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Recent advances in annulations enabled by nucleophilic Lewis base/metal dual catalysis☆

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ABSTRACT

Metal/nucleophilic Lewis base dual catalysis has been recognized as a reliable and promising strategy for finishing ideal organic synthesis over the past decades. The new strategy can usually achieve some chemical reactions that cannot be realized by the traditionally mono-catalytic system, dramatically expanding the synthetic utility of chemical transformations by leveraging additional activation modes. Thus considerable progress has been made in the synthesis of a wide range of heterocyclic and biologically active compounds by using the combination of diversely metal/nucleophilic Lewis base dual catalysts, including metal/phosphine, metal/*N*-heterocyclic carbene (NHC) and metal/tertiary amine dual catalysis systems. In this review, we describe a comprehensive and updated advance of metal/nucleophilic Lewis base dual catalytic annualtion reactions, meanwhile, the related mechanism and the application of these annulation strategies in natural product total synthesis will be highlighted in detail.

1. Introduction

Dual catalysis is a powerful and reliable synthetic strategy for the construction of a wide range of pharmaceuticals and bioactive natural products. In dual catalysis, two different catalysts activate diverse reactive substrates concurrently by either cooperative or relay catalytic process in a single chemical transformation. Thus it can realize unprecedented chemical transformations that could not be achieved by either of the catalysts alone. In the past decades, numerous progress on dual catalysis involving metal/metal, metal/organocatalyst and organo/organocatalyst has attracted considerable attention. In particular, the combination of transition metal with organocatalysis has attracted interest from a large number of research groups since the proof of concept was reported in 2001 [1,2]. And a large number of unprecedented annualtion reactions involving transition metal with organocatalyst dual catalysis have been developed in laboratories worldwide [3–10].

As a class of organocatalysts, nucleophilic Lewis bases, mainly including tertiary phosphine, *N*-heterocyclic carbene (NHC) and tertiary amine catalysts, have emerged as promising and versatile catalysts over the last few decades. For each reported nucleophilic Lewis base-catalyzed reaction, the reactive substrates are limited to electron-deficient olefins, alkynes, aldehydes, ketones and imines. Nevertheless, the electron-rich substrates, which are commonly used in metal catalysis, often suffer from significant limitations, including slow conversion, poor selectivity, or even no reaction at all. In recent years, by mimicking the characteristic of biosystems, the strategy of metal/Lewis base dual catalysis has been explored by organic chemists for achieving important transformations that are unobtainable through single-catalyst systems [11–14]. In such systems, metal catalysts are widely used in bond-breaking and bond-forming events, and nucleophilic Lewis base catalysts exhibit a excellent tolerance of functionalities with a unique level of regio- and stereocontrol. Thus two distinct catalysts can work either cooperatively or independently to fulfill ideal organic synthesis in one operation, dramatically reducing solvents, waste, time, *etc*.

The utilization of dual catalysts in a single reaction to realize correspondingly chemical synthesis has witnessed continuous success. In mechanism, dual catalysis was divided into two types including cooperative dual catalysis and relay or sequential catalysis. Dual cooperative catalysis describes the concept of two different catalysts working together synergistically without interfering with one another but rather by simultaneously activating two different reactive species, one an electrophile **A** and the other a nucleophile **B**. In relay or sequential catalysis, the intermediate **A-B** was first obtained in the presence of catalyst 1, and then intermediate **A-B** was transformed into the desired product **C** under catalyst 2

☆ Dedication to Prof. Lixin Dai on the Occasion of His Centenary Birthday.

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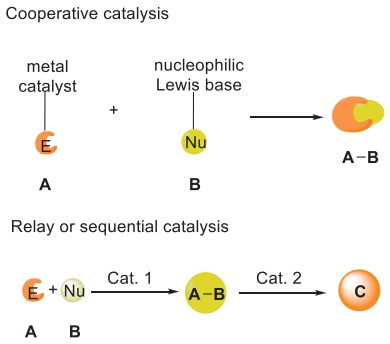


Scheme 1. Metal/nucleophilic Lewis base dual catalysis.

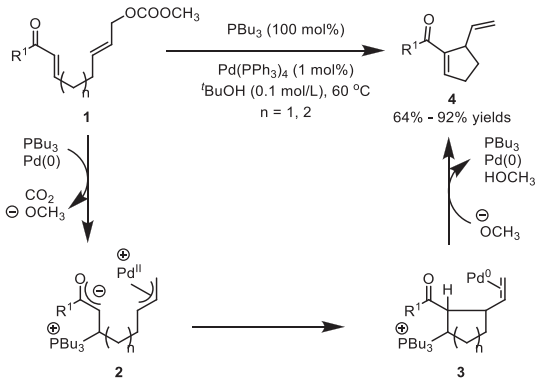
(Scheme 1). In dual catalytic system, some more reactive intermediates and sophisticated transformations may produce, the key to the realization of dual catalysis system is thus that each catalyst precisely activate the corresponding substrates. In other words, The compatibility problems is critical for the success of dual transition metal/nucleophilic Lewis base catalytic system. For this reason, the combination of diverse catalysts for cooperative or relay activation requires a combination of strategy and empiricism in evaluating compatible systems for the ultimate goal of exploring new reaction modes.

Given the power and efficiency of dual transition metal/nucleophilic Lewis base catalytic annualtion reactions in constructing valuable ring structures, and their remarkable applications in pharmaceuticals and bioactive natural products synthesis. Enormous efforts have been devoted to the development of highly efficient protocols for the synthesis of this motifs *via* dual transition metal/Lewis base catalytic cycloaddition reactions in the past decade. Thus a comprehensive and update review focusing on recent advancements in transition metal/nucleophilic Lewis base catalytic system-empowered annulation reactions and its applications in the total synthesis of natural products is essential. In this review, we summarize and classify the related research works based on different catalytic pathways such as transition metal/phosphines, transition metal/amines and transition metal/NHC dual catalysis. We sincerely hope that this tutorial review will act as a handy reference for synthetic chemists interested in exploring and discovering more types of multiple catalytic reactions.

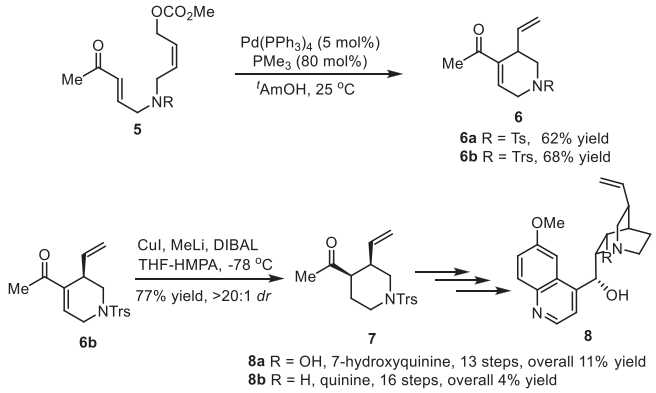
2. Application of phosphine/metal dual catalytic system in annulation reaction

2.1. Phosphine/metal cooperatively catalytic annulations

Owning a pair of nonbonding electron pairs, tertiary phosphines are not only applied as ligands that coordinate with the metal center, but also can be directly used as organocatalysts to catalyze the chemical reactions [15–20]. That is to say, in the dual catalytic system, tertiary phosphines can coordinate with the transition metals involved, which will result in the deactivation of catalytic system, thereby diminishing or even preventing the individual reactivity of each substrate. Thus rare examples have been reported involving transition metal/phosphine dual catalytic system. In 2003, Krische and coworkers were the first to resolve the compatibility problems of palladium complex and tertiary phosphines, realizing the intramolecular enone cycloallylation reactions by applying $Pd(PPh_3)_4$ and PBu_3 cooperatively catalytic system. In this report, the authors used allylic carbonates as latent "nonclassical" electrophiles, achieving the precise activation of nucleophilic (enone) and electrophilic (allyl carbonate) partners through phosphine addition and metallo-π-allyllation, respectively. In mecha-



Scheme 2. Phosphine/palladium cooperative catalyzed cycloallylation.



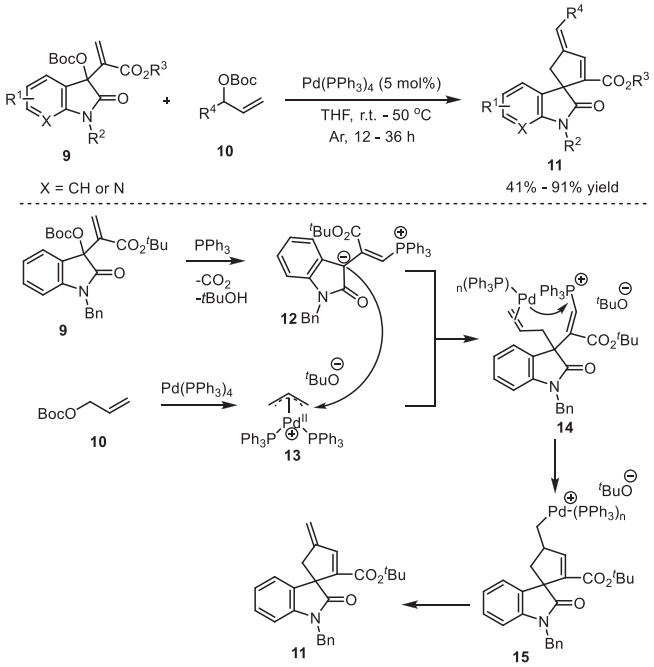
Scheme 3. Totally synthesis of (±)-quinine and (±)-7-hydroxyquinine.

nism, the authors thought that the lifetime of the transiently generated enolate would be extended through solvation in the form of hydrogen-bond interactions, in which capture of the metallo π-allyl intermediate would be facilitated (Scheme 2) [21].

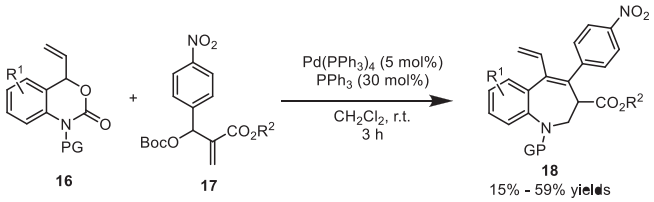
Using the phosphine/palladium cooperative catalytic system, Krische and coworkers realized concise stereoselective synthesis of (±)−7-hydroxyquinine and (±)-quinine. As shown in Scheme 3, (±)-7-hydroxyquinine **8a** was obtained in 13 steps and 11% overall yield from aminoacetaldehyde diethyl acetal. And (±)-quinine **8b** was synthesized in 16 steps and 4% overall yield from commercial aminoacetaldehyde diethyl acetal (Scheme 3) [22].

Despite those efforts, phosphine/palladium cooperative catalytic system has not seen widespread use up to date, This mainly unsolved challenge in the design of such a cooperative system has been the difficulty of controlling compatibility problems. Until 2019, Chen and coworkers reported an auto-tandem cooperative catalysis for Morita–Baylis–Hillman carbonates from isatins and allylic carbonates using a simple $Pd(PPh_3)_4$ precursor, affoding a spectrum of spirooxindoles incorporating a 4-methylene-2-cyclopentene motif in good yields with chemoselectivity [23]. In mechanism, the authors thought that dissociated phosphine from $Pd(PPh_3)_4$ generated phosphorus ylides **12** and the Pd concurrently led to π-allylpalladium complexes **13**. And they underwent a γ-regioselective allylic-allylic alkylation reaction (**14**), followed by a cascade intramolecular Heck-type coupling to produce the desired spirooxindoles **11**. It was worth noted that the authors first realized the phosphine/palladium cooperative catalyzed asymmetric cycloaddition reaction, obtaining high yield with moderate *ee* value (Scheme 4).

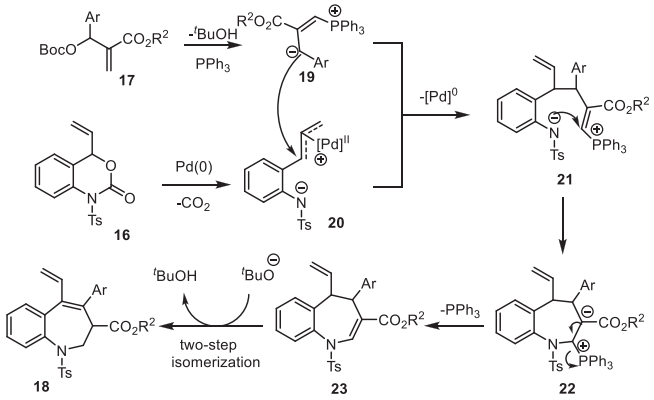
Azepine derivatives are abundant in many natural products, bioactive molecules, and pharmaceuticals. Thus, the development of an efficient catalytic system for the construction of these molecules is still needed. In 2019, Li and co-workers devel-



Scheme 4. Auto-tandem cooperatively catalysis for Morita–Baylis–Hillman carbonates from isatins and allylic carbonates.



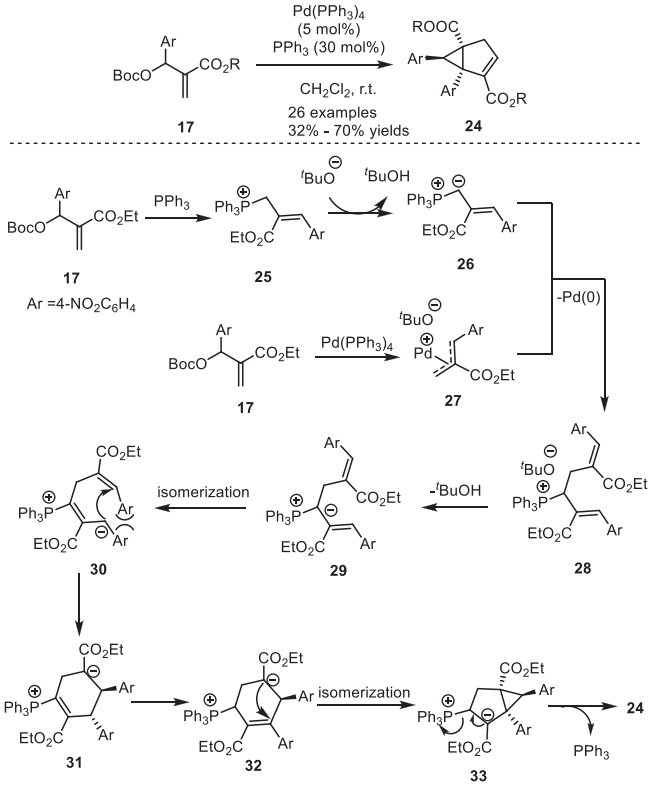
Scheme 5. Phosphine/palladium cooperatively catalytic [3 + 4] annulation reaction of Morita–Baylis–Hillman carbonates and vinyl benzoxazinanones.



Scheme 6. A possible mechanism for phosphine/palladium cooperative catalytic [3 + 4] annulation reaction.

oped a phosphine/palladium cooperatively catalytic [3 + 4] annulation reaction of Morita–Baylis–Hillman carbonates and vinyl benzoxazinanones, providing a range of vinyl 2,3-dihydro-1*H*-benzo[*b*]azepine derivatives in moderate to good yields and diastereoselectivities (Scheme 5) [24].

A plausible mechanism is presented, as outlined in Scheme 6. The reaction was first triggered by nucleophilic attack of PPh_3 on MBH carbonates **17** to yield zwitterion **19**, Simultaneously, **16** and $Pd(PPh_3)_4$ produced the π-allylpalladium complex **20**. Next, the γ-regioselective addition of the zwitterionic intermediate **19** to the



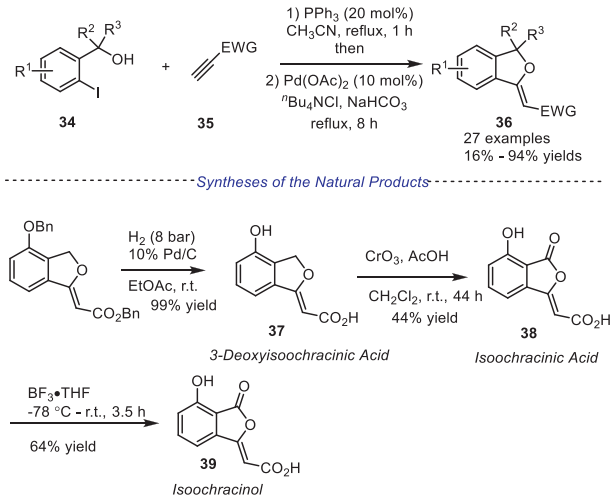
Scheme 7. A possible mechanism for phosphine/palladium cooperative catalytic successive [2 + 3]/[2 + 1] cycloadditions.

π-allylpalladium complex **20** gave the intermediate **21** and regenerated Pd(0) catalyst. An intramolecular Michael addition occurred to produce the intermediate **22**. Then the electron-transfer process and subsequent β-elimination of PPh_3 afforded the corresponding intermediate **23**. Finally, two-step isomerization of C=C bond produced the observed adducts **18** in the presence of base (Scheme 6).

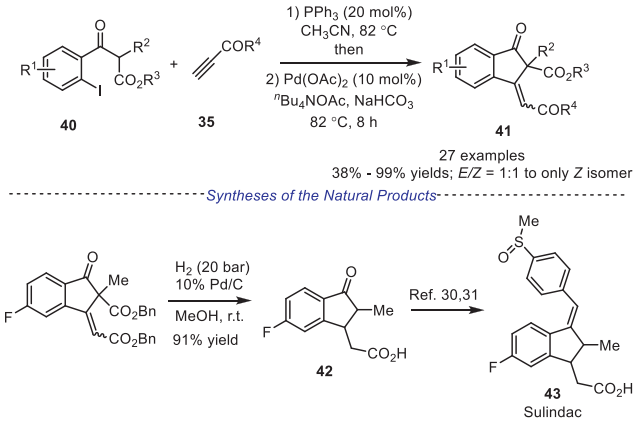
In 2021, Li and coworkers reported a phosphine/palladium cooperatively catalytic successive [2 + 3]/[2 + 1] cycloadditions of MBH carbonates, leading to the desired bicyclo[3.1.0]hexenes **24** in moderate to good yields [25]. For the mechanism, the authors found that one molecule of MBH carbonates with PPh_3 produced a tertiary phosphine-tethered allylic P-ylide **26**. Simultaneously, another molecule of MBH carbonates coordinated with $Pd(PPh_3)_4$ to obtain π-allylpalladium complex **27**. Subsequently, an α-regioselective allylic alkylation (**28**), dehydrogenation (**29**), proton shift (**30**), ring-closure produced intermediate **31**. Finally, a sequential isomerization (**32**), annulation (**33**) and regeneration of the PPh_3 catalyst led to the desired adducts **24** (Scheme 7).

2.2. Phosphine/metal sequentially catalytic annulations

In dual catalysis, sequential catalysis (or tandem/cascade catalysis) is a very powerful and efficient approach in organic synthesis. In this field, the two catalysts are operating in series; the first catalyst activates the substrates toward the formation of the reactive intermediate, which is then transformed in the next catalytic cycle in the presence of the second catalyst, and leads to the desired product [26]. The key challenge in sequential catalysis is to aviod deactivation of two catalysts by interaction. In 2009, Wu and coworkers first resolved the compatibility problems and reported a silver triflate and triphenylphosphine sequential catalyzed domino reaction of the three-component reaction of 2-alkynylbenzaldehyde, amine, and α,β-unsaturated ketone [27]. In



Scheme 8. Phosphine/palladium relay catalytic cycloaddition reaction.



Scheme 9. Phosphine/palladium sequential catalytic Michael−Heck annulation of 2-iodobenzylmalonates.

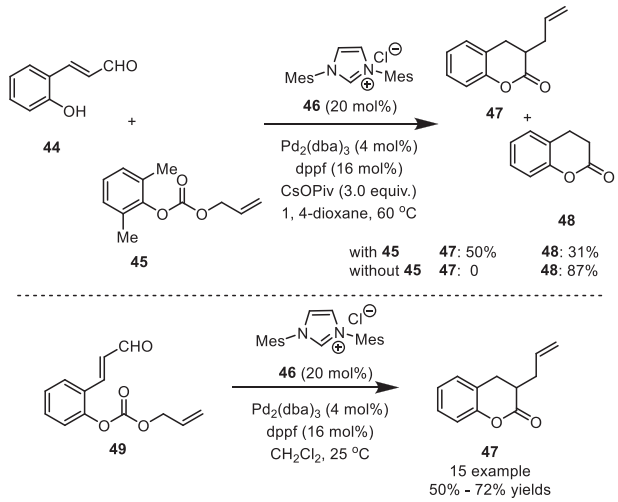
2012, Kwon and coworkers developed a phosphine/palladium sequentially catalytic annulation reaction. Notably, the reaction underwent sequential phosphine-catalyzed nucleophilic addition followed by $Pd(PPh_3)_4$-catalyzed Heck cyclization. In addition, the authors accomplished concise total syntheses of 3-deoxyisoochacinic acid (**37**), isoochracinic acid (**38**), and isoochracinol (**39**) (Scheme 8) [28].

In 2015, Kwon and coworkers used 2-iodobenzylmalonates and methyl propiolate as reactive substrates to test the viability of Michael-Heck annulation in forming carbocycles. Under phosphine/palladium sequential catalysis, the tandem Michael-Heck annulation proceeded smoothly, affording the desired alkylidene indane **41** in 38%-99% yields with moderate *Z*/*E* selectivity [29]. The experiment result suggested that the salt additives had a significant effect on the yield, and an excellent yield was achieved when using tetra-*n*-butylammonium acetate as the additive. It was worth noted that alkylidene indane could be translated into a nonsteroidal anti-inflammatory drug (Sulindac) **43** from known literature (Scheme 9) [30,31].

3. Application of NHC/metal dual catalytic system in annulations

3.1. NHC/metal cooperatively catalytic annulations

N-Heterocyclic carbene (NHC) catalysis is recognized as a powerful tool for the construction of complex organic frameworks from

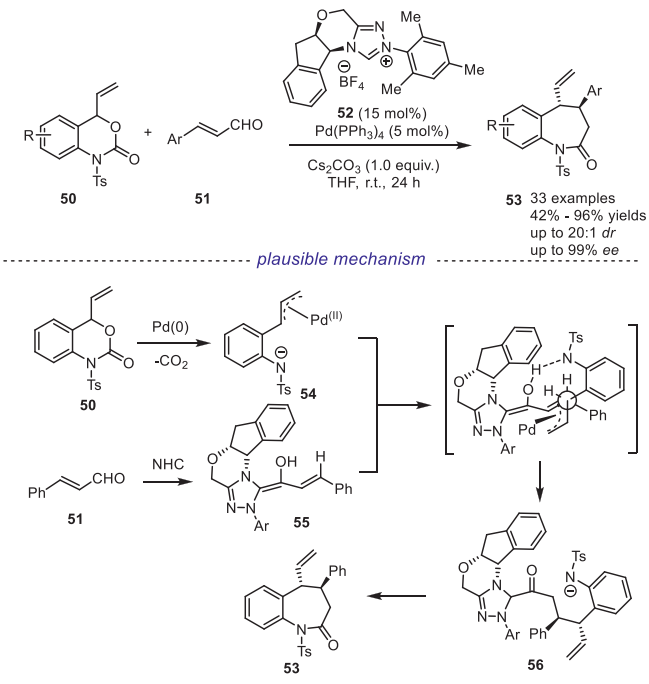


Scheme 10. Cooperative NHC/palladium catalysis approach to access a variety of 3-allyl dihydrocoumarin derivatives.

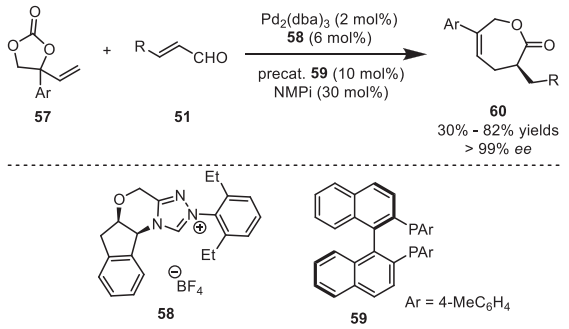
simple and readily available starting materials [32–38]. However, NHC catalysis is typically limited to established substrate classes and reaction modes. Thus cooperative combination of transition-metal catalysis and NHC catalysis could dramatically expand the scope of NHC catalysis and provide access to currently inaccessible reaction pathways. In 2014, Scheidt and coworkers reported a new cooperative NHC/palladium catalytic approach to access a variety of 3-allyl dihydrocoumarin derivatives. Initially, the authors investigated the intermolecular reaction of **44** with allyl carbonate **45** using a cooperative NHC-Pd catalysis system. Obviously, the undesired dihydrocoumarin **48** was obtained as a competing by-product [39]. The authors hypothesized that the phenolic proton promoted the tautomerization of the NHC-enolate to the NHC-acyl adduct. To overcome this limitation, they designed a new substrate (*o*-alloc aldehyde **49**) to mask the phenol with the allyl source. Thus the desired allylated dihydrocoumarins **47** were produced in 50%-72% yields (Scheme 10).

In 2016, Glorius and coworkers developed an asymmetric cooperative system for the intermolecular [4 + 3] cycloaddition reaction that combines transition-metal/NHC organocatalytic system [40]. This asymmetric process was first to demonstrate the compatibility of these two important catalytic modes and efficiently afforded annulated 1-benzazepine products with excellent regio- and enantioselectivities. A plausible “cooperative activation” concept was proposed in this paper: First, the coordination of vinyl benzoxazinanone **50** to the palladium catalyst formed an electrophilic allyl-palladium(II) complex **54** upon decarboxylation, simultaneously, the nucleophilic addition of NHC organocatalyst to the enal **51** gave rise to the NHC-homoenolate **55**. Then, the NHC-homoenolate **55** underwent conjugate addition to the allyl-palladium(II) complex, affording the acyl azolium **56** and released the palladium catalyst. Finally, this species underwent *N*-acylation cyclization to furnish the final product **53** and regenerated the NHC organocatalyst **52** (Scheme 11).

Later, Glorius and coworkers reported the detailed mechanistic studies involving a palladium catalyst and an NHC organocatalyst dual catalytic systems. This result revealed that the NHC, besides its role as an organocatalyst, also fortuitously acts as a ligand on the active metal catalyst [41]. In 2018, Glorius and coworkers expected to report an enantioselective [2 + 5] annulations involving such NHC/transition metal cooperativity to generate challenging ε-caprolactones in a highly enantioselective fashion [42]. Unfortunately, no product was detected when the authors used NHC precatalyst **58** and monodentate PPh_3, the authors thought



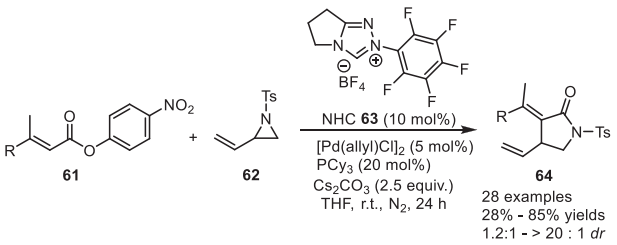
Scheme 11. The intermolecular [4 + 3] cycloaddition reaction that combines Pd/NHC cooperative system and plausible mechanism.



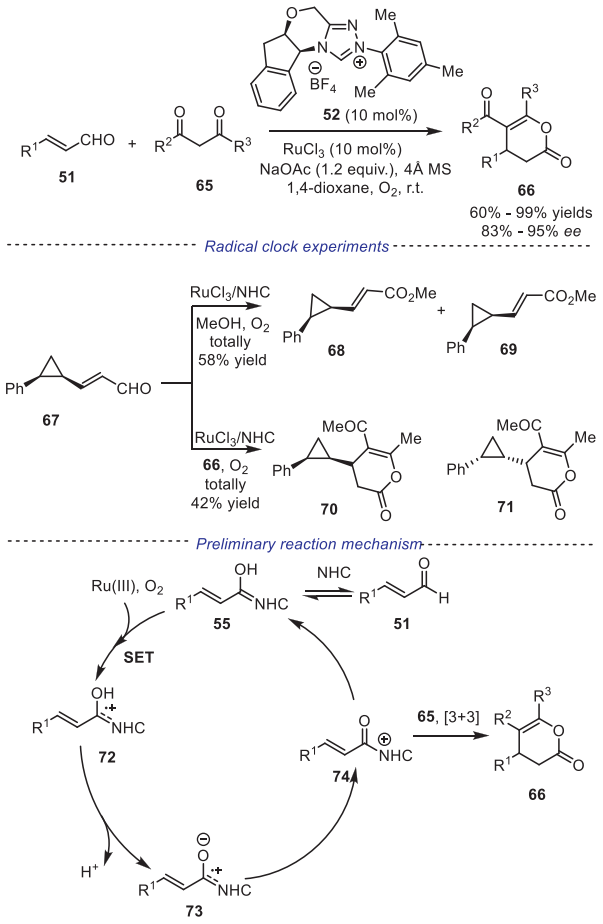
Scheme 12. The intermolecular [2 + 5] cycloaddition reaction that combines NHC/Pd cooperative system.

that NHC **58** could easily compete with the weakly coordinating PPh_3 for ligation to Pd, which inhibited the reaction. In this context, the authors questioned whether the ligation of NHC to the transition metal was prevented and the NHC was only operative in the organocatalytic cycle, which would thus provide access to currently inaccessible reaction pathways by allowing the fine-tuning of both catalytic systems. Based on this strategy, some more strongly chelating bidentate ligands were used to optimize the reaction condition. When a more bulky and electron-rich ligand (*R*)-Tol-BINAP was used, the desired product **60** was obtained in 76% yield with excellent *ee* (>99% *ee*). Further mechanistic studies showed that use of a bidentate phosphine ligand played key role in preventing the binding of NHC to the transition metal and thereby the success of this transformation (Scheme 12).

In 2020, Du and coworkers used 3-substituted but–2-enoates and 1-tosyl-2-vinylaziridine as reactive substrates, developing a cooperative NHC/palladium-catalyzed [2 + 3] annulation system [43]. In this dual catalytic system, the NHC catalyst and the palladium catalyst could work well independently instead of quenching each other, affording the desired (*E*)−3-ethylidene-4-vinylpyrrolidin-2-one skeletons in medium to good yields (Scheme 13).

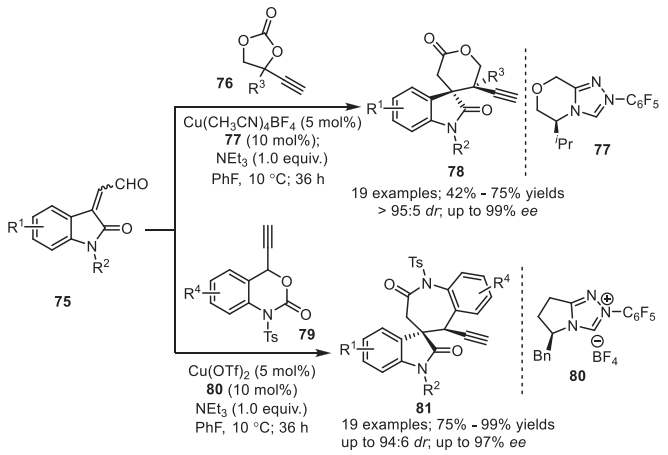


Scheme 13. Cooperative NHC/palladium [2 + 3] annulation of 3-substituted but–2-enoates and 1-tosyl-2-vinylaziridine.

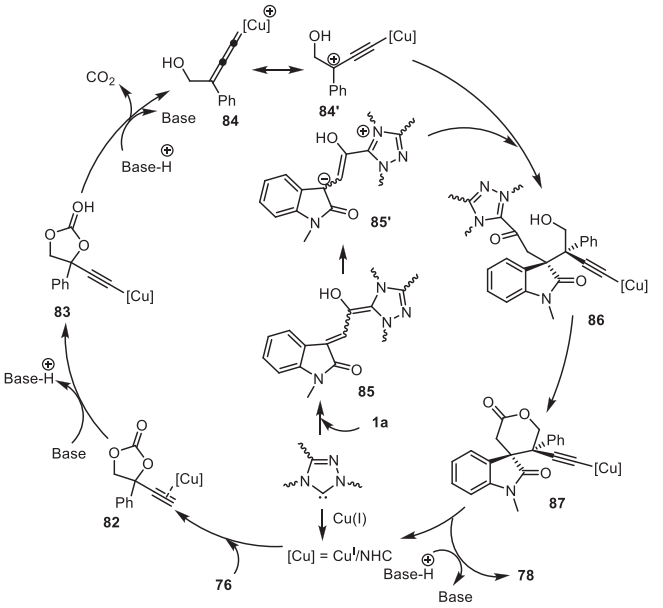


Scheme 14. $RuCl_3$/NHC dual cooperative catalytic [3 + 3] cycloaddition.

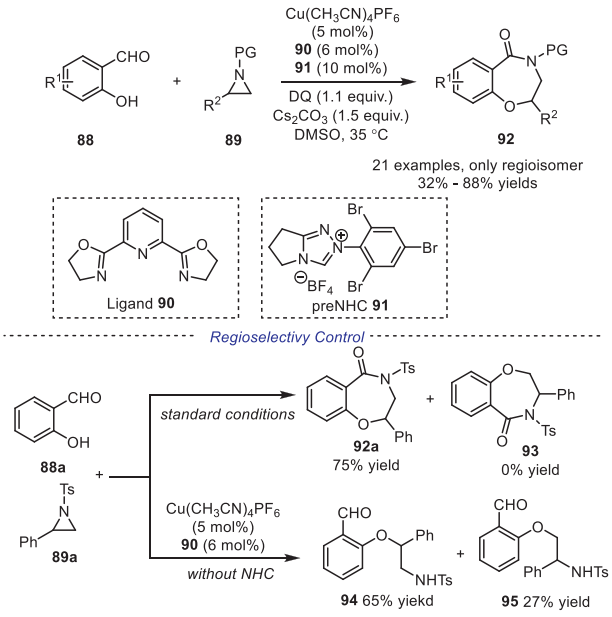
Besides Pd/NHC cooperatively catalytic system, Huang and coworkers reported an enantioselective [3 + 3] cycloaddition reaction by $RuCl_3$/NHC catalytic system [44]. In this reaction, the α,β-unsaturated acylazolium intermediate reacted selectively with 1,3-dicarbonyl compounds or ketones at either the β- or γ-carbon, producing polysubstituted chiral lactones in high yield and with excellent enantioselectivity (up to 98% yield, 94% *ee*). The authors thought that the key oxidation step in this reaction was a Ru-mediated SET process. In order to determine the nature of the radical, the radical clock experiments were carried out, the result showed the relative configurations of the cyclopropanes were perfectly preserved during both the oxidation and the annulation, which suggested the radical was strictly localized at the carbonyl carbon, with little resonance to the corresponding β-radical isomer. According to this, a plausible mechanism was proposed as shown in Scheme 14. Initially, the enal reacted with the NHC to yield a homoenolate **55**, $RuCl_3$ then oxidized the homoenolate by an SET process. The resulting radicalcation was deprotonated



Scheme 15. NHC/copper cooperatively catalyzed [3 + 3] and [3 + 4] annulations between isatin-derived enals.



Scheme 16. A possible mechanism for NHC/copper cooperatively catalyzed [3 + 3] and [3 + 4] annulations between isatin-derived enals.



Scheme 17. Copper/NHC cooperatively catalyzed [3 + 4] annulation of salicylaldehydes with aziridines.

to give a zwitterionic radical species. Consequently, a second SET by Ru led to the α,β-unsaturated acylazolium, which undergoes [3 + 3] annulation with the 1,3-dicarbonyl compound (Scheme 14).

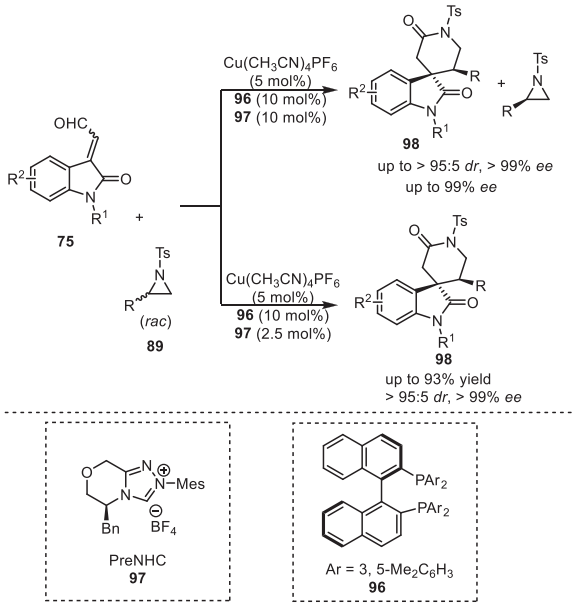
Copper-catalyzed asymmetric decarboxylation of ethynylethylene carbonates and ethynyl benzoxazinanones that generates nucleophile/copper-allenylidene bifunctional intermediates, provides a powerful approach to build chiral heterocycles. Inspired by this, cooperative dual catalytic system involving copper catalyst has received comprehensive interest. In 2019, Gong and coworkers reported a NHC/copper cooperatively catalyzed [3 + 3] and [3 + 4] annulations between isatin-derived enals **75** with ethynylethylene carbonates **76** and ethynyl benzoxazinanones **79**, affording the chiral spirooxindole derivatives with high structural diversity and enantiopurity (Scheme 15) [45]. The experiment result showed that a chiral copper/NHC complex might form and participate in the control of stereochemistry, together with the chiral NHC catalyst.

Thus the authors proposed a plausible reaction mechanism. Initially, the active species **82** was formed by substrate **76** coordinating with a Cu(I)/NHC complex. Then sequential deprotonation/decarboxylation of **82** gave a copper-allenylidene intermediate (**84** or **84′**). Simultaneously, the Breslow intermediate **85′** was produced by the addition of NHC organocatalyst to the enal **75**, which would thereafter react with copper-allenylidene intermediate **84** to generate an intermediate **86**. Finally, *O*-acylation cyclization and protonation furnished the final product **78** and regenerated the NHC organocatalyst and the copper catalyst (Scheme 16).

In 2020, Ye and Zhang utilized the copper/*N*-heterocyclic carbene dual catalytic system, developing a cooperatively catalyzed [3 + 4] annulation of salicylaldehydes with aziridines [46]. The reaction proceeded smoothly under the optimized reaction conditions, producing the desired 1,4-benzoxazepinones in good yields with exclusive regioselectivity. Further study showed that the addition of NHC to the salicylaldehyde afforded the Breslow intermediate, which played a predominant role in improving the regioselectivity (Scheme 17).

Catalytic kinetic resolution and dynamic kinetic asymmetric transformation of racemic mixtures is of great significance in synthetic chemistry. In 2021, Gong and Song reported a highly efficient chiral copper/NHC cooperatively catalytic systems for kinetically controlled processes, producing enantioenriched spirooxindolyl lactams in good yields with stereoselectivity by asymmetric [3 + 3] annulation [47]. The experiment result showed that NHC not only was applied as organocatalyst in the reaction, but also played the key role in improving the catalytic activity of the copper complex as an additional ligand. It was worthy noted that kinetic resolution and dynamic kinetic asymmetric reaction could be switched by changing the loading of NHC, respectively. Namely, the use of 2.5 mol% $Cu(CH_3CN)_4PF_6$, 5 mol% diphosphine **96** and 5 mol% NHC **97** was confirmed as the best optimized catalyst system for the catalytic kinetic resolution, while the presence of 5 mol% $Cu(CH_3CN)_4PF_6$, 10 mol% diphosphine **96** and 2.5 mol% NHC **97** was found as the best dual system for the dynamic kinetic asymmetric transformation (Scheme 18). More recently, the authors realized an asymmetric [3 + 3] cycloaddition of racemic vinyl epoxides with isatin-derived enals, providing straightforward access to highly enantioenriched 3,3′-disubstituted oxindoles in good yields with good diastereoselectivity and excellent enantioselectivity [48].

γ-Butyrolactones display important structural skeletons that widely occur in natural molecules, pharmaceuticals, and functional materials. Therefore, highly efficient access to and fully charac-



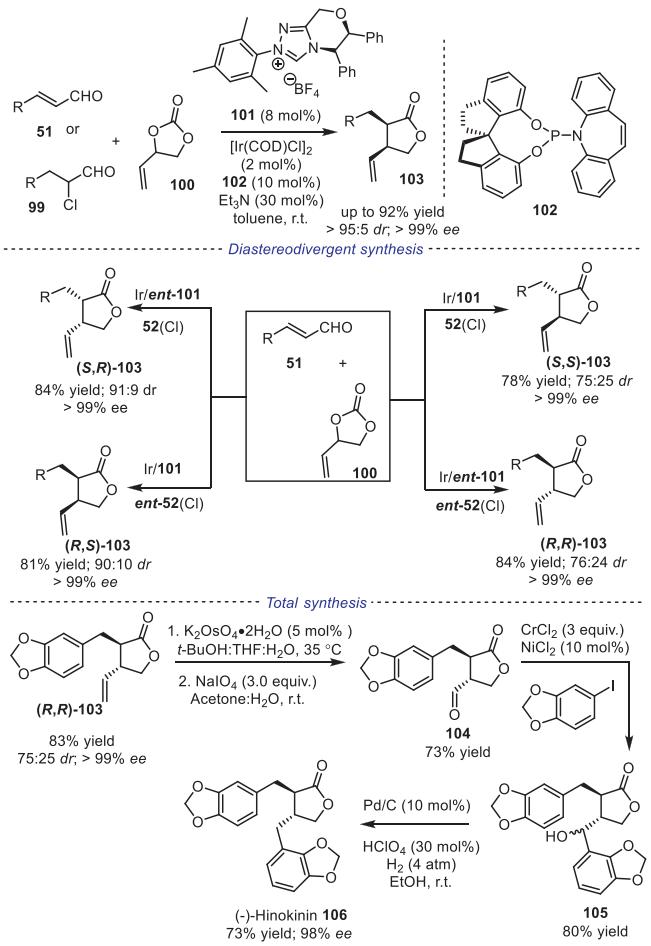
Scheme 18. NHC/copper cooperatively catalyzed [3 + 3] cycloaddition of aziridines.

terizing all possible stereoisomers of γ-butyrolactones are still needed. In 2020, Glorius and coworkers reported a stereodivergent NHC/Ir dual catalytic [2 + 3] cycloaddition reaction, providing all four stereoisomers of α,β-disubstituted γ-butyrolactones in good yields with excellent enantioselectivity by switching the four possible combinations of NHC precatalyst **101** (Cl) with the P–olefin ligand **102**. In addition, the obtained product was applied for total synthesis of the naturally occurring lignan (-)-hinokinin, which displayed anti-inflammatory, antimicrobial and modulatory effects on human GABA (γ-aminobutyric acid) transporter activities (Scheme 19) [49].

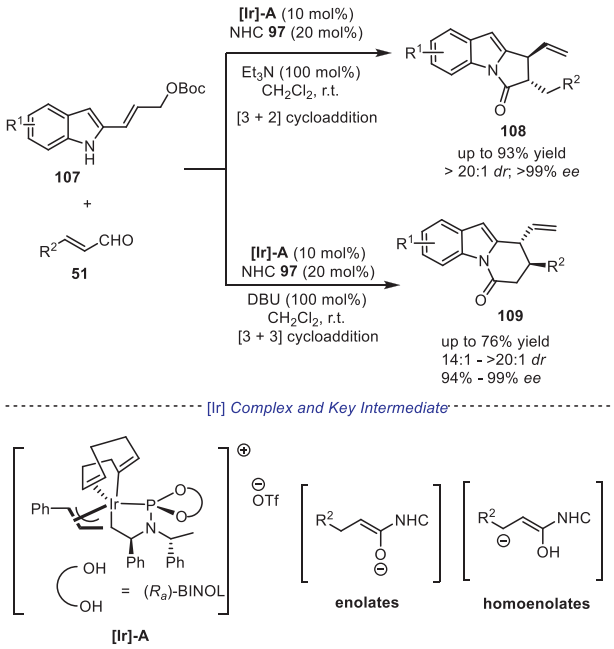
In 2015, Glorius and coworkers reported a switchable asymmetric annulation reaction with aromatic azomethine imines, in which homoenolate and enolate intermediates derived from enals could be switched under the catalysis of NHC in a rational and predictable manner [50]. In 2021, Deng and coworkers applied this strategy to realize the stereoselective and regiodivergent reactions of enals *via* cooperative NHC/iridium catalysis system [51]. According to Glorius's reports, an effective proton concentration would determine conversions between homoenolate and enolate forms. Thus the authors first used Et_3N (100 mol%) as a base in the presence of the iridium complex [Ir]-A and *N*-heterocyclic carbene in CH_2Cl_2 at room temperature, the [2 + 3] cycloaddition reaction could proceed smoothly *via* enolate intermediate, producing pyrrolo[1,2-a]indoles in good yields with regio-, diastereo- and enantioselectivities. When the strong organic base DBU (100 mol%) was used in $PhCF_3$, The homoenolate-derived products pyridine[1,2-a]indoles were obtained with complete regioselectivities. Similar to Glorius's reports, all four stereoisomers of these products could be afforded by the pairwise combination of two chiral catalysts. In mechanism, the authors found that the ligand exchange did not occur when the NHC was used with the Ir complex ligated in the reactive system, which was different from Glorius's reaction system (Scheme 20).

3.2. NHC/metal relay catalytic annulations

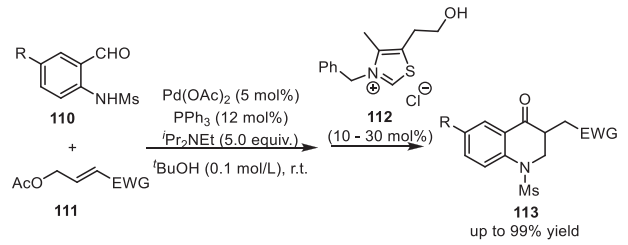
Besides cooperatively dual catalytic system, the dual catalysis involving relay catalysis by means of the combination of an NHC organocatalyst and a transition-metal catalyst has also emerged as a powerful strategy for the development of new reactions. In 2006,



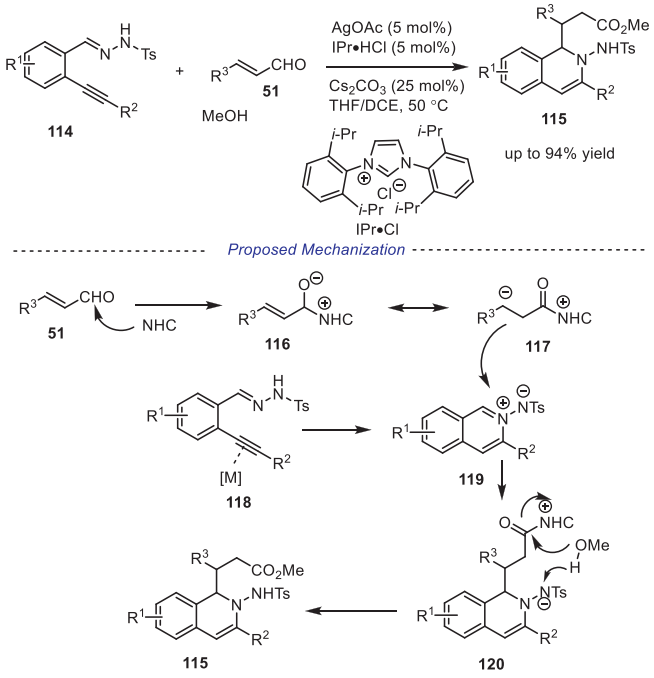
Scheme 19. NHC/Ir dual catalytic [2 + 3] cycloaddition of *trans*-cinnamaldehyde and vinylethylene carbonate.



Scheme 20. NHC/iridium catalysis enables stereoselective and regiodivergent [2 + 3] and [3 + 3] annulation reactions.



Scheme 21. Palladium/NHC relay catalytic domino reaction.

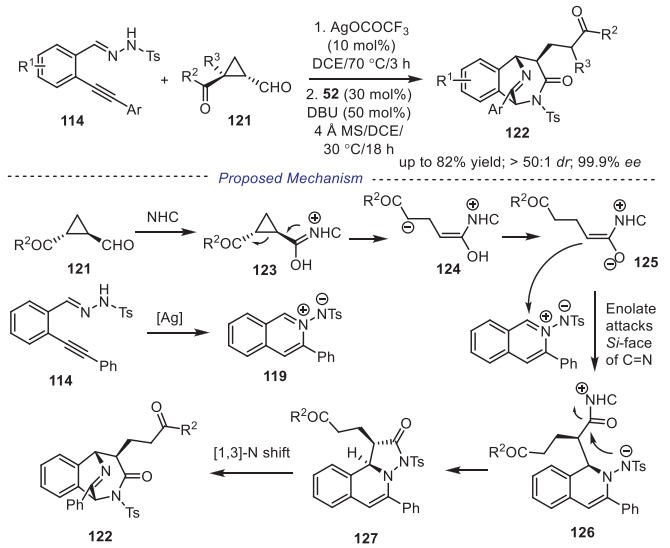


Scheme 22. Ag/NHC relay catalytic three-component reaction of *N*′-(2-alkynylbenzylidene)-hydrazide, methanol with α,β-unsaturated aldehyde.

Hamada and coworkers reported a palladium/NHC relay catalytic domino reaction including palladium-catalyzed allylic amination-NHC-catalyzed Stetter reaction cascade, affording the 3-substituted 2,3-dihydroquinolin-4-ones **113** in high yields [52]. The authors found that the reaction rate was increased in the presence of 1.0 equiv. of acetic acid, that is to say, ammonium salt (AcOH-Pr_2NEt) would function as Brønsted acid and accelerate the reaction (Scheme 21).

N′-(2-Alkynylbenzylidene)hydrazide is usually used as substrate in the Ag-catalyzed 6-*endo*-cyclization, producing the isoquinolinium-2-yl amide which is a good electrophile [53–55]. Thus the 1,2-dihydroisoquinoline core can be applied in dual relay catalytic cycloaddition. In 2010, Wu and coworkers disclosed Ag/NHC relay catalytic three-component reaction of *N*′-(2-alkynylbenzylidene)-hydrazide, methanol with α,β-unsaturated aldehyde, producing the 2-amino-1,2-dihydroisoquinolines **115** in good yield [56]. In mechanization, the isoquinolinium-2-yl amide **119** was first obtained by Ag-catalyzed 6-*endo*-cyclization of *N*′-(2-alkynylbenzylidene)hydrazide. Next, the Breslow intermediate **117** was obtained under the catalysis of NHC catalyst, which would attack the isoquinolinium-2-yl amide **119** to generate intermediate **120**. Finally, deprotonation of methanol and nucleophilic addition of carbonyl compound to produce the desired 2-amino-1, 2-dihydroisoquinoline **115** (Scheme 22).

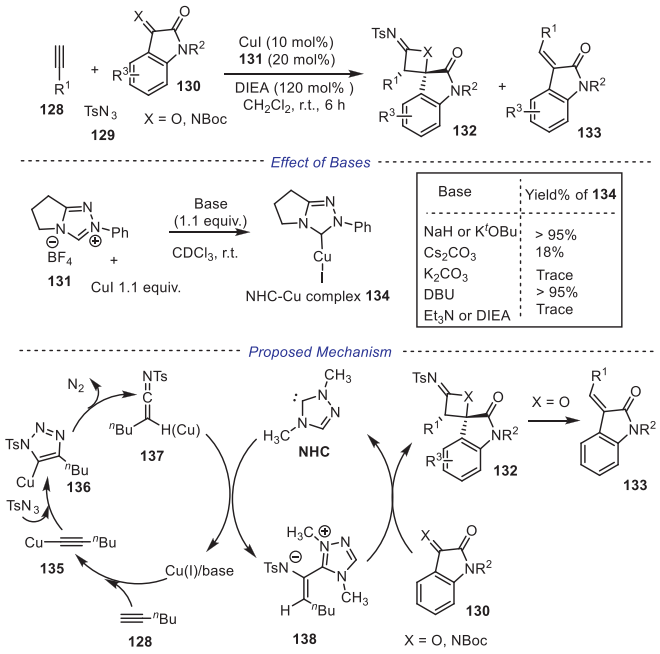
Under NHC catalysis, cyclopropanecarbaldehydes could act as an α-nucleophile or a γ-nucleophile in different reactions by *in-*



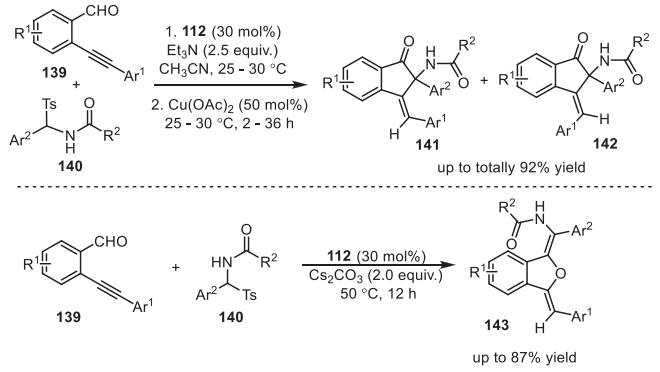
Scheme 23. Ag/NHC relay cataltytic domino annulation reaction of *N*′-(2-alkynylbenzylidene)hydrazides with cyclopropane-carbaldehydes.

situ formation of enolate intermediates [57–59]. In 2020, Cheng and coworkers reported a Ag/NHC relay cataltytic domino annulation reaction, providing an efficient approach for the construction of a variety of (1*R*,4*R*,5*S*)−4-(acylethyl)−11-aryl-2-tosyl-1,2,4,5-tetrahydro-5,1-(azenometheno)benzo[*c*]azepin-3-one **122** [60]. In experiment, the reaction proceeded smoothly under catalysis of $AgOCOCF_3$ (10 mol%) to obtain the intermediate **119**, which then underwent an NHC-catalyzed annulation to produce the desired adducts **122**. Under respective optimized reaction conditions, the authors studied the substrate scope of *N*′-(2-alkynylbenzylidene)hydrazides with cyclopropane-carbaldehydes, and the corresponding products **122** were obtained in moderate to good yields, with excellent enantioselectivity and diastereoselectivity. Based on the results of experiments, a possible mechanism was proposed for this transformation. First, the *N*-iminoisoquinolinium ylide intermediate **119** was formed by an Ag-catalyzed 6-*endo*-cyclization of *N*′-(2-alkynylbenzylidene)-hydrazide, the enolate intermediate 125, on the other hand, was generated *in situ* from the cyclopropane-carbaldehydes under catalysis of NHC, which then attacked the C=N bond of isoquinolinium ylide **119** yielded the intermediate **126**. Finally, an intramolecular lactamization, following by 1,3-shift of the amide nitrogen producing the desired adduct **122** (Scheme 23).

In 2014, Chi and coworkers realized a Cu/NHC relay catalytic three-component domino reaction, the reaction involved a copper-catalyzed activation of alkynes and activation of ketenimine intermediates by an *N*-heterocyclic carbene organocatalyst. Studying the compatibility of Cu and NHC catalysts [61], the authors found that strong base promoted the coordination of NHC and copper compared with weak bases. That was say, under 'weak' base conditions, there was a controllable kinetic/thermodynamic window that allowed the carbene organocatalyst and Cu metal catalyst to coexist with a meaningful level of concentrations. The experiment result confirmed this conclusion, when the authors used NHC/Cu catalyst in a ratio of 1:1 gave much better results (10 mol% each, 79% yield) than using the preformed NHC–Cu complex (10% yield), which suggested that the two catalysts (NHC and Cu) independently (rather than as the metal-carbene complex form) work in the presence of weak bases. In addition, mechanism of the three-component domino reaction was illustrated in Scheme 24. Initially, Cu-catalyzed activation of alkyne to react with TsN_3 to obtain the ketenimine intermediate **137**, which was then activated by the



Scheme 24. Cu/NHC catalyzed relay activation of alkynes for stereoselective reactions.

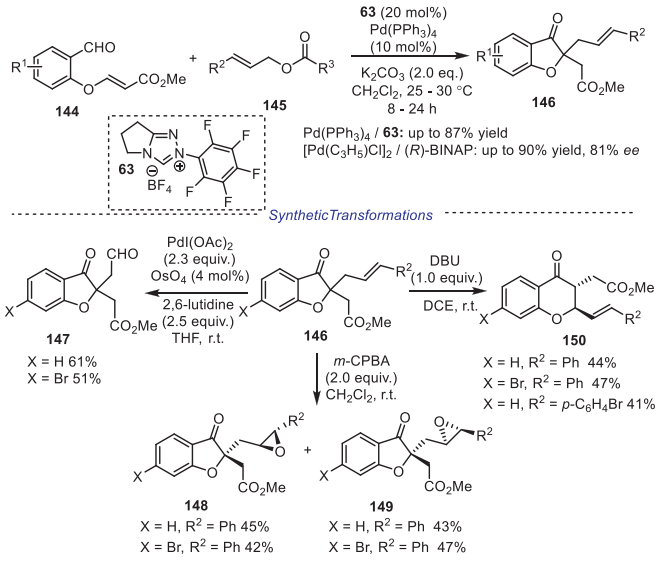


Scheme 25. NHC/Cu relay catalysis in the reaction of *o*-alkynylbenzaldehydes with *N*-acylimines.

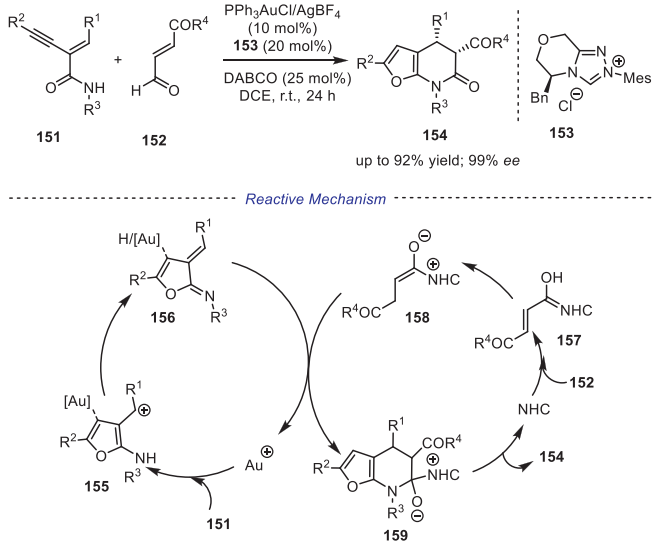
NHC organocatalyst to form azolium enamide intermediate **138**. The intermediate reacted with reactive ketones and imines to form the desired product **132**, which was simultaneously transformed to alkene product **133** when the N-protected isatins were used as reactive substrates (Scheme 24).

1-Indanone scaffolds are widely present in agrochemicals and pharmaceuticals. In 2018, Cheng and coworkers disclosed an efficient approach for the construction of a pair of *Z*- and *E*-2-amido-3-benzylidene-1-indanones in 47%–92% total yields by using NHC/Cu relay catalysis [62]. Optimization of reaction conditions suggested that the reaction media and temperature played decisive roles on the cascade catalysis in question. In addition, this work also provided simple and efficient methods for the highly selective synthesis of multifunctionalized 1,3-dihydroisobenzofuran derivatives from the same reactants by using NHC/Cs_2CO_3 relay catalytic system (Scheme 25).

In the same year, Cheng and coworkers reported an efficient NHC/Pd relay catalytic method for the synthesis of 2,2-disubstituted benzofuran-3-ones in moderated to good yields, the reaction underwent a cascade Stetter reaction and regioselective allylation [63]. When the reaction was performed in toluene at 0 °C, using $[Pd(C_3H_5)Cl]_2$/(*R*)-BINAP as the chiral palladium catalyst, the optically active 2-allylbenzofuran-3-one-2-acetates were unprecedentedly obtained in 54%-90% yields with 68%-81% *ee*, respectively. In addition, the obtained products could be easily converted into different polyfunctionalized compounds under suitable catalytic conditions, which demonstrated the valuable synthetic utility of the resulting products (Scheme 26).

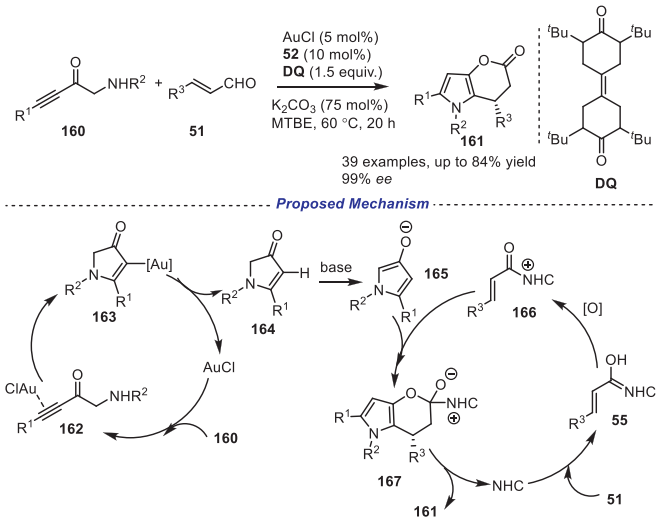


Scheme 26. NHC/Pd cascade catalytic method for the synthesis of 2,2-disubstituted benzofuran-3-ones.



Scheme 27. Au/NHC relay catalytic cycloisomerization/cyclization reactions of ynamides and enals.

In 2020, Chi and coworkers reported an Au/NHC relay catalytic enantioselective cycloisomerization/cyclization reactions of ynamides and enals, forming the bicyclic lactam products with excellent diastereo- and enantioselectivities [64]. Control experiment showed that the use of $AgPF_6$ was essential to release the active gold catalyst from PPh_3AuCl, while $AgPF_6$ alone did not have the ability to activate the alkyne substrate in the absence of PPh_3AuCl. Thus the authors proposed a possible mechanism. As outlined in Scheme 27. Initially, α,β-unsaturated *N*-sulfonyl ketimine **156** as a key intermediate was obtained by successive Au-catalyzed the activation of ynamide and isomerization. Next, treatment of enal with NHC formed Breslow intermedaite **157** that underwent a proton shift to give an azolium enolate intermediate **158**. Finally, the



Scheme 28. Au/oxidative NHC relay catalytic cascade annulation of α-aminoynones and enals.

bicyclic lactam product **154** was afforded by azadiene Diels–Alder reactions and regenerated the both Au and NHC catalysts (Scheme 27).

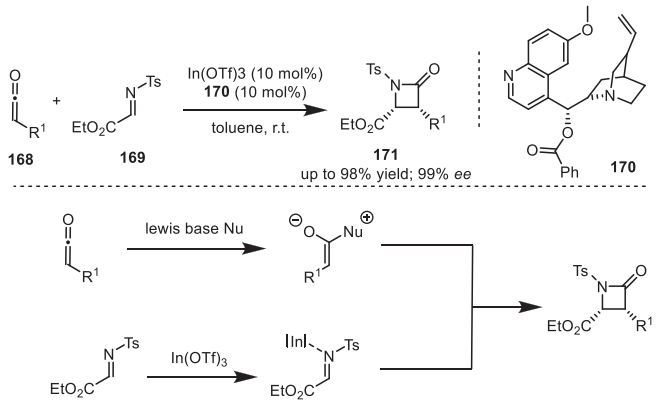
Success in the NHC and transition metal dual catalytic system mainly focused on the cycloaddition of homoenolate/enolate intermediates with various dipoles possessing nucleophilic and electrophilic moieties generated under transition metal catalysis. More recently, Lu and coworkers reported an Au/oxidative NHC relay catalytic annulation of α-amino-ynones and enals, in which pyrrolin-4-one (generated *in situ* from α-amino-ynones under Au catalysis) served as a highly effective doubly nucleophilic synthon, affording pyrrole-fused lactones **161** in good to high yields with excellent enantioselectivities [65]. The authors proposed a possible mechanism as showed in Scheme 28. First, enolate **165** was produced by cascade Au-catalyzed intramolecular cyclization of α-amino-ynones, protonolysis of intermediate **164** and deprotonation of pyrrolin-4-one. Concurrently, the Breslow intermediate **55** (producing by reaction of enal with NHC) underwent oxidation to form an α,β-unsaturated acyl intermediate **166**. Next, successively enolate conjugate addition and alkoxide cyclization occurred to form intermediate **167**, which finally underwent elimination to produce **161** with regenearation of the NHC catalyst (Scheme 28).

4. Application of tertiary amine/metal cooperatively catalytic system in annulations

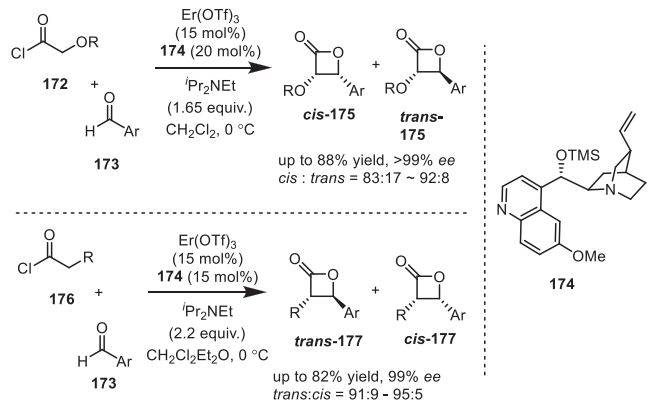
4.1. Tertiary amine/metal cooperatively catalytic annulations

The tertiary amines own a pair of nonbonding electron pairs, which represent the most commonly recognized form of nucleophilic Lewis base catalysts [66,67]. As the development of Lewis base catalysis, tertiary amine catalysts have proven to be effective catalysts for a range of synthetic transformations. In this review, we summarize recent progress in this area, and the diverse reactivities, various reaction modes and proposed mechanisms will be described in detail.

The Wynberg reaction reported in 1982 [68], has found widespread applications for the addition of ketene to di- and trichloroaldehydes and ketones. However, the Wynberg reaction involving substituted ketenes has been hampered by the tendency of these ketenes to dimerize under nucleophilic catalysis. In 2002, Lectka and coworkers reported a [2 + 2] cycloaddition reaction by using tertiary amine/In(OTf)$_3$ dual catalysis [69]. According to experiment result, the authors thought that a chiral Lewis base was paired with an achiral Lewis acidic metal salt to effect a high-yielding synthesis of optically enriched β-lactam products. Later, the authors validated the reaction mechanism by systematically mechanism experiment (Scheme 29) [70].



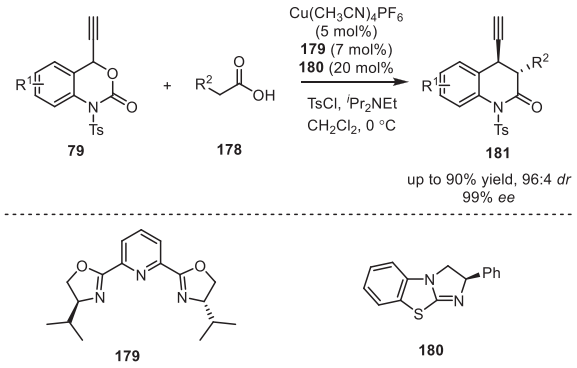
Scheme 29. Tertiary amine/In(OTf)$_3$ cocatalyzed [2 + 2] cycloaddition of ketene with imine.



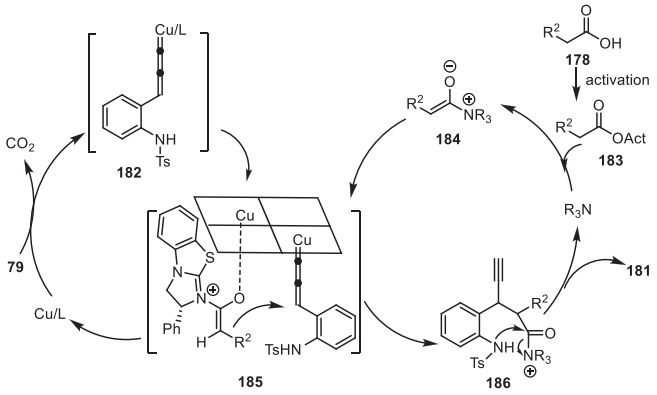
Scheme 30. Tertiary amine/Sc(OTf)$_3$ co-catalyzed [2 + 2] cycloaddition reaction of substituted ketenes with unactivated arylaldehydes.

In 2005, Calter and coworkers described a tertiary amine/Sc(OTf)$_3$ co-catalyzed [2 + 2] cycloaddition reaction of substituted ketenes with unactivated arylaldehydes, affording β-lactones in high diastereo- and enantioselectivity [71]. According to the experiment result, the authors thought that the diastereoselectivity of adducts depended on the substitution of the acid chloride. The reaction of aliphatic acid chlorides with aldehydes produced predominantly the *trans*-isomers, and the substrates alkoxyacetyl chlorides favored formation of the *cis*-isomer (Scheme 30).

The reaction of copper complexes with propargylic esters generates copper–allenylidene complexes, which turn out to be versatile intermediates and allow the development of various propargylation reactions. In 2017, Gong and coworkers established a cooperative isothiourea/copper co-catalyzed asymmetric decarboxylative [2 + 4] annulation of 4-ethynyl dihydrobenzooxazinones and carboxylic acids, yielding optically active 3,4-dihydroquinolin-2-one derivatives in good yields with excellent stereoselectivities [72]. Optimization of reaction suggested that the matched chirality of chiral ligand and organocatalyst played the key role in controlling diastereoselectivity. In addition, the enantioselectivity was predominantly determined by organocatalyst, even if the achiral copper complex, in combination with chiral isothiourea **180**, still obtained a high enantioselectivity. Subsequently, the substrate scope and limitation was investigated, and found that simple propargylic



Scheme 31. Cooperative tertiary amine/copper co-catalyzed asymmetric decarboxylative [2 + 4] annulation of 4-ethynyl dihydrobenzooxazinones.

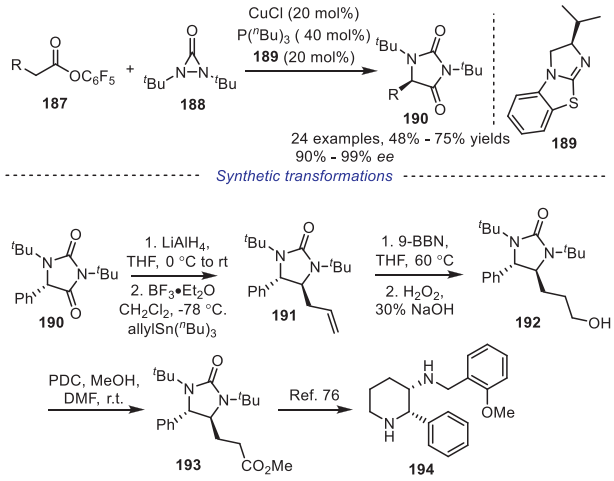


Scheme 32. A plausible mechanism for isothiourea/copper co-catalyzed asymmetric decarboxylative [2 + 4] annulation.

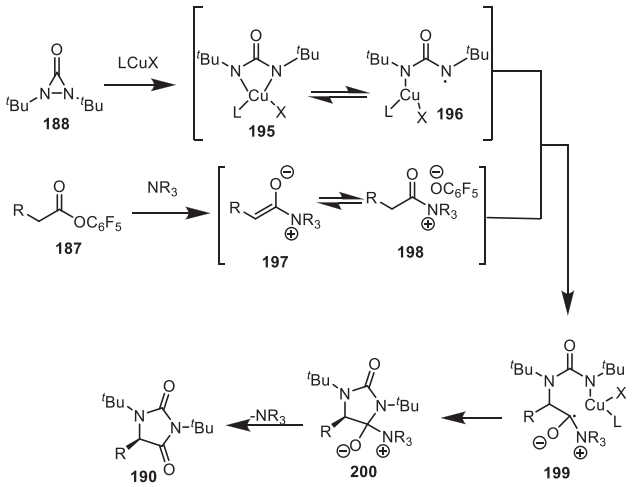
acetate or 3-phenylpropanoic acid was not suitable substrates in the reaction (Scheme 31). Almost simultaneously, Wu and coworkers reported a similar experiment result [73].

According to the results of experimental results and the previous reports, a plausible mechanism was presented. As shown in Scheme 32, the decarboxylation of **79** with a copper complex generated the copper–allenylidene intermediate **182**. Concurrently, a C1 ammonium enolate intermediate **184** was obtained by the treatment of a chiral isothiourea catalyst with an active electrophilic species **183**. The intermediate **186** was generated by an enantioselective nucleophilic addition of **182** to the γ-carbon atom of **184**. The authors thought that the copper complex [74] might play a dual role in which one copper participated in the decarboxylation of **79** to give the copper–allenylidene complex, and the other acted as a counterion bonded to the C1 ammonium *Z*-enolate (**185**). Finally, a lactamization reaction of the intermediate **186** produced the 3,4-dihydroquinolin-2-one **181** and released the chiral isothiourea catalyst (Scheme 32).

Hydantoins as core structural elements have significant application potential in natural products and pharmaceuticals. In 2018, Gong and coworkers developed an isothiourea/copper cooperative catalytic strategy for the preparation of highly enantioenriched hydantoins by an enantioselective α-amination of esters [75]. The reaction proceeded smoothly at 70 °C in the presence of an isothiourea catalyst and a copper chloride−tributylphosphine complex by using $CHCl_3$ as a reaction solvent, affording the desired hydantoin **190** in good yield with enantioselectivity. It's worth mentioning that this work provided simple and efficient methods for the highly efficient synthesis of an ester **193**, which could be transformed into (+)-CP-99994 (a high affinity NK1 antagonist) by following Shi's procedure (Scheme 33) [76].



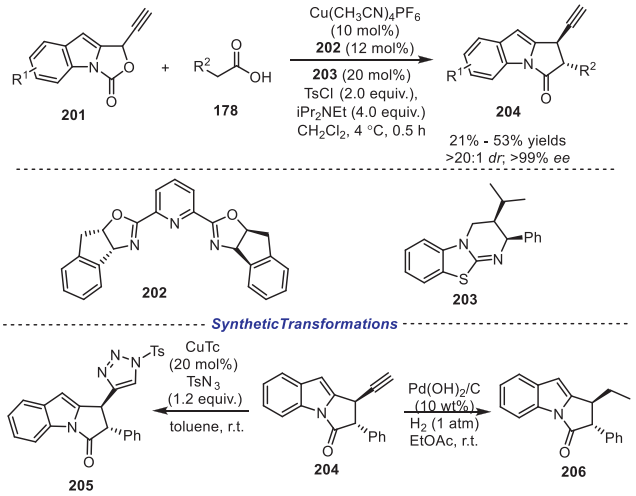
Scheme 33. Isothiourea/copper cooperative catalysis strategy for the preparation of highly enantioenriched hydantoins.



Scheme 34. A plausible mechanism for isothiourea/copper cooperative catalysis strategy for the preparation of highly enantioenriched hydantoins.

Based on the experimental results, a plausible mechanism of this α-amination of esters was proposed as shown in Scheme 34. An acylation reaction of the ester **187** with a chiral isothiourea produced a chiral acylammonium **197**. Simultaneously, the four-membered Cu(III) species **195** or a Cu(II) radical species **196** was obtained by the cleavage of the N−N bond of diaziridinone **188** in the presence of Cu(I) catalyst. The electron paramagnetic resonance (EPR) showed that the radical intermediate **196** might be the active copper species in the cooperative catalytic cycle. Next, the chiral intermediate **199** was produced by the treatment of the acylammonium **197** with Cu(II) species **196**. Subsequently, continuously reductive elimination of **199** and an intramolecular amidation reaction of **200** gave the enantioenriched hydantoin **190** and regenerated the catalyst (Scheme 34).

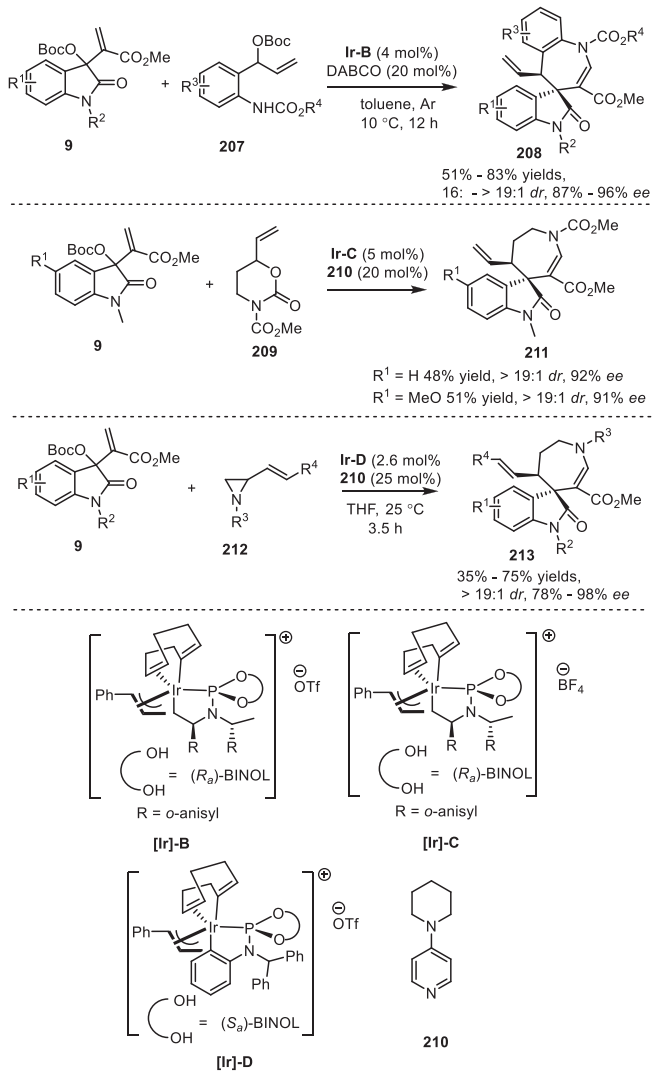
In 2021, Deng and coworkers reported an asymmetric decarboxylative [2 + 3] cycloaddition of ethynyl indoloxazolidones with carboxylic acids by using isothiourea/copper synergistic catalysis [77]. In this reaction, a novel indolyl copper-allenylidene amphiphilic intermediates generated *via* copper-mediated decarboxylation of ethynyl indoloxazolidones and prepared a wide range of pyrrolo[1,2-a]indoles with excellent stereoselectivity. In addition, the resulting products could underwent click reaction and reduction reaction to give the desired 1,2,3-triazole and chiral indoline, respectively (Scheme 35).



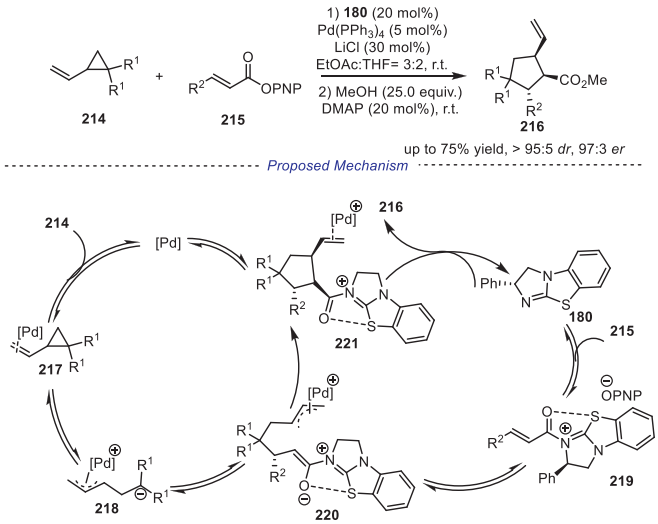
Scheme 35. Isothiourea/copper synergistic catalyzed [2 + 3]-cycloaddition of ethynyl indoloxazolidones.

The Morita–Baylis–Hillman (MBH) adducts have emerged as powerful synthons in organic synthesis [78,79]. In 2019, Chen and coworkers developed an efficient tertiary amine/iridium complexes cooperatively catalytic strategy for construction of valuable 4-azepane or 4-piperidine motifs by a [3 + 4] or [3 + 3] annulation pattern [80]. It was worth noting that the chiral iridium complex induced the stereocontrol in this reaction, a common tertiary amine (DABCO), in combination with chiral iridium complex, could offer a high enantioselectivity, which differed from the known tertiary amine/metal catalysis. The substrate scopes and limitations of the cooperative catalytic strategy were also investigated under the optimized conditions. Besides carbamate-functionalized allylic carbonate **207**, the cyclic vinyl carbamate **209** and vinyl N-Ts aziridines **212** could be applied for the reactions of Morita–Baylis–Hillman carbonates by using tertiary amine/iridium complexes cooperative catalysis. Additionally, the obtained products could be further converted into more complex compounds under suitable catalytic conditions, which demonstrated the valuable synthetic utility of the product (Scheme 36). In 2021, the authors also realized asymmetric [3 + 4] annulations between isatin-derived Morita−Baylis−Hillman carbonates and two types of vinyl carbonates by using synergistically tertiary amines and palladium catalytic system, affording a range of oxepane frameworks in moderate to good yields with high stereocontrol [81].

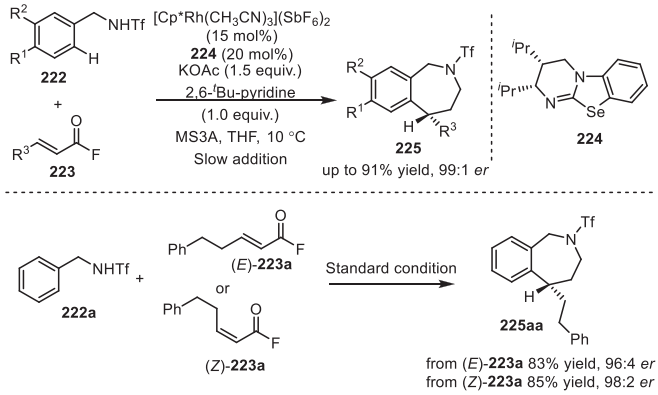
Vinylcyclopropanes have emerged as promising and powerful substrates for palladium-catalyzed [3 + 2] cycloadditions. In 2022, Smith and coworkers reported an isothiourea/palladium cooperative catalyzed enantioselective [2 + 3] cycloaddition of vinylcyclopropanes and α,β-unsaturated esters [82]. After extensive condition screening, it was found that the optimal conditions required achiral $Pd(PPh_3)_4$/chiral isothiourea dual catalytic system in EtOAc:THF (3:2) at room temperature under argon atmosphere, the functionalised cyclopentanes **216** were generated in good yields and excellent diastereo- and enantioselectivity. It was worth noting that the salt additive (LiCl) played a significant role in obtaining high levels of diastereo- and enantioselectivity because of the addition of Cl^- ions generally increases the rate of π-σ-π isomerization within Pd π-allyl intermediates [83–85]. The authors proposed a reactive mechanism showed in Scheme 37. Initially, π-allyl-palladium intermediate **218** was obtained by treatment of vinylcyclopropane **214** with $Pd(PPh_3)_4$. Concurrently, isothiourea **180** underwent reversible *N*-acylation with PNP ester **215**, giving α,β-unsaturated C1 ammonium intermediate **219**. Subsequently, continuous Michael addition (**220**), intramolecular ring



Scheme 36. An efficient tertiary amine/iridium complexes cooperatively catalytic strategy for construction of valuable 4-azepane or 4-piperidine motifs.



Scheme 37. Isothiourea/palladium cooperative catalyzed enantioselective [2 + 3] cycloaddition of vinylcyclopropanes and α,β-unsaturated esters.

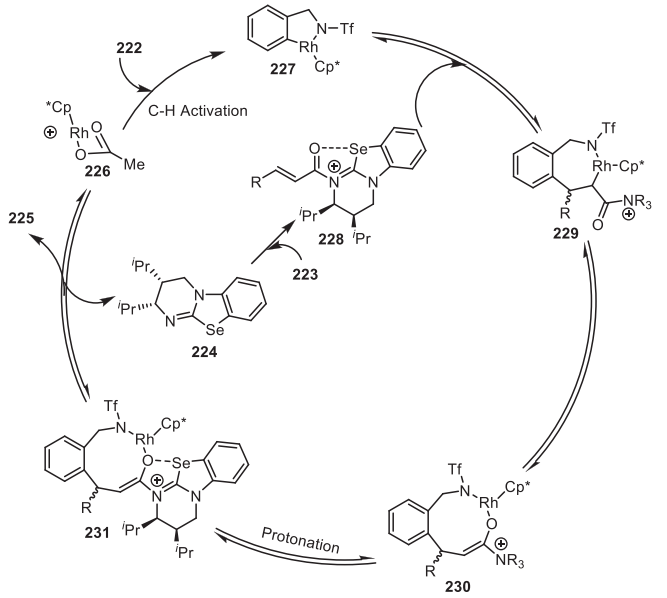


Scheme 38. Tertiary amine/Cp*Rh cooperative catalytic C–H bond functionalization.

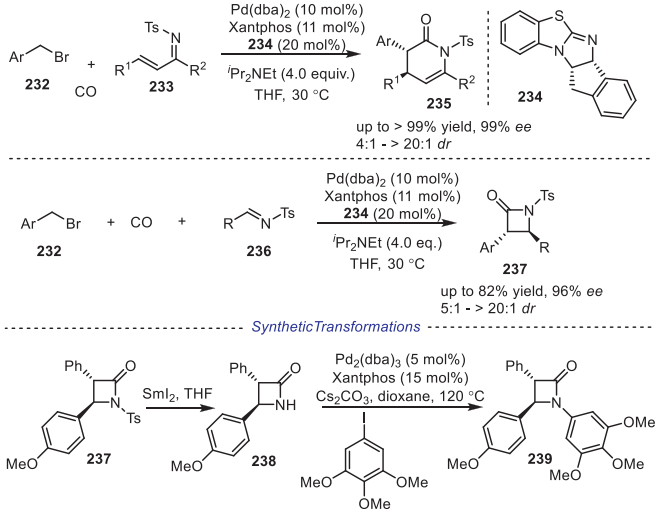
closure generated cyclopentane **221**. Finally, decomplexation of the palladium catalyst and irreversible turnover of the isothiourea catalyst by *para*-nitrophenoxide furnished the desired products **216** (Scheme 37).

C–H bond functionalizations have emerged as powerful methods for the construction of valuable organic molecules. More recently, Matsunaga and coworkers disclosed a cooperative catalytic system composed of an achiral Cp*Rh catalyst and a chiral tertiary amine catalyst, for an enantioselective C–H functionalization reaction [86]. The experiment result demonstrated that the cooperative catalytic systems were highly tolerant of functional groups to give a wide range of target products **225** in high enantioselectivities. Notably, the authors found that the slow addition of **223** might suppress not only its decomposition but also a possible racemic background reaction between a metallacycle intermediate and **223**, thus increasing the yield and resulting in a significant improvement of the enantioselectivity. In addition, further study suggested that the isomerization of (*Z*)–**223** to (*E*)–**223** was negligible, which showed that the isomerization of 223 occurred under the reaction conditions and/or that the insertion of the double bond was reversible and the insertion step was less likely to be enantio–determining step (Scheme 38).

A plausible mechanism for this cooperative catalytic process was outlined in Scheme 39. Initially, a cationic Cp*Rh(III) species **226** was obtained from $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ and KOAc, which reacted with **222** to form a metallacycle intermediate **227**. Meanwhile, a C1 ammonium intermediate **228** was generated by the nucleophilic attack of tertiary amine to α,β-unsaturated precursor **223**. The authors thought that the conformation of **228** could be fixed by a noncovalent interaction between the acyl oxygen atom and the selenium atom from the catalyst. Next, the acyl ammonium **228** coordinated with metallacycle **227**, followed by the insertion of the C–C double bond to afford C-enolate **229**, which subsequent furnished a O-enolate **230** by an isomerization. Finally, protonation of **230** to give **231** and subsequent cyclization between the directing group and the acyl ammonium moiety furnished the product **225** (Scheme 39).



Scheme 39. A plausible mechanism for tertiary amine/Cp*Rh cooperative catalytic C–H bond functionalizations.

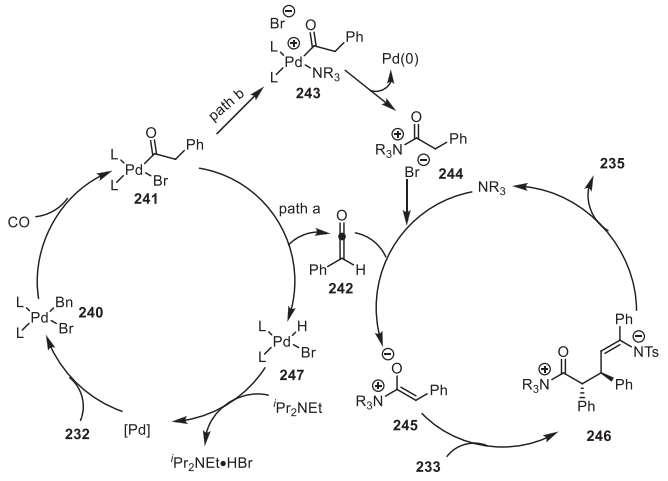


Scheme 40. Isothiourea/palladium relay catalytic asymmetric annulation reaction of bromides, CO and ketimine.

4.2. Tertiary amine / metal relay catalytic annulations

Tertiary amine/metal relay catalysis has found widespread applications in organic synthesis. For this type of chemistry, the C1 ammonium enolate generated from the nucleophilic addition of a tertiary amine to a preformed or *in situ* generated ketene is pivotal. Thus developing a general route to the catalytic generation of chiral C1-ammonium enolates from simple starting materials has become an active research field. In 2019, Gong and coworkers applied palladium-catalyzed carbonylation reaction to isothiourea/metal reply catalysis [87]. Using inexpensive CO as the C1 source, the authors envisioned that a ketene intermediate first generated by palladium-catalyzed carbonylation reaction, which next formed C1-ammonium enolate in the presence of a chiral isothiourea catalyst. Here the authors reported an isothiourea/palladium relay catalytic asymmetric [1 + 1 + 4] annulation reaction of bromides **232**, CO and ketimine **233**, delivering the desired products **235** in good yields with high enantioselectivities. This strategy owned well substrate tolerance, and *N*-tosylimine **236** could be applied as reactive substrate to give the corresponding β-lactams **237** with high enantio– and diastereoselectivities and good yields. In addition, an antiproliferative agent **239** could be obtained by two-step classical transformations (Scheme 40).

The authors proposed a plausible mechanism, as showed in Scheme 41. Initially, the oxidative addition reaction of palladium catalyst to benzyl bromide **232** generated the intermediate **240**, which then underwent an insertion reaction with CO to gener-



Scheme 41. A plausible mechanism for isothiourea/palladium relay catalytic asymmetric annulation reaction.

ate acylpalladium **241**. Next, the authors thought that two possible paths might occur: one is that the acylpalladium intermediate **241** bearing α,β-hydrogen might be transformed to the ketene **242** through β-hydride elimination, which then reacted with isothiourea catalyst **234** to form the key C1-ammonium enolate intermediate **245**; other alternative pathway was to generate **245** from acylpalladium **241**, which coordinated with catalyst **234** to give an intermediate **243**, and then generating an ammonium salt **244** by reductive elimination. In the presence of a base, the salt could transform into ammonium enolate **245**. Finally, successive Michael addition and intramolecular cyclization generated the corresponding dihydropyridone **235** (Scheme 41).

5. Conclusions

Dual catalysis has proven an efficient strategy to achieve unprecedented transformations and selectivity that are not available using a single catalyst. The combination of diverse catalysts has been applied widely to the synthesis of fine chemicals, pharmaceuticals, and materials. As described in this review, we have summarized the recent advances on nucleophilic Lewis base/metal dual catalyzed cyclization reactions. The combination of metal with a variety of nucleophilic Lewis base catalysts, such as phosphines, *N*-heterocyclic carbenes (NHC) and tertiary amines, has enabled a large number of unprecedented cycloaddition reactions by employing appropriate reactive precursors. Obviously, these reported methodologies show a bright prospect to further design and discover new reaction modes and realize challenging chemical transformations that had not been possible using either nucleophilic Lewis base or the metal catalyst alone.

Despite these significant achievements made in this area, there are still great challenges that need to be resolved. For example, catalyst compatibility issues still pose constraints on the effective combination of versatile activation modes. In addition, the catalyst loading of Lewis base required is fairly high (usually 10–30 mol%). Therefore, the development of the design of new, highly active Lewis base catalysts and highly efficient synthetic strategies is becoming more attractive. Undoubtedly, the concept of green chemistry and sustainable development will prompt chemists to develop new avenues to solve these problems, such as performing reactions in aqueous media, lowering the loading of catalysts and developing universal dual catalytic module. As this perspective has illustrated, we hope that, in due time, a general system involving dual catalysis will appear to advance the development of practical organic synthesis in the future.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled “Recent Advances in Annulations Enabled by Nucleophilic Lewis Base/Metal Dual Catalysis”.

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