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Nickel-Catalyzed C–H Bond Functionalization Utilizing an *N*,*N*′-Bidentate Directing Group

Naoto Chatani

Abstract This review discusses the use of nickel catalysts and *N*,*N*′-bidentate directing groups, such as 2-pyridinylmethylamine, 8-aminoquinoline, and derivatives thereof, which constitute a powerful combination for the chelation-assisted functionalization of C–H bonds.

Keywords C–H activation · C–H functionalization · Chelation assistance · Nickel

Contents

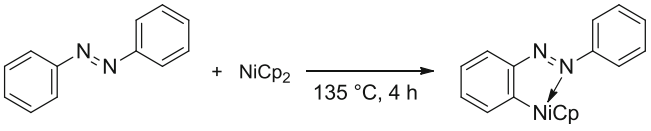
N. Chatani (✉)
Department of Applied Chemistry, Osaka University, Suita, Osaka 565-0871, Japan
e-mail: chatani@chem.eng.osaka-u.ac.jp

1 Introduction

A wide variety of transition metal complexes, such as Pd, Ru, Rh, and Ir, have been used as catalysts in a variety of catalytic functionalizations of C–H bonds, such as arylation, alkenylation, alkylation, carbonylation, dehydrogenation, amination, oxidation, silylation, and borylation [1–9]. Among the transition metal complexes used thus far in the functionalization of C–H bonds, the most powerful and extensively studied involve Pd complexes. Pd complexes are known to show a high catalytic activity in a wide variety of functionalization reactions of C–H bonds. Because of this, many groups are now using Pd catalysts in the development of such functionalization reactions. Mechanistic studies of the Pd-catalyzed functionalization of C–H bonds, including stoichiometric reactions, have also been conducted. However, the recent focus on developing synthetic methodology for various functionalization reactions using less costly and more abundant first row metals, such as Fe, Co, Ni, and Cu, is a challenging task. Ni catalysts are of particular interest in this area [10, 11].

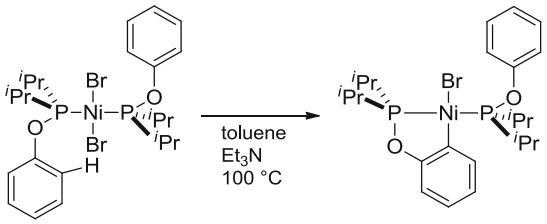
In 1963, an early example of the stoichiometric cyclometalation of C–H bonds was reported by Kleiman and Dubeck (Scheme 1) [12]. Thus, the reaction of azobenzene with $NiCp_2$ resulted in the formation of a cyclometalated complex. Although the mechanism responsible was not discussed, the cleavage appeared to proceed through σ-bond metathesis. A chelation-assisted cylometalation using Pd complexes was also reported by Cope and coworkers in 1965 [13]. Since then, cyclopalladation has been extensively studied [14, 15], in which the cleavage of C–H bonds proceeds through an S_EAr-type or concerted metalation–deprotonation (CMD) mechanism. A wide variety of new reactions have arisen from the cyclopalladated intermediates. In contrast, examples of stoichiometric amounts of Ni complexes involving the activation of C–H bonds are still very rare. In 2014, Zargarian finally reported on a stoichiometric reaction of bis(phosphinite) derivatives with $NiBr_2$, in which the cleavage of C–H bonds was proposed to proceed through a S_EAr-type mechanism based on the observation that electron-donating substituents facilitate the reaction (Scheme 2) [16].

A pioneering example of the Ni-catalyzed functionalization of C–H bonds was reported by Cavell, who reported on the Ni(0)-catalyzed alkylation of C–H bonds in imidazolium salts with alkenes leading to the production of linear alkylation products [17]. The addition of 2 equiv. of PPh_3 is essential for the effective catalytic reaction. The oxidative addition of C–H bonds to $Ni(PPh_3)_n$, which is generated in situ, was proposed to initiate the catalytic cycle (Scheme 3).

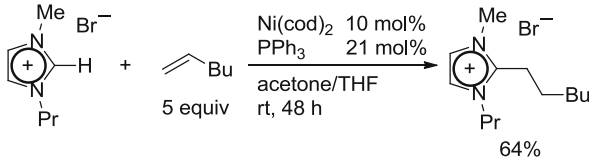


Scheme 1 Cyclometalation using $NiCp_2$ complex

Scheme 2 Cyclometalation using $NiBr_2$



Scheme 3 Imidazolium C–H/alkene coupling reaction



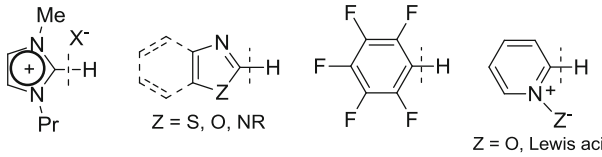


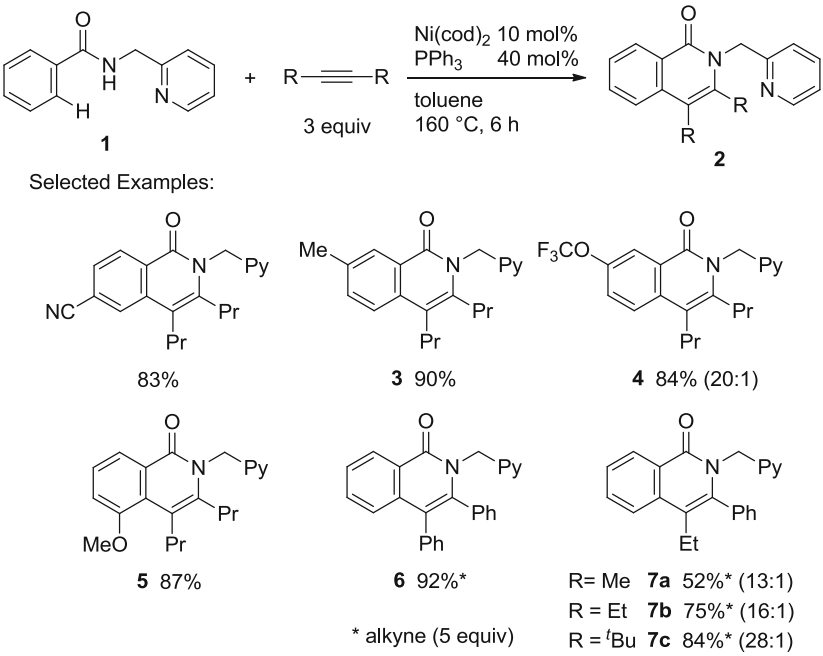
Fig. 1 Representative substrates applicable to the Ni-catalyzed functionalization of C–H bonds

Following this pioneering report, a number of the Ni-catalyzed functionalization of C–H bonds have been reported. However, the functionalization of C–H bonds catalyzed by Ni complexes is limited to C–H bonds in specific aromatic systems, such as pyridine or activated pyridine derivatives and highly perfluorinated benzene and azole derivatives, in which an acidic C–H bond is present (Fig. 1) [18]. On the other hand, examples of the nickel-catalyzed activation of non-acidic C–H bonds in benzene rings are rare. Recently, Chatani reported on the use of a powerful combination of a Ni catalyst and an *N*,*N*′-bidentate directing group in the chelation-assisted functionalization of C–H bonds, which is a promising chelation system for developing new types of Ni-catalyzed functionalization of C–H bonds. Since then, various transformations of C–H bonds catalyzed by Ni complexes have been reported [19, 20]. This review focuses on the Ni-catalyzed functionalization of C–H bonds by taking advantage of *N*,*N*′-bidentate directing groups. A pioneering example of an *N*,*N*′-bidentate directing group was reported by Daugulis [21].

2 C(sp^2)-H Activation

2.1 Oxidative Cycloaddition of C(sp^2)–H Bonds with Alkynes

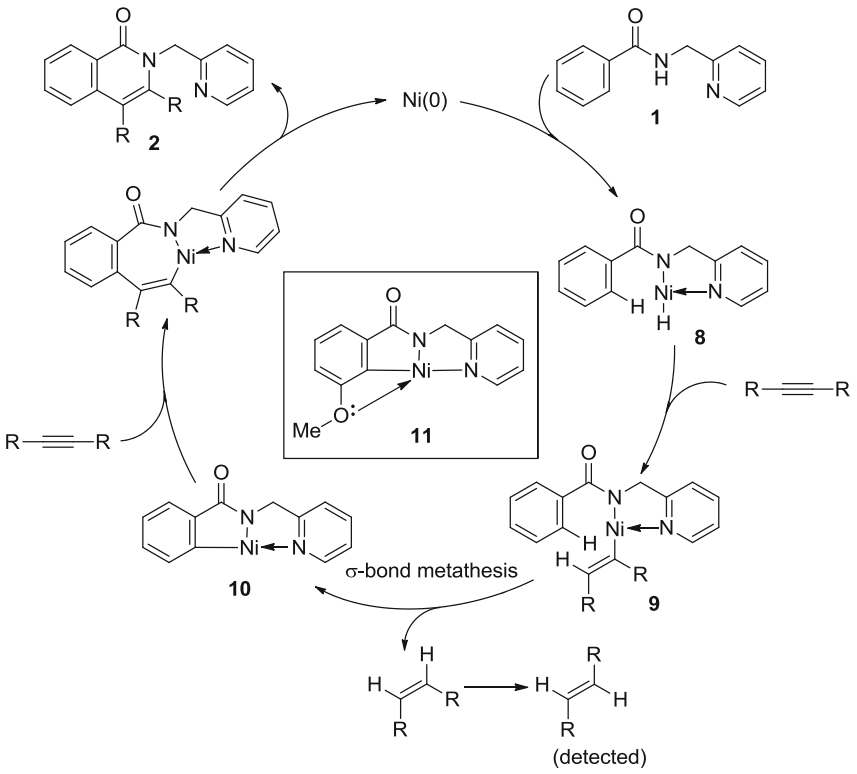
In 2011, Chatani and coworkers reported on the Ni(0)-catalyzed oxidative cycloaddition of aromatic amides **1** to internal alkynes for the synthesis of isoquinolone derivatives **2** (Scheme 4) [22]. A similar transformation was previously reported



Scheme 4 Ni-catalyzed oxidative cycloaddition reaction with alkynes

using Rh(III) as the catalyst [23, 24]. However, the reaction does not require the addition of a metal oxidant or an intramolecular sacrificed oxidizing substituent in the substrate, in contrast to the Rh(III) system. Instead, an alkyne functioned as the hydrogen acceptor. Later, Pd(II) [25] and Ru(II) were also found to catalyze oxidative cycloaddition of aromatic amides to internal alkynes leading to isoquinolones [26] (for the Ru(II)-catalyzed isoquinolone synthesis utilizing an 8-aminoquinoline directing group, see [27]). However, the use of an inexpensive and abundant metal, such as Ni as the catalyst, is significant. A key to the success of this reaction was the utilization of a 2-pyridinylmethylamine moiety as the directing group. Among the directing groups examined, a 2-pyridinylmethylamine was found to be a superior directing group.

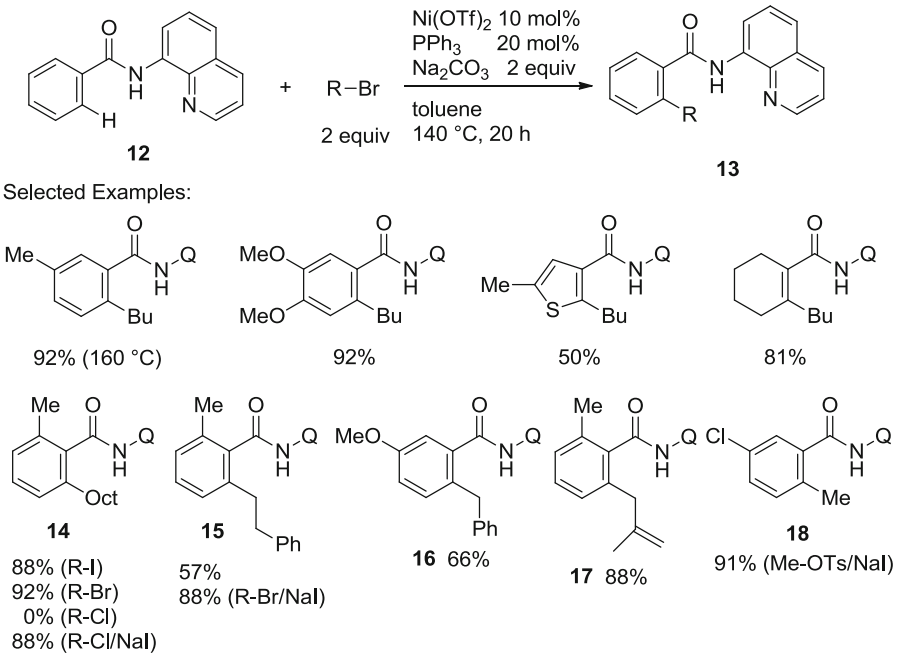
Various functional groups, such as methoxy, amino, trifluoromethoxy, acetyl, cyano, and acetal groups, are tolerated in the reaction. The reaction of a *meta*-methyl- and trifluoromethoxy-substituted aromatic amide gave **3** and **4**, respectively, in which the less-hindered C–H bond was selectively cleaved. In sharp contrast, in the case of a *meta*-methoxy-substituted substrate, the hindered C–H bonds were cleaved to afford **5**. The difference in regioselectivity between **4** and **5** is worthy of attention. These results suggest that steric effects are a major factor in this type of reaction, but the electronic nature of the substituents also can have a significant effect on the regioselectivity of the reaction if they contain a lone pair of electrons. Diphenylacetylene also participates in the oxidative cycloaddition, as in **6**. Unsymmetrical alkynes and phenyl alkyl alkynes regioselectively gave the



Scheme 5 A proposed reaction mechanism for the Ni-catalyzed oxidative cycloaddition with alkynes

corresponding isoquinolones **7**, in which the phenyl group is attached to the carbon adjacent to a nitrogen atom. The regioselectivity increased with increasing size of the alkyl group.

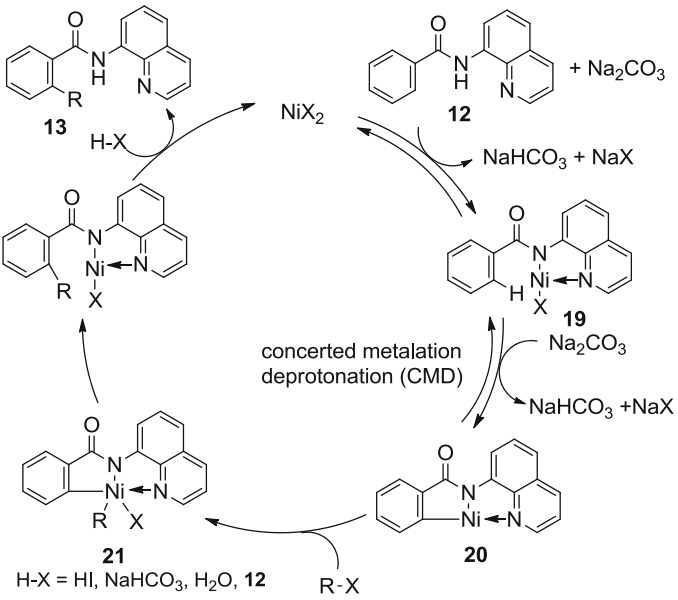
A proposed mechanism for the oxidative cycloaddition with alkynes is shown in Scheme 5. The reaction starts from the coordination of the pyridine nitrogen in the amide **1** to the nickel(0) center followed by the oxidative addition of a N–H bond to give the nickel hydride complex **8**. The insertion of the alkyne into the Ni–H bond of **8** affords the vinyl nickel complex **9**. Cleavage of the *ortho*-C–H bond with the concomitant formation of an alkene (experimentally detected) gives the *ortho*-metalated complex **10**. The cleavage of C–H bonds is proposed to proceed through σ-bond metathesis. Insertion of the alkyne into the C–Ni bond in complex **10**, followed by a reductive elimination, results in the formation of an isoquinolone **2**, with regeneration of the active nickel(0) species. The proposed intermediate, which switches the regioselectivity of *meta*-methoxy substrate, is depicted as the complex **11**. According to the proposed mechanism, in which the alkyne functions as a hydrogen acceptor, 2 equiv. of alkynes is required and 1 equiv. of alkenes would be formed. In fact, stilbene was formed in 81% yield, which is comparable to that for **6** (92%) in the reaction of **1** with diphenylacetylene.



Scheme 6 Ni-catalyzed alkylation of C–H bonds with primary alkyl halides

2.2 *Alkylation of C(sp^2)–H Bonds*

The direct arylation of C–H bonds with aryl halides or pseudo halides has been extensively studied to construct biaryls as one of the alternative cross-coupling reactions because biaryls find widespread applications as building blocks for organic materials, fine chemicals, and pharmaceuticals. In sharp contrast, examples of the direct alkylation of C–H bonds with alkyl halides are limited because the oxidative addition of alkyl halides to transition metal complexes is an unfavorable process and the resulting alkylmetal complexes tend to undergo β-hydride elimination (for a review on C–H alkylation, see [28]). In 2013, Chatani reported on the Ni(II)-catalyzed alkylation of C–H bonds in aromatic amides **12** with alkyl halides (Scheme 6) [29, 30]. Among various directing groups tested, only an 8-aminoquinoline directing group gave the alkylation products **13**. The addition of PPh_3 was essential for the success of the reaction. In the absence of PPh_3, no product was formed. The addition of NaI was also found to promote the reaction. An alkyl chloride showed no reactivity, but the reaction with an alkyl chloride in the presence of 2 equiv. of NaI dramatically increased the product yield, as in **14**. The addition of NaI was also effective in the case of reactions with relatively less-reactive alkyl bromides, as in **15**. Not only alkyl halides but also benzyl bromide and allyl bromide were also applicable to the reaction, as in **16** and **17**. Because examples of the methylation of C(sp^2)–H bonds with methyl halides

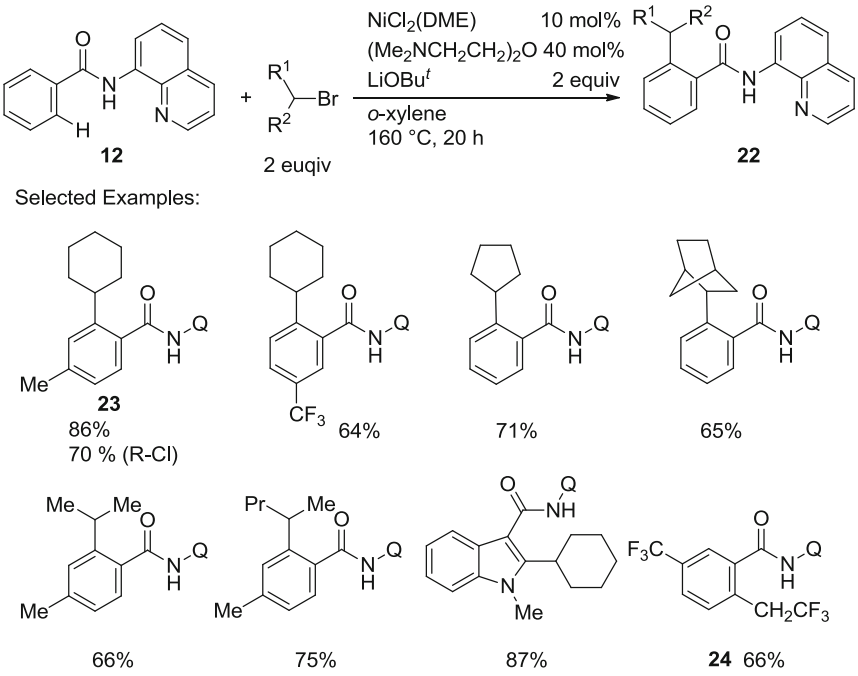


Scheme 7 A proposed reaction mechanism for the Ni-catalyzed alkylation of C–H bonds

(or pseudohalide) are very rare, the methylation of C–H bonds continues to be a significant challenge. The use of a combination of methyl tosylate/NaI afforded the methylation product **18** in 91% yield.

To gain insights into the reaction mechanism, various mechanistic experiments, including deuterium-labeling experiments, competition experiments, radical clock experiments, and radical trap experiments, have been carried out. These mechanistic studies indicated that (1) the cleavage of C–H bonds is reversible, (2) a free radical is not involved, and (3) Ni(II) is a key catalytic species. A proposed mechanism for the Ni-catalyzed alkylation of C–H bonds is shown in Scheme 7 [29, 30]. The coordination of amide **12** to the Ni(II) center gives the nickel complex **19** with the concomitant generation of HX. This step is accelerated by the base. The complex **19** undergoes cyclometalation to give the *ortho*-metalated complex **20**. The cleavage of C–H bonds appears to proceed via a CMD (concerted metalation deprotonation) mechanism [31]. This step is a reversible and rapid step and is not the rate-determining step. The oxidative addition of R–X gives the Ni(IV) species **21**, which undergoes reductive elimination followed by protonation to afford the alkylation product **13** with the regeneration of Ni(II) species.

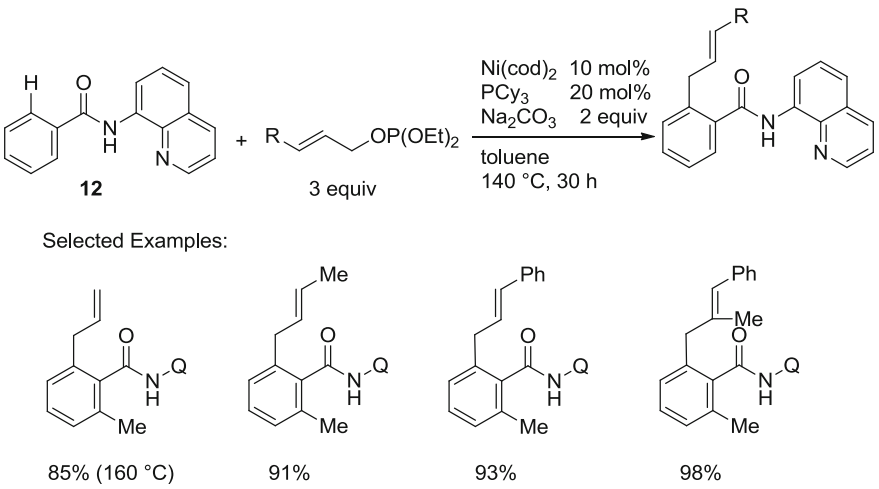
The reaction with secondary halides under the reaction conditions suitable for the reaction with primary alkyl bromides gave no alkylation products (Scheme 6). However, Ackermann recently successfully found the optimal reaction conditions for the Ni(II)-catalyzed alkylation of C–H bonds with secondary alkyl halides using essentially the same chelation system (Scheme 8) [32]. The reaction gave the mono-alkylation products **22** with excellent selectivity. More significantly, less-reactive



Scheme 8 Ni-catalyzed alkylation of C–H bonds with secondary alkyl halides and trifluoroethyl halide

secondary alkyl chlorides were also applicable to the reaction, as in **23**. Various secondary alkyl bromides including cyclic and acyclic halides participate in the reaction without any evidence of isomerization or rearrangement. Similar to the results reported by Chatani and coworkers [29, 30], H/D exchange took place only at the *ortho*-position, providing a strong support for the occurrence of a reversible C–H bond cleavage. In addition, competition experiments showed that electron-withdrawing groups on the aromatic ring facilitate the reaction. The trifluoroethylation of C–H bonds was also achieved, as in **24**.

It was found that a variety of groups, such as alkyl, benzyl, allyl, and methyl groups, can be installed at the *ortho*-position in the Ni-catalyzed reaction of C–H bonds with alkyl halides or pseudohalides (Schemes 6 and 8) [29, 30, 32]. Zeng recently reported on the Ni(0)-catalyzed *ortho*-allylation of C–H bonds in aromatic amides using an 8-aminoquinoline as the directing group with allyl phosphates (Scheme 9) [33]. In this reaction, Ni(II) complexes also showed catalytic activity, but $Ni(cod)_2/PCy_3$ was the most active catalyst. This C–H allylation proceeds with complete α- and *E*-selectivity. The addition of 2,4-di-*tert*-butyl-4-methylphenol (BHT), a radical scavenger, had no obvious effect on the conversion, suggesting that a free radical is not involved in the reaction pathway.

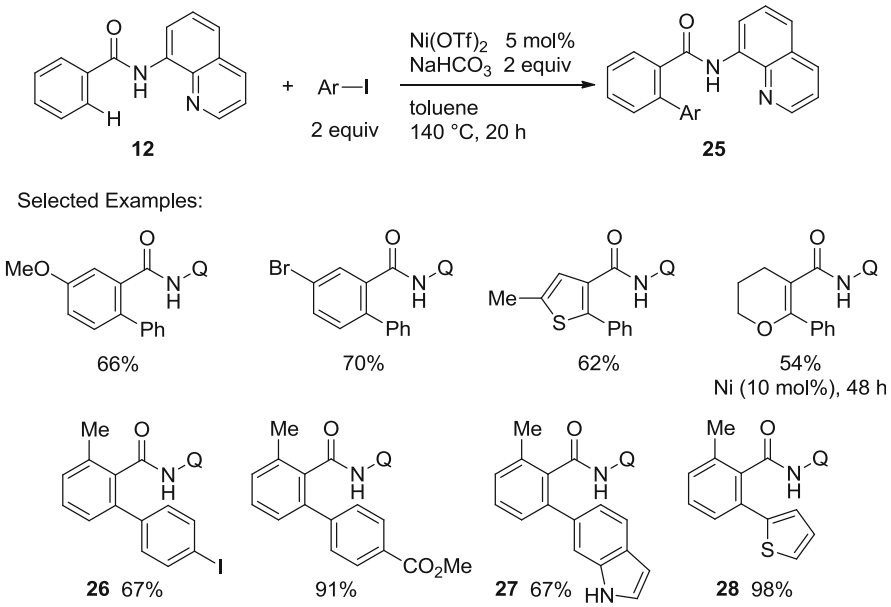


Scheme 9 Ni-catalyzed allylation of C–H bonds with ally phosphates

2.3 Arylation of C(sp^2)–H Bonds

Chatani recently developed the Ni(II)-catalyzed arylation of aromatic amides containing an 8-aminoquinoline as the directing group with aryl iodides as coupling partners (Scheme 10) [34]. In this system only the 8-aminoquinoline moiety gave the desired *ortho*-phenylation product. Unlike the alkylation of C–H bonds shown in Scheme 6 [29, 30], the addition of a phosphine ligand was not required for the reaction to proceed. The reaction showed a high efficiency with broad functional group tolerance. The scope of the reaction is broad with regard to both aromatic amide and coupling partner. The reaction with 1,4-diiodebenzene gave **26**, in which one of the iodides remained intact. Some heteroaromatic iodides, such as 7-iodo-1H-indole and 2-iodothiophene, also participate in the arylation of C–H bonds as coupling partners to give **27** and **28**, respectively.

To gain insights into the reaction mechanism, several mechanistic experiments, including deuterium-labeling experiments, competition experiments, radical trapping experiments, and Hammett studies, have been conducted. The results of deuterium-labeling experiments indicated that the cleavage of C–H bonds is reversible and it does not appear to be the rate-determining step. The competition experiments and Hammett studies indicated that the presence of an electron-withdrawing group in the aromatic amides and an electron-donating group in the aryl iodides accelerates the reaction, suggesting that the reductive elimination step appears to be the rate-determining step. The reaction was not completely inhibited in the presence of the radical scavenger, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO). A proposed mechanism, based on the above observations, for the Ni-catalyzed alkylation of C–H bonds is shown in Scheme 11. The mechanism is essentially the same as that proposed for the alkylation of C–H bonds shown in

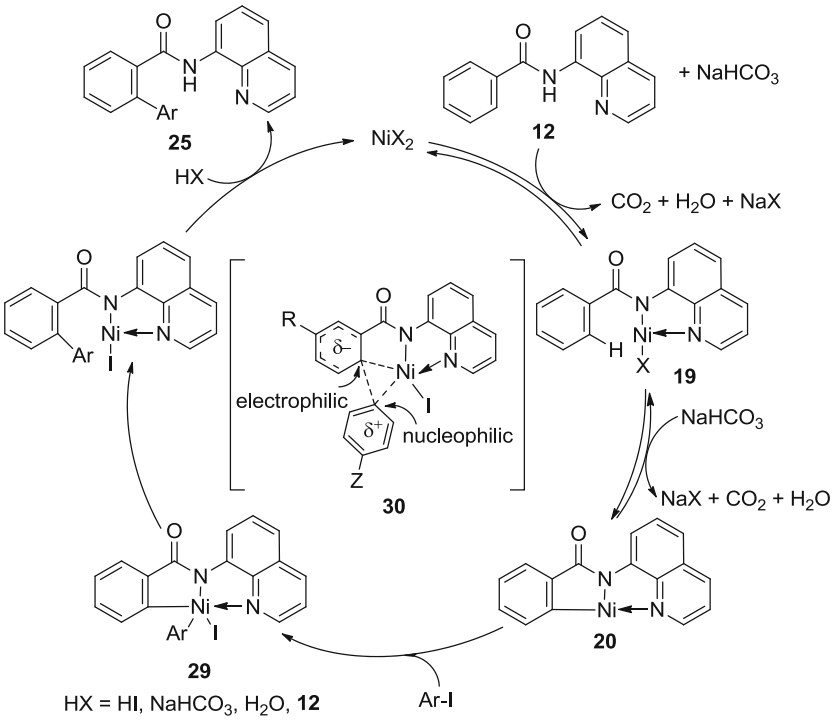


Scheme 10 Ni-catalyzed arylation of C–H bonds with aryl iodides

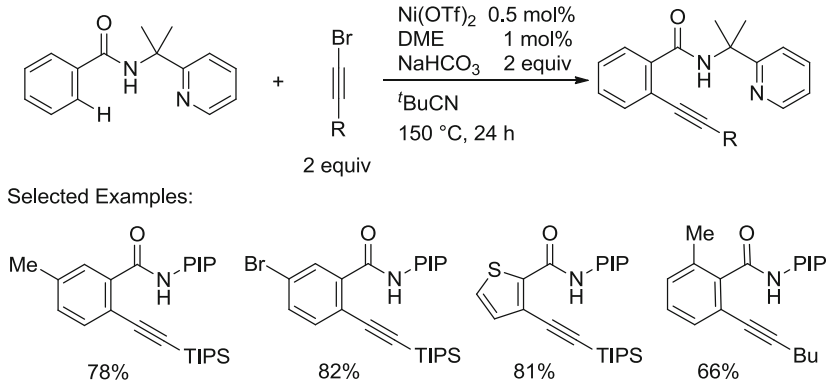
Scheme 7. The oxidative addition of Ar–I to the cyclometalated Ni(II) complex **20** leads to the formation of the Ni(IV) species **29**, which undergoes a reductive elimination followed by protonation to give the final arylation product **25** with the regeneration of the active Ni(II) species. Based on competition experiments and Hammett studies, the reductive elimination, which appears to be the rate-determining step, would proceed through the transition state **30** in which a developing negative charge is stabilized by electron-withdrawing groups **R** on the aromatic amides and a developing positive charge is stabilized by electron-donating groups **Z** on the aryl iodides.

2.4 Alkynylation of C(sp^2)–H Bonds

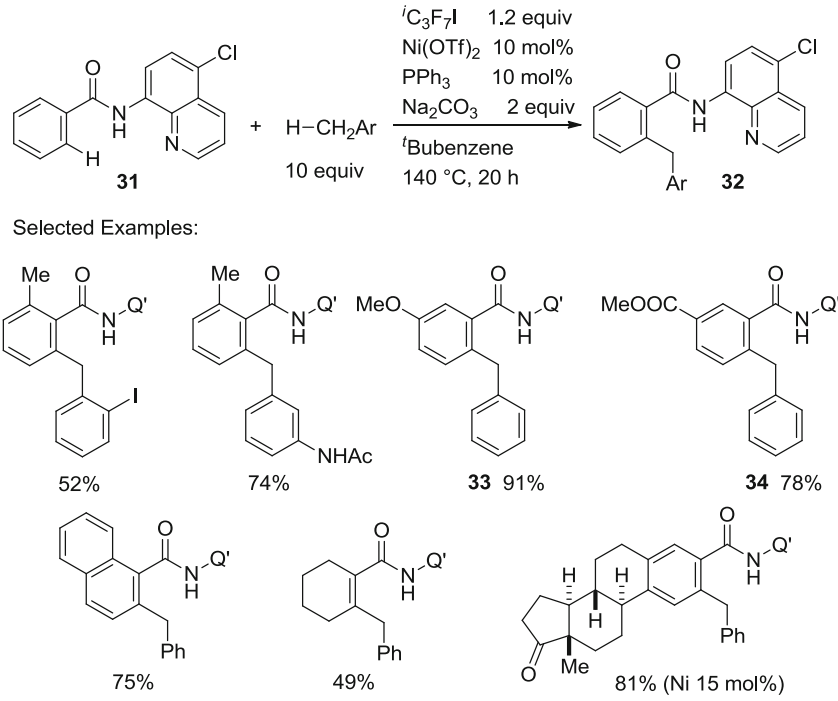
Shi recently reported on the Ni(II)-catalyzed alkynylation of aromatic amides containing a (pyridine-2-yl)isopropylamine (PIP) as the directing group with ethynyl bromides as coupling partners (Scheme 12) [35]. When *meta*-substituted aromatic amides were employed, the alkynylation occurred at the sterically more accessible position. A wide variety of functional group were tolerated. The scope of the reaction with respect to ethynyl bromides was wide. Not only a triisopropylsilyl (TIPS) group but also a trimethylsilyl (TMS), alkyl, and aryl-substituted alkynes were applicable to the reaction. The reaction proceeded with a high catalyst turnover number (TON) of up to 196.



Scheme 11 A proposed reaction mechanism for the Ni-catalyzed arylation of C–H bonds



Scheme 12 Ni-catalyzed alkynylation of C–H bonds with ethynyl bromides

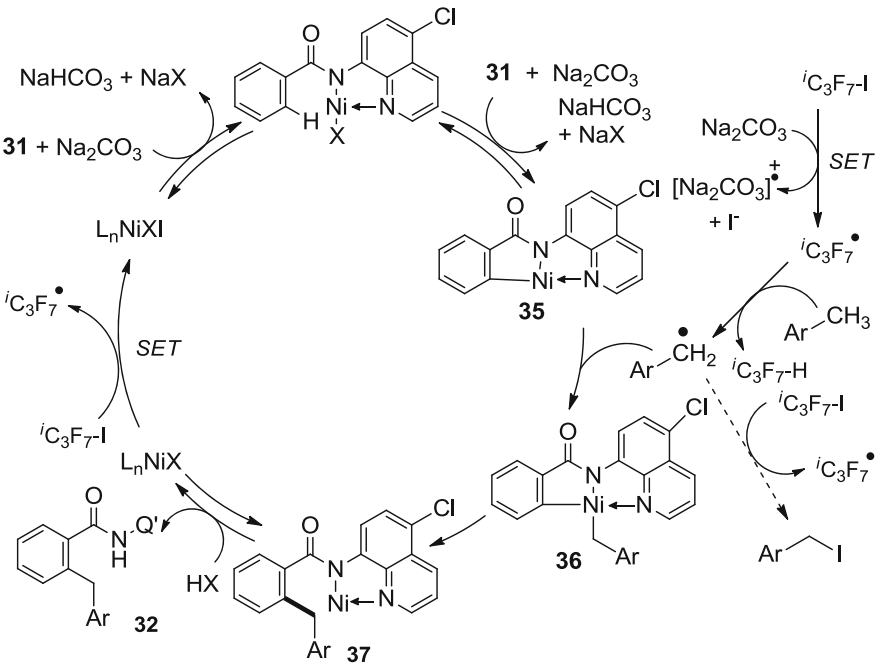


Scheme 13 Ni(II)-catalyzed benzylation of C–H bonds via cross-dehydrogenative coupling of C–H bonds

2.5 *Cross-Dehydrogenative Coupling of C(sp^2)–H Bonds with Toluene C–H Bonds*

Among catalytic functionalizations of C–H bonds developed so far, cross-dehydrogenative coupling of C–H bonds is one of the most ideal C–H functionalizations because the new C–C bond is formed by the direct connection of two different C–H bonds, thus avoiding the generation of stoichiometric amounts of halogenated or organometallic byproducts [36–38]. However, most of the examples reported so far involve the coupling of C(sp^2)–H/C(sp^2)–H bonds. Chatani reported on the Ni(II)-catalyzed benzylation of *ortho*-C–H bonds in aromatic amides with toluene derivatives using an 8-amino-5-choloroquinoline as the directing group (Scheme 13) [39]. The reaction is tolerant to a wide variety of functional groups. When *meta*-substituted aromatic amides were used, benzylation products were selectively obtained through the cleavage of the less-hindered C–H bonds, as in **33** and **34**.

A proposed mechanism is depicted in Scheme 14. The most important issue to be understood is the nature of the actual benzylation species and how it is generated. The generation of a benzyl radical species is proposed as the key species, which is generated by the SET (single-electron transfer) from the base, Na_2CO_3 to $^{i}C_3F_7I$ to

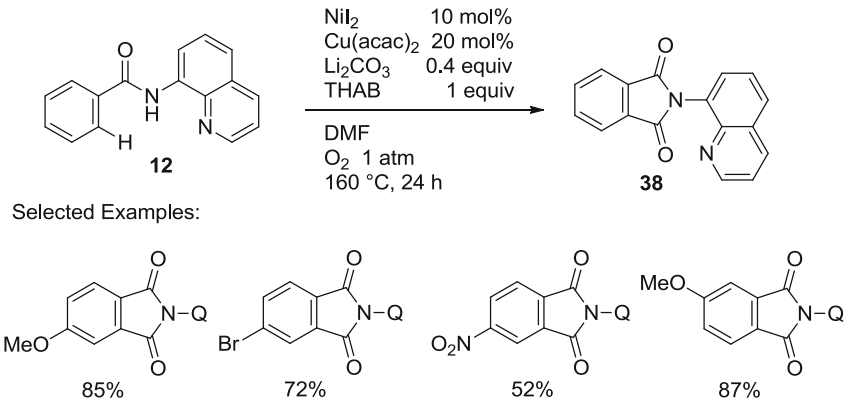


Scheme 14 A proposed reaction mechanism for the Ni-catalyzed cross-dehydrogenative coupling of C–H bonds with toluene C–H bonds

generate a $^{i}C_3F_7$ radical. The radical abstracts a hydrogen from toluene to give a benzyl radical, which reacts with the cyclometalated complex **35** to generate a Ni (III) complex **36**. Reductive elimination from **36** releases the benzylation product **32** and a Ni(I) complex. The Ni(I) complex abstracts an iodine atom from $^{i}C_3F_7I$ to generate Ni(II) complex and a $^{i}C_3F_7$ radical. In fact, the addition of TEMPO completely quenched the reaction, suggesting that a free radical species is involved in the reaction. The generation of benzyl iodide as the electrophilic counter partner also cannot be excluded.

2.6 Carbonylation of C(sp^2)–H Bonds

The use of *N*,*N*′-bidentate directing group in the carbonylation of C–H bonds has been achieved by the use of carbon monoxide (CO) as the carbonyl source in conjunction with $Ru_3(CO)_{12}$ [40] or $Co(acac)_2$ as the catalysts [41]. Ge recently reported on the Ni(II)/Cu(II)-catalyzed carbonylation of benzamides containing an 8-aminoquinoline as the directing group with DMF as the carbonyl source (Scheme 15) [42]. The presence of both a Ni and a Cu catalyst was required for the reaction to proceed. The product yield was improved by the addition of a



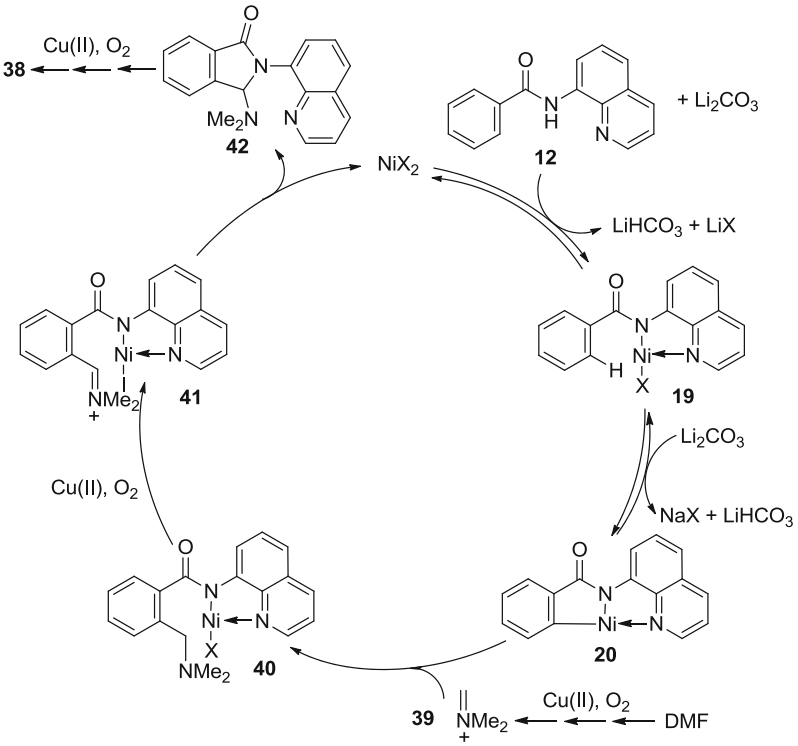
Scheme 15 Ni(II)-catalyzed carbonylation of C–H bonds

quaternary ammonium salt, tetraheptylammonium bromide (THAB). The reaction shows a high functional group compatibility. When ^{13}C-labeled DMF, the carbonyl group being labeled, was used as the solvent, only a trace amount of ^{13}C was incorporated into the product **38**, indicating that the carbonyl group in DMF is not the source of CO. The results from some control experiments with various nitrogen-containing solvents resulted in the suggestion that the source of the incorporated CO in **38** is mainly the methyl group in DMF.

A deuterium-labeling experiment was carried out to probe the reaction mechanism. The results indicated that the H/D exchange at the *ortho*-position is reversible. A proposed mechanism is shown in Scheme 16. An iminium species **39**, which is proposed as the CO source, is generated in situ from DMF via a multistep process under Cu(II) catalyst with O_2. The reaction of cyclometalated complex **20** with **39** resulted in the formation of **40**, which is oxidized by Cu(II) under O_2 to give **41**. An intramolecular nucleophilic addition gives the intermediate **42**, which is followed by oxidation and hydrolysis to afford the phthalimide **38**.

2.7 C–S Bond Formation

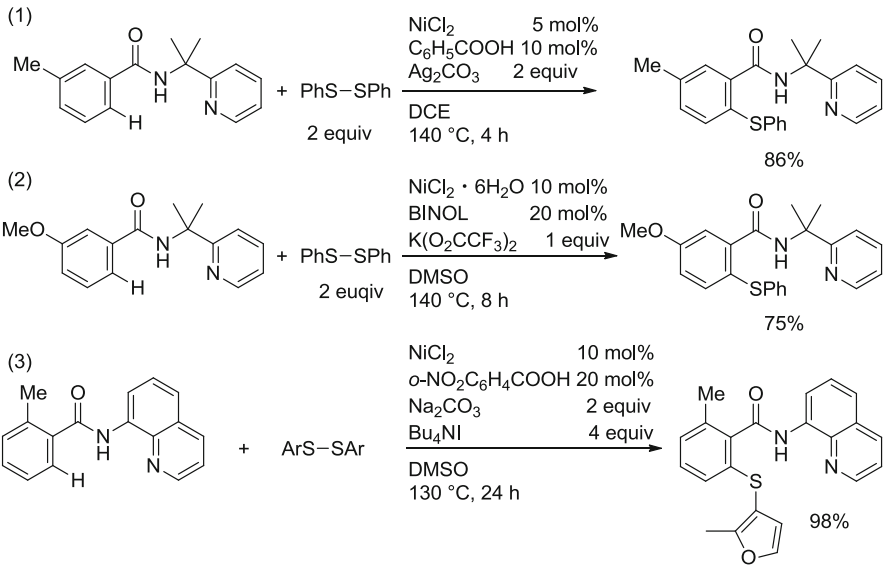
Around the same time, the Lu, Shi, and Zhang groups independently reported on the Ni(II)-catalyzed thiolation of C–H bonds with disulfides, in which two different *N*, *N*′-directing groups were used as the directing group (Scheme 17). Lu (Scheme 17a) [43] and Shi (Scheme 17b) [44] used a PIP directing group and Zhang used an 8-aminoquinoline as the directing group (Scheme 17c) [45]. In all cases, the reactions showed a high degree of functional group tolerance. The scope of the reaction regarding aromatic amides and diaryl disulfides was broad. Curiously, Lu found that the addition of TEMPO inhibited the reaction, but in Shi and Zhang's systems, the addition of TEMPO had no effect on the efficiency of the reaction.



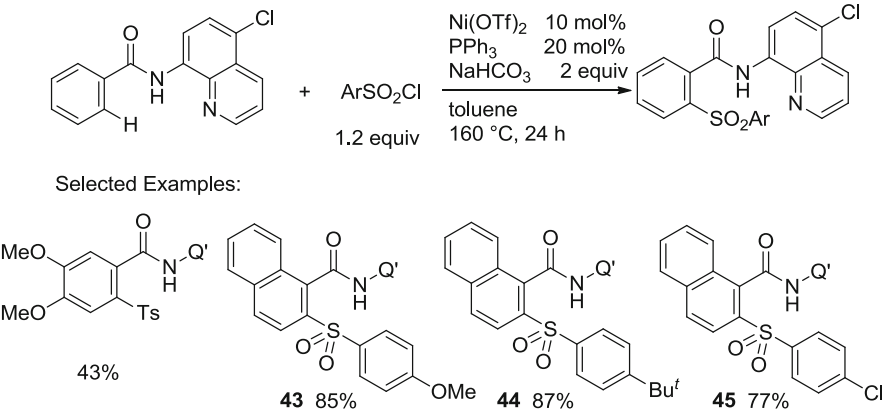
Scheme 16 A proposed reaction mechanism for the Ni-catalyzed carbonylation reaction

Based on their contradictory results, a different mechanism was proposed. Lu proposed a Ni(II)/Ni(III) catalytic cycle, in which the cyclometalated complex **20** reacts with a phenylsulfide radical to generate a Ni(III) intermediate, which is similar to the pathway from **35** to **37** in Scheme 14. However, Shi and Zhang proposed a Ni(II)/Ni(IV) cycle, in which diaryl disulfides undergo oxidative addition to the cyclometalated complex **20** to afford a Ni(IV) intermediate.

Chatani recently reported that the reaction of aromatic amides that contain a 5-chloro-8-aminoquinoine moiety as the directing group with arylsulfonyl chlorides in the presence of $Ni(OTf)_2$ as the catalyst results in sulfonylation at the *ortho*-position (Scheme 18) [46]. A blocking substituent, chloride, is required to avoid the sulfonylation at the quinoline ring at the 5-position. Various arylsulfonyl chlorides can be used as the coupling partner, as in **43**–**45**.



Scheme 17 Ni-catalyzed thiolation of C–H bonds with disulfides

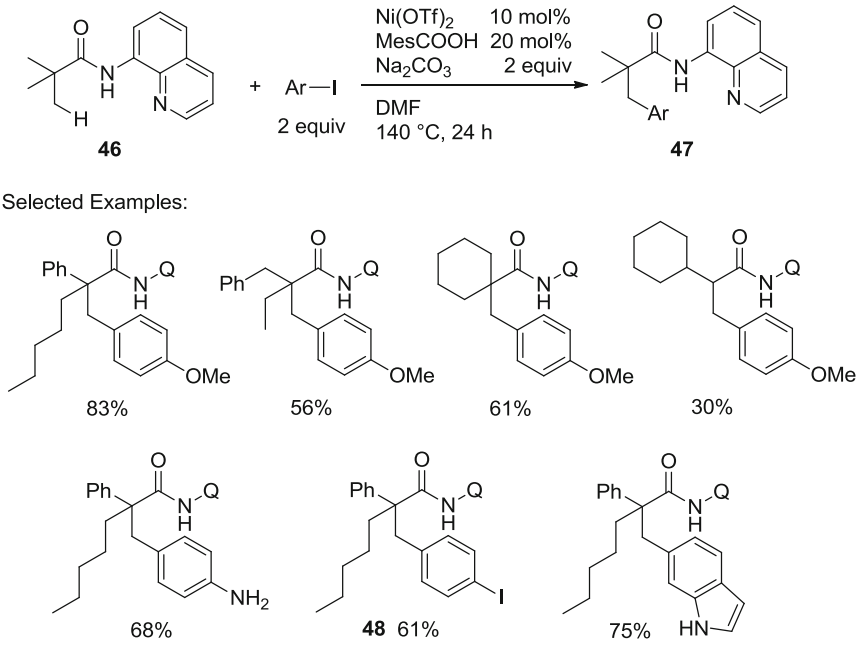


Scheme 18 Ni-catalyzed sulfonylation of C–H bonds

3 C(sp^3)–H Activation

3.1 Arylation of C(sp^3)–H Bonds

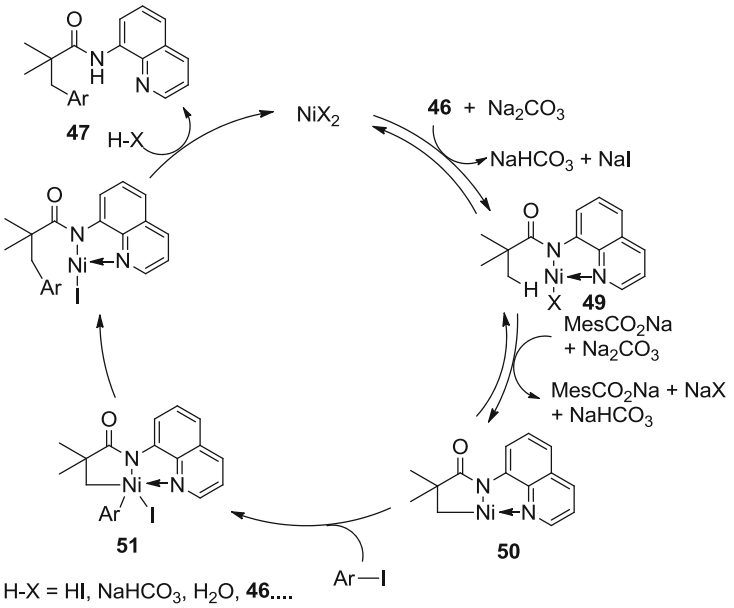
A wide variety of catalytic functionalizations of C(sp^2)–H have already been developed to date and have had a significant impact not only in the field of organic chemistry but also in related fields of chemistry. The methods have been applied to the synthesis of synthetically useful compounds, such as materials, fine chemicals,



Scheme 19 Ni-catalyzed arylation of C–H bonds with aryl iodides

and pharmaceuticals. Much attention has been currently focused on the functionalization of C(sp^3)–H bonds, which continues to be a challenging issue. In 2014, Chatani reported the first example of the Ni(II)-catalyzed β-arylation of C(sp^3)–H bonds in aliphatic amides with aryl iodides (Scheme 19) [47]. Among the directing groups evaluated, only an 8-aminoquinoline was successful directing group. The addition of a sterically bulky carboxylic acid, such as 2,4,6-trimethylbenzoic acid (MesCOOH) as an additive, improved the efficiency of the reaction. The reaction was also significantly affected by the base used. Na_2CO_3 was found to be the best base for this reaction. Among the solvents examined, DMF was the solvent of choice. Curiously, not only Ni(II) complexes, such as $Ni(OTf)_2$, $NiCl_2$, and $Ni(OAc)_2$, but also a Ni(0) complex $Ni(cod)_2$ showed a high catalytic activity. The reaction took place only at the β-position. The reaction shows a high efficiency with a broad functional group tolerance. Even an iodide survived under the reaction conditions, as in **48**.

The reaction mechanism appears to be similar to those proposed for the alkylation and arylation of C(sp^2)–H bonds (Schemes 7 and 11). Mechanistic studies indicated that (1) the C–H bond cleavage is reversible and is not a difficult process, even in the case of strong C(sp^3)–H bonds; (2) the oxidation of a Ni(0) species to a Ni(II) species occurs, which is the actual catalytic species, by the Ar–I with the generation of the respective Ar–H; and (3) a single-electron transfer (SET) was not involved, based on radical trapping experiments with TEMPO. A proposed mechanism for the reaction is shown in Scheme 20. Coordination of the amide **46** to the

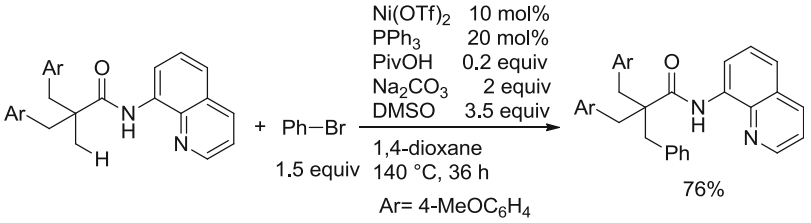


Scheme 20 A proposed reaction mechanism for the Ni-catalyzed arylation of C–H bonds

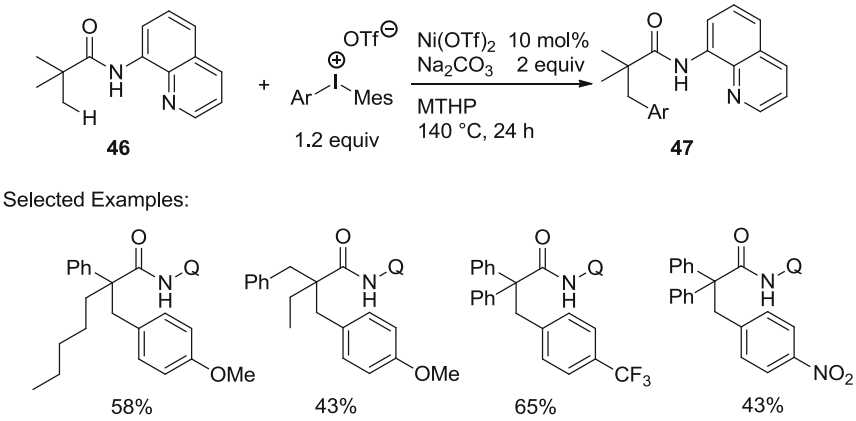
Ni(II) center followed by ligand exchange with the concomitant generation of HX gives the Ni complex **49**. The C–H bond in complex **49** undergoes cleavage at the β-position to give **50** via a CMD mechanism. The oxidative addition of an aryl iodide gives the high-valent Ni(IV) complex **51**, which undergoes reductive elimination followed by protonation to complete the catalytic cycle with the formation of the desired arylation product **47** with the regeneration of Ni(II). The cleavage of C–H bonds is reversible. The role of the carboxylic acid appears to be to accelerate the cleavage of C–H bonds and the reductive elimination step.

You also reported on the use of a similar system for the Ni(II)-catalyzed arylation of C(sp^3)–H bonds in aliphatic amides using an 8-aminoquinoline as a bidentate auxiliary directing group (Scheme 21) [48]. The addition of PPh_3 and DMSO improved the product yield. It is noteworthy that aryl bromides can be used as the coupling partner in this system, but the yield of the corresponding arylation products was slightly lower than those in the reaction with aryl iodides. The reaction was compatible with various functional groups, such as ketones, esters, amides, aldehydes, and cyano groups.

Since Sanford reported the first example of the Pd-catalyzed arylation of C–H bonds with diaryliodonium salts as coupling partners [49], the utilization of diaryliodonium salts in the functionalization of C–H bonds has been of great interest. However, all examples involved the use of Pd, Pt, and Cu as the catalyst. Chatani reported that diaryliodonium salts can also be used as coupling partners for the arylation of C(sp^3)–H bonds in place of aryl iodides using Ni(II) as the catalyst (Scheme 22) [50]. Arylated products were obtained in good yields even in the



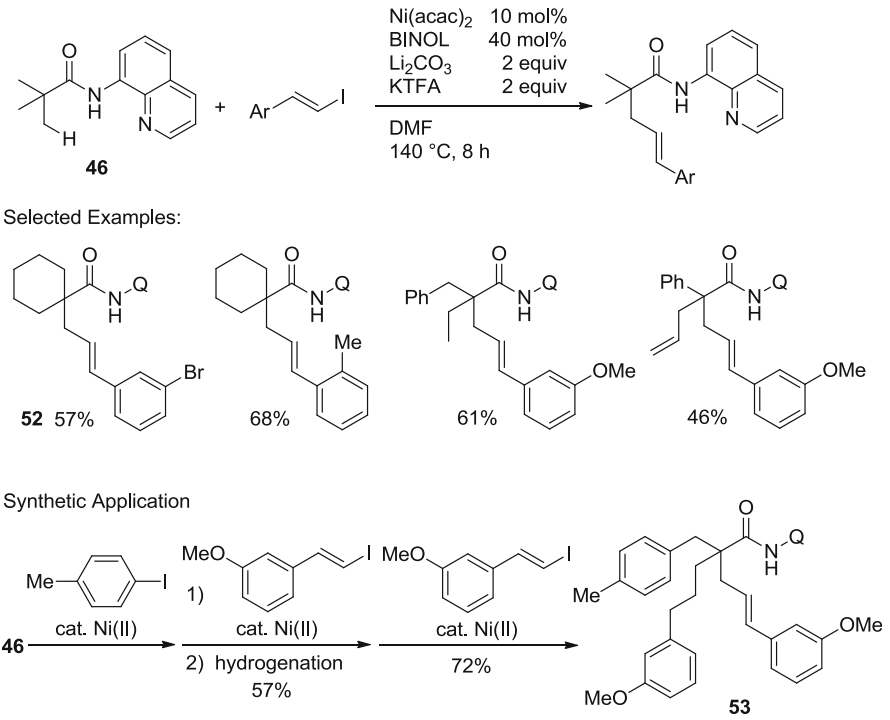
Scheme 21 Ni-catalyzed arylation of C–H bonds with aryl halides



Scheme 22 Ni-catalyzed arylation of C–H bonds with diaryliodonium salts

absence of a carboxylic acid. The effect of the counter anion of the diaryliodonium salt was examined. Among the anions screened, a triflate was found to be a superior counterion. The use of tetrafluoroborates (BF_4^-) and hexafluorophosphates (PF_6^-) as counterions resulted in no reaction. Among the solvents examined, 4-methyltetrahydro-2H-pyrane (MTHP) was determined to be the solvent of choice. A competition experiment using electronically different diaryliodonium salts indicated that an electron-donating group facilitates the reaction, which is a similar tendency to that observed in the reaction with aryl iodides [47]. The addition of TEMPO had no effect on the reaction.

Alkenylation was also achieved using a Ni(II) catalyst and an 8-aminoquinoline directing group (Scheme 23) [51]. BINOL (1,1′-bi-2-naphthol) provided the best results among the various additives examined. The yield was improved when a combination of Li_2CO_3 and potassium trifluoroacetate (KTFA) along with BINOL was used. Various functional groups were tolerated under the reaction conditions. Even a bromo group remained intact, as in **52**. As a synthetic application of this alkenylation, a highly functionalized carboxamide **53** was prepared via a sequence involving a Ni(II)-catalyzed arylation step, Ni(II)-alkenylation, hydrogenation under Pd/C, and Ni(II)-catalyzed alkenylation.

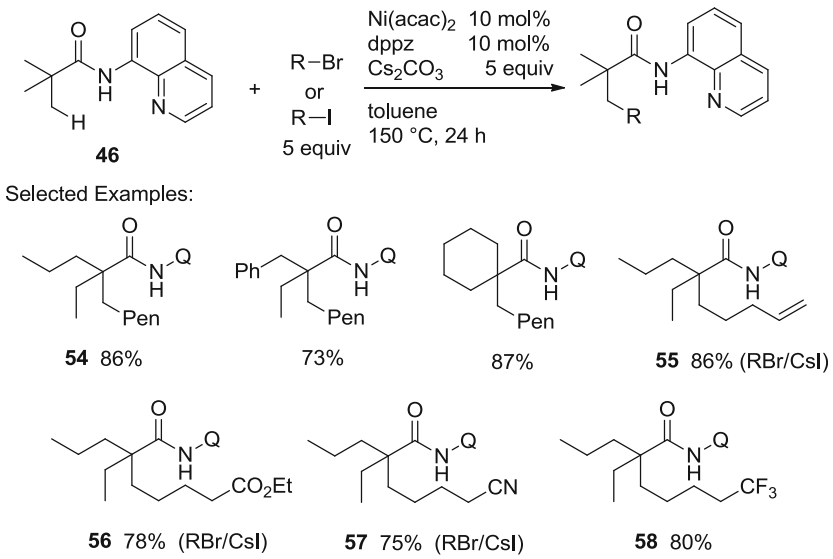


Scheme 23 Ni-catalyzed alkenylation of C–H bonds with aryl iodides

3.2 *Alkylation of C(sp^3)–H Bonds*

Ge reported on the Ni(II)-catalyzed alkylation of C(sp^3)–H bonds with alkyl halides by taking advantage of an 8-aminoquinoline directing group (Scheme 24) [52]. In sharp contrast to the arylation of C(sp^3)–H bonds [47], $Ni(cod)_2$ was not active as a catalyst. It was found that various phosphine ligands improved the product yield. Among the phosphine ligands screened, 1,2-bis(diphenylphosphino)benzene (dppbz) gave the best result. The reaction tolerated various functional groups, such as terminal alkenes (**55**), esters (**56**), cyano groups (**57**), and trifluoromethyl groups (**58**). It was found that alkyl iodides could be replaced with alkyl bromides with the addition of CsI, as in **55**–**57**.

In contrast to the mechanism proposed by Chatani (Schemes 7, 11, and 20), which involves a Ni(II)/Ni(IV) catalytic cycle, a Ni(II)/Ni(III) cycle was proposed. When TEMPO was added, the yield of the product **54** was decreased: 0 equiv. 86%, 3 equiv. 46%, and 8 equiv. trace. In addition, the corresponding pentyl TEMP ether was isolated. On the basis of these observations, a Ni(II)/Ni(III) catalytic cycle was proposed. The cyclometalated complex **50** reacts with an alkyl radical, which is generated through SET from a Ni(I) species to an alkyl halide with the concomitant generation of a Ni(II) species. In this catalytic system, H/D exchange did not take



Scheme 24 Ni-catalyzed alkylation of C–H bonds with primary alkyl halides

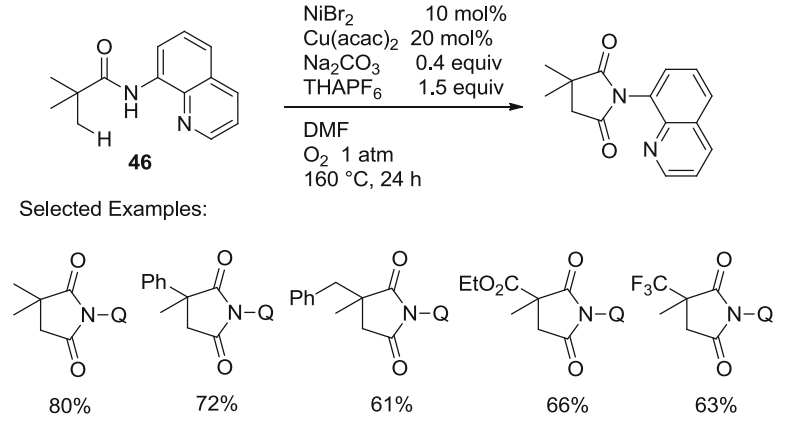
place, suggesting that the cleavage of C–H bonds is irreversible, which is contrary to finding reported by Chatani [47].

3.3 Carbonylation of C(sp^3)–H Bonds

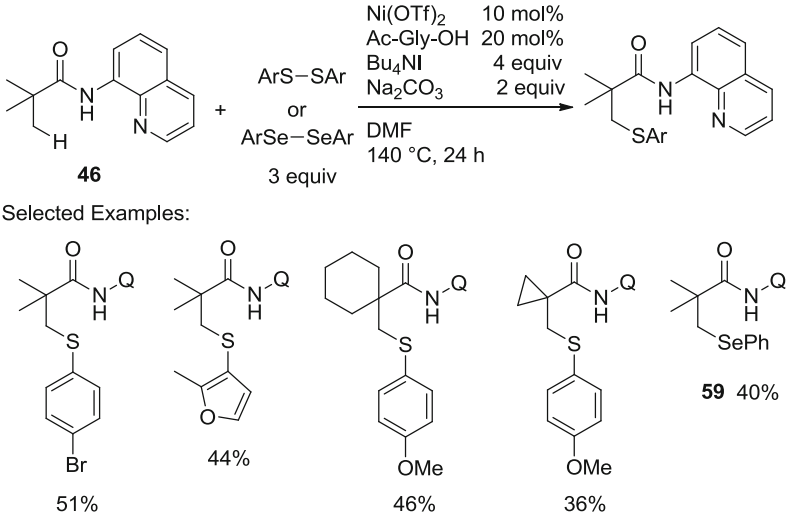
Ge reported on the Ni(II)/Cu(II)-catalyzed carbonylation of C(sp^2)–H bonds in aromatic amides containing an 8-aminoquinoline as the directing group with DMF as the carbonyl source (Scheme 15) [42]. This catalytic system was applicable to the carbonylation of C(sp^3)–H bonds (Scheme 25) [42]. A quaternary α-carbon to the carbonyl group in the substrates is required for the carbonylation to proceed. Contrary to the carbonylation of C(sp^2)–H bonds, in which the cleavage of C–H bonds is reversible, the cleavage of C–H bonds was irreversible in the carbonylation of C(sp^3)–H bonds, suggesting that the rate-determining step is the cyclometalation.

3.4 C–S Bond Formation

Zhang reported on the Ni(II)-catalyzed thiolation of C(sp^3)–H bonds in aliphatic amides containing an 8-aminoquinoline directing group with diaryl disulfides (Scheme 26) [53]. All examples involved the use of aliphatic amides having no hydrogen at the α-position. Diphenyl diselenide was also applicable to the reaction,



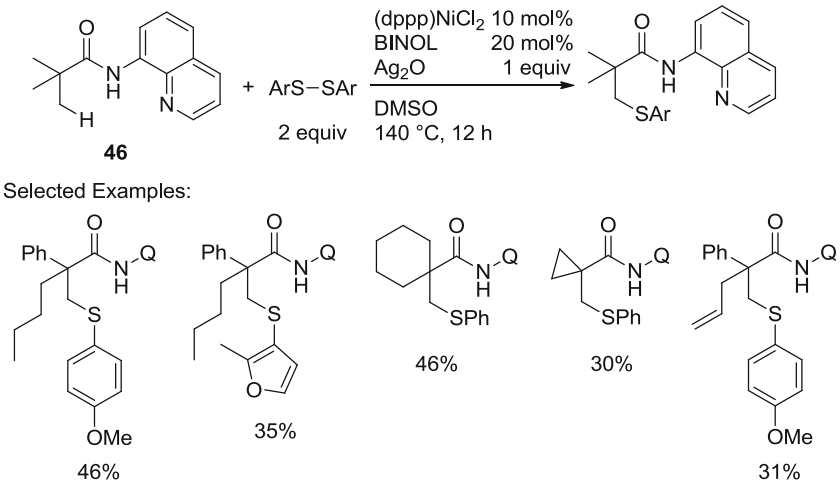
Scheme 25 Ni(II)-catalyzed carbonylation of C(sp^3)–H bonds



Scheme 26 Ni-catalyzed thiolation of C–H bonds with diaryl sulfides

as in **59**. The addition of TEMPO or BHF had a negligible effect on the reaction, suggesting that the reaction does not proceed through a free radical mechanism. The results of deuterium-labeling experiments indicated that H/D exchange took place only at the β-position indicating that the cleavage of C–H bonds is reversible.

Around the same time, Shi also developed the Ni(II)-catalyzed thiolation of C (sp^3)–H bonds in aliphatic amides with diaryl disulfides (Scheme 27) [54]. Mechanistic experiments using 1,4-dinitrobenzene, TEMPO, and 1,4-diphenylethylene indicated that a thioaryl radical is not involved in the reaction. Zhang and Shi proposed a Ni(II)/Ni(IV) catalytic cycle for the Ni(II)-catalyzed thiolation.



Scheme 27 Ni-catalyzed thiolation of C–H bonds with diaryl sulfides

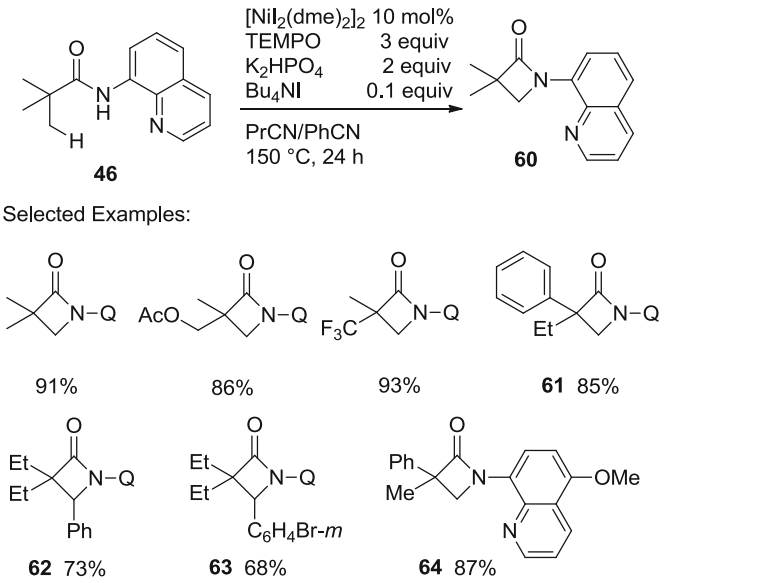
3.5 C–N Bond Formation

Ge reported on the TEMPO-assisted Ni(II)-catalyzed intramolecular cyclization of C–H bonds in aliphatic amides leading to the formation of β-lactam derivatives with the assistance of an 8-aminoquinoline directing group (Scheme 28) [55]. Amidation took place at the methyl C–H bond preferentially over phenyl C–H bonds, as in **61**. If the substrate did not contain a methyl group at the β-position, the reaction took place at the benzylic C–H bonds, as in **62** and **63**. A 5-methoxy-8-aminoquinoline can be used as the directing group, as in **64**, and the directing group can be easily removed under oxidation conditions using cerium (IV) ammonium nitrate (CAN).

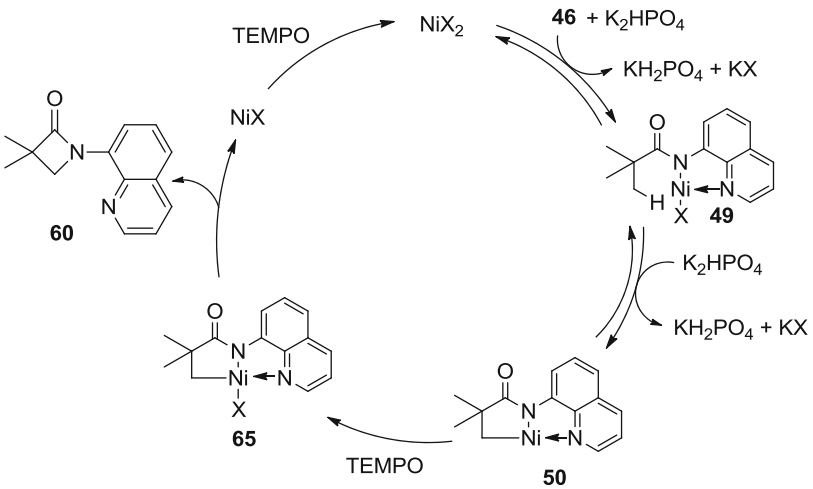
A Ni(II)/Ni(III) catalytic cycle is proposed (Scheme 29). Catalysis is initiated by the coordination of **46** to Ni(II) followed by a ligand exchange and the cleavage of C–H bonds gives the cyclometalated Ni(II) complex **50**, which is oxidized to the Ni (III) species **65** by TEMPO. Reductive elimination gives the desired product **60** with the generation of a Ni(I) species that is oxidized to Ni(II) species by TEMPO.

4 Elaboration of Directing Groups

Three different directing groups, such as 2-pyridinylmethylamine, 8-aminoquinoline or derivatives thereof, and (pyridine-2-yl)isopropylamine moieties, have been used as the directing group in Ni-catalyzed chelation-assisted C–H functionalization reactions. These directing groups are easily converted to other synthetically useful functional groups. Deprotection of an 8-aminoquinline moiety to carboxylic acids was easily achieved by hydrolysis under acidic conditions

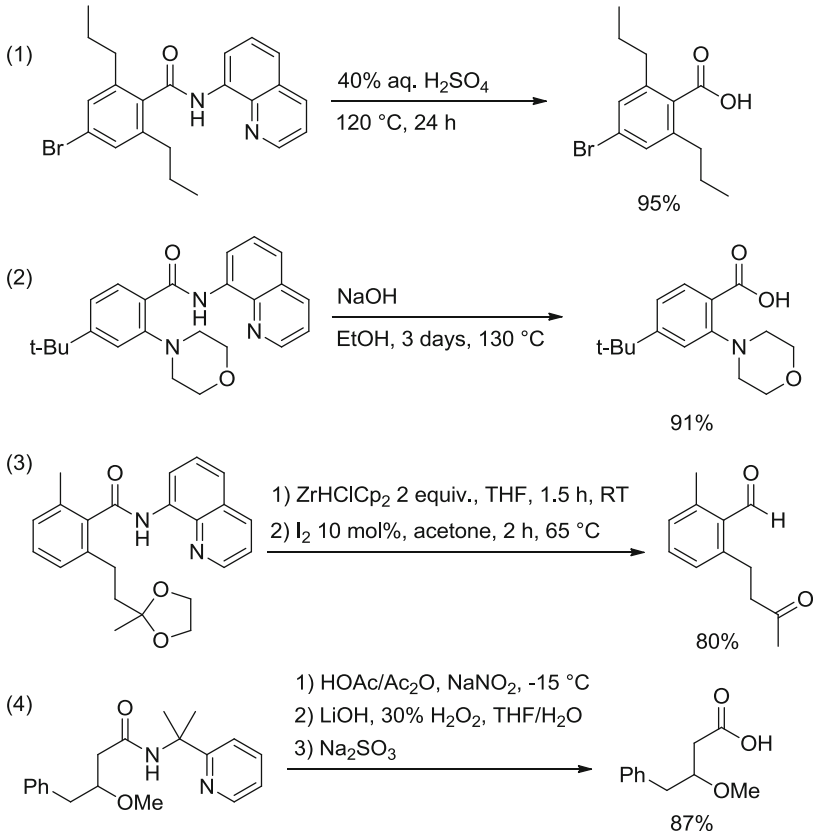


Scheme 28 Ni-catalyzed intramolecular amidation of C–H bonds



Scheme 29 A proposed reaction mechanism for the Ni-catalyzed amidation of C–H bonds

(Scheme 30a) [56] or basic conditions [57] (Scheme 30b). The 8-aminoquinoline moiety was removed by treatment with HCl in refluxing methanol [58] or BF_3•Et_2O in methanol at 100°C to give the corresponding ester [59]. The 8-aminoquinoline moiety was converted into the corresponding aldehydes via a reaction with Schwartz's reagent ($ZrHClCp_2$) [60] (Scheme 30c). The 2-pyridinyl-isopropylamine moiety can also be easily removed by a mild sequence consisting

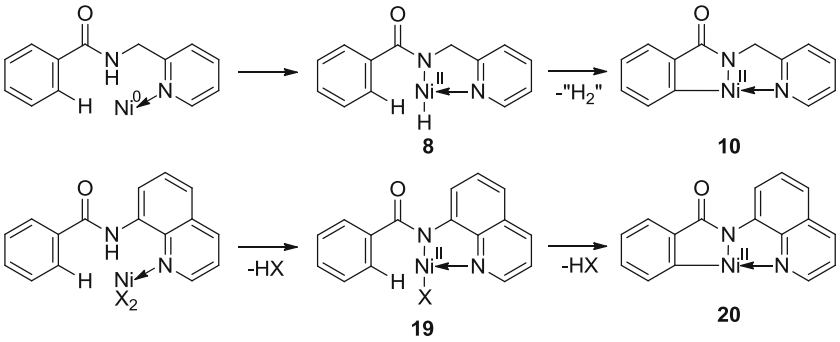


Scheme 30 Elaboration of directing groups

of *N*-nitrosylation, treatment with LiOOH, and reduction with Na_2SO_3 [61] (Scheme 30d).

5 Conclusions

A new chelation system using an *N*,*N*′-bidentate directing group has enabled the development of various types of Ni-catalyzed functionalizations of C–H bonds. In the case of previously reported systems, substrates that were applicable to the Ni-catalyzed functionalization of C–H bonds were limited to specific structures, such as pyridine or activated pyridine derivatives and highly perfluorinated benzene and azole derivatives, all of which contain an acidic C–H bond (Fig. 1) [17]. However, the combination of a Ni catalyst and an *N*,*N*′-bidentate directing group was found to be an excellent combination for the development of various Ni-catalyzed chelation-assisted functionalizations of C–H bonds, since the report by Chatani and



Scheme 31 Difference between Ni(0)/2-pyridineylmethylamine and Ni(II)/8-aminoquinoline systems

coworkers in 2011, on the use of an *N*,*N*′-bidentate directing group in the first example of the Ni-catalyzed chelation-assisted functionalization of C–H bonds [20].

The cleavage of C–H bonds in these Ni-catalyzed chelation systems appears to involve two different mechanisms depending on the system in use (Scheme 31). Substrates applicable to the *N*,*N*′-bidentate chelation system involve amides, which contain both an sp^2 nitrogen and the NH bonds. In both cases, the coordination of the sp^2 nitrogen to the Ni center initiates the catalysis. In the case of the Ni(0)/2-pyridineylmethylamine system, the cleavage of C–H bonds proceeds via σ-bond metathesis. In contrast, a CMD mechanism is operative in the case of Ni(II)/8-aminoquinoline. In any case, the catalytic Ni species forms a chemical bond to an sp^3 nitrogen by the coordination of sp^2 nitrogen followed by the reaction with a NH bond, as in **8** and **19**. This N–Ni bond formation is a key for the activation of *ortho*-C–H bonds.

One of the most important issues to be addressed in this area involves the mechanism responsible for the reaction. In sharp contrast to the Pd-catalyzed functionalization of C–H bonds, mechanistic studies dealing with the Ni-catalyzed functionalization of C–H bonds are limited. The oxidation state of the Ni intermediates is unclear. Catalytic Ni(II)/Ni(IV) or Ni(II)/Ni(III) cycles have been proposed, although no direct experimental evidences exist [62, 63]. The role of the guinoline ring is also unclear. In addition to serving as a directing group [64], it is likely that it plays other roles in the overall reaction. One possibility is that the 8-aminoquinoline moiety functions as an electron reservoir to stabilize the high-valent and unstable Ni(III) or Ni(IV) complex (for a review on redox non-innocent ligands, see [65]).

Reactions using a Ni catalyst and an *N*,*N*′-bidentate directing group have started to appear in the literature only in the last few years. As more mechanistic information emerges, new and more exciting advances can be anticipated.

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