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Highlight Review

Dual Activation in N-Heterocyclic Carbene-organocatalysis

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Abstract

N-Heterocyclic carbene (NHC)-catalyzed transformations have found increasing interest in the last years. Recently, dual catalytic approaches using NHCs in combination with a second catalyst such as another organocatalyst or a metal-based catalyst or by the NHC itself have emerged. The careful choice of the proper combination of catalysts allows two compatible yet independent catalytic systems in one-pot to undergo tandem processes. Moreover, simultaneous action of two activators in a bond-forming event enables new reactivity, which often cannot be achieved by monocatalytic approaches.

♦ Introduction

The chemistry of "umpolung," which in German originally means "reversal of polarity," provides alternative ways of retrosynthetic disconnection.[1] The catalytic version of umpolung transformations using N-heterocyclic carbenes (NHCs) has been attracting increased attention over the last years.[2] NHCs exhibit special electronic properties, which enable several attractive modes of action (Figure 1). Their most prominent catalytic action is the umpolung of aldehydes (Figure 1, modes 1, 2, and 3). The highly nucleophilic C2 carbon of an NHC adds to the aldehyde leading to the tetrahedral zwitterionic intermediate (1). Now, the positively charged azolium ring acidifies the α-C–H bond derived from the aldehyde to form an enamine species (Breslow intermediate) (2).[3] This enamine can efficiently add to various electrophiles to form a zwitterion (3). Thereafter, the azolium moiety behaves as a good leaving group releasing the product and regenerating the free NHC catalyst (4). This process was independently extended to the catalytic homoenolate formation from α,β-unsaturated aldehydes by the groups of Glorius and Bode (5), followed by the release of the NHC from the formed acyl azolium species by nucleophilic attack (6).[4] Whereas the NHC moiety in modes 1, 3, and 5 acts as an electron-donating group, in modes 2, 4, and 6 the NHC derived azolium moiety acts as an electron-withdrawing group. The balance of these properties is one of the unique characteristics of NHC in organocatalysis.

Catalysis by NHCs alone has found many applications, but is also quite limited in terms of reaction types.[2] The parallel use of an additional catalyst or catalytically active entity can lead to improved levels of selectivity and reactivity, but also to completely new classes of reactions. However, until recently, problems of incompatibility between the NHC and other catalysts had precluded this dual mode of action. In this highlight review, some recent breakthroughs in NHC-organocatalysis powered by another metal- or organo-cocatalyzed process will be discussed, together with a recently discovered dual mode of activation in a concerted transition state using an NHC catalyst only.

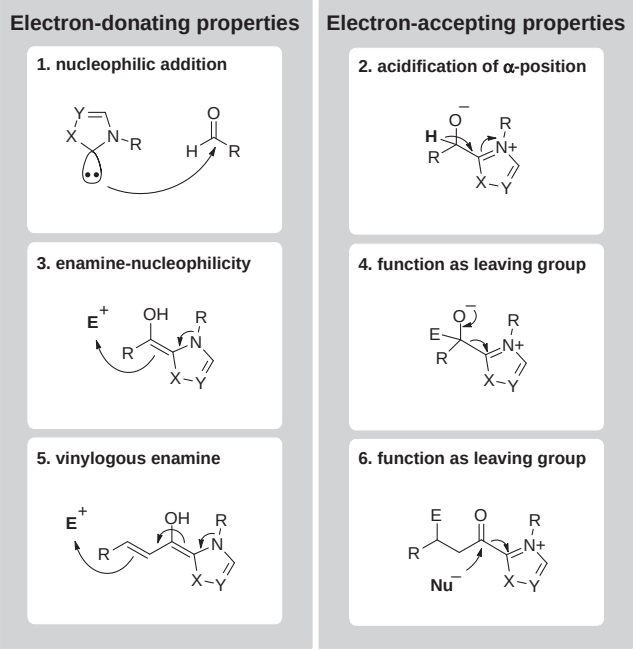

Figure 1. Classification of some of the most important inherent modes of action of NHC catalysts.

♦ Tandem NHC- and Metal Catalysis

Combining NHC-catalyzed umpolung with transition-metal-catalyzed processes is of particular interest and an attractive approach to realize new reactivity or modes of action. However, the Lewis basic nature of carbenes and the generally Lewis acidic character of metals often result in complex formation and poisoning of each other. Indeed, especially late transition metals, which possess soft character, have strong inclination for stable complexation with NHCs and this fact has been utilized extensively in transition-metal-catalyzed chemical transformations.[5] This strong interaction has precluded the development of cooperative catalyst systems. The first disclosure of success on this challenging topic was a one-pot sequential Pd-catalyzed allylic amination–thiazolylidene-catalyzed Stetter reaction to

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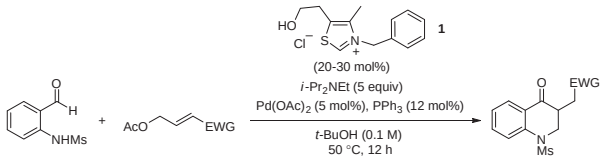
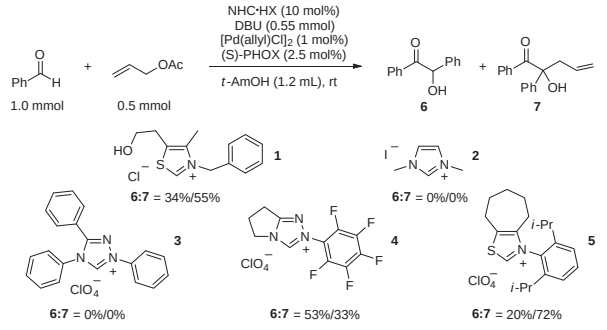
afford dihydroquinolinones by Hamada and co-workers (Scheme 1).[6] The key to this success was the use of the commercially available thiazolium salt **1** as a precursor of the carbene catalyst. It seems that the corresponding thiazolium-derived carbene does not irreversibly bind to palladium so that the free carbene and palladium catalyst are able to coexist in the same reaction solution.



Scheme 1. Hamada's tandem-catalysis.[6]

Glorius et al. developed another sequential process using NHC and palladium catalysts, a benzoin formation by NHC-catalysis followed by palladium-catalyzed allylic alkylation thereof (Scheme 2).[7] The carbene used by Hamada derived from precursor **1** showed catalytic activity despite the second step, however, allylic alkylation does not proceed smoothly. The electron-rich carbenes derived from imidazolium salt **2** and Enders' triazolium **3** were not even able to yield benzoin, which is the product of the first cycle. This strongly indicates that the free imidazolylidene or triazolylidene is poisoned by irreversibly binding to palladium. Interestingly, the electron-poor triazolylidene formed from **4** affords the desired tertiary alcohol **7** in 33% yield. This result supports the above rationalization. Further optimization of the catalyst structure elucidated the newly developed *N*-(2,6-diisopropylphenyl)thiazolylidene (derived from **5**) fused with a 7-membered ring to be the most active catalyst giving the best conversion and best ratio of desired allylation product **7** to benzoin **6**.

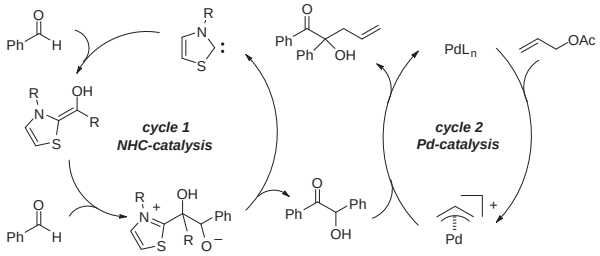


Scheme 2. Studies on the compatibility of NHC and palladium.[7]

The proposed reaction mechanism is described below (Scheme 3). The NHC catalysis produces the nucleophile (benzoin **6** from cycle 1) for the subsequent palladium-catalyzed allylic alkylation (cycle 2).

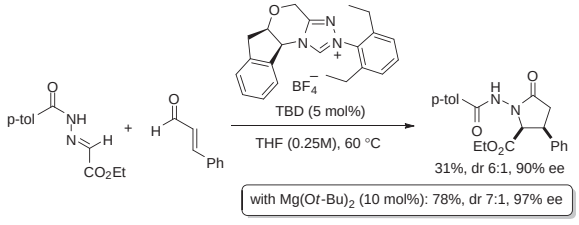
♦ *Cooperative Catalysis by NHC and Metal: Simultaneous Activation of Reactants*

Cooperative catalysis is a rapidly growing research area



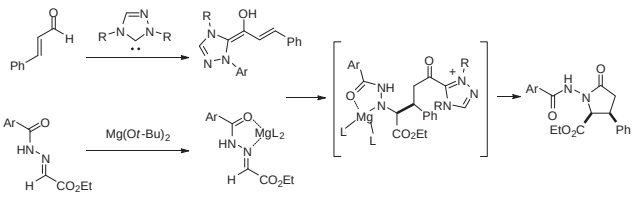
Scheme 3. Benzoin condensation–Pd-allylic alkylation-tandem catalysis by Glorius.[7]

since it enables new transformations by activation of multiple components in the reaction mixture.[8] Regarding NHC catalysis, the Scheidt group made a number of important breakthroughs, demonstrating the simultaneous catalytic activation of two reaction partners in the same step using NHC and metal catalyst (Scheme 4).[9] While the NHC activates the α,β-unsaturated aldehyde to generate the homoenolate equivalent, a magnesium salt activates the acyl hydrazone. Key to success in this concurrent process is the choice of Lewis acidic *early* metals, taking advantage of their relatively weak associative interaction with NHCs. A remarkable enhancement of yield and ee was observed *in the presence of* magnesium co-catalyst [Mg(O*t*-Bu)$_2$] at low catalyst loading. On the other hand, use of strong Lewis acids such as magnesium triflate shuts down the reaction.



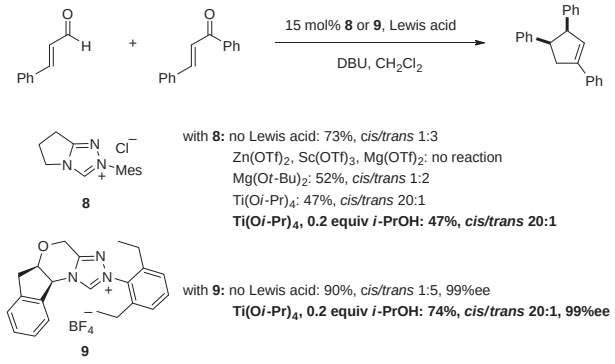
Scheme 4. Scheidt's cooperative catalysis of NHC and Lewis acid.[9]

It was reasoned that Mg activates and bridges the two reaction partners in a chelating fashion to render the addition of the catalytically formed homoenolate more facile (Scheme 5).



Scheme 5. Simultaneous action of two compatible catalysts for a C–C bond formation.[9]

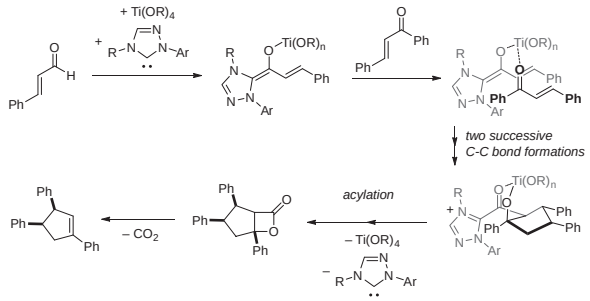
In course, Scheidt showed that the addition of an appropriate Lewis acid can have a huge impact on the diastereoselectivity of NHC-catalyzed cyclopentene formation (Scheme 6).[10] The deactivation of the NHC catalyst formed from **8** is observed upon employing strong Lewis acids such as metal triflates presumably due to strong binding of the NHC to the metal center. As seen



Scheme 6. Scheidt's enantioselective cyclopentene formation.[10]

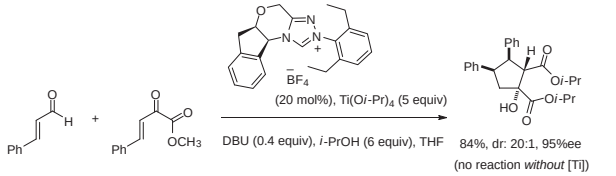
already, attenuation of affinity between them using magnesium *tert*-butoxide does not result in poisoning of the NHC catalyst although improvement in neither yield nor dr is observed in this case. Titanium tetraisopropoxide obviously interacts with the chalcone since a dramatic enhancement of diastereoselectivity with reversed stereochemistry is observed. Addition of catalytic amounts of isopropyl alcohol improves the yield, presumably by facilitating the dissociation of the titanium catalyst from the intermediate. The chiral NHC-precatalyst **9** can successfully be used to yield the product under essentially perfect control of stereochemistry (*cis*/*trans* 20:1, 99% ee). In this case, the titanium catalyst improves the diastereoselectivity of the C–C bond formation without erosion of enantiomeric excess.

Scheidt proposed that the titanium complex activates not only the chalcone but also preorganizes homoenolate and chalcone to favor their spatial alignment leading to high degrees of *cis*-selectivity (Scheme 7).



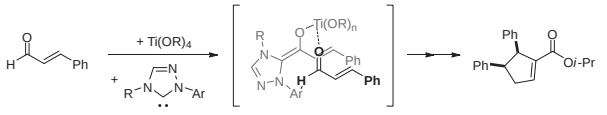
Scheme 7. Proposed model of activation and preorganization of reactants.[10]

In line with this dual concerted action of NHC and titanium catalysts mentioned above, Scheidt expanded the scope of the reaction using β,γ-unsaturated-α-ketoesters as Michael acceptors (Scheme 8).[11] In this reaction, use of NHC *only* does not afford the desired product, whereas NHC-catalyzed homoenolate formation in combination with the activation of electrophiles with titanium tetraisopropoxide gives the highly functionalized cyclopentanes in good yields with excellent drs and ee values. This achievement is rather important since the effect of the second activator (used in overstoichiometric amounts) was crucial to get the desired reactivity in contrast to the previous examples shown above, where the second catalyst was used to enhance selectivity.



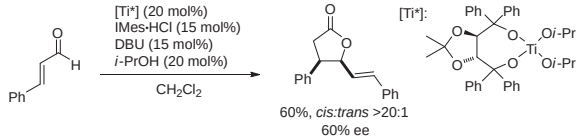
Scheme 8. Synthesis of a highly funtionalized cyclopentane.[11]

Recently, the group of Scheidt reported an NHC-catalyzed/Ti-mediated enantioselective dimerization of enals.[12] The dimerization of enals catalyzed by NHC usually affords γ-butyrolactones[4] via 1,2-addition of the catalytic homoenolate to electrophiles. However, Scheidt realized the 1,4-addition of homoenolate equivalents to enals over traditional 1,2-addition giving γ-butyrolactones. The authors hypothesize again that the titanium salt preorganizes the enal with the catalytic homoenolate as well as it activates the enal. These actions of titanium might explain that the reaction proceeds in favor of the observed 1,4-addition of homoenolate to enal instead of the commonly seen 1,2-addition. Lack of titanium catalyst does not furnish the formation of the desired product (Scheme 9).



Scheme 9. Cyclopentene formation via dimerization of enals.[12]

Scheidt showed another important ability of enantioselective NHC–Lewis acid cooperative catalysis. Until this work appeared in the literature, all the enantioselective NHC-catalyses had relied on chiral NHCs for enantioinduction.[2] However, Scheidt demonstrated the first example of enantioinduction using *a chiral Lewis acid catalyst* in combination with *an achiral NHC*.[10a] The *achiral* NHC dimerizes *trans*-cinnamaldehyde to γ-butyrolactone with perfect diastereoselectivity and 60% ee assisted by a Ti-TADDOL complex (Scheme 10). In spite of the unsatisfactory selectivity at this moment, these results prompt further extensive studies on the NHC-catalyzed enantioselective reactions. The large number and the modular nature of chiral Lewis acid complexes renders these investigations promising.[13]

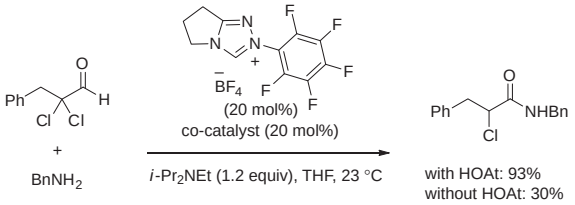


Scheme 10. Enantioselective lactone formation assisted by a chiral Lewis acid.[10a]

♦ *Sequential Organocatalyses in One-Pot*

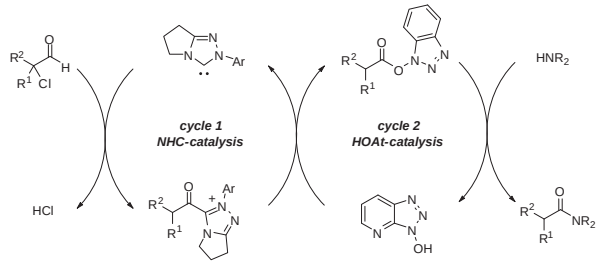
The continuous quest for new types of NHC-catalyzed processes has found some important synergetic actions of NHC-

and other organocatalysts. Vora and Rovis reported an orthogonal amide formation by NHC- and HOAt relay catalysis (Scheme 11).[14] Conventional amide bond formation relies on stoichiometric activation of the carboxylic acid functionality to couple with amines. The authors[15] and also others[16] reported on the NHC-catalyzed redox-esterformation using alcohols as nucleophiles. With the intention of finding atom-economical catalytic methods for amide formation, they utilized HOAt (1-hydroxy-7-azabenzotriazole) as co-catalyst with the underlying hypothesis that HOAt could take part in this redox process resulting in the catalytic formation of an active ester and thus facilitate amide bond formation. Indeed, the reaction with NHC and HOAt as catalysts yields the amide in 93% yield, whereas in contrast to an accompanied amide product with imine and α-monohalogenated carboxylic acid of only 30% yield is obtained *without any cocatalyst*. Several commonly used activators for acylation such as HOBt (1-hydroxybenzotriazole), and DMAP (4-dimethylaminopyridine) as well as highly electron-deficient pentafluorophenol show similar activity.



Scheme 11. NHC–HOAt co-catalyzed redox amidation by Rovis.[14]

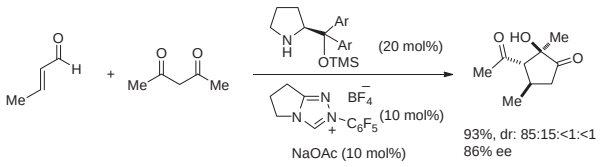
A variety of α-reducable aldehydes such as α-halo-, epoxy-, aziridino-, and α,β-unsaturated aldehydes were tolerated in this method in coupling with primary, secondary, and aromatic amines. The authors proposed a sequential two catalytic cycle cascade (Scheme 12). The α-reducable aldehyde is redox-isomerized by the NHC to form the acyl azolium species, which is attacked by HOAt to form activated ester releasing the NHC catalyst back to the first catalytic cycle. This active carboxylate is trapped by the desired amine to furnish the amide bond formation.



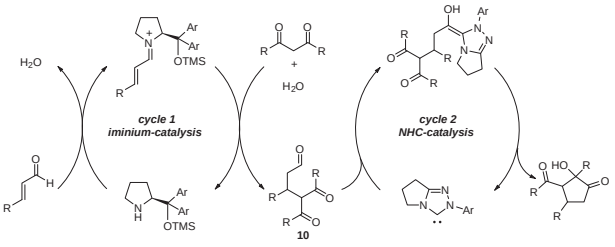
Scheme 12. Sequential NHC–HOAt catalysis by Rovis.[15]

Moreover, Lathrop and Rovis reported an enantioselective synthesis of functionalized cyclopentanones utilizing NHC-catalysis in combination with iminium catalysis (Scheme 13).[17]

Enantioselective addition of an active methylene compound to an enal catalyzed by a secondary amine followed by the intramolecular crossed benzoin cyclization between ketone and



Scheme 13. Achiral NHC meets chiral secondary amine.[17]

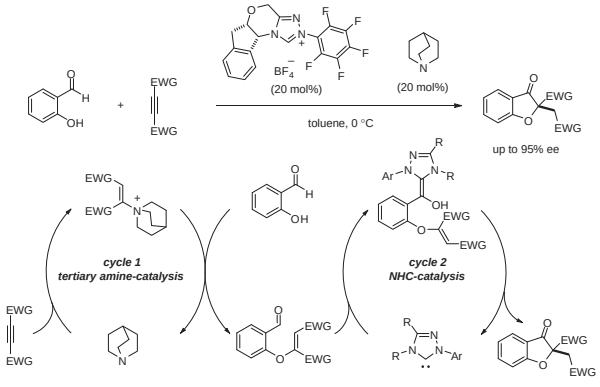


Scheme 14. Sequential C–C-bond formation catalyzed by secondary amine and NHC.[17]

aldehyde, as pioneered by Suzuki[18] and Enders,[19] led to the targeted product (Scheme 14).

Very importantly, in a stepwise non-one-pot process, this product could only be obtained in 65% yield with 58% ee (vs. 93% yield with 86% ee in one-pot fashion) due to the erosion of enantioenrichment of the intermediate aldehyde via the retro-Michael reaction *in the absence of NHC catalyst*. Herein, the NHC functions as a shuttle to convert the relatively unstable Michael addition product **10** to the cyclopentanone so that the loss of the optical purity can be minimized. This system clearly shows the power of multicatalytic sequential catalysis involving NHC catalysts.

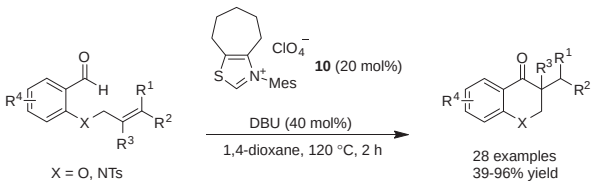
Moreover, Rovis and co-workers developed an asymmetric Michael/Stetter reaction of salicylaldehydes and activated alkynes via multicatalysis (Scheme 15).[20] The Michael addition of a salicylaldehyde to an activated alkyne is catalyzed by quinuclidine and the subsequent enantioselective Stetter reaction is promoted by a chiral triazolium-derived carbene. In this cascade, quinuclidine serves also as base to generate a free carbene from the triazolium salt in addition to promoting the Michael addition.



Scheme 15. Dual catalytic approach to enantioselective benzofuranone formation.[20]

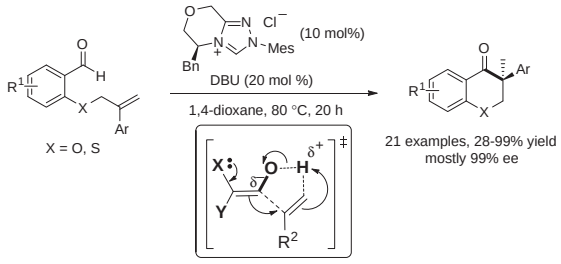
♦ *Dual Activation by NHC Only: Utilizing a Concerted Transition State*

Finally, dual activation can also occur by the Breslow intermediate only. Recently, we have discovered the NHC-catalyzed hydroacylation of electron-neutral olefins and this was utilized for the formation of chromanones (Scheme 16).[21] Our original thiazolylidene catalyst derived from **10** promotes this unprecedented process particularly efficiently.



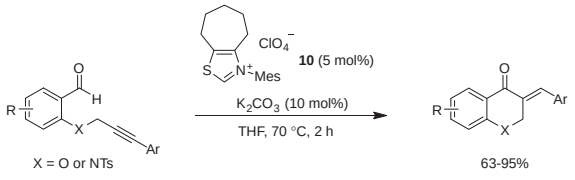
Scheme 16. Hydroacylation of electron-neutral olefins.[21a]

Remarkably, utilizing a chiral NHC, the substrates bearing an aryl group at the internal position of double bond undergo the hydroacylation forming a quaternary all-carbon stereocenter with excellent enantiomeric excess (mostly 99% ee).[21b,21c] Theoretical and mechanistic investigations point at a concerted though highly asynchronous process, in which the alkene is activated by interaction with the positively polarized proton of the enol moiety. This sets the stage for the attack of the enamine onto the activated alkene (Scheme 17).



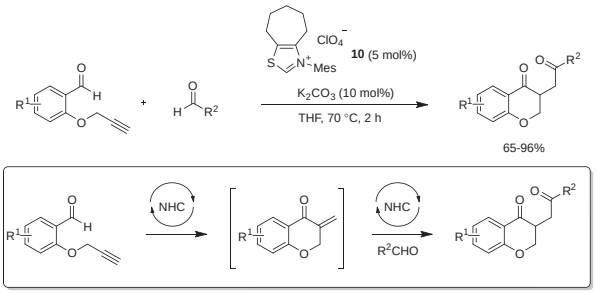
Scheme 17. Highly enantioselective hydroacylation of electron-neutral olefins.[21b]

Very recently, we have also reported the intermolecular hydroacylation of cyclopropenes, the first intermolecular hydroacylation of electron-neutral olefins.[21d] In addition, the NHC derived from **10** also catalyzed an intramolecular addition of aldehydes across unactivated triple bonds (Scheme 18).[21e] Substrates bearing internal alkynes were cyclized to chromanones with an exocyclic double bond.



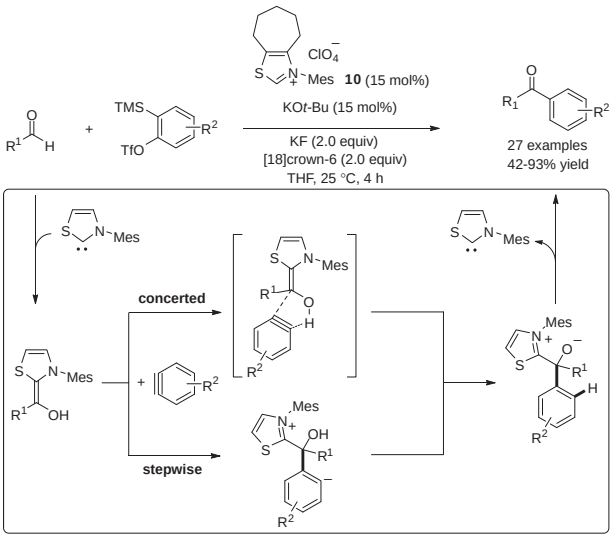
Scheme 18. Glorius' hydroacylation of electron-neutral triple bonds.[21e]

Notably, a tandem process of the hydroacylation and Stetter reaction is observed in case simple *O*-propargylated salicylaldehydes are used in combination with another aldehydes (Scheme 19). In this process, the NHC derived from **10** demonstrates its unique effectiveness to avoid undesired benzoin- and Stetter products.



Scheme 19. Tandem hydroacylation–Stetter reactions.[21e]

Our new catalyst **10** also enabled the organocatalytic hydroacylation of arynes.[21f–21h] The acylanion equivalent generated by NHC derived from **10** reacts with benzynes generated in situ to yield a series of ketones (Scheme 20). Two possible mechanisms for this unprecedented reaction are shown below. The stepwise mechanism involving a nucleophilic attack of the acyl anion equivalent to benzyne followed by protonation of the aryl anion or the concerted [3 + 2]-dipolar cycloaddition type mechanism.[22]



Scheme 20. Glorius' hydroacylation of arynes.[21f]

♦ *Conclusion*

The research on catalytic transformations involving NHC catalysts has entered a new and exciting phase. Recent successful investigations of dual catalysis, tandem or cooperative NHC–metal or organocatalysis, have shown the vast potential of new types of reactions by virtue of careful fine-tuning of both catalysts' architectures and balancing Lewis

basicity of NHC and Lewis acidity of metal-based catalyst. Combining NHC-catalysis and other organocatalysis has opened up possibilities to realize unique reactivity and selectivity, which cannot be seen in monocatalytic systems. Finally, a dual activation mode was also found in the concerted transition state of an only-NHC-catalyzed process. Given the vast possibilities of combination of NHCs and metals or organocatalysts, many brand-new styles of reaction should certainly be explored in the near future by using compatible catalyst-pairs or even more additional catalysts. Let's go/Ikuze!

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