1

History of Directed C—H Bond Activation and its Discovery

Susmita Mondal[1,], Sumit Ghosh[2,*], Asim Kumar Ghosh[2], and Alakananda Hajra[2]*

[1] *Department of Chemistry, Central Ayurveda Research Institute, 4-CN Block, Bidhannagar, Kolkata, 700091, West Bengal, India*
[2] *Department of Chemistry, Visva-Bharati (A Central University), Santiniketan, 731235, West Bengal, India*

1.1 Introduction

C—H Functionalization is a groundbreaking technique in synthetic organic chemistry that allows the direct transformation of C—H bonds into C—C or C—X (X = heteroatom) bonds [1]. However, regioselective functionalization of C—H bonds is a highly challenging task due to its ubiquitous nature [2]. Thus, in past decades, pre-functionalization was performed on starting molecules for further functionalization [3]. Within this realm, transition metal-catalyzed C—H bond activation for the construction of C—C and C—X bonds is one of the most significant and challenging fields of research due to its more research-laboratory-friendly conditions, high efficiency, and selective C—H functionalization [4]. A molecular complex can be built from readily available simple hydrocarbon counterparts by using this strategy [5]. Therefore, functional-group-assisted site-selective C—H bond activation for functionalization shows great promise to researchers. The coordination of transition metal catalysts with the directing group controls the site selectivity of the reaction. The pioneering work in the field was reported by Lewis and Murai in 1986 who reported regioselective mono- and di-*ortho*-alkylations of phenol with ethylene, which proceed through the formation of ruthenium phosphite complex [6]. After that, various directing group-assisted chelation-controlled C—H activation strategies have been developed for the incorporation of various functional groups like amide, anilide, imine, heterocyclic, amine, carboxylic acid, ester, ketone, and hydroxyl [7]. There are mainly two types of directing group-assisted C—H functionalizations: one is the built-in directing group-assisted C—H bond functionalization and another is the removable directing group-assisted C—H bond functionalization. The built-in directing group is already present in the functionalized molecule; thus, it reduces the step economic issue, whereas the

*These authors have first authorship and have equal contribution.

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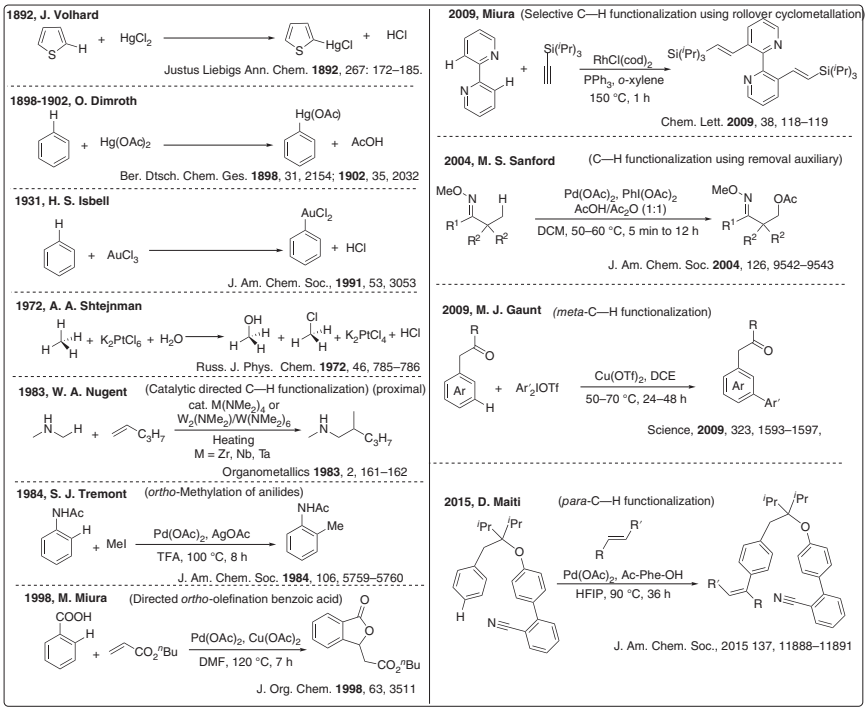


Figure 1.1 Schematic representation of the evolution of C–H activation.

removal directing group may be pre-installed or installed *in situ* in a molecule to achieve a favored coordination with the metal for selective C—H bond functionalization. In the former directing group, there is a possibility of unprecedented reactions due to the weak coordination ability to a metal, but the removal directing group has an optimum coordinating ability toward the metal catalyst and is widely used for the functionalization of a non-biased C—H bond.

Therefore, a brief overview on the history of directed C—H functionalization is much needed. Our group has also worked on directed C—H functionalization [8]. In this chapter, we have presented a strategic evaluation of directing group-assisted selective C—H bond functionalization via C–H activation. We have included early discoveries on stoichiometric metal-promoted proximal C—H bond activation, directing group (both built-in functional group and removal directing group)-assisted catalytic proximal C—H bond functionalization, and directing group-assisted distal (both *meta* & *para*) C—H bond activation in this chapter. Figure 1.1 represents the historical evolution of C—H bond activation.

1.2 Importance of C–H Activation

C—H Bond activation allows the synthesis of compounds without the requirement of pre-halogenated or pre-functionalized starting materials, which are typically

required in traditional methods; hence, this approach is more environmentally friendly. On the other hand, C—H bond activation simplifies the synthetic process by reducing the number of steps needed. It also allows for the direct functionalization of hydrocarbons, which are the primary raw materials derived from oil and natural gas used in the chemical industry. Not only that, it has a significant interest in late-stage modification in the pharmaceutical and material industries.

1.3 Early Discoveries in Stoichiometric Metal-promoted Proximal C—H Bond Functionalization

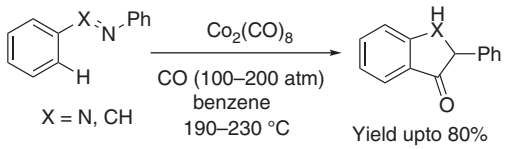
In 1937, A. Farkas and L. Farkas first discovered the interaction between a C—H bond and a transition metal during the catalytic exchange of benzene and D_2 on a platinum foil [9]. After that, Garnett [10] and Parshall [11] also reported the metal atom interaction with either aromatic or aliphatic C—H bond. These discoveries inspired researchers to activate unreactive C—H bonds for functionalization purposes. In this regard, in 1955 and 1956, Murahashi and Horiie [12] carried out Co-promoted C—H carbonylation with carbon monoxide of a Schiff base and azobenzene, respectively (Scheme 1.1a). The following two reactions proceeded through the formation of a five-membered cobaltacycle. After that, a number of research groups were actively involved in the carbonylation of different moieties via C—H bond activation. In 1958, Rosenthal et al. [13] reported Co-promoted *ortho*-carbonylation of benzophenone oxime (Scheme 1.1b), and Bagga et al. [14] developed Fe-promoted carbonylation of a Schiff base (Scheme 1.1c). Other metallacycles like nickelacycle [15], ferrocycle [16], platinacycle [17], and palladacycle [17] (formed from corresponding metal complexes with the interaction of *N*-atom of organic core) have been isolated, which may serve as a directing group for C—H functionalization via the activation of a C—H bond. In this connection, Fahey group [18] used palladacycles formed from the reaction of azobenzene and $PdCl_2$ for halogenation (chlorination and bromination) of azobenzenes (Scheme 1.1d). Komiya group [19] used a ruthenium hydride complex for the deuteration of a C—H bond with DCl (Scheme 1.1e).

1.4 Directing Group-assisted Catalytic Proximal C—H Bond Functionalization

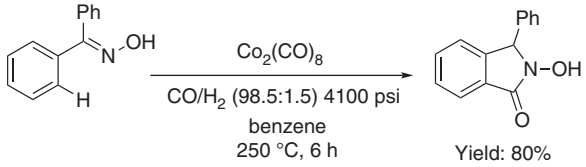
1.4.1 In-built Functional-Group-directed Proximal C—H Bond Functionalization

In the previous section, we have discussed transition-metal-complex-mediated C—H bond activation for functionalization. Meanwhile, catalytic-directed C—H activation was first done by Nugent et al. [20] in 1983, who reported C—H bond activation of dimethylamine for alkylation with alkenes using a metal dimethylamide precursor (Scheme 1.2).

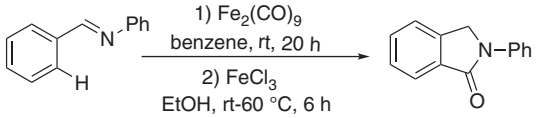
(a) Co-promoted C—H carbonylation of a Schiff base and azobenzene by Murahashi et al.



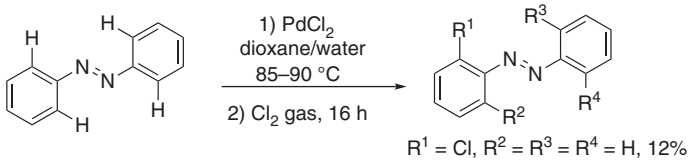
(b) Co-promoted ortho-carbonylation of benzophenone oxime by Rosenthal et al.



(c) Fe-promoted carbonylation of a Schiff base by Bagga et al.

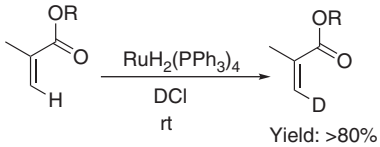


(d) Chlorination of azobenzene by Fahey et al.

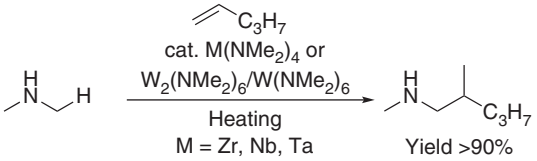


R^1 = Cl, R^2 = R^3 = R^4 = H, 12%
R^1 = R^3 = Cl, R^2 = R^4 = H, 30%
R^1 = R^2 = R^3 = Cl, R^4 = H, 33%
R^1 = R^2 = R^3 = R^4 = Cl, 3%

(e) Ruthenium hydride complex promoted euteration of a C—H bond with DCl by Komiya group

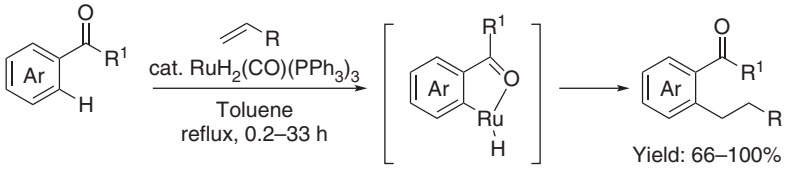


Scheme 1.1 Pioneering reports on directed C–H functionalization reactions.



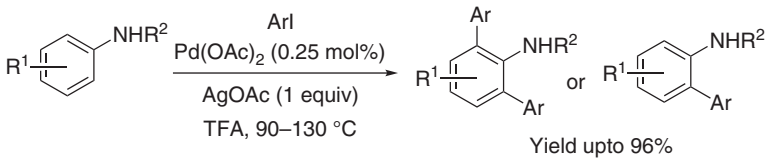
Scheme 1.2 C–H bond activation of dimethylamine for alkylation.

One of the essential catalytic C—H activation reactions was reported by Murai et al. [21] in 1993 (Scheme 1.3). They used a ketone as a directing group for the regioselective *ortho*-C—H alkylation of aromatic ketones with alkenes. The reaction proceeds through a metallacycle, which was the key intermediate of the reaction.



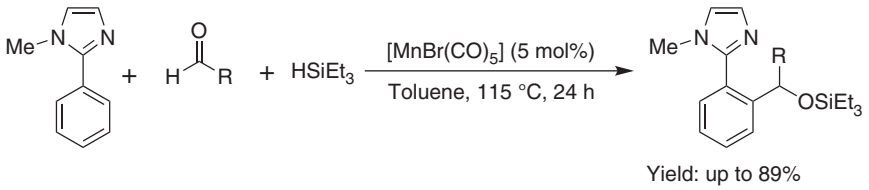
Scheme 1.3 Regioselective *ortho*-C—H alkylation of aromatic ketones.

After that, numerous research works have been published on this field using various functional groups as directing moiety, such as carbonyl, amine, amides, hydroxyl, carboxylic acid, and sulfonic acid derivatives. Daugulis and Zaitsev [22] reported palladium-catalyzed *ortho*-arylation (both mono- and di-) of anilides using amide as a directing group and aryl iodides as an arylating agent in 2005 (Scheme 1.4). The method is highly tolerant to functional groups showing up to 1000 turnovers for this reaction.



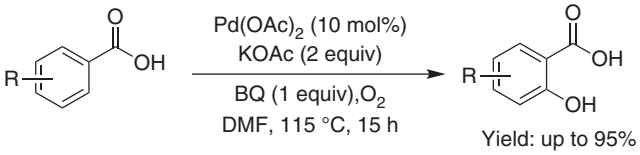
Scheme 1.4 Palladium-catalyzed *ortho*-arylation of anilides.

Kuninobu et al. [23] developed a method for direct aryl C—H addition to aldehyde using *N*-containing directing group in the presence of 5 mol% [$MnBr(CO)_5$] in toluene (Scheme 1.5). This present protocol could be applied for asymmetric transformation using an aromatic compound with a chiral substituent.



Scheme 1.5 Mn-catalyzed remote C—H addition to aldehyde.

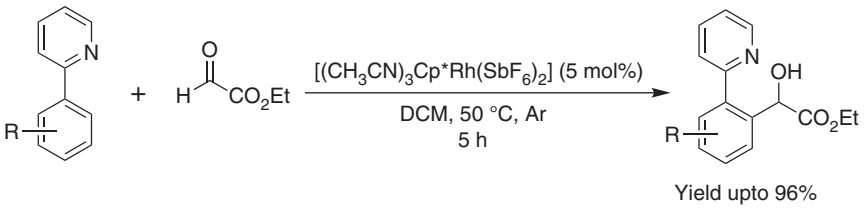
In 2009, Zhang and Yu [24] developed a versatile method for *ortho*-hydroxylation of benzoic acids using Pd catalyst under O_2 atmosphere (Scheme 1.6). Mechanistic investigations suggested that direct oxygenation took the place of aryl-Pd species



Scheme 1.6 Pd-catalyzed *ortho*-hydroxylation of acid derivatives.

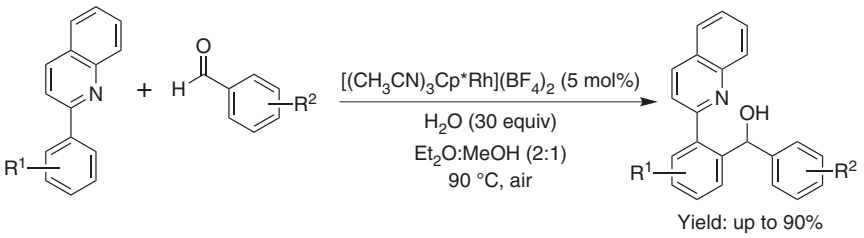
from molecular O_2. A wide range of functional groups were well tolerable in the reaction.

Rhodium-catalyzed Grignard-type arylation of activated aldehyde was described by Li and co-workers [25] in 2011 (Scheme 1.7). Remote C—H addition of activated aldehyde occurred at the *ortho*-position of the phenyl ring of 2-phenyl pyridine derivatives assisted by pyridine ring in the presence of 5 mol% $[(CH_3CN)_3Cp^*Rh(SbF_6)_2]$.



Scheme 1.7 Arylation of activated aldehyde.

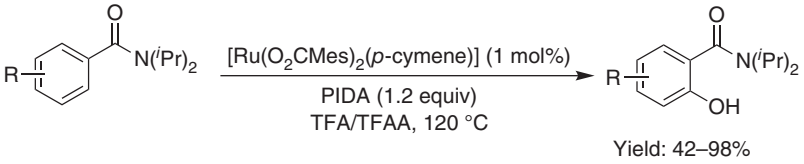
The following year, Shi and co-workers [26] also reported *N*-directing group-assisted remote aryl C—H addition to activated aldehydes to produce biaryl methanols in the presence of Rh(III) catalyst (Scheme 1.8). The present reaction is compatible with water and air.



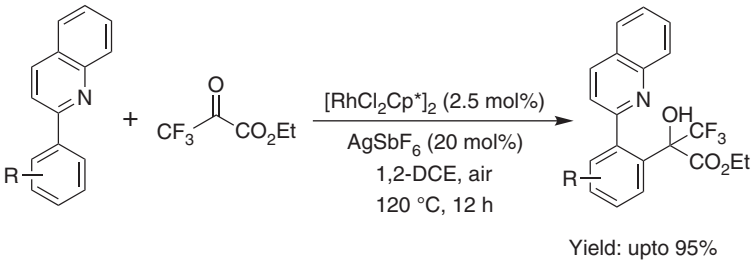
Scheme 1.8 C–H addition of 2-arylquinolines to activated aldehyde.

In the same year, Ackermann and co-workers [27] reported ruthenium-catalyzed remote C—H hydroxylation of benzamide derivatives using PIDA as an oxidant in trifluoroacetic acid/trifluoroacetic anhydride (TFA/TFAA) solvent mixture using Ru-catalyst (Scheme 1.9).

Shi and co-workers [28] described a Rh-catalyzed direct intermolecular aromatic C—H bond nucleophilic addition to ketones directed by quinoline (Scheme 1.10). A wide variety of quinoline derivatives were well tolerable in this transformation.

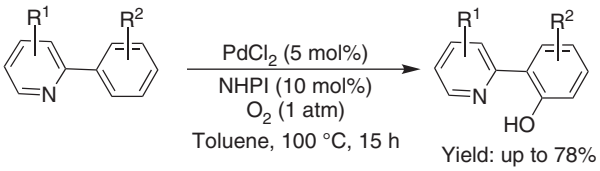


Scheme 1.9 Ruthenium-catalyzed hydroxylation of benzamides.



Scheme 1.10 Rh(III)-catalyzed remote C–H addition to ketones.

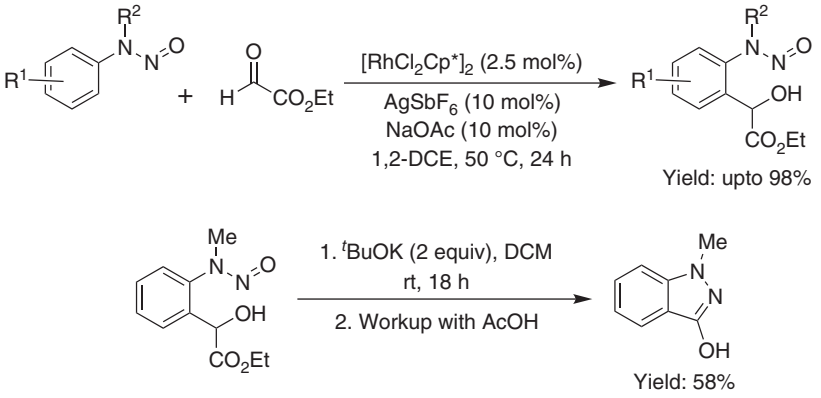
In 2013, Jiao and co-workers [29] described a direct C(sp^2)—H hydroxylation of 2-phenylpyridines using $PdCl_2$ as a catalyst and *N*-hydroxyphthalimide (NHPI) as a co-catalyst in toluene at 100 °C (Scheme 1.11). They used molecular O_2 as a green oxidant. Here, pyridine ring acted as a directing group for the C-2 hydroxylation of arenes. A variety of 2-phenylpyridines underwent reaction under optimized reaction conditions and produced desired products in moderate-to-good yields.



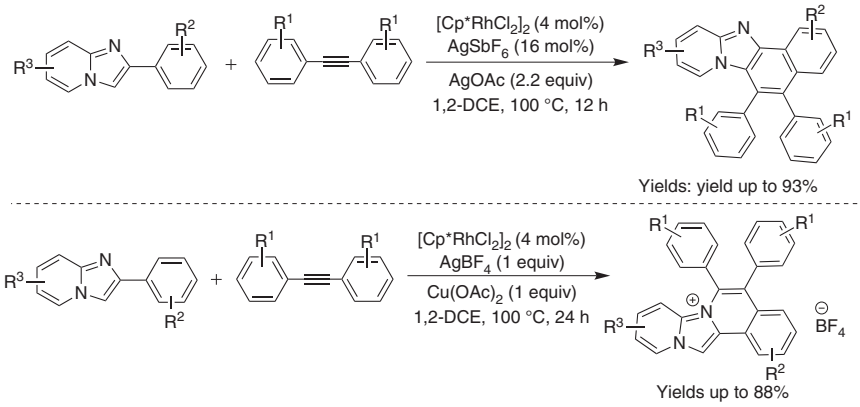
Scheme 1.11 Pyridine-directed hydroxylation of arenes.

The following year, Zhu and co-workers [30] described Rh(III)-catalyzed *N*-nitroso-directed C—H addition to ethyl-2-oxoacetate at the *ortho*-position of *N*-nitrosoaniline derivatives (Scheme 1.12). They also synthesized indazoles from the ethyl 2-hydroxy-2-(2-(methyl(nitroso)amino)phenyl)acetate derivatives via intramolecular cycloaddition.

Rh(III)-catalyzed divergent C—H activation of 2-phenylimidazo[1,2-*a*]pyridines with alkynes has been described by Li and co-workers [31] in 2015 (Scheme 1.13). Selective mono vs twofold C—H activation has been attained by using 4 mol% $[Cp^*RhCl_2]_2$. In the presence of AgOAc, 5,6-disubstituted naphtho[1′,2′:4,5]imidazo [1,2-*a*]pyridines were obtained by the chelation-assisted C—H activation at the benzene ring followed by rollover C—H activation. In addition, the reaction afforded a fused isoquinolinium via C—C and C—N coupling employing $AgBF_4$ as a co-oxidant.

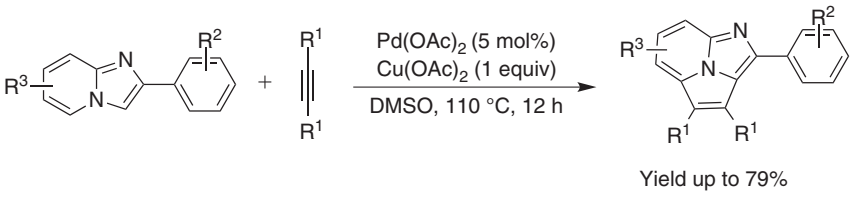


Scheme 1.12 Rh(III)-catalyzed remote C–H addition to ethyl 2-oxoacetate.



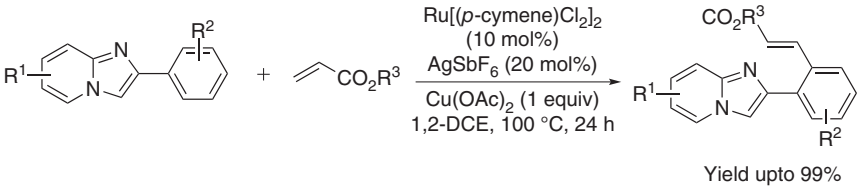
Scheme 1.13 Rh(III)-catalyzed C–H activation of 2-phenylimidazo[1,2-*a*]pyridines.

In 2015, Hajra and co-workers [32] reported a Pd-catalyzed direct dehydrogenative annulation of imidazo[1,2-*a*]pyridines with diarylalkynes through dual cleavage of C—H bonds (Scheme 1.14). This protocol provides a straightforward route for the synthesis of π-conjugated polyaromatic heterocycles from readily available imidazo[1,2-*a*]pyridines. A variety of 2,3,4-triarylphenyl-1,7*b*-diaza-cyclopenta[*cd*] indene derivatives were obtained in high yields by this protocol.



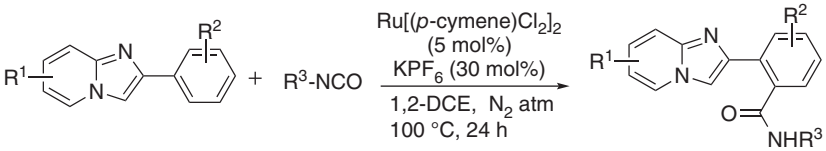
Scheme 1.14 Pd-catalyzed dehydrogenative annulations of imidazopyridines.

In 2015, Sawant's research group [33] described the Ru-catalyzed alkenylation of 2-phenylimidazo[1,2-*a*]pyridine with an alkene to give *ortho*-monoalkenylated products in good yields (Scheme 1.15). The reaction was performed with $[RuCl_2(p\text{-cymene})]_2$ in the presence of $AgSbF_6$ and $Cu(OAc)_2{\cdot}H_2O$ in 1,2-DCE at 100 °C for 24 hours. The reaction proceeded regioselectively through *ortho*-C—H bond activation via the formation of a five-membered ruthenacycle intermediate.



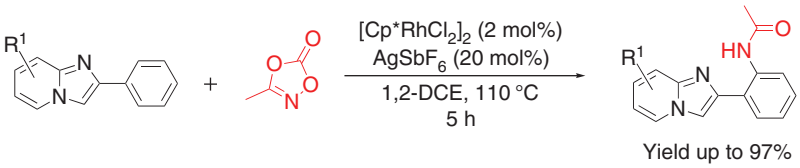
Scheme 1.15 Ruthenium-catalyzed alkenylation of 2-phenylimidazo[1,2-*a*]pyridine.

In 2016, Sakhuja and co-workers [34] developed a convergent and efficient methodology for the regioselective synthesis of *ortho*-amidated imidazoheterocycles via a facile $C(sp^2)$—H bond functionalization with aryl isocyanates employing $[Ru(p\text{-cymene})Cl_2]_2$ and KPF_6 in catalytic amounts (Scheme 1.16). A library of *ortho*-amidated 2-arylimidazo[1,2-*a*]pyridine derivatives with broad functionalities was synthesized in moderate-to-good yields. This present protocol could be applied for other imidazo-fused heterocycles such as imidazo[2,1-*b*]thiazole, benzo[*d*]imidazo[2,1-*b*]thiazole, and imidazo[1,2-*a*]pyrimidine.



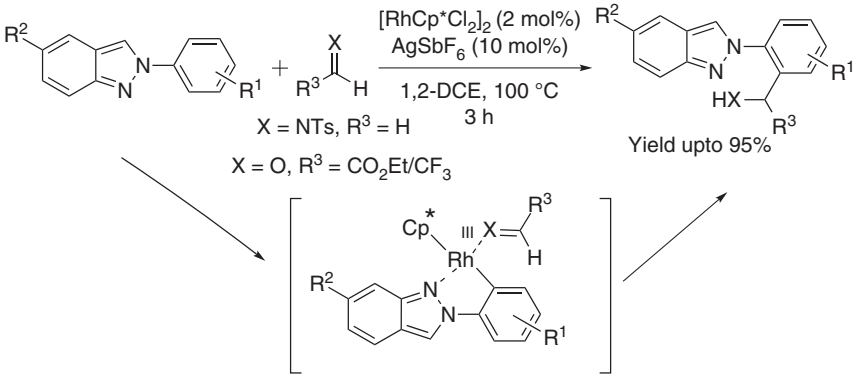
Scheme 1.16 Ru(II)-catalyzed *ortho*-amidation of imidazoheterocycles with isocyanates.

In 2019, Hajra and co-workers [35] reported a rhodium-catalyzed *ortho*-selective C—H amidation reaction of 2-arylimidazoheterocycles with dioxazolones to afford *N*-(2-(imidazo[1,2-*a*]pyridin-2-yl)phenyl)acetamide derivatives through C—H activation (Scheme 1.17). A variety of acetamide derivatives was formed in good-to-excellent yields.



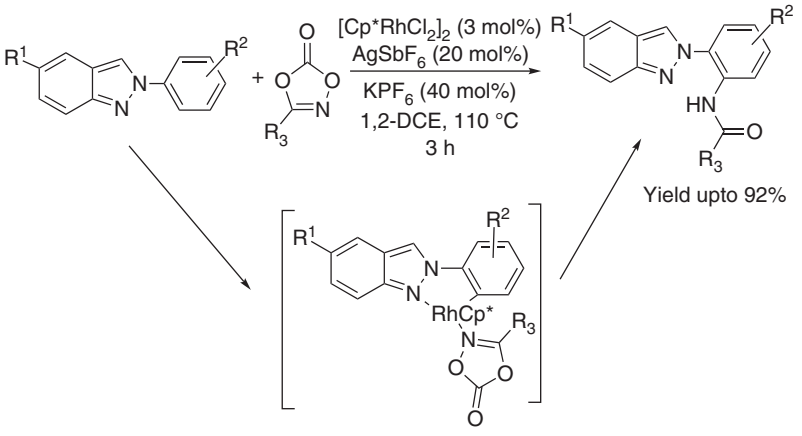
Scheme 1.17 Rhodium-catalyzed *ortho*-selective C—H amidation reaction of 2-arylimidazoheterocycles.

In 2020, Hajra and co-workers [36] reported $[Cp^*RhCl_2]_2$-catalyzed directed C—H functionalization of 2-arylindazoles with *N*-sulfonylformaldimines and activated aldehydes like ethyl glyoxalate and 2,2,2-trifluoroacetaldehyde (Scheme 1.18). A variety of *N*-benzylarylsulfonamide derivatives and hydroxyl derivatives were produced under optimized reaction conditions with good-to-excellent yields. The present protocol is also applicable in large-scale synthesis. To establish the mechanistic pathway of the reaction, they performed kinetic isotopic effect studies, which suggested that C—H activation step may be the rate-limiting step of the reaction.



Scheme 1.18 Rhodium-catalyzed C–H functionalization of 2-arylindazoles with *N*-sulfonylformaldimines.

In the same year, the same group [37] also developed an efficient protocol for the rhodium-catalyzed directed *ortho*-C—H amidation of 2-arylindazoles (Scheme 1.19). A variety of 2-arylindazoles underwent reaction effectively with a wide range of dioxazolones having alkyl, aryl, and heteroaryl functionalities



Scheme 1.19 Rhodium-catalyzed C–H amidation of 2-arylindazoles.

to form a series of *N*-(2-(2*H*-indazol-2-yl)phenyl)acetamide derivatives in excellent yields. To show the synthetic applicability of the reaction, they hydrolyzed the amide derivatives to amines by using 10 mol% KOH as a hydrolyzing agent. Mechanistic experiments suggested that C—H bond cleavage may be the rate-determining step of the reaction.

1.4.2 Removable Directing Group-assisted Proximal C—H Bond Functionalization

For removable directing group assisted C—H bond activation, a removable directing group must be installed in the substrate molecule, which involves chelation with the metal center activating one position of the substrate. After completing the reaction, the directing group can be removed without any difficulties. Now, this strategy has been extensively used by scientists due to its high efficacy. In this regard, in 1972, Breslow group [38] made selective C—H abstraction of 3α-cholestanol, using benzophenone moiety, connected through an ester linkage as a removal directing group. There are three main categories of removable directing groups: (i) pre-installed and post-removable directing groups, (ii) traceless directing group, and (iii) transient directing group. All these three categories are elaborately explained below.

1.4.2.1 Pre-installed and Post-removable Directing Groups-assisted C—H Bond Activation

In this activation process, two additional steps for installation and removal of directing group are required to achieve a selective C—H activation. The most explored designed bidentate directing groups are quinoline-, oxazole-, pyrazole-, pyridine-, triazole-based directing groups having an *N*,*N*-coordinating site for metal coordination; pyridine *N*-oxide-, oxalyl amide-, amino-acid-based directing groups having *N*,*O*-coordinating sites; and thiomethyl aniline-, sulfinyl aniline-based directing groups having *N*,*S*-coordinating sites, which are shown in Figure 1.2.

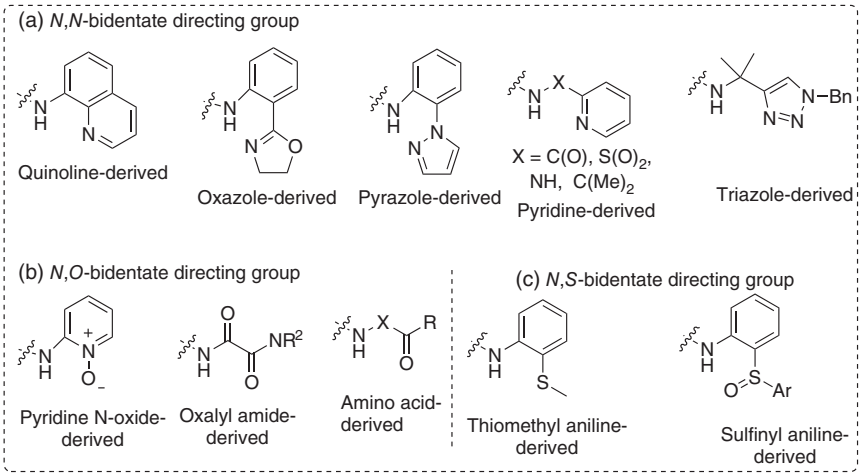
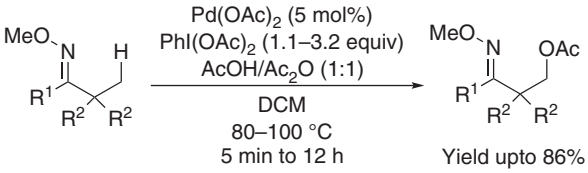


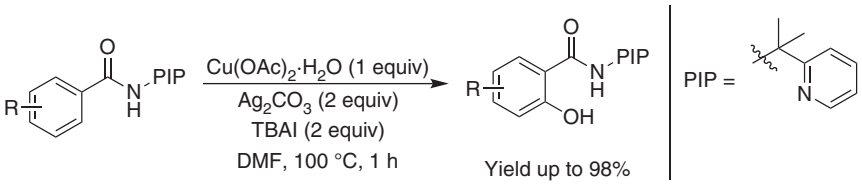
Figure 1.2 Some bidentate directing group.

One of the early examples on this topic was reported by Sanford and co-workers [39] in 2004. They carried out the Pd(II)-catalyzed acetoxylation of unactivated sp^3-C—H bond of ketone derivatives using an oxime moiety as a removable directing group (Scheme 1.20). In this method, $PhI(OAc)_2$ was used as a stoichiometric oxidant.



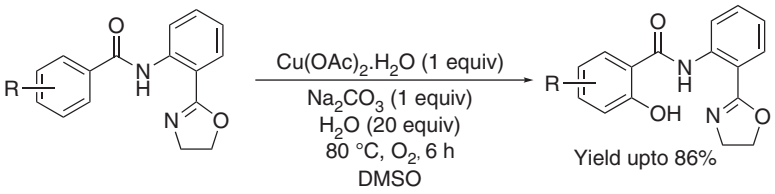
Scheme 1.20 Pd(II)-catalyzed acetoxylation of ketone derivatives.

In 2005, Yu and co-workers [40] reported that oxazole, which was prepared from the parent acid, can also serve as a directing group for the functionalization of sp^3-C—H bonds of acid derivatives. Considering the significance of removable directing groups, various removable directing groups have now been employed in C—H functionalization reactions of a variety of substrates. Later, Shi group [41] developed copper-mediated C—H hydroxylation of arenes and heteroarenes using a bidentate directing group derived from 2-(pyridine-2-yl)isopropylamine (PIP-amine) (Scheme 1.21). The optimized reaction condition was achieved using 1 equiv $Cu(OAc)_2 \cdot H_2O$, 2 equiv Ag_2CO_3, and 2 equiv TBAI in DMF at 100 °C.



Scheme 1.21 Hydroxylation of arenes.

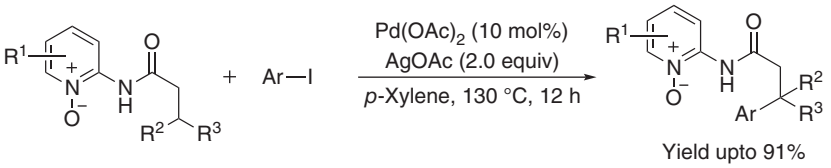
In 2015, Lin and co-workers [42] reported directing group-promoted *ortho*-C—H hydroxylation of aryl C—H bond using Cu(II) catalyst and molecular oxygen as the sole oxidant (Scheme 1.22). The reaction proceeded through the formation of an acetoxylated product.



Scheme 1.22 Cu-catalyzed hydroxylation of arenes.

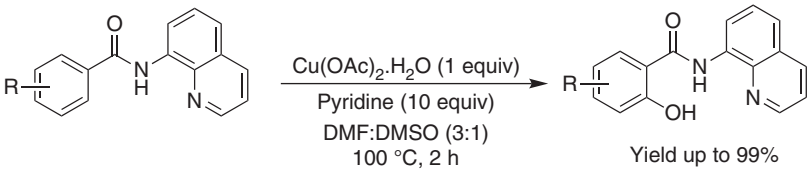
In 2015, Lu and co-workers [43] developed a novel method for arylation of unactivated at β- or γ-Csp^3—H bonds in aliphatic amides with aryl iodides using $Pd(OAc)_2$

as a catatist and pyridine *N*-oxides as a directing group (Scheme 1.23). Here, pyridine N—O$^-$ and amide N—H group was found to play a key chelation-assisted role in activating Csp^3—H bond. The reaction proceeded through the formation of palladabicyclic intermediate, which was confirmed by HR-MS and ^{1}H NMR methods.



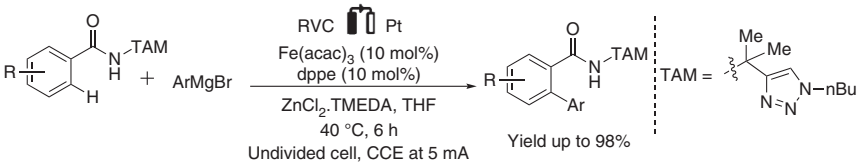
Scheme 1.23 Arylation of unactivated Csp^3—H bonds in aliphatic amides.

The following year, hydroxylation of arenes was also developed by Singh and Jana [44] using 8-aminoquinoline as a directing group, inexpensive copper(II)acetate monohydrate as a catalyst, and pyridine as a ligand (Scheme 1.24). A wide range of functional groups were well tolerable in this transformation.



Scheme 1.24 Direct hydroxylation of arenes.

Iron is the most naturally abundant transition metal in comparison with other precious 5d and 4d transition metals, such as iridium, palladium, and rhodium. In 2019, Ackermann and co-workers [45] reported unprecedented iron-catalyzed C—H activation for arylation through oxidation-induced reductive elimination by electrocatalysis at room temperature (Scheme 1.25). They used a triazole-based removal directing group.



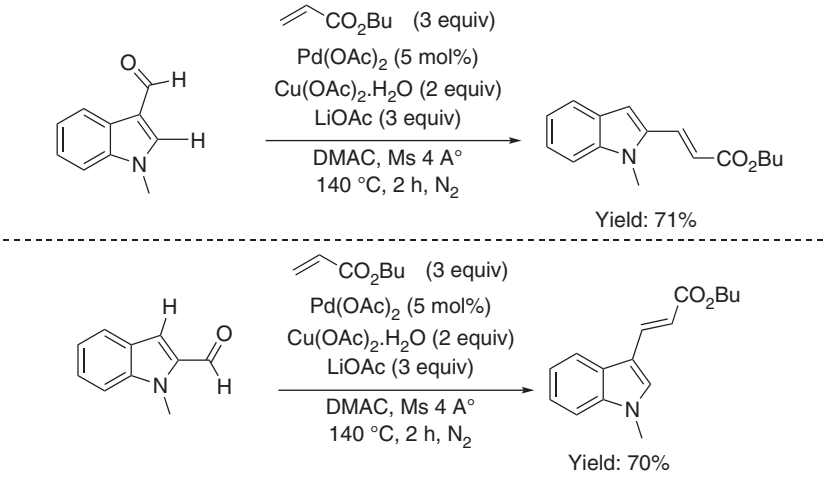
Scheme 1.25 Arylation of acid derivatives.

1.4.2.2 Traceless Directing Group-assisted C—H Bond Functionalization

A traceless directing group is either installed beforehand or is inherently present in naturally or commercially available compounds, which assists in selective C—H bond activation for functionalization and is spontaneously released after completion

of C—H functionalization. In this section, we briefly discuss the discovery of traceless directing group-assisted C—H bond functionalization.

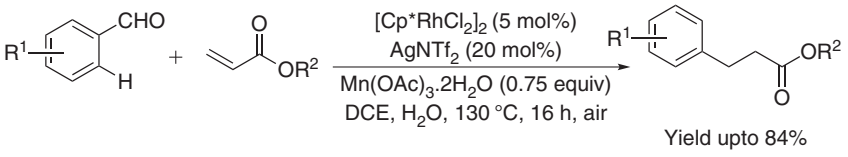
In 2008, Satoh and Miura group [46] first used carboxylic acid moiety as a traceless directing group for the C2- and C3-alkenylation of *N*-substituted indole derivatives using Pd/Cu catalytic system (Scheme 1.26). Protodecarboxylation occurred in one pot under the optimized conditions. Similarly, they also explored the reaction with pyrrole-, furan-, and thiophenecarboxylic acids, and all underwent decarboxylative vinylation efficiently.



Scheme 1.26 C2- and C3-alkenylation of *N*-substituted indole derivatives.

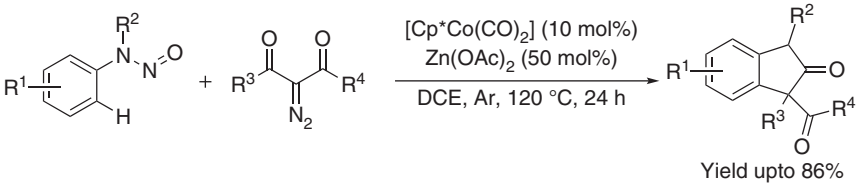
Inspired by their result, a number of groups like carboxaldehyde, *N*-oxide, nitrones, *N*-nitroso, *N*—N bond-based, S=O bond-based, and SiR_3-based directing groups were used as traceless directing groups by various researchers [4c, 47]. In this section, we briefly discuss the discovery of traceless directing group-assisted C—H bond functionalization by different research groups.

In 2020, Shi and co-workers [48] reported Rh(III)-catalyzed regioselective *ortho*-alkylation of aromatic aldehydes using aldehyde as a traceless directing group. The reaction was performed in aerobic atmospheric conditions (Scheme 1.27). The addition of a trace amount of water was found to enhance the yield of the reaction. They have been used with various acrylates and acrylic acids as alkylating agents.



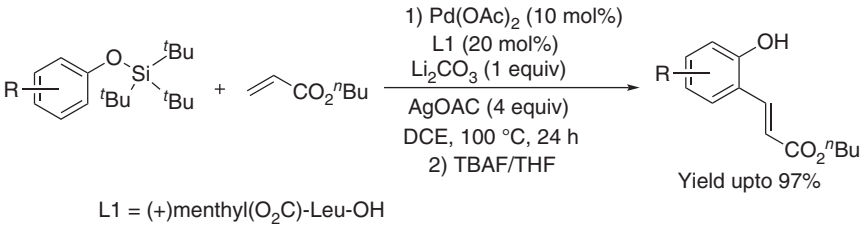
Scheme 1.27 Alkylation of aromatic aldehydes.

In 2018, Zeng and co-workers [49] reported an unprecedented method for the cyclization of *N*-nitrosoanilines with α-diazo-β-ketoesters for the formation of 3,3-disubstituted 2-oxindoles (Scheme 1.28). The reaction was catalyzed by cobalt(III) catalyst and proceeded through a combined C—H activation/Wolff rearrangement process. Density functional theory (DFT) studies were carried out by them, which suggested that the reaction proceeded through the trapping of ketene intermediates by cobalt metallocycles.



Scheme 1.28 Synthesis of 3,3-disubstituted 2-oxindoles.

Gevorgyan and co-workers [50] reported Pd(II)-catalyzed *ortho*-C—H alkenylation of phenols using di-*tert*-butylsilanol as a traceless directing group (Scheme 1.29). They synthesized a diverse range of alkenylated phenols in good-to-excellent yields. To show the synthetic applicability of the reaction, they also explored the alkenylation reaction of benzofuranone and estrone derivatives.

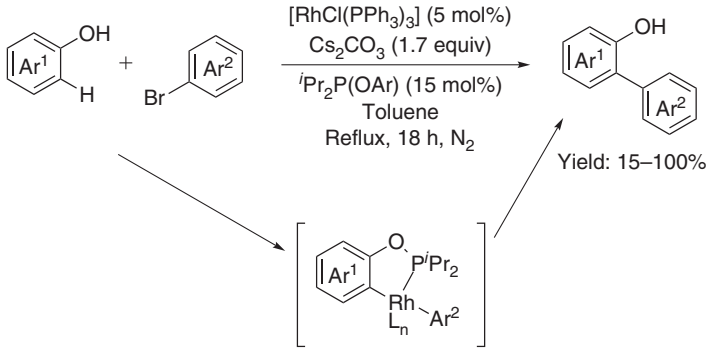


Scheme 1.29 Synthesis of 3,3-disubstituted 2-oxindoles.

1.4.2.3 Transient Directing Group (TDG)-assisted C—H Bond Activation

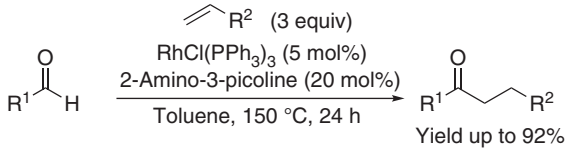
The installation and removal of these directing groups require two additional steps, which compromises the step-economical nature of the overall C—H activation strategy. Moreover, in some cases, installing and removing the directing groups is difficult. To overcome this drawback, researchers have developed the concept of a transient directing group, which can be easily incorporated into the substrate and easily removed from the product *in situ* during the functionalization; no extra additional step is required. The substrate scope of functionalization by using a transient directing group is limited to alcohols, carbonyl compounds, and amines. In this regard, phosphinites are used as directing groups for alcohol compounds, and imines for carbonyl and amine derivatives [51]. In this part, we have very briefly discussed the strategic evaluation of the transient directing group.

In 1969, Parshall et al. [52] first demonstrated that ruthenium, rhodium, and cobalt complexes of triphenylphosphite underwent cyclometallation at the *ortho*-position of one of the phenoxy groups of triphenylphosphite. They explored only stoichiometric C—H cyclometallations without further functionalizations. With the help of their concept, Lewis and Smith [6] successfully applied this transient phosphite DG to catalytic *ortho*-C—H alkylations of phenols by means of the first ruthenium-catalyzed alkene hydroarylation. In the year 2002, Bedford et al. [53] used phosphinite as a transient directing group for the Rh(I)-catalyzed arylation of phenol derivatives using aryl halides as a coupling partner (Scheme 1.30). The reaction proceeded through the formation of the rhodacycle with phosphinite. Inspired by their result, various groups like Bedford, Bergman, Ellman, Cole-Hamilton, Ye, Oi, and Inoue successfully explored phosphite or phosphinite as a transient directing group for *ortho*-selective alkylation and arylation of phenol derivatives [54].



Scheme 1.30 Arylation of phenols.

Imines are broadly explored as transient directing groups for various functionalization through C—H of aldehydes, ketones, etc. Imines can be easily synthesized by the condensation of carbonyl compounds and amines; besides, they can be readily removed upon hydrolysis. In 1997, Jun et al. [55] first used an imine as a transient directing group for the hydroacylation of aldehydes with alkenes via the activation of the aldehyde C—H bond (Scheme 1.31). They used 2-amino-3-picolin for the generation of the transient directing group.

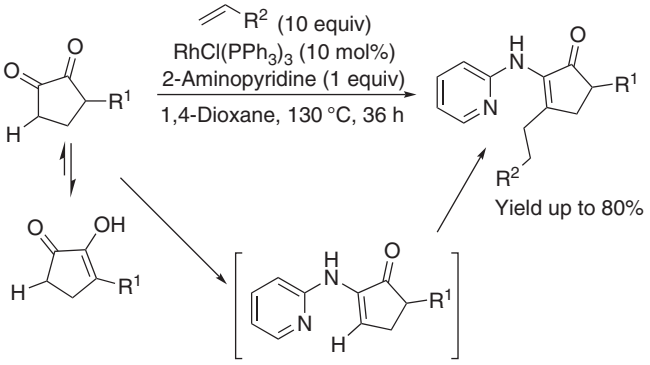


Scheme 1.31 Hydroacylation of aldehydes.

Subsequently, in 2000, Jun group [56] also explored Rh-catalyzed *ortho*-C—H alkylation reaction of the aldimine with tert-butylethylene using 2-amino-3-picoline as amine for formation of imine. Inspired by their work, many researchers successfully

utilized imine as a transient directing group, for various functionalization like alkylation, arylation, alkenylation, amination, and halogenation of a variety of substrates: aldehyde C—H bonds, *ortho*-C—H bonds of aromatic aldehydes or ketones, the atroposelective C—H bond of biaryl carbonyl compounds, *ortho*-C—H bonds of ferrocene derivatives, benzylic C(sp^3)—H bonds of aromatic aldehydes, β- or γ-C(sp^3)—H bonds of aliphatic amines, and δ-C(sp^3)—H bond of aryl amines [57].

Some groups also explored enamine as a transient directing group for C—H functionalization. In 2012, Dong group [58] pioneered the use of an enamine as a transient directing group for Rh-catalyzed alkylation of the cyclic 1,2-diketone using 2-aminopyridine directing group (Scheme 1.32). The reaction proceeded through the coordination of pyridine nitrogen to the Rh-center. Subsequently, they also explored a similar strategy for the Rh-catalyzed α-alkylation of the ketone [59].



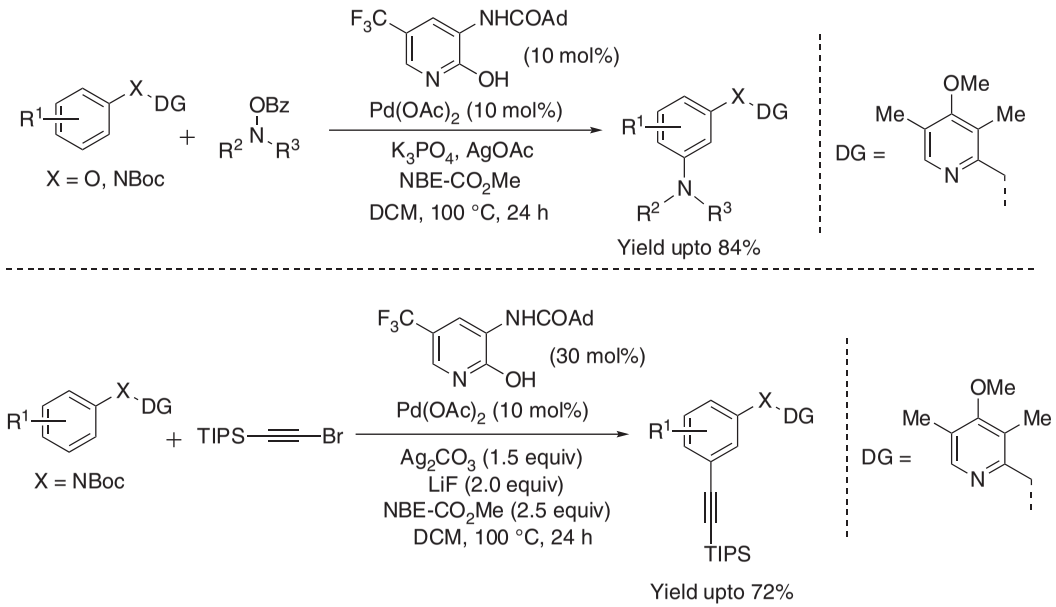
Scheme 1.32 Rh-catalyzed alkylation of the cyclic 1,2-diketone.

1.5 Directed Distal C—H Bond Functionalization

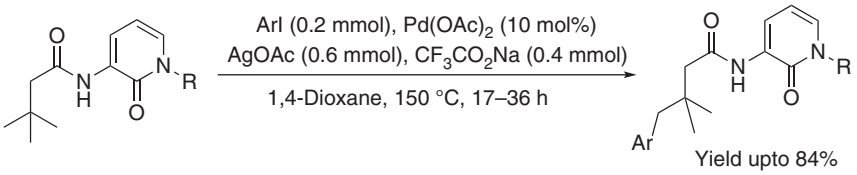
1.5.1 *meta*-C—H Bond Functionalization

In 2016, Yu and co-workers [60] first reported Pd(II)-catalyzed *meta*-C—H amination and alkynylation of aniline and phenol substrates using either *N*-benzoyloxyamines or alkynyl bromides as electrophilic reagents in presence of modified norbornene (methyl bicyclo[2.2.1]hept-2-ene-2-carboxylate) as a transient mediator and monoprotected 3-amino-2-hydroxypyridine ligands (Scheme 1.33). A variety of substrates, including different heterocycles like indole, indoline, and indazole, effectively reacted to produce the desired products in moderate-to-high yields.

Maiti and co-workers [61] developed a new protocol for selective β- and γ-C(sp^3)—H activation and arylation of aromatic and aliphatic carboxylic acid derivatives using a new traceless removal bidentate directing group, 3-amino-1-methyl-1*H*pyridin-2-one (AMP), using Pd catalyst (Scheme 1.34). To show the generality of the strategy, they also explored arylation at β- and γ-positions of C(sp^2)—H of the amide



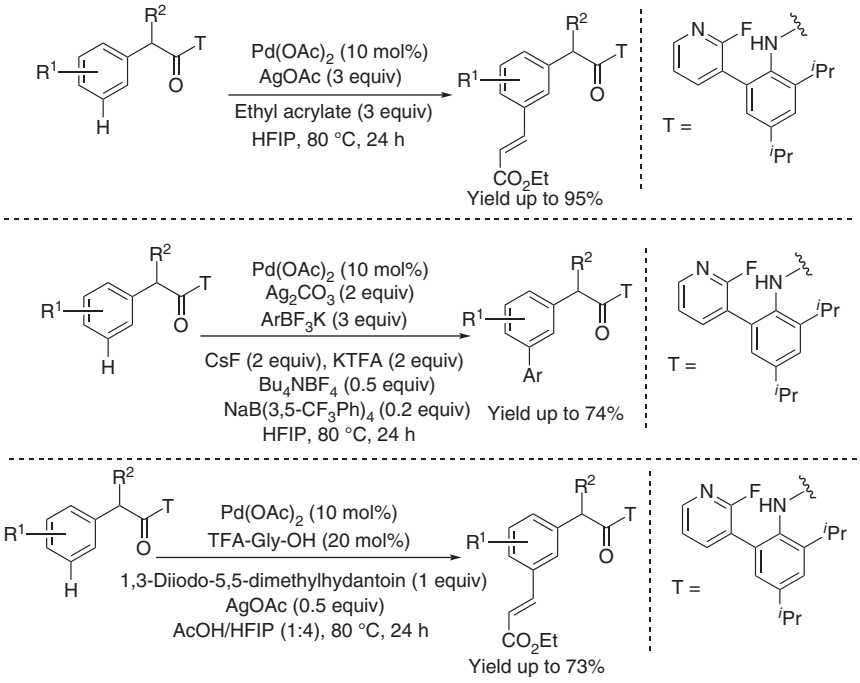
Scheme 1.33 *meta*-C—H amination and alkynylation of arenes.



Scheme 1.34 γ-C(sp^3)–H arylation of carboxylic acid derivatives.

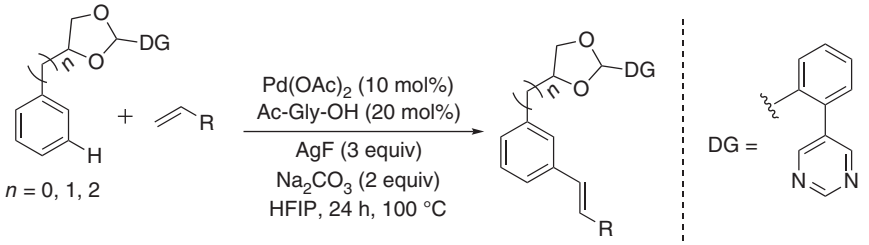
analogs. They also explored the γ-arylation of a chiral amino acid derivative like phthalimide-protected L-valine amide.

Yu group [62] used a pyridine-based U-shaped template for a diverse range of *meta*-C—H functionalizations of phenylacetic acid scaffolds using Pd catalyst. They explored *meta*-C—H olefination using ethyl/methyl acrylate derivatives, *meta*-C—H arylation with $ArBF_3K$, and *meta*-C—H iodination using 1,3-diiodo-5,5-dimethylhydantoin as the iodination reagent (Scheme 1.35). In all cases, the desired products were formed in moderate-to-good yields.



Scheme 1.35 *meta*-C–H alkynylation of phenylacetic acid scaffolds.

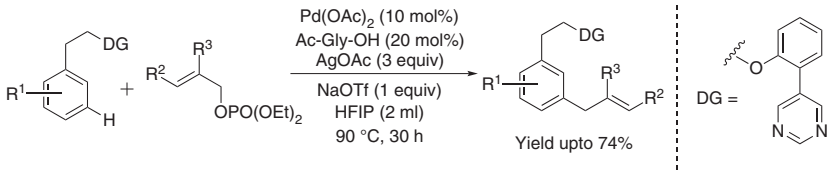
In 2019, Wang and co-workers [63] developed Pd(II)-catalyzed *meta*-C—H olefination of arene-tethered diols across different linker lengths attached to an easy removal well-designed pyrimidine template (Scheme 1.36). A variety of 3-phenylpropane-1,2-diol frameworks having electron-withdrawing and electron-donating groups efficiently underwent reaction under the optimized reaction



Scheme 1.36 Pd-catalyzed *meta*-C–H alkenylation of arenes.

conditions. To show the synthetic applicability of the reaction, they synthesized various diol-based natural products, such as coumarins, phenylpropanoids, stilbenes, and chalcones. They also performed the gram-scale reaction. Moreover, they also carried out different experimental and computational studies, including ^{1}H NMR, ESI-MS and IR, and DFT, to clarify the mechanistic complexity.

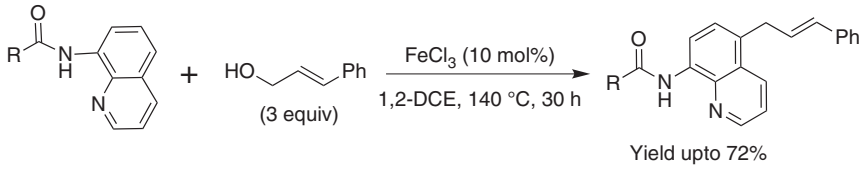
Introduction of different functionalities at distal positions in arenes in a regioselective manner is a challenging task. In 2020, Maiti and co-workers [64] reported pyrimidine-based auxiliary-directed palladium-catalyzed *meta*-C—H allylation of arenes using allyl phosphate as an allylating agent (Scheme 1.37). Here, the pyrimidine directing group of substrate coordinated to the palladium center, which enhances C—H activation. In this reaction, 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) solvent played a critical role by lowering the energy of transition states and intermediates via its interactions with both catalysts and substrates. A variety of substrates like phenethyl ether, phenol, benzylsulfonyl ester, phenethylsulfonyl ester, phenylacetic acid, hydrocinnamic acid, and 2-phenylbenzoic acid derivatives were efficiently reacted under the optimized reaction conditions. They also synthesized eugenol derivative under the optimized reaction conditions. Various spectral analyses like ^{1}H NMR, ^{31}P NMR, ESI-MS, kinetic study, and DFT computations were performed to understand the mechanistic pathway of the reaction. The experimental results suggested that the reaction proceeded through a ligand-mediated *meta*-C—H activation followed by the addition of allyl to form a Pd-π-allyl complex, which finally had a turnover determining C—C bond formation step, leading to the formation of *meta*-allylated product.



Scheme 1.37 *meta*-C–H allylation of arenes.

1.5.2 *para*-C–H Bond Functionalization

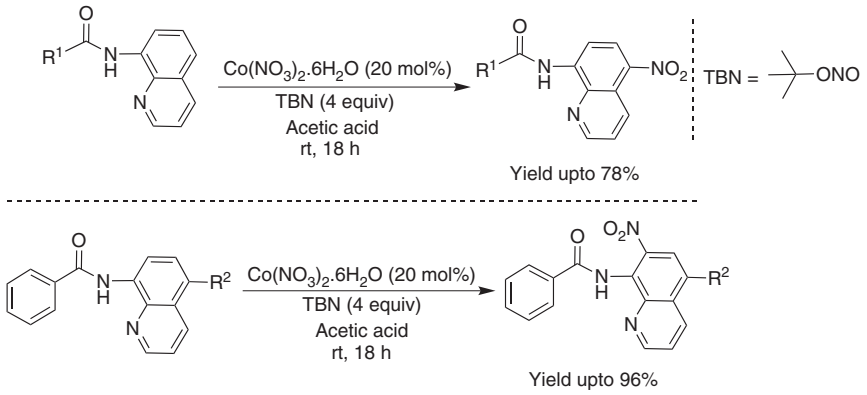
In 2014, Cong and Zeng [65] reported iron-catalyzed remote C-5 allylation of quinolines with allyl alcohol. The optimized reaction condition was achieved by using



Scheme 1.38 Iron-catalyzed C-5 allylation of quinolones.

10 mol% $FeCl_3$ in 1,2-DCE at 140 °C (Scheme 1.38). Irrespective of the nature of the allyl alcohol, only the *E*-isomeric product was obtained under the optimized reaction condition.

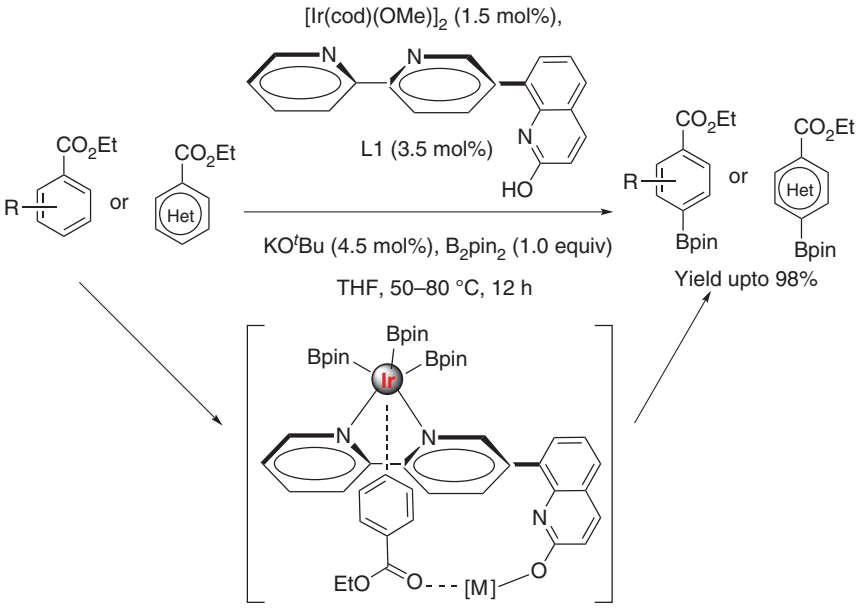
In 2016, Ribas and co-workers [66] developed a facile and efficient approach for direct C-5 nitration of quinoline scaffolds using commercially available *tert*-butyl nitrite (TBN) as the nitrating reagent in the presence of Co catalyst (Scheme 1.39). The mechanistic pathway of this protocol involves the SET pathway. 5-Substituted-8-aminoquinoline derivatives undergo nitration at the C-7 position under the optimized reaction conditions.



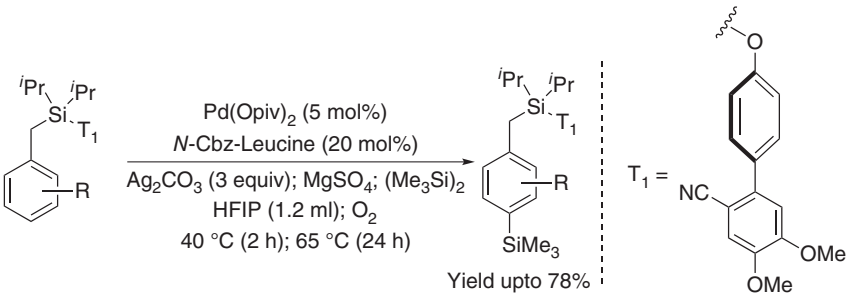
Scheme 1.39 Co-catalyzed nitration of quinolone.

Noncovalent interactions play a key role in controlling the chemical reactivity of similar types of C—H bonds within the substrate. In 2017, using noncovalent interaction between the substrate and an L-shaped ligand having a pendant noncovalent interacting site, Chattopadhyay and co-workers [67] developed an efficient method for Ir-catalyzed *para*-C—H borylation of aromatic esters (Scheme 1.40). They used an L-shaped ligand in which bipyridine was the core moiety, which provided an unprecedented controlling factor to activate selectively at the *para*-position of ester. A wide variety of substrates with different functional groups selectively borylated at the *para*-position and produced the desired products in good-to-excellent yields.

The development of regioselective C—Si bond formation reactions is extremely important due to the natural abundance and non-toxic nature of silicon [68]. Maiti and co-workers [69] developed a template-assisted regioselective *para*-silylation of toluene derivatives (Scheme 1.41). They designed the templates depending on their experimental and computational studies. They chose a dimethoxy-substituted



Scheme 1.40 Ir-catalyzed C-5 allylation of quinolones.

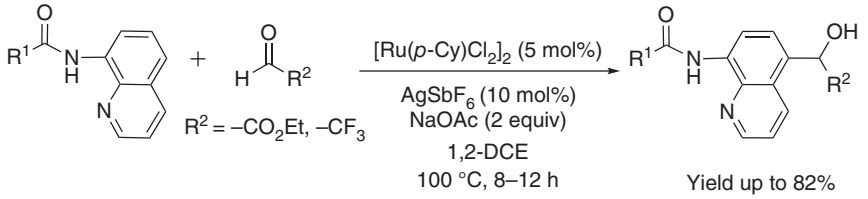


Scheme 1.41 Regioselective *para*-silylation of toluene derivatives.

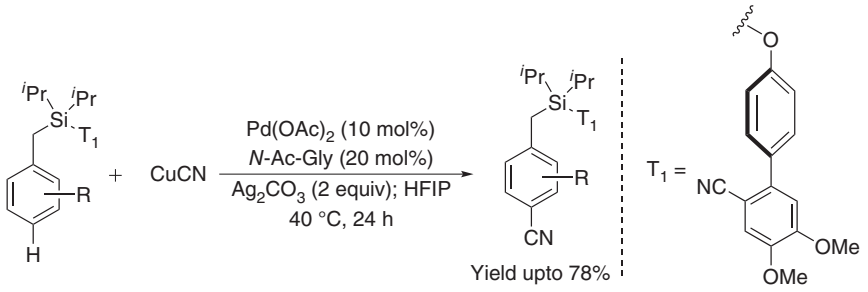
cyano-based D-shaped template, which helped the *para*-C—H bond activation. Kinetic, spectroscopic, and computational studies shed light on the reaction mechanism. The reaction was also applicable in gram-scale synthesis. The synthetic advantage of this reaction is that the strategy was applied for the synthesis of potential lipophilic bioisostere of γ-aminobutyric acid (GABA).

Mondal and Hajra [70] developed a convenient protocol for the site-selective C—H addition of 8-aminoquinoline to ethyl glyoxalate via a ruthenium-catalyzed C—H activation under mild conditions (Scheme 1.42). This method describes selective functionalization at the C-5 position of quinoline ring. The reaction is not air- or moisture-sensitive.

Using the same template shown above, Maiti group [71] reported Pd(II)-catalyzed *para*-selective cyanation of arenes using CuCN as a cyanating agent (Scheme 1.43). This protocol holds its efficacy regardless of substrate electronic bias.

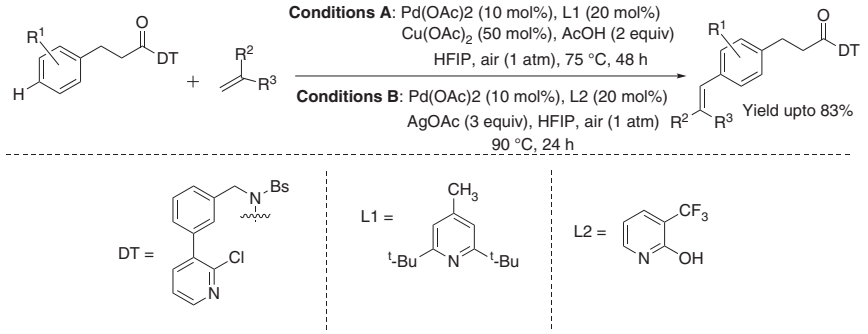


Scheme 1.42 Functionalization of 8-aminoquinoline amide.



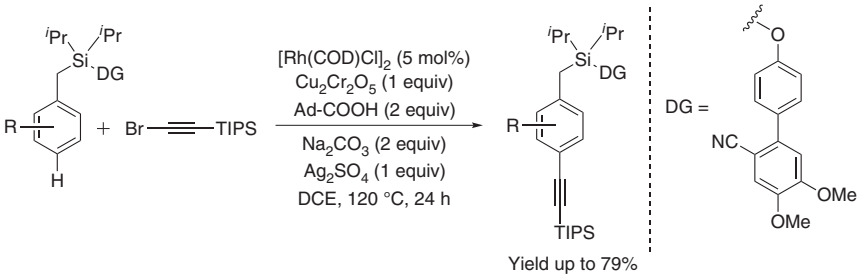
Scheme 1.43 H–Bonded template for regioselective *para*-cyanation of arenes.

Li and co-workers [72] reported an unprecedented Pd-catalyzed *para*-C—H alkenylation of arenes using a readily recycled pyridine-based *para*-directing template (DT) (Scheme 1.44). They explored the reaction by using three classes of arenes like phenylpropanoic acids, 2-phenyl benzoic acids, and benzyl alcohols as model substrates. A variety of alkenes, including perfluoroalkenes, efficiently reacted under the optimized reaction conditions. They have used air as the green terminal oxidant. They also scaled up their reaction into a 3 mmol scale.



Scheme 1.44 Pd-catalyzed para-C–H alkenylation of arenes.

Regioselective C—H alkynylation of arenes via C—H activation is a challenging yet highly desirable transformation. A directing group having a suitable geometric orientation may help the transition metal catalyst to activate *para*-C—H bond. In this regard, Maiti and co-workers [73] developed a reusable dimethoxy-substituted cyano-based D-shaped template route for the unprecedented *para*-C—H



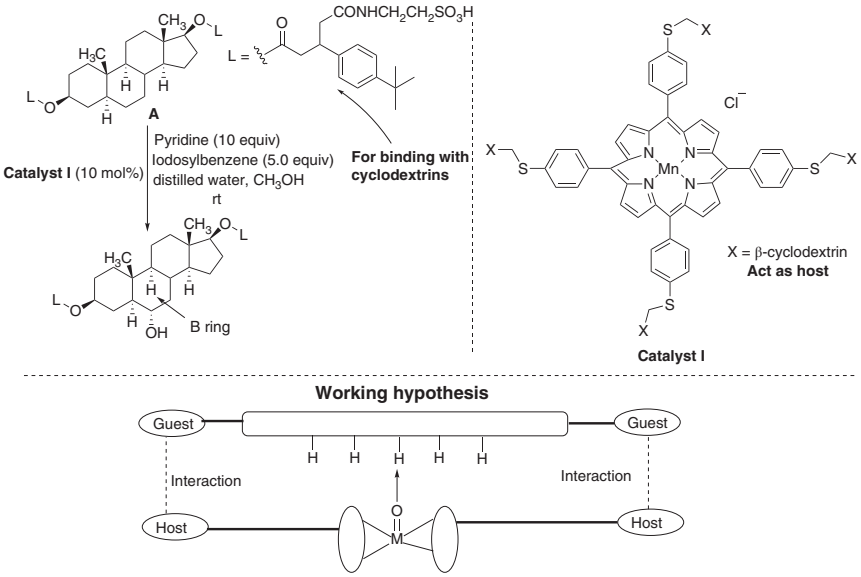
Scheme 1.45 Template-assisted *para*-C–H alkynylation of arenes.

alkynylation of arenes (Scheme 1.45). The reaction was catalyzed by Rh catalyst. This present protocol was well tolerated with a variety of substituents on the arene ring. Moreover, they also performed a late-stage modification of the product and functional group inter-conversion. To understand the mechanistic pathways, they performed computational studies, which suggested that the C—H activation step was not the overall rate-determining step; instead, migratory insertion of the alkyne to arenes was the overall rate-determining step.

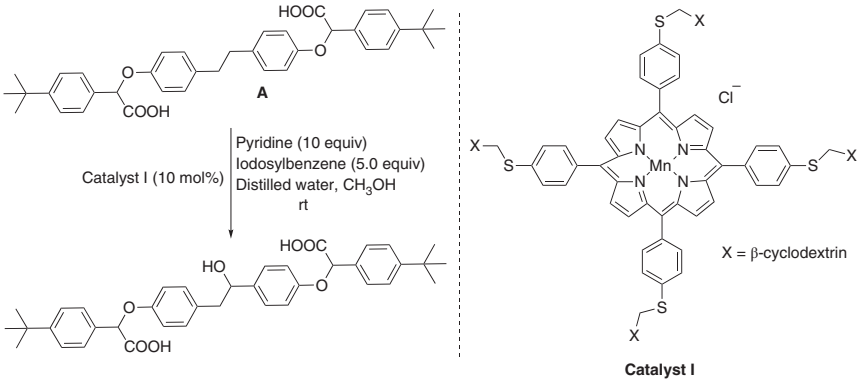
1.5.3 Remote C–H Functionalization

Functionalization of remote C—H bonds, especially when the reaction site is distant from the directing group, is a major challenge in synthetic chemistry. This difficulty arises mainly because the reaction typically requires the formation of a macrocyclic metallacycle, which is a large, ring-shaped intermediate where a metal center coordinates with the substrate to guide the reaction. In this context, enzymes can also act as catalysts and can perform a reaction at a specific position of the bound substrate. In 1997, Breslow et al. [74] used manganese-porphyrin-carrying four β-cyclodextrin groups for selective hydroxylation of unactivated carbons in substrates, such as steroids, under the following optimized reaction conditions: 10 mol% of manganese catalyst (**Catalyst I**) and 5 equiv of iodosobenzene in water in the presence of 10 equiv of pyridine (Scheme 1.46). Molecular models suggested that two *tert*-butylphenyl groups of the substrate bound with the two *trans*-cyclodextrin rings of catalyst and placed the steroid ring B of steroid **A** directly above the metalloporphyrin ring and made it free for oxidation. 40% Conversion was found under the optimized reaction conditions.

In the same year (1997), the same group (Breslow group) [75] used manganese porphyrin, which had four β-cyclodextrin groups for site-selective hydroxylation of a substrate **A**. *Tert*-butylphenyl groups of substrate **A** could hydrophobically bind into the cyclodextrin cavities of the catalyst (Scheme 1.47). The turnover number of the catalyst was high. They also explored the reaction in a steroid derivative, and hydroxylation occurred regio- and stereoselectively at a single unactivated carbon atom with fewer turnovers. With a simple dihydrostilbene substrate, the hydroxylations occurred at the speed of corresponding cytochrome P450 enzymes and with hundreds of turnovers.

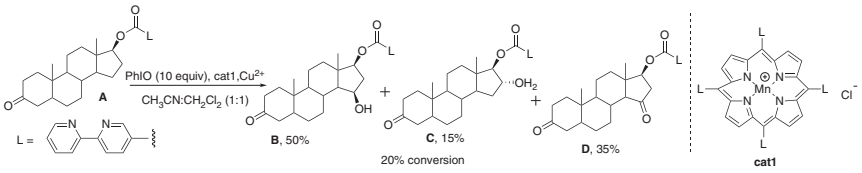


Scheme 1.46 Site-selective hydroxylation of steroids.



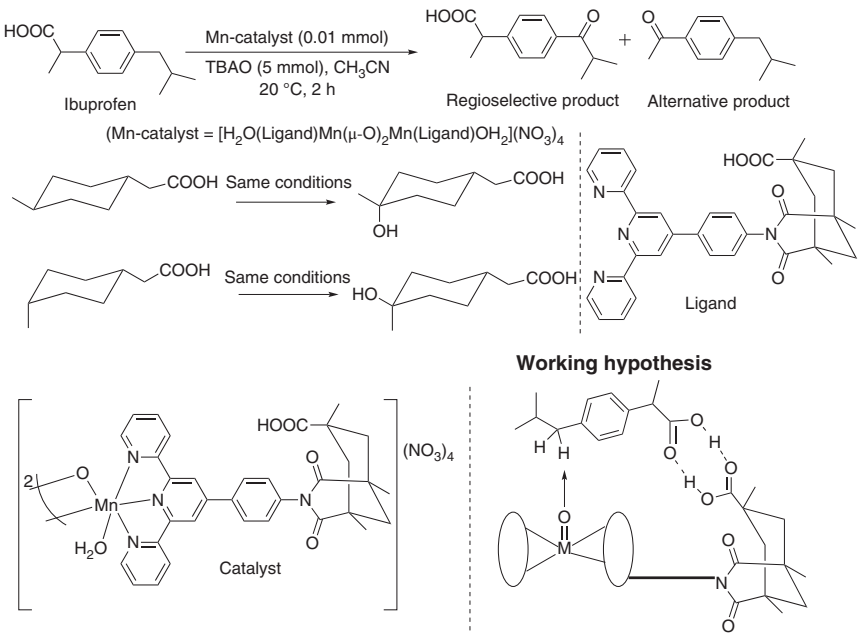
Scheme 1.47 An artificial cytochrome P450-catalyzed regio- and stereoselective hydroxylation of unactivated carbons.

In 2001, the same group (Breslow group) [76] developed a method for regioselective hydroxylation of unactivated C—H bonds of steroids by using new manganese-porphyrin-carrying metal coordinating groups. The auxiliary group of the substrate molecule coordinated with the metal ion of the porphyrin bipyridyl, which was preceded by a geometrically controlled oxidation. The metal chosen for coordination was Cu^{2+}. The androstane derivatives **A** underwent oxidation in the presence of 0.5 equiv of manganese porphyrin catalyst and 2 mmol of $Cu(OTf)_2$ and 10 equiv of iodosylbenzene (PhIO) as an oxidant. Under this condition, overall 20% of total conversion was found by the formation of a mixture of products **B**, **C**, and **D**, yielding 50%, 15%, and 35%, respectively (Scheme 1.48). They also explored the reaction with the epiandrosterone derivative.



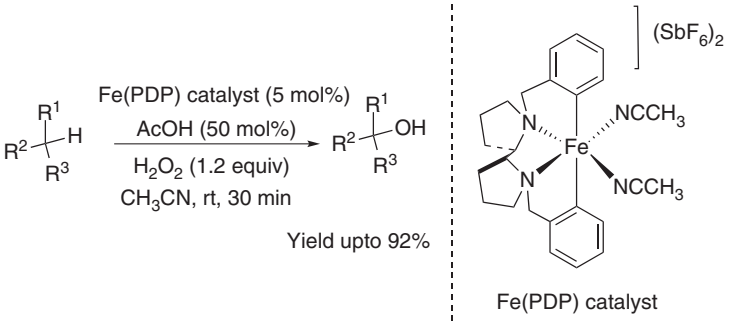
Scheme 1.48 Manganese-porphyrin-catalyzed regioselective hydroxylation.

Crabtree and co-workers [77] used molecular recognition through a hydrogen bonding strategy for regioselective C(sp^3)—H using —COOH group as a recognition group. In 2007, they reported the nonporphyrin-di-μ-oxo dimanganese-catalyzed highly regioselective oxygenation at saturated C—H bonds of ibuprofen and (4-methylcyclohexyl)acetic acid (both *cis* and *trans*) (Scheme 1.49). The turnover number of this reaction was 9100. Control experiments suggested that hydrogen bonding played a key role in orienting the substrate toward high selectivity.

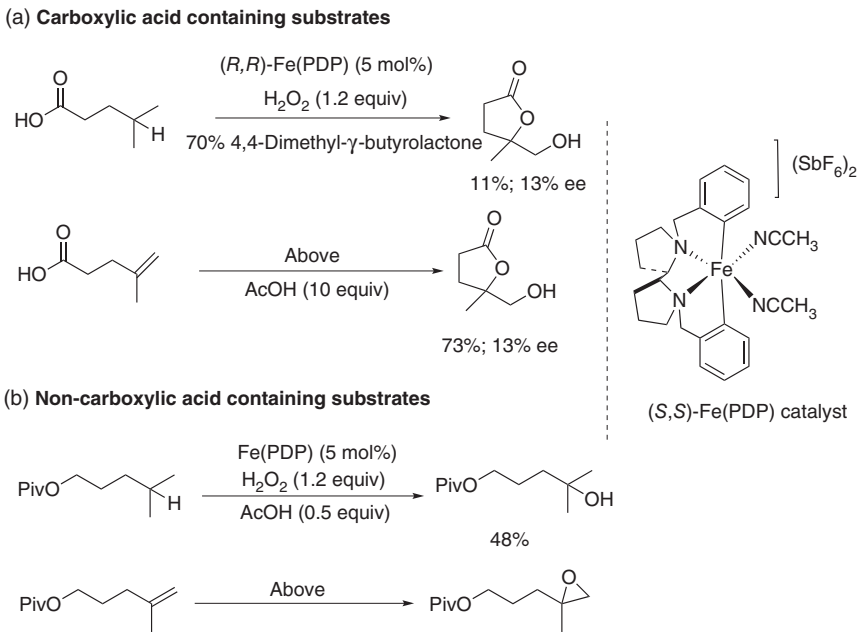


Scheme 1.49 Di-μ-oxo dimanganese-catalyzed regioselective oxygenation.

In 2007, Chen and White [78] developed an electrophilic iron catalyst [Fe(PDP)] having a bulky ligand framework for unactivated sp^3 C—H bond oxidation using hydrogen peroxide (H_2O_2) as an inexpensive, environmentally friendly oxidant. A broad variety of substrates got oxidized at the unactivated C(sp^3)—H bond under the optimized reaction conditions. The site of oxidation of the bonds depended upon the electronic and steric environment of the C—H bond. When carboxylic functionality was present in the substrate, it led to the formation of lactone through oxidation (Schemes 1.50 and 1.51).



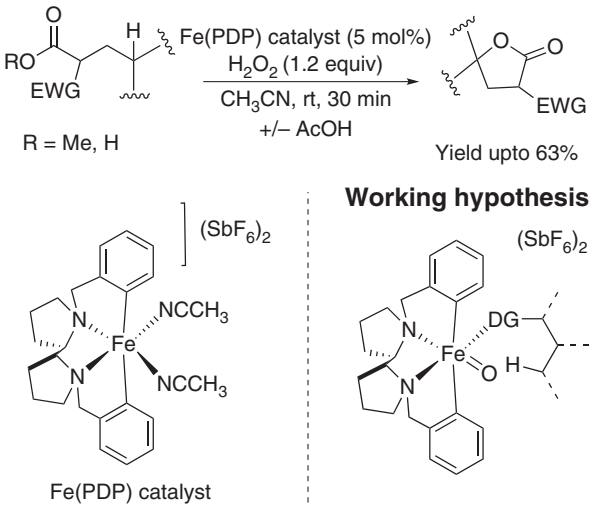
Scheme 1.50 Fe-catalyzed hydroxylation of unactivated sp^3 C—H bonds.



Scheme 1.51 Fe-catalyzed regio- and stereoselective hydroxylation of unactivated carbons.

In 2011, the same group (White group) [79] reported a nonheme iron hydroxylase complex, [Fe(PDP)]-catalyzed site-selective aliphatic C—H hydroxylation of carboxylic and non-carboxylic acid derivatives, using H_2O_2 as a terminal oxidant (Scheme 1.52). They performed a taxane-based radical trap experiment, and under the reaction condition, it rearranges to a nortaxane skeleton. They demonstrated that 13% ee was obtained when they used a chiral Fe(PDP) catalyst.

The following year (2012), the same group (White group) [80] described nonheme iron complex, Fe(PDP)-catalyzed C—H lactonization followed by hydroxylation of carboxylic acids derivatives. Iron complex Fe(PDP) catalyst was suitable for overcoming the unfavorable electronic, steric, and stereoelectronic biases of carboxylic



Scheme 1.52 Di-μ-oxo dimanganese-catalyzed regioselective C–H hydroxylation.

acid moieties for the C—H hydroxylations. In a demonstration of the power of this directing effect, C—H oxidation was diverted away from an electronically favored C-1 H abstraction/rearrangement pathway in the paclitaxel framework to enable installation of C-2 oxidation in the naturally occurring oxidation state and stereoconfiguration. A series of linear methyl esters having an electron-withdrawing acetoxy (-OAc) group were favorable for this reaction. Interestingly, they also succeeded in C-2 hydroxylation on a medicinally important class of molecules like taxane.

1.6 Conclusions

Transition-metal-catalyzed directed C—H bond activation for construction of C—C and C—heteroatom bond has widely expanded in the last few decades, and now, it has become a major research topic among synthetic organic chemists. The pioneering work in this field was reported by Lewis group [81] in 1985 for the Ru-catalyzed *ortho*-C—H deuteration of phenol using phosphite as a transient directing group. After that, a variety of functionalization like arylation, alkylation, alkynylation, olefination, carbonylation, amination, and halogenations have been developed by different research groups. In this chapter, we tried to give an overview on different strategies for directed selective and efficient C—H bond functionalization via C—H activation. We included early discoveries on stoichiometric metal-promoted proximal C—H bond activation, directing group (both built-in functional group and removal directing group)-assisted catalytic proximal C—H bond functionalization, and directing group-assisted distal (both *meta* & *para*) C—H bond activation. We believe that this chapter will motivate the researcher to further explore this field. Although this field has been explored extensively, according to green chemistry aspect, the development of user-friendly waste-free

reaction conditions and modification of catalysts, which are not air or moisture sensitive, is highly desirable and is a challenging work in the near future. We envisage that numerous environmentally friendly C—H activation reactions with industrial potential will be explored.

Acknowledgments

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