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N-Heterocyclic carbene/palladium synergistic catalysis in organic synthesis†

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The cooperation of two distinct catalytic cycles to activate different reactive centers leading to a chemical transformation has been classified as synergistic catalysis. The synergistic combination of NHC with palladium catalysis has emerged as a powerful strategy in the last few years. Merging the ability of NHCs to inverse the polarity of a functional group with the unique reactivity of palladium enables transformations that cannot be accomplished by either of these catalysts alone. Despite the associated challenges, such as quenching of catalysts, reactivity mismatch *etc.*, significant development has been achieved in the field of NHC/Pd synergistic catalysis. The recent incorporation of photoredox catalysis with NHC/Pd synergistic catalysis has further advanced this area. This review highlights the developments made in the area of NHC/Pd synergistic catalysis.

1. Introduction

Development of novel catalytic processes for the synthesis of useful organic molecules is the leading area of research in chemistry. One of the most recent developments in this area is the use of several catalysts in a single reaction to facilitate desired chemical changes.[1] Among these approaches, synergistic catalysis (cooperative catalysis), the process by which at least two distinct catalysts collaborate through their independent catalytic cycles, resulting in activated complexes that then participate in a chemical reaction, has gained much attention.[2] Along with offering several advantages such as enabling challenging transformations, and enhancements in yields, reactivity and stereoselectivity, cooperative catalysis has also faced some challenges like reactivity mismatch, quenching of catalysts, *etc.* Thus, a strategic blend of planning and practical methods is essential to effectively combine catalysts and achieve desired transformations.

Organocatalysts have been extensively studied in the past few decades because of their potent catalytic activity.[3] N-Heterocyclic carbenes (NHCs), in particular, are highly effective organocatalysts, due to their ability to reverse the

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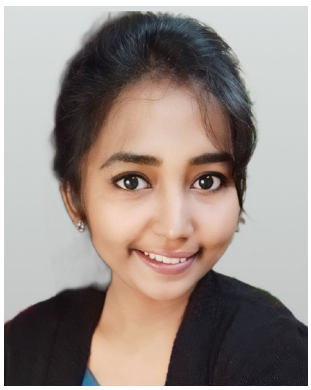
† Celebrating the 100th birthday of Prof. Sukh Dev.



Chhanda Debnath

Chhanda Debnath was born in West Bengal, India. She completed her undergraduate studies at Kanchrapara College, University of Kalyani, and earned an M.Sc. degree in Chemistry from the University of Kalyani, India. She is currently pursuing her Ph.D at the Indian Institute of Science Education and Research, Berhampur, India under the supervision of Dr Shikha Gandhi. She has been a recipient of the Prime Minister Research Fellowship since 2022. Her current research interests include NHC as well as palladium catalysis for the development of novel organic transformations.

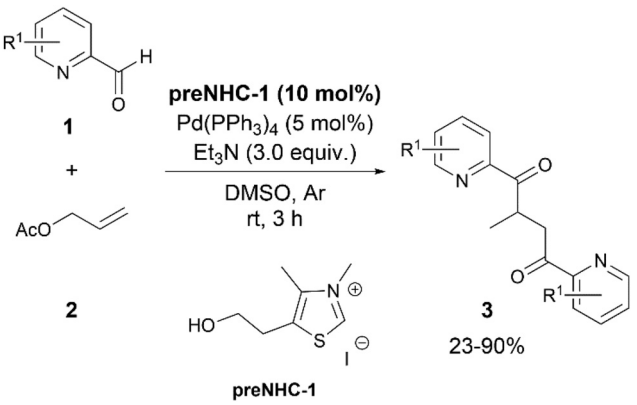
Saswat Ranjan Bhoi

Saswat Ranjan Bhoi was born in Odisha, India. He completed his BSMS dual degree in 2023 with a major in Chemical Sciences from the Indian Institute of Science Education and Research Berhampur, India. He completed his MS thesis project under the guidance of Dr Shikha Gandhi. His work focuses on palladium catalysis and NHC/palladium synergistic catalysis.

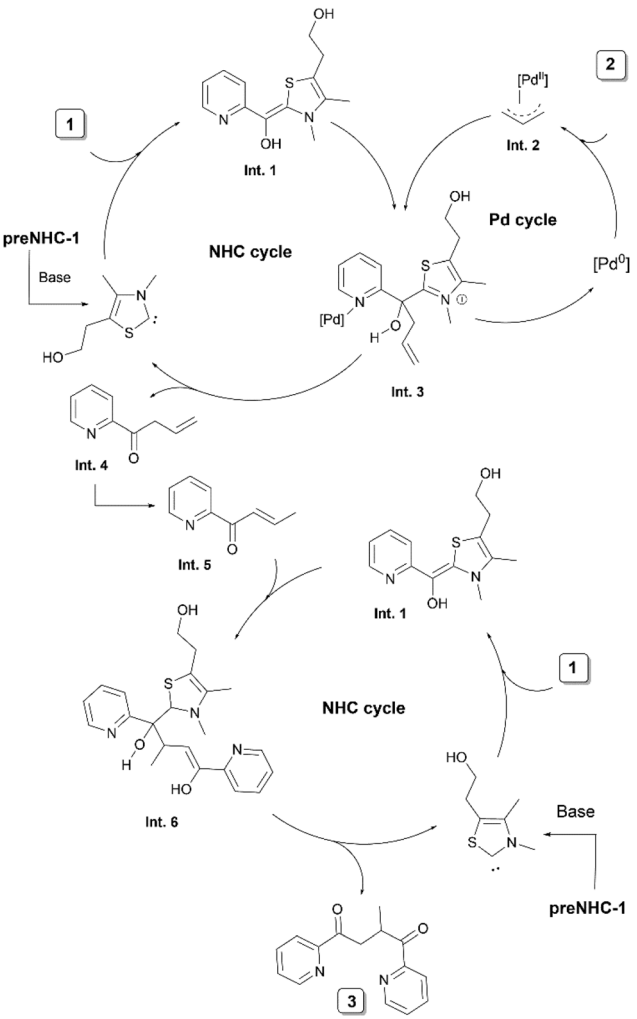
polarity of a functional group (umpolung) and their wide applicability in asymmetric synthesis.[4] In order to enhance the utilization of NHC catalysis, multiple research teams have overcome the constraints of NHC single catalysis through an array of cooperative systems that employ an NHC catalyst with another catalyst.[5] Over the years, the merging of NHC organocatalysis with transition-metal catalysis in a cooperative manner has gained popularity.[1c,5] Due to the coordinating ability of NHCs with transition metals, which might render both the catalysts inactive, this approach offered a significant challenge. Nonetheless, several groups have successfully combined NHC catalysis synergistically with different transition metals like Pd, Ru, Cu, Ni, Ir, Co, and Au.[6–11] Among these, Pd has emerged as the most employed transition metal in synergistic catalysis with NHCs. This combination has been successfully utilized for the synthesis of diverse molecules. To date, no comprehensive review focusing exclusively on NHC/palladium synergistic catalysis has been published. This review covers the progress made in this area. The review is structured into two segments. The first segment covers the applications of NHC/palladium synergistic catalysis using aldehydes as substrates and the second one covers the developments using α,β-unsaturated carbonyl systems. When an NHC reacts with an aldehyde, it leads to the formation of a Breslow intermediate,[12] whereas, in the case of α,β-unsaturated carbonyls, an extended Breslow intermediate[13] is formed.

2. Aldehydes as substrates

In 2014, Liu and his group reported an application of NHC/palladium synergistic catalysis for the synthesis of 1,4-diones employing pyridine-2-carbaldehydes **1** and allyl acetate **2** as substrates (Scheme 1).[14] In their initial attempts utilizing Pd $(PPh_3)_4$, **preNHC-1**, and triethylamine, the product **3** was isolated in 53% yield as a 2 : 1 coupling product. The addition of **1** (as a 1 M DMSO solution) using a syringe pump within 2 hours increased the yield of **3** to 90%. Pyridine-3-carbalde-



Scheme 1 NHC/Pd synergistically catalysed coupling of pyridine-2-aldehydes and allylic acetate.



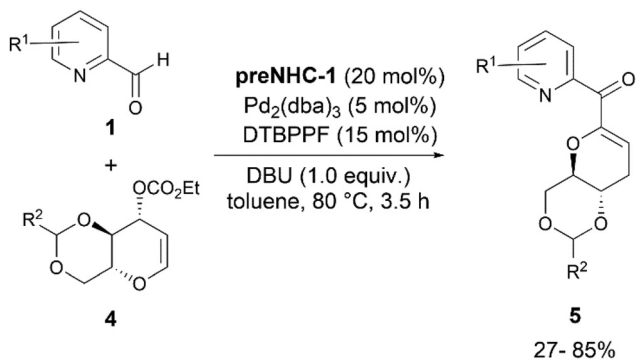
Scheme 2 Proposed mechanism of NHC/Pd synergistically catalysed coupling of pyridine-2-carbaldehydes and allylic acetate.

Shikha Gandhi

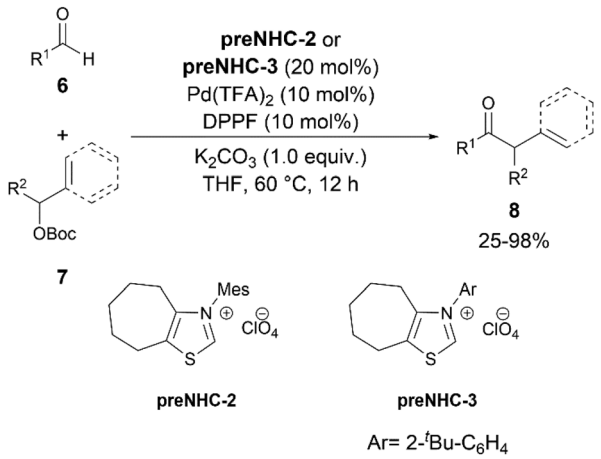
Shikha Gandhi was born in Punjab, India. She completed her Ph.D degree in 2009 under the supervision of Prof. Vinod K. Singh at Indian Institute of Technology, Kanpur. She subsequently worked as a post-doctoral fellow at the Max Planck Institut für Kohlenforschung, Mülheim, Germany with Prof. Benjamin List. She is a recipient of the Alexander von Humboldt post-doctoral fellowship. Currently she is an Assistant Professor of Chemistry at the Indian Institute of Science Education and Research, Berhampur, Odisha. She was awarded the Thieme Chemistry Journal Award in 2019. Her research interests are focused on asymmetric catalysis and the development of new methodologies in organic synthesis.

hydes and pyridine-4-carbaldehydes did not form the desired product under the same reaction conditions, indicating an important role of the *ortho*-N in the reaction. The authors observed that replacement of **1** by benzaldehyde led to the formation of benzoin as the sole product under the same reaction conditions.

The authors proposed a mechanism involving a synergistic action of the NHC and palladium catalysts (Scheme 2). The initial addition of the NHC to pyridine-2-carbaldehydes **1** forms a nucleophilic Breslow intermediate **Int. 1**. In parallel, a π-allyl Pd complex **Int. 2** is generated from **2**. The co-ordination of the N-atom of the pyridine ring with the palladium of the π-allyl complex facilitates the convergence of the intermediates. Subsequent nucleophilic addition of the Breslow intermediate to the π-allyl Pd complex yields the intermediate **Int. 3**. Catalyst removal leads to a β,γ-unsaturated ketone **Int. 4**, which upon subsequent proton transfer in the basic medium forms an α,β-unsaturated ketone **Int. 5**. This is followed by the Michael addition of **Int. 5** with another Breslow intermediate **Int. 1**, ultimately forming the compound **3** *via* **Int. 6**.

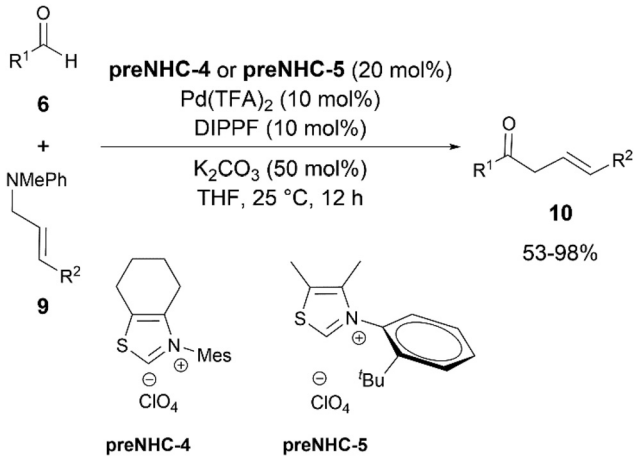


Scheme 3 *C*-Glycosylation *via* NHC/Pd synergistic catalysis.

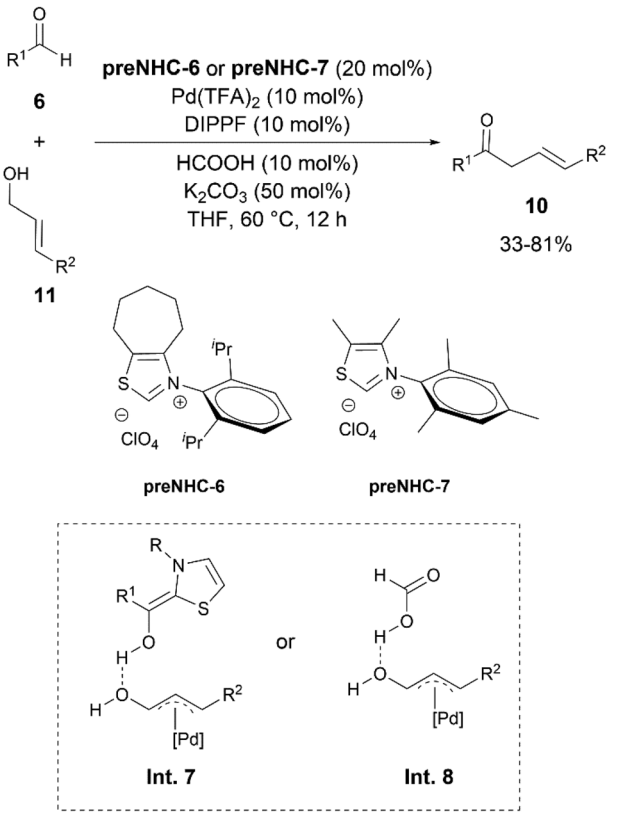


Scheme 4 NHC/Pd synergistically catalysed C(sp^2)–H benzylation or allylation of general aldehydes.

The same group extended the applications of NHC/Pd synergistic catalysis to couple glycals **4** with **1** (Scheme 3).[15] A preliminary study with $Pd(PPh_3)_4$, DPPB, **preNHC-1**, and triethylamine in DCM at 50 °C gave the desired *C*-glycoside product **5** in 20% yield along with a 22% yield of the *O*-glycoside, formed by the attack of ethanol, generated during decarboxylation of the electrophile. A further screening of Pd



Scheme 5 Coupling of aliphatic aldehydes and allylic amines by NHC/Pd synergistic catalysis.

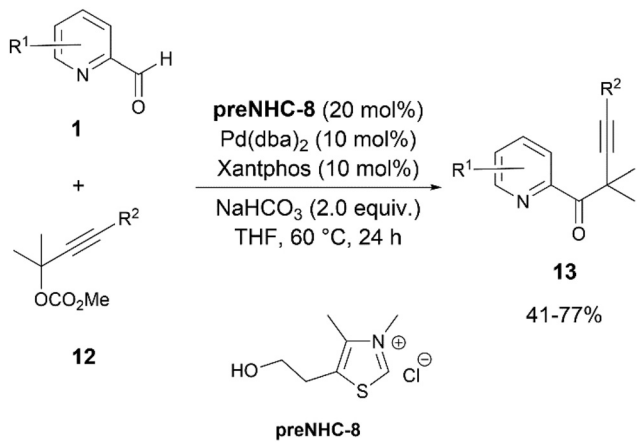


Scheme 6 Synthesis of β,γ-unsaturated ketones by NHC/Pd synergistic catalysis.

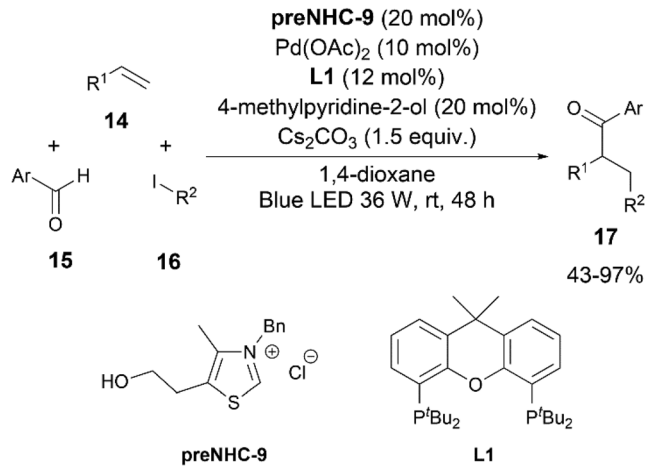
catalysts, ligands, and bases improved the yield of the desired product to 85%. The use of a Pd(II) catalyst as the palladium source did not give the desired product.

The first development of a C(sp^2)–H benzylation and allylation of general aldehydes was achieved by Ohmiya and team in 2018 (Scheme 4).[16] They reported an NHC/palladium catalysed synergistic coupling of aldehydes **6** and benzyl *tert*-butyl carbonates or allylic carbonates **7**. This development provided a new synthetic pathway to α-arylated ketones and β,γ-unsaturated ketones **8**. A combination of thiazolium **preNHCs 2** or **3** and Pd $(TFA)_2$-DPPF catalysts was found to be optimal for the reaction. Based on the observation that DPPF was found to be the most suitable ligand for the reaction, the authors implied that the bulkiness of the bidentate ligand might prevent the unwanted coordination of the NHC to the Pd.

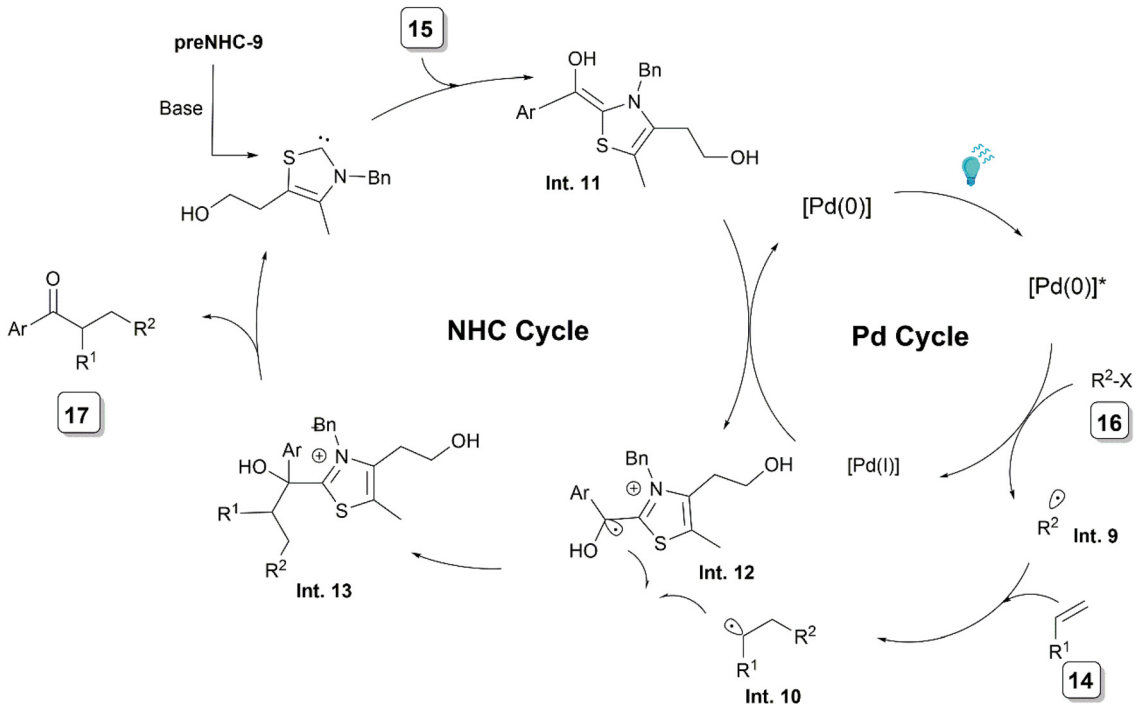
The same group, in the subsequent year, reported a synergistic NHC/palladium catalytic system for the acylation of aliphatic aldehydes **6** with allylic amines **9** *via* C–N bond cleavage (Scheme 5).[17] $Pd(TFA)_2$ was used as the Pd catalyst and DIPPF in place of DPPF was found to be the optimal ligand to synthesise β,γ-unsaturated ketones **10**. Thiazolium NHCs were



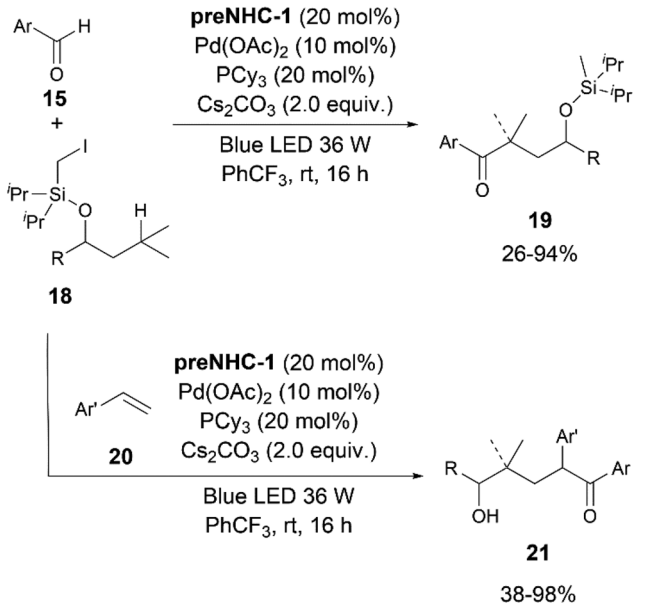
Scheme 7 Coupling of pyridine-2-carbaldehydes and propargylic carbonates *via* NHC/Pd synergistic catalysis.



Scheme 9 Photoredox NHC/Pd synergistically catalysed alkylacylation of alkenes.



Scheme 8 Proposed mechanism of photoredox NHC/Pd synergistically catalysed alkylacylation of alkenes.

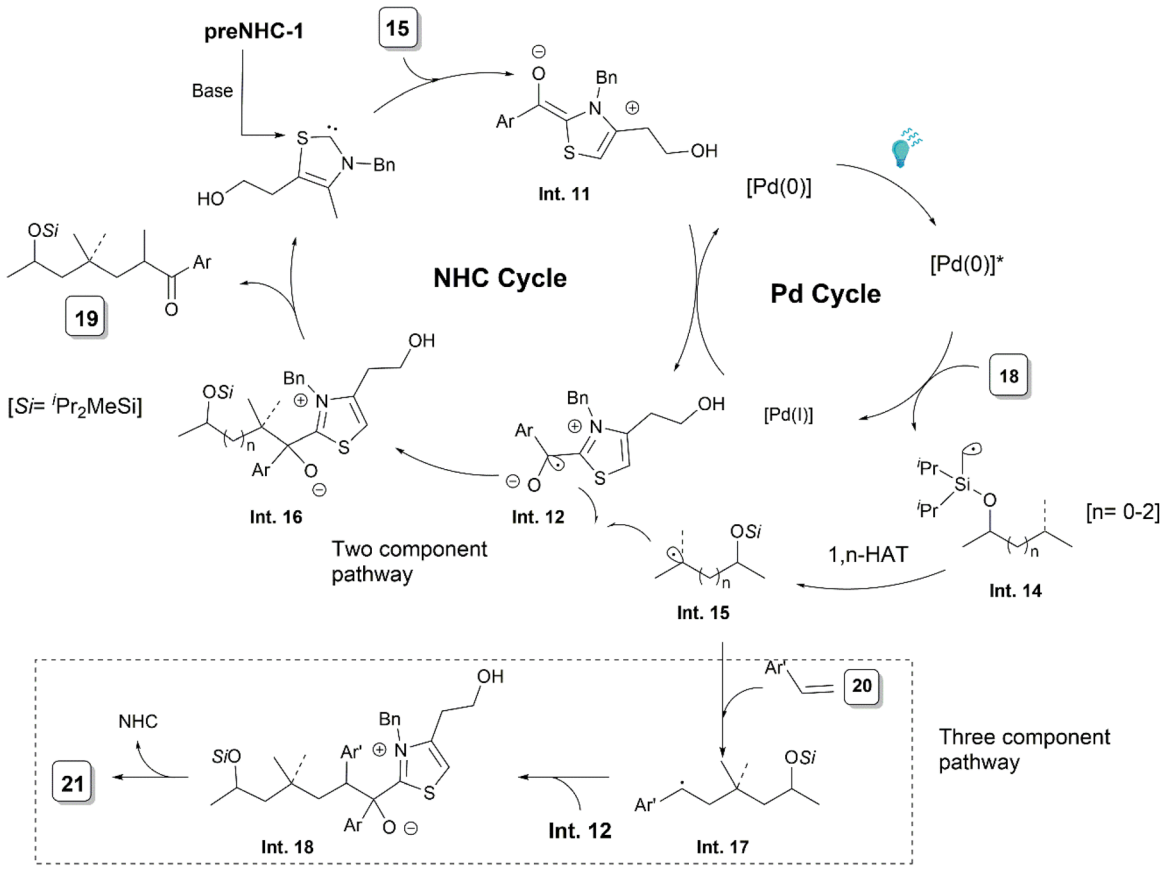


Scheme 10 Photoredox NHC/Pd synergistically catalysed alkyl C(sp^3)–H functionalization.

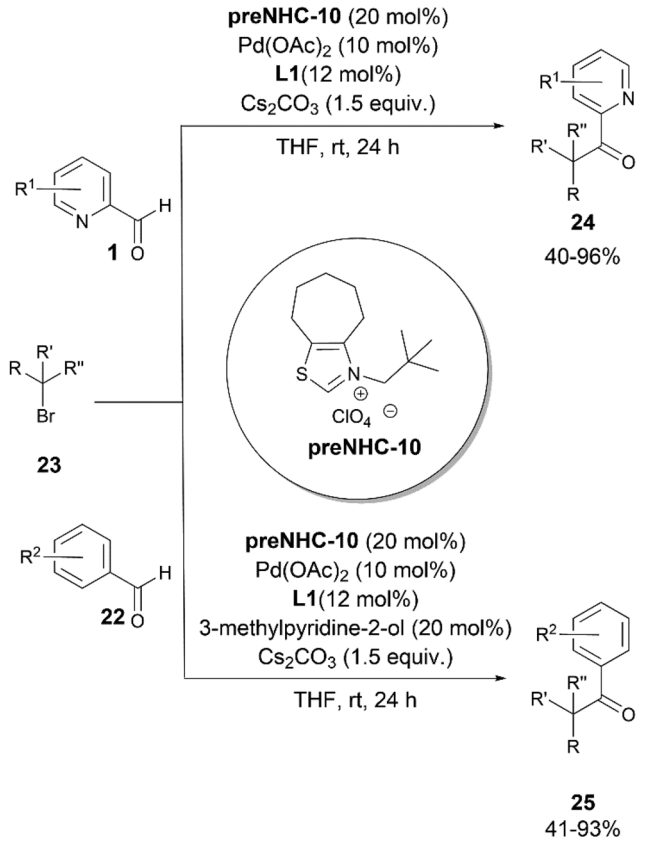
found to be compatible catalysts for this transformation whereas imidazolium and triazolium NHCs were not suitable.

A dehydrative allylation between widely available aldehydes **6** and allylic alcohols **11** was also developed by the group of Ohmiya in 2019 to afford β,γ-unsaturated ketones **10** (Scheme 6).[18] The addition of a catalytic amount of formic acid was found to be beneficial for the reaction. Furan- and pyridine-based allylic alcohols also reacted to produce the corresponding ketones **10**. Aromatic aldehydes did not react under the reaction conditions. However, the authors did not provide an explanation for this. Based on the DFT calculations, a reaction pathway involving intermediacy of intermediates **Int. 7** or **8**, formed *via* the assistance of the Breslow intermediate (as a Brønsted acid) or formic acid in the oxidative addition step, was proposed.

A further advancement in the field of NHC/palladium synergistic catalysis was brought by Wang and co-workers through the development of the reaction of the Breslow intermediate of **1** with the π-allyl complexes derived from propargylic carbonates **12** (Scheme 7).[19] The thiazolium **preNHC-8** and $Pd(dba)_2$ appeared to be the most effective catalysts. A bidentate ligand, Xantphos, was found to be the most suitable, while the monodentate ligand triphenylphosphine failed to give the desired product **13**. This reaction could be applied to



Scheme 11 Proposed mechanism of photoredox NHC/Pd synergistically catalysed alkyl C(sp^3)–H functionalisation.



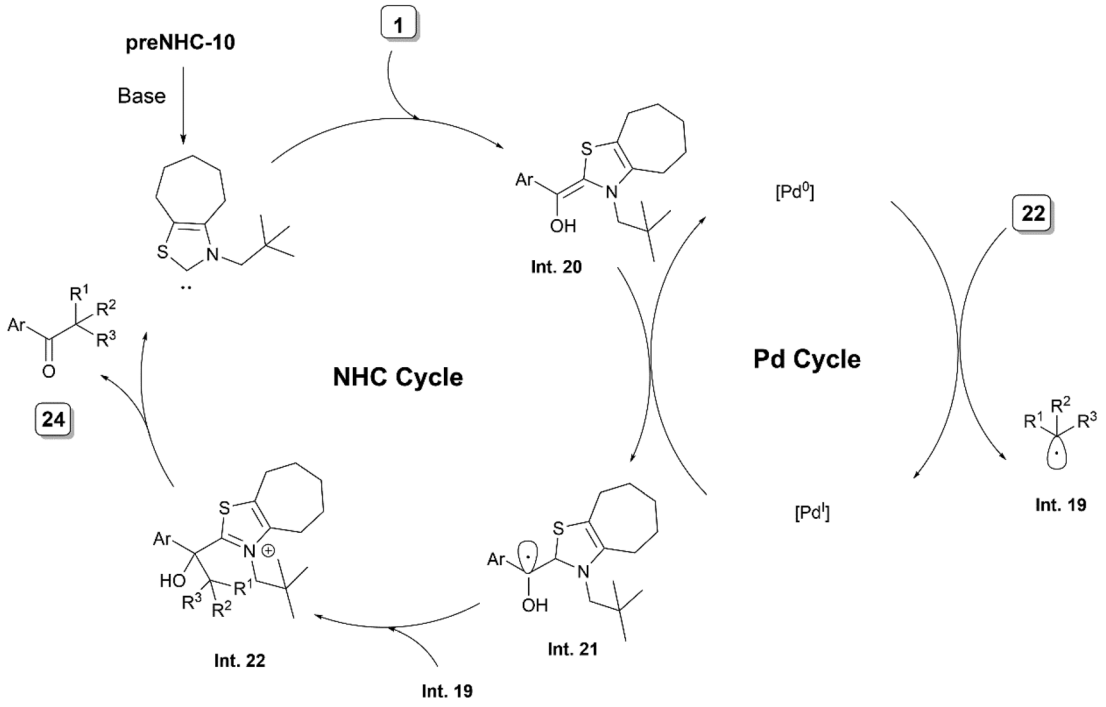
Scheme 12 NHC/Pd synergistic catalysis for coupling of aromatic aldehydes and alkyl bromides.

propargylic carbonates with naphthyl, thienyl, or *n*-butyl groups along with differently substituted aryl groups.

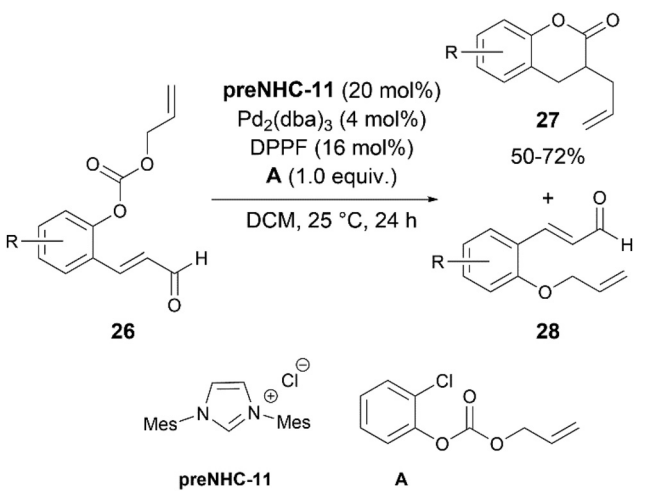
In 2022, Ye and his team opened a new vista in the field of NHC/palladium cooperative catalysis through the incorporation of photoredox catalysis (Scheme 8).[20] They reported a photoredox[21] cooperative NHC/Pd-catalyzed alkylacylation of simple alkenes **14** with aldehydes **15** and unactivated alkyl halides **16**. The reaction was efficiently catalysed by using catalytic amounts of $Pd(OAc)_2$, a bidentate phosphine, and **preNHC-9** along with a base and 4-methylpyridine-2-ol as an additive under blue LED irradiation. Although the clear role of the additive was not elucidated, it could be acting as a competitive ligand. Based on UV-visible absorption spectroscopy studies of a combination of substrates and catalysts, a palladium species was proposed to be the photocatalyst for the reaction.

The plausible catalytic cycle involved the generation of an alkyl radical species **Int. 9** and a Pd(I) species from the photoexcited Pd(0) complex and an alkyl halide (Scheme 9). The addition of **Int. 9** to the alkene **14** generates the alkyl radical **Int. 10**. Concurrently, Breslow intermediate **Int. 11**, formed from the NHC and aldehyde **15**, undergoes SET with Pd(I), generating ketyl radical **Int. 12** and Pd(0). The coupling of radicals **Int. 10** and **Int. 12** leads to **Int. 13**, which releases the product **17** along with the regeneration of the NHC.

In the subsequent year, the Ye group published another report on photoredox cooperative NHC/Pd-catalyzed ketone synthesis *via* activation of $C(sp^3)$–H bonds (Scheme 10).[22] A variety of aromatic aldehydes **15** could be coupled to different iodomethylsilyl ethers **18**. The reaction proceeded *via* a 1,*n*-HAT from the $C(sp^3)$–H by the initially generated silyl methyl radicals under photoredox conditions. The methodology was



Scheme 13 Proposed mechanism of NHC/Pd synergistic catalysis for coupling of aliphatic aldehydes with alkyl bromides.



Scheme 14 Synthesis of 3-allyl dihydrocoumarins by NHC/Pd synergistic catalysis.

also extended to a three-component reaction by the addition of styrenes. ε-Hydroxylketones could be synthesized in good yields after a desilylation step.

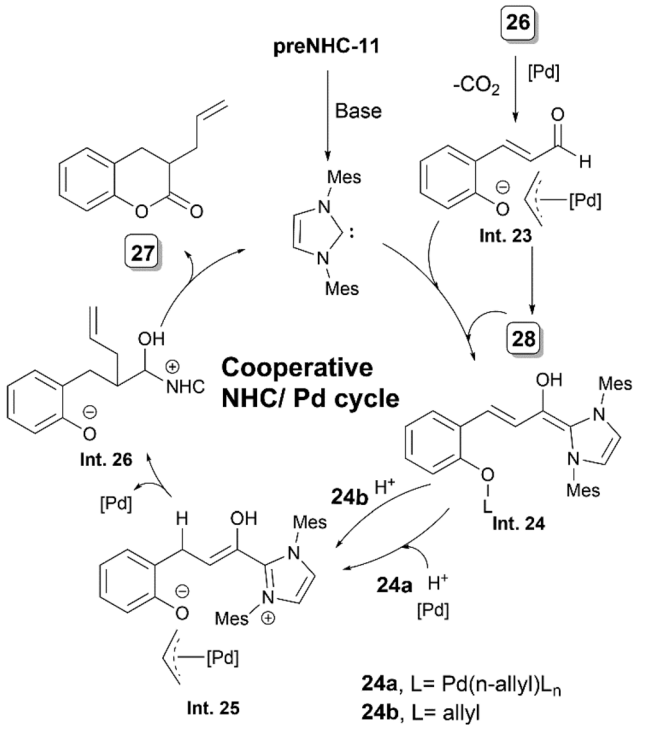
A probable catalytic cycle was proposed by the authors (Scheme 11). The Pd(0) species upon excitation with the blue light, after a SET to iodomethylsilyl ether **18**, produces a Pd(I) complex and radical **Int. 14**. A subsequent intramolecular 1,*n*-hydrogen atom transfer (HAT) leads to radical **Int. 15**. A single electron oxidation of the Breslow intermediate **Int. 11**, generated from the NHC and aldehyde, by Pd(I), leads to the radical species **Int. 12**. A subsequent combination of the radicals **Int. 12** and **Int. 15** forms **Int. 16**, which then releases the product and eliminates the NHC. In the presence of styrene, the radical **Int. 15** attacks the styrene to form the benzylic radical **Int. 17**, which couples with the ketyl radical **Int. 12** to give the product **21**.

Recently, the same group reported the direct C–H alkylation of aldehydes **1** and **22** with alkyl bromides **23** using an NHC/Pd synergistic system (Scheme 12).[23] The method provided a direct access to ketones **24** and **25**. The reactions with aldehydes **22** required the addition of 3-methyl-pyridin-2-ol as an additive to provide the desired ketones. The feasibility of the reaction at rt has been ascribed to the coordination of the pyridine nitrogen to Pd(0), facilitating the SET from the Pd(0) complex to the alkyl bromide. Secondary, tertiary and benzylic alkyl bromides could be employed as coupling partners under the reaction conditions. The proposed reaction mechanism proceeding *via* the coupling of alkyl radical **Int. 19** and ketyl radical **Int. 21**, generated from Breslow **Int. 20**, was supported by the mechanistic studies performed by the authors (Scheme 13).

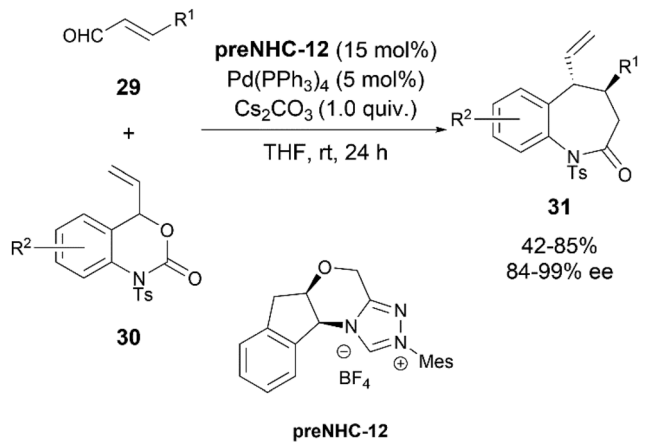
3. For α,β-unsaturated carbonyls

Scheidt's group applied NHC–Pd synergistic catalysis for the synthesis of 3-allyl dihydrocoumarin derivatives **27** *via* the allylation and acylation of *O*-alloc α,β-unsaturated aldehydes **26** (Scheme 14).[24] **preNHC-11** was found to be the most suitable catalyst for this transformation. They also postulated that the inclusion of a bidentate ligand could inhibit irreversible Pd–NHC binding, hence preventing catalytic quenching. During the course of the reaction, formation of **28** was observed, indicating this to be an intermediate in the reaction.

The authors proposed a mechanism where *O*-alloc aldehyde **26** is rapidly consumed, and palladium insertion precedes NHC addition (Scheme 15). Intermediate **Int. 23** or aldehyde **28** enters the catalytic cycle, adding on to the NHC to form



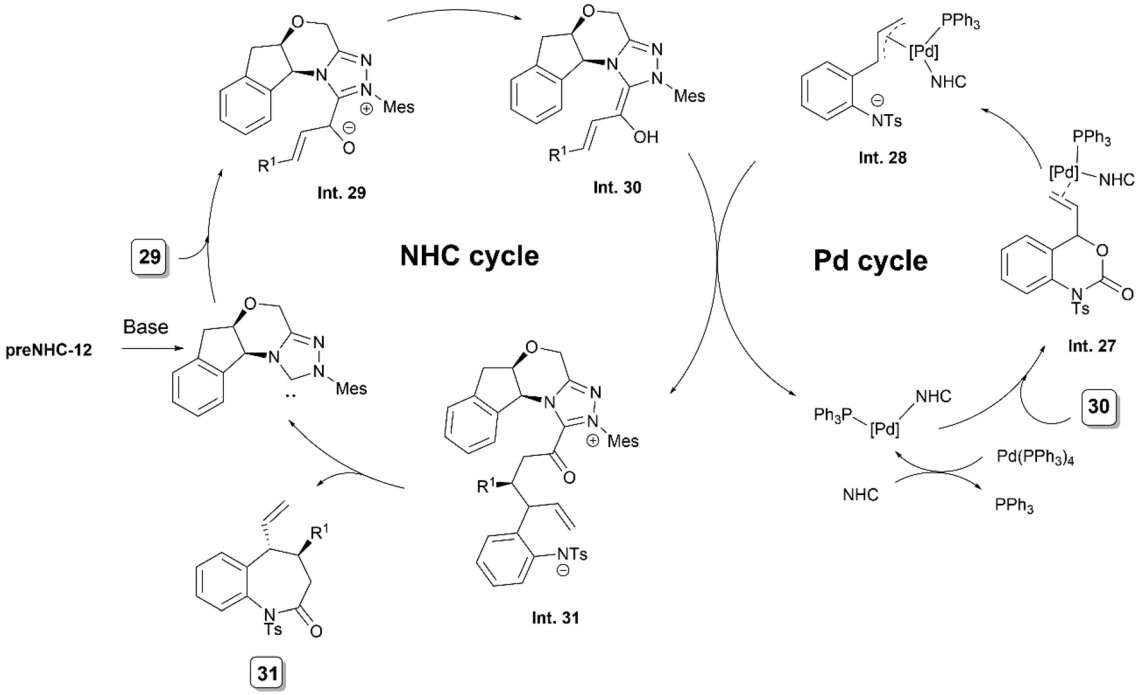
Scheme 15 Mechanism of NHC/Pd synergistic catalysis for synthesis of 3-allyl dihydrocoumarins.



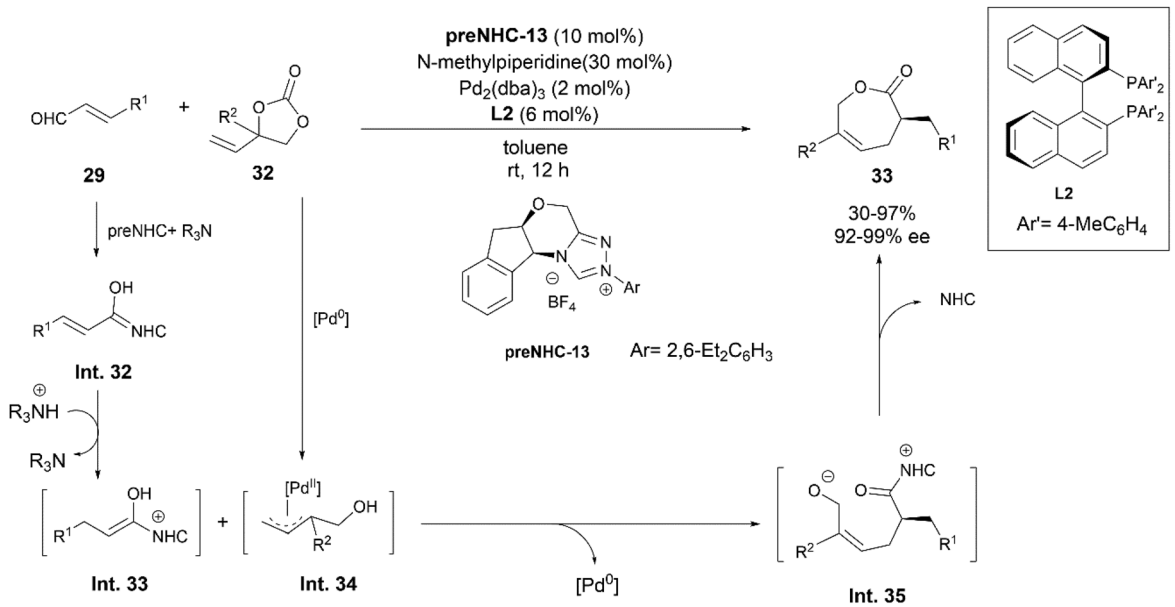
Scheme 16 Enantioselective umpolung [2 + 5] annulation of enals and vinyl oxazinanones *via* NHC/Pd synergistic catalysis.

extended Breslow intermediates **Int. 24a** or **24b**. β-Protonation of **Int. 24b**, or β-protonation and palladium insertion of **24a**, leads to the intermediate **Int. 25**. An ionic interaction between the phenoxide anion and Pd[π-allyl]L_n species facilitates a pseudo-intramolecular allylation, leading to **Int. 26**. Intramolecular acylation of allylated acyl azolium **Int. 26** completes the catalytic cycle, yielding the desired product **27** and regenerating the NHC catalyst.

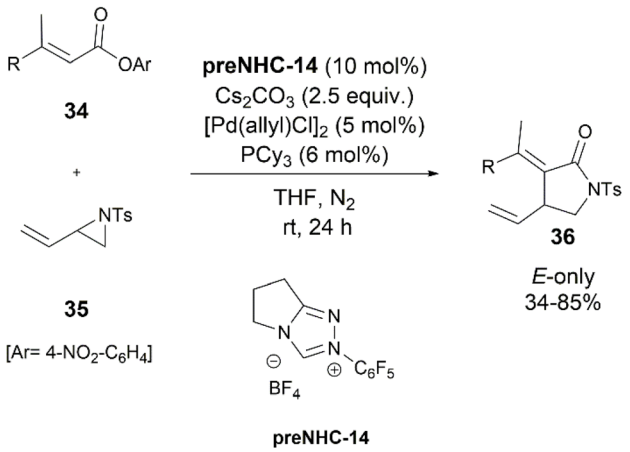
In 2016, the Glorius group reported a synergistic NHC/palladium catalyzed asymmetric synthesis of benzazepines **31** (Scheme 16).[25] The reaction proceeded *via* the nucleophilic addition of NHC generated homoenolates from enals **29** to the π-allyl Pd-species generated from **30**, followed by cyclisation. This also constituted the first example of asymmetric NHC-Pd synergistic catalysis for an intermolecular reaction. Under the optimized reaction conditions employing NHC precatalyst



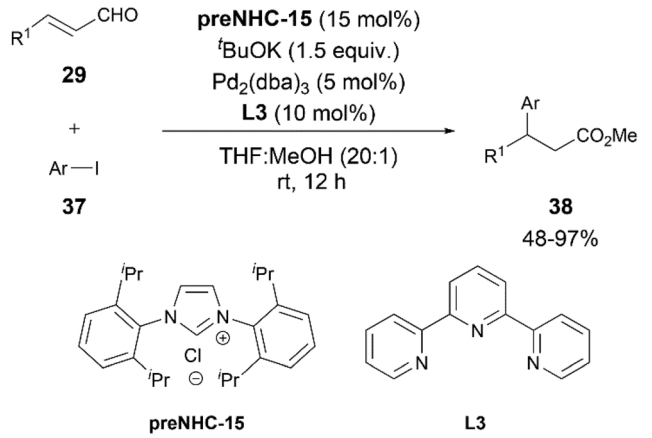
Scheme 17 Proposed mechanism of NHC/Pd synergistically catalysed umpolung annulation of enals and vinyl oxazinanones.



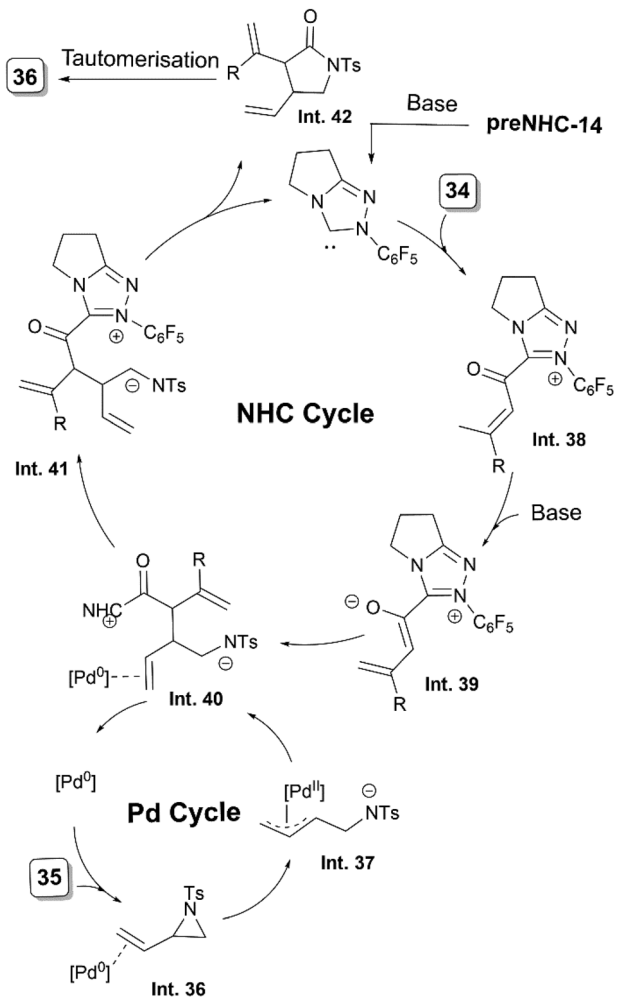
Scheme 18 NHC/Pd synergistic catalysis for enantioselective [2 + 5] annulation of enals and vinylethylene carbonates.



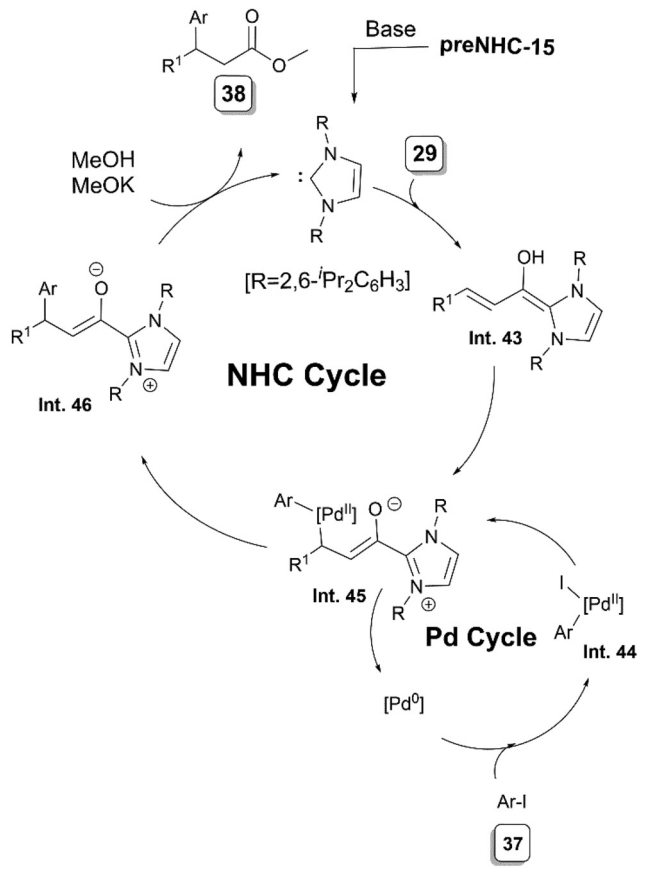
Scheme 19 NHC/Pd synergistic catalysis for [3 + 2] annulation of vinyl enolates and vinyl aziridines.



Scheme 21 Umpolung 1,4 addition of aryl iodides to α,β-unsaturated aldehydes using NHC/Pd synergistic catalysis.



Scheme 20 Proposed mechanism of [3 + 2] annulation of vinyl enolates and vinyl aziridines *via* NHC/Pd synergistic catalysis.



Scheme 22 Proposed mechanism of NHC/Pd synergistically catalysed umpolung 1,4-addition of aryl iodides to enals.

preNHC-12 (15 mol%), $Pd(PPh_3)_4$ (5 mol%) and Cs_2CO_3 (1 equiv.) in THF, the products could be obtained in high yields (up to 85%) and enantioselectivities (up to 99% ee).

In the following year, the group published the details of the mechanistic investigations on their above mentioned cooperative asymmetric NHC/palladium catalyzed transformation.[26]

These suggested a dual role of the NHC catalyst, both as an organocatalyst and as a chiral ligand for palladium. ESI-MS analysis supported the presence of a mixed ligand palladium complex ([Pd(π-allyl)(NHC)(PPh_3)]). The absence of a phosphine ligand resulted in no product formation, indicating its crucial role. The effect of varying the phosphine ligand on the enantioselectivity indicated its role in the enantio-determining step.

As per the proposed mechanism, the coordination of vinyl benzoxazinanone **30** to the NHC–Pd–phosphine complex initiates the formation of an electrophilic allyl–palladium complex **Int. 28** *via* **Int. 27** (Scheme 17). Simultaneously, NHC addition to enal **29** generates a homoenolate intermediate **Int. 30**. Conjugate addition of **Int. 30** to **Int. 28** leads to the intermediate **Int. 31**. The subsequent step involves *N*-acylation cyclisation to yield the final product **31**, regenerating the NHC catalyst.

In 2018, Glorius and his team took up the challenge to form ε-caprolactones enantioselectively using NHC–Pd synergistic catalysis (Scheme 18).[27] [5 + 2] annulation of vinylethylene carbonates **32** and α,β-unsaturated aldehydes **29** using a chiral NHC as well as a chiral phosphine ligand led to the desired products in high yields and enantioselectivities. Their studies indicated that the use of a bidentate ligand inhibited the coordination of the NHC to Pd, leaving the role of the NHC as that of an organocatalyst only.

Based on their mechanistic studies, they postulated that the reaction is initiated by the formation of the extended Breslow intermediate (**Int. 32**) of **29** which upon protonation forms a *Z*-enol intermediate **Int. 33** (Scheme 18). The attack of **Int. 33** at the terminal position of the Pd–π-allyl complex **Int. 34**, followed by a cyclization step leads to formation of **33** *via* **Int. 35** with regeneration of the free NHC and Pd catalysts.

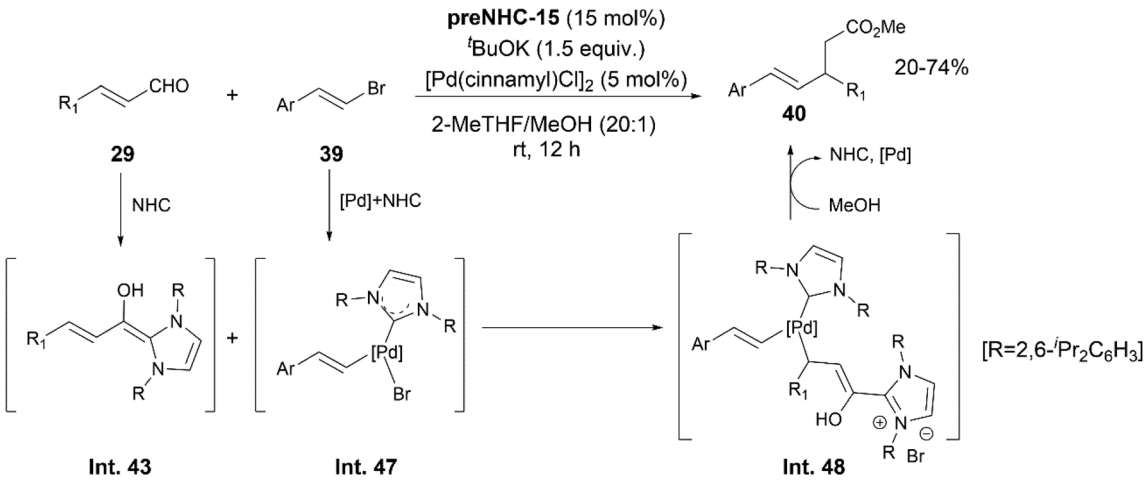
Later, in 2020, Du and coworkers reported the first example of synergistic NHC/palladium catalyzed reactions of vinyl enolates **34** with vinylaziridine **35** for the simple (3 + 2) synthesis of the (*E*)-3-ethylidene-4-vinylpyrrolidin-2-ones **36** (Scheme 19).[28] They also discovered that having an excess of **35** was crucial for this change due to dimerization of **35** in the reaction.

As proposed by the authors, an initial coordination of the vinyl aziridine with Pd (**Int. 36**) facilitates its ring opening and leads to an (η^3-allyl)palladium complex **Int. 37** (Scheme 20). A simultaneous activation of vinyl enolate **34** by the NHC, forms the intermediate **Int. 38**, which undergoes a γ-H deprotonation to form the nucleophilic NHC-bound vinyl enolate **Int. 39**. The attack of **Int. 39** on the π-allyl complex **Int. 37** present in the reaction medium results in the C–C bond formation. Removal of Pd and the subsequent *N*-acylation forms the annulated intermediate **Int. 42** *via* **Int. 41** and regenerates the NHC. Subsequently, the more stable product **36** is formed from **Int. 42** by tautomerisation.

To enhance the utility of NHC-bound nucleophilic intermediates in C–C bond-forming processes, in 2020, Mao and Walsh reported the first 1,4-addition of aryl iodides **37** to enals **29** (Scheme 21).[29] A combination of **preNHC-15**, *t*BuOK as the base with $Pd_2(dba)_3$ and terpyridine ligand **L3** was found to be the most suitable combination for the desired arylation. The addition of MeOH to the reaction led to the regeneration of the NHC and formation of β,β-diarylpropanoates.

In the organocatalytic cycle, the NHC leads to the formation of NHC bound homoenolate intermediate **Int. 43** whereas oxidative addition of palladium into aryl iodide **37** generates the intermediate **Int. 44** (Scheme 22). The homoenolate **Int. 43** then attacks the palladium, displacing the iodide and leading to the formation of a Pd–C bond (**Int. 45**). Upon reductive elimination, **Int. 45** leads to **Int. 46**, which is followed by liberation of the NHC by MeOH and formation of the desired product **38**.

Mao extended the same strategy for 1,4 addition of vinyl bromides **39** to cinnamaldehyde **29**, which led to the formation of γ,δ-unsaturated carbonyl derivatives **40** (Scheme 23).[30] Based on some experiments, the authors postulated the NHC to be the catalyst as well as ligand in the reaction. Intermediates **Int. 43** and **Int. 47** were proposed to be



Scheme 23 Umpolung 1,4-addition of vinyl bromides to enals *via* NHC/Pd synergistic catalysis.

generated *via* the activation of substrates **29** and **39** by the NHC and Pd catalysts, respectively. A combination of these two intermediates, followed by a reductive elimination and NHC regeneration aided by MeOH, led to the desired product **40** *via* **Int. 48**.

4. Conclusion

The field of NHC/palladium synergistic catalysis has witnessed significant developments over the last decade, showcasing its potential in several synthetic transformations. The reactions of Breslow as well as extended Breslow intermediates, generated from the activation of aldehydes and α,β-unsaturated carbonyls by NHCs, with a diverse range of substrates activated by palladium complexes have enabled several transformations that could not be accomplished by either of these catalysts alone. Innovative extensions, such as the incorporation of photoredox catalysis, have further expanded the scope of NHC/palladium synergistic catalysis. The development of new synthetic pathways, such as alkylacylation of alkenes and activation of $C(sp^3)$–H bonds, highlights the adaptability of this collaborative strategy to address challenges posed by unreactive substrates. Despite the progress made, challenges such as reactivity mismatch and catalyst quenching persist. Ongoing efforts are required to refine reaction conditions, and catalyst and ligand selection for enhanced efficiency and a broader substrate scope. The development of enantioselective processes using NHC/palladium synergistic catalysis has not gained much momentum, in spite of the significant advancement in the enantioselective transformations catalysed by NHCs and palladium catalysts separately.

The cooperative catalysis with NHCs and palladium represents a vibrant and promising pathway in synthetic chemistry. As research in this field progresses, NHC/palladium synergistic catalysis is poised to make substantial contributions to the development of innovative synthetic methodologies.

Conflicts of interest

The authors have no conflict of interest to declare.

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