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1. *Meta*-C−H Bond Functionalization's in Organic Synthesis

Dr. Debapratim Das

Assistant Professor,
Department of Chemistry,
School of Basic and Applied Sciences,
Adamas University,
Kolkata, West Bengal, India.

Abstract:

Transition metal-catalyzed C-H bond functionalization is one of the important synthetic tools which is largely used in industry and academia for the synthesis of drug molecules, organic materials, organic polymers, natural products etc. in step economic and more efficient way. It involves inert C-H bond activation with the help of transition metal salts followed by some functionalization which converts the C-H bond to a C-C or C-heteroatom bond. The use of a directing group has emerged as a promising technique to do C-H bond functionalization in a site-selective manner. In an aromatic system, proximal C-H functionalization or ortho-C-H functionalization is broadly explored. In it, several functional groups can be incorporated with the help of different functional groups under transition metal catalysis.

Recently with the help of several specially designed directing groups, distal C-H functionalization or meta/para-C-H functionalization is also possible. In this chapter, we will mainly discuss the meta-C-H functionalization.

1.1 Introduction to C-H Bond Functionalization:

Earlier region-selectivity of the upcoming group to an aromatic system was guided by the electronic nature of the functional group attached to the aromatic system. If the electron-donating group is attached to the aromatic system, it will direct the upcoming electrophiles to *ortho*/*para*-position and upcoming nucleophiles to *meta*-position. Similarly, if an electron-withdrawing group is attached to the aromatic system, it will direct the upcoming electrophiles to *meta*-position and upcoming nucleophiles to *ortho/para*-position. Those mainly involve electrophilic and nucleophilic aromatic substitution reactions.

In the last few decades, C-H bond functionalization has emerged as an important toolbox in synthetic organic chemistry.[1] It represents the controlled functionalization of specific C-H bonds, even in presence of more reactive functional groups. Earlier, it was achieved by radical functionalization or aerobic oxidation followed by the incorporation of a desired functional group to construct the structure. But recently, it can be performed by the activation of non-reactive/less reactive C-H bond with the help of transition metal salts and then transforming it to C-C or C-heteroatom bond. The C-H bond functionalization can occur in two path-way, (i) *via* classical insertion into C-H bond (outer-sphere mechanism) or (ii) *via* chelation assisted C-H bond cleavage (inner-sphere mechanism).[2]

Transition metal salt first cleaves the C-H bond and forms a C-Metal bond, then insertion of some other functional group followed by proto-demetallation gives desired C-H functionalized product (Figure 1.1a). In Chelation assisted C-H bond cleavage, regio-selectivity of coupling depends on the directing group. It first directs the metal catalyst to bind to the desired site and C-H bond activation takes place. Then functional group binds to the metal centre followed by proto-demetallation produces the desired product (Figure 1.1b).

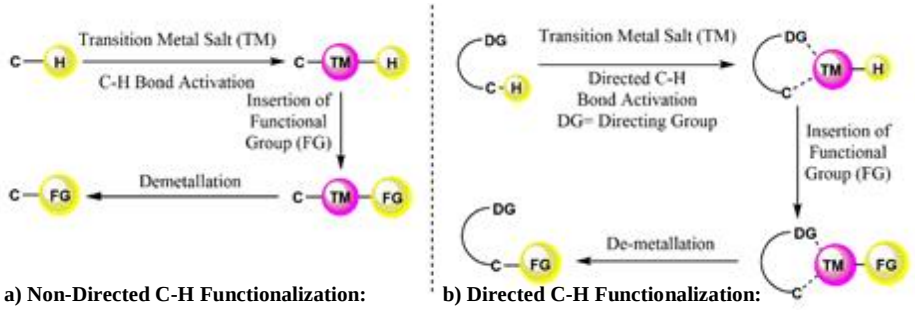

Figure 1.1: C-H bond Functionalization

1.2 *Meta*-C-H Functionalization:

The directing group guided C-H functionalization with the help of transition metal salts was started with *ortho*-C-H functionalization of the aromatic system. In these cases, the organometallic intermediate is a five- to six-membered metallocyclic system. But activating distal C-H bonds are quite difficult because of a few facts, a) designing long-chain template, which will eventually end up in the formation of the energetically unfavourable large membered macrocyclic transition state, b) close proximity of the coordinating heteroatom in the template toward the *meta*-C−H bond and c) selectivity between *ortho*- and distal-C-H bond activation. Now, this can be easily possible *via* distal C-H bond functionalization. Hence with the help of a specially designed template *meta*/*para*-C-H functionalization can be done with the help of transition metal salts in a site-selective manner (figure 1.2).[3] In the case of the *meta*-functionalization transition state is eleven- to twelve-membered metallocyclic system.

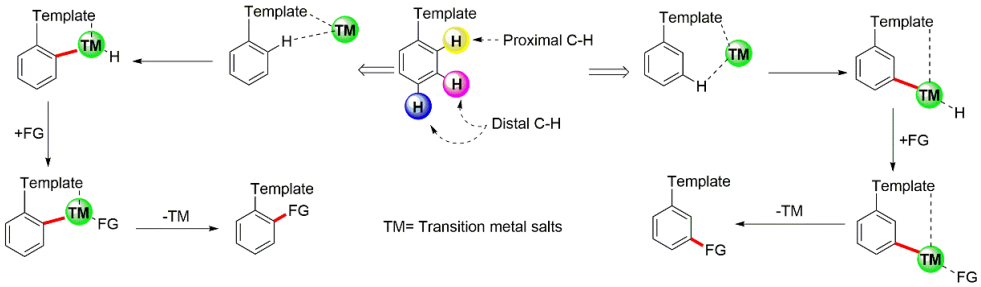

Figure 1.2: Different types of directed C-H bond functionalization

First, *meta*-C-H functionalization was reported by a cyano based template to a toluene derivative under Pd-catalysis (Figure 1.3).[4]

Treatment of compound **1** with ethyl acrylate under Pd-catalysis give compound **2** with high selectivity of *meta*-C-H functionalized product over *ortho via* reaction intermediate **3**. The beautifully designed template almost selectively binds to the *meta*-position of the arene and furnish desired product with high selectivity. There is an equal possibility of a Fridel-Crafts olefination by Pd (II) salts acting as Lewis acids. As a result, the need for a different functionalization was inevitable, to prove the movement of the reaction through an 11−12 membered metallacycle.

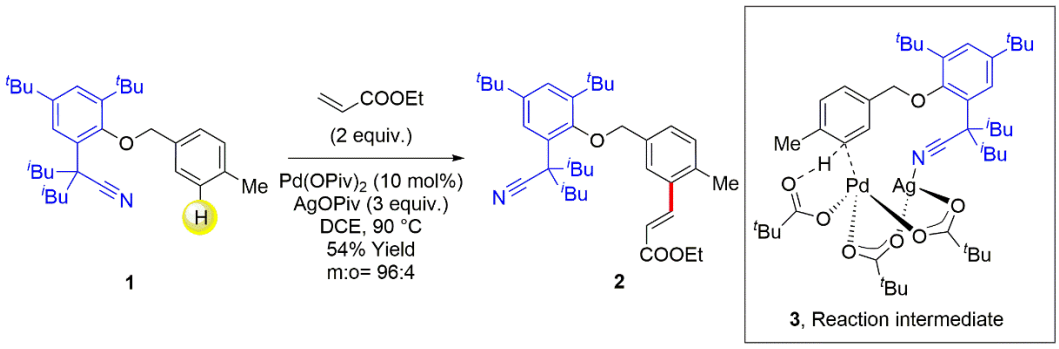

Figure 1.3: Template-based metal olefination of toluene derivatives

Several others CN-based templates are also able to furnish metal-selective functionalization. U-shaped cyano-based template attached to hydrocinammic acid (**4**) *via* amide linkage also able to do *meta*-C-H olefination (**6**) under Pd-catalysis with the help of *N*-protected amino acids as a ligand (Figure 1.4).[4] The use of N-protected amino acids is very crucial here. It acts as a bidentate chelating ligand as well as a proton acceptor.

Theoretical calculation proves the concept. Even further regioselectivity also can be improved by using different mono-protected amino acid derivatives. Not only *meta*-olefination, *meta*-arylation (**5**) is also can be performed using this protocol using aryl-BPin derivatives as the arylating partner.

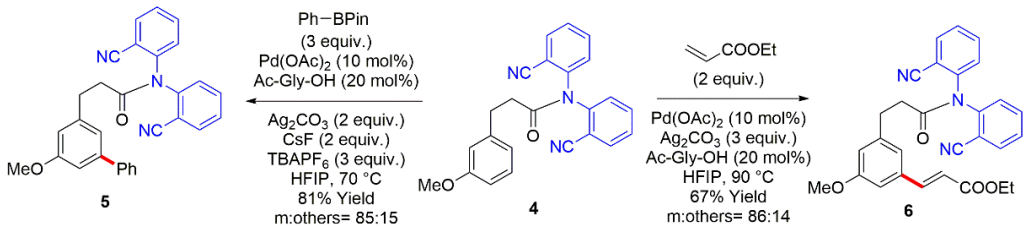

Figure 1.4: *Meta*-functionalization of hydrocinammic acid

Several different functional groups based templates are also able to do *meta*-C-H functionalization. When we move from arene derivatives to heteroarene derivatives, with the purpose of functionalizing the distal *meta*-position it has to think through bonds that are more than 10 atoms away from the respective H-atom. So, successful *meta*-functionalization for heteroarenes is little bit difficult. But designing a suitable template can solve the purpose. For example, in case of tetrahydro-quinoline derivative (**7**), installation of a cyano-based template *via* amide linkage can be a solution for it.

Using the template under Pd-catalysis and mono-protected amino acid derivatives as a ligand can do successful *meta*-olefination (**8**) using acrylate derivative as the olefinating agent *via* reaction intermediate **9** (Figure 1.5).[5]

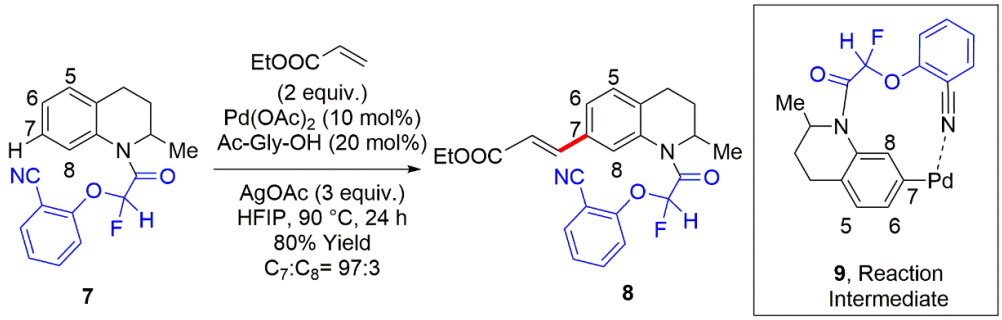

Figure 1.5: *Meta*-functionalization of heteroarene (tetrahydro-quinoline derivative)

All the U-Shaped templates deliver the products in many arene derivatives, irrespective of their electronic nature and different substituents present, with excellent *meta*-selectivity. With the help of *N*-acyl protected amino acid ligands and Pd-catalysis, they preferably bind the expected position. But other than the U-shaped template several other templates also furnishes products with the desired regio-selectivity. Using carbonyl linkages, used for site-selective C-H functionalization of tetrahydroquinolines, is not effective in indolines because of the electronic nature and conformational property of indolines. So in those cases, a differently designed template is required. A cyano-based template having sulfonyl linkage can solve the purpose, which is also easily de-attachable. Toluene derivative (**10**) having cyano-based template attached *via* sulfonyl linkage can furnish *meta*-olefinated derivative **11** under Pd-catalysis (Figure 1.6a).[6] Mechanistic study shows that reaction is proceeding *via* a 12 membered palladocycle intermediate **12**. Just like C-analogue templates, Si-templates also serve the role in efficient way. Toluene derivative **13** connected with a cyano-template having O-Si bond linkage is able to furnish *meta*-olefinated derivative **14** under palladium catalysis (Figure 1.6b).[7] Adding and removing the Si-linkage is even easier.

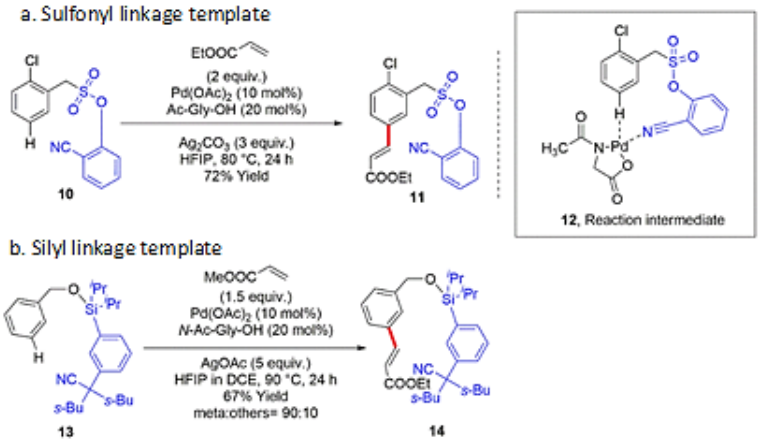

Figure 1.6: *Meta*-C-H functionalization using cyano-templated connected via sulfonyl and sillyl linkage.

Phosphate linkages also have been used to get desired regioselective functionalization. Toluene derivative **15** connected with a cyano-template having phosphate bond linkage is able to furnish *meta*-olefinated derivative **16** under palladium catalysis (Figure 1.7).[8] Easy installation and easy removals make it more effective in the synthesis of di- or tri-alkylated arene derivatives, which have wide importance in organic electronics and optoelectronics.[9]

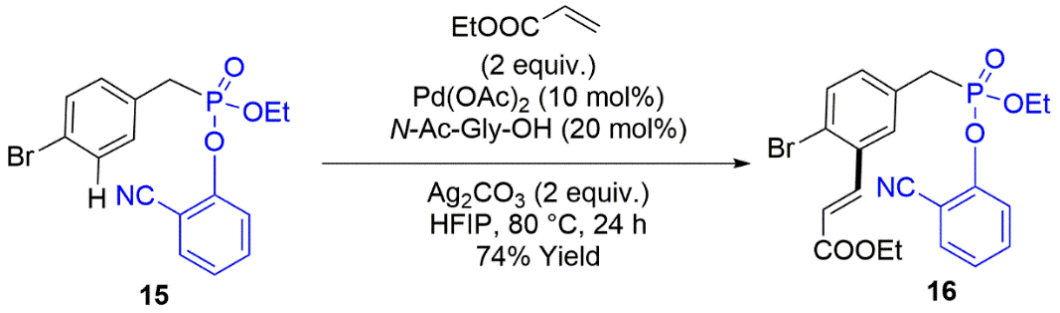

Figure 1.7: *Meta*-C-H functionalization using cyano-templated connected *via* phosphate linkage.

Boron-derivatives also can be used as a template for the desired *meta*-functionalization (Figure 1.8). For example, the following cyano-based boron template can do *meta*-olefination of arene (conversion of **17** to **18**).[10] The advantage of using this template is that upon de-protection it directly provides boronic acid derivative, which can be used as an arylating agent in Suzuki reaction for further use. In this case for the desired functionalization, metal−H coordination must dodge metal-B coordination. Earlier literature reports say that *N*-Methyliminodiacetic acid (MIDA) boronate esters are suppressed metal−B coordination for Suzuki coupling reaction. Hence, this type of boronate ester having a ether-linked cyano-based template can be used for *meta*-functionalization.

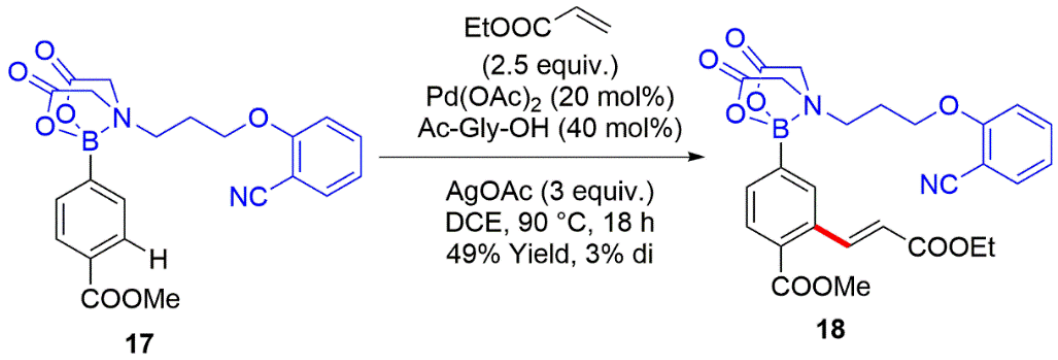

Figure 1.8: *Meta*-C-H functionalization using cyano-templated connected via boron linkage.

In most of the *meta*-C-H functionalizations, CN-based templates having several different linkages are used. But the CN-group has some back-draws too. CN-group is itself a relatively weak coordinating group compared to other directing groups. Hence, if any other strong coordinating element or solvents are present in the system, it will be detached from the metal side. As a result, *meta*-activation will not occur.

Other than this, CN has two types of coordination possibilities with metals, i) end-on and ii) side-on. Only end-on coordination furnish desired stereo-selective product. But if side-on coordination occurs with metals, it is unable to do *meta*-activation. So to replace those cyano-based templates, different templates containing nitrogen-based heterocycle were designed. For example, biaryl pyridine containing template attached *via* ester linkage with the arene (**19**) converts it to its *meta*-C-H olefinated derivative **20** under Pd-catalysis in the almost site-selective manner (Figure 1.9).[11]

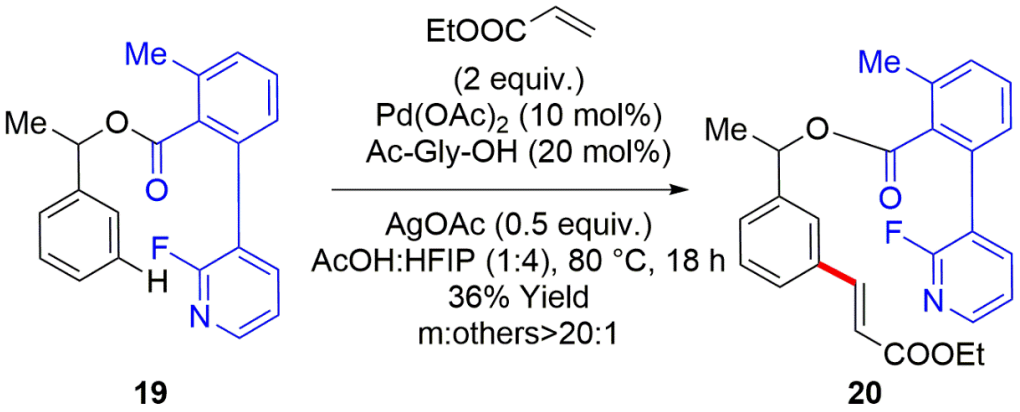

Figure 1.9: *Meta*-C-H functionalization using biaryl pyridine containing template

Heterocyclic template attached to an arene (**21**) *via* a sulfonyl linkage also can be used for *meta*-C-H olefination (**22**) *via* reaction intermediate **23** (Figure 1.10).[12] As heterocyclic template 8-nitro quinolone can be used, which will give stable pallado-cycle intermediate. Results show that incorporation of 8-substituted quinolone is more efficient than using a pyridyl template. Theoretical studies also show that having OMe- and NO_2- group at C8-position of quinolone provide better yields and regio-selectivity. Coordination by the oxygen atom of NO_2- or OMe- group was assumed to endorse strong chelation with metal and smoothen the synthesis of *meta*-olefinated derivatives.

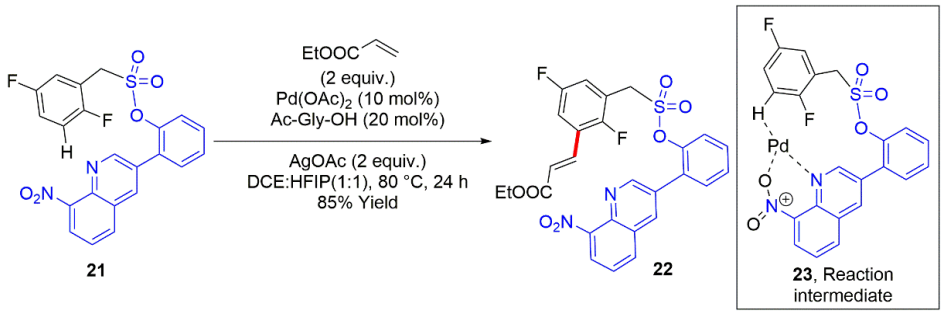

Figure 1.10: *Meta*-C-H functionalization using heterocycle template linked via sulfonyl linkage

In some cases, *meta*-C-H functionalization wouldn't happen due to the entropic barrier. This can be overcome by using a template connected to the arene by a long-chain alkyl system. For example, propyl to octyl benzene can be functionalized in their respective position using some strong coordinating heterocyclic templates, mainly pyrimidine.

Using this protocol compound **24** can be converted to its *meta*-olefinated derivative **25** under Pd-catalysis via reaction intermediate **26** (Figure 1.11).[13]

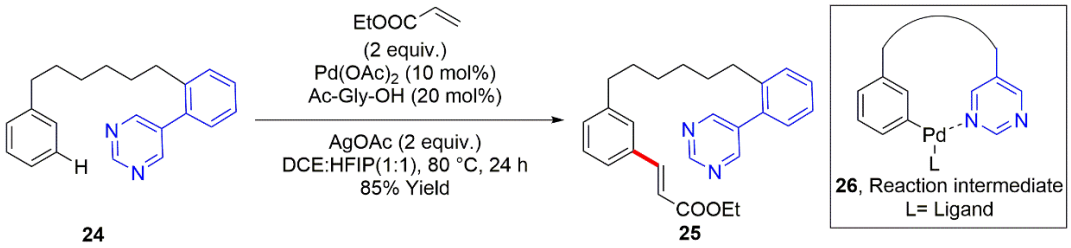

Figure 1.11: *Meta*-C-H functionalization using heterocycle template linked *via* long-chain alkyl group

Not only pyrimidyl template, triazyl-based template also can be used to do regio-selective *meta*-C-H bond functionalization. Using the bi-functional template having traizine and attached arene having CN-functional group (**27**), is able to do *meta*-C-H olefination of a phenol derivative **28** (Figure 1.12).[14]

Triazine group can be synthesized from cyanuric chloride and unable to do *ortho*-functionalized product. Using this template, synthesis of bio-active molecule TMC-95 A-D is also achieved in a step-economic and efficient way *via* a central scaffold derivative.

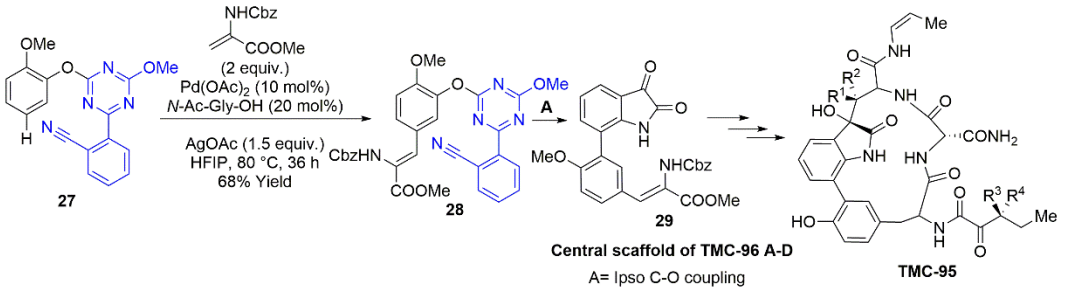

Figure 1.12: *Meta*-C-H functionalization using cyano-based triazine derivative

1.2.1 Ru-catalyzed *meta*-C-H functionalization:

Generally, *meta*-C-H functionalizations are carried out using well-designed template under Pd or Rh-catalysis. Those occur *via* 10-12 membered metallo-cycle intermediate. But other than this, using small directing group *meta*-C-H functionalization of arene is possible under cheaper Ru-catalysis.

This type of *meta*-C-H functionalization involves the formation of cyclollation. With the help of small directing groups, Ru-catalyst activates the *ortho*-C-H bond of the arene, and the newly formed Ru-C bond acts as a Friedel-Craft type of directing group which further to *para*-C-H bond activation with respect to itself. Overall, it looks like *meta*-C-H bond activation with respect to the directing group (Figure 1.13).

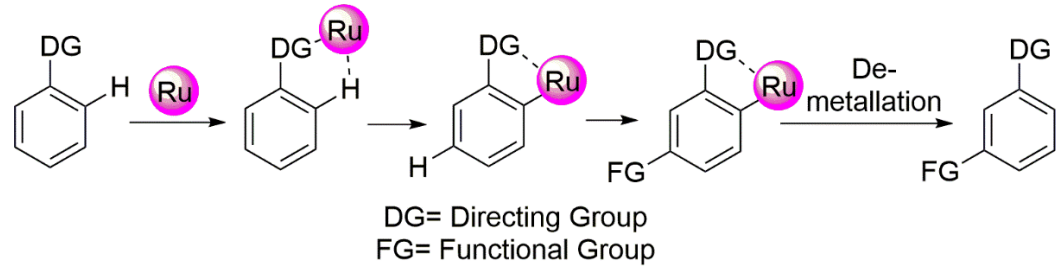

Figure 1.13: Ru-catalyzed *meta*-C-H functionalization

2-Phenyl pyridine (**30**) is one of the most used substrates used for transition metal-catalyzed C-H bond functionalization. Several transition metal salts are used for the *ortho*-C-H bond activation of this moiety *via* coordination with *N*-atom of the pyridyl group. But using a suitable catalyst and suitable reaction conditions, *meta*-C-H functionalization of the phenyl moiety is also possible. If 2-phenyl pyridine is treated with Ru-catalysis, it first coordinates to the *ortho*-position, which substantially activate the *para*-C-H bond with respect to the Ru-C sigma bond. Overall *meta*-C-H bond activation is observed with respect to the pyridyl directing group. Then several reagents react in a Friedel-Craft type of reaction. Using this protocol several groups, like, alkyl (**31**/**34**),[15,16] aryl-sulfonyl (**32**),[17] bromine (**33**)[18] etc. group can be incorporated in the *meta*-position in a regio-selective way (Figure 1.14). Other than those, several functional groups also can be incorporated into the *meta*-position.

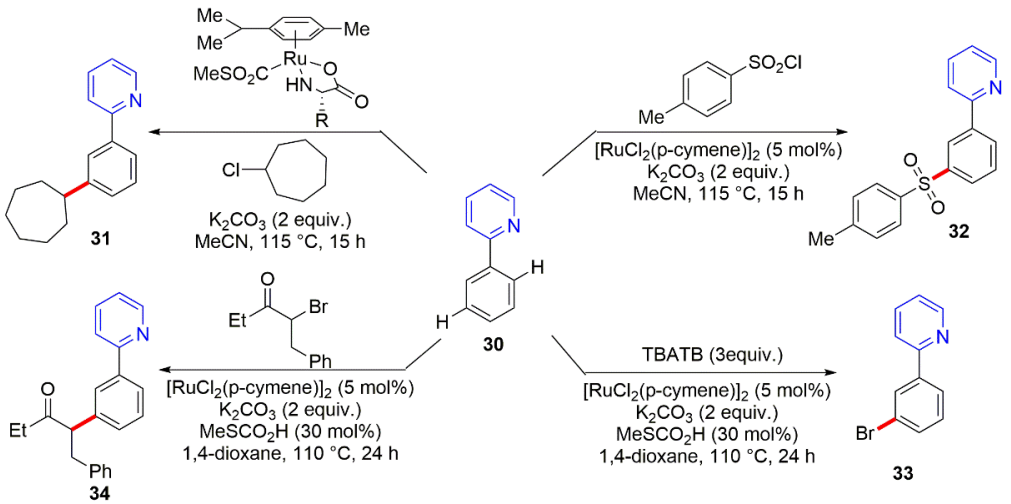

Figure 1.14: Different Ru-catalyzed *meta*-C-H functionaizations

Other than pyridyl group directly attached to the arene moiety, 2-pyrimidyl protected phenol or aniline moieties also can be converted into its *meta*-functionalized derivative sing such type of protocol. Ru-catalyst in presence of mono-protected amino acids successfully binds to the *ortho*-position of the arene moiety by coordinating with the *N*-atom of the pyrimidyl group. Eventually, this organometallic intermediate activates the *meta*-position.

Using this protocol, *meta*-alkylation of 2-pyrimidyl protected phenol or aniline moieties (**35**) are developed (Figure 1.15).[19]

The de-protection of the 2-pyrimidyl group can convert it to *meta*-substituted aniline or phenol derivatives in one step, which is not possible via electrophilic aromatic substitution because of the electron-donating nature of $–NH_2$ and –OH group. Under Ru(II)-catalysis using this C-H functionalization technique *meta*-alkylation of the arene (**35**) is developed using secondary and tertiary alkyl bromide. As a result *meta*-alkylated aniline derivative (**36**) and *meta*-alkylated phenol derivative (**37**) can be easily synthesized.

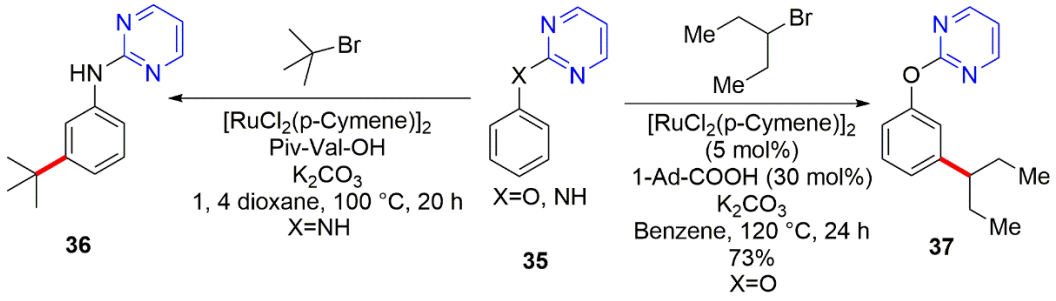

Figure 1.15: Different Ru-catalyzed *meta*-C-H functionalization's of phenol and aniline derivatives using 2-pyrimidyl directing group

Several other *meta*-C-H activations of arene moieties are also developed using different small coordinating directing groups under Ru-catalyzed conditions.

1.2.2 Para-C-H functionalization of arenes:

For the last few decades, fantastic progress has been made for *ortho*-C-H activation of arene derivatives with the assistance of several directing groups. After that, different template-assisted *meta*-C-H functionalization has been also developed with great selectivity and yield. Not only *meta*-C-H functionalization, using more higher analogue or specially designed template it's now able to do selective *para*-C-H functionalization.[2]

Mainly biaryl cyano-based template solves the purpose. But the major obstacles associated while designing the template are a) synthesizing long-chain template, b) formation of the large membered macrocyclic transition state, which is energetically not so favourable, c) close proximity of the coordinating heteroatom in the template toward the *para*-C−H bond (Figure 1.16).

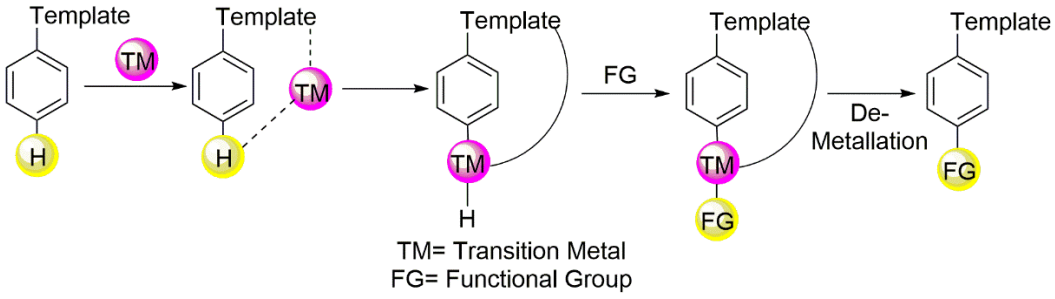

Figure 1.16: *Para*-C-H functionalization

1.3 Conclusion:

Distal C-H bond functionalization is emerging as an immense Figure in synthetic organic chemistry. Among them, various meta-C-H bond functionalization techniques in the synthesis of drug discovery, natural products etc. emerged as quite efficient techniques because of their step-economic benefit. Several directing templates already have been developed to furnish the desired functionalization. Those mainly involve the cyano-group as the key chelating group attached to the substrate via several removable linkages (like, ether, sulfonyl, phosphorous, silyl, heterocycle etc.). Other than those, several N-heterocyclic templates also show promising results. Most of the developed reactions are under Pd-catalysis. But several other metal salts (like Rh, Ru, and Cu etc.) also show promising results. Not only meta-C-H functionalization, further improvement already has been developed. Designing more suitable templates, para-C-H functionalization of arenes has already been developed by several research groups. Though many questions arise about the efficiency of those distal (meta/para)-C-H functionalization through atom economy, because of the use of a relatively big template to furnish the desired functionalization and additionally the use of several additives (like, ligands, oxidants etc.), which are not recyclable. However, the advent of distal C−H functionalization has been impressive and seeing the rapid progress in this field, we hope all the shortcomings will be addressed in near future.

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