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Recent Advances in the Application of Group–10 Transition Metal Based Catalysts in C–H Activation and Functionalization

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Abstract

The importance of C–H bond activation in a simple molecule to form a molecule with enhanced functionality can be easily understood from a study of biological processes at a molecular level where, for example, a specific enzyme selectively activates a chemically inert C–H bond and functionalises it to a useful product. This strategy is now being used for large scale industrial processes and has both social and environmental benefits. C–H bond functionalization is also of major importance in catalysis because of the possibility of constructing complex structural motifs from relatively simple precursors. However, functionalization of a chemically inert C–H bond needs specific catalysts or reaction conditions that can selectively activate a particular C–H bond, leaving others intact. To achieve this target, various metal catalyzed or mediated reactions have been employed. Keeping the growing importance of this emerging field in mind, we now present recent advances in the field of C–H activation and functionalization using group 10 transition metal catalysts. Attempts have also been made to discuss the future of group 10 transition metals in catalysis.
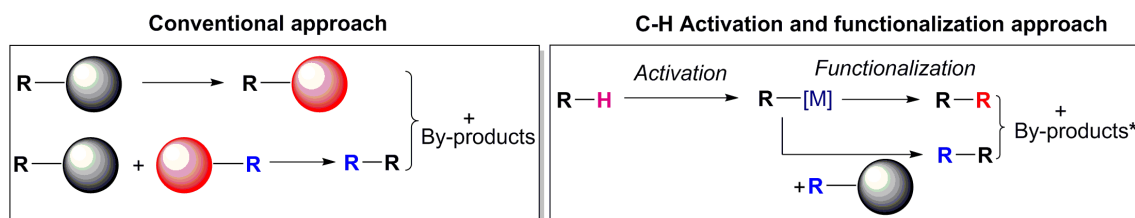
Keywords: C–H activation, Functionalization, Group 10 metal–based catalyst.

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1. Introduction

Nature is a rich source of molecules having C–H bonds, starting from the very basic hydrocarbon methane to complex molecules such as proteins and enzymes. C–H bonds, which behave like "*noble gases*" in the context of their stability, have been the subject of intense research in the last few decades [1], as processes that showed that the C–H bond could be activated, were discovered. This is due to the advancement in the field of organometallic chemistry, where it has been shown that it is possible to convert the stable or *inert* C–H bond into various functionalities [1d,2]. Because of this ability to convert the C–H moiety into C–C and C–X (X = N, O, S, F *etc.*) bonds, this field now has applications in sectors including energy, pharmaceuticals, natural products, agrochemicals, polymers and feedstock commodity chemicals [3]. Generally, C-H activation is relatively environmentally benign, which is a need of contemporary science. Conventionally, the formation of a functional group in a molecule requires pre−functionalization of one or more starting materials and multi−steps are needed to get the final product with the likelihood of producing toxic by-products [4]. For example, for amidation of aryl halides, Pd−catalyzed amination or Cu-catalyzed reactions have been used, in which the success of the reaction depends on the presence of these reagents [5, 6]. Contrarily, functionalization of the C–H moiety using organometallic catalysts is both atom−economic and step−economic (**Figure 1**) [4c−d,7]. In the latter case, both the formation of side products and the number of reaction steps are generally lower and the yields of the desired products higher than with conventional chemical synthesis [4c−d,7]. This fact is further supported by the views of Nobel laureate Prof. E. Negishi. According to him "*many more d−block transition metal−catalyzed green organic synthetic methods will be and will have to be discovered and developed for a sustainable 21st century and beyond*" [8].
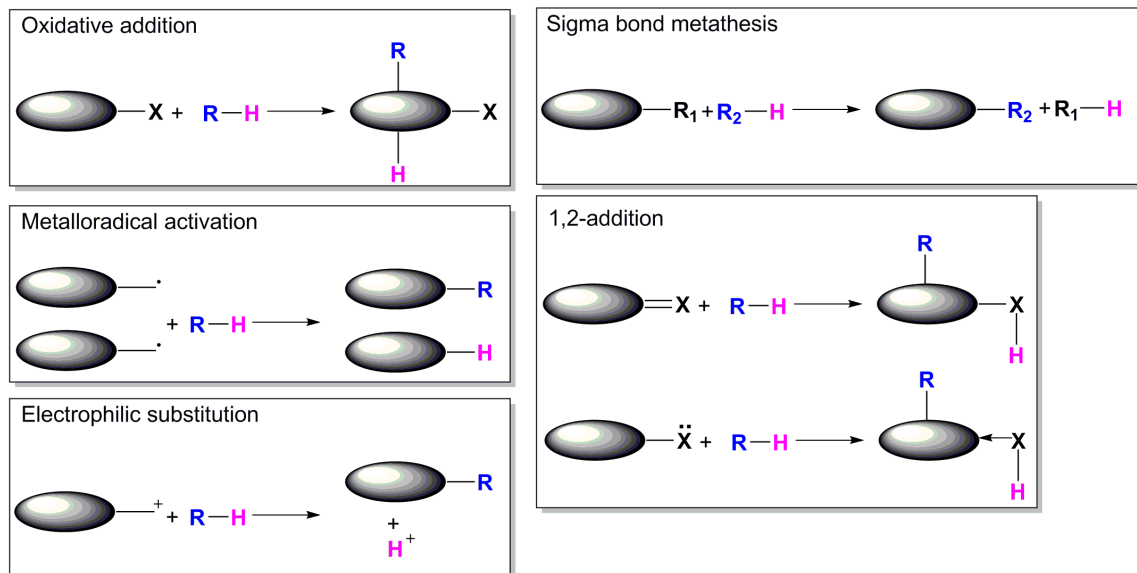
Figure 1: Difference between the installation of a functional group by a typical conventional conversion (left) and by C-H activation and functionalization method (right). Circles in color denote random functional groups. * Indicates less toxic by-product/s.

However, the transformation of a C–H bond in a less useful compound to form a more useful compound having C–B, C–C, C–Si, C–N, C–O, C–F or C–S bonds is quite challenging. This is because of the inherently inert nature (bond energies of $C(sp^3)$-H and $C(sp^2)$–H bonds range from 90-110 kcal/mol) and low selectivity of C–H bonds [2h]. Additional problems associated with the activation of C–H bonds are their low dipole moments, low HOMO and high LUMO energy levels [9]. Furthermore, the activation methods developed should be able to introduce different functionalities under the same reaction conditions [1c,10]. Because of the previously described limitations of the C–H bond in a molecule it is necessary to activate this bond (making it more reactive) as the first step, followed by its subsequent functionalization [1a]. The activation process can be achieved effectively by using transition metal catalysts and others [1c,11]. It is well−known that complexes based on transition metal can react and activate C–H bonds to produce C–M bonds, which undergo functionalization to produce required functional materials [3]. Another advantage of transition metal−based C–H activation is that M–C bonds are generally more reactive than the starting materials and can be readily converted into numerous other functionalities [12]. In particular, group 10 metals have a unique ability to activate C–H bond through the formation of square planar metal complexes [13]. Furthermore, metals of this group have the ability to circumvent the kinetic barrier associated with the C–H bond as the activation of the C–H bond is thermodynamically unfavorable. Additionally, the presence of a ligand directing group also has synergistic effect on the region-selective activation of C–H bonds [13] using this group of metals. The last few decades have witnessed a dramatic advancement in the use and application of transition metal catalyzed C–H bond activation reactions. Many research papers and reviews are being published in this area every year. Herein, we present some major recent advancements in the field of C–H activation and functionalization using group 10 metal (Ni, Pd and Pt) catalysts and their applications.

2. Types of C–H Activation Reaction

Many articles have been published which deal with the types of C-H activation reactions and their mechanisms. For interested readers, we provide here a glimpse of the types of C–H activation reactions. Further details on the topic are provided in references [2a, 14]. Around a decade ago, Labinger and Bercaw [14a] divided C–H activation reaction into five subtypes depending upon their stoichiometry [14]. These are oxidative addition, σ−bond metathesis, metalloradical activation, 1,2−addition and electrophilic substitution. Oxidative addition reactions are generally exhibited by electron-rich transition metal, in complexes, including Pt. These reactions proceed through the formation of a three-membered ring followed by an increase in metal oxidation state by two. On the other hand, σ-bond metathesis reactions are mainly exhibited by metals with a d^0 electron configuration including elements of group 3-5 and involves a four-centered, four-electron transition state and without any change in the formal oxidation state of the metal [14b]. Metalloradical activation includes rhodium(II) catalyzed reversible cleavage of R–H bonds. In 1,2-addition reactions, either a lone pair present on a heteroatom or the double bond between metal and nonmetal (M=N or M=C) plays a significant role. Hence, this mechanism of C–H activation occurs either with late transition metal amide/alkoxy bonds or with early/middle transition metal-ligand multiple bonds [14b]. In the electrophilic activation type of reaction, functionalized alkanes are formed directly without the appearance of organometallic species, which actually form during the reaction. In other words, a metal ion attacks an electron rich carbon atom followed by removal of proton. This type of reaction is shown by several late transition metal ions including Pd^{2+}, Pt^{2+} and/or Pt^{4+} in polar solvents. In addition to these mechanisms, ambiphilic metal ligand activation (AMLA) or concerted metalation-deprotonation (CMD) are also known.

Oxidative addition	Sigma bond metathesis
Metalloradical activation	1,2-addition
Electrophilic substitution	

Figure 2: Types of C-H activation reaction. Oval shapes denote a metal atom.

3. Group 10 metals-based complexes for C–H activation and its application
3.1. Nickel-based catalysts

The catalytic efficiency of first row transition metals is well documented [1e, 3, 15]. Among those, Ni-based catalysts have attracted attention due to their low toxicity and low cost in comparison to other catalytic systems [16]. Ni also has a high potential for C−H bond activation in isolated model systems, in the gas phase, and is less expensive in comparison to 4d- and 5d-elements, though the latter are more reactive [16, 17]. Ni-based catalysts have been used for the synthesis of biologically active agents such as febuxostat, tafamidid and texaline. The very first example of the Ni complex (Cp$_2$Ni) as a C–H activator was reported about half a century ago for the activation of azobenzene (**Scheme 1**) [18].
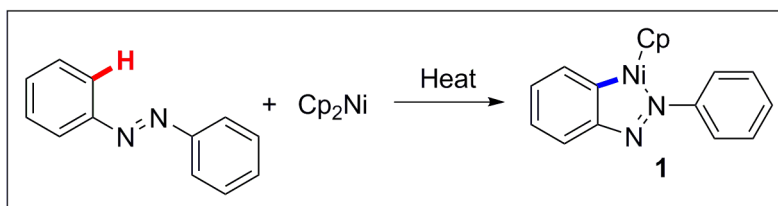
In this section, we will focus on selected important reports on Ni catalyzed reactions. Comprehensive details of Ni catalyzed reactions are available in references [16,19].

3.1.1. C(sp^3)–H activation and functionalization

After the discovery of the first Ni-catalyzed C–H arylations of azoles with aryl halides by Itami's and Miura's groups [20], several new Ni-catalyzed activations and functionalizations of aromatic rings have been reported. Chatani and co-workers [21], by taking advantage of bidentate chelation, reported the first example of Ni(II)-catalyzed functionalization (arylation) of C(sp^3)–H bonds (methyl and methylene) in aliphatic amides with diaryliodonium salts (**Scheme 2**). The use of diaryliodonium salt was preferred over aryl halides as the former required relatively milder reaction conditions than the latter. This base-sensitive reaction showed high functional group compatibility and versatility (methoxy, ester, and chloride groups compatible). Furthermore, the 8-aminoquinoline (8-AQ) moiety which serves as a ligand-directing group could be easily removed and converted to more useful functional groups. It was observed that the electron donating aryl groups resulted in slightly higher yields than electron withdrawing aryl groups and the reaction was also sensitive to the structure of the amide used (aliphatic amides possessing no hydrogen at the α-position reacted exclusively at the methyl group while methylene and benzene C−H bonds were not arylated). Still, quinoline N and NH bonds were important for the feasibility of the reaction, as in the absence of these bonds (i.e. in the presence of other directing group), the reaction failed. Similarly, the diaryliodonium counterion also affected the reaction (triflate or chloride salt gave the arylated product while with tetrafluoroborates and hexafluorophosphates as counterions failed to give any product). The mechanistic studies indicated that cleavage of the C−H bond was a reversible step and that it occurs before the oxidative addition of the diaryliodonium salt.
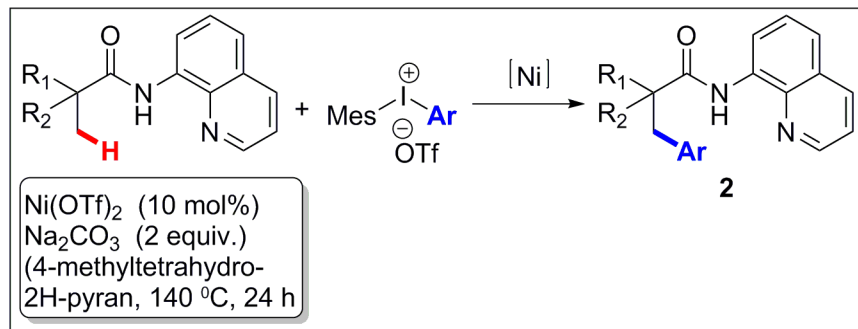
For this C(sp³)–H bonds arylation, the authors proposed a catalytic cycle (**Figure 3**, shown with one representative substrate) involving the following steps: (i) coordination of amide to the Ni center followed by ligand exchange giving the Ni complex (**3**), (ii) reversible cyclometalation to give **4**, (iii) oxidative addition of the diaryliodonium salt with the concomitant generation of 2-iodo-1,3,5-trimethylbenzene (Mes−I) giving the high valent Ni(IV) complex **5** stabilized by an 8-AQ group, (iv) reductive elimination of **5** and, (v) protonation to afford the desired arylation product with the regeneration of Ni(II) [21].
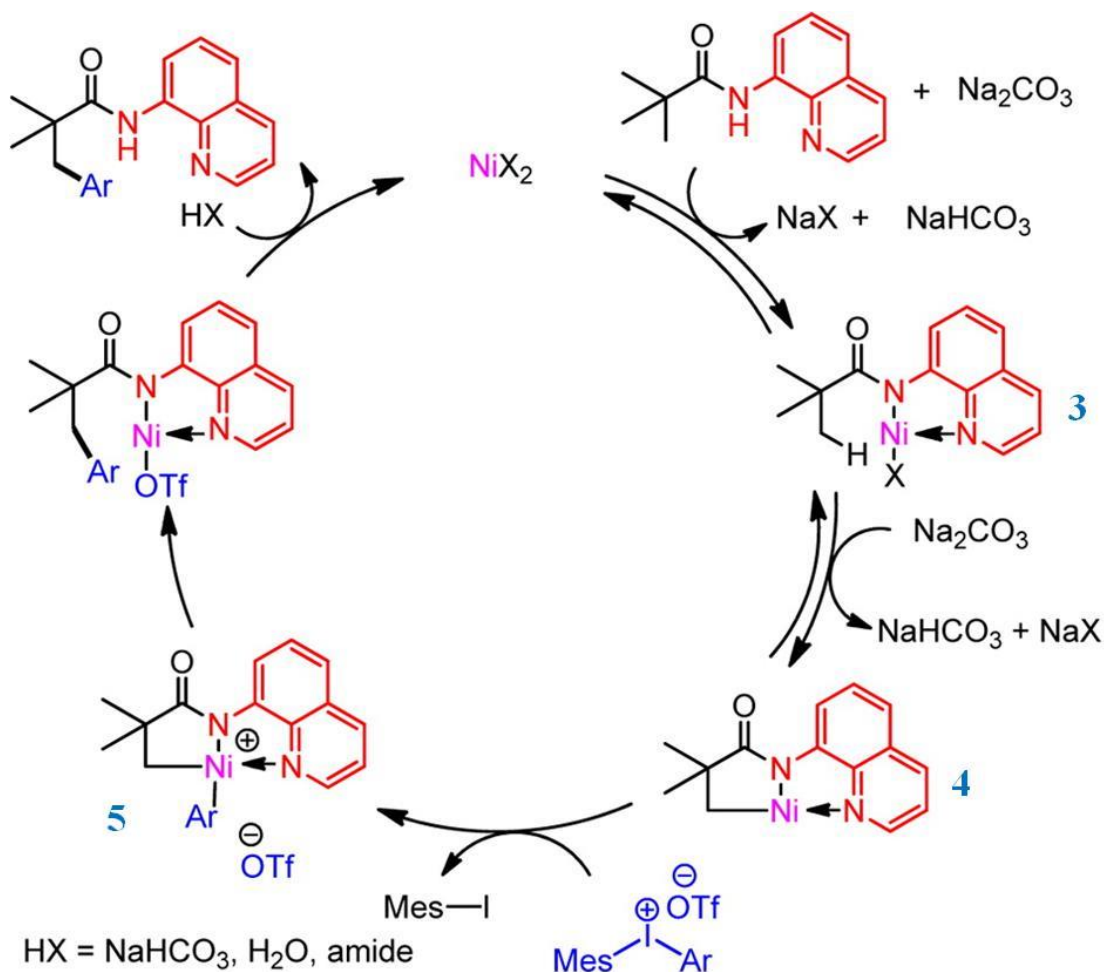
Figure 3: Proposed mechanism for Nickel-catalyzed arylation of aliphatic amides with diaryliodonium salt ("Reprinted with permission from M. Iyanaga, Y. Aihara, N. Chatani, J. Org. Chem. 79 (2014) 11933−11939 [ref. 21]. Copyright (2015) American Chemical Society).

Recently, Ge and co-workers reported a site-selective intramolecular amidation using 8-AQ [22]. This functionalization method was reported to be highly selective and efficient as C–H bonds of β-methyl groups were preferred over the γ-methyl or β-methylene groups and allows effective functionalization of benzylic 2° C(sp^3)–H bonds (**Scheme 3**). Furthermore, a good functional group tolerance was also observed as good to excellent yields (7-93%) of the products were obtained with 2,2-disubstituted propanamides bearing both the linear and cyclic chains. For the smooth conversion of reactant to desired products, the presence of tertiary α-C was necessary. The authors showed that a range of β-lactam could be produced by the oxidative cleavage of the 8-

amino-5-methoxyquinoline. A similar observation (presence of tertiary α-C) was made for the alkylation of aliphatic amides (**Scheme 3**) [23]. Analogous to the previous report, the same group reported a regioselective alkylation of $C(sp^3)$−H bonds in 2,2-disubstituted propionamide with a 8-aminoquinolinyl group as the amide moiety for the construction of $C(sp^3)$–$C(sp^3)$ bond (**Scheme 3**). Among sp^3 C–H bonds, methyl C–H bonds were preferred over methylene C−H bonds. Contrary to Pd-catalyzed functionalization, a predominant preference for the sp^3 C−H bonds of methyl group over the sp^2 C−H bonds of phenyl group was also observed. Under optimized conditions, several 2,2-disubstituted propanamides gave products in good to excellent yields and showed compatibility with the functional groups including alkene, cyano, ester, and trifluoromethyl. Interestingly, the alkyl iodide was found to be replaceable with chloride/bromide with addition of CsI. However, benzylic halide, allylic halide, secondary alkyl halides and benzyl bromide failed to give the desired products.
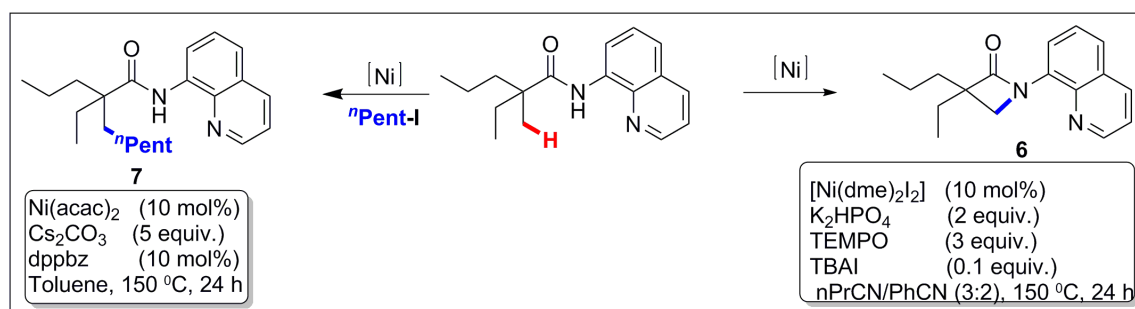

However, for the construction of $C(sp^3)$–$C(sp^2)$ bonds at unactivated β-$C(sp^3)$–H bond, another potential method has been reported recently (**Scheme 4**) [24]. In these types of functionalization 8-AQ was also found to provide a better chelate-assisted functionality than other directing groups such as pyridin-2-ylmethanamine and 2-(methylthio)aniline. Interestingly, under optimized conditions, the reaction yielded products incorporating both electron donating and accepting groups including alkyloxy, ketone, ester, amide, acetamido, and even frees amino groups. Furthermore, the reaction was also found to be successful with both aryl iodide and bromide, which is one of the first chelation-assisted arylation of unactivated $C(sp^3)$–H bonds. Prior to this, Chatani and Aihara had also reported the arylation of β C−(sp^3) of methyl and methylene containing 8-AQ moiety [25]. However, among the halides, only *para*-substituted aryl iodides

(electron rich aryl iodide gave better yield) were found to undergo transformation, while aryl bromide, triflates and *ortho*-substituted aryl iodide were unable to give any product (**Scheme 4**). Furthermore, the reaction was found to depend on the structure of the amide (aliphatic amides possessing no hydrogen at the α-position reacted efficiently). The authors also suggested that the reaction proceeds through a Ni(II)/Ni(IV) catalytic cycle, rather than a Ni(0)/Ni(II) catalytic cycle. This reaction too gave no product in the presence of other chelate assisting groups like N-2-naphthylbenzamaide, its ester and others. The authors found that both Ni(II) and Ni(0) were effective in the formation of coupling products.
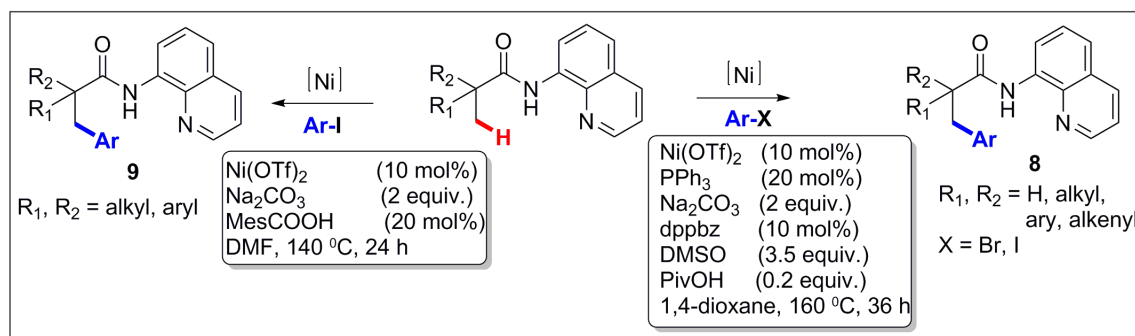
Unlike the previous examples of $C(sp^3)$ arylation at the β-position, $C(sp^3)$ arylation at the α-position has also been reported. Since the $C(sp^3)$–H bond adjacent to oxygen atom in ether derivatives has relatively low bond dissociation energies (BDE), it can be cleaved easily. So, $C(sp^3)$–H bonds adjacent to or at the α-position to oxygen atoms (ether derivatives) and carbonyl groups (ketones) are pre-activated and can be easily functionalized. Keeping this fact in mind, a first Ni-catalyzed oxidative arylation of *ortho* $C(sp^3)$–H bonds of tetrahydrofuran and 1,4-dioxane have been reported (**Scheme 5**) [26]. This method successfully demonstrated that the introduction of a range of aryl groups and the formation of α-arylated ethers proceeded *via* radical pathway.
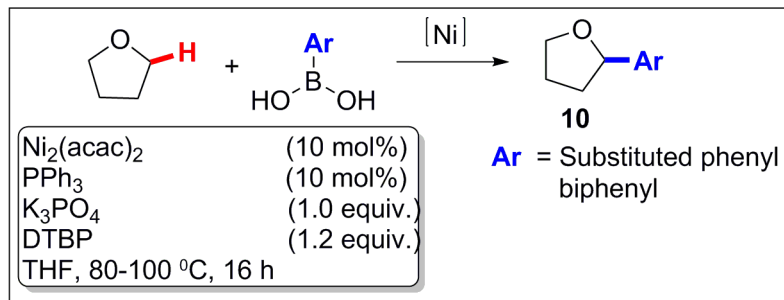
When neutral NHC complexes or cationic compounds were treated with KO^{t}Bu, C–H bond α to the nitrile group underwent activation to yield cyclized products (**Scheme 6**) [27]. This base-catalyzed intra-molecular nitrile C–H bond activation in Ni NHC complexes also afforded a nickelacycle.
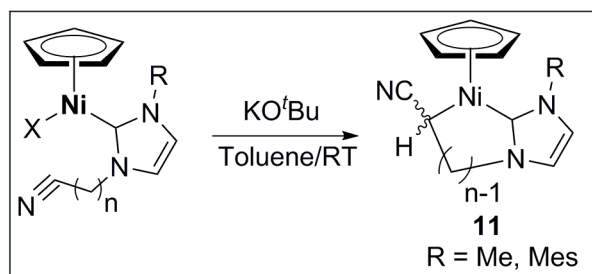
A similar intramolecular C(sp^3)–H arylation in benzamide was described in a molecule in which the C–H bond adjacent to the N-atom was activated (**Scheme 7)** [28]. Interestingly, this transformation was feasible with substoichiometric amount of both 1,10-phenanthroline and Ni(COD)$_2$. However, a higher catalyst loading was required in case of 1,10-phenanthroline. A preferential arylation of more highly ssubstituted C–H bond and the inability of 1° C–H bond arylation indicated that the reaction possibly proceeds through the involvement of alkyl radicals. Both aryl chloride and bromide gave products in good to moderate yield. The method was successfully demonstrated for the syntheses of electronically diverse isoindolinone products.
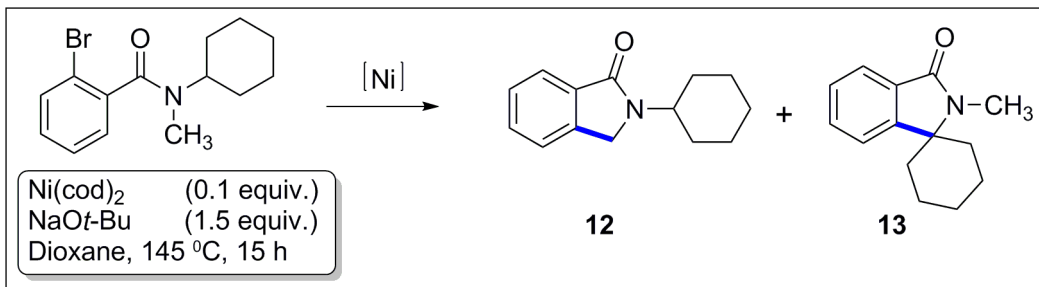
For the synthesis of substituted dihydropyridone derivatives, which is an important scaffold for the synthesis of nitrogen-containing six-membered heterocycles, Hiyama et al. [29] reported a novel double activation and functionalization which included both $C(sp^2)$–H and $C(sp^3)$–H bonds in N,N-bis(1-arylalkyl) formamides (**Scheme 8**). The reaction was reported to proceed through a dehydrogenative [4+2] cycloaddition reaction with alkynes. The mechanistic studies indicated that the hydrogenation of the alkyne takes place in a manner distinct from simple addition of free H_2 across the alkynes.
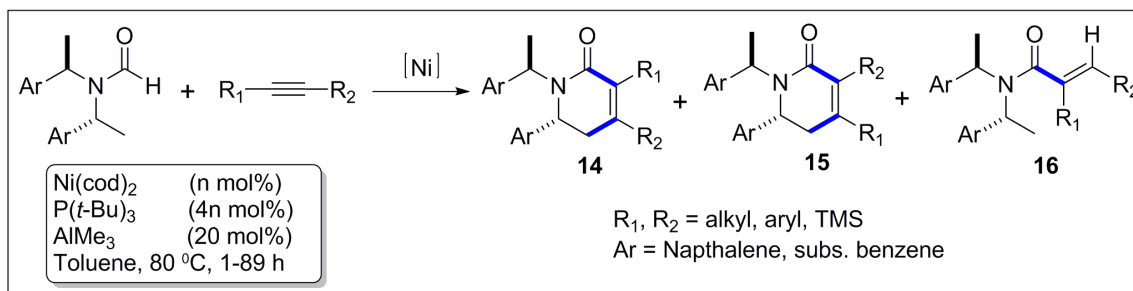
3.1.2. $C(sp^2)$–H activation and functionalization

The activation of $C(sp^2)$–H bonds followed by functionalization is quite rare. In most of the cases, functionalization takes place in molecules where the *ortho*-Hs are acidic or a specific functional group is present [30]. Recently, the first example of Ni catalyzed *ortho* alkylation of benzamides and acrylamide derivatives with unactivated alkyl halides has been reported (**Scheme 9**) [30]. The 8-AQ moiety acts as a bidentate ligand and provides chelation site to the catalyst. In the absence of these coordination sites and amide protons no product was formed. The reaction showed high functional group compatibility. In reactions of *meta*-substituted aromatic amides, the reaction proceeds in a highly selective manner at the less hindered C–H bond [30], indicating

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steric controlled regioselectivity of the reaction. Like the example discussed in **Scheme 2**, this reaction was also sensitive to the substituent present at the α-C and also affected by the "*salt-effect*". Furthermore, a similar mechanism, as shown in **Figure 3**, was suggested by the authors (coordination of amide to the Ni center followed by ligand exchange with concomitant generation of HX gives Ni complex, reversible cyclometalation, oxidative addition of alkyl bromide followed by reductive elimination and protonation to afford the desired alkylated product).
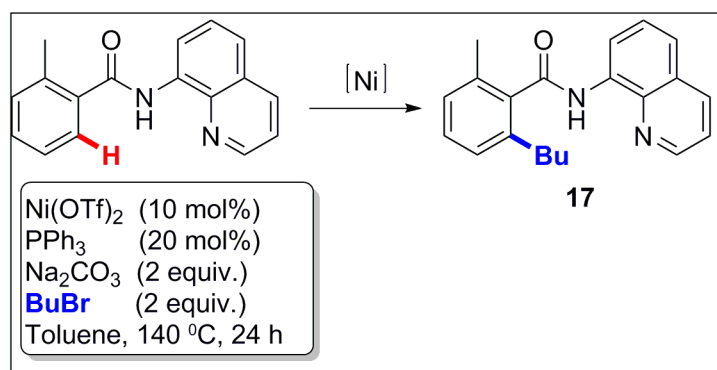
Going one step ahead, recently, a more versatile method for the alkylation with secondary alkyl bromide using Ni(II) as catalyst has been reported (**Scheme 10**) [31]. This method was found to perform well in non-polar solvents (toluene), which is different from the alkylation conditions used for primary alkyl halides. Under optimized conditions, 52%-86% of the alkylated product was reported. This method, like the previous one, was also found to be suitable in the fluorination of the arene ring, and thus may find applications in the synthesis of biologically active agents. Competitive studies indicated that substrates with electron withdrawing groups were more reactive. The preliminary mechanistic studies indicated the C–H metalation was reversible and the acidity of the C–H bond to be cleaved was important for reaction to proceed smoothly.
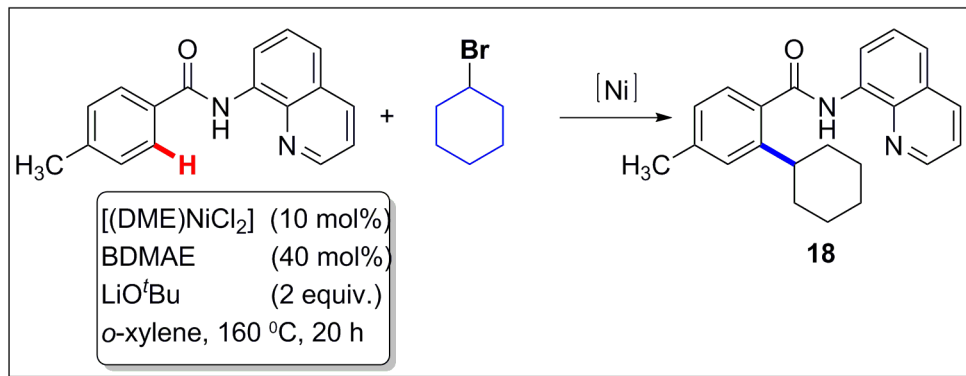
Zeng et al. [32] developed a Ni catalyzed C−H allylation with allyl phosphates. Using this reaction, allyl scaffolds can be installed into the *ortho* site of benzamides to get mono and di-allyl products with high selectivity (**Scheme 11**). There was not much electronic effect of allyl-scaffold on the reaction and the C−H allylation proceeds with complete α- and E-selectivity, and the related olefin-migration isomer was not detected. However, changing the methyl substituent on second coupling partner (benzamide) greatly affected the product. Also, when allylation was tried with cinnamyl alcohol, ether, acetate, and carbonate as allyl partners, no product was formed. The installation was found to be governed by steric hindrance of the allyl partners. The kinetic isotopic effect (KIE) and competitive studies indicated concerted-metalation-deprotonation (CMD) mechanism for the cleavage of the *ortho* C–H bond.
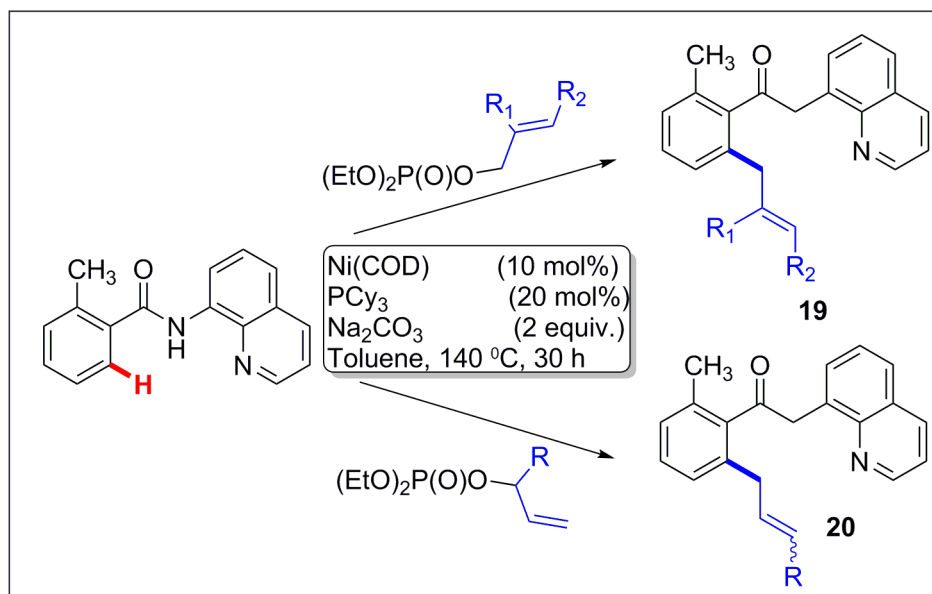
There are reports claiming the alkylation of benzoxazole using a Pd(II) catalyst [33]. However, when a small variation was made in the structure *i.e.* benzothiazole, no product was detected using the same Pd(II) catalyst. Contrarily, a catalytic system composed of another element from the same group, *i.e.* Ni(II)/diglyme/terpyridine, was able to produce alkylated benzothiazole in moderate amounts (**Scheme 12**) [33]. Such a reaction was proposed to go through (i) formation of an alkyl radical triggered by a single electron transfer from an electron-rich heteroarylnickelate complex to the alkyl halide, (ii) recombination of the formed radical with the heteroarylnickel, and (iii) reductive elimination.
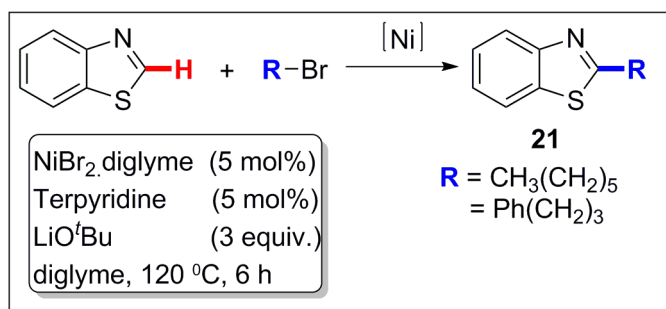
During the coupling of two different rings, the nature of the leaving group is also an important factor. More often, carbon-based leaving groups, especially carboxylic acids are considered as better leaving groups because of their low cost, good air and moisture stability, and ready availability [34]. An extensive Ni-catalyzed decarboxylative arylation method has been reported by Zhang et al. (**Scheme 13**) [34]. Yields of up to 83% were achieved using the combination of $NiCl_2/PCy_3$ as catalyst, 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl) as the ligand and silver carbonate as the oxidant. This new method can be employed for the synthesis of benzoxazoles, oxazoles and benzothioazole bearing varieties of functional groups such as methoxy, methyl, halo (fluoro, chloro, and bromo), ester, nitro, and trifluoromethyl. Moreover, the reaction was found to give the desired product with 2-nitrobenzoic acids having electron donating and electron withdrawing groups in the C4, C5, or C6 positions. However, the method uses costly solvent (trifluoromethyl)-benzene and high temperatures, which would limit the applicability of this method on a large scale.
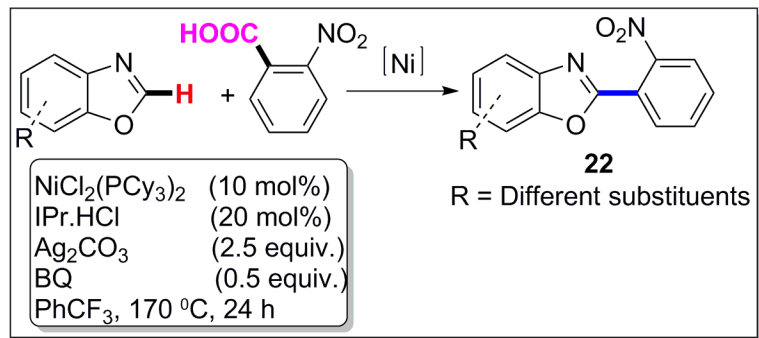
Recently, using terminal alkynes and benzeneselenol, a Ni(II) catalyzed synthesis of monoseleno-substituted 1,3-dienes has been reported (**Scheme 14**) [35]. The reaction gave a good yield of the product under mild condition. Various alkynes with different functionalities can be used for the synthesis of selenium-functionalized dienes. The unique properties of the catalytic system enable the exclusive formation of one type of diene in the stable *s*-gauche conformation.
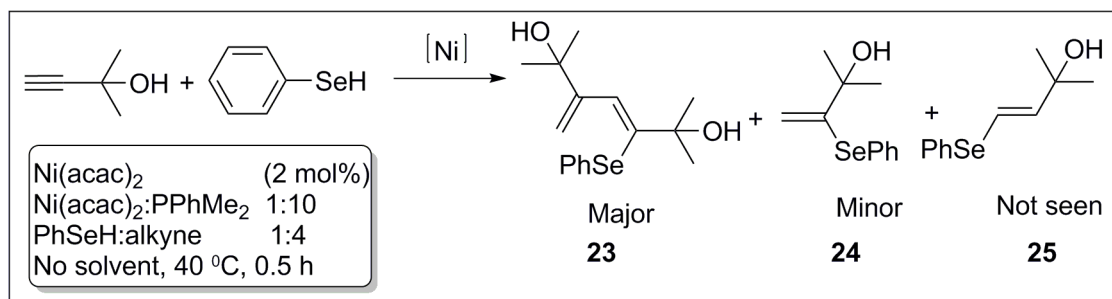
For the alkylation of N-aromatic heterocycles, which have a range of applications in the pharmaceutical industry and for drug development, a novel Ni-catalyzed direct C(sp^2)–H bond alkylation has been reported (**Scheme 15**) [36]. Under optimized condition, 100% conversion of the starting materials was reported to occur at room temperature. The authors used a Grignard reagent as a new and efficient coupling partner for directing group free N-aromatic heterocycles alkylation, which was the first of its kind. Contrary to this, when Pd/Fe was used in place of Ni, only a trace or no product was obtained. A similar observation was made when benzimidazole derivatives were used as substrates.
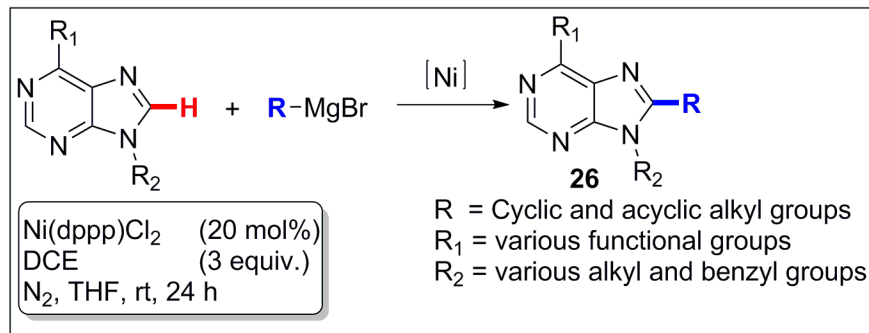
Similarly, a direct C–H functionalization of azole with aryl boronic acids using a crystalline porous metal–organic framework, $Ni_2(BDC)_2(DABCO)$, as an efficient heterogeneous catalyst has been reported (**Scheme 16**) [37]. The catalytic system, which is first of its kind, was found to show better activity than other Ni, Cu and Co-based catalysts and salts. This material is quite attractive as the catalyst can be reused several times. Interestingly, the recovered catalyst gave its best performance for six sequential runs, and this reduced to 77% of its original activity in the seventh run.
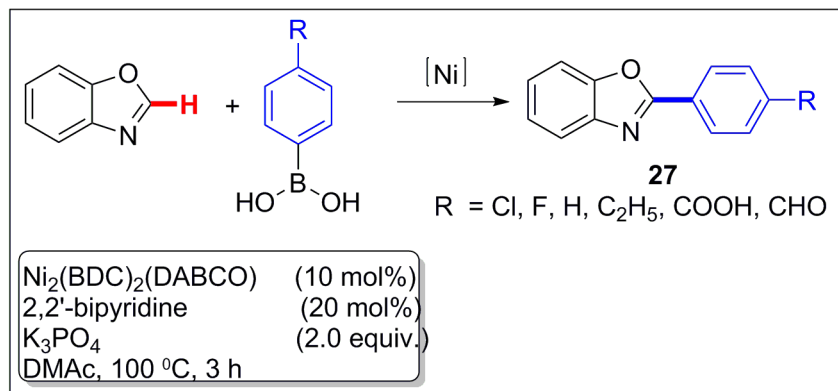
Cooperative catalysis is another dimension of C–H activation and functionalization, in which a transition metal-based catalyst is supported by another inorganic or organic moiety [38]. Anand and Sunoj found a similar cooperativity of Lewis acid ($AlMe_3$) [38a] during C–H activation by Ni(0) catalyst. A dual activation was observed in this system that was attributed to formyl $C(sp^2)$−H first followed by benzyl methyl $C(sp^3)$−H. The authors reported that the cooperativity was kinetic in origin. It was due to the significant stabilization of the vital transition states as compared to the non-cooperative pathways. The rate-determining oxidative insertion has been found to be 14

kcal/mol lower in energy with the Lewis acid coordination than in its absence. A mechanistic study for bimetallic Ni–Al-catalyzed hydro hetero-arylation of styrene with benzimidazole based on C–H bond activation [39] showed a similar result in which the presence/absence of Al-based co-catalyst affected the formation of product (**Scheme 17**). The authors identified a mode of chemically region-selective switching for C–H bond functionalization of benzimidazole derivatives. The cooperative interaction between Ni and Al created a steric environment for obtaining the linear product. However, when AlMe$_3$ was removed from the reaction, a branched product formation was preferred (**Figure 4**). Moreover, AlMe$_3$ had also a good impact on the rate of the reaction.
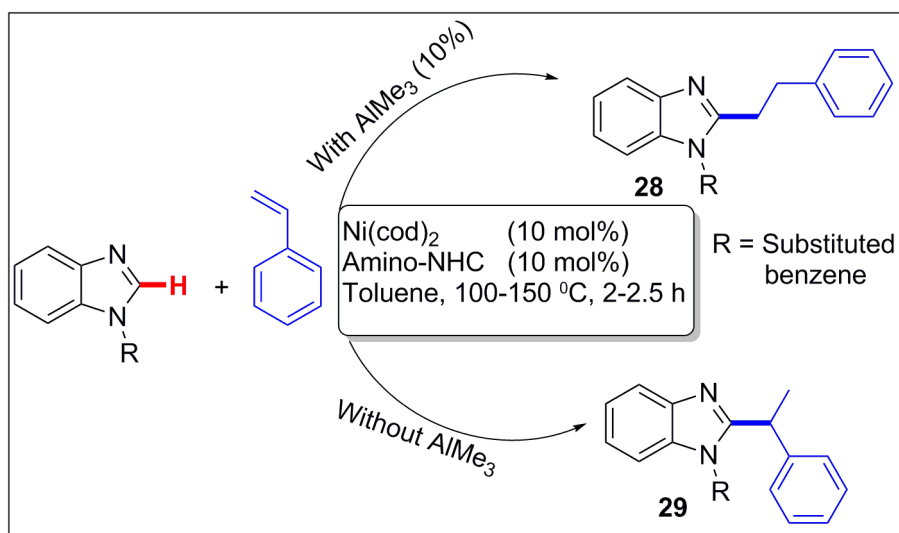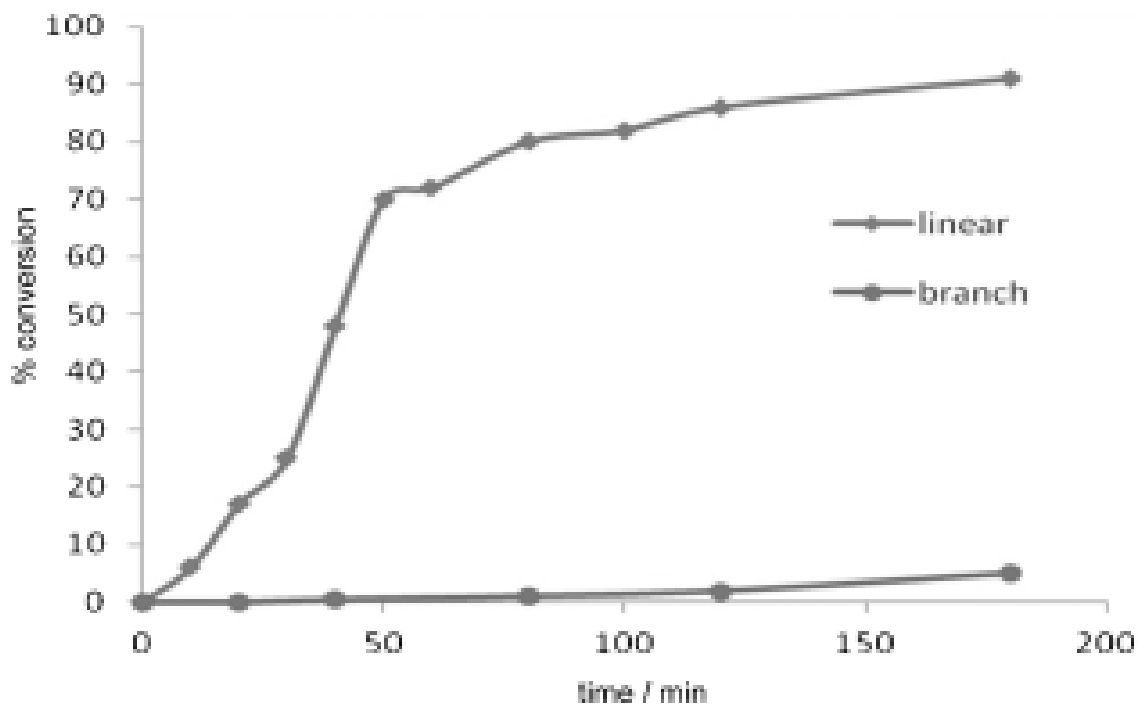
Figure 4: The reaction rate profile for the reaction of benzimidazole and styrene in the presence (diamonds) and absence of $AlMe_3$ (circles) (Reproduced with permission from ref. 39).

A unique carbide cluster has been reported in which the methyl group attached to Ni atom was transformed into the carbido and the carbyne ligands through triple C−H bond activation of methyl group, which is uncommon for late transition metal compounds (**Scheme 18**). Furthermore, the selective formation of C−C bond was attributed to carbon atoms that were originally bonded to the Ni atoms in the complex [40].

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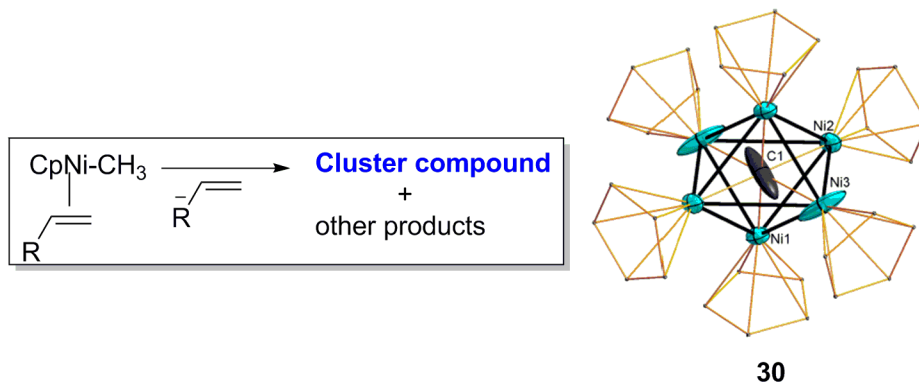
Rokob and co-workers [17] found an interesting pattern of C–H activation in regioisomeric complexes of phenylpyridines and Ni(II). The ESI-MS studies in the vapor phase indicated the presence of the species $[Ni(phpy)_m]^{2+}$ with m = 3-5 and $[NiCl(phpy)_n]^+$ with n = 1-3 (**Scheme 19**). A significant C−H bond activation was observed in a complex comprising of 2-phpy *i.e.* $[NiCl(phpy)_2]^+$ while for its regioisomers (3- and 4-phpy), it was either suppressed or occurred only at high temperature. The activation of the C–H bond was initiated from the coordination of 2-phpy *via* the nitrogen lone pair, one of the two *ortho*-C−H bonds comes into close proximity to the metal center, which enables subsequent bond activation.
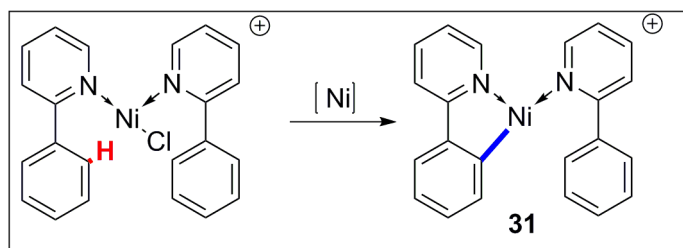
3.2. Palladium-Catalyzed Reactions

Transition metal catalyzed intermolecular cross-coupling of inert C−H bonds has recently emerged as a powerful method for C−C bond formation [41]. The first example of Pd as C−H activator was reported for the synthesis of olefinated arenes from benzene using Pd(OAc)$_2$ [42]. Since then similar Pd-catalyzed reactions have been reported from time to time [43]. Pd complexes are attractive candidates for the activation and functionalization of C–H bonds for many reasons. These include compatibility with different functional groups so that it allows installation of C−N, C−O, C−S, C−X, and C−C bonds, participates in cyclometallation with a wide variety of directing groups and, unlike many other transition metals, readily promotes C–H activation at both sp^2 and sp^3 C–H sites and require mild condition in most of the cases [3]. All these properties of Pd complexes make them suitable candidates for C–H activation and functionalization.

3.2.1. C(sp^3)–H activation and functionalization

Cyclopropane is an attractive moiety in terms of its biological activity and is readily available in many natural products [44]. However, its installation into the molecule is a tedious job. Keeping this problem in mind, Nacci and co-workers

developed an unusual double C–H activation in arylmethyl ketones, which upon treatment with styrenes gave cyclopropanated products (**Scheme 20**) [45]. For this purpose, they used a combination of Pd(OAc)$_2$, Cu(OAc)$_2$, and dioxygen in molten tetrabutylammonium acetate (TBAA). When the same reaction was conducted in conventional solvents, no product was formed. Similarly, among the diff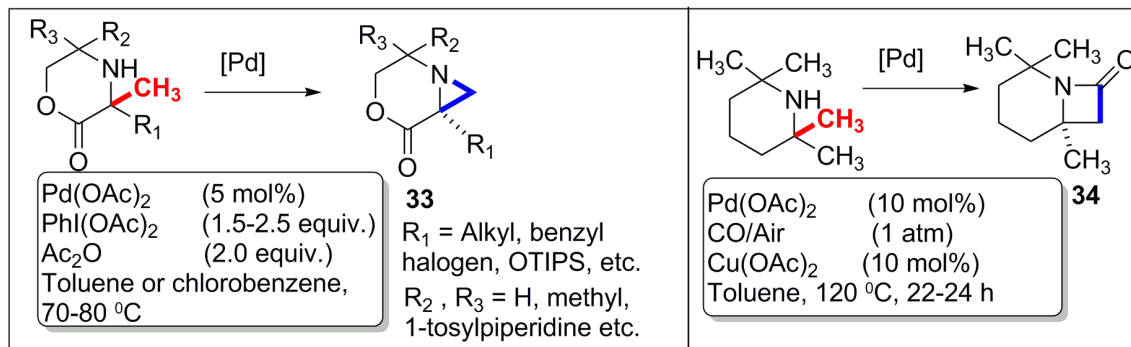erent bases used, acetate gave the best result. Since molecular oxygen was involved in the reaction, this reaction can be carried out in aerobic condition. The ready availability of starting materials (ketones and styrenes), high yields, no special need of pre-functionalization and the eco-friendly nature (water as by-product and ionic liquid as solvent) were the main features of this method. However, this method was not applicable for the ketones and alkenes with long aliphatic chains as it resulted in the formation of dehydrogenated by-products. Furthermore, when this reaction was conducted using a nano-Pd catalyst, it gave no product.

Pd(OAc)$_2$ (5 mol%)
Cu(OAc)$_2$ (1 equiv.)
O$_2$
TBAA (molten), 100 ^{0}C, 6-8 h

32
R$_1$ & R$_2$ = Functional groups
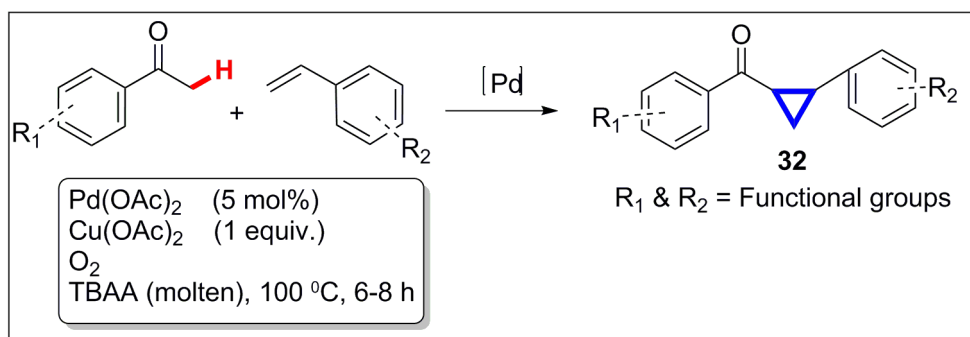
For the synthesis of aliphatic amines, which are important moieties in pharmaceutical field, a C–H functionalization platform is highly desirable. For this purpose, recently, Gaunt et al. [46] reported a new Pd-catalyzed C–H bond activation that proceeds through a four-membered ring cyclopalladation pathway, which was different from the classical 5-membered ring formation pathways and occurred at β-position (**Scheme 21**). With this methodology, they selectively transformed a methyl group adjacent to unprotected secondary amine (fully aliphatic unactivated amines) into synthetically versatile nitrogen heterocycles including aziridines and β-lactams.

22

R₃, R₂, NH, **CH₃**, O, R₁, O →[Pd]→ R₃, R₂, N, O, R₁, O

Pd(OAc)₂ (5 mol%)
PhI(OAc)₂ (1.5-2.5 equiv.)
Ac₂O (2.0 equiv.)
Toluene or chlorobenzene, 70-80 °C

33
R₁ = Alkyl, benzyl
halogen, OTIPS, etc.
R₂ , R₃ = H, methyl,
1-tosylpiperidine etc.

H₃C, CH₃, NH, **CH₃**, CH₃ →[Pd]→ H₃C, CH₃, N, O, CH₃

Pd(OAc)₂ (10 mol%)
CO/Air (1 atm)
Cu(OAc)₂ (10 mol%)
Toluene, 120 °C, 22-24 h

34

Similarly, 3-pinanamine is another natural product containing 1° amine and is endowed with intriguing biological activities. However, the structural complexity of this molecule often hinders the synthesis of its derivatives and thus biological profiling. Considering this challenge, Wan and co-workers recently reported a rare functionalization of this aliphatic amine at the remote δ-position, which is first of its kind [47]. They achieved a region- and stereo-selective functionalization of the methylene $C(sp^3)$−H bond present at the remote δ-position (**Scheme 22**) [47]. With the help of this method, pinamine derivatives with a range of functionalities can be arylated easily.

H, **H**, HN, O, N; H₃C, H, CH₃ CH₃ + **Ar**-X →|Pd|→ H, **Ar**, HN, O, N; H₃C, H, CH₃ CH₃ **35**

Pd(OAc)₂ (10 mol%)
Ag₂CO₃ (1.0 equiv.)
Toluene, 130 °C, 24 h
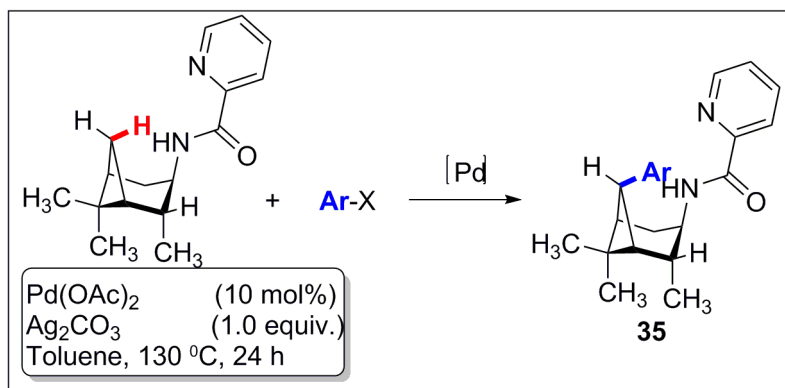
N-heterocyclic carbene (NHC)-containing catalytic systems have been thoroughly exploited for activation and functionalization. The use of NHC ligands with different metal partners often produces valuable enantio-enriched substituted indolines and azaindolines [48,49]. Kündig et al. [49] studied the detailed scope and limitations of Pd-NHC-catalyzed complexes in asymmetric $C(sp^3)$−H activation (**Scheme 23**). The authors used racemic mixtures of the carbamate which underwent regiodivergent reactions to afford single regioisomeric, enantiopure *trans*-2,3-substituted indolines with high chiral induction. It was found that the enantiopurity of the product depends upon the chirality of

the catalyst used. However, C–H bonds at, or adjacent to, tertiary centers could not be touched by this method.
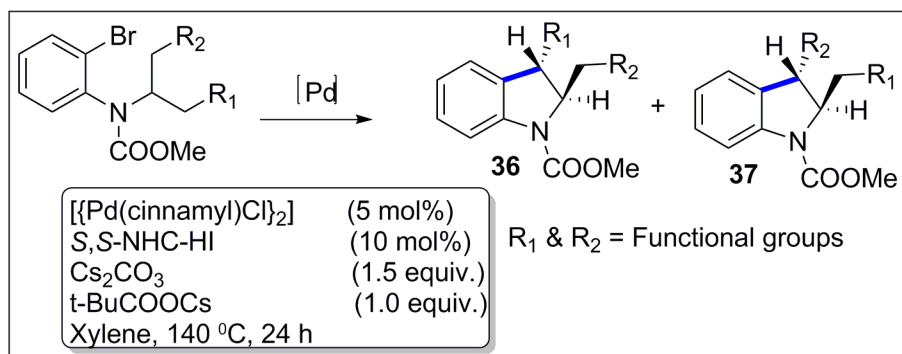

In another study, Munz and Strassner [50] recently reported detailed mechanistic studies (regioselectivity and the catalytic activity) on the C–H functionalization of alkanes by Pd catalysts with chelating NHC complexes using both experimental and DFT calculations. The results indicated that the C–H activation step takes place at the Pd(II) complex followed by oxidation by bromine to the +IV oxidation state. Furthermore, the C–H activation step controls the reaction rate, whereas the *iso*-selectivity was determined within the oxidation step to Pd(IV). In addition to this, a different mechanism was responsible at higher halide loadings.

A C–H activation step followed by C−N bond formation is a promising way of obtaining N-containing heterocycles including amide, amine, alkaloids etc. For this purpose, activation and functionalization of both $C(sp^2)$–H and $C(sp^3)$–H have been reported. While the activation of $C(sp^2)$−H bonds is most often triggered by an interaction between the π electrons and the catalyst, the activation mode for unactivated $C(sp^3)$−H bonds is a matter of debate and less well understood [51]. Glorious et al. [51] reported the first example of Pd-catalyzed synthesis of indoline products from many differently substituted anilides (**Scheme 24**). In this reaction, they reported the activation of $C(sp^3)$–H instead of the presence of $C(sp^2)$–H bond. Under optimized conditions, the reaction gave high yields (> 80 %) using AgOAc as oxidant and Na_2CO_3 as base. It was noted that no product was formed when polar solvents like DMSO, DMF and MeCN were used and the reaction was sensitive to water. Instead of tolerability of wide range of functional groups (ethers, sulfones, and carboxylic esters, such as thioethers, acetals, silanes,

24

ketones, bromide, olefin, and aldehyde), this method does not give satisfactory result when the acetyl functionality is replaced by pivaloyl, benzoyl, trifluoroacetyl, carbamates, sulfonamides, free primary or secondary amines.
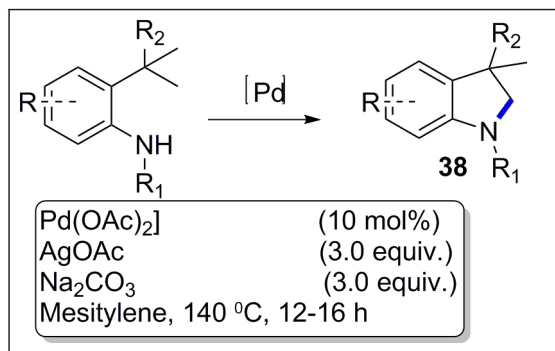
Recently, for the installation of aryl group into acyclic and cyclic amides containing β-methylene $C(sp^3)$–H bonds, a new ligand-enabled methylene $C(sp^3)$−H activation method has been reported (**Scheme 25**) [52]. In this method, a mutually repulsive and electron-rich quinoline ligand (2,6-dialkoxypyridine and 2-alkoxyquinoline) was used to insert Pd(II) into β-methylene $C(sp^3)$–H bonds. It was observed that the reaction proceeded only in the presence of the ligand.
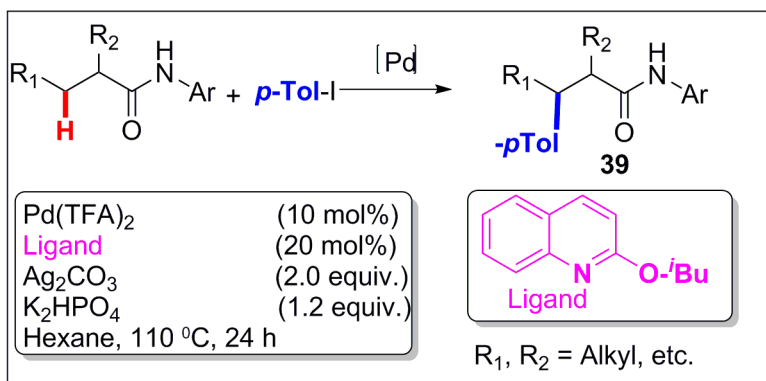
The first enantioselective α-allylation of aldehydes with terminal alkenes has been reported by using the combination of asymmetric counter anion catalysis and Pd-catalyzed allylic C–H activation (**Scheme 26**) [53]. The reported method uses enolizable aldehyde and a mild oxidizing agent. When diphenylmethanamine was used as base, which is a common one in asymmetric allylic alkylation of allylic alcohols and aldehydes, a trace amount of product was obtained. This was probably due the oxidation

of base into diphenylmethanimine. To overcome this problem, achiral tertiary carbon-bearing amine was used when the reaction went well. Under optimized conditions, the base cumylamine gave the product in good yield with high enantiopurity. With this method, one can proceed with a wide range of unactivated allylarenes. Since the enantioselectivity of the product was not affected by the electronic nature and substitution pattern of the arene moiety, one can get the product in 84 to 90% enantiomeric excess (*ee*). However, the reaction was affected by the nature of the aryl ring.
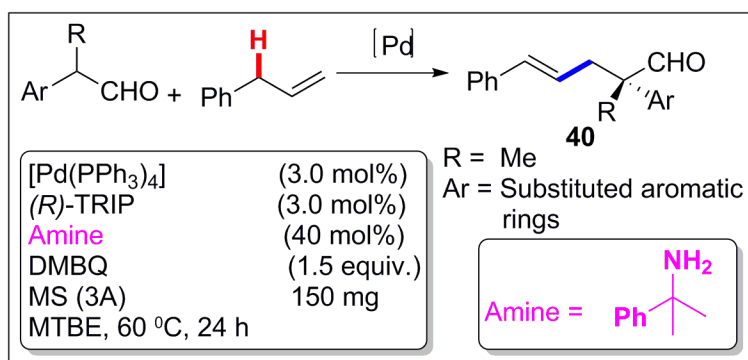
Ligand-directed cyclization is an appealing method for ring-forming reactions and has been used for a long time [3, 54]. Examples of ligand-directed activation and cyclization have already been discussed in the previous section. Using the same concept, alkylation of unactivated β-methylene $C(sp^3)$−H bonds of α-amino acid substrates using the 8-AQ auxiliary, a Pd(II)-catalyzed method has been reported which tolerated a broad range of alkyl iodides and proceeds with high diastereoselectivity (**Scheme 27**) [55]. The optimized reaction condition dictated that the presence of 4-Cl-$C_6H_4SO_2NH_2$ and NaOCN was crucial. Among alkyl halides, several branched and linear iodides with a wide range of functional groups were compatible in the reaction. Interestingly, TIPS-protected terminal alkyne unit containing alkyl iodide was also found to react conveniently, thus giving another dimension for coupling to afford new materials with intriguing properties. This method is specifically useful for the synthesis of β,β-hetero-dialkyl- and β-alkyl-β-aryl-α-amino acids. A single-crystal X-ray structure of a new palladacycle intermediate was also reported.

Methyl C(sp^3-H) alkylation/arylation **41**

Pd(OAc)$_2$ (10 mol%)
Ag$_2$CO$_3$ (0.8 equiv)
(OBn)$_2$PO$_2$H (0.3 equiv.)
^{t}BuOH/ DCE (1/1)
N$_2$, 60 ^{0}C, 12 h

or

Pd(OAc)$_2$ (10 mol%)
AgBF$_4$ (1.3 equiv)
^{t}BuOH/ DCE (2/1)
N$_2$, 75 ^{0}C, 4 h

Methylene C(sp^3-H) alkylation/arylation **42**

Pd(OAc)$_2$ (10 mol%)
Ag$_2$CO$_3$ (1.5 equiv)
NaOCN (2.0 equiv)
Sulfonamide (0.3 equiv.)
N$_2$, 1,4-dioxane, 80 ^{0}C, 20 h

or

Pd(OAc)$_2$ (10 mol%)
AgOAc (1.5 equiv)
^{t}BuOH/ DCE (2/1)
N$_2$, 90 ^{0}C, 13 h

SO$_2$NH$_2$

Cl
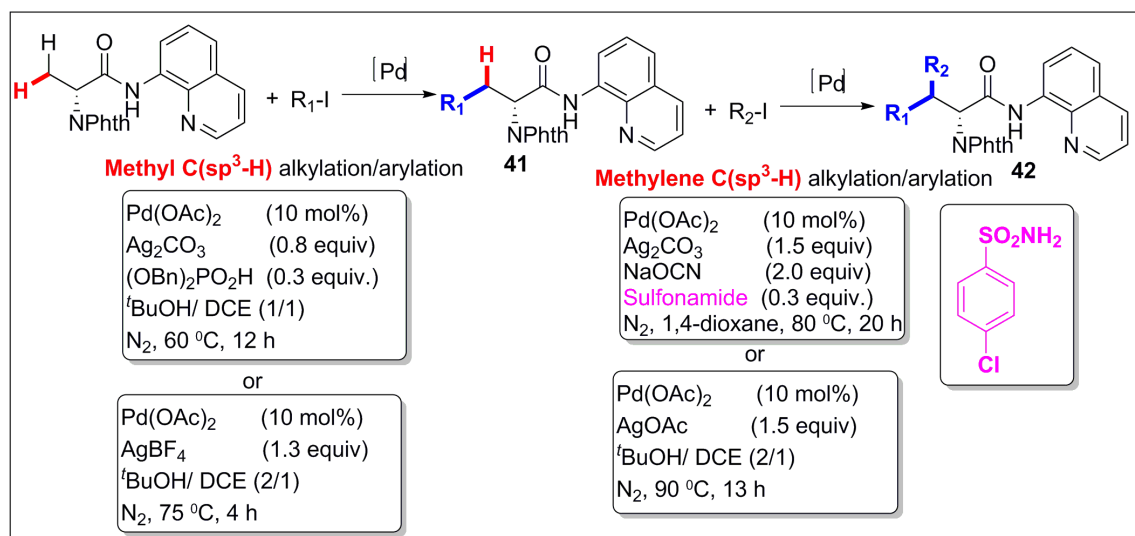
3.2.2. C(sp^2)−H activation and functionalization

Because of the importance of alkylated heterocycles in medicinal chemistry, polymer chemistry and as an alternative to conventional Friedel-Craft alkylation, several new methods and results have been reported. Miura et al. [33] reported a Pd-catalyzed C−H alkylation of electron-deficient arenes and azoles possessing β-hydrogen with unactivated alkyl bromides and chlorides (**Scheme 28**). The mechanistic studies indicated that the formation of C−C bond was metal dependent and proceeds through reductive elimination. This method was very similar to the Ni-catalyzed alkylation of benzothiazole (**Scheme 12**) [33]. In this work, they only change was the catalytic system and the ligand.

[{PdCl(n^3-C$_3$H$_5$)}$_2$] (3.75 mol%)
PBu$_3$ (30 mol%)
LiO^{t}Bu (3 equiv.)
diglyme, 120 ^{0}C, 4 h

43

R = Cyclic and acyclic alkyl group
X = Cl, Br, I
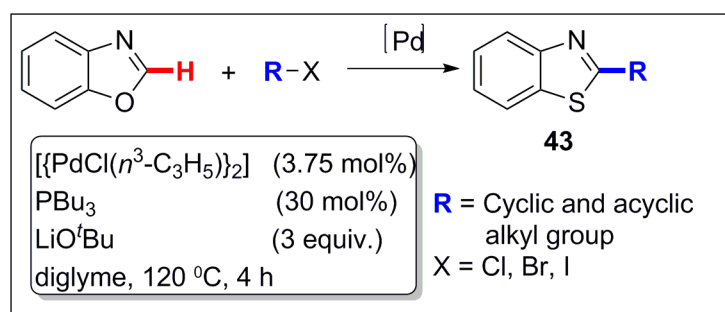
For the synthesis of alkylated pyridine derivatives, Fu et al. [41] reported an extraordinary gram scale example of the Pd-catalyzed cross-coupling of secondary and tertiary aliphatic electrophiles with pyridine N-oxides (**Scheme 29**). They found application of this method in the alkylation of naturally occurring alkaloids such as

quinine, cinchonine and in the coupling of steroids and alkyl pyridine derivatives. They suggested that the C−Br bond cleavage may proceed through a hybrid organometallic-radical mechanism. However, the protection was necessary to prevent double alkylation, the mono-substituted pyridine N-oxides reacted efficiently to give the desired product. The authors noted that a pre-synthesized Pd(OAc)$_2$dppf complex gave 90% yield of the alkylated product.
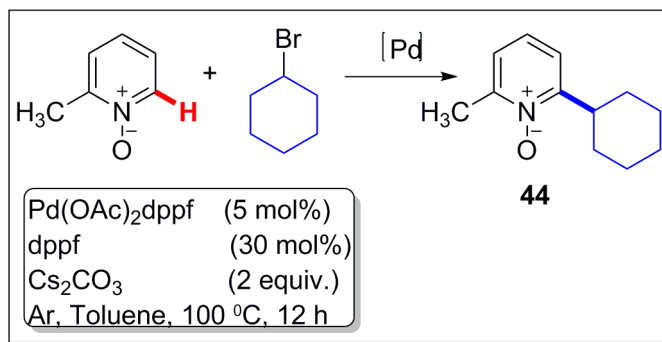

Following this report, Zhou et al. [56] reported a Pd-catalyzed method for the alkylation of heteroarenes using 2° and 3° alkyl halides, in which the addition of alkyl radical to neutral heteroarenes was suggested. The reported method can be employed for regioselective alkylation of electron-deficient pyridines with unactivated 2° and 3° alkyl halides. Other than this, furans, thiophenes, pyrroles, and their benzoid-fused derivatives can also be alkylated (**Scheme 30**). However, the presence of electron-withdrawing groups (aldehydes, ketones, and nitriles) was necessary as they played an important role for substrate activation and regiocontrol. The proposed mechanism stated that the catalytic cycle starts from conversion of alkyl halide to alkyl radical by one electron transfer from the catalyst (Pd^0), which itself gets converted into [(dppp)Pd^{I}X]. It is then followed by radical addition to a heteroarene, back electron transfer to [(dppp)Pd^{I}X] and deprotonation to furnish the product (**Figure 5**).
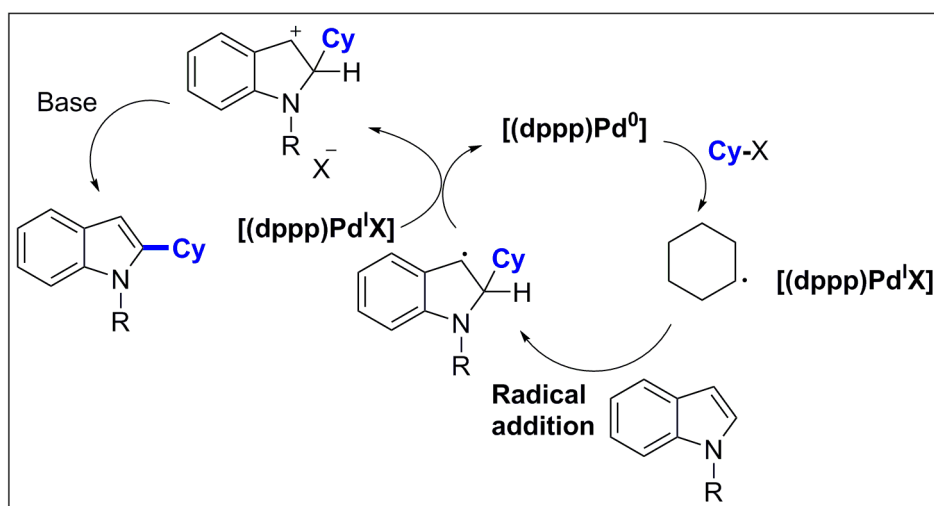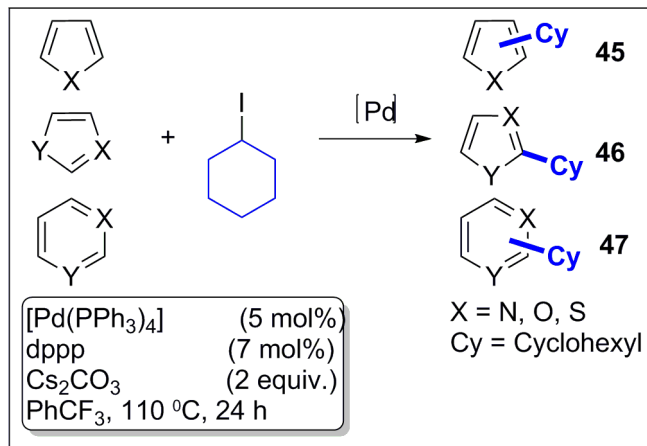
Figure 5: Proposed catalytic pathway for the alkylation of heteroarenes (Reproduced with permission from ref. 56).

Benzothiophenes are sulfur-containing compounds having application in opto-electronics, pharmaceuticals, dyes, liquid crystals, agrochemicals, etc. [57]. Considering their wide ranging applications, Colobert et al. [58] recently reported a synthetic method of dibenzothiophene-S-oxides in excellent yields using differently substituted 2-bromo-diarylsulfinyl moieties and Pd(OAc)$_2$ as the catalyst with KOAc as the base (**Scheme 31**). The reaction was carried out at high temperature (130 °C) in dimethylacetamide solvent. The dibenzothiophene-S-oxides can be easily reduced to the corresponding dibenzothiophenes using standard methodologies (sulfoxides → thioethers). However, when the same reaction was carried out using Pd(OAc)$_2$ catalyst, Ag$_2$CO$_3$ as base in

apolar solvent (1,3,5-triflurorbenzene) heated by microwave (135 °C), only a trace amount of product was obtained.
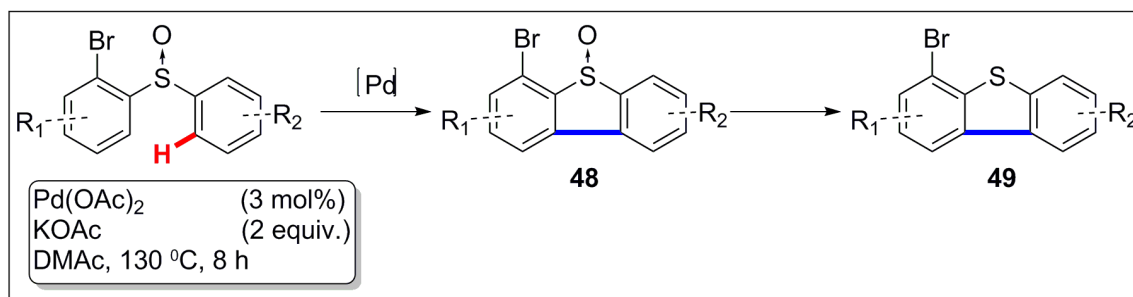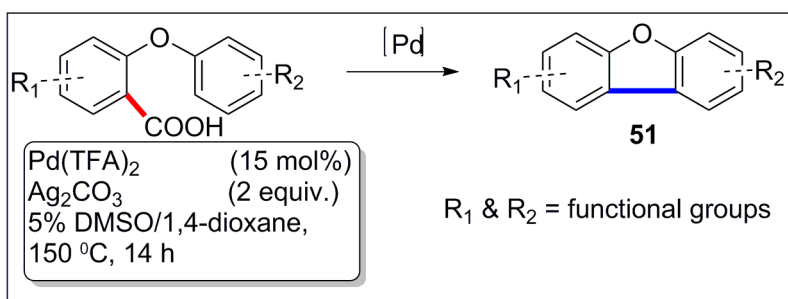

Prior to this report, a Pd(II)-catalyzed synthesis of dibenzothiophene was reported (**Scheme 32)** [59]. In the reported method, AgOAc was used as the oxidant in presence of *p*-fluoroiodobenzene additive and acetic acid as solvent. The method was applied to the synthesis of dibenzothiophenes from simple benzyl phenyl sulfoxides. In the absence of additive, a low yield of the product was reported. The dibenzothiophene prepared by this protocol could be used further for the synthesis of polycyclic aromatic hydrocarbons.
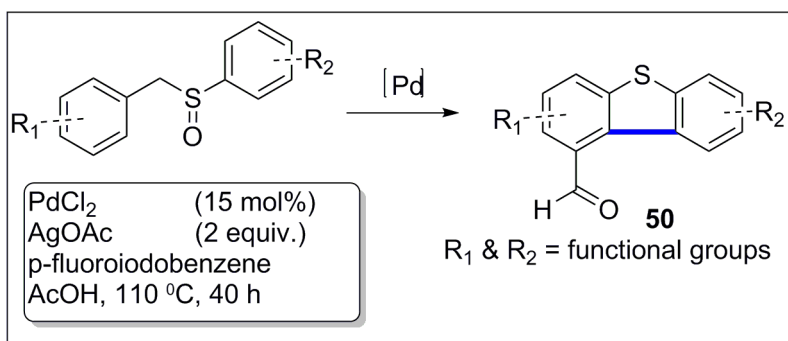
As stated earlier, carboxylate groups are well known for their ability to provide carbon frameworks with low cost and diversity [60, 61]. By the coupling of benzoic acids with arenes a library of biaryl compounds can be prepared at low cost [60, 61]. For this purpose, a highly chemo- and region-selective, efficient Pd-catalyzed intra-molecular direct arylation of benzoic acids by a tandem decarboxylation/C–H activation method was reported by Glorious and co-workers (**Scheme 33**) [61]. In these direct arylation reactions, the COOH group acts as a halide-free leaving group that provides a handle for obtaining high levels of regioselectivity. A variety of dibenzofuran derivatives was

synthesized using this method. Functional groups including fluoride, chloride, bromide, and double bond were easily tolerated in this process.

$$R_1 \text{---} \underset{\text{COOH}}{\bigcirc\!-\!O\!-\!\bigcirc} \text{---} R_2 \quad \xrightarrow{[Pd]} \quad R_1 \text{---} \bigcirc\!-\!O\!-\!\bigcirc \text{---} R_2$$

51

Pd(TFA)$_2$ (15 mol%)
Ag$_2$CO$_3$ (2 equiv.)
5% DMSO/1,4-dioxane,
150 ^{0}C, 14 h

R$_1$ & R$_2$ = functional groups

Liu et al. [54] reported the synthesis of substituted dibenzofuran by phenol-directed C–H activation/C−O cyclization using air as an oxidant (**Scheme 34**). The turnover-limiting step of the process was found to be C−O reductive elimination instead of C–H activation. This reaction can tolerate a variety of functional groups. When K$_2$CO$_3$ was used as base and the Cu(II)/Ag(I) salt as oxidant in mesitylene (solvent), no product was formed. However, under optimized conditions when K$_2$CO$_3$ was used as base, air as oxidant and MesCOONa as additive, a yield of 90% was obtained. The selectivity of the above method was seen even in the presence of NH$_2$ group at the same position. Using this approach, the authors successfully demonstrated its use in arylation of estrone and two-photon responsive calcium caging agent.

$$R_1 \text{---} \underset{\text{HHO}}{\bigcirc\!-\!\bigcirc} \text{---} R_2 \quad \xrightarrow{[Pd]} \quad \textbf{51}$$

R$_1$ & R$_2$ = functional groups

Pd(OAc)$_2$ (5 mol%)
IPr   (10 mol%)
Air
K$_2$CO$_3$ (2 equiv.)
MesCOONa (0.5 equiv.)
Mesitylene, 120 ^{0}C, 24 h
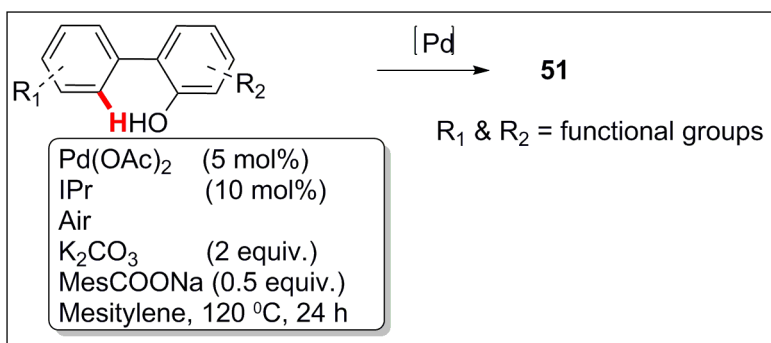
A mixture of Pd/Cu catalysts were reported for use in decarboxylative/direct C–H alkenylations of heteroarenes with α-fluoroacrylic acid (**Scheme 35**) [62]. This work extends the boundaries of the current highly attractive field of catalytic C–H functionalization of molecules since it involves, for the first time, the acrylic acid series

as coupling partners in direct C–H alkenylation. The method can be employed for the synthesis of heteroarylated monofluoroalkenes which, in turn, is useful as biomolecules.
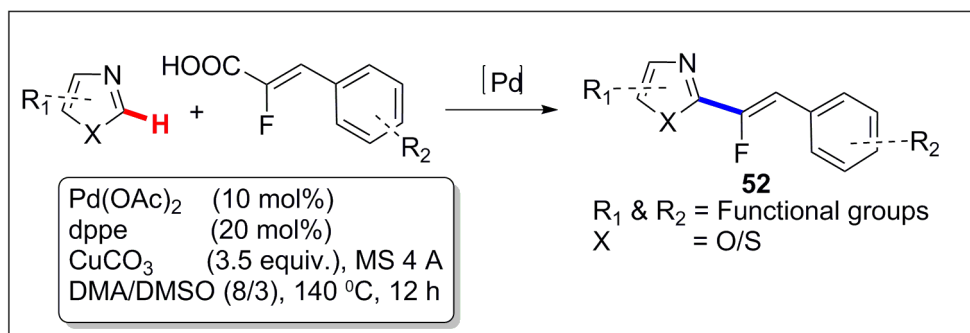
Zhao et al. [63] reported a one pot high yielding Pd-catalyzed *ortho* $C(sp^2)$–H alkenylation *via* a rarely reported seven-membered palladacycle at the ε-position (**Scheme 36**). They used oxalyl amide as a directing group, $(n\text{-BuO})_2PO_2H$ as additive and Ag_2CO_3 as oxidant. The directing group (oxalyl amide) could be easily introduced and removed under mild conditions, thus presenting a practical protocol for the synthesis of alkenylated arenes. In the report, a good substrate scope and functional group tolerance were observed. The mechanistic studies with one of the substrates indicated the formation Pd-complex in toluene, which in presence of dibutyl phosphate additive and terminal alkene converted to the desired alkenylation product through seven-membered palladacycle intermediate (**Figure 6**).
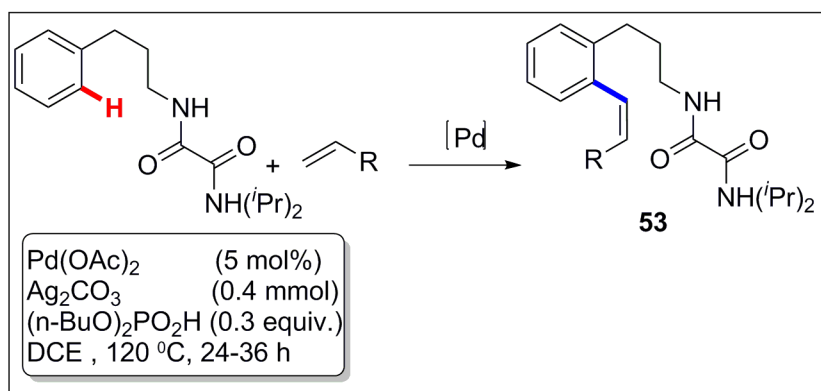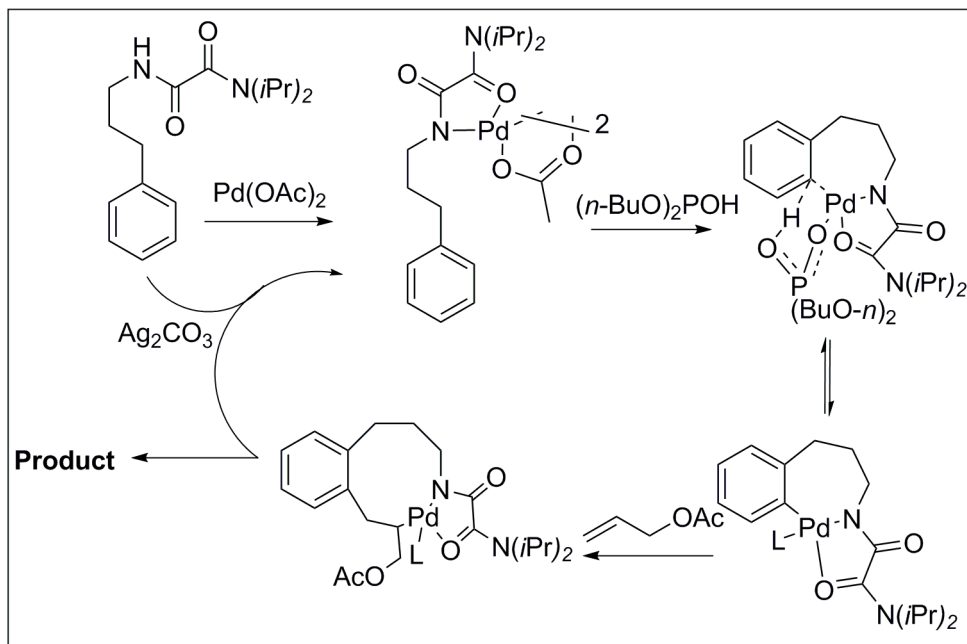
Figure 6: Formation of one of the products *via* a rarely reported seven-membered palladacycle (Reproduced with permission from ref. 63).

For the activation and alkenylation of sydnones, (**Scheme 37**) which has a range of applications, a catalytic mixture consisting of Pd/Ag has been used [64]. The reaction was carried out under milder condition using DCM as solvent and gave good to moderate yields of the products. As outlined by the authors, the proposed mechanism for the alkenylation of 3-arylsydnones involved the following pathways: electronic attack of Pd^{II} on 3-arylsydnone and subsequent deprotonation to form species **A**, formation of intermediate **B** by insertion into alkene followed β-hydride elimination to give the desired product and regeneration of Pd^0 (**Figure 7**).
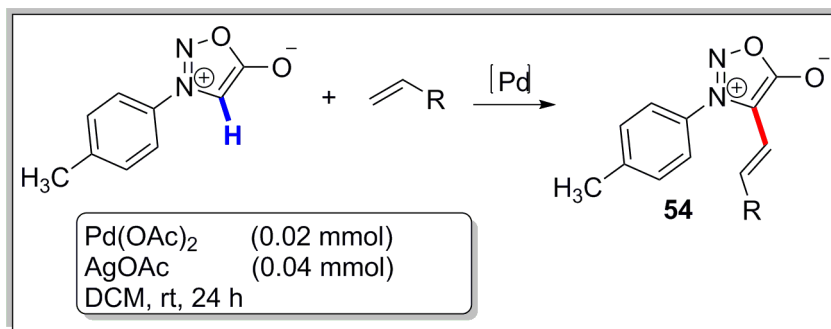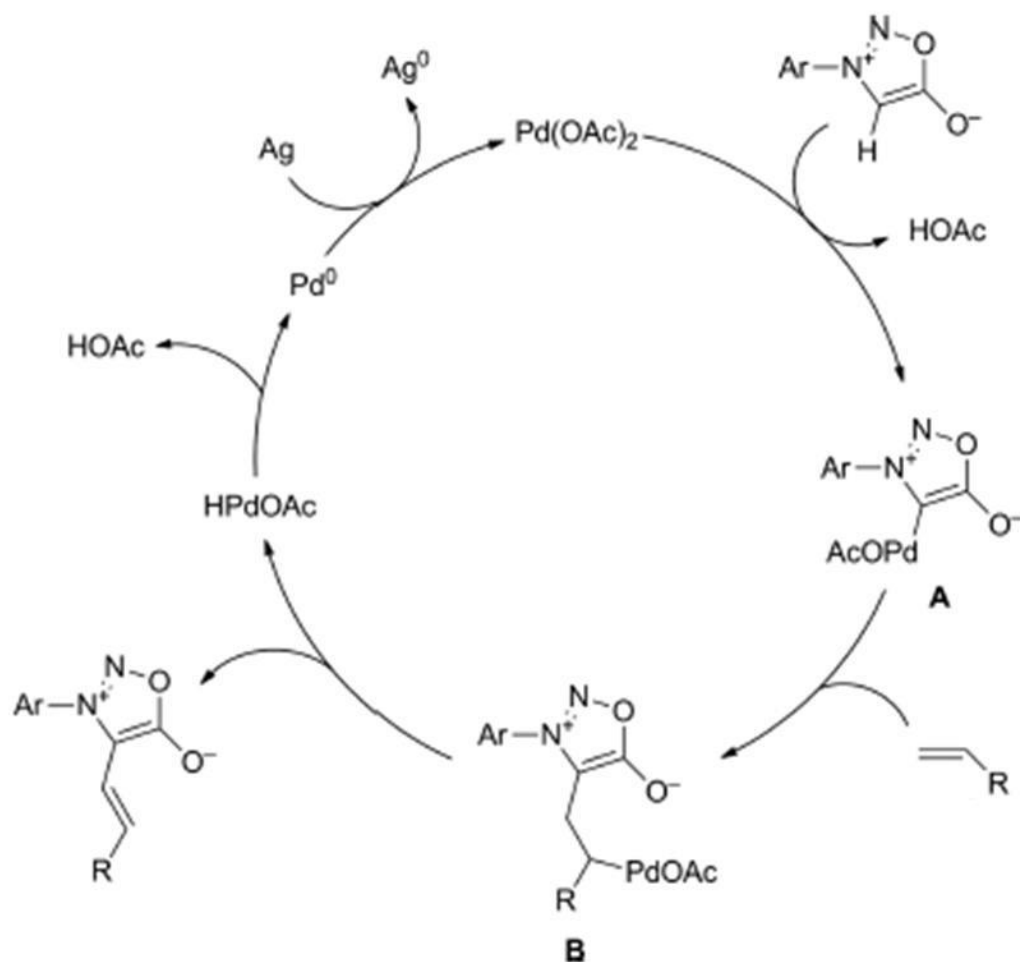
Figure 7: Possible mechanism for the alkenylation of 3-arylsydnones (Reproduced with permission from ref. 64).

For the synthesis and derivatization of biologically important substituted indoles, several new methods are being reported. Glorious et al. [65] reported an alternative to the Heck coupling reaction for efficient one pot synthesis of functionalized indoles from commercially available anilines using Pd through intra-molecular oxidative coupling (**Scheme 38**) [65]. Due to the non-electrophilic aromatic palladation nature of this reaction, a large variety of anilines was successfully employed. The reaction proceeds through σ bond-metathesis or deprotonation pathway. This method, unlike other used $Cu(OAc)_2$ as oxidant, K_2CO_3 as base and DMF as solvent. The conversion was complete

within 3 h at 80 °C (72% yield of the isolated product), or within less than 15 min. at 140 °C, even when only 5 mol% Pd(OAc)$_2$ was used.
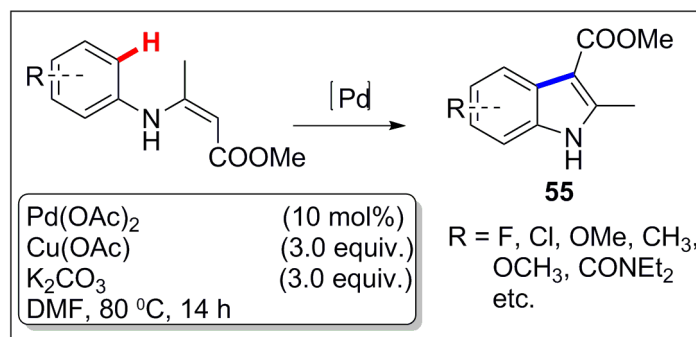
Tan and Hartwig [66] used Pd-catalyzed direct amination of aromatic C–H bonds with oxime esters under redox neutral conditions (**Scheme 39**). For amination, they used hydroxylamine derivatives as nitrogen source, instead of nitrene insertion into an aromatic C–H bond or oxidative amination of arenes with amine derivatives, as these two methods require high catalyst loading. On the other hand, when hydroxylamine derivatives were used as nitrogen source, reaction was found to proceed with a range of complexes and with low catalyst loading. The authors noted that the reaction proceeds through a Pd(II) complex generated from N−O bond oxidative addition.
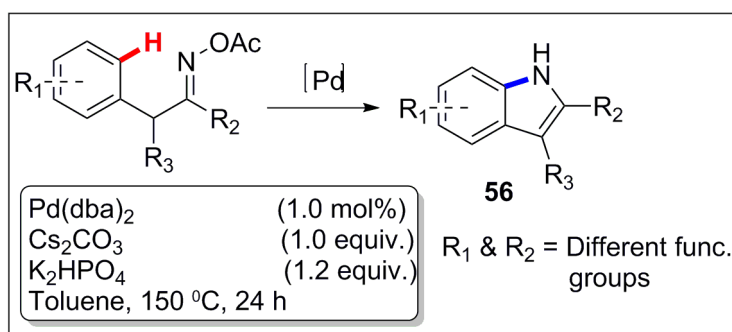
A Pd-catalyzed dehydrogenative coupling between diarylamines and olefins has been reported (**Scheme 40**) [67]. This method can be utilized with readily available olefins without using any directing group or functionalities. The authors suggested the mechanism of olefinated intermediate formation through *ortho* palladation, olefin coordination followed by β-migratory insertion. The reaction afforded good to moderate amount of products with symmetrical and unsymmetrical diphenylamines,

terminal/internal olefins and cyclic olefins (mono and dienes). It was found that different styrenes with diphenylamine result in 1,2- (major) and 1,3- (minor) diarylated indoles with a ratio of 99:1 in most of the cases. Furthermore, with unsymmetrical diarylamines, cyclization was preferred for the electron-deficient aromatic ring.
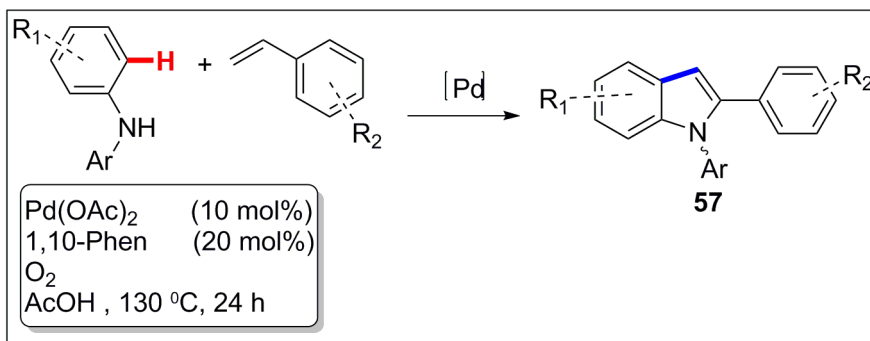
Similarly, for the synthesis of substituted 2-quinolones atom economic carbonylative cyclization of N-aryl-pyridine-2-amines and internal alkynes by C–H activation was reported by Wu et al. (**Scheme 41**) [68]. The elongation of the carbon chain was carried out by using CO, which was generated *in-situ* using solid [Mo(CO)$_6$] instead of using gaseous CO. The method reported a good functional group tolerance and easily removable directing group. This method was in line with the method for quinolone synthesis which utilizes either gaseous CO or CO containing complex as CO source [69].
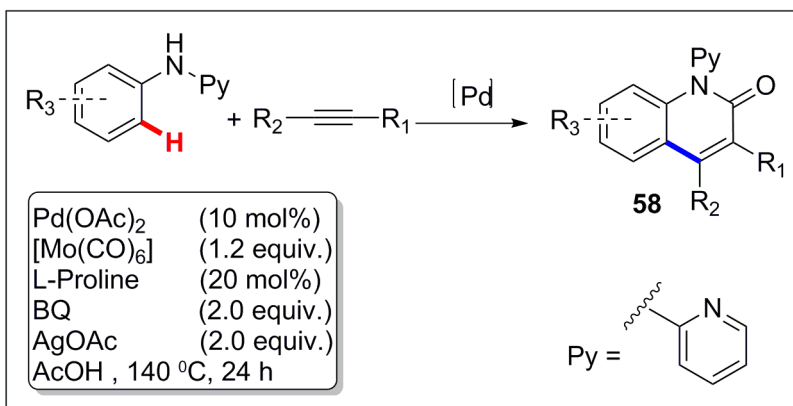
Lipshutz et al. [70] reported an unusual effect of cationic Pd in Suzuki-Miyaura reaction without using any metal oxidants or acid (**Scheme 42**). The authors found facile C–H activation of aromatic moiety followed by cross-couplings at room temperature. The cationic Pd(II) catalyst enhances not only the rate of C–H activation but also that for

transmetallation with an arylboronic acid. The yield of the reaction was less than 1% when neutral Pd(II) catalyst was used. In this reaction, the solvent played an important role. For example, the yield was 38% when solvent was acetone while the yield was increased to 96% in ethyl acetate. The aniline moiety was the directing group, which helped the cationic Pd catalyst to activate the *ortho* H.
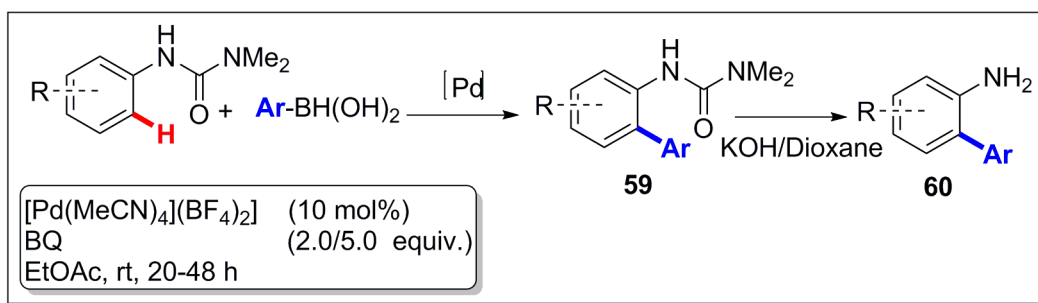

3.3. Platinum-Catalyzed Reactions

3.3.1. C(sp^3)–H and C(sp^2)–H activation and functionalization

The first catalytic reaction that comes to the mind of organometallic chemists is the Shilov system, which changed the direction of this ever growing field. In 1972, Shilov and co-workers discovered the first homogenous oxidation of alkane using a mixture of Pt(II) and Pt(IV) salts [71]. They used an aqueous solution of Pt(II) salts for the conversion of methane to alcohol (actually a mixture of alcohols) and other products (**Scheme 43**). In the process, the first step (C–H activation) is reported to be the rate determining step of the catalytic cycle [72]. In a recent atomistic simulation study on the Shilov system *cis-* and *trans*-PtCl$_2$(H$_2$O)(CH$_4$) σ-complexes within a realistic solvent environment shows that the complexes easily release a proton to the bulk solution [73]. According to the study, they do so through easy C–H bond cleavage forming a transient 5-coordinated Pt–H species which keeps the initial formal oxidation state Pt(II). The process does not involve coordination of water molecules, whereas those from the hydration sphere accept the proton. However, the main problems associated with this system were the slow rate, unstable catalysts, use of oxidant Pt(IV) and low methanol conversion [74]. The problems were well tackled using N-ligated Pt complexes, called the "*Periana system*" [75]. The "*Periana-catalytica*" based on (bpym)PtCl$_2$(bpym = 2,2′-

bipyrimidine) operates by C–H activation in concentrated H_2SO_4 at ~ 200 °C. This Pt-based catalyst, (κ^2-2,2'-bipyrimidyl)-Pt(II)dichloride converts methane to methanol quantitatively and selectively (**Scheme 43**). In spite of this, the high cost of Pt and large amount of catalyst required restricted its applicability [74].
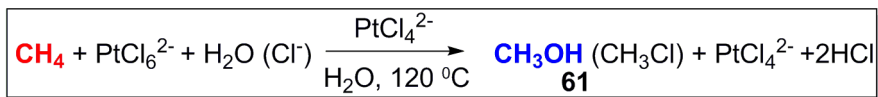
Shilov system
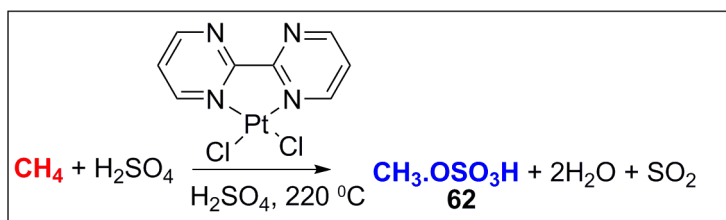
Periyana system

It has been proposed that the cationic complex [(NH−bpym)Pt(X)$_2$](X=Cl or OSO$_3$H) (**Scheme 44**) is the active component, which is responsible for the conversion of methane to methyl bisulfate and the protonation of bpym nitrogen is a crucial step [76].
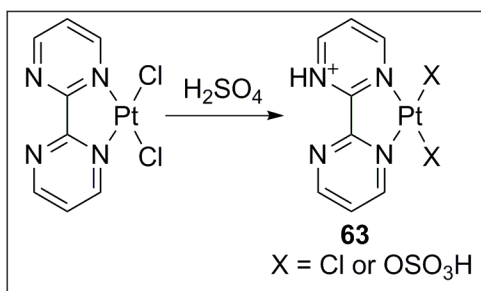
To validate this hypothesis and to further understand effects of protonation on reactivity, Sanford et al. [76d] replaced the bipyrimidine ligand on Pt with the cationic quaternized nitrogen-containing N-methyl-2,2'-bipyrimidininum (NCH$_3$−bpym) ligand (**Scheme 45**). Upon evaluation of catalytic activity in H/D exchange reactions of CH$_4$ (with D$_2$SO$_4$) and benzene (with CF$_3$CO$_2$D), it was observed that the efficiency of cationic quaternized ligand was comparable to the neutral "*Periana-Catalytica*", probably due to the *in situ* formation of the same active catalyst in both cases.
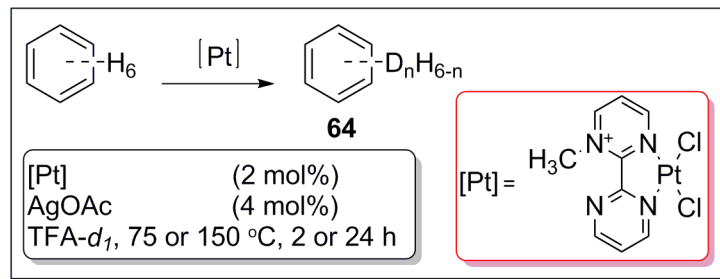
Prior to this, the same group reported the application of dicationic-bipyridine-based ligands in Pt- and Pd-catalyzed arene H/D exchange and oxidation reactions [77]. When these complexes were used as catalysts for H/D exchange between [D$_4$]acetic acid and benzene, they found a very a high catalytic activity with turnover frequencies (TOFs) in the range of 0.05-0.1 s^{-1} after 15 minutes at 150 °C (**Scheme 46**). On the other hand, the *Periana* catalyst [bpymPtCl$_2$] was reported to show TOFs of 0.003 s^{-1}. Interestingly, for H/D exchange between benzene and [D$_4$]AcOH at 100 °C, the catalytic activity (in terms of TONs) was very high compared to [bpymPtCl$_2$].
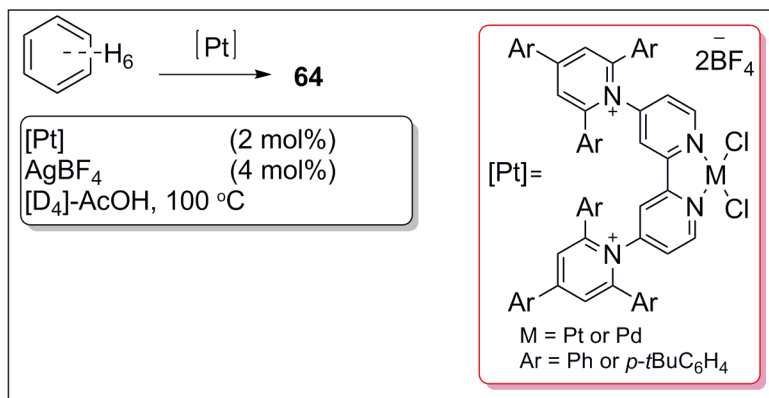
Recently Periana and co-workers [78] showed that functionalization of ethane occurs rapidly and selectively to EtOSO$_3$H (ethanol ester of sulphuric acid) as the initial product at rates that are ∼144 times higher (∼100 per CH bond) than for methane with the *Periana-Catalytica* system (**Scheme 47**). This was attributed to the different mechanism which led to much faster functionalization of Pt(II)−Et compared to Pt(II)−Me.
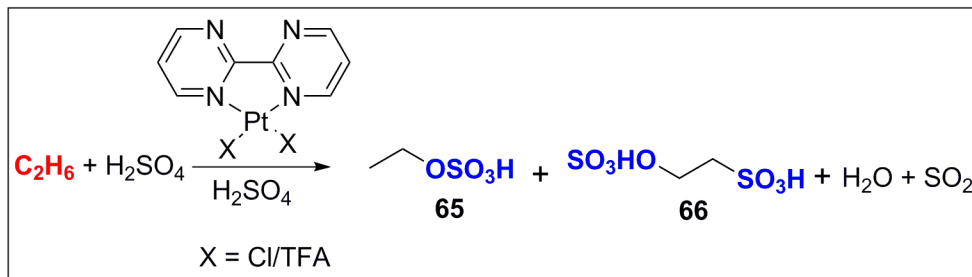
Labinger et al. [79] isolated η^3-cyclohexenyl and indenyl Pt(II) and Pd(II) diimine complexes of C–H activated product and showed that strong oxidants are able to liberate functionalized organic products. The same author recently reviewed a detailed electrophilic activation by Pt and other metals including late transition metals such as Zn and Hg. The author pointed out that some issues which were still persist include low selectivity, slow reaction rate, and difficulty in scale-up to an industrial level. However, according to the author, a practical application of electrophilic functionalization of alkanes may well appear in the not too distant future [80]. Trifluoroethanol (TFE) is considered inert to the oxidation reaction due to the presence of strong electron-withdrawing moieties and is used as solvent for oxidation reactions [81]. During the oxidation of methane in TFE, Neumann et al. [81] observed that instead of methane, TFE undergoes an oxidation reaction. The oxidation reaction which was carried out in the presence of O_2, Pt(dppz)Cl$_2$ and H_2SO_4, oxidized TFE to trifluoroethyltrifluoracetate, $CF_3C(O)OCH_2CF_3$ as the major product with minor products (~ 2 %) including trifluoroacetaldehyde CF_3CHO and its acetal $CF_3CH(OCH_2CF_3)_2$ (**Scheme 48**). However, the same reaction was not observed when Pt(phen)Cl$_2$ was used. It was found that the Pt C–H bond activation was the rate determining step. Overall, this research opens up new potential pathways for oxidation by activation of relatively inert C–H bonds such as those adjacent to strongly electron-withdrawing groups.
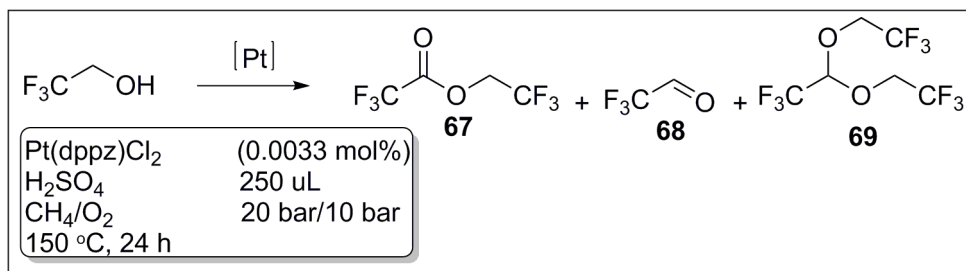
The thermolysis study of the Pt(II) *bis*-hydroxo complex in d$_6$-benzene showed a sequential activation of the C–D bonds of the solvent at each Pt–OH moiety to produce the diphenyl complex and water (**Scheme 49**) [82]. The C–D bond activations observed were largely mediated by Pt(0) particles, as the speculated conversion of *bis*-hydroxo Pt(II) complex to its deuterated derivatives takes place through different pathways and mechanisms. In dilute solution, the bis-hydroxy Pt complex slowly converted into the product *via* an electrophilic substitution (ES) mechanism, which was strongly inhibited by the by-product (water). On the other hand, in concentrated samples, the conversion was catalyzed by elemental Pt(0) particles and was found to be faster than the ES mechanism.
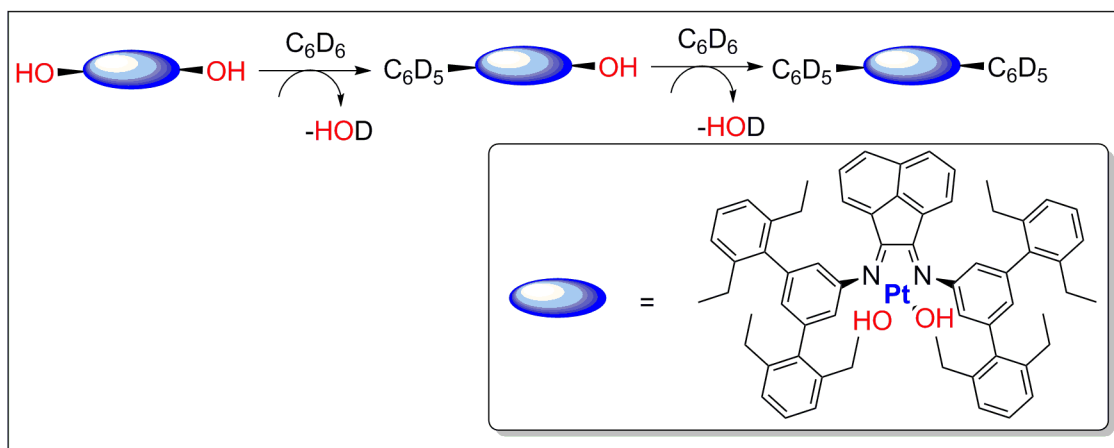
To determine the basicity of selectivity of C−H bond activation of anisole by electrophilic methyl Pt(II) complexes, a study has been reported by Puddephatt and co-workers [83]. When the Pt(II) complex reacts with anisole in TFE, it produces methane as the major product (90%) with two minor anisyl complexes (10% collectively). Competitive study of the anisole with the deuterated counterpart gave an isotope effect kH/kD = 3.6. The authors concluded that the anisole C−H bond cleavage step in anisole activation, or the anisyl−H bond-forming step in protonolysis, was responsible for the selectivity in these reactions. Recently, Love et al. [84a] reported Pt(II)-catalyzed methylation of imine (**Scheme 50**). During the C–H activation of methylated imine products, the presence of a 6-membered platinacycle was noted by the authors. Interestingly, they also found that in some cases, C(sp^3)−H activation was preferred over C(sp^2)−F activation. Furthermore, preferential activation of the methyl C(sp^3)−H bond to

form a 6-membered metalacycle rather than activation of a C(sp^2)−H bond was also reported. The reason for selectivity was attributed to the preferred endo-metalation over exo-metalation [84]. Further, the presence of two *ortho* methyl groups was also found to affect the selectivity as two methyl groups were found to act as barriers to C–F activation.
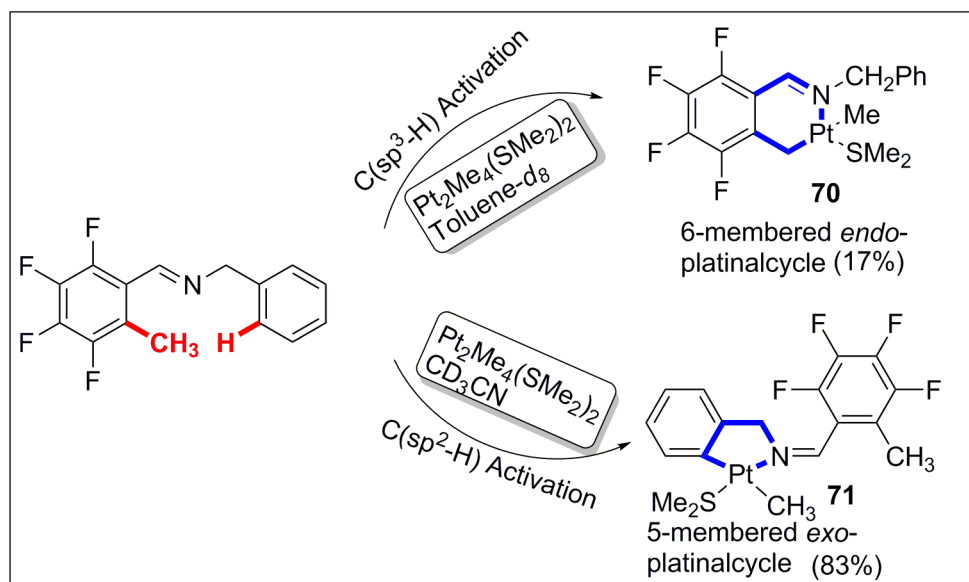
A rare C–H bond activation followed by C−C bond cleavage has been reported using Pt-triflimidate pre-catalysts (**Scheme 51**) [85]. The authors, based on different analytical results, proposed that the initial C−H activation of the substrate led to carbocation generation and rearrangement to break two C−C bonds followed by catalytic releases of a bicyclic product (1,2,4,7,7a-pentahydroindene). A minor change in the chemical structure of catalyst led to large variation in results. For example, in some cases, the reaction gave satisfactory yield within a few minutes, while in some cases the reaction was incomplete even after a month. Similarly, the reaction was found to proceed well in aromatic polar solvents (94% yield in *o*-dichlorobenzene), while it failed in coordinating solvents. Overall, under optimized conditions, 87% yield was achieved after 1 h at 70 °C in *o*-dichlorobenzene. It was also reported that the catalysis required a single open coordination site at the Pt center. The catalytic cycle for this reaction involves the following steps: (i) initiation involving the displacement of NTf$_2^−$ by neutral cyclopropane substrate at the Pt center forms the cationic Pt olefin complex **A**, (ii) C−H activation at C9 yields the cationic Pt(IV) alkyl hydride complex **B**, (iii) generation of

carbocation **C** by acidic proton transfers from the Pt center to the pendent olefin moiety, (iv) conversion of **C** into **D** or **E** by cyclopropane ring-opening to the carbocationic center, (v) if **D** is formed, it again undergoes rearrangement to give **E**, (v) breaking of C2−C3 bond in **E** forms the product complex **F** and (vi) elimination of Pt introduces double bond character to the C9−C2 and C3−C7 bonds (**Figure 8**).
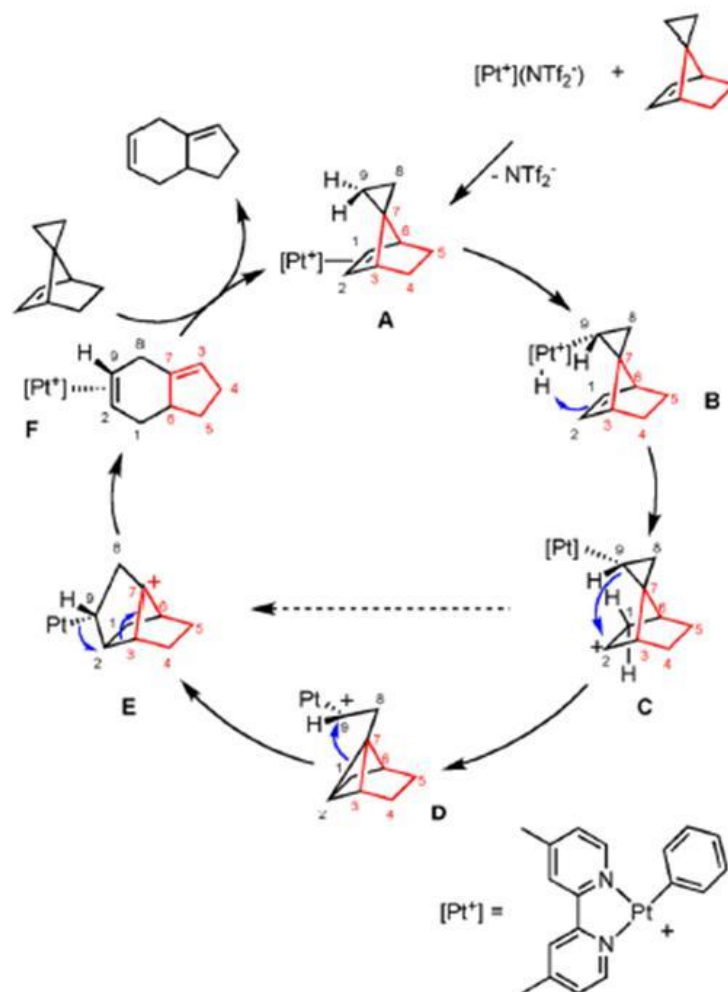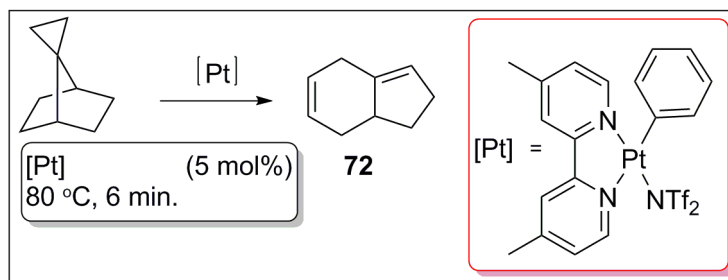
Figure 8: Possible pathways for the catalytic rearrangement of spiro[bicyclo[2.2.1]hept-2-ene-7,1'-cyclopropane] to 1,2,4,7,7a-pentahydroindene ("Reprinted with permission from M.A. Bowring, R.G. Bergman, T.D. Tilley, J. Am. Chem. Soc. 135 (2013) 13121−13128 [ref. 85]. Copyright (2015) American Chemical Society).

The reductive elimination reaction is often the product-forming step in both catalytic cycles and stoichiometric transformations leading to formation of C−C, C−H, or C−X bonds [86]. Pt(IV) species are compounds known to readily undergo reductive elimination, often ...... initial loss of a ligand to generate a five coordinate intermediate [86]. Such a reductive elimination reaction of the cyclometalated Pt(IV) compounds was reported by Calvet and co-workers [86]. They reported a selective elimination reaction to produce $C(sp^3)−C(sp^2)$ coupling followed by cyclometalation and subsequent loss of methane (**Scheme 52**). During the metalation, $C(sp^2)−H$ bond activation was observed for compound containing a smaller SMe_2 ligand while competition between $C(sp^2)−H$ and $C(sp^3)−H$ bond activation was observed for the bulkier triphenylphosphine analogue [86].
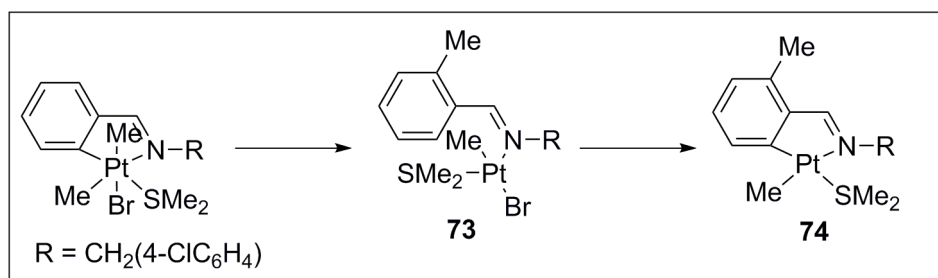
Although *ortho*-platinated benzylamine complexes are highly stable both in the solid state and in solution, an interesting activation of the γ-H on the chiral phenylamine auxiliary has been reported in the presence of excess of Pt(II) ions (**Scheme 53**) [87]. However, no product was obtained in the absence of external Pt ions. The reaction involved the activation of an aromatic proton which resulted into a new C−C bond formation between the aromatic γ-C of the *ortho* platinated chiral phenylamine and the α-C of the alkynyl phosphine ligand and formed a new six-membered P-C chelate. The mechanistic studies indicated that the P → Pt bonds remain kinetically inert throughout the coupling reaction, which, in turn proceeds *via* a reaction mechanism in which both the *ortho* platinated benzylamine and the Ph_2P moiety remained coordinated to the same Pt

ion throughout the course of the coupling reaction. Overall, the reaction involved the activation of an aromatic proton adjacent to the Pt−C bond and the formation of a vinylidene intermediate, which also triggered the unexpected migration of the P−C bonds during the coupling reaction.
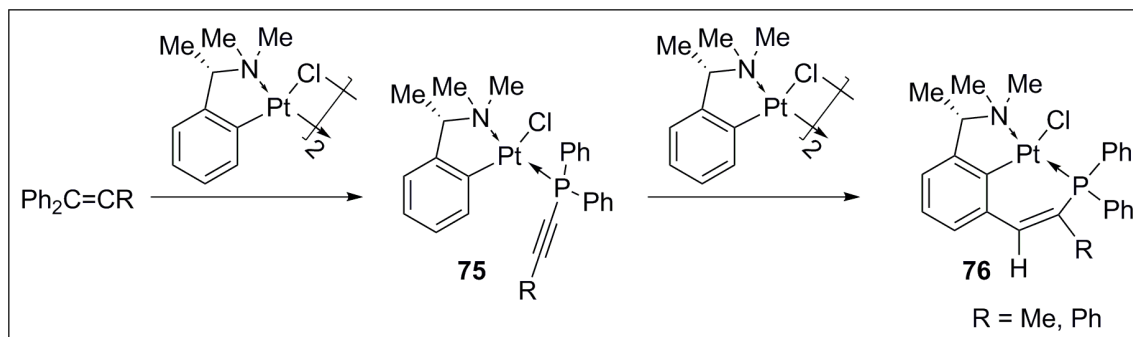
A regiospecific activation of C(naphthyl)–H bonds in a group of naphthylazo-2'-hydroxyarene ligands was also reported using allyl Pt(II) complex $[(\eta^3\text{-}C_4H_7)Pt(\mu\text{-}Cl)]_2$ [88]. In this system, the position of the primary donor (diazene group) controlled the sites of metalation. For instance, C2(naphthyl)–H bond activation has been achieved when the diazene group was at the C1 position. Contrary to this, C3(naphthyl)–H bond activation has been observed when the primary donor was attached to the C2 atom. These differences in regiospecificity were attributed to the formation of five-membered carboplatinacycle ring formation followed by N,O-chelation. Solvents such as benzene, toluene, and *ortho*-, *meta*-, and *para*-xylene, considered as "*innocent*" solvents were found to undergo "formal insertion" *i.e.* intermolecular C–H activation leading to C−C coupling through seven membered metalacycles to produce metalated biaryls during the reaction of Pt(II) compounds and imines (**Scheme 54**) [89]. The stability of the platinacycle was found to depend upon the steric hindrance (arene methyl) and basicity (imine nitrogen) as the order of stability *p*-xylyl < *m*-xylyl < *o*-xylyl < tolyl < phenyl. Furthermore, the presence of C−Cl bonds in the *ortho* positions of the imine plays a crucial role in the process that takes place through a Pt(IV) intermediate. Overall, this is a general procedure for C−C coupling arising from intermolecular C–H activation of arene solvents.
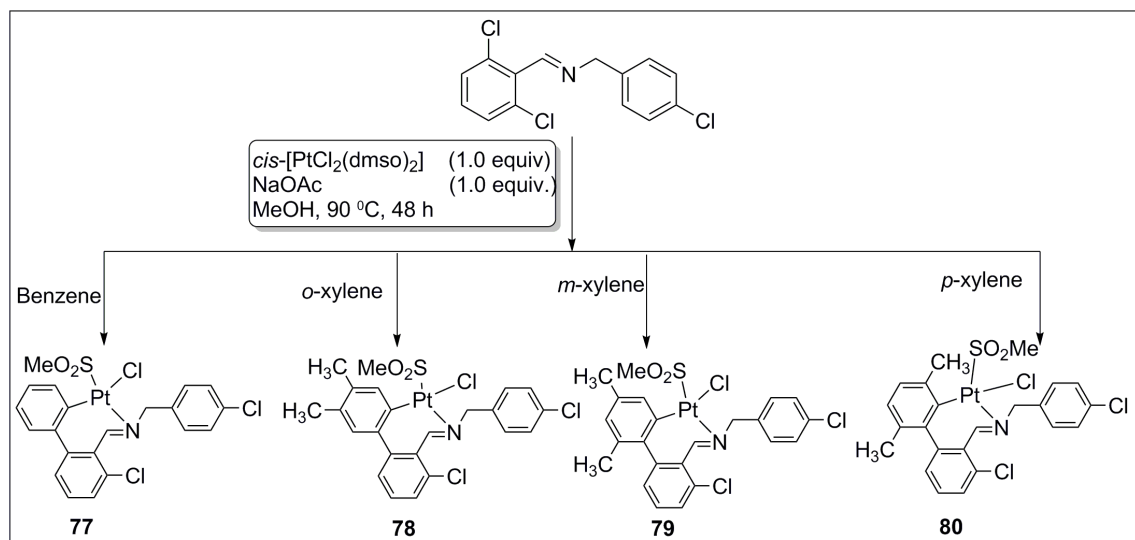
One can change the steric and electronic properties of Pt complexes containing NHC ligand by modifying the environment around the ligand. Conejero et al. [90] found that by doing so, an intermolecular C–H bond activation can be achieved in some arenes. When they used unsaturated 14-electron, T-shaped NHC-modified Pt(II) catalyst, C–H bond activation in benzene, toluene and other fluoro aromatic compounds was found in regioselective manner. In such a system, C–H bond activation processes proceed through oxidative addition and reductive elimination mechanisms *via* unstable Pt(IV) intermediates. Site selectivity controlled by steric factors was also observed in the C–H arylation of arene substrates with diaryliodonium salts using Na_2PtCl_4 (**Scheme 55**) [91]. This method could be used to couple naphthalene with a variety of substituted aryliodonium salts. Interestingly, the arylation of naphthalene using Pt catalyst takes place at the site opposite to site arylated by Pd catalyst. According to the authors, it was the first report of arylation of simple arenes in which intermolecular Pt(II/IV) catalytic cycle takes place. Furthermore, the kinetic study shows that neither oxidation nor C−H cleavage was the rate-determining step, instead C−C bond-forming reductive elimination was the rate-limiting step.

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R-⟨benzene⟩ + [Ar₂I]TFA →[Pt] R-⟨benzene⟩-Ar

81

Na₂PtCl₄ (2.5-5.0 mol%)
TFA/AcOH (0-32 equiv.)
Bu₄NOTf, 100-120 °C, 72 h
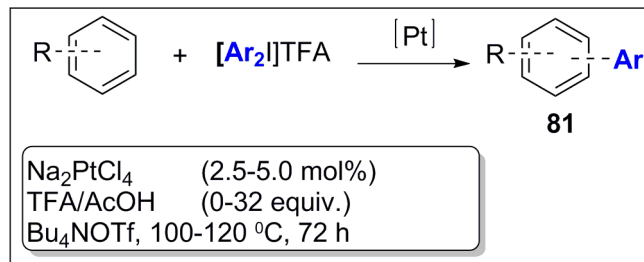
4. Future outlook and challenges

Based on the facts presented in this review, it is worthwhile saying that transition metal-based catalysts have a bright future, especially for group 10 metal-based catalysts. This is due to their versatility and compatibility in both homogenous and heterogeneous catalysis. Many findings are being reported for the activation and functionalization of simple aromatics, heteroaromatics, alkane etc. New functional groups can be installed and biphenyl moieties can be cyclized simply using group 10 metal catalysts with air as the oxidant. Several pharmaceutically important alkaloid moieties can be functionalized, which have given opportunity to the medicinal chemists to develop a library of compounds. With the aid of catalysts, syntheses of compounds bearing anti-tubercular and anti-malarial properties have also been accomplished. Furthermore, indoline that is an important component of vinca alkaloids has also been synthesized. The increasing demand for low cost, efficient energy sources is creating an immense pressure on the scientific communities to develop alternative energy sources. In this context also, C–H activation and functionalization is proving promising. New laboratory methods are being reported for the functionalization of alkanes. *Double* and *triple* C–H activation using this series of metal catalyst are fascinating and attracting the interest of researchers worldwide. Additionally, methods are being reported in which C–H activation led to the activation of C–C bonds, which in turn is in high demand [85]. In the majority of the reactions, the leaving group is either water or carbon dioxide, which is environmentally benign. The computational study is also playing an important role in this field by helping us to understand the mechanistic pathways. However, some challenges still remain and need to overcome. The main problems associated with this field are the development of more general methods for asymmetric catalysis, C–H functionalization to complex, multi-functional substrates [3] and practical conversion of transformed alkanes to value-added

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products cost-effectively [14a]. Furthermore, most of the reported methods were carried out in harsh conditions. Also the requirement for the use of stoichiometric amounts of expensive and/or moisture-sensitive organometallic coupling partners leads to the generation of stoichiometric amounts of often-toxic metal wastes [11b, 34]. These are some of the major drawbacks of the use of transition metal-based catalytic systems, which should be addressed.

5. Conclusion

In conclusion, we have reviewed some of the recent studies on the catalytic application of group 10 metals in C–H activation. These catalysts are important in terms of industrial applications, as many pharmaceutically active agents can be synthesized using these metal catalysts. Furthermore, new methods are being reported for the conversion of alkane to alcohols.

Acknowledgements

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