Recent advances in nickel-catalyzed C–H bond functionalized reactions

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Abstract

The direct C–H bond functionalization has been one of the most active research fields in organic chemistry not only due to the significance in basic studies of inert C–H bond chemistry but also due to the step economy feature in potential synthetic application. In the past decades, transition-metal-catalyzed direct and selective functionalization of C–H bonds has emerged as a straightforward and environmentally friendly synthetic tool, which is also a long-standing goal that continues to drive discovery in organic synthesis. The precious late transition metals have been proved to play key roles to facilitate highly efficient transformations through C-H functionalization. However, the relatively high price, low natural abundance and partly strong toxicity limited their application. Nickel, compared to precious transition metals, is showing great potential for C–H bond functionalizations because of its low cost, unique reactivity profiles and easy availability in the earth's crust. This tutorial review summarizes the recent advances in nickel-mediated direct C–H bond functionalizations and C−C bond forming reactions.

Keywords: C–H bond activation, functionalized reaction, C–C bond formation, nickel catalysts

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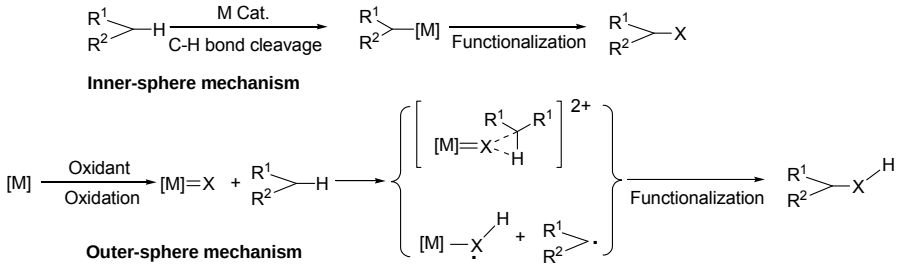
1. Introduction

Direct functionalization of unactivated carbon-hydrogen (C-H) bonds has been a focal point of experimental and theoretical research and plays an important role among these synthesis routes.[1-7] A relatively inert C–H bond is activated, and the hydrogen atom acts essentially as a leaving group. This technology allows one to bypass the installation and subsequent removal of classical leaving groups and to reduce wastes as well as some precautions (such as protecting group manipulations) typical in the handling of promiscuous amine reagents. While developing a capable reactant or catalyst system that is chemo-, regio-, and stereoselective is highly challenging, various researchers have made significant contributions to this field.[8-15] In the past decades, transition-metal-catalyzed direct and selective functionalization of C–H bonds has emerged as a straightforward and environmentally friendly synthetic tool, which is also a long-standing goal that continues to drive discovery in organic synthesis. Thus research on this subject has been attracting increasing interest amongst organic chemists, and various high efficiency and versatile protocols have been explored.[16,17]

In 2006, a simpler vision on the most common C-H bond functionalization mechanisms was provided by Sanford who described these as "inner-sphere" and "outersphere" mechanisms (Scheme 1).[18-20] As defined by Sanford, the "inner-sphere" mechanism comprises two steps that involve the cleavage of the C-H bond leading to the formation of a transition metal alkyl or aryl derivative and the functionalization of this intermediate by an external reagent (or the metal center) to lead to final product. Concerning the "outer-sphere" mechanism, the first species formed is a high oxidation state metal complex containing an activated ligand. This reactive species can evolve by two different pathways, one is the direct insertion in the C-H bond and the second is a hydrogen atom abstraction/radical rebound furnishing the C-H bond functionalization product.



Scheme 1

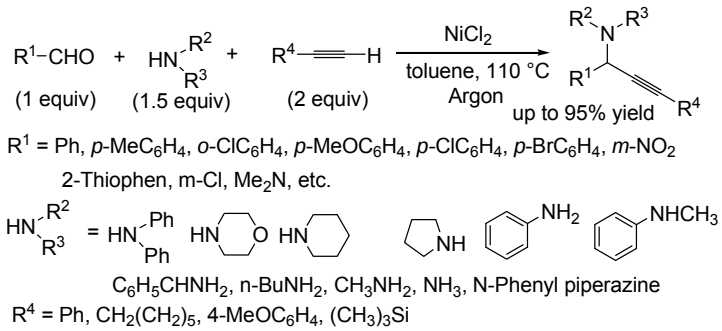
In the past decades, most attention has been paid to the development of late transition metals, mainly due to some advantages in terms of the diversity and tunability of the catalysts and their robustness. The precious late transition metals, for example, palladium, ruthenium, rhenium and iridium catalysts have been shown to be effective for this catalytic system and have been proved to play key roles to facilitate highly efficient transformations through C-H activation. However, the relatively high price, low natural abundance and partly strong toxicity limited their application. Nickel is an abundant 1st row transition metal found in group 10 of the periodic table. Nickel

contains ten d-electrons in a neutral Ni(0) species and can exist in a variety of oxidation states Ni(0)–Ni(IV), the lower oxidation states Ni(0) and Ni(II) are the most common, while Ni(I) and the higher oxidation states Ni(III) and Ni(IV) are quite rare.[21] Nickel compared to precious late transition metals, is easily available in the earth's crust. In spite of showing great potential in the direct C–H bond functionalizations because of its low cost and unique reactivity profiles, the metal is comparatively underutilized.[22] During the past several years, an increasing number of nickel catalyzed C–H functionalizations have appeared in the literature. This review will discuss recent discoveries in nickel-catalyzed C-H bond functionalized reactions and highlight the scope and the mechanism of these reactions.

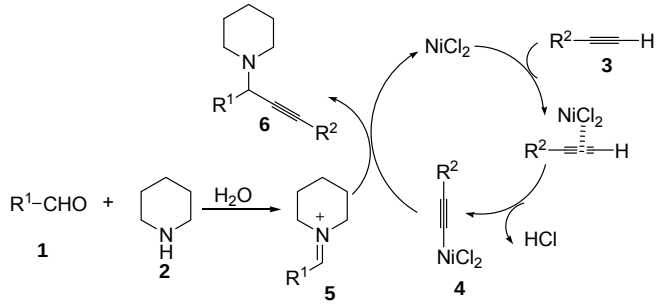
2. Csp^1-H Bond Functionalizations

Carbon–carbon bond-formation reactions are among the most important processes in chemistry because they enable key steps in building more complex molecules from simple precursors. In the past several years, Nickel-catalyzed functionalization of C–H bonds for constructing new C-C bonds has emerged as a straightforward and environmentally friendly synthetic tool, which is also a long-standing goal that continues to drive discovery in organic synthesis.

Samai *et al*[23] developed an efficient $NiCl_2$-catalyzed one pot coupling of aldehydes, amines afforded a diverse range of propargylamines in up to 95% yields (Scheme 2). The reaction had high atom efficiency, since water is the only byproduct. A possible mechanism (Scheme 3) was proposed for the probable sequence of events involving the activation of the C–H bond of alkyne **3** by $NiCl_2$. The nickel–acetylide intermediate **4** generated by the reaction of acetylene and $NiCl_2$ reacted with the iminium ion **5** (generated in situ from aldehyde **1** and amine **2**) to give the corresponding propargylamine **6**.



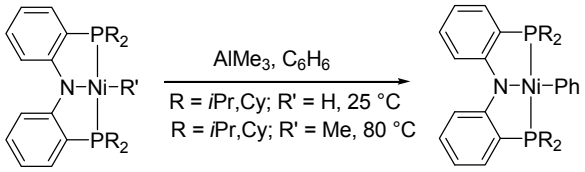
Scheme 2



Scheme 3

3. Csp^2-H Bond Functionalization

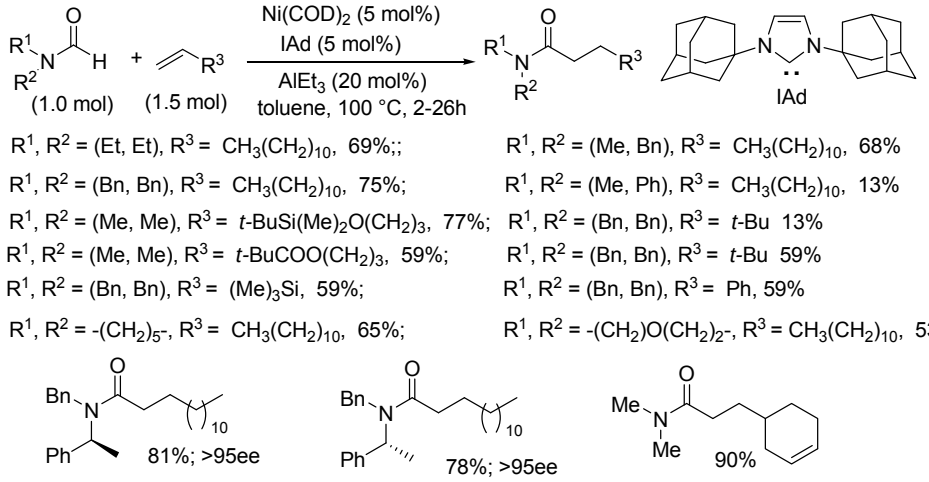
In 2006, Liang *et al*[24] have reported an efficient intermolecular arene C-H activation protocol mediated by Ni(II) complexes under mild conditions. These studies directed to describe the reaction mechanism and reactivity with applicable hydrocarbons are currently underway. Later, Muto et al[25] studied mechanistic of a C−H/ C−O biaryl coupling of 1,3-azoles and aryl pivalates using $Ni(cod)_2$/dcype as catalyst. This study not only supports a catalytic cycle consisting of C−O oxidative addition, C−H nickelation, and reductive elimination but also provides insight into the dramatic ligand effect in C−H/C−O coupling. Investigations on kinetic studies and kinetic isotope effect disclose that the C−H nickelation is the turnover-limiting step in the catalytic cycle.



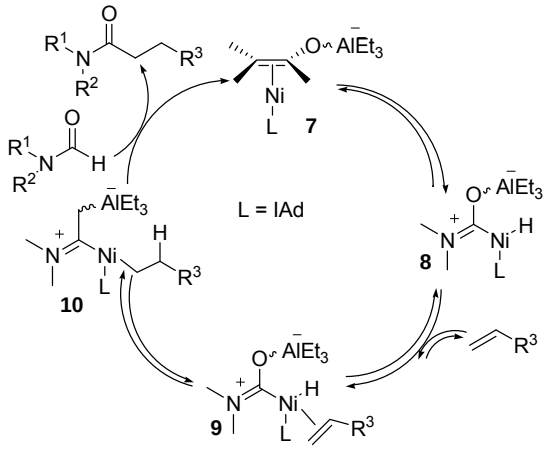
Scheme 4

3.1. Aldehydes of C–H activation

Nakao and coworkers[26] developed regioselective hydrocarbamoylation of alkenes mediated by nickel/Lewis acid cooperative catalysis (Scheme 5). This catalytic system achieved the exceptionally high regioselectivity and would be highly useful as a protocol to access variously functionalized amides as well as a novel transformation of *anti*-Markovnikov selective functionalization of alkenes. The proposed catalytic cycle was shown in Scheme 6. Formamides coordinating to the Lewis acid catalyst through their carbonyl oxygen would undergo the oxidative addition of the C(sp^2)-H bond to a nickel(0) species to give nickel hydride **8** via the formation of 2-formamidenickel intermediate **7**. Alkenes coordinate to the nickel center of **8** to form **9**, which undergoes migratory insertion to give alkylnickel **10**. Reductive elimination followed by ligand exchange reactions provides alkanamides and regenerate **7** to complete the catalytic cycle.

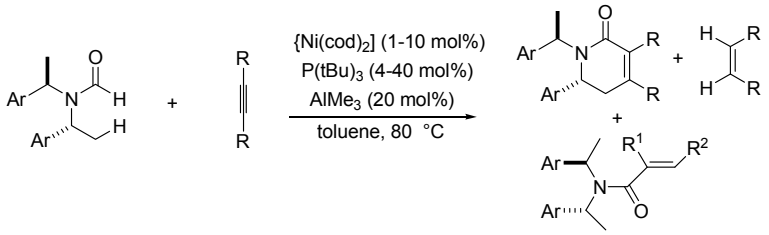


Scheme 5

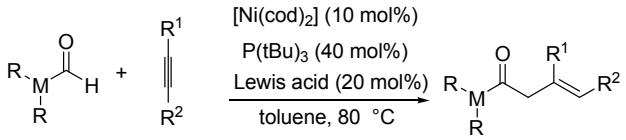


Scheme 6

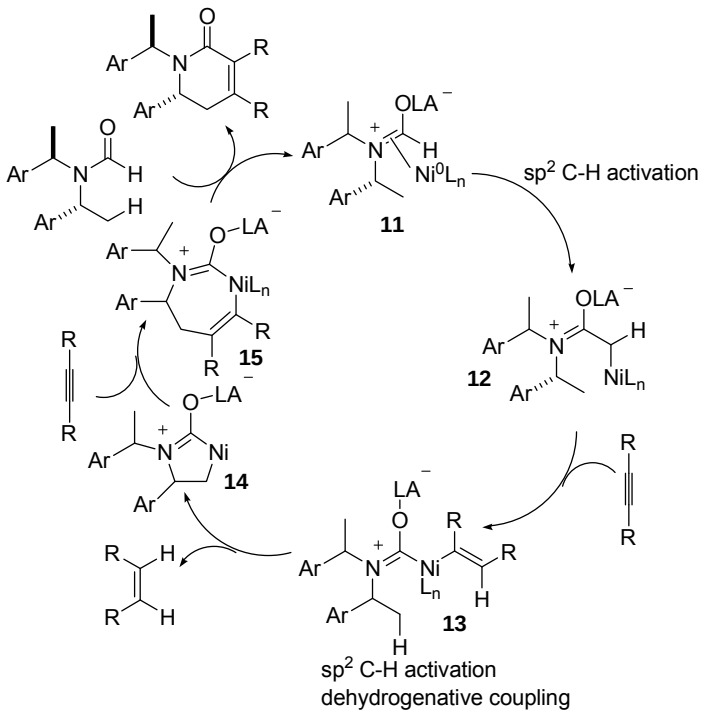
In 2011, Hiyama and co-workers[27] made a significant achievement for the development of cycloaddition of formamides and alkynes through activation of both C(sp^2)-H and C(sp^3)-H bonds (Scheme 7). Hiyama *et al.*[28] originally discovered a nickel catalyst system that facilitates hydrocarbamoylation of unsaturated bonds such as alkynes (Scheme 8 cod=cyclooctadiene). This study reveal that Lewis acid plays a critical role in activating the formamides towards C(sp^2)-H activation.[29,30] With this Lewis-acid assistance, [Ni] oxidatively adds the C(sp^2)-H bond of the formamide. Alkyne insertion followed by C-C bond-forming reductive elimination provides highly substituted acrylamides.



Scheme 7



Scheme 8



Scheme 9

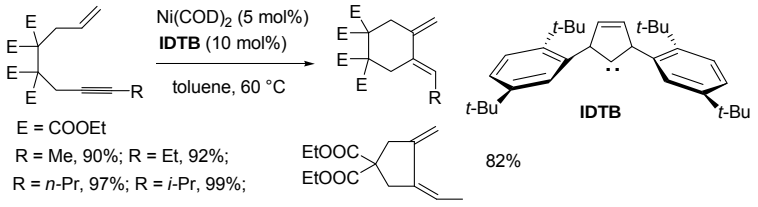
Building upon this work, Hiyama and co-workers[31] found *N*,*N*-bis(1-arylalkyl) formamides not only undergo the Lewis acid-assisted oxidative addition of the formamide C(sp^2)-H bond, the resultant nickel intermediate inserts an alkyne and undergoes a second C-H activation (Scheme 9). That is, intermediate **13** converts to intermediate **14** through cyclometalation of the alkyl C(sp^3)-H bond and extrusion of a reduced alkyne (i.e., an alkene). Although this type of cyclometalation is prevalent for platinum metals, cyclometalation on nickel is much less prevalent.[32-34] In addition,

examples of Ni-based cyclometalation has been mainly limited to the activation of C(sp^2)-H bonds.[35,36] In contrast this nickelacycle **14** inserts a second alkyne and reductively eliminates the dihydropyridone product to complete the catalytic cycle.

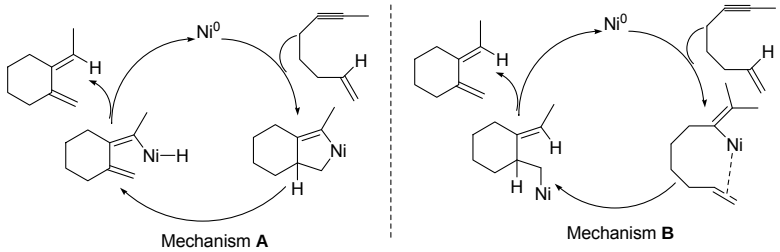
The work of Hiyama and co-workers is certainly an outstanding contribution in the field of cross-dehydrogenative coupling. Key to their success was an optimal steric environment around the metal center to promote cyclometalation/ dehydrogenative coupling. These findings mark the entry of a cheaper, first-row transition metal catalyst nickel in mediating C-C bond formation through the challenging C(sp^3)-H activation.

3.2. Olefin and aromatic C–H activation

In 2008, Tekavec and Louie[37] developed the cycloisomerization of enynes to afford 1,3-dienes using the combination of Ni(0) and an N-heterocyclic carbene acted as a precatalyst (Scheme 10). During the course of the reaction, a nickel hydride was formed from oxidative addition of the ortho C–H on the carbene ligand. In mechanism A (Scheme 11), the enyne undergoes oxidative coupling with the Ni(0) catalyst to generate a metallacyclopentene. This metallacyclopentene undergoes β-hydride elimination to provide a vinyl nickel hydride. Then the vinyl nickel hydride reductively eliminates to yield the observed 1,3-diene. Alternatively, in mechanism B (Scheme 11), the alkyne component of the enyne undergoes hydrometalation with a Ni–H complex to produces a vinyl nickel species. The pendant olefin then inserts into the vinyl nickel bond thereby forming an alkyl nickel species. β-Hydride elimination and reductive elimination affords the observed 1,3-diene. The combination of $Ni(cod)_2$ and IDTB catalyzes the cycloisomerization of enynes to synthetically valuable cyclic 1,3-dienes. Deuterium labeling studies suggest that the active catalyst species is a Ni–H species generated via a rare Ni(0) C–H activation.

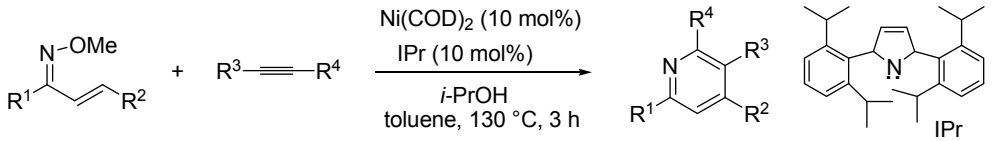


Scheme 10



Scheme 11

Yoshida *et al*[38] developed a nickel-catalyzed cycloaddition of α,β-unsaturated oximes with alkynes to afford 2,3,4,6-tetrasubstituted pyridine derivatives (Scheme 12 and 13). The reaction involved oxidative addition of the NO bond of α,β-unsaturated oximes to Ni(0) and subsequent alkyne insertion to an N-Ni bond, followed by intramolecular cyclization. It was also found that α,β-unsaturated oximes participate in the nickelcatalyzed reaction with alkynes to furnish pyridine derivatives. Based on the results, a proposed reaction pathway was show in Scheme 14. The oxidative addition of an oxime NO bond to an Ni(0) complex initiated the reaction, followed by insertion of an alkyne into an N-Ni bond to generate intermediate **17**. The subsequent intramolecular insertion of the olefin produces intermediate **18**. The methoxy ligand on the nickel would then be replaced with *i*-PrOH to provide **19**. This ligand-exchange reaction of intermediate **18** with *i*-PrOH to lead to intermediate **19** is the rate-determining step in the catalytic process. β-Hydride elimination will give **20**, and a second β-hydride elimination, with aromatization of the six-membered heterocycle, would provide pyridine **21**.



$R^1 = R^2 = Ph$, $R^3 = R^4 = Pr$, 75%; $R^1 = Ph$, $R^2 = Me$, $R^3 = R^4 = Pr$, 71%;

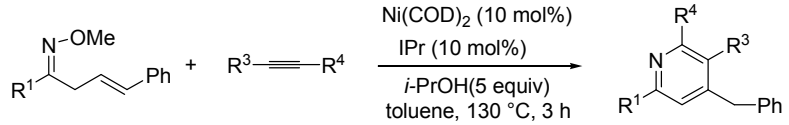
$R^1 = Me$, $R^2 = Ph$, $R^3 = R^4 = Pr$, 29%; R^1, = *t*-Bu, $R^2 = Me$, $R^3 = R^4 = Pr$, 70%;

$R^1 = 4\text{-}CF_3\text{-}C_6H_4$, $R^2 = Ph$, $R^3 = R^4 = Pr$, 85%; R^1, = 4-MeO-C_6H_4, $R^2 = Ph$, $R^3 = R^4 = Pr$, 78%;

$R^1 = Ph$, $R^2 = 4\text{-}F\text{-}C_6H_4$, $R^3 = R^4 = Pr$, 85%; R^1, = Ph, $R^2 = 4\text{-}MeO\text{-}C_6H_4$, $R^3 = R^4 = Pr$, 83%;

$R^1 = Ph$, $R^2 = Ph$, $R^3 = Pr$, $R^4 = Me$ 85% (Ratio of regioisomers = 2:1)

Scheme 12

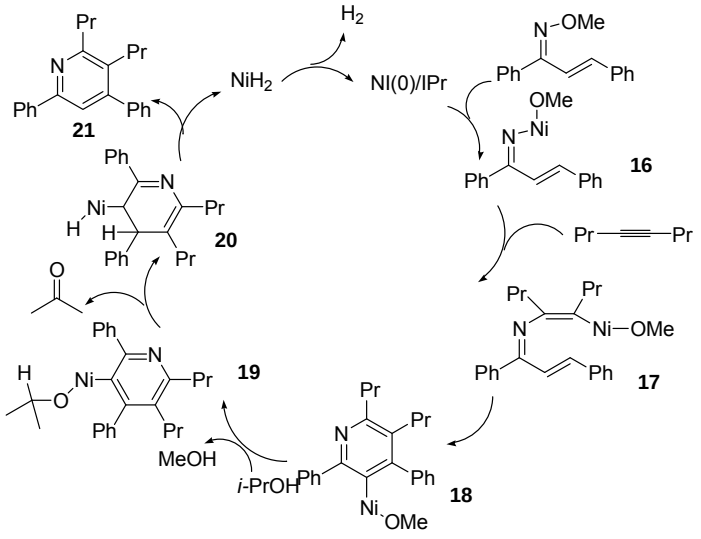


$R^1 = Ph$, $R^3 = R^4 = Pr$, 75%; $R^1 = 4\text{-}F\text{-}C_6H_4$, $R^3 = R^4 = Pr$, 67%;

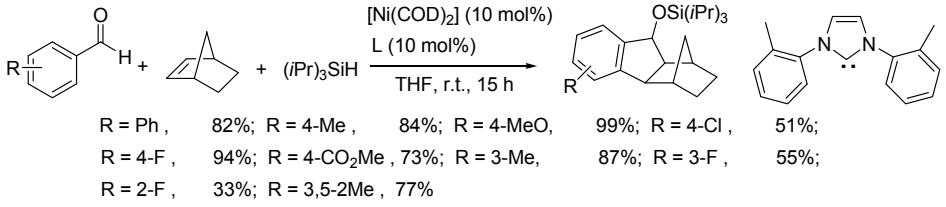
$R^1 = 4\text{-}MeO\text{-}C_6H_4$, $R^3 = R^4 = Pr$, 23%; $R^1 = Ph$, $R^3 = Pr$, $R^4 = Me$ 59%
(Ratio of regioisomers = 5:1)

Scheme 13

In 2011, Ogata and coworkers[39] reported a diastereoselective three-component coupling reaction between aryl aldehydes, norbornenes (norobornadiene), and silanes leading to silylated indanol derivatives using a [Ni(cod)$_2$]/N-heterocyclic carbene catalyst system (Scheme 15). This was the first example of a nickel-catalyzed reductive three-component reaction involving aromatic C-H bond activation of aryl aldehydes. A possible pathway for the three-component reaction is shown in Scheme 16.

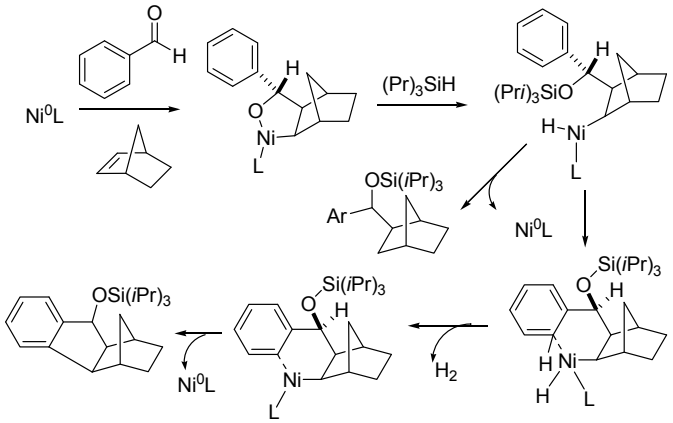


Scheme 14



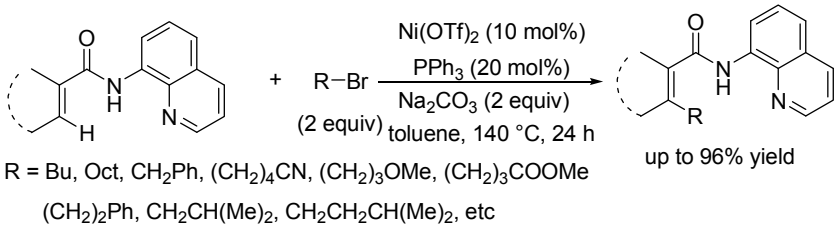
R = Ph , 82%; R = 4-Me , 84%; R = 4-MeO, 99%; R = 4-Cl , 51%;
R = 4-F , 94%; R = 4-CO_2Me , 73%; R = 3-Me, 87%; R = 3-F , 55%;
R = 2-F , 33%; R = 3,5-2Me , 77%

Scheme 15



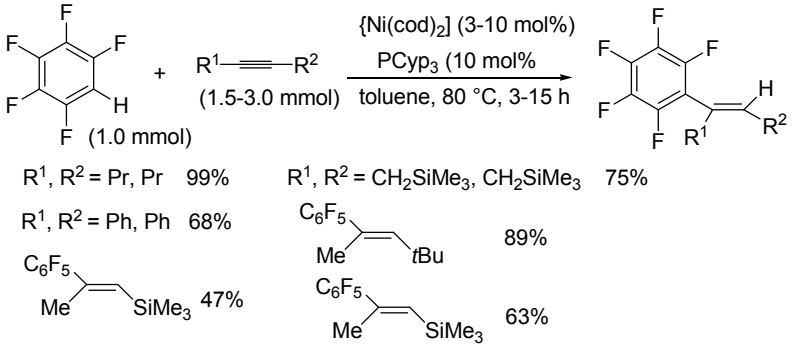
Scheme 16

In 2013, Yoshinori and Naoto[40] described the alkylation of the ortho C–H bonds in benzamides and acrylamides containing an 8-aminoquinoline moiety as a bidentate directing group with unactivated alkyl halides using nickel complexes as catalysts in good yields (Scheme 17). The reaction showed high functional group compatibility. In reactions of *meta*-substituted aromatic amides, the reaction smoothly proceeds in a highly selective manner at the less hindered C–H bond.



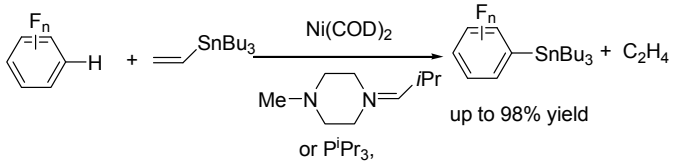
Scheme 17

Nakao et al[41] found a Ni catalyst for the activation of C-H over C-F bonds of polyfluoroarenes and demonstrated their direct alkenyl- and alkylation to allow efficient synthesis of a variety of polyfluoroarenes having alkenyl and alkyl groups in regio- and stereoselective manners (Scheme 18). Experimental and theoretical mechanistic studies determine the origin of the dramatic ligand effect on the Ni catalysis for C-H activation of polyfluoroarenes.



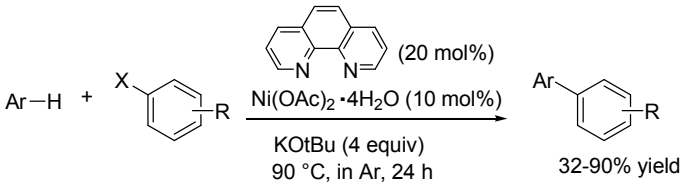
Scheme 18

In 2010, Johnson and coworkers[42] reported the nickel-catalyzed reaction of fluorinated arenes and pyridines with vinyl stannanes does not provide the expected vinyl compounds via C-F activation but rather provides new Sn-C bonds via C-H functionalization with the loss of ethylene (Scheme 19). Unlike the B-C bonds used in the Miyaura-Suzuki coupling reaction, which are readily obtained via direct borylation of C-H bonds, the reaction provides a novel unanticipated methodology for the direct conversion of C-H bonds to carbon-heteroatom bonds.

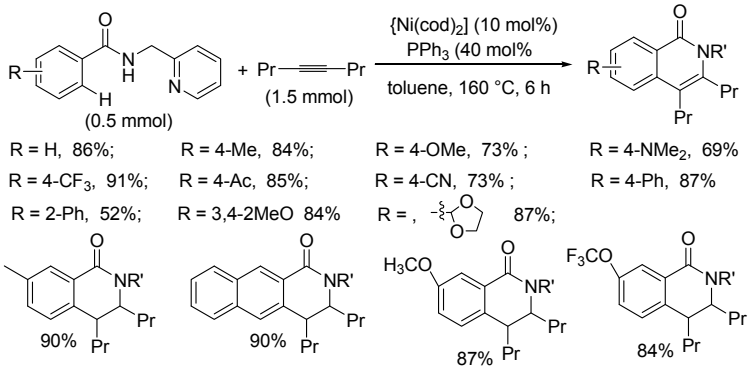


Scheme 19

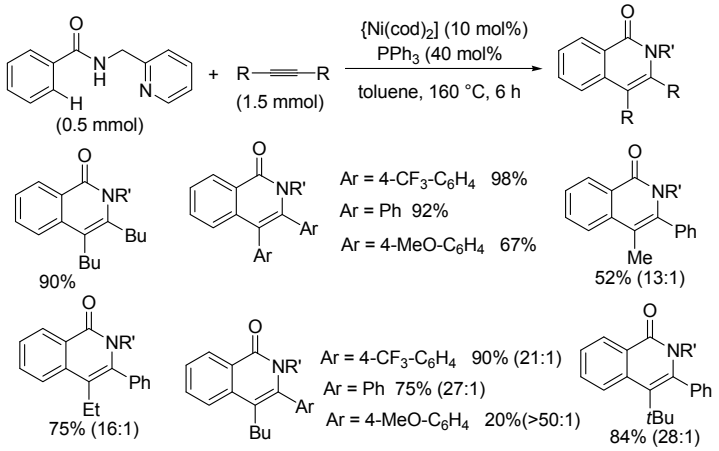
Later, Mao and coworkers[43] reported $Ni(OAc)_2 \cdot 4H_2O$ could catalyze the direct C–H arylation of unactivated arenes with aryl halides in presence of 1,10-phenanthroline without using additives (Scheme 20). This protocol provides more useful C–H arylation via activation of aromatic C-H Bond. Shiota *et al*[44] achieved the first example of the Ni-catalyzed transformation of ortho C-H bonds utilizing chelation assistance and realized the regioselective oxidative cycloaddition of aromatic amides to alkynes (Scheme 21 and 22).



Scheme 20

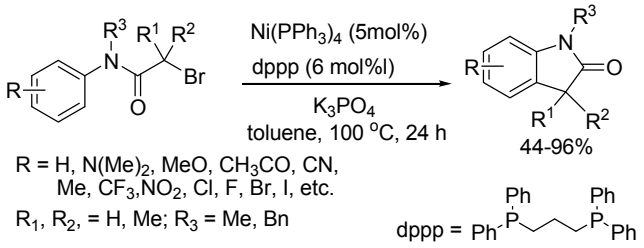


Scheme 21



Scheme 22

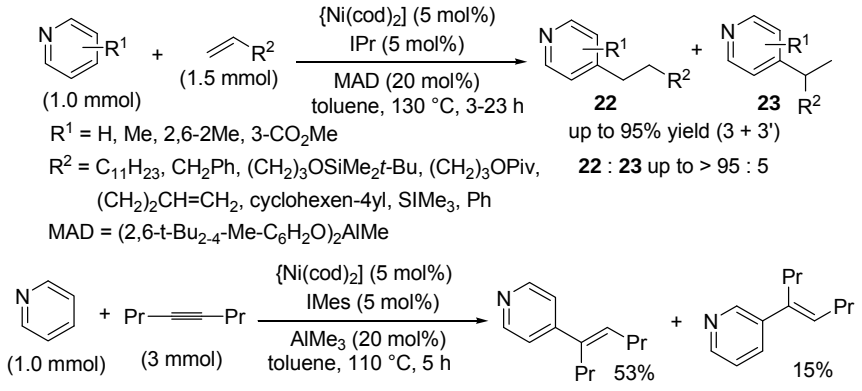
In 2013, Lei and coworkers[45] developed the aromatic C–H alkylation with tertiary or secondary alkyl–Br bonds for the construction of indolones using nickel catalysis (Scheme 23). Various functional groups were well tolerated in the reaction. Moreover, the challenging secondary alkyl bromides were well introduced in this transformation. Radical trapping and photocatalysis conditions exhibited that it is most likely to be a radical process for this aromatic C–H alkylation.



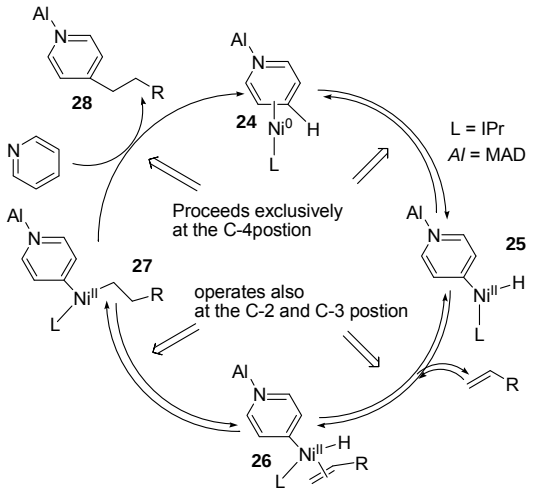
Scheme 23

3.3. Heteroaromatic C–H activation

A pyridine core plays a key role in a number of natural products, pharmaceuticals and functional materials. Because a wide variety of pyridine derivatives are available, a strategy to install substituents directly into a preformed pyridine core has advantages in terms of step economy as well as versatility. In 2010, Nakao *et al*[46] achieved the direct C-4-selective alkylation of pyridines using nickel/Lewis acid cooperative catalysis with an N-heterocyclic carbene ligand (Scheme 24). In this reaction, a variety of substituents on both alkenes and pyridine are tolerated to give linear 4-alkylpyridines in modest to good yields. The addition across styrene, on the other hand, gives branched 4-alkylpyridines. These results imply a catalytic cycle initiated by oxidative addition of the C(4)-H bond of pyridine coordinating to MAD, which is kinetically favored over that of the C(2)-H and C(3)-H bonds, through η^2-arene nickel species **24** (Scheme 25). Coordination and migratory insertion of alkenes into the Ni-H bond of nickel(II) intermediate **25** takes place to give alkylnickel **26** through **25**, and subsequent reductive elimination gives C-4-alkylated pyridines **28** and regenerates **24**.

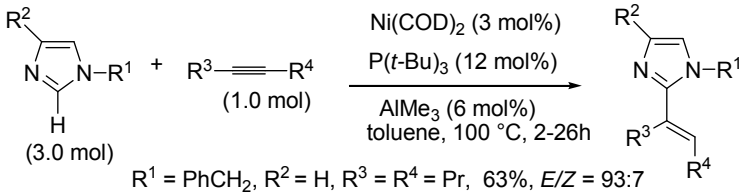


Scheme 24



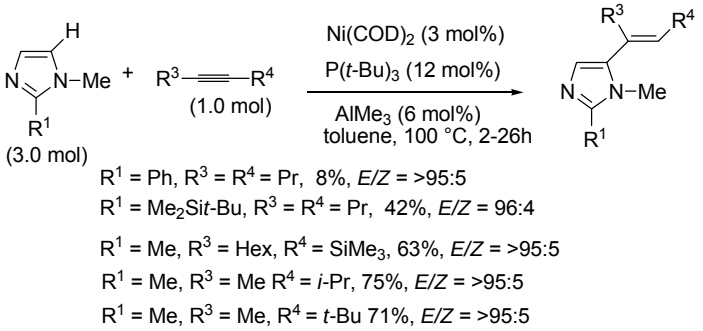
Scheme 25

The imidazole ring is an important structural motif encountered in numerous biologically active compounds ranging from natural products to pharmaceuticals.[47] In 2009, Nakao and coworkers[48] found Nickel/Lewis acid binary catalysis was effective to direct regioselective alkenylation of imidazoles through C–H bond activation and stereoselective insertion of alkynes (Scheme 26 and 27). Use of P(*t*-Bu)$_3$ as a ligand allowed exclusive regioselective C(2)-alkenylation, while PCyp$_3$ was found effective for C(5)-alkenylation of C(2)-substituted imidazoles. Results of the reaction revealed a broad scope of imidazoles and internal alkynes to give trisubstituted ethenes with highly regio- and stereoselectivities in modest to good yields.



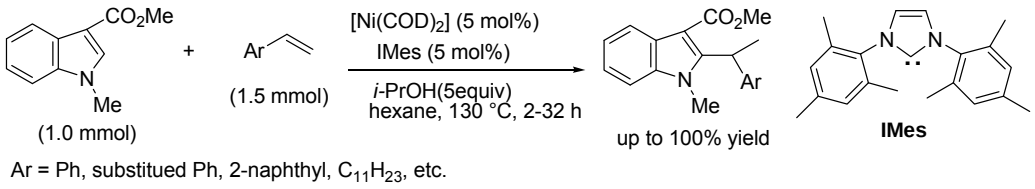
R^1 = $PhCH_2$, R^2 = H, R^3 = R^4 = Pr, 63%, *E/Z* = 93:7
R^1 = Ph, R^2 = H, R^3 = R^4 = Pr, 42%, *E/Z* = 92:8
R^1 = Me, R^2 = Ph, R^3 = R^4 = Pr, 63%, *E/Z* = >99:1
R^1 = Me, R^2 = H, R^3 = R^4 = Ph 75%, *E/Z* = <1:99
R^1 = Me, R^2 = H, R^3 = R^4 = 4-$MeOC_6H_4$ 53%, *E/Z* = <1:99
R^1 = Me, R^2 = H, R^3 = Ph, R^4 = $SiMe_3$, 69%, *E/Z* = 20:80
R^1 = Me, R^2 = H, R^3 = Hex, R^4 = $SiMe_3$, 60%, *E/Z* = >99:1

Scheme 26

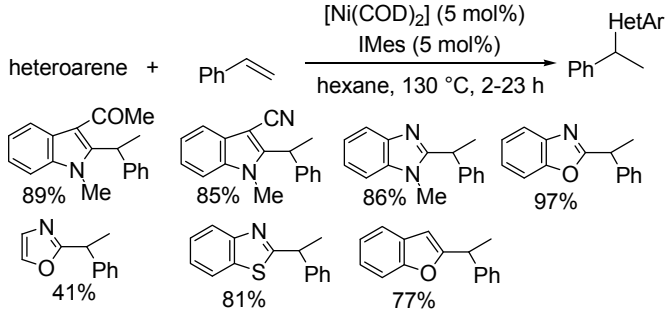


Scheme 27

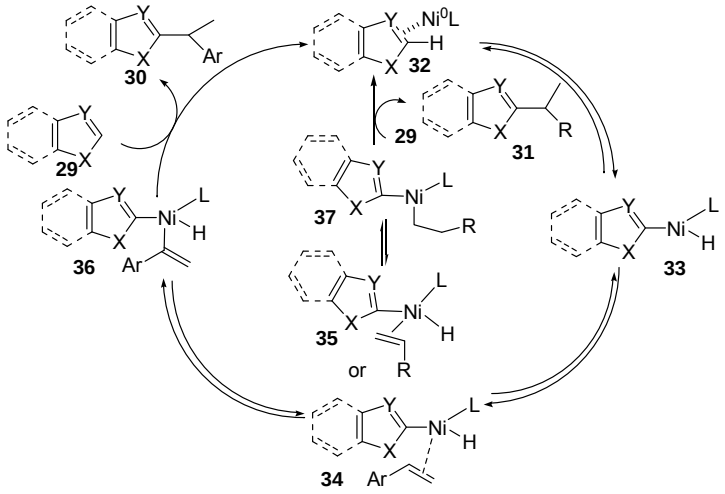
Nakao, Hiyama and coworkers[49] demonstrated the nickel-catalyzed hydroheteroarylation of vinylarenes to exclusively give a variety of 1,1-diarylethanes that contain a heteroaryl motif (Scheme 28 and 29). The use of relatively electron-poor heteroarenes in this reaction is complementary to the well documented Friedel–Crafts-type hydroarylation of vinylarenes with electron-rich arenes to give a wide variety of 1,1-diarylethanes. A plausible catalytic cycle that is initiated by reversible oxidative addition of an Ar-H bond to the nickel(0)/IMes catalyst to give nickel hydride **33** through η^2-arenenickel **32** (Scheme 30). The coordination of vinylarenes **34** and subsequent hydronickelation are both reversible and give 1-arylethylnickel **36**, that reductively eliminates 1,1-diarylethanes irreversibly to regenerate **32**. The final step could be the rate-determining step, as has been discussed previously for the nickel-catalyzed hydrocyanation[50] and hydroalkynylation[51] of vinylarenes. The primary reaction pathway could compete with the coordination and migratory insertion of alkenes to give 1,2-diarylethanes via **35** and **37**.



Scheme 28

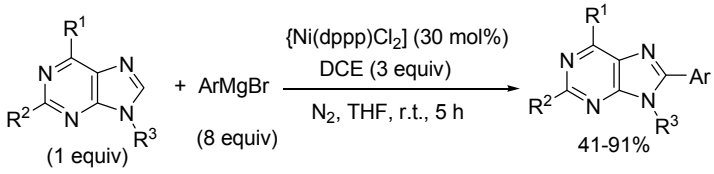


Scheme 29



Scheme 30

Qu et al[52] developed a useful process for nickel-catalyzed direct sp^2 C–H bond arylation of purines at room temperature in good yields (Scheme 31). This reaction was the first example that uses Grignard reagent as the coupling partner to perform direct sp^2 C–H bond arylation of N-aromatic heterocycles without a directing group. This approach provided a new access to a variety of C8-arylpurines which are potentially of great importance in medicinal chemistry. A possible mechanism that accounts for C–H bonds arylation of purine with Grignard reagents is presented in Scheme 32. Combination of **38** and Ni(dppp)Cl_2 provides the metalated intermediate **39**. Subsequently, an (aryl)-nickel(II) intermediate **40** is generated by transmetalation between aryl Grignard reagent and the metalated intermediate **39**. Followed by reductive elimination to produce the desired product **41**, the Ni(0) species **42** is generated, which is reoxidized to Ni(II) species by DCE to complete the catalytic cycle.



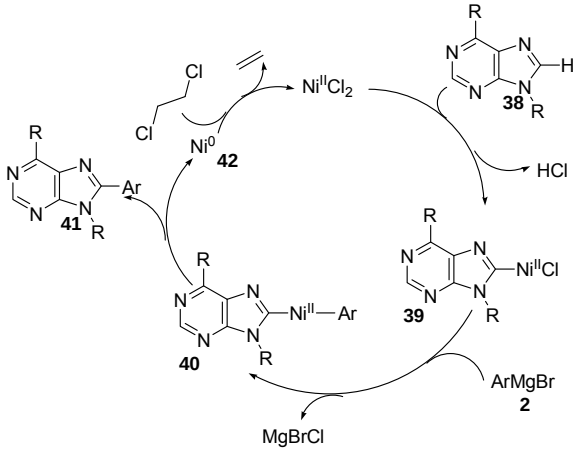
R^1 = OMe, Ph, Bn, Cl, Benzylthio

R^2 = H, Cl

R^3 = Bn, Phenethyl, Me, Et, *n*-Pr, cyclopentyl, *n*-Bu

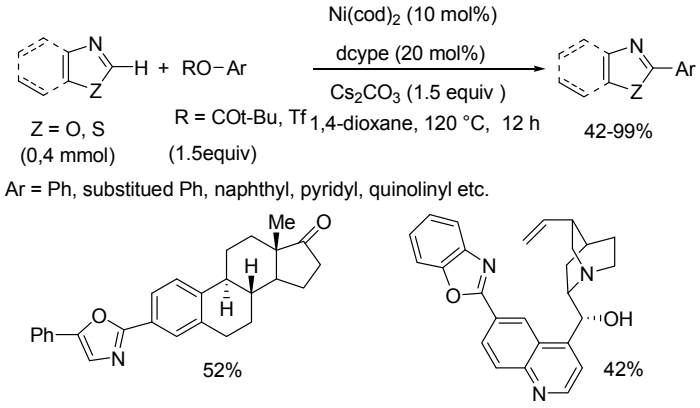
Ar = 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-EtC_6H_4,3,5-2MeC_6H_4, 4-PhC_6H_4, 2-MeC_6H_4

Scheme 31



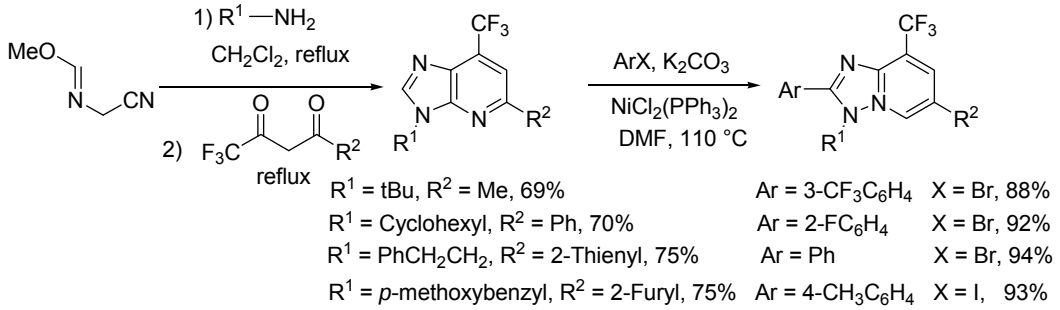
Scheme 32

Itami and coworkers[53] described the C–H bond arylation of azoles with phenol derivatives including esters, carbamates, carbonates, sulfamates, triflates, tosylates, and mesylates using a $Ni(cod)_2$/dcype catalytic system (Scheme 33). The reaction provided the synthesis of a series of privileged 2-arylazoles including biologically active alkaloids, and the functionalizing estrone and quinine were obtained in 52% and 42% yield.

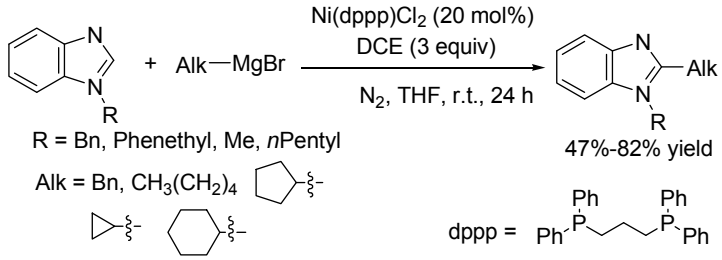


Scheme 33

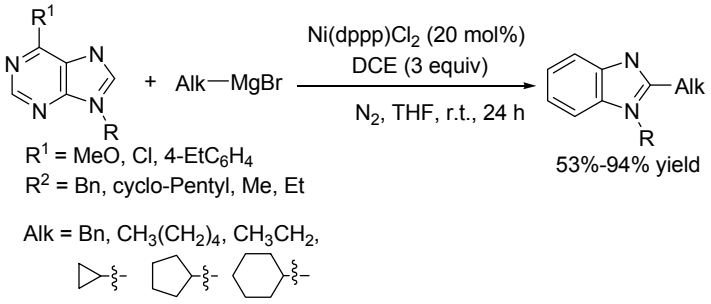
In 2012, Iaroshenko et al[54] reported the arylation of imidazo[4,5-b]pyridines known as 1-deazapurines catalyzed by transition-metal (Scheme 34). 1-Deazapurines were generated from 5-aminoimidazoles by the reaction of methyl N-(cyanomethyl)formimidate with primary amines. Later, Qu and coworkers[55] developed a method for nickel-catalyzed direct sp^2 C–H bond alkylation of N-aromatic heterocycles using a Grignard reagent as the coupling partner (Scheme 35 and Scheme 36). In this process, a variety of alkylated N-aromatic heterocycles with potentially of great importance in medicinal chemistry were obtained under mild condition.



Scheme 34



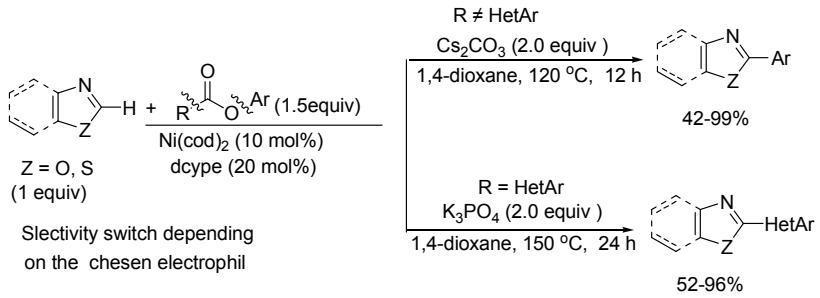
Scheme 35



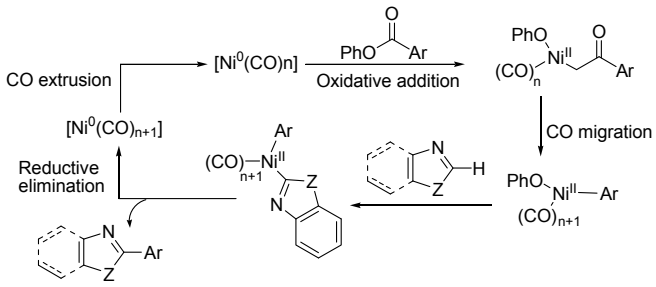
Scheme 36

In early 2012, Itami *et al*[56] disclosed a C-H arylation of azoles with C-O electrophiles, catalyzed by the combination [Ni(cod)$_2$]/dcype (cod=1,5-cyclooctadiene, dcype=1,2-bis-(dicyclohexylphosphino)ethane) (Scheme 37). This catalyst system was highly efficient for the coupling of esters, carbamates, sulfamates, triflates, tosylates, and mesylates with several compounds with an acidic C-H group, such as benzoxazoles, oxazoles, benzothiazoles, and thiazoles. Not surprisingly, the use of simpler alkyl ethers (C-OMe) as electrophiles did not give any conversion at all, thus illustrating the greater inertness associated with the C-OMe bond.[57-60] Interestingly, the coupling of benzoxazole with phenyl thiophene-2-carboxylate did not give the expected C-H/C-O coupling process, but the formation of the corresponding bis(heteroaryl) backbone. In the reaction, a wide variety of heteroaromatic phenyl esters, including furans, thiophenes, pyridines, thiazoles, and quinolones were smoothly coupled with benzoxazoles,

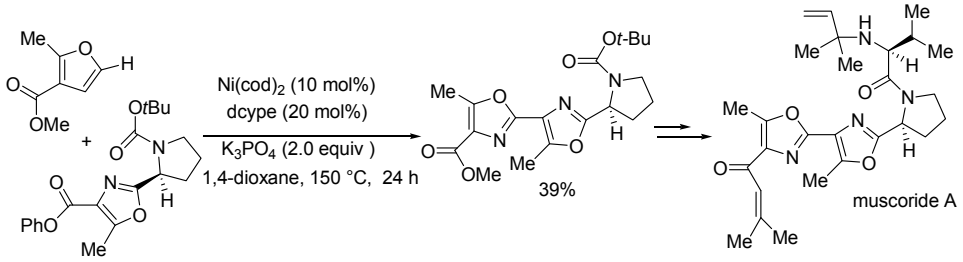
oxazoles, and thiazoles, to access bis(heteroaryl) motifs in a straightforward fashion. The authors reasonably speculated that the decarbonylative C-H arylation protocol involved a Ni0/NiII catalytic cycle (Scheme 38).[61] This novel C–H arylation reaction was successfully applied to a convergent formal synthesis of natural product muscoride A with exceptional antibacterial activity (Scheme 39).



Scheme 37



Scheme 38

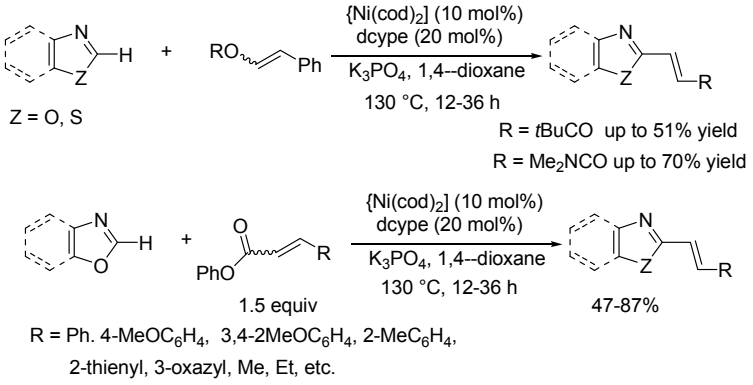


Scheme 39

The novel decarbonylative C-H arylation reported by Itami et al. will open up new opportunities and stimulate the development of new concepts and ideas within the field of Ni-catalyzed reactions, which is probably one of the most vibrant and promising branches of current research in organic and organometallic chemistry.[62]

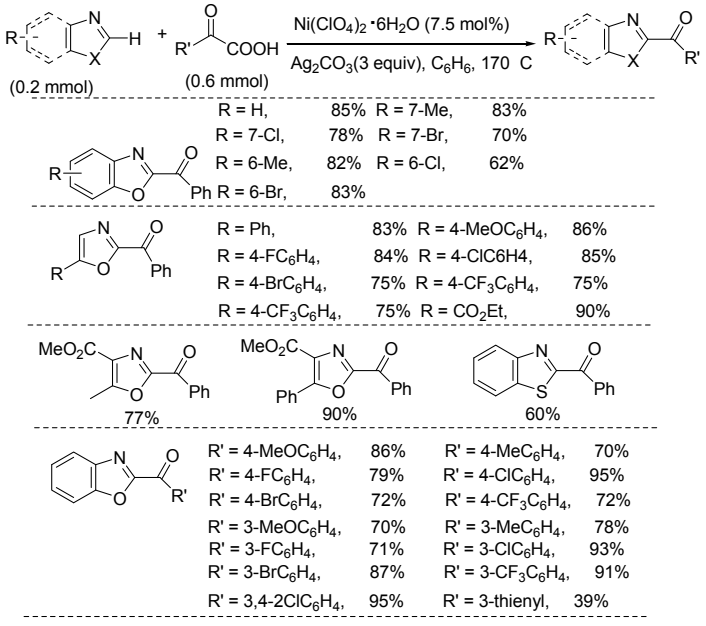
Transition metal catalyzed alkenylation is one of the most reliable methods for making alkenyl-substituted arenes as exemplified by the Mizoroki–Heck reaction.[63] In 2013, Yamaguchi and

coworkers[64] developed Ni/dcype catalyzed C-H/C-O alkenylation and decarbonylative C-H alkenylation two novel C-H alkenylations of azoles (Scheme 40). These newly developed azole alkenylation reactions were successfully applied to the convergent formal synthesis of siphonazole B.[65]



Scheme 40

Recently, Zhang, Ge and coworkers[66] developed an efficient Ni-catalyzed ligand-free direct decarboxylative acylation of azole derivatives by means of sp^2 C-H bond functionalization with good to excellent yields (Scheme 41). This transformation is the first example of decarboxylative cross-coupling reactions using Ni catalysis by a C-H bond functionalization pathway, and provides an useful complementary protocol to access important heteroaryl ketone derivatives in the field of synthesis and medicine.

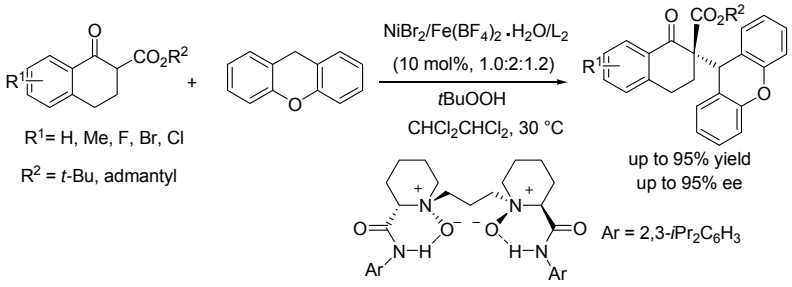


Scheme 41

4. Csp^3-H Bond Functionalizations

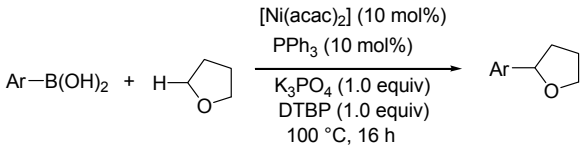
Direct functionalization of unactivated C(sp^3)–H bond has been a focal point of experimental and theoretical research and play important roles among these synthesis routes. In recent year, more attention has been paid to the development of nickel catalysis directly catalyse C(sp^3)–H functionalization and achieve some challenging research results.

Catalytic asymmetric cross-dehydrogenative coupling reaction (CDC reaction) has attracted great attention because it provides efficient methods to construct versatile and useful building blocks.[67-73] Under oxidative conditions, two C–H bonds could be directly coupled to form a new C–C bond without prior installation of functional groups. In 2013, Feng group[74] developed catalytic asymmetric cross-dehydrogenative coupling of β-ketoesters and xanthene using a cooperative bimetallic catalyst system (Scheme 42). Various optically active xanthene derivatives bearing a quaternary stereogenic carbon center were obtained in up to 90% yields with up to 99% ee under mild conditions.



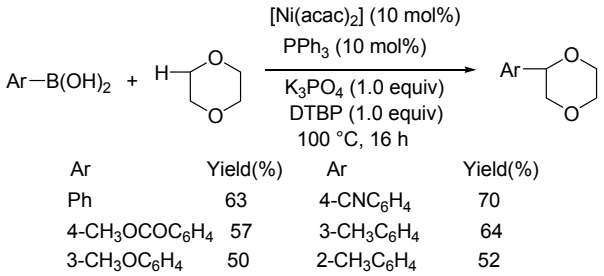
Scheme 42

Lei and coworkers[75] demonstrated the nickel-catalyzed oxidative arylation of C(sp^3)-H bonds in moderate to good yield (Scheme 43-45). Several substituted arylboronic acids and various C(sp^3)-H bonds were approved to be suitable substrates for this novel transformation. This process provides an effective method for the introduction of simple ether derivatives to synthese α-arylated ethers. Preliminary mechanistic studies suggest that this reaction possiblly proceed through a radical pathway.

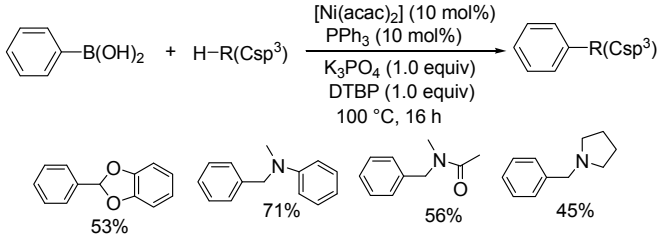


Ar	Yield(%)	Ar	Yield(%)
Ph	88	4-MeOC$_6$H$_4$	93
4-CH$_3$COC$_6$H$_4$	78	4-CF$_3$C$_6$H$_4$	52
4-FC$_6$H$_4$	86	4-ClC$_6$H$_4$	84
2-CH$_3$C$_6$H$_4$	84	nathph-2-yl	52

Scheme 43

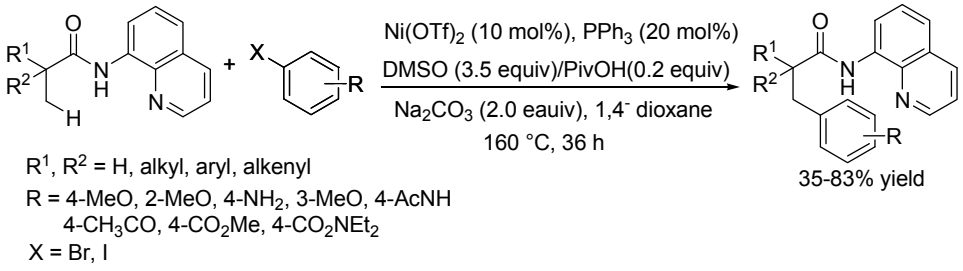


Scheme 44

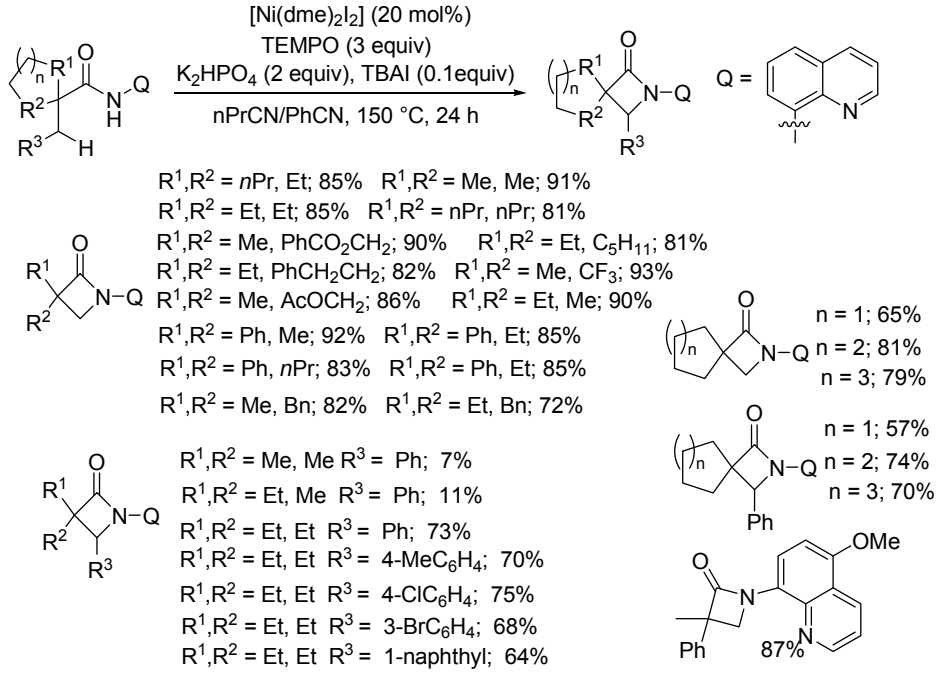


Scheme 45

In 2014, You[76] disclosed the nickel-catalyzed unactivated β-C(sp^3)–H bond arylation of aliphatic acid derivatives with aryl iodides/bromides via bidentate chelation-assistance of an 8-aminoquinoline moiety (Scheme 46). These preliminary results in the reaction indicate the intrinsic catalytic potential of nickel metal for unactivated C(sp3)–H bond arylation. Ge[77] developed a a nickel-catalyzed sp^3 C-H bond functionalization process for site-selective intramolecular dehydrogenative cyclization reaction of 2,2-disubstituted propionamides (Scheme 47). The reaction suits to the C-H bonds of β-methyl groups over the γ-methyl or β-methylene groups. Additionally, a predominant preference for the β-methyl C-H bonds over the aromatic sp^2 C-H bonds was observed. Moreover, this process also allows for the effective functionalization of benzylic secondary sp^3 C-H bonds. Naoto[78] still reported the similar studies on the direct arylation of C-(sp^3)−H (methyl and methylene) bonds in aliphatic amides containing an 8-aminoquinoline moiety as a bidentate directing group with aryl halides catalyzed by Ni catalysis.

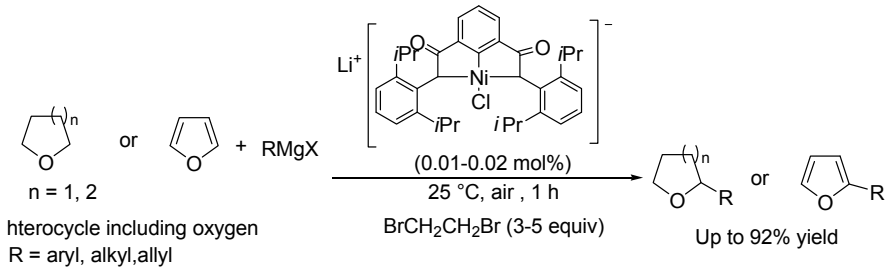


Scheme 46



Scheme 47

In 2014, Gartia *et al*[79] described the catalytic coupling of Grignard reagents with the C–H bond of oxygen containing heterocyclic compounds such as tetrahydrofuran catalysed by nickel(II) complex (Scheme 48). The nickel(II) complex showed excellent activity in catalyzing C–H activation and further coupling with various Grignard reagents. The effective activation of the C–H bond proceeded under ambient reaction conditions with a short reaction time (1–2 h) and catalyst loading as low as 0.01 mol%. This catalytic route could prove to be an efficient method for the preparation of synthetically and pharmaceutically relevant molecules by activation of sp3 C–H bonds in various heterocycles.



Scheme 48

5 Conclusions

Over the past decades, there has been an explosive growth in the development of methods for C–H functionalization and the application of these technologies for the synthesis of complex targets such

as natural products and pharmaceutical agents. Various nickel salts or complexes are extensively used as catalyst for these reactions due to their high efficiency and low cost. This review presented an overview of the area of nickel-catalyzed direct C–H bond functionalizations and C−C bond forming reactions via Csp–H, Csp^2–H and Csp^3–H bond activation. Nickel-catalyzed C-H bond functionalized reactions which lead to the formation of C–C bonds have been recognized as one of important strategies in synthetic organic chemistry. Some important breakthroughs in the study of nickel-catalyzed direct C-H activations demonstrated that Nickel-catalyzed reactions are broadly applicable to a variety of research fields related to organic synthesis. Important developments have come true to extend the substrate scope, particularly, including simple arenes, electron-deficient aromatic and heteroaromatic substrates.

From a synthetic point of view, nickel-catalyzed direct C–H bond functionalizations provide novel and efficient tools for constructing various useful compounds. Gathering mechanistic insights could help us to understand the nature of these reactions and lead to the discovery of unique reactivities of metal catalysts. However, there are still some major challenges that need to be addressed in this rapidly developing area. Most mechanisms proposed in this study are preliminary methods lacking solid and thorough experimental and theoretical studies. Moreover, only a few reactions with chiral ligands could realize asymmetric catalysis. Enantioselective C−H functionalization and $C(sp^3)$−H functionalization may represent significant challenges for further catalyst/reaction developments, etc. To overcome these central challenges, an increasing demand for the robust catalytic systems will continue to drive the field forward towards the development of ideal C–H bond activation. With increased exploitation of nickel catalysts, new exciting and innovative achievements are expected to appear in the near future.

Acknowledgements

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