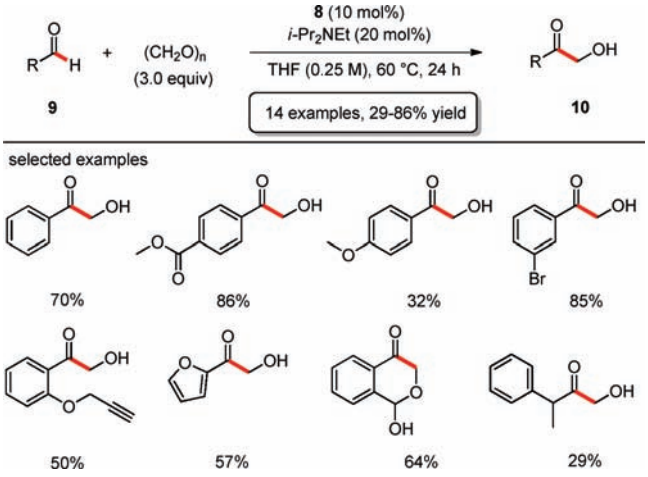


TABLE 1. NHC-Catalyzed Hydroxymethylation of Aldehydes[20]

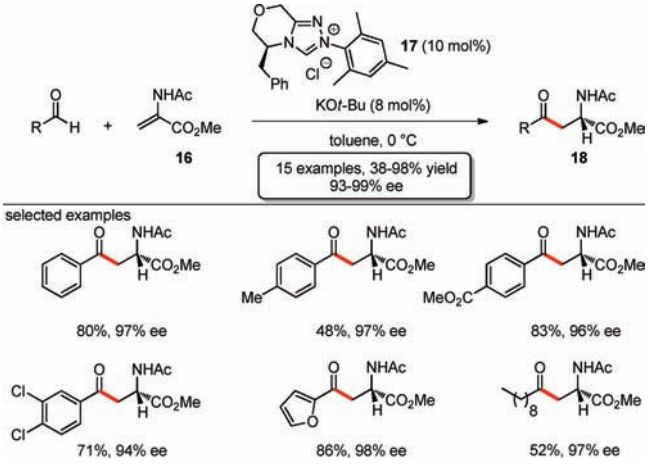


3. Recent Advances in the Stetter Reaction

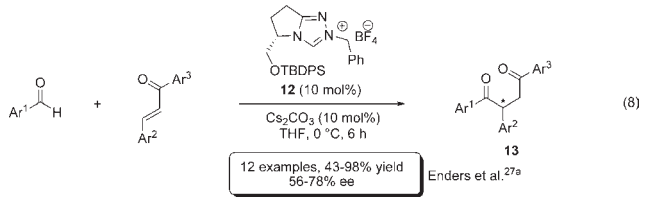
Ever since the seminal work of Stetter in 1973, the NHC-catalyzed addition of aldehydes to Michael acceptors, the Stetter reaction, is widely used as a catalytic pathway for the synthesis of 1,4-bifunctional compounds such as 1,4-diketones, 4-ketonitriles, and 4-ketoesters.[24] This is valuable, since it leads to an "unnatural" functional group distance, which is difficult to realize using traditional methods. Stetter and co-workers succeeded to selectively cross-couple a variety of aromatic and aliphatic aldehydes with a variety of Michael acceptors in an intermolecular fashion. The catalytic intramolecular version of this reaction was developed by Ciganek in 1995 leading to the formation of benzo-annulated furanones and pyranones.[25] The Stetter reaction can be utilized for the controlled formation of new stereocenters in the product. The intramolecular Stetter reaction and its variants have received a lot of attention recently, and a number of reviews have addressed various aspects of this reaction.[2c,f,26] In view of these excellent reviews, a detailed discussion of the intramolecular Stetter reaction is not attempted in this Account.

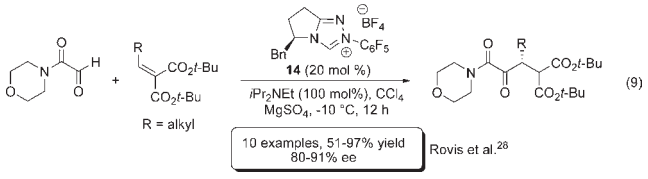
Although NHC catalysts and reaction protocols are well established for the enantioselective intramolecular version, the asymmetric *intermolecular* Stetter reaction still remains a formidable challenge. This is partly because the Michael acceptors containing a β-substituent (except chalcones) usually show diminished reactivity in the Stetter reaction. Recently, Enders and co-workers reported the asymmetric intermolecular Stetter reaction of aromatic aldehydes and chalcones catalyzed by the NHC derived from triazolium salt **12** leading to 1,4-diketones **13** in moderate to excellent yields (49−98%) and moderate to good enantioselectivities (56−78% ee).[27a] Impressively, the enantiomeric excess of the products could be enhanced up to 99% ee by a single recrystallization (eq 8). The presence of the *N*-benzyl substituent in **12** was crucial for activity and high levels of selectivity in this intermolecular Stetter reaction, demonstrating the importance of the *N*-substituent of triazolium-based catalysts.[27c] Independently, Rovis and co-workers reported the asymmetric intermolecular Stetter reaction of a glyoxamide and alkylidenemalonates.[28] However, excellent enantioselectivities were obtained only for a morpholine-derived glyoxamide. A variety of β-substituted alkylidenemalonates underwent this reaction in good yield with high asymmetric induction in the presence of a phenylalanine-derived NHC catalyst **14** (eq 9). A limitation of this method was the use of alkylidene malonate with two ester groups, which diminishes the opportunity for further derivatization. In view of this, the Rovis group recently developed a highly enantioselective and diastereoselective intermolecular Stetter reaction of a glyoxamide and alkylidene ketoamides leading to 1,4-dicarbonyl compounds, which are amenable for further derivatization to synthetically useful intermediates in organic synthesis (eq 10).[29] Subsequently, they used nitroalkenes as viable Michael acceptors in intermolecular Stetter reaction using a new chiral NHC precatalyst **15**. By utilizing the stereoelectronic as well as steric effects induced by the fluoro and isopropyl substituents in **15**, a highly enantioselective Stetter reaction of nitroalkenes and heteroaryl aldehydes was developed (eq 11).[30] However, the use of heteroaromatic

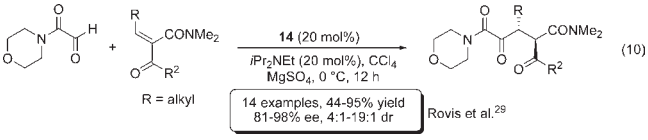
TABLE 2. NHC-Catalyzed Intermolecular Stetter Reaction[32]

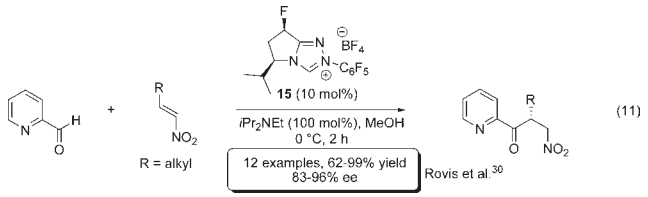


aldehyde was crucial for high levels of reactivity and selectivity.









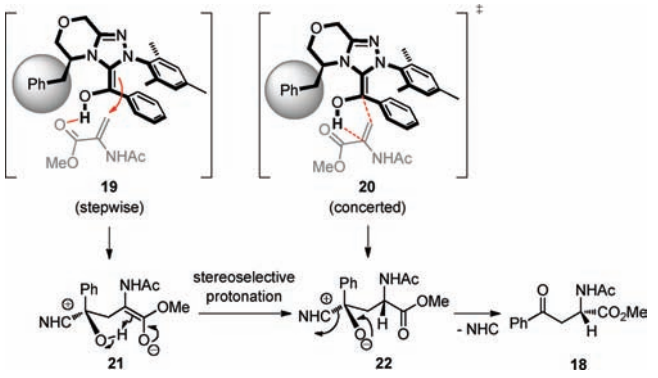
We envisioned the synthesis of enantioenriched α-amino acid derivatives by an intermolecular enantioselective Stetter reaction using *N*-acylamido acrylate **16** as the Michael acceptor. In this process, the two important steps, the C−C bond formation between the Breslow intermediate and the Michael acceptor as well as an asymmetric protonation are efficiently merged. A variety of aldehydes reacted with the dehydroamino ester **16** in the presence of NHC generated from L-phenyl alaninol derived triazolium salt **17**[2c,31] yielding α-amino acid derivatives **18** in excellent yield and stereoinduction (Table 2).[32]

The mechanism and mode of asymmetric induction are still unclear, but can be rationalized as follows. First, the reaction between the free carbene derived from **17** and the aldehyde leads to the formation of a nucleophilic Breslow intermediate (Scheme 2). The Michael acceptor **16** approaches from the bottom face in an *anti* fashion, most likely supported by a hydrogen bond between the enol hydrogen and the carbonyl oxygen of the Michael acceptor (**19**, Scheme 2). In this process, ester enolate **21** bearing a new but transient stereocenter is formed highly stereoselectively. The stereochemistry is relayed to the α-position by a stereoselective protonation of the transiently formed enolate. Finally, the NHC is released, destroying the initially formed stereocenter and forming the final product **18**. Alternatively, a concerted transition state **20** could directly generate intermediate **22**. This reaction is remarkable because of the rather low electronic activation of substrate **16** and because it represents the first asymmetric intermolecular Stetter reaction that generates only an α-stereocenter.

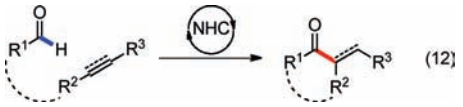
4. NHC-Catalyzed Reaction of Aldehydes with Unconventional Electrophiles

Although the NHC-catalyzed umpolung of aldehydes and the subsequent interception of the nucleophilic acyl anion intermediates with various electrophiles, such as aldehydes, ketones, imines, and activated, C=C double bonds, is well-known, the analogous transformations with unconventional electrophiles such as unactivated C−C multiple bonds

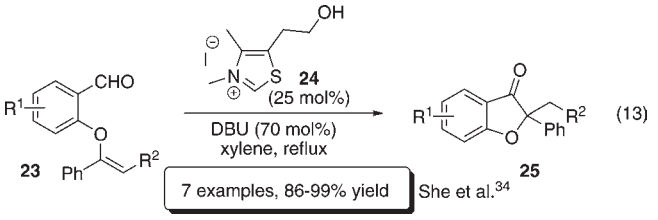
SCHEME 2. Proposed Mechanistic Pathways for the Enantioselective Stetter Reaction[32]



(eq 12) and activated alkyl halides was largely unexplored. In contrast, the transition metal catalyzed hydroacylation of unactivated C−C multiple bonds, the insertion into the C_{formyl}-H bond of aldehydes is established.[33]



4.1. Hydroacylation of Electron-Neutral Double Bonds. The intramolecular nucleophilic addition reaction of acyl anion equivalents to enol ethers catalyzed by the NHC generated from readily available thiazolium salt **24** was developed by She and co-workers,[34] leading to the formation of benzofuranones **25** in excellent yield (eq 13). The exact mechanism of this transformation (concerted or stepwise involving an oxonium species) is not clear.



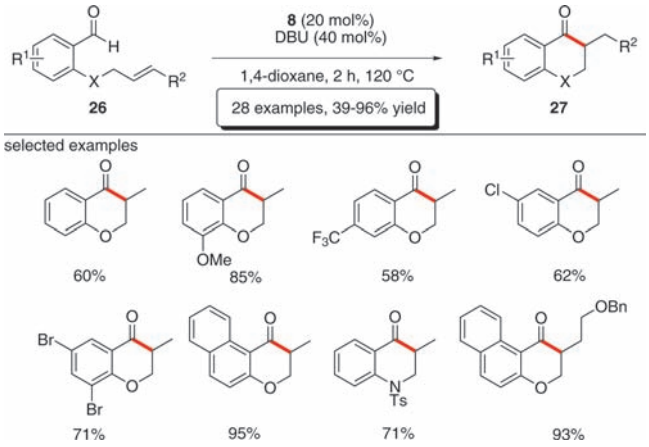
Recent investigations in our laboratory revealed novel reactivity profiles of the carbene generated from the thiazolium salt **8**. We commenced with the NHC-organocatalyzed cyclization of 2-allyloxy benzaldehydes **26** to the corresponding chromanones **27**, the intramolecular hydroacylation of unactivated C=C-double bonds.[35] Gratifyingly, among the wide range of NHCs screened, the carbene generated from **8** by deprotonation with DBU showed the best reactivity, providing the desired functionalized chromanones in moderate to excellent yield. This new methodology was applied to a range of substrates with electron-donating and -withdrawing substituents on the aromatic ring as well as the substituent on the allyl moiety (Table 3).

A likely mechanism starts with the addition of NHC to the carbonyl group of 2-allyloxy benzaldehyde to form Breslow intermediate **28** (Scheme 3). In a concerted transition state **29**, this could add as a nucleophile to the olefin of the allyl moiety and the resulting zwitterionic tetrahedral intermediate **30** liberates the desired product and the catalyst. The similarity to Conia-ene type transition states (same polarity of reacting olefins) and reverse-Cope elimination type ones as suggested by Rovis (five-membered transition state) is striking.[36,37] It should be noted in this context that the possibility of addition of Breslow intermediates[4] to Michael acceptors in a concerted manner analogous to the reverse Cope elimination was previously mentioned by Rovis and Read de Alaniz.[37] Furthermore, density functional theory calculations were performed by Grimme et al.[38] to get more insight into the crucial step of the reaction, that is, whether the proton migration or the C−C bond formation occurs first. These studies support a concerted but highly asynchronous transition state.[38]

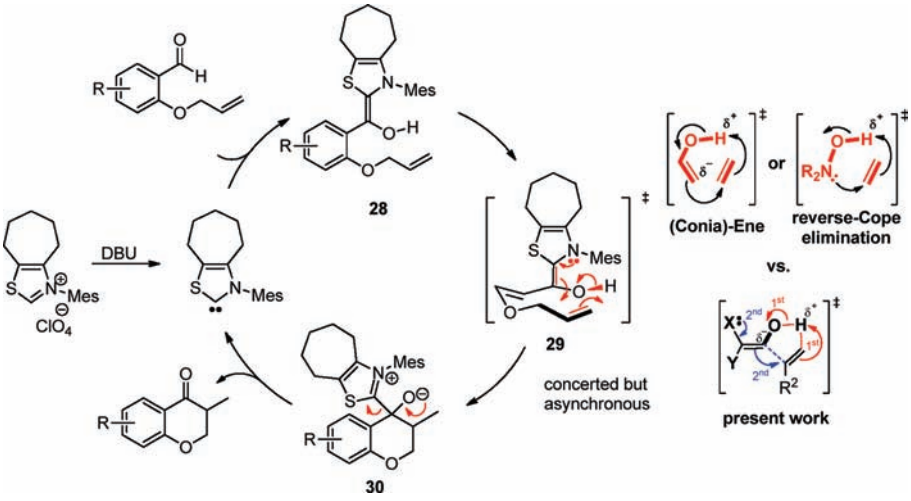
Subsequently, we applied this methodology to the highly asymmetric NHC-catalyzed intramolecular hydroacylation of unactivated olefins leading to the formation of an all-carbon quarternary stereocenter in the biologically and pharmaceutically important chromanone structure.[38] The carbene generated from **17** showed exceptionally high reactivity and selectivity affording differently substituted chromanones, most of them with 99% ee (Table 4). This extraordinarily high level of enantioinduction also speaks in favor of a concerted mechanism. Another indication comes from the first intermolecular hydroacylation of cyclopropenes that we have reported very recently (Table 5).[39] Experiments with deuterated substrates demonstrated that the hydroacylation is a *syn* addition process. With this latter transformation, a general NHC-catalyzed intermolecular hydroacylation of truly unactivated olefins seems to be within reach.

4.2. Hydroacylation of Electron-Neutral Triple Bonds. In view of these interesting results, we then focused our attention on the hydroacylation of unactivated triple bonds. Treatment of unactivated internal alkynes **31** with the carbene generated from **8** by deprotonation with K_2CO_3 resulted in the smooth formation of benzylidene chromanone **32**, bearing a synthetically valuable exocyclic olefin, as a single isomer.[40] Variations on both aromatic rings are well tolerated, providing good yields for electron-donating and electron-withdrawing substituents (Table 6). Interestingly, competition experiments carried out using electronically different alkynes revealed (1) reversible formation of the

TABLE 3. NHC-Catalyzed Hydroacylation of Unactivated Double Bonds[35]

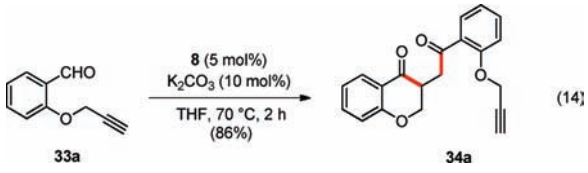


SCHEME 3. Proposed Mechanism for the Hydroacylation of Unactivated Double Bonds[35,38]

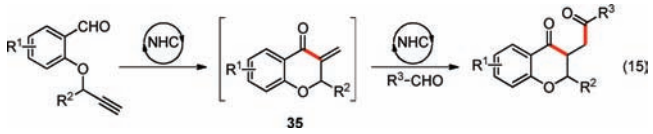


Breslow intermediate and (2) a key role of the alkyne in the rate determining step, since electron-poor alkynes reacted faster than electron-rich ones.

We continued with the organocatalyzed hydroacylation of unactivated terminal alkynes. Surprisingly, treatment of **33a** with **8** and K_2CO_3 did not result in the formation of the expected enone, but it led to the formation of chromanone **34a**, presumably by the addition of a second molecule of **33a** to the intermediate enone (eq 14).



In view of this unprecedented reactivity, we decided to employ a second aldehyde as the coupling partner for enone **35**. It was envisioned that this will constitute a dually NHC-catalyzed hydroacylation cascade comprising an initial hydroacylation of an unactivated triple bond and a subsequent intermolecular Stetter reaction (eq 15).



Reaction of the 2-propargyloxy aldehydes **33** with a second coupling aldehyde catalyzed by NHC generated from **8** resulted in the formation of chromanone with a 1,4-diketone motif in excellent yield. It is noteworthy that these reactions require only rather low catalyst loading (5 mol %) and proceed with high level of selectivity. A variety of substrates with different substitution patterns

TABLE 4. NHC-Catalyzed Enantioselective Hydroacylation of Unactivated Olefins[38]

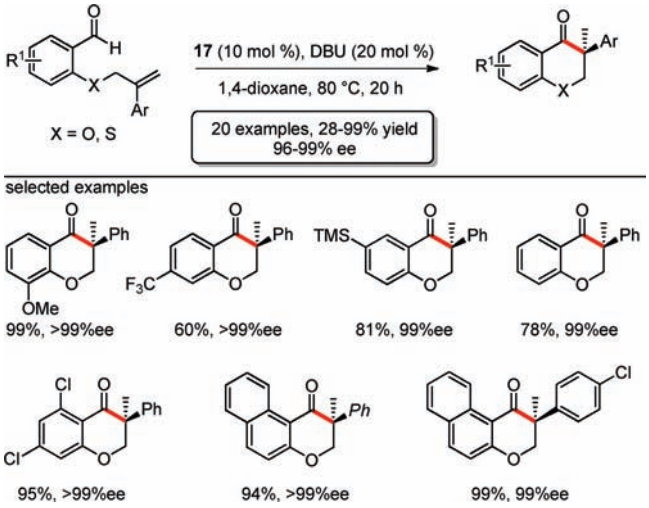


TABLE 5. First intermolecular NHC-Catalyzed Hydroacylation of Cyclopropenes[39]

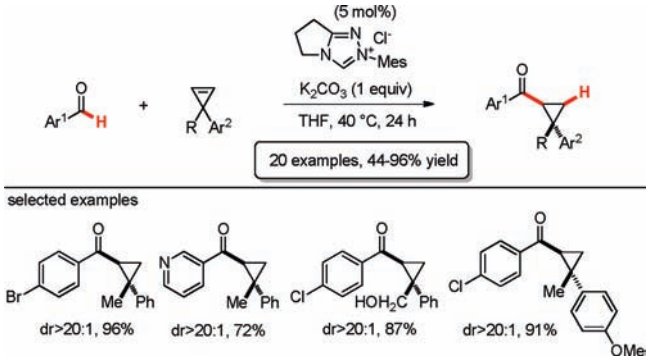
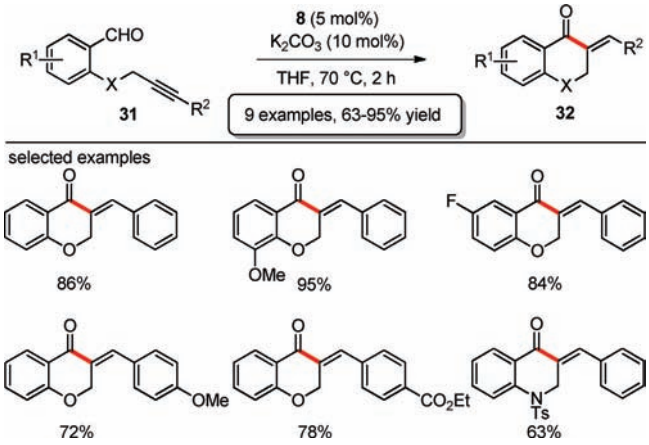


TABLE 6. NHC-Catalyzed Hydroacylation of Unactivated Internal Alkynes[40]



afforded the chromanones in good to excellent yield (Table 7). Gratifyingly, a substituent on the progargylic moiety was also well tolerated, giving the product in 70% with a *trans/cis* ratio of 3:1. In addition, a variety of coupling aldehydes **36** including heterocyclic and aliphatic ones have been examined, and in all cases the reaction

TABLE 7. NHC-Catalyzed Hydroacylation–Stetter Cascade[40]

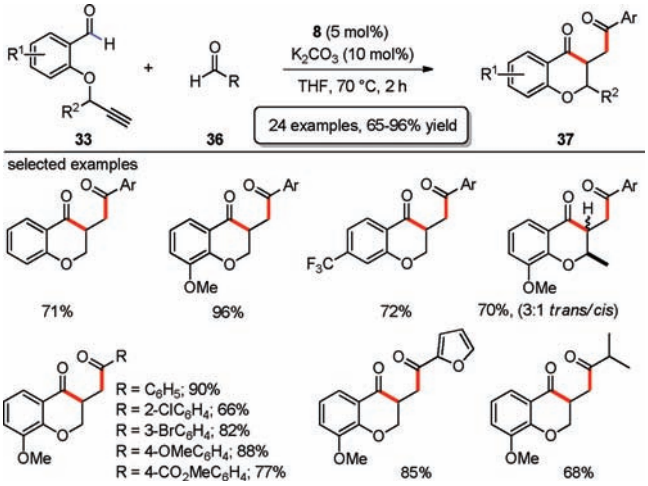
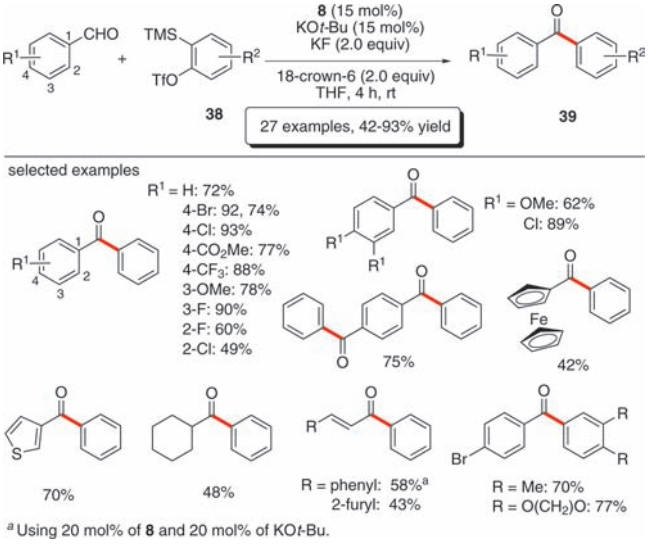


TABLE 8. NHC-Catalyzed Hydroacylation of Arynes[41]



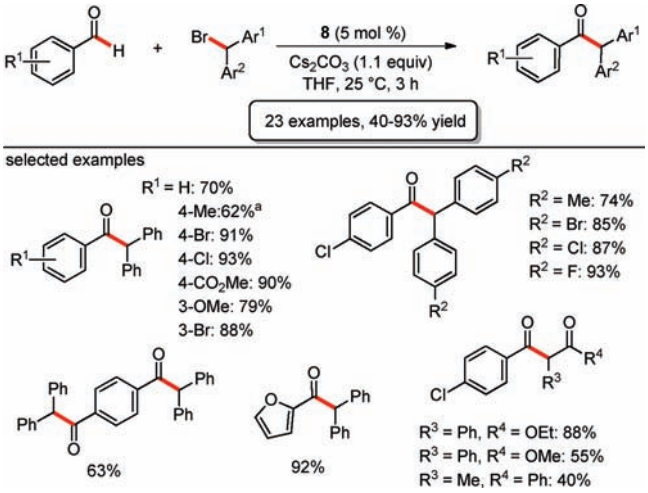
[a] Using 20 mol% of **8** and 20 mol% of KO*t*-Bu.

resulted in the smooth formation of the expected chromanone derivative.

4.3. Hydroacylation of Arynes. Encouraged by these results, we then turned our attention to a class of highly reactive intermediates in organic synthesis, namely, arynes. Although arynes have been extensively utilized in transition-metal-catalyzed reactions, their application in organocatalytic processes is scarce presumably due to the inherent reactivity of arynes toward nucleophiles. Interestingly, the insertion of arynes into the C_{formyl}–H bond of aldehydes, the intermolecular hydroacylation of arynes, was unknown. Again, the proper choice of the carbene was key to success. The reaction of a wide variety of aldehydes with the aryne generated in situ from 2-trimethylsilylaryl triflate **38** using 2.0 equiv each of KF and 18-crown-6 in the presence of carbene generated from **8** by deprotonation using KO*t*-Bu resulted in the formation of the aryl ketones **39** in moderate to excellent yield (Table 8).[41] This process provides an attractive transition metal-free synthetic strategy to a wide range of aryl ketones and is particularly appealing by virtue of the high levels of chemoselectivity observed.

Mechanistic studies indicate that the electronic nature of the aldehydes plays a prominent role in the rate-determining step,[42] with electron-poor aldehydes reacting faster than the electron-rich ones. Also, competition experiments carried out using electronically dissimilar arynes revealed no preference in product formation, indicating that the

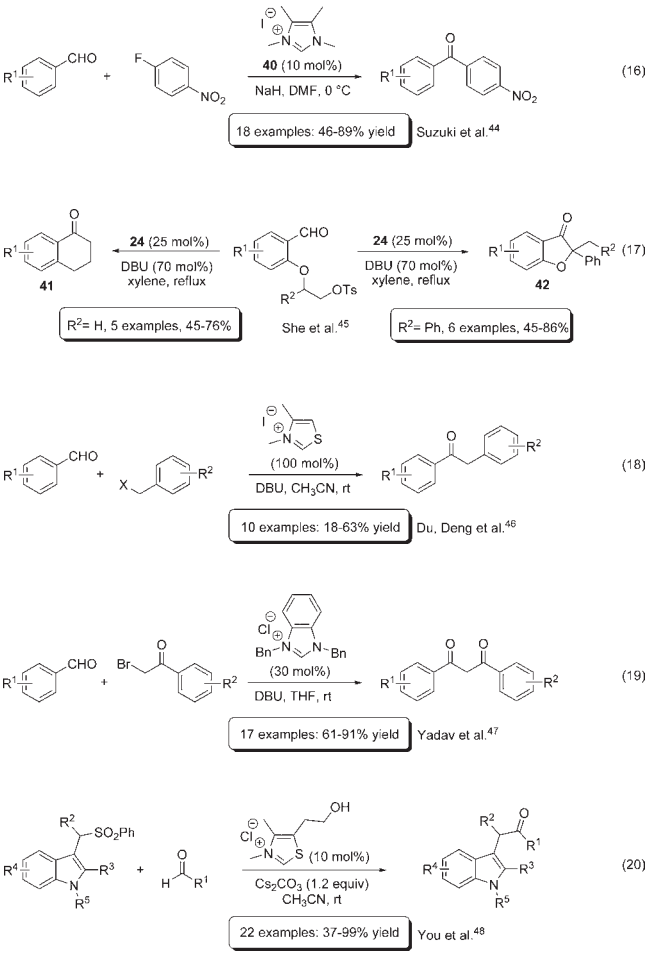
TABLE 9. NHC-Catalyzed C−H Alkylation of Aldehydes[49]



[a]Using 20 mol % of **8** and 1.4 equiv of Cs_2CO_3.

electronic nature of the aryne may not be important for the rate-determining step.

4.4. Nucleophilic Substitution Reactions. Besides the NHC-catalyzed addition of aldehydes to carbonyl compounds, activated or unactivated C−C multiple bonds, NHCs have been utilized for the nucleophilic substitution reaction.[43] The underlying principle in these reactions is the addition of acyl anion equivalents to activated alkyl or aryl halides. Suzuki and co-workers reported that the carbene generated from **40** catalyzed nucleophilic acylation of fluorobenzene derivatives possessing electron-withdrawing groups leading to the formation of aryl ketones proceeding via an addition−elimination mechanism (eq 16).[44] An intramolecular nucleophilic substitution reaction catalyzed by NHCs for the facile construction of benzopyrones and benzofuranones has been uncovered by She et al. (eq 17).[45] When R^2 is a phenyl group, the expected benzopyrone **41** was not formed but resulted in the formation of benzofuranones **42**. Very recently, NHC-*mediated* cross-coupling of aromatic aldehydes with benzyl halides leading to the synthesis of α-aryl ketones has been developed by Deng et al. (eq 18).[46] Although this method used stoichiometric amounts of NHC, this is the first example of intermolecular nucleophilic acylation of aromatic aldehydes with benzyl halides. Additionally, nucleophilic acylation of α-haloketones with aldehydes leading to the formation of 1,3-diketones has been reported by Yadav and co-workers (eq 19).[47] It should be mentioned in this context that conceptually similar NHC-catalyzed cross-coupling of aldehydes with arylsulfonyl indoles proceeding via an intermolecular Stetter-like reaction has been reported by You et al. (eq 20).[48]



The NHC-catalyzed hydroacylation of alkyl halides is a valuable topic, and we have developed the cross-coupling of

(hetero)aromatic aldehydes with diarylbromomethanes.[49] Even under mild reaction conditions with low catalyst loading, a variety of aromatic aldehydes were converted to diaryl acetophenone derivatives in good yields (Table 9). In addition, α-halo ketones and esters can also be used as aldehyde reaction partners, which lead to the efficient formation of β-ketoester and β-diketone derivatives in moderate to good yields. Mechanistic experiments favor a stepwise S_N1 pathway involving the formation of a diphenylmethyl carbonium ion, which is eventually attacked by the Breslow intermediate.

5. Conclusion

In summary, this Account has outlined several useful NHC-catalyzed transformations that bring to light the diverse reactivity and versatility of NHCs. We have uncovered new reactivity profiles of NHCs including the hydroacylation of electron-neutral double and triple bonds and arynes. The new reactivity was possible by the design of novel NHC precursors. Understanding the underlying mechanism and the electronic and steric properties of NHCs[1e] will allow the design of more sophisticated NHCs having numerous applications. It is anticipated that the simplicity of the synthetic strategies that are highlighted here will inspire a broad range of new applications of NHCs in organocatalysis. However, to be clear: in most cases, the efficiencies of the transformations are not yet at a sufficient level and future research also has to address this.

BIOGRAPHICAL INFORMATION

Akkattu T. Biju received his Ph.D. in 2006 under the guidance of Dr. Vijay Nair at NIIST Trivandrum. Subsequently, he was a postdoctoral fellow at NTU Taipei (Prof. Tien-Yau Luh). At present, he is a postdoctoral fellow in the research group of Professor F. Glorius at the WWU Münster. His research interests are focused on the synthesis of new N-heterocyclic carbenes and their application in catalysis. In June 2011, he started his independent research career at the National Chemical Laboratory (CSIR), Pune, India.

Nadine Kuhl studied Chemistry at Westfälische-Wilhelms Universität Münster. After a research stay with Prof. Jennifer A. Love at the University of British Columbia, Vancouver, she joined the research group of Prof. Frank Glorius at the Westfälische-Wilhelms Universität where she received her degree in organic chemistry in 2010. At present, she is a Ph.D. student in the group of Prof. Frank Glorius with a scholarship of the Fonds der Chemischen Industrie. Her research interests are focused on the development of new N-heterocyclic carbene catalyzed transformations and new methodologies in the field of transition metal-catalyzed C−H activations.

Frank Glorius was educated in chemistry at the Universität Hannover, Stanford University (Prof. Paul A. Wender), the Max-Planck-Institut für Kohlenforschung and Universität Basel (Prof. Andreas Pfaltz), and Harvard University (Prof. David A. Evans). In 2001, he began his independent research career at the Max-Planck-Institut für Kohlenforschung in Germany (Prof. Alois Fürstner) and in 2004 was promoted to Associate Professor for Organic Chemistry at the Philipps-Universität Marburg. Since 2007, he has been Full Professor at the Westfälische Wilhelms-Universität Münster. His research focuses on the development of new concepts for catalysis and their implementation in organic synthesis.

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FOOTNOTES

*To whom correspondence should be addressed. E-mail: glorius@uni-muenster.de.

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