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Review

Recent Strategies in Nickel-Catalyzed C–H Bond Functionalization for Nitrogen-Containing Heterocycles

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Abstract: *N*-heterocycles are ubiquitous in natural products, pharmaceuticals, organic materials, and numerous functional molecules. Among the current synthetic approaches, transition metal-catalyzed C–H functionalization has gained considerable attention in recent years due to its advantages of simplicity, high atomic economy, and the ready availability of starting materials. In the field of *N*-heterocycle synthesis via C–H functionalization, nickel has been recognized as one of the most important catalysts. In this review, we will introduce nickel-catalyzed intramolecular and intermolecular pathways for *N*-heterocycle synthesis from 2008 to 2021.

Keywords: nickel-catalyzed; *N*-heterocycle; C–H functionalization

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1. Introduction

N-heterocycles are the most abundant type of heterocyclic organic compounds. Based on their electronic properties, *N*-heterocycles could be subdivided into aliphatic *N*-heterocycles and aromatic *N*-heterocycles. Furthermore, they are mainly classified based on their ring size into three-, four-, five-, six-, and seven-membered *N*-heterocycles [1–6]. Nitrogen-containing heterocyclic compounds have unique biological activity, low toxicity, and high internal absorption, making them potent medicines and bioactive compounds [7–13]. For example, the 2-pyridone ring in camptothecin has been linked to significant antitumor activity [12] and a 4-pyridinone ring comprises the skeleton of the fluoroquinolone antibiotic, levofloxacin [13]. So far, pursuing the means to efficiently synthesize *N*-heterocycles has been a key target for organic and pharmaceutical chemists.

In recent years, C–H functionalization has become one of the most effective approaches to constructing C–C bonds and C–heteroatomic bonds [14–19]. This process can convert C–H bonds into the corresponding C–X bonds (X = C, O, N, S, F, Cl, Br, Si, etc.) in a single step. Compared with the traditional organic synthetic strategies, this method can effectively avoid the pre-functionalization of starting materials, reduce the use of chemical reagents, and shorten the count of reaction steps, thus greatly improving the efficiency of the reaction. Within this field, transition metal-catalyzed C–H bond functionalization is an important approach due to its advantages of simplicity, efficiency, and environmental benignity [20,21]. The uses of Pd, Rh, Ir, and other common noble-metal catalysts have been widely reported with regard to the construction of *N*-heterocycles through C–H bond functionalization reactions [22–24]. In addition, some cheap first-row metal catalysts, including Ni, Cu, Co, Mn, etc., have also been used to realize these processes with success [25–28]. Nickel is located at the top of group VIII in the fourth period of the periodic table. Compared with other transition metal catalysts, nickel catalysts have attracted much attention because of their low cost, widespread availability, and high conversion rates [29,30]. Furthermore, nickel exists in various oxidation states, giving rise to different redox pathways in different

catalytic processes. Due to this unique property, nickel can be used to catalyze cross-coupling, insertion, and cyclization reactions alike [31–33]. Hence, nickel is one of the most important transition metal catalysts for the synthesis of *N*-heterocycles.

Recently, some related reviews on transition metal-catalyzed C–H functionalization for the construction of diverse nitrogen-containing heterocycles have been reported [34–41]. However, most of them focused mainly on Pd, Rh, Co, and Cu catalysts [34–40]; only one report from the Cramer group briefly illustrated their Ni-catalyzed asymmetric C–H bond functionalization for chiral *N*-heterocycles [41]. In this review, we will briefly introduce the recent progress in the field of nickel-catalyzed *N*-heterocycle synthesis by C–H functionalization via intramolecular and intermolecular pathways, respectively (Figure 1).

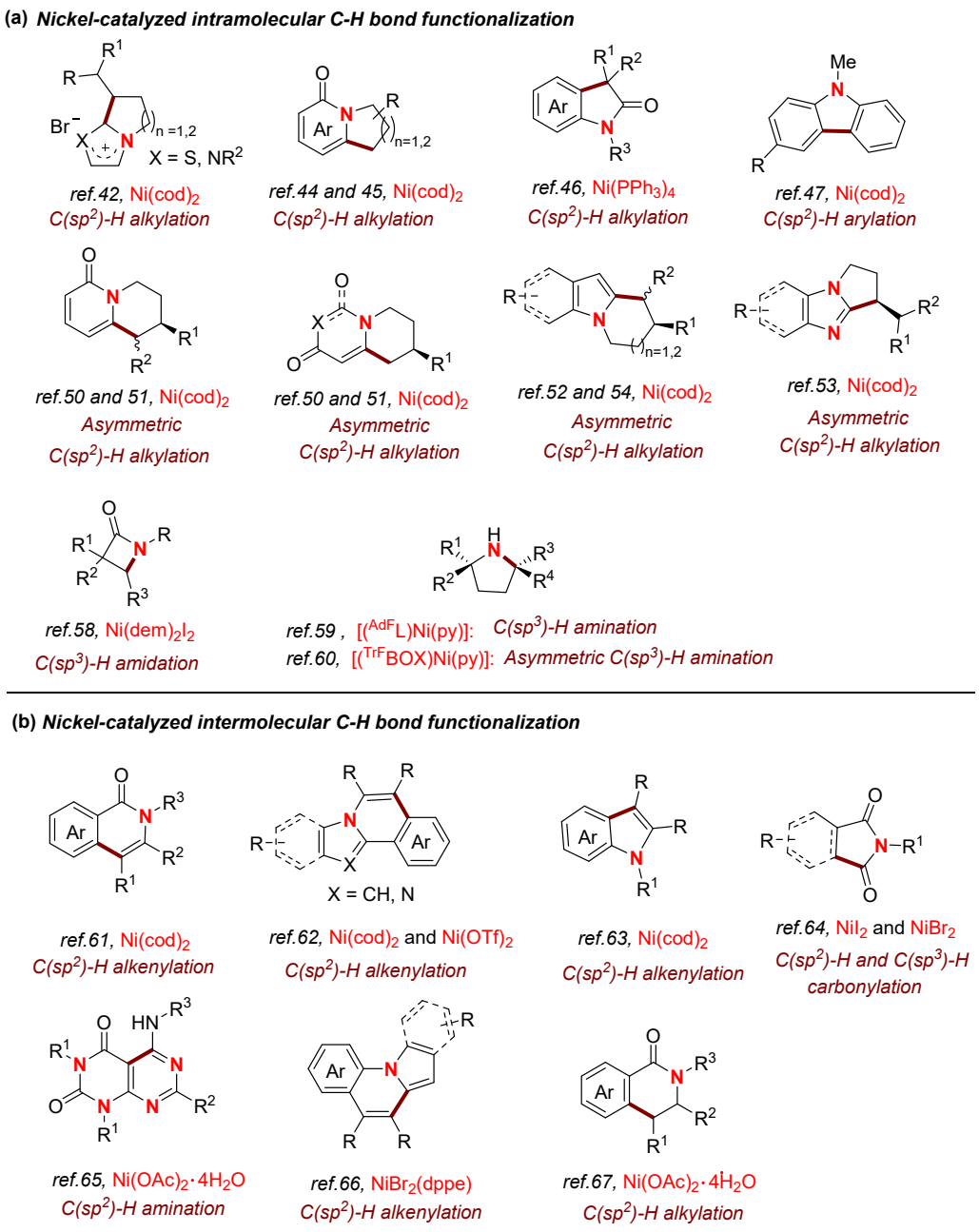
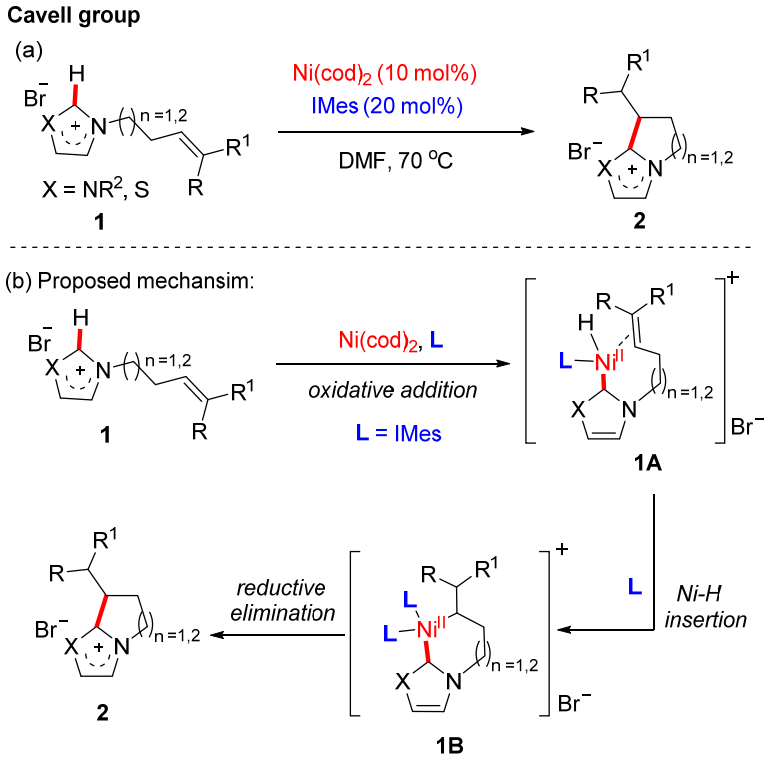


Figure 1. Outline of nickel-catalyzed C–H functionalization for *N*-heterocycle synthesis.

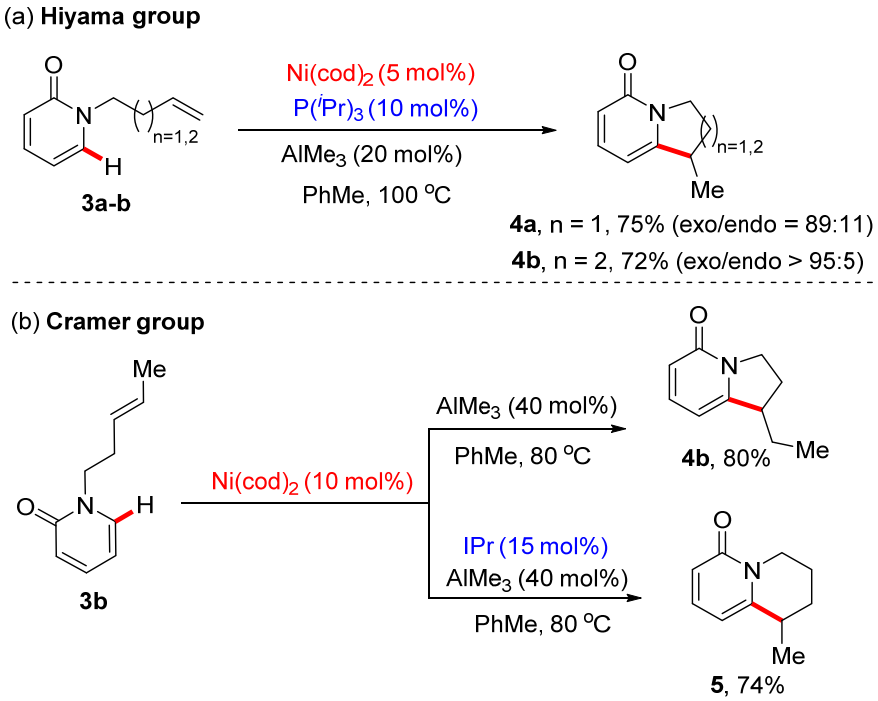
2. Nickel-Catalyzed Intramolecular C–H Bond Functionalization

In the past two decades, transition metal-catalyzed C–H bond functionalization has developed into a direct and effective approach for the construction of different *N*-heterocyclic compounds. In 2008, the Cavell group reported a Ni-catalyzed intramolecular C(sp^2)–H alkylation reaction employing different alkenyl-substituted imidazolium salts as substrates, $Ni(cod)_2$ as a catalyst, and *N*-heterocyclic carbene IMes as a ligand [42]. Using this strategy, various kinds of five- and six-membered fused-ring imidazolium and thiazolium salts were constructed in moderate to quantitative yields (Scheme 1a). Mechanistic studies hinted that the carbene-Ni-alkyl intermediate **1B** is formed through a Ni(0)-oxidative addition of substrate **1** and a subsequent intramolecular Ni–H insertion process. Subsequently, this carbene-Ni-alkyl intermediate **1B** affords the desired product **2** through a reductive elimination process (Scheme 1b). It should be noted that these fused-ring imidazolium and thiazolium salts are potential components of synthetic drugs and ionic liquids [43,44].



Scheme 1. (**a**) $Ni(cod)_2$-catalyzed intramolecular C(sp^2)–H alkylation of alkenyl-substituted imidazolium salts; (**b**) Proposed mechanism.

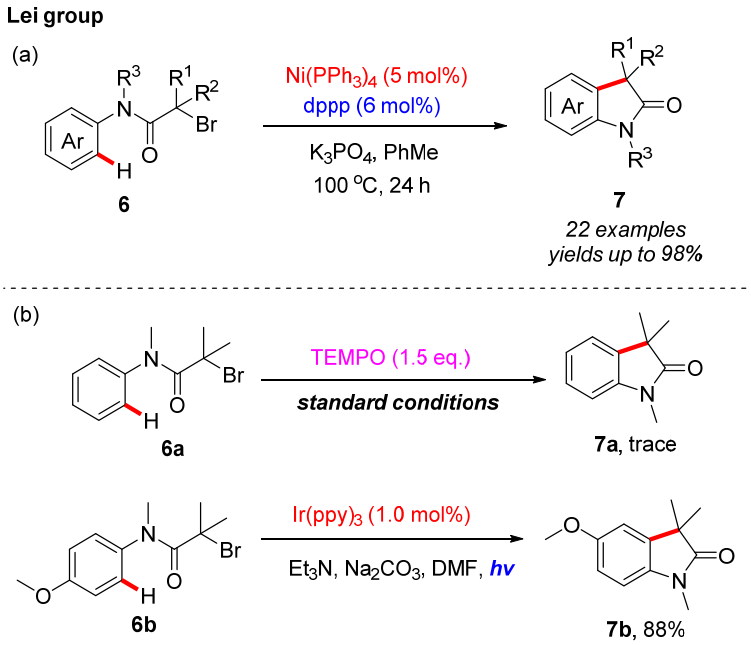
Pyridone skeletons are widely present in a variety of important biologically active heterocyclic compounds [12,13,45]. Therefore, the development of novel, effective, and rapid methods for obtaining these heterocyclic compounds is of interest to synthetic and medicinal chemists. In 2009, the Nakao and Hiyama group developed a $Ni(cod)_2/AlMe_3$ co-catalyzed intramolecular C–H alkylation of alkenyl-substituted pyridones **3** in the presence of P(*i*-Pr)$_3$ as a ligand [46]. In this reaction, $AlMe_3$ acts as an important Lewis acid to assist the reaction by activating the carbonyl group of the substrate. The intramolecular insertion of the unsaturated bond was achieved, leading to the synthesis of the five-membered fused-ring pyridone derivatives **4a-b** in good yields (Scheme 2a). Notably, this intramolecular alkylation process mainly gave rise to *exo*-cyclization products, although theoretically the reaction could occur at both ends of the double bond, leading to the formation of both *exo* and *endo* products. Thereafter, control over the cyclization mode of this reaction has become the focus of the subsequent related research.



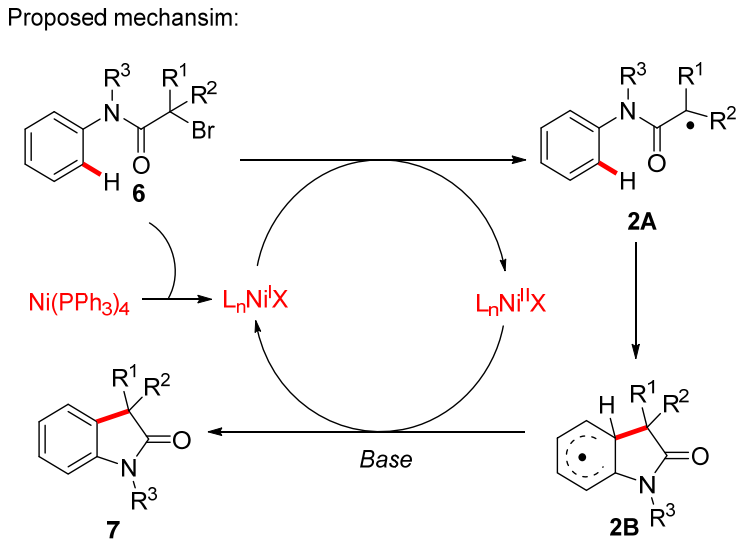
Scheme 2. (**a**) Ni(cod)$_2$-catalyzed intramolecular C–H alkylation of alkenyl-substituted pyridones in the presence of P(*i*-Pr)$_3$ as a ligand; (**b**) Ni(cod)$_2$-catalyzed ligand-controlled intramolecular C–H alkylation of alkenyl-substituted pyridines.

In 2015, Cramer developed a Ni-catalyzed ligand-controlled intramolecular C–H alkylation of alkenyl-substituted pyridone **3b** [47]. Investigative experiments indicated that the regioselectivity of the cyclization reaction is controlled by the ligand and is completely independent of the ring size and the olefin substitution pattern. On the one hand, when the Ni(cod)$_2$ catalyst is used alone, this reaction gives the *exo*-selective cyclization product **4b**. On the other hand, when an additional bulky *N*-heterocyclic carbene IPr is added as a ligand to the catalytic system, the reaction leads to the *endo*-cyclization product **5** (Scheme 2b).

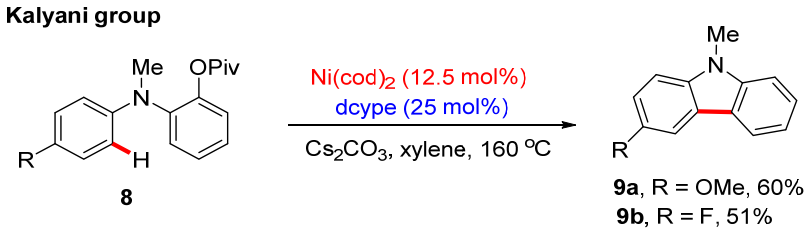
In addition, Lei and co-workers reported Ni(PPh$_3$)$_4$-catalyzed intramolecular C(sp^2)–H alkylation exploiting the alkyl–Br bonds [48]. Substrates with different functional groups were well tolerated in this reaction, and the desired indolones were obtained in moderate to good yields (Scheme 3a). Both visible photocatalysis and radical trapping experiments indicated that a radical process might be involved in this process (Scheme 3b). Furthermore, a mechanism involving a Ni(I)/Ni(II) catalytic cycle was proposed (Scheme 4). It is believed that the Ni(I) species is formed through a SET process between Ni(PPh$_3$)$_4$ and the alkyl bromide substrate **6**. Afterwards, a second SET between the Ni(I)species and substrate **6** generates the radical species **2A** and the Ni(II) species. Next, the intramolecular radical addition provides the intermediate **2B**. Finally, the further oxidation of this intermediate with the Ni(II) species yields the desired product **7** and the Ni(I) species. Meanwhile, the Kalyani group also demonstrated an effective method for the synthesis of carbazoles **9** through Ni(cod)$_2$-catalyzed intramolecular C–H arylation employing aryl pivalates **8** as starting materials [49]. In the substrate scope study, two carbazoles were isolated in moderate yields (Scheme 5). Mechanistic studies indicate that a CMD-type C–H activation step might be involved in this process.



Scheme 3. (**a**) $Ni(PPh_3)_4$-catalyzed intramolecular $C(sp^2)$–H alkylation utilizing alkyl–Br bonds for the synthesis of indolones; (**b**) Radical trapping and visible photocatalysis experiments.



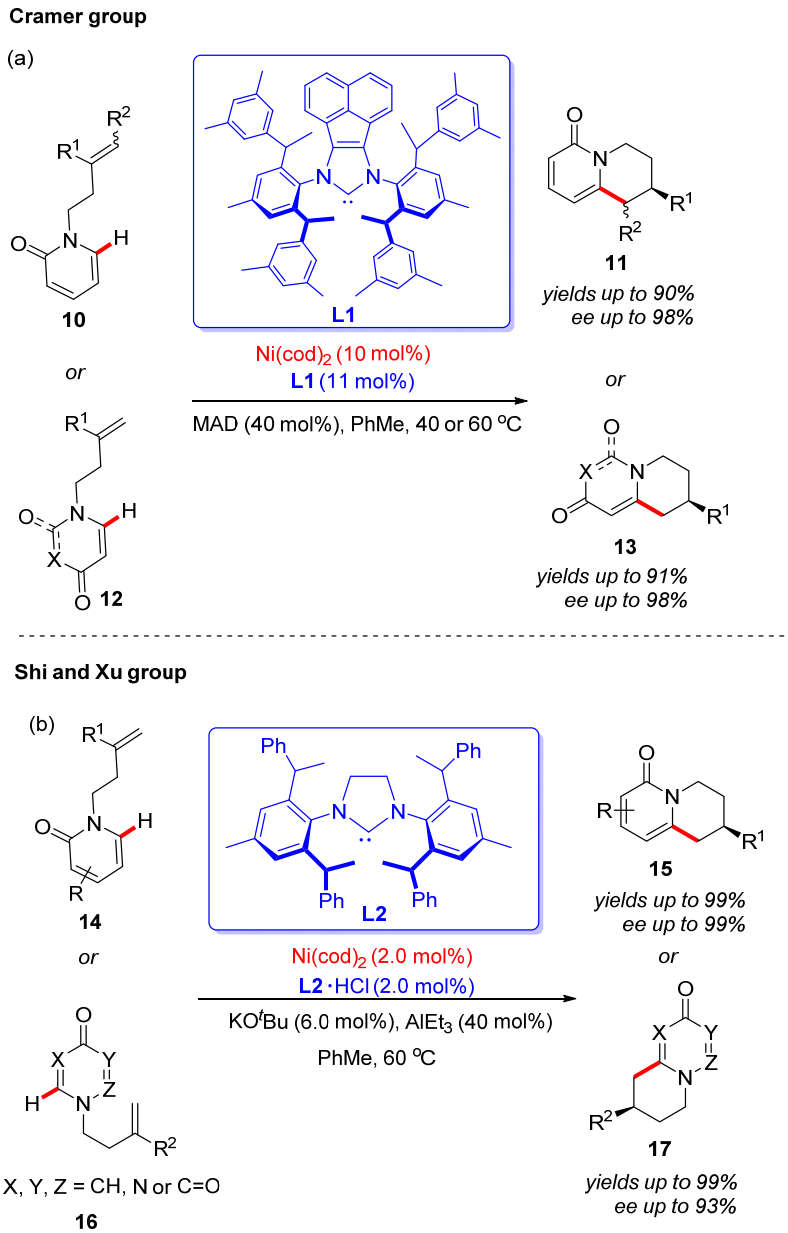
Scheme 4. Proposed mechanism of $Ni(PPh_3)_4$-catalyzed intramolecular $C(sp^2)$–H alkylation utilizing alkyl–Br bonds.



Scheme 5. $Ni(cod)_2$-catalyzed intramolecular C–H arylation of aryl pivalates.

In recent years, chiral *N*-heterocycle synthesis has become an unmistakably critical target [50,51]. Encouraged by previous reports, the Cramer group reported a $Ni(cod)_2$-catalyzed chiral ligand-enabled enantioselective intramolecular C–H alkylation reaction [52].

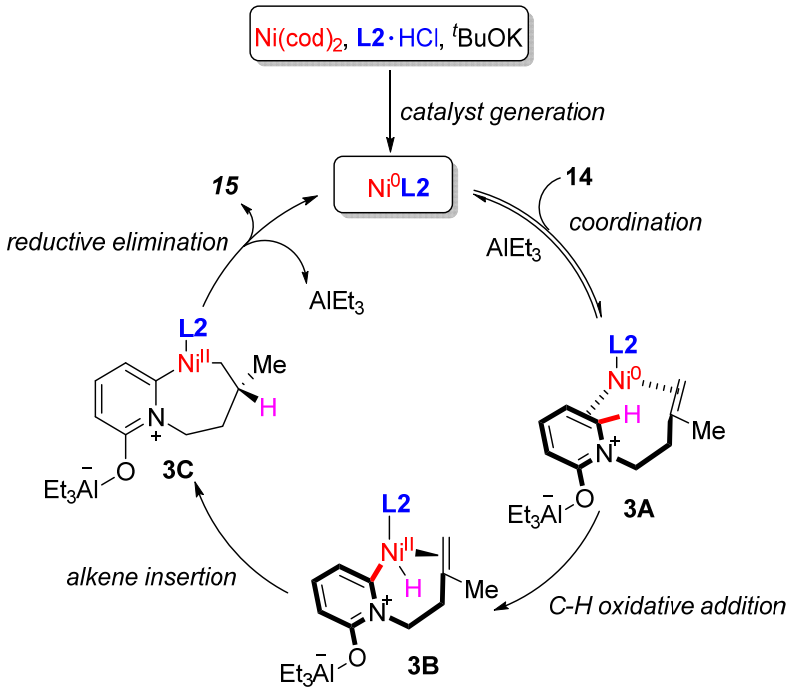
Various kinds of chiral bicyclic heterocycle products were isolated in good yields and excellent enantioselectivities (Scheme 6a). It is worth noting that a bulky chiral *N*-heterocyclic carbene ligand **L1** was demonstrated as the most effective chiral ligand for this asymmetric process. MAD was proved as the optimal Lewis acid. Under mild reaction conditions, alkenyl-substituted 2-pyridone substrates **10** were converted to the corresponding six-membered fused-ring 2-pyridone derivatives **11** in good yields (up to 91% isolated yields) and excellent enantioselectivities (up to 98% *ee*). In addition, 4-pyridone and uracil compounds could also be used as reaction substrates to obtain chiral bicyclic heterocycles with good yields (up to 93% isolated yields) and excellent enantioselectivities (up to 98% *ee*). The experimental results show that the substituents of the substrates have little effect on the reaction, and the chirality of the target product is exclusively controlled by the chiral ligand.



Scheme 6. (**a**) Ni(cod)$_2$-catalyzed and chiral *N*-heterocyclic carbene ligand **L1**-enabled enantioselective intramolecular C–H alkylation reaction; (**b**) Ni(cod)$_2$-catalyzed enantioselective intramolecular *endo*-selective C–H alkylation in the presence of the chiral bulky *N*-heterocyclic carbene hydrochloride **L2●HCl**.

Meanwhile, the Shi and Xu group also demonstrated Ni(cod)$_2$-catalyzed enantioselective intramolecular *endo*-selective C–H alkylation of *N*-alkenyl-substituted 2-pyridones, isoquinolines, quinolinones, and 4-pyrimidones [53]. With this novel method, the desired chiral bicyclic heterocycle products **15** and **17** could be obtained in up to 99% *ee* and 99% isolated yields in the presence of the chiral bulky *N*-heterocyclic carbene hydrochloride **L2●HCl** (Scheme 6b). It is believed that the electron-rich nature of the ligand **L2●HCl** is favorable for the nickel-catalyzed C–H oxidative addition process, while the bulky nature of **L2●HCl** favors the alkene insertion and reductive elimination processes. Moreover, the use of commercially available AlEt$_3$ as a co-catalyst promotes this process.

A plausible catalytic cycle is depicted in Scheme 7. It was proposed that this process is initiated by the generation of the **L2**-Ni(0) catalyst, followed by the Ni/Al dual coordination of substrate **14** to produce the Ni-complex **3A**. Next, the C–H bond oxidative addition of the Ni(0) center generates the Ni–H complex **3B**. Subsequently, a seven-membered ring intermediate **3C** is formed through an *anti*-Markovnikov alkene insertion. Finally, the reductive elimination of intermediate **3C** affords the desired product **15** and regenerates the catalyst for the following cycle.

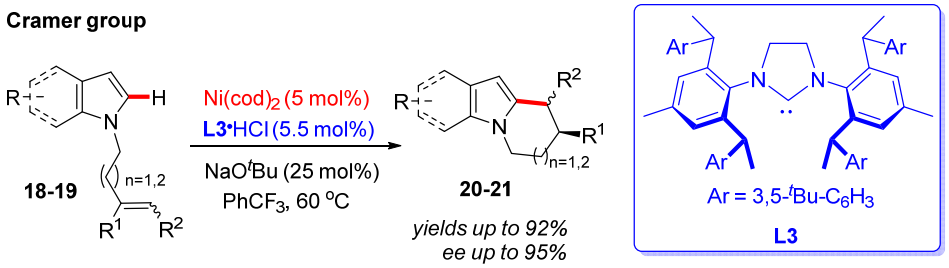


Scheme 7. Proposed mechanism of Ni(cod)$_2$-catalyzed chiral ligand-enabled enantioselective intramolecular C–H alkylation reaction.

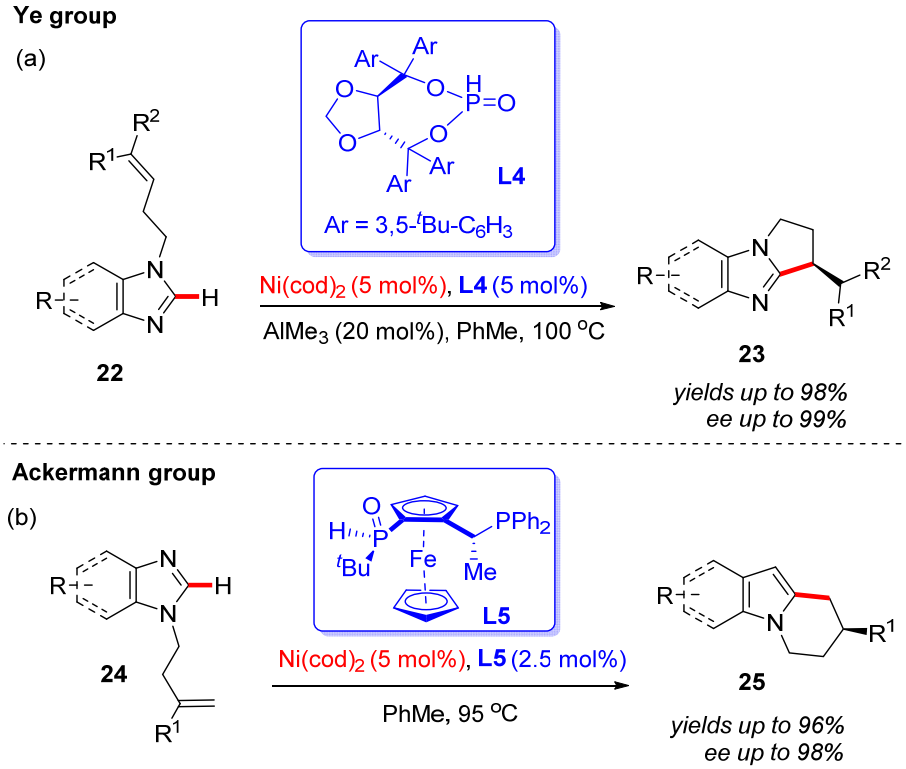
Meanwhile, the Carmer group also reported the Ni(cod)-catalyzed enantioselective C–H functionalization of *N*-alkenyl-substituted indoles **18** and pyrroles **19** to construct various chiral tetrahydropyridoindoles **20** and tetrahydroindolizines **21** under mild reaction conditions [54]. It was pointed out that the development of a novel bulky chiral *N*-heterocyclic carbene hydrochloride **L3●HCl** is key to the success of this process. Without the essential Lewis acids, including AlMe$_3$, AlEt$_3$, and MAD, both chiral tetrahydropyridoindoles **20** and tetrahydroindolizines **21** were obtained in excellent yields (up to 92% isolated yields) and enantioselectivities (up to 95% *ee*) (Scheme 8).

In 2018, the Ye group reported the novel enantioselective Ni/Al co-catalyzed intramolecular *exo*-selective C–H cyclization of *N*-alkenyl-substituted imidazoles **22** [55]. By employing a chiral bis(*t*-butyl)phenyl-containing SPO ligand **L4**, different kinds of chiral five-membered fused-ring imidazole derivatives **23** were isolated in up to 98% yield and 99% *ee* (Scheme 9a). In the following year, Ackermann and co-workers also reported a complementary method for the synthesis of chiral six-membered fused-ring imidazole

derivatives **25** through an enantioselective Ni(0)-catalyzed C–H functionalization reaction [56]. In this strategy, the *endo*-selective C–H cyclization of *N*-alkenyl-substituted imidazoles **24** was catalyzed by a $Ni(cod)_2$ catalyst and chiral JoSPOphos ligand **L5** without additional aluminum reagents, providing the desired products **25** in up to 96% yield and 98% *ee* (Scheme 9b).



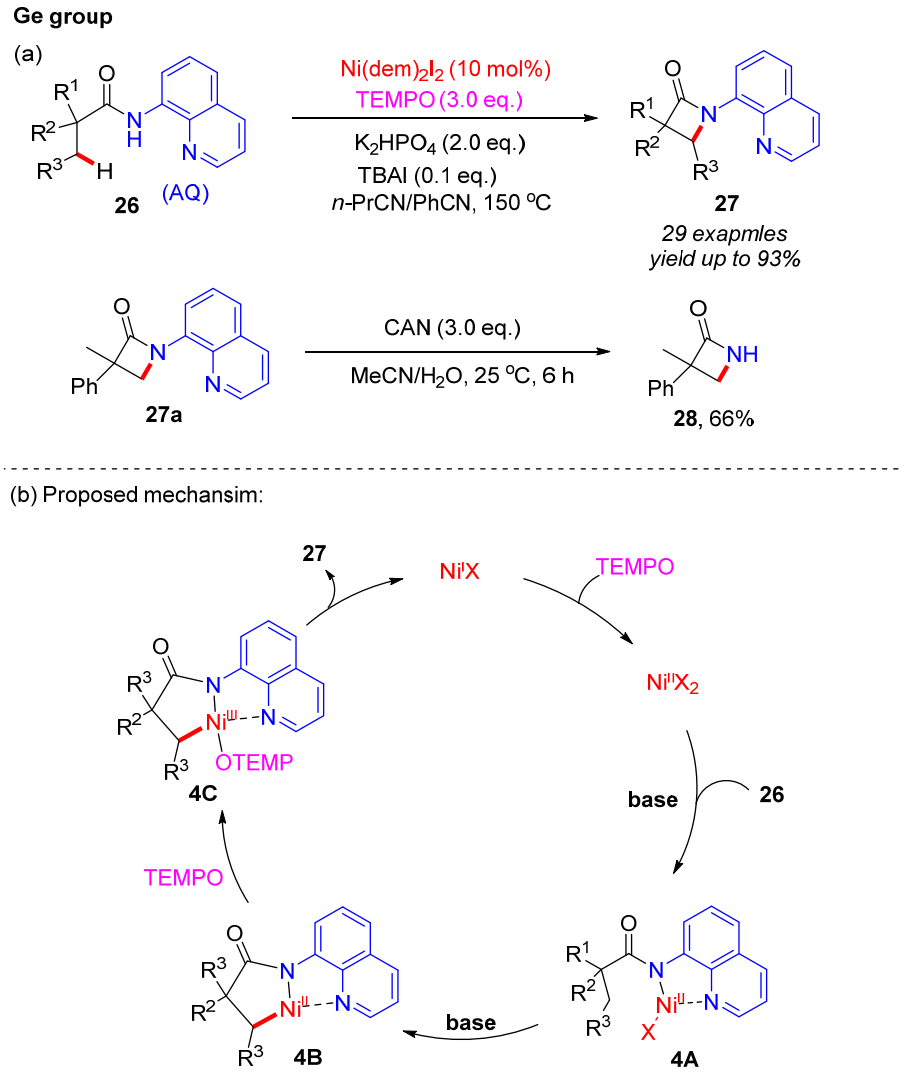
Scheme 8. $Ni(cod)_2$-catalyzed enantioselective C–H functionalization of *N*-alkenyl-substituted indoles and pyrroles.



Scheme 9. (**a**) Ni/Al co-catalyzed intramolecular *exo*-selective C–H cyclization of *N*-alkenyl-substituted imidazoles employing a chiral bis(*t*-butyl)phenyl-containing SPO ligand **L4**; (**b**) $Ni(cod)_2$-catalyzed enantioselective C–H functionalization of *N*-alkenyl-substituted imidazoles employing a chiral JoSPOphos ligand **L5**.

Recently, directing the group-assisted transition metal-catalyzed C–H bond functionalization has become an important approach for constructing C–C and C–heteroatom bonds [57–59]. In 2014, Ge and co-workers reported an 8-aminoquinoline (8-AQ)-assisted nickel(II)-catalyzed intramolecular C–H bond dehydrogenative cyclization of aliphatic amides [60]. The unactivated $C(sp^3)$–H bonds of 2,2-disubstituted propionamides **26** were activated and various kinds of β-lactam derivatives **27** were prepared in good yields (Scheme 10a). As for the substrate scope, a tertiary α-carbon atom was found to be required for this reaction, and a predominant preference for the β-methyl $C(sp^3)$–H bonds over the γ-methyl $C(sp^3)$–H bonds, β-methylene $C(sp^3)$–H bonds, and aromatic $C(sp^2)$–H bonds

was observed. Furthermore, benzylic secondary C(sp^3)–H bond functionalization has also been achieved via this protocol. In addition, product **27a** was easily converted to the desired 3-methyl-3-phenylazetidin-2-one **28** in 66% isolated yield in the presence of CAN and the MeCN-H_2O co-solvent.

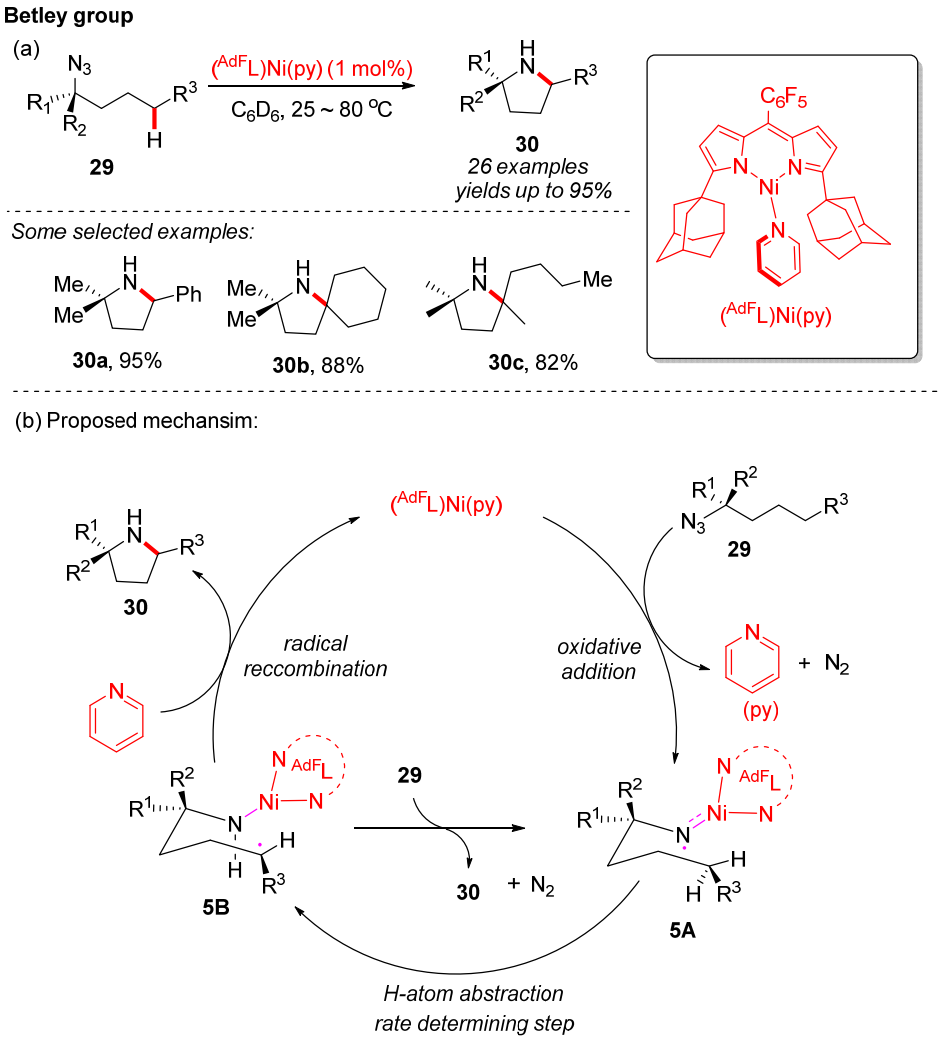


Scheme 10. (**a**) 8-Aminoquinoline (8-AQ)-assisted nickel(II)-catalyzed intramolecular C–H bond dehydrogenative cyclization of aliphatic amide; (**b**) Proposed mechanism.

A plausible catalytic pathway for the above transformation is proposed in Scheme 10b. It is envisioned that this process is initiated by the coordination of the amide to Ni(II), followed by a base-promoted ligand exchange, providing the nickel intermediate **4A**. Next, the cyclonickelation of intermediate **4A** produces the Ni(II) complex **4B**, which can be further oxidized by TEMPO into the Ni(III) species **4C** through a single-electron transfer process. Finally, the reductive elimination of the intermediate **4C** releases the desired product and the Ni(I) species. Meanwhile, Ni(I) is re-oxidized to Ni(II) by TEMPO.

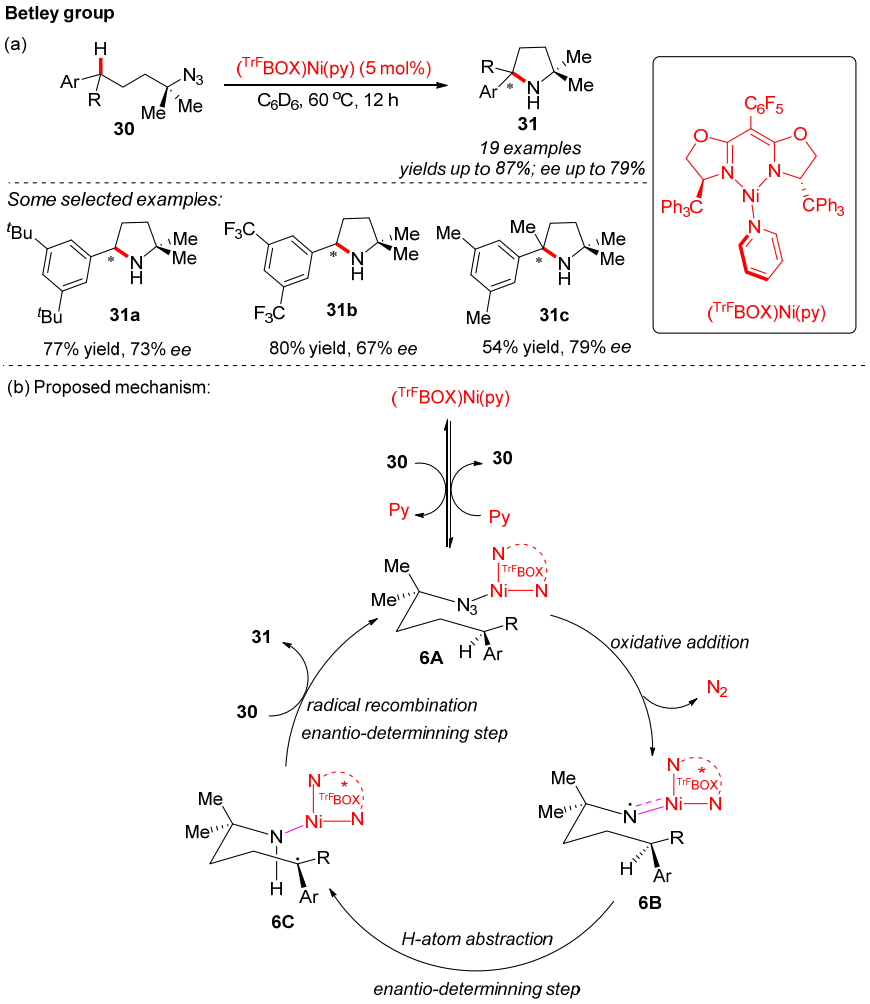
Very recently, the Betley group reported an intramolecular C–H bond amination of aliphatic azides to afford pyrrolidine derivatives, catalyzed by a dipyrrin-supported nickel catalyst [(^{AdF}L)Ni(py)] under mild conditions [61]. Aliphatic azides **29** containing different sites, including benzylic, tertiary, secondary, and primary C–H bonds, gave rise to the desired pyrrolidines **30** in good yields (Scheme 11a). Furthermore, this reaction also exhibited high chemoselectivity and broad functional group compatibility. It is worth noting that this strategy was used to prepare the indolizidine skeletons—commonly found in many alkaloids—through the sequential cyclization of azide substrates containing ester

groups. Furthermore, a possible catalytic cycle is also proposed (Scheme 11b). The initial ligand exchange and subsequent oxidative addition between the substrate **29** and the nickel catalyst [(^{AdF}L)Ni(py)] provides the corresponding nickel iminyl species **5A**, pyridine, and nitrogen gas. Next, hydrogen atom abstraction within this intermediate, followed by a radical recombination process, affords the pyrrolidine product **30**. Finally, the ligand exchange between pyridine or substrate **29** with the nickel iminyl species **5A** facilitates the release of the pyrrolidine product **30**.



Scheme 11. (**a**) Dipyrrin-supported nickel catalyst [(^{AdF}L)Ni(py)]-catalyzed intramolecular C–H bond amination of aliphatic azides; (**b**) Proposed mechanism.

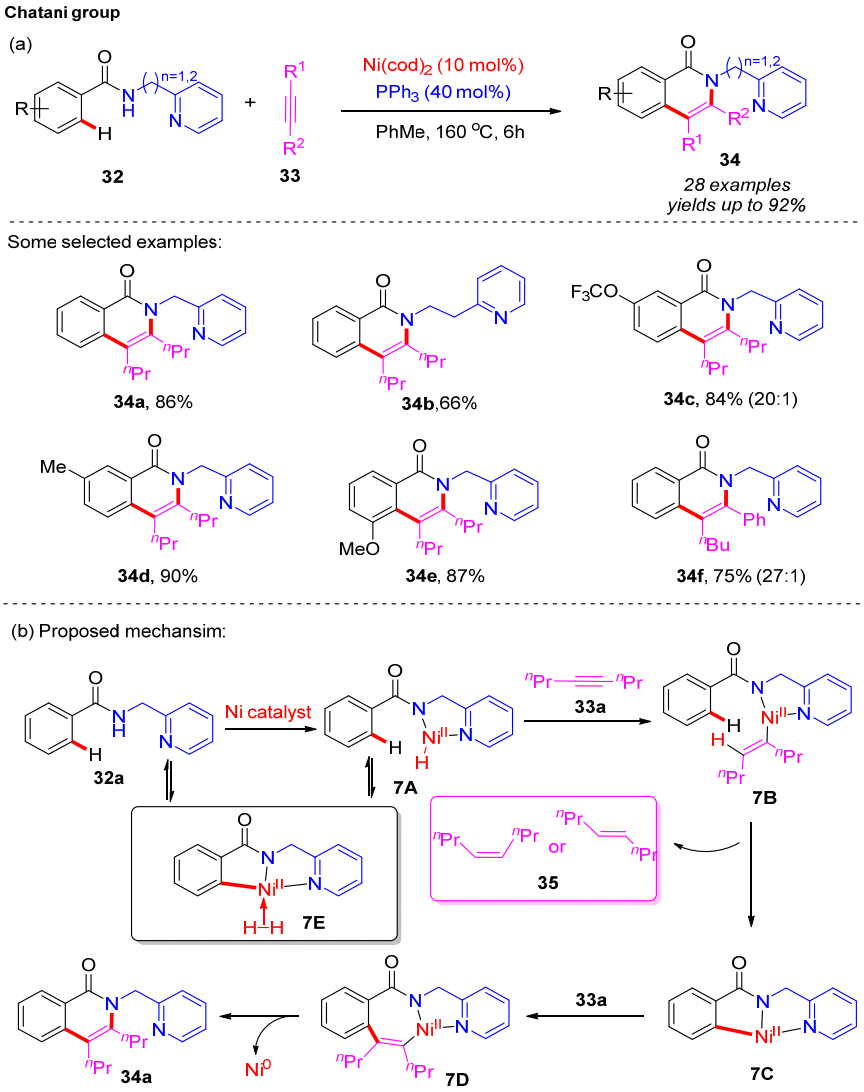
The same group later developed a novel chiral nickel catalyst [(^{TrF}BOX)Ni(py)] to achieve the intramolecular enantioselective C–H amination of aliphatic azides [62]. Different chiral pyrrolidines **32** were prepared in good yields (up to 87% isolated yields) and moderate enantioselectivities (up to 79% *ee*) (Scheme 12a). A proposed mechanism is depicted in Scheme 12b. Chiral nickel catalyst [(^{TrF}BOX)Ni(py)] first undergoes ligand exchange with substrate **30** to form the azide intermediate **6A**. Nitrogen gas is then released from the azide intermediate **6A** to yield the nickel iminyl species **6B**. The intramolecular hydrogen atom abstraction of **6B** generates the radical intermediate **6C**. Finally, the pyrrolidine product **31** is formed through a radical recombination process, aided by the ligand substitution with substrate **30**.



Scheme 12. (**a**) An intramolecular enantioselective C–H amination of aliphatic azides catalyzed by a novel chiral nickel catalyst [(^{TrF}BOX)Ni(py)]; (**b**) Proposed mechanism.

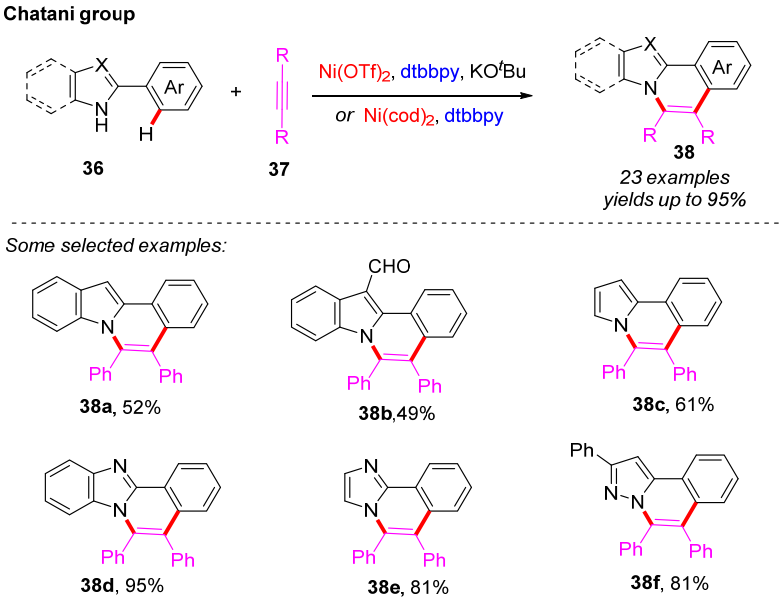
3. Nickel-Catalyzed Intermolecular C–H Bond Functionalization

Compared to intramolecular C–H bond functionalization, intermolecular C–H bond functionalization is more challenging. In 2011, Chatani and co-workers reported the first example of a Ni(cod)$_2$-catalyzed directing-group-assisted *ortho*-C–H functionalization of aromatic amides with alkynes for the construction of isoquinolone derivatives [63]. Ph_3P was used as an essential ligand for stabilizing the nickel catalyst. Initial investigations showed that 2-pyridinylmethylamine was the optimal directing group. In the substrate scope, an array of isoquinolone derivatives were generated in moderate to good yields. Aromatic amides **32c-d** bearing the electron-donating groups (Me and OCF_3) at the *meta*-position on the aromatic ring afforded the less-hindered isoquinolone products **34c-d** in excellent yields, while aromatic amide **32e** with a *meta*-methoxy group gave the hindered product **34e**, which might have been caused by the coordination of an oxygen atom to the nickel catalyst. Furthermore, the unsymmetrical *n*-butylphenylacetylene could also be converted to the product **34f** in good yield (Scheme 13a). A proposed mechanism is depicted in Scheme 13b. First, the coordination of the amide substrate **32a**, with the nickel catalyst followed by N–H bond activation, provides the nickel hydride species **7A**. The subsequent alkyne insertion of the nickel hydride species **7A** produces vinylnickel complex **7B**. Next, the *ortho*-C–H bond cleavage of complex **7B** provides the *ortho*-metalated complex **7C** and the corresponding alkynes **35**. Finally, the second alkyne insertion and the sequential reductive elimination processes afford the desired isoquinolone product **34a** and regenerate the nickel catalyst.

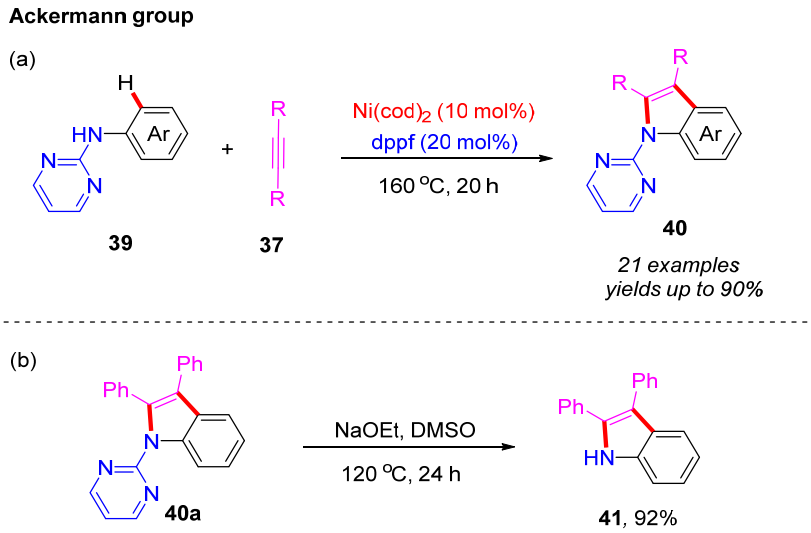


Scheme 13. (**a**) Ni(cod)$_2$-catalyzed directing-group-assisted *ortho*-C–H functionalization of aromatic amides with alkynes; (**b**) Proposed mechanism.

The same group later reported on the development of a new catalytic system for the nickel-catalyzed oxidative C–H/N–H annulation of 2-aryl-pyrrole, benzimidazole, imidazole, indole, and pyrazole derivatives with symmetrical alkynes [64]. Various kinds of isoquinoline derivatives, including indolo-isoquinolines, pyrrolo-isoquinolines, benzimidazo-isoquinolines, imidazo-isoquinolines, and pyrazolo-isoquinolines, were isolated in good yields (Scheme 14). Furthermore, this strategy exhibits a very board substrate scope and high functional group compatibility. The Ni(0) species is proposed as the key catalytic species in this reaction. It is noteworthy that, theoretically, both the Ni(0) and the Ni(II) catalysts can promote this process. Notably, a strong base is required in the case of the Ni(II) system, whereas no base is needed in the Ni(0) system. In 2013, the Ackermann group presented a Ni(cod)$_2$-catalyzed C–H oxidative annulation of *N*-arylpyrimidin-2-amines with alkynes [65]. This novel C–H/N–H bond functionalization strategy afforded a wide array of substituted indoles **40** in good yields (Scheme 15a). In addition, the 2-pyrimidyl group could be easily removed from the substituted indoles **40a** to produce the NH-free indoles **41** in 92% isolated yield (Scheme 15b).



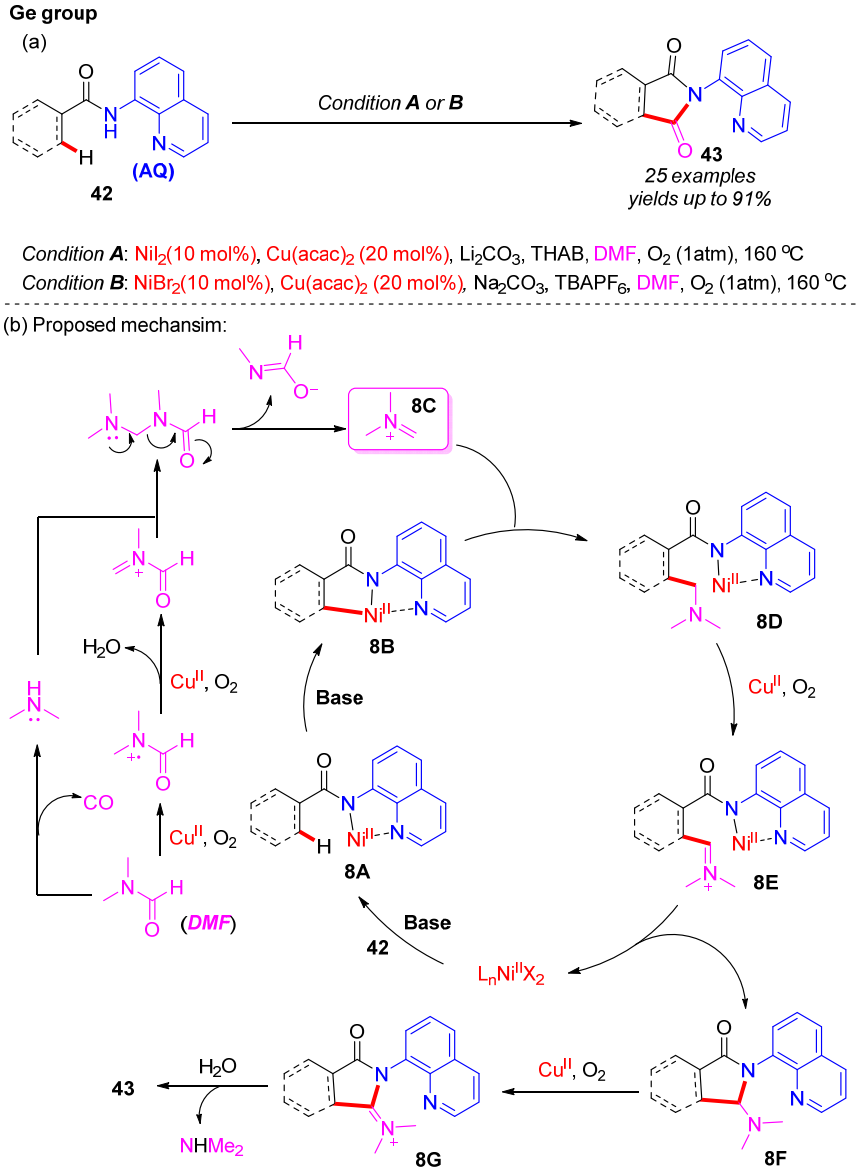
Scheme 14. Nickel-catalyzed oxidative C–H/N–H annulation of 2-aryl-pyrrole, benzimidazole, imidazole, indole, and pyrazole derivatives with symmetrical alkynes.



Scheme 15. (**a**) Ni(cod)$_2$-catalyzed C–H oxidative annulation of *N*-arylpyrimidin-2-amines with symmetrical alkynes; (**b**) Removal experiment of 2-pyrimidyl group.

In 2015, the Ge group developed Ni/Cu co-catalyzed 8-aminoquinoline (8-AQ)-assisted direct C–H carbonylation of amides by using DMF as the CO source under an O_2 atmosphere [66]. In this strategy, a variety of aromatic or aliphatic amides were used to construct various isoindoline-1,3-diones and pyrrole-2,5-diones in good yields (Scheme 16a). Furthermore, both the C(sp^2)–H and the C(sp^3)–H bond functionalization processes have shown broad functional group compatibility and good selectivity. Notably, the quinolin-8-yl moiety could be readily removed by treatment with ammonia to give the NH-free product. Mechanistic studies indicate that the nucleophile is generated by the Ni-catalyzed C–H activation of the amides and that the electrophile results from DMF with the copper species under the O_2 atmosphere. A plausible catalytic cycle is proposed in Scheme 16b. The nickel complex **8A** is initially formed through the coordination of the amide substrate to the Ni(II) catalyst, followed by a ligand exchange step. The subsequent cyclometallation of the nickel complex **8A** generates the intermediate **8B** through a C–H bond activation step. Meanwhile, under copper catalysis and the O_2 atmosphere, DMF provides the electrophilic

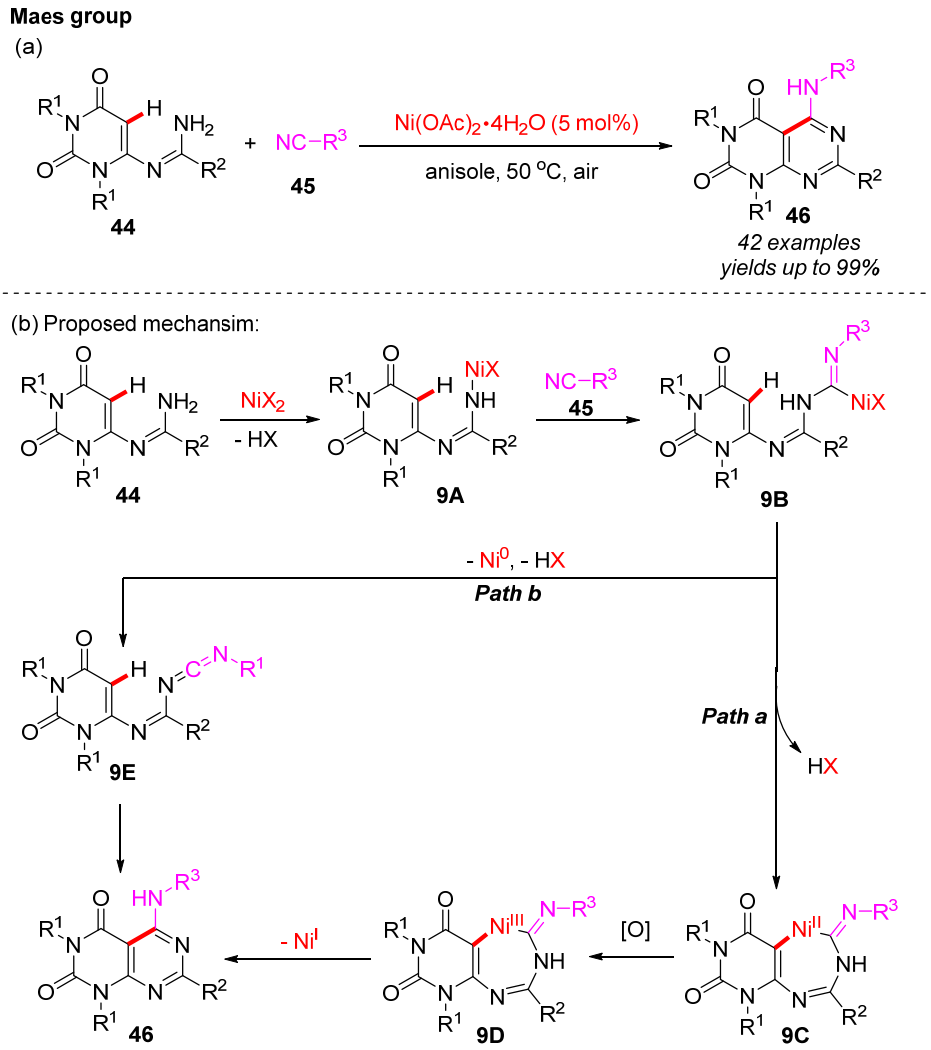
species **8C**. Then, the intermediate **8D** is formed by a nucleophilic addition process, and it is further oxidated to the intermediate **8E** at a subsequent step. Finally, the sequential intramolecular nucleophilic addition, oxidation, and hydrolysis of this intermediate afford the desired product **44**.



Scheme 16. (**a**) Ni/Cu co-catalyzed 8-aminoquinoline (8-AQ)-assisted direct C–H carbonylation of amides by using DMF as the CO source under O_2 atmosphere; (**b**) Proposed mechanism.

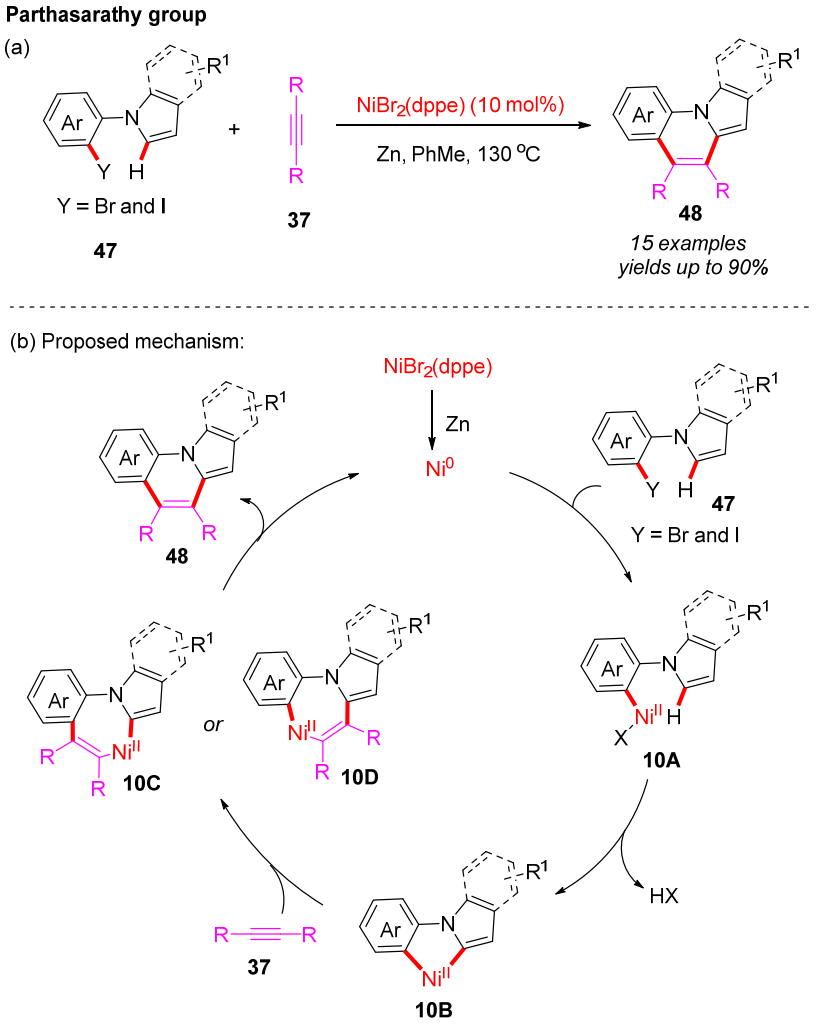
In 2020, a Ni(II)-catalyzed oxidative isocyanide insertion/C–H amination reaction was reported by the Maes group. The process proceeded in anisole as a solvent under an air atmosphere at a moderate temperature [67]. Various *N*-uracil-amidines and isocyanides were used to construct poly-substituted pyrimidouracils in moderate to excellent yields (Scheme 17a). The *N*-uracil-amidines bearing different functional groups were well-suited for this reaction. Moreover, a broad range of isocyanides, including primary, secondary, and tertiary aliphatic, benzyl, and aromatic isocyanides were also compatible in this C–H functionalization strategy. As shown in Scheme 17b, a plausible catalytic cycle is proposed. It starts with the formation of the amidine nickel intermediate **9A**. The subsequent insertion of the isocyanide **45** yields the amidine nickel intermediate **9B**, which is converted to a nickel ring intermediate **9C** via C–H bond functionalization. Subsequently, the cyclic Ni(III)

intermediate **9D** is formed through an oxidative SET process. The sequential reductive elimination gives the product **46** and the Ni(I) species, which eventually undergoes a second SET oxidation to regenerate the active Ni(II) catalyst. Alternatively, the elimination of the β-hydride of intermediate **9B** yields the carbodiimide **9E**, which is further transformed to the product **46**.



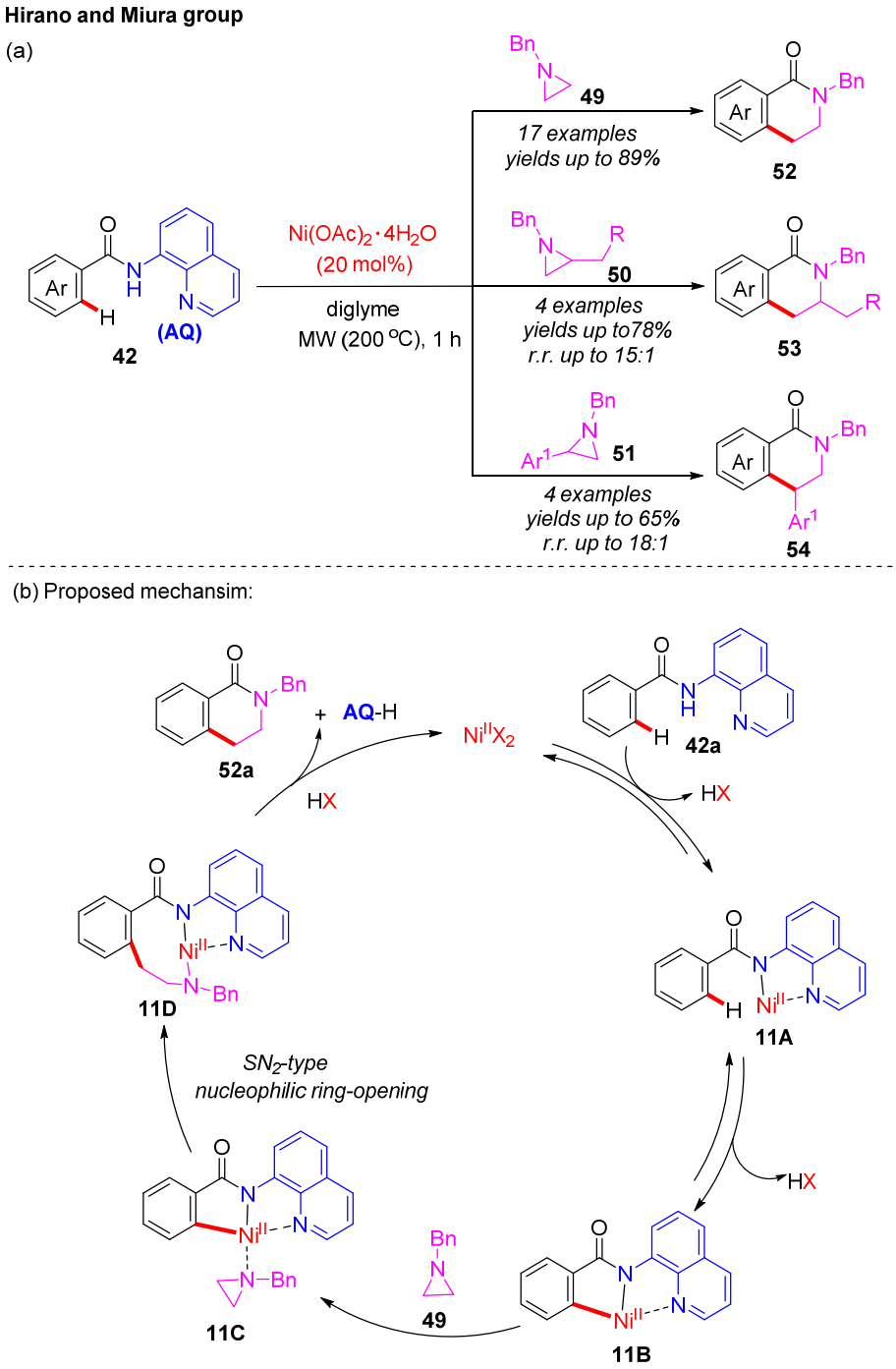
Scheme 17. (**a**) Ni(II)-catalyzed oxidative isocyanide insertion/C–H amination reaction; (**b**) Proposed mechanism.

Meanwhile, the Parthasarathy group also presented the nickel-catalyzed C–H annulation of 1-(2-iodophenyl)-1*H*-pyrrole or 1-(2-bromoaryl)-1*H*-indole with alkynes [68]. The Ni/Zn combination of C–H annulations is reported to have constructed different pyrroloquinoline and indoloquinoline derivatives for the first time in good yields (Scheme 18a). In addition, a possible reaction pathway is proposed (Scheme 18b). First of all, the Ni(II) catalyst is reduced by zinc to the active Ni(0) complex. The oxidative addition reaction of substrate **47** to the Ni(0) complex yields the Ni(II) intermediate **10A**, which is further transformed to the five-membered nickel intermediate **10B**. Then, the alkyne insertion process of this intermediate generates either seven-membered nickel intermediate **10C** or **10D**. Finally, the reductive elimination of **10C** or **10D** provides the product **48** and regenerates the active Ni(0) complex.



Scheme 18. (**a**) Ni-catalyzed C–H annulation of 1-(2-iodophenyl)-1*H*-pyrrole or 1-(2-bromoaryl)-1*H*-indole with alkynes; (**b**) Proposed mechanism.

In 2021, the Hirano and Miura group reported a Ni-catalyzed and 8-aminoquinoline (8-AQ)-assisted C–H alkylation of benzamides with alkyl- and aryl-substituted aziridines [69]. This strategy provides an important complementary approach to preparing benzolactams in moderate to good yields (Scheme 19a). Moreover, 8-aminoquinolinyl, as the directing group, could be spontaneously removed via an intramolecular amidation process. The regioselectivities of the products are determined by the nature of their own substituents. The controlled experiments indicated that an SN_2-type nucleophilic ring-opening pathway may be involved in the C–C formation step. The plausible reaction mechanism is depicted in Scheme 19b. The reversible chelation of benzamide **42a** with the Ni(II) catalyst generates the nickel complex **11A**. Next, the reversible C–H cleavage of the nickel complex **11A** provides the intermediate **11B**. Subsequently, the coordination of aziridine **49** with the intermediate **11B**, followed by an SN_2-type nucleophilic ring-opening process, gives the intermediate **11D**. The final protonolysis and intramolecular amidation provide the desired product **52a**, 8-aminoquinoline (AQ-H), and the Ni(II) catalyst.



Scheme 19. (**a**) Ni-catalyzed and 8-aminoquinoline (8-AQ)-assisted C–H alkylation of benzamides with aziridines; (**b**) Proposed mechanism.

4. Conclusions

Transition metal-catalyzed C–H functionalization has become an important approach for the synthesis of nitrogen-containing heterocycles. Previous reports often use Pd, Rh, Co, and Cu catalysts. In this review, we provide a robust discussion of the recent advances of nickel-catalyzed C–H functionalization in heterocycle synthesis. The first part mainly introduces the nickel-catalyzed intramolecular C–H alkylation and arylation reactions and their role in constructing different heterocycle compounds, including imidazolium and thiazolium salts, pyridones, indolones, dibenzofurans, and others. Furthermore, various chiral derivatives of simple heterocyclic compounds, such as pyridine, 2-pyridone, isoquinoline,

quinolinone, 4-pyrimidone, and imidazoles, have been obtained through Ni-catalyzed asymmetric C–H functionalization with a chiral ligand. Additionally, intramolecular C–H amination catalyzed by the nickel catalysts provides an important approach to preparing azetidin-2-one and cyclopentylamine derivatives. The second part mainly describes the nickel-catalyzed intermolecular C–H/N–H annulation reactions, leading to the synthesis of isoquinolones, isoquinoline, indoles, isoindoline-1,3-diones, and pyrrole-2,5-diones by using different directing groups, including pyridinylmethylamine, pyrimidin-2-amine, 8-aminoquinoline, and others. While some significant work has been accomplished using these directing groups, there are still many avenues for improvement and utilization in this field. In general, these directing groups often need to be pre-installed on the substrates to promote the C–H functionalization reactions, which limits the efficiency of the process. Therefore, transient ligand-enabled nickel-catalyzed C–H functionalization would be an ideal strategy for heterocycle synthesis. We hope this review will provide some insights for readers and inspire them to explore more novel approaches in nickel-catalyzed C–H functionalization and their utility in heterocycle synthesis.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

IMes	1,3-Bis(2,4,6-trimethylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene
cod	1,5-Cyclooctadiene
IPr	1,3-Bis(2,6-diisopropylphenyl)imidazole-2-ylidene
dppe	1,2-Bis(diphenylphosphino)ethane
dppp	1,3-Bis(diphenylphosphino)propane
CMD	Concerted metalation deprotonation
MAD	Methylaluminum bis(2,6-di-*tert*-butyl 4-methylphenoxide)
SPO	Secondary phosphine oxide
JoSPOphos	(*R*)-1-[(*R*)-*Ter*t-butylphosphinoyl]-2-[(*R*)-1-(diphenylphosphino)ethyl]ferrocene
CAN	Ceric ammonium nitrate
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
SET	Single electron transfer
acac	Acetylacetone
DMF	*N*,*N*-Dimethyl Formamide
SET	Single electron transfer
^{AdF}L	1,9-Di(1-adamantyl)-5-perfluorophenyldipyrrin
py	Pyridine
^{TrF}BOX	Trityl-5-perfluorophenylbisoxazoline
dtbbpy	4,4′-Di-*tert*-butyl-2,2′-bipyridine
ppy	(2-Pyridinyl)phenyl
THAB	Tetra-*n*-hexylammonium benzoate
$TBAPF_6$	Tetrabutylammonium hexafluorophosphate
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dme	Dimethyl ether

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