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Review

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Exploring NHCs as organocatalysts: a modern synthetic tool

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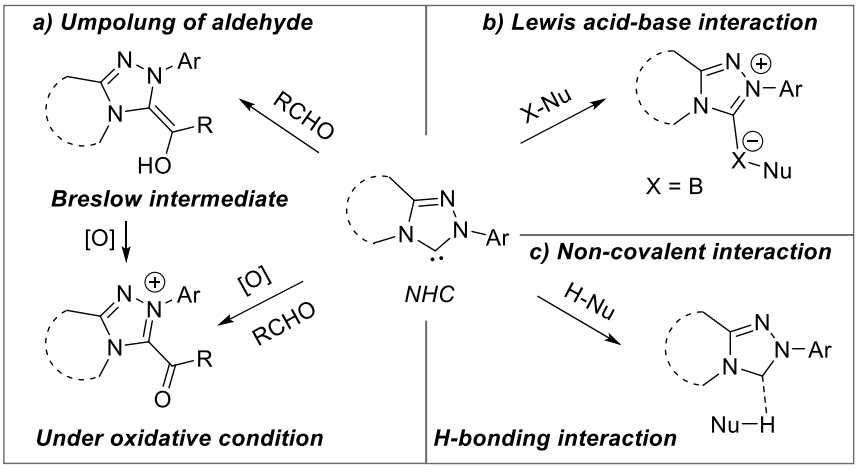
Abstract

N-Heterocyclic Carbenes (NHCs) have emerged as powerful organocatalysts in modern synthetic chemistry offering unique reactivity and selectivity under mild conditions. This review explores the evolution, mechanistic underpinnings and broad utility of NHCs in organocatalysis. In this review, we begin by outlining the fundamental principles underlying NHC organocatalysis followed by a discussion of the emerging trends that are driving innovation in this dynamic field. Based on distinct substrate activation modes, we categorize NHC organocatalysis into three major classes: (a) NHCs functioning as nucleophilic organocatalysts, (b) NHCs acting as Lewis base organocatalysts and (c) NHCs serving as non-covalent organocatalysts. Particular focus is given to their role in umpolung reactions, annulations and cascade processes which have significantly expanded the synthetic toolbox for constructing complex molecular architectures. Advances in catalyst design, including chiral NHCs, have further enhanced their applicability in asymmetric synthesis. Through a comprehensive analysis of recent developments, this review highlights how NHCs continue to shape the future of sustainable and efficient organic synthesis.



Keywords: N-Heterocyclic carbenes, organocatalysts, nucleophilic, Lewis-base, n-covalent

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1. Introduction

Organocatalysis has emerged as a powerful and versatile strategy in modern organic synthesis, offering an alternative to traditional catalysis involving metals or enzymes.[1] It involves the acceleration of chemical reactions using small, non-metallic organic molecules that are typically easy to access, stable under ambient conditions and environmentally friendly. While the foundational principles of organocatalysis date back over a century, it was only in the early 21st century that the field experienced a surge in development particularly with the advent of enantioselective organocatalysis.[2-4] The appeal of organocatalysis lies in its operational simplicity and compatibility with a wide range of reaction conditions. These catalysts typically function under mild conditions, tolerate moisture and air and avoid the toxicity and environmental concerns associated with many metal-based systems. One of the most significant contributions of organocatalysis is its role in asymmetric synthesis, enabling the efficient construction of chiral molecules with high enantioselectivity—an essential feature in the development of pharmaceuticals, agrochemicals, and fine chemicals.[5-6] Moreover, many organocatalysts can be derived from naturally occurring chiral sources such as amino acids, alkaloids and carbohydrates.

Similar to other organocatalysts, N-heterocyclic carbenes (NHCs) have emerged as highly effective tools in contemporary organic synthesis.[7-9] They have been employed in a wide range of both asymmetric and non-asymmetric transformations, showcasing catalytic capabilities comparable to well-established organocatalysts such as amines and phosphoric acids. Different structural classes of NHCs commonly used in organocatalysis are illustrated in Figure 1.

The remarkable stability of NHCs is attributed to a combination of electronic and steric factors with electronic stabilization playing a more dominant role. In particular, the nitrogen atoms positioned on either side of the central carbene carbon play a crucial role in stabilizing the species. They stabilize the carbene centre by withdrawing electron density through σ-bond inductive effects while simultaneously donating their lone pairs into the vacant p orbital of the carbene carbon *via* mesomeric interaction (Figure 2).[10-11]

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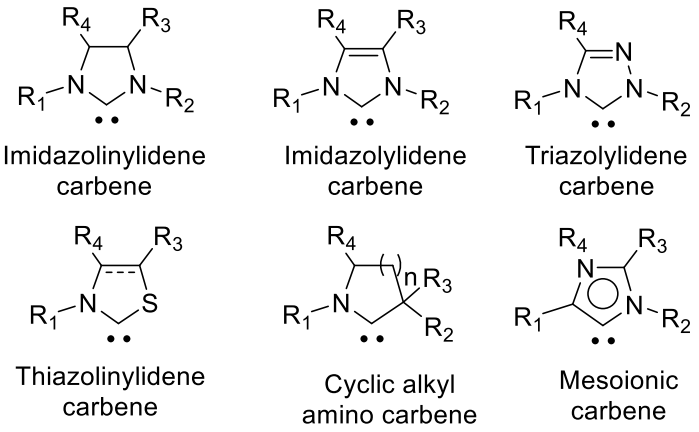

Figure 1. Different types of N-Heterocyclic Carbenes.

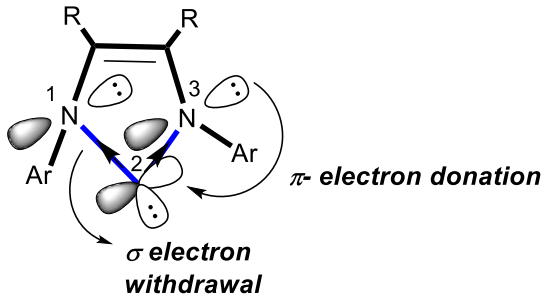

Figure 2. Electronic Stabilization of N-Heterocyclic Carbenes.

This dual interaction enhances the nucleophilicity of the carbene centre and helps maintain its electro-neutrality. Unlike classical carbenes, NHCs possess a singlet ground state and adopt bent sp^2 hybridized geometry at the carbene carbon due to their cyclic framework. This structure is further reinforced by the partial double-bond character of the C2–N bond, which typically exhibits a bond length of approximately 1.37 Å. Moreover, bulky groups attached to the nitrogen centres provide steric protection to the carbene carbon, effectively preventing dimerization (Figure 3).

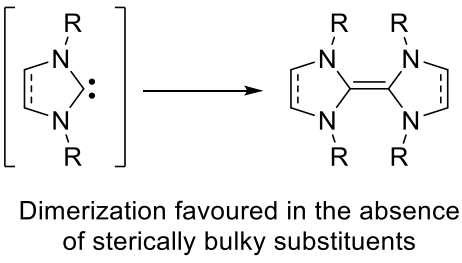

Figure 3. Wanzlick equilibrium of N-Heterocyclic carbenes.

The strong σ-donating ability of N-heterocyclic carbenes (NHCs) has made them highly valued as ligands in transition metal catalysis.[12-17] NHCs possess a higher electron density than trialkylphosphines, resulting in organometallic complexes with enhanced stability compared to those formed with phosphine ligands. This

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enhanced stability has facilitated the development of key transformations such as the Heck reaction, olefin metathesis, and various cross-coupling reactions using NHC-containing metal catalysts. Beyond their role as ligands, NHCs themselves have emerged as powerful catalysts in metal-free organic reactions.[7-9] Over the past thirty years, they have been widely employed as versatile organocatalysts for the synthesis of a broad range of heterocycles, carbocycles and acyclic compounds. The broad utility of NHCs arises from their easily tunable steric and electronic characteristics which enable the nucleophilic carbene to engage in multiple modes of reactivity with diverse substrates. In this review, we first introduce the fundamental principles of NHC organocatalysis, followed by an overview of emerging trends shaping this rapidly evolving field. Based on the substrate activation strategies, we classified NHC organocatalysis into three major categories, a) NHC as a nucleophilic organocatalyst, b) HNC as a Lewis Base organocatalyst, c) NHC as a non-covalent organocatalyst. It is important to note that, in the first two cases, NHC activates the substrate *via* strong covalent interaction where as in last cases substrate is activated *via* non-covalent interaction.

2. NHC as a Nucleophilic Organocatalysts

N-Heterocyclic Carbenes (NHCs) act as powerful nucleophilic catalysts in organic chemistry due to their ability to donate electron density from the carbene center. In catalysis, NHCs typically react with carbonyl-containing substrates, such as aldehydes, to form reactive intermediates like the Breslow intermediate. This enables key transformations, including umpolung (polarity reversal) of the carbonyl carbon, facilitating reactions such as the benzoin condensation and Stetter reaction. Their strong σ-donating nature and tunable steric/electronic properties make NHCs versatile tools in modern synthetic methodologies.[18]

2.1. NHC-catalyzed polarity inversion of aldehydes

N-Heterocyclic carbenes (NHCs) have gained significant attention in modern organic synthesis as highly effective nucleophilic catalysts. Characterized by a divalent carbon atom bearing a lone pair of electrons, NHCs are strong σ-donors and exhibit exceptional nucleophilicity. This allows them to engage directly with electrophilic substrates, often initiating catalytic cycles through the formation of key reactive intermediates. One of the characteristic features of NHCs as nucleophilic catalysts is their ability to invert the typical reactivity of carbonyl compounds—a process known as umpolung catalysis. The first organocatalytic application of N-heterocyclic carbenes (NHCs) was recognized in the benzoin condensation, a reaction that proceeds *via* umpolung (polarity inversion) of aldehydes.[18] This transformation enables the coupling of two aldehyde molecules to form α-hydroxy ketones (benzoins). Historically, the benzoin condensation was first discovered by Wöhler and Liebig in 1832 who utilized catalytic amounts of cyanide anions to promote the dimerization of aldehydes in an atom-economical manner.[19] The introduction of NHCs as catalysts for this reaction marked a significant advancement, offering a metal-free alternative to cyanide with improved functional group tolerance and mechanistic versatility. Over a century after the original discovery of the benzoin condensation, Ukai and co-workers reported a similar transformation using a naturally occurring thiazolium salt as a catalyst in the presence of a base.[20-21] However, the mechanism underlying Ukai's reaction remained unclear at the time. It was not until 1958 that Breslow proposed a mechanistic model that has since gained widespread acceptance.[22] The catalytic cycle for the benzoin condensation using an N-heterocyclic carbene (NHC) as a nucleophilic organocatalyst is illustrated in Scheme 1. In this cycle, the azolium salt **(I)** is sufficiently acidic to undergo deprotonation under mild basic conditions, generating the active nucleophilic carbene species **(II)**. This carbene then adds to an aldehyde, forming a tetrahedral intermediate **(III)**, which upon proton transfer

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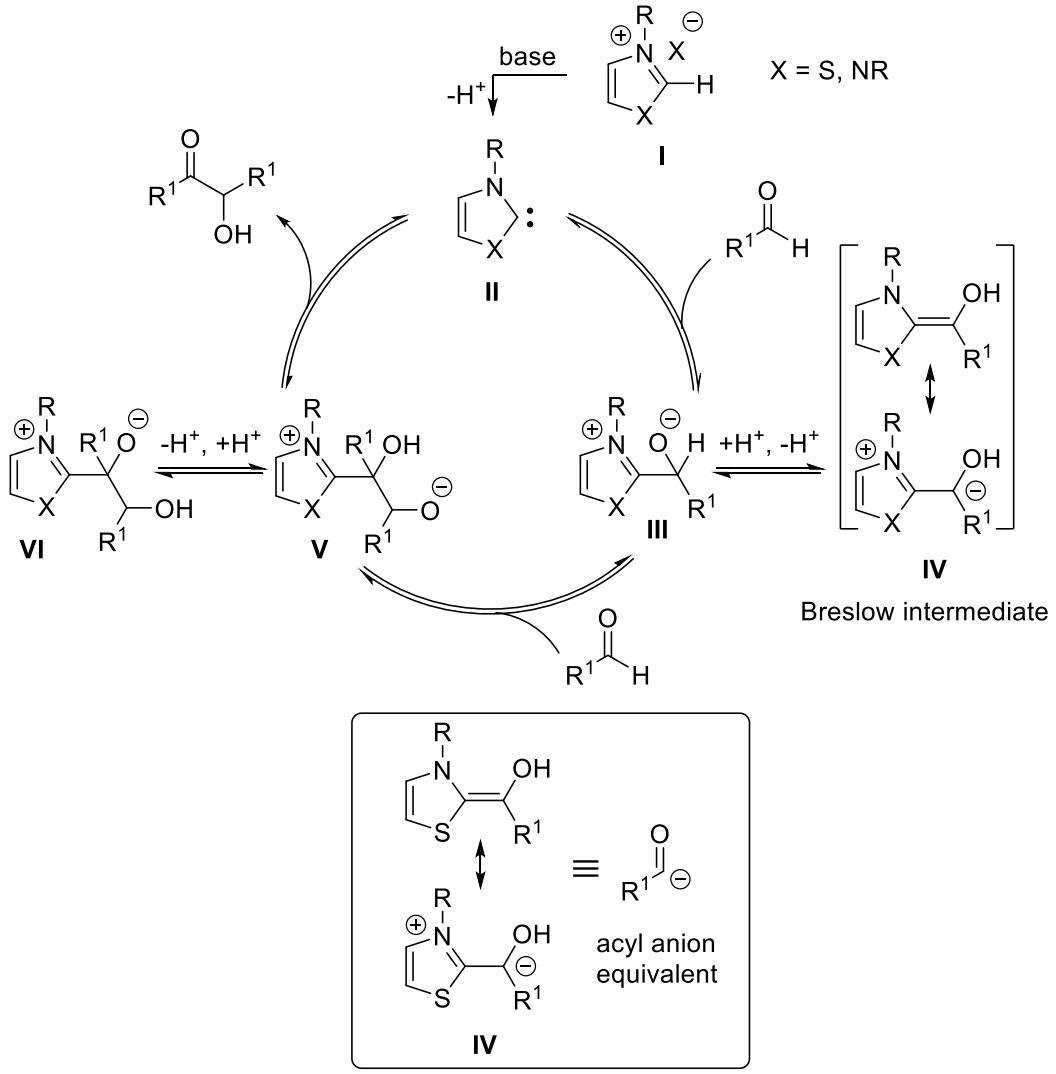
yields a resonance-stabilized enamine species **(IV)**, commonly referred to as the Breslow intermediate. In this intermediate, the originally electrophilic carbon of the aldehyde is rendered nucleophilic, a phenomenon known as "umpolung", as defined by Seebach. The electron-rich enaminol intermediate **(IV)**, also considered an acyl anion equivalent**,** subsequently reacts with a second molecule of aldehyde to form intermediate **V**. Through a sequence of proton transfer steps, this is converted to intermediate **VI**, which then undergoes rearrangement and catalyst regeneration, ultimately furnishing the benzoin product and restoring the active carbene species **II**.



Scheme 1. Mechanistic pathway of the benzoin condensation *via* Breslow Intermediate.

Significant efforts have been directed toward developing enantioselective variants of benzoin condensation. A key milestone was achieved in 1966, when Sheehan reported the first example of an intermolecular asymmetric benzoin condensation using a chiral thiazolium salt, which afforded the benzoin product in 22% enantiomeric excess (*ee*) and 9% isolated yield.[23] This pioneering work spurred extensive research aimed at designing more efficient and selective chiral catalysts for asymmetric benzoin synthesis. Over the following decades, a wide range of chiral thiazolium and triazolium salts were developed and applied to this transformation. A notable improvement in both yield and enantioselectivity was observed when the catalyst system shifted from thiazolium to triazolium-based scaffolds. Ultimately, a major breakthrough came

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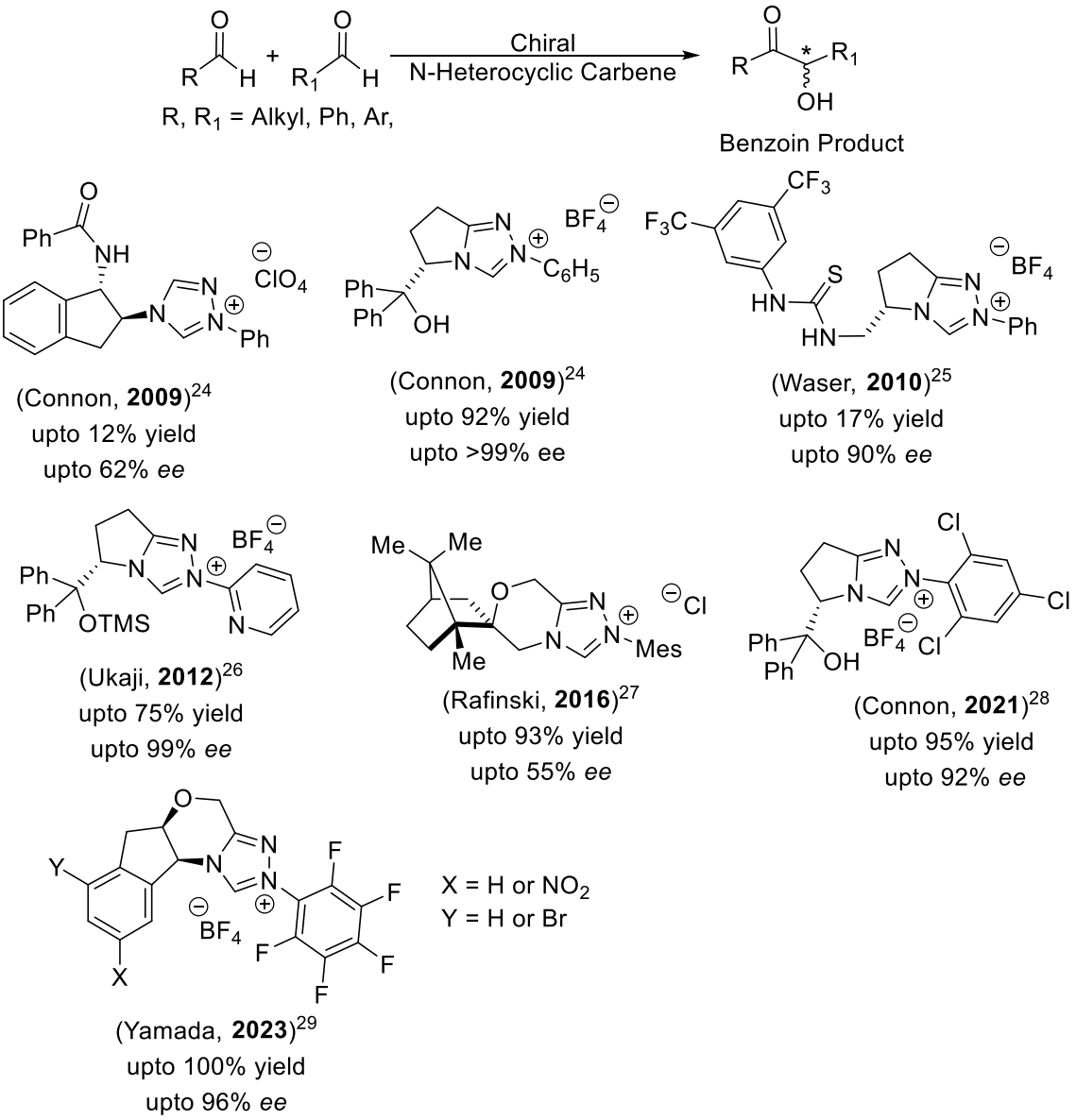
in 2009, when Connon *et. al* introduced a triazolium-based NHC catalyst that delivered excellent reactivity along with high levels of enantioselectivity, setting a new benchmark for asymmetric benzoin catalysis (Scheme 2).[24] Owing to its success, this reaction has become a benchmark for evaluating newly developed NHC catalytic systems, with numerous research groups continuing to explore novel scaffold designs through its application (Scheme 2).[25-28] In 2023, Yamada *et. al* demonstrated that remote electronic modification of N-heterocyclic carbenes (NHCs) effectively enhanced the catalytic asymmetric benzoin reaction.[29] The introduction of remote electron-withdrawing substituents on the NHC improved the enantioselectivity of the reaction, albeit with a reduction in reaction rate. These substituents not only helped prevent racemization of highly enolizable substrates but also contributed to the overall reaction efficiency.



Scheme 2. N-Heterocyclic carbene in enantioselective benzoin condensation.

The ability of N-heterocyclic carbenes (NHCs) to generate acyl anion equivalents has played a pivotal role in expanding the landscape of organocatalytic transformations. These nucleophilic intermediates readily react with a broad range of electrophiles—including aldehydes, ketones, imines, and various Michael acceptors—

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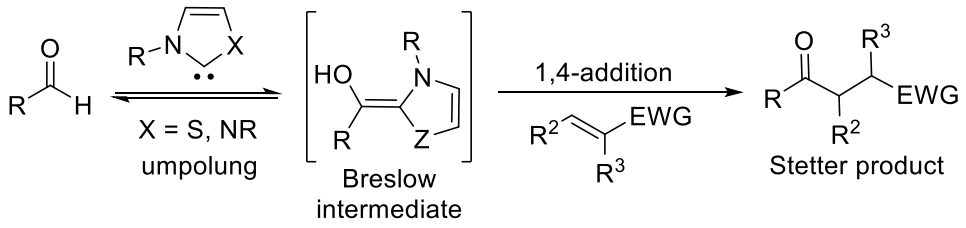
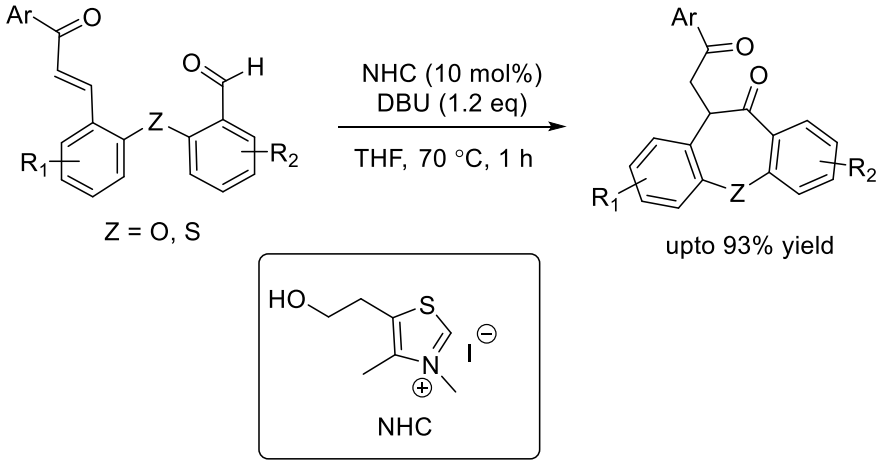
facilitating the construction of complex molecular frameworks.[30-31] Among the most notable examples the Stetter reaction which represent classical 1,4-addition processes proceeding through NHC-stabilized acyl anion species (Scheme 2). Advances in this field have broadened the scope of compatible Michael acceptors to include α,β-unsaturated ketones, esters, nitriles, nitrates, sulfones and phosphates, enabling efficient conjugate addition (hydroacylation) reactions. These methodologies offer streamlined access to a variety of 1,4-bifunctional compounds—such as 1,4-diketones, 4-ketonitriles, and 4-ketoesters—which are often difficult to synthesize using traditional approaches, thereby highlighting the synthetic utility and versatility of NHC catalysis.



Scheme 3. Stetter reactions involving NHC-mediated umpolung of aldehydes.

The first intramolecular enantioselective Stetter reaction was reported by Enders and co-workers in 1995, nearly two decades after Stetter's original discovery. In this pioneering study, a chiral triazolium salt was employed to synthesize a benzopyran derivative, affording the desired chromanone product in up to 73% yield and 60% enantiomeric excess (*ee*).[32] Building on this foundation, the Rovis group made substantial contributions to the development of asymmetric Stetter reactions by designing novel chiral triazolium pre-catalysts. Their studies demonstrated that fused-ring chiral triazolium salts significantly improved both yield and enantioselectivity in intramolecular variants of the reaction. A major milestone was reached in 2008, when Enders and Rovis independently reported the first successful NHC-catalyzed enantioselective intermolecular Stetter reaction, marking a significant advancement in the field of asymmetric organocatalysis.[33-34] Recently, Suresh *et. al* reported an NHC-catalyzed transformation that enables the synthesis of dibenzo-fused seven-membered heterocyclic compounds through an intramolecular Stetter reaction conducted under ambient conditions. This method efficiently affords a variety of dibenzo[b,f]oxepine and dibenzo[b,f]thiepine derivatives in very good to excellent yields (Scheme 4).[35]



Scheme 4. Intramolecular stetter reactions involving NHC-mediated umpolung of aldehydes.

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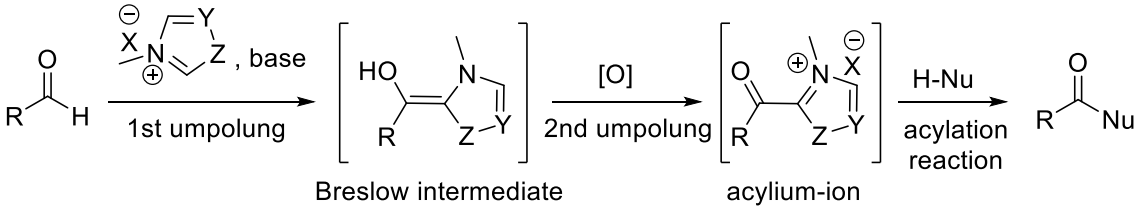
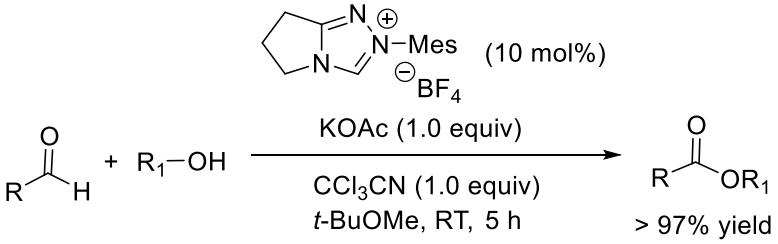
2.2. NHC-Promoted generation of acylium ions

N-Heterocyclic carbenes (NHCs) are highly versatile organocatalysts capable of generating a variety of reactive intermediates either with different substrates or with the same substrate under varying reaction conditions. Due to their nucleophilic nature, NHCs readily react with aldehydes to form electron-rich Breslow intermediates, which can be subsequently oxidized to acyl azolium salts under oxidative conditions (Scheme 5). This transformation represents a formal double umpolung of the aldehyde functionality—first through the formation of the Breslow intermediate followed by its oxidation. Oxidation can proceed either via internal redox processes involving functionalized aldehydes (such as α,β-unsaturated or α-halo aldehydes) or through the use of external oxidants with simple aldehydes employing either inorganic or organic oxidizing agents.[36-37] The resulting redox-active acyl donors are capable of transferring the acyl group to suitable nucleophiles. As such, oxidative NHC catalysis offers a powerful platform for the development of mild and efficient acylation reactions. Notably, this approach allows for the creation of a chiral environment around the activated carbonyl group when chiral NHC catalysts are employed, thereby enabling enantioselective transformations. Among these, the NHC-catalyzed oxidative kinetic resolution of alcohols via asymmetric acylation has emerged as a well-studied and impactful reaction.[38-39] Significant contributions in this area have been made by the research groups of Studer, Zhao, Yamada, Wang, Chi and others.[40]



Scheme 5. Oxidative transformation of the Breslow intermediate and its synthetic applications.

An unconventional NHC-catalyzed intermolecular O-acylation reaction has been developed using CCl_3CN as a key reagent (Scheme 6).[41] This method enables the synthesis of a broad range of esters from various aldehydes—including aliphatic, aromatic, heteroaromatic, enals, and ynals—as well as from primary and secondary alcohols. It is also compatible with naturally derived substrates such as steroids, terpenes, and carbohydrates, in addition to phenols, hemiacetals, hemiaminals, and hydroxylamines. The proposed mechanism involves the formation of a reactive acyl azolium intermediate via hydride transfer from the initial NHC–aldehyde adduct to CCl_3CN. The reduced form of CCl_3CN is subsequently isolated from the reaction mixture after base-promoted elimination of in situ generated 2,2,2-trichloroethan-1-imine.



Scheme 6. Oxidative esterification of aldehydes promoted by CCl_3CN.

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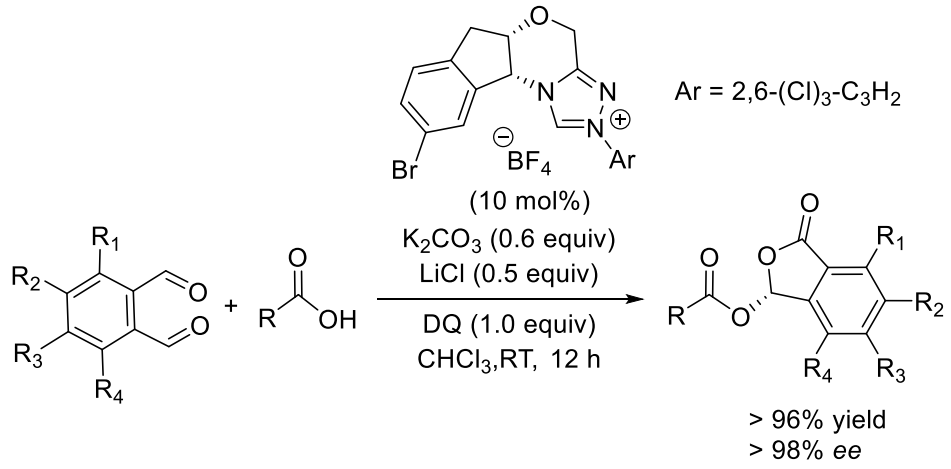
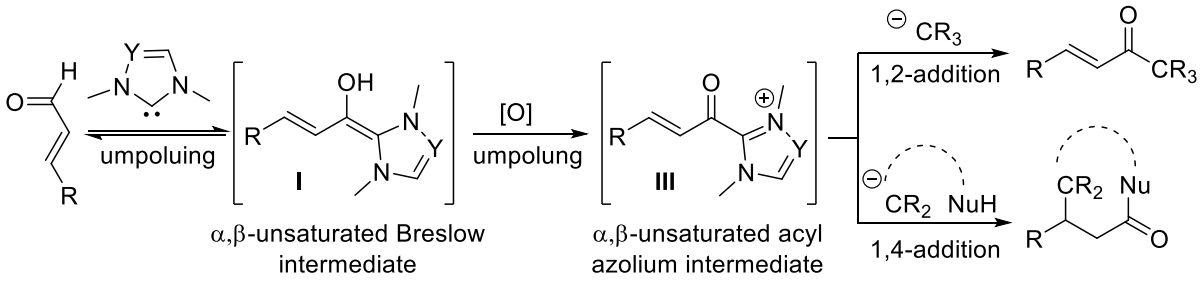
Chiral phthalidyl esters have been synthesized from *ortho*-phthalaldehydes and carboxylic acids via NHC-catalyzed intramolecular acetalization reactions, carried out in the presence of DQ (3,3′,5,5′-tetra-*tert*-butyldiphenoquinone) (Scheme 7).[42]



Scheme 7. NHC-catalyzed oxidative asymmetric acetalization of carboxylic acids.

2.3. NHC catalyzed α,β-unsaturated acylium-ion formation

Studer and Bode independently reported that the conjugated Breslow intermediate (I) can undergo further umpolung to form the α,β-unsaturated acyl azolium intermediate (III) under oxidative conditions (Scheme 8).[43-44] This intermediate (III) is a versatile species for carbon–carbon bond formation, enabling both 1,2- and 1,4-addition reactions with soft carbon nucleophiles. In the case of 1,4-addition, the nucleophile must possess an additional nucleophilic site to facilitate a subsequent 1,2-addition to the acyl azolium. This step is crucial for the release of the NHC catalyst and the completion of the catalytic cycle. The primary application of in situ generated α,β-unsaturated acyl azolium intermediates lies in annulation reactions, enabling the synthesis of cyclic compounds from various bis-nucleophiles.



Scheme 8. Oxidation of conjugated Breslow intermediate and its utility.

Lactone derivatives belonging to the pyran series were synthesized via NHC-catalyzed oxidative reactions between α,β-unsaturated aldehydes and substrates such as benzofuran-3-ones, benzyl ketones, and pyrrolin-4-ones. These transformations proceeded through a Michael addition followed by lactonization. Specifically, benzofuran-3-ones were coupled with (hetero)aryl- and alkyl-substituted enals to afford benzofuran-fused pyrones. The reaction, conducted using a triazolium pre-catalyst based on N-mesitylpyrrolidine (10 mol%),

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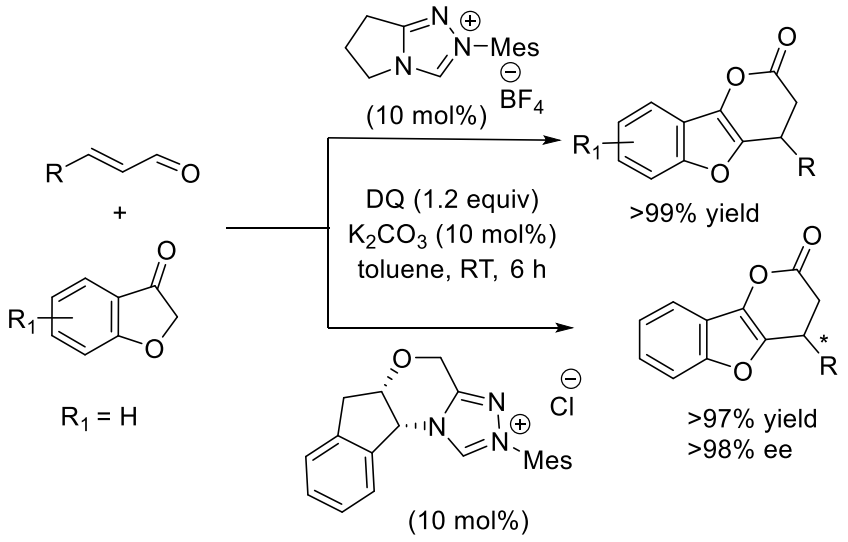
K_2CO_3 (10 mol%), and DQ (1.2 equivalents), delivered the desired products in yields ranging from 47% to 99%. Excellent enantioselectivity (96–98% ee) was achieved by employing a chiral NHC catalyst (Scheme 9).[45]



Scheme 9. NHC-catalyzed oxidative reaction of enals with benzofuran-3-ones.

3. NHC as Lewis Base Catalyst

N-heterocyclic carbenes (NHCs) have emerged as increasingly versatile catalysts in organic synthesis. It is worthwhile to mention that NHC carbenes have been extensively used as Lewis base catalyst in the C-C coupling reaction.[46-47] Although extensively applied as nucleophilic catalysts in transformations involving aldehydes, their role in nucleophilic addition reactions with boron- and silicon-based reagents has also gained significant attention. These reactions exploit the strong σ-donating nature of NHCs, enabling them to function effectively as Lewis bases (LBs). Weakly Lewis acidic boron and silicon compounds, which are generally inert on their own, can be activated through coordination with a Lewis base.[48] As shown in Figure 4, this interaction leads to the formation of a hypervalent intermediate, accompanied by electron density redistribution.[49] This process renders the central atom of the Lewis acid electron-deficient, while increasing the nucleophilicity of the peripheral substituents. The resulting activated nucleophile is then capable of transferring to an appropriate electrophilic acceptor.

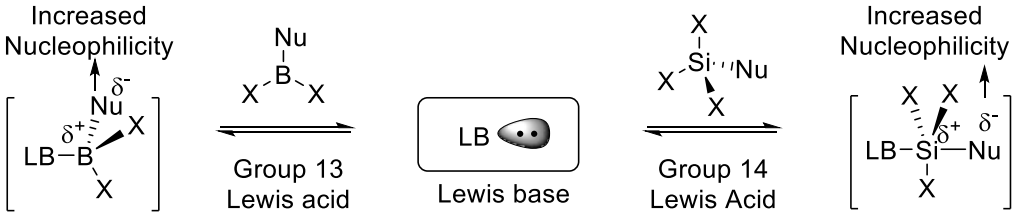


Figure 4. Redistribution of electron density through donor-acceptor interaction.

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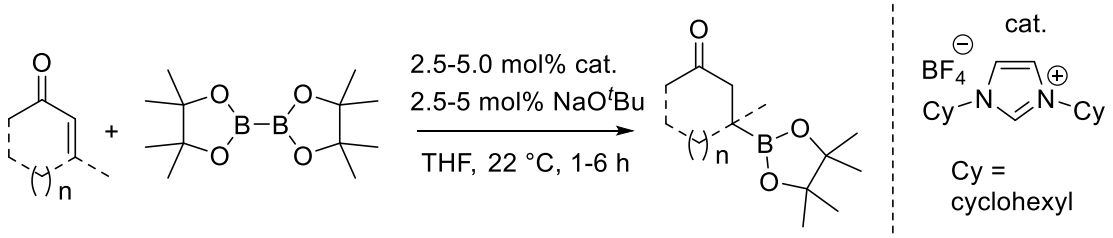
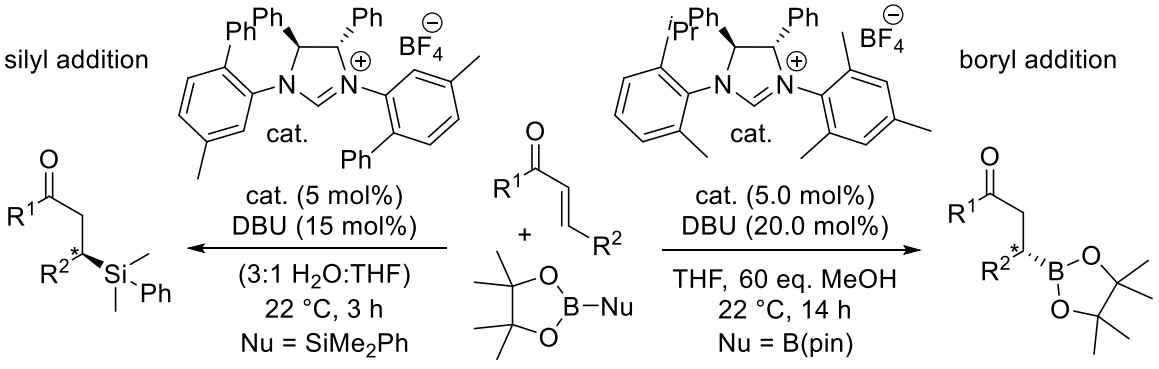
3.1. NHC-driven addition reactions using boron reagents

Hoveyda *et. al* demonstrated that imidazolium-derived carbenes can activate the B–B bond in bis(pinacolato)diboron, enabling the catalytic formation of carbon–boron bonds (Scheme 10).[50] This transformation led to the synthesis of β-boron-substituted ketones *via* conjugate addition to enones. The authors proposed that the reaction initiates with coordination of the free NHC to one of the boron atoms in bis(pinacolato)diboron, forming an activated NHC–$B_2(pin)_2$ adduct. This species then facilitates the transfer of a nucleophilic boron moiety to the β-position of the enone. Supporting this mechanism, Marder and co-workers provided structural evidence for the formation of NHC–boron adducts by characterizing the crystal structure of the resulting complex.



Scheme 10. N-heterocyclic carbene-mediated boryl conjugate addition.

The same group developed NHC-catalyzed enantioselective silyl and boryl conjugate additions to α,β-unsaturated carbonyl compounds, building upon their earlier concept (Scheme 11).[51-52] In the case of the silyl addition, the reaction proceeds via NHC-mediated activation of the boron–silicon reagent [Me_2PhSi–B(pin)], enabling selective transfer of the silyl group to the β-position of the Michael acceptor. The observed selectivity arises from the high Lewis acidity of boron, which preferentially coordinates to the NHC, thereby activating the silicon atom for transfer. Initial studies of the boryl conjugate addition showed limited enantioselective conversion. It was hypothesized that this was due to the formation of a less stable NHC–boron complex, likely resulting from steric hindrance between the bulky NHC and bis(pinacolato)diboron. The addition of methanol was found to address this issue effectively. It was proposed that methanol exchanged with one of the pinacol units of the diboron reagent, generating a more sterically accessible species capable of coordinating to the NHC and promoting the reaction efficiently.



Scheme 11. NHC-enabled enantioselective conjugate addition of silyl and boryl groups.

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3.2 N-Heterocyclic carbene-catalyzed nucleophilic additions involving silicon reagents

N-Heterocyclic carbenes (NHCs) have been shown to act either as catalysts or initiators in a variety of organic transformations involving silicon-containing compounds (Figure 5).[53] Representative examples include the sila-Stetter reaction (I) (Scheme 12); 1,2-additions such as cyanosilylation, trifluoromethylsilylation, and stannylsilylation (II-VII); the Mukaiyama aldol reaction (VIII); aziridine ring-opening reactions (IX); group-transfer polymerization of acrylate monomers using silyl ketene acetal initiators; ring-opening polymerization of cyclic siloxanes and the reduction of CO_2 to methanol using hydrosilanes (X), among others.

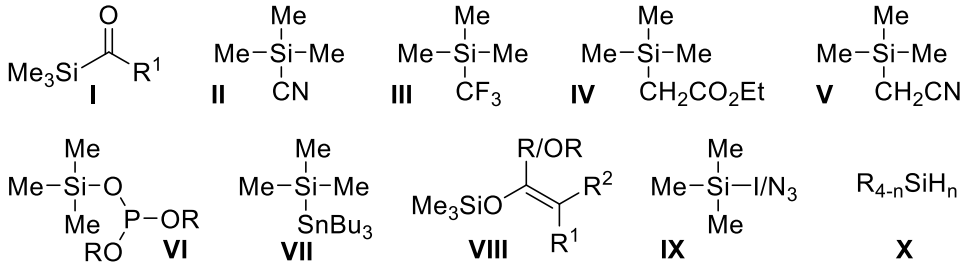
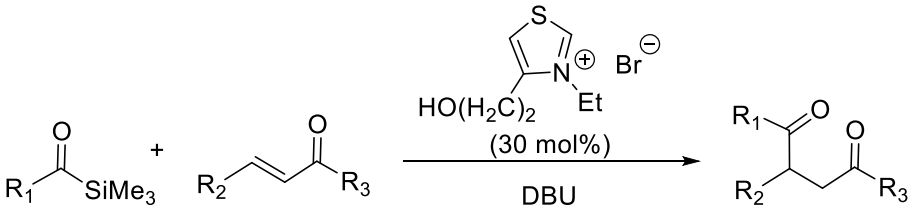


Figure 5. Organosilicon reagents in NHC-catalyzed transformations.



Scheme 12. NHC-catalyzed sila-Stetter reaction.

4. NHC as a Non-covalent Organocatalyst

N-Heterocyclic Carbene (NHC) catalyzed non-covalent interactions represent a growing area in organocatalysis, where the NHC catalyst does not form a covalent bond with the substrate but instead influences reactivity through weak interactions such as hydrogen bonding, π–π stacking, or electrostatic forces. These interactions can help stabilize transition states, organize substrates in a favourable orientation or enhance selectivity in complex reactions. This non-covalent mode expands the versatility of NHCs beyond traditional covalent catalysis, offering new pathways for asymmetric induction and fine control over reaction mechanisms in organic synthesis.[54-56]

Hedrick and Waymouth *et. al* demonstrated NHC-catalyzed transesterification of methyl benzoate using a substantial excess of alcohol (20 equivalents) to drive the reaction to completion (Scheme 13).[57] They explored the influence of NHC structure by varying the N-substituents from aryl to alkyl groups and examined the reactivity of different alcohols from primary to tertiary. A notable decline in conversion was observed when shifting from ethanol to 2-propanol with GC-MS conversions dropping from 85% to 11% using an N-mesityl-substituted NHC. In contrast, the use of a less sterically hindered and more basic N-methyl-substituted NHC

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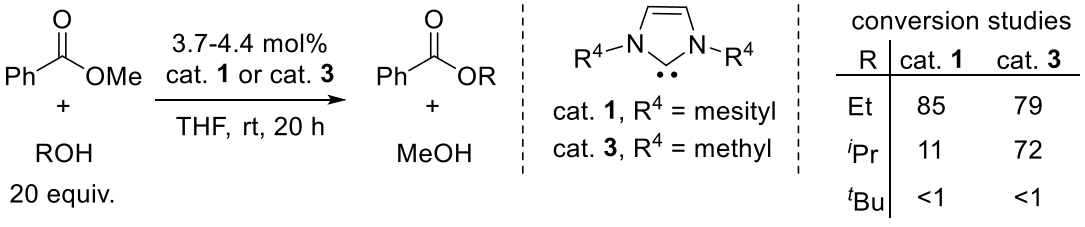
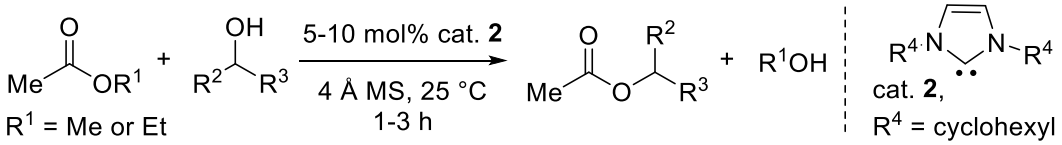
improved the formation of isopropyl esters, achieving 72% conversion. Transesterification with tertiary alcohols, however, remained unsuccessful regardless of the NHC structure.



Scheme 13. NHC catalyzed transesterification reaction.

Nolan's group further addressed the reactivity challenges associated with NHC-catalyzed acylation of secondary alcohols by employing excess methyl acetate as the acylating agent and a more nucleophilic N-cyclohexyl-substituted imidazole-based NHC catalyst (Scheme 14).[58] This approach enabled efficient acylation of a broad range of commercially available secondary alcohols—including acyclic, aliphatic cyclic, and aromatic cyclic types—with good to excellent yields. However, cyclohexanols bearing bulky substituents at the α-position relative to the hydroxy group exhibited significantly reduced reaction rates due to steric hindrance. Additionally, the acylation of a tertiary alcohol, 1-adamantanol, required a higher catalyst loading (20 mol%) and extended reaction times to afford isolable amounts of the desired product. Notably, the method also demonstrated high selectivity for primary over secondary alcohols, achieving selectivity ratios of up to 9:1.



Scheme 14. The NHC-catalyzed transesterification of branched alcohols.

Using a similar catalytic system, Nolan and coworkers further explored the transesterification of phosphorus esters.[59] By carefully optimizing reaction parameters—such as employing 2 equivalents of benzyl alcohol and controlling the reaction time—they achieved high selectivity for the mono-transesterification of dimethyl methylphosphonate, obtaining the mono-benzyl ester in 75% yield. Prolonged reaction times or higher alcohol equivalents shifted the product distribution toward the dibenzyl ester, resulting in a roughly 2:1 ratio of dibenzyl to mono-benzyl ester. In these transesterification reactions, the NHC is proposed to function primarily as a nucleophilic catalyst.

Computational studies by Hu *et. al* provided strong evidence for a non-covalent, hydrogen-bonding mode of NHC catalysis in transesterification reactions (Scheme 15).[60] Both nucleophilic and Brønsted base activation pathways were evaluated using DFT calculations. The results indicated that the most favorable mechanism involves a neutral, hydrogen-bonded complex between the carbene and alcohol. In this pathway, the NHC does not deprotonate the alcohol; rather, it facilitates a proton transfer from the incoming alcohol to the departing one through a concerted mechanism involving four-membered ring transition states (A and C) and a neutral tetrahedral intermediate (B) with no ionic intermediates formed.

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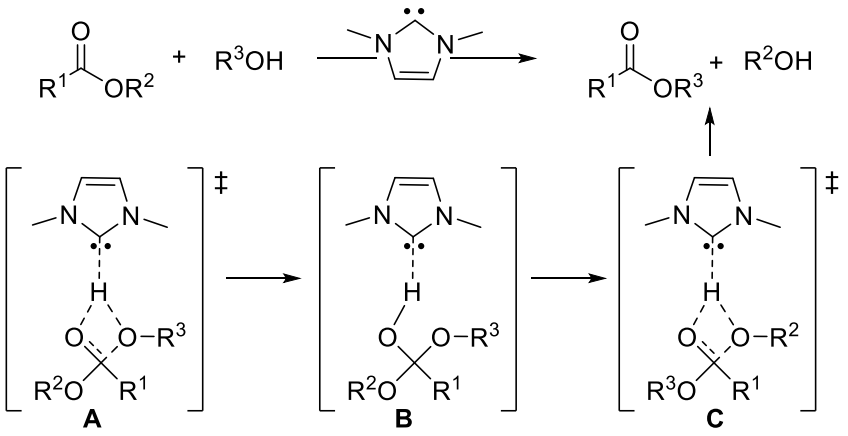
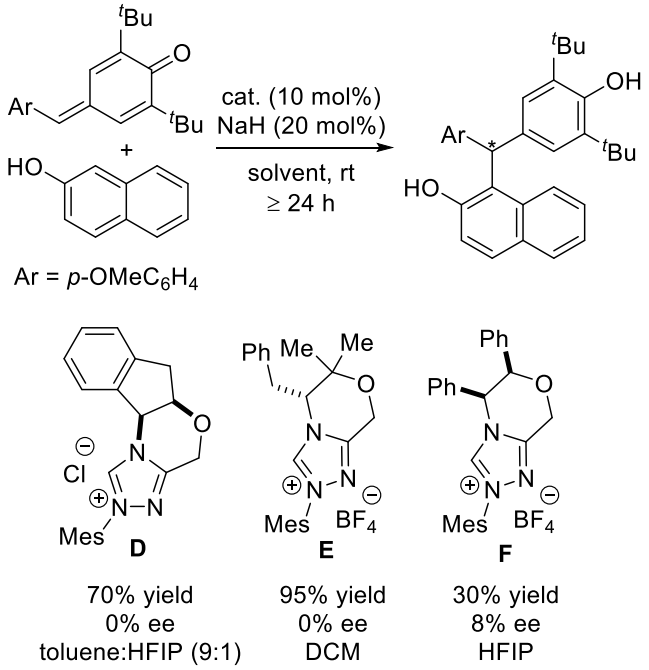


Scheme 15. Transition states and intermediates proposed by Hu for NHC-catalyzed transesterification.

Recently, Anand's group attempted to develop an enantioselective method for synthesizing unsymmetrical triarylmethane derivatives via the 1,6-conjugate addition of 2-naphthols to p-quinone methides, employing a chiral NHC as a non-covalent catalyst (Scheme 16).[61-62] A variety of reaction conditions and NHC precursors derived from chiral amino alcohols were screened for this transformation. Among them, pre-catalysts **D** and **E** delivered the desired addition products in 70% and 95% isolated yields, respectively. However, both reactions resulted in racemic mixtures when conducted at room temperature. Lowering the reaction temperature to sub-zero failed to improve enantioselectivity. A slight enhancement in enantioselectivity (8% ee) was observed when using pre-catalyst **F** in hexafluoroisopropanol (HFIP) as the solvent, although the yield dropped to 30%.



Scheme 16. NHC-catalyzed enantioselective 1,6-conjugate addition.

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5. Conclusions

N-Heterocyclic carbenes (NHCs) have firmly established themselves as a highly adaptable and influential class of organocatalysts, significantly broadening the capabilities of modern synthetic chemistry. Their exceptional nucleophilicity and ability to stabilize a range of reactive intermediates—such as acyl anion equivalents and azolium enolates—enable access to a variety of previously challenging transformations. Importantly, NHCs operate efficiently under mild, metal-free conditions, which not only enhances functional group compatibility but also aligns with principles of green chemistry. Their structural tunability—achieved through strategic modification of both the heterocyclic core and the substituents—allows for precise control over catalyst reactivity and selectivity. This versatility has led to their successful application in diverse reaction types, including umpolung additions, annulation reactions and asymmetric syntheses. As research in this field advances, innovations in catalyst design and reaction development continue to unlock new synthetic pathways. Given their proven effectiveness, environmental benefits, and adaptability, NHCs are expected to remain central to both academic research and industrial applications, driving the next generation of sustainable synthetic strategies.

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