Remote C—H Bond Functionalizations
Methods and Strategies in Organic Synthesis
Remote C—H Bond Functionalizations
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### 11 Radically Initiated Distal C(sp\(^3\))–H Functionalization

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Innovation and implementation of science and technology is a defining parameter to determine the progress of a civilization. Inquisitive minds are constantly devoted in empowering the human civilization by elegant discoveries and their subsequent applications in practical life. Organic chemistry, being a prime component of modern science, has served the human society in a way that has pronounced to be a boon for the present era. In one hand organic chemistry has unfolded the mechanistic intricacies of biorelevant reactivity, while on the other hand it has uncovered the methods to synthesize the molecular architecture that can either mimic the biological activity or can alter the same. Additionally, organic chemistry has profound industrial application including agrochemicals, food industry, dyes industry, polymer industry, and so on. As a whole, organic chemistry has become an inseparable component in our daily life. However, the genesis of these applications and large scale synthesis used to be initiated at synthetic laboratory. The ground breaking discoveries by erudite chemist have thus proved the intellectual supremacy of human race. However, the efficacy of synthetic methods is dependent on the step economy, atom economy, and environment benignity. Never ending aspiration to search such fruitful methods continues to challenge the chemist and inspire new chemical transformations. Accounting these existing literature precedents in the form of a concise summary, which would be the tutorial resources for future generation to accomplish successive progress, is undeniably one of the best efforts to intensify the expansion of chemical synthesis.

C—H bond being the fundamental backbone of organic compounds, the potential of a C–H functionalization to amend a molecule overrides traditional routes on grounds of step and atom economy. This has triggered the development of various strategies with the aim to alter the physicochemical properties of specific compounds or add on molecular complexity. Irrespective of aliphatic or aromatic setup, the C—H bonds, vicinal to a functional group, are relatively easier to functionalize either by exploiting its acidity or by taking the advantage of its coordinating ability to the metal. Moving further toward distal positions, C–H functionalization is engrossed with several issues including the intrinsic inertness as well as regioselectivity due
to the overabundance of multiple C—H bonds with subtle reactivity differences. Therefore, a curious quest was always followed to execute distal C–H functionalization with precise site selectivity. In its itinerary thus far, a number of elegant approaches have been conceived to install functional group at distal location with precise and predictable selectivity. In this book, an attempt is made to provide a broad overview on contemporary advancements in the field of distal C–H functionalization. Eminent researchers, who are known for their significant contributions in distinguished research areas, have penned down their collective efforts to outline a coherent and comprehensive discussion about different strategies for distal C–H functionalization.

Chapter 2 introduces to the realm of directing group (DG) assisted distal arene meta-functionalization. Precise control on regioselectivity is one of the most important aspects in arene C–H functionalization. Arenes bearing heteroatom containing functionality, which is famously known as directing group (DG), were extensively exploited for proximal ortho-C–H activation. Extending such DG-assisted distal meta-functionalization strategy required proper template engineering that would ensure the meta-selective C–H activation. In this context, Yu and coworkers disclosed a “U”-shaped template for meta-selective alkenylation. Thereafter, Yu, Maiti, Tan, Li, and others embarked on exploring the scope of meta-functionalizations employing several templates. Gao and Li have collectively penned down in delineating a monograph on recent development of transition metal-catalyzed, template assisted distal meta-C–H functionalization.

Chapter 3 deals with the involvement of the Catellani reaction for distal functionalization of (pseudo)halo arenes. Transition metal-catalyzed cross-coupling reactions have revolutionized the art of modern synthesis. While aryl halides or pseudo-halides produced ipso-functionalized compounds, a new class of reactivity of aryl (pseudo)halide was developed by Catellani utilizing the combination of strained bicyclic olefin, norbornene (NBE), and palladium. A phenylnorbornylpalladium(II) (PNP) dimeric Pd-catalyst was successfully employed to furnish \( o,o' \)-disubstituted vinylarenes starting from aryl iodides, alkyl iodide, and olefin in a regioselective manner. This Pd–NBE cooperative catalysis was expanded further for a diverse class of substrates including NH-indoles and NH-pyrroles, arenes bearing directing group (DG), and arylboron compounds by several eminent scientists. Several electrophiles were utilized for ortho-functionalization, and various nucleophiles were used as terminating reagent for ipso-functionalization. In Chapter 3, Juntao Ye and Mark Lautens have provided a vivid description about the development of arene C–H functionalization relying on Pd–NBE catalysis. The discussion was initially focused on the processes initiated with Pd(0) and subsequent discussion was made on the protocols initiated with Pd(II). However, a large part of Chapter 3 was devoted in portraying synthetic applicability of the Pd–NBE cooperative catalysis.

The seminal work by Catellani on di-functionalization of aryl (pseudo)halides evolved in 1997. In later years, enormous efforts have been devoted in expanding the scope of this Pd–NBE cooperative catalysis in a relayed C–H activation process. In this context, Dong and Yu independently pioneered a directing group assisted meta-C–H functionalization utilizing the concept of Catellani reaction.
An ortho-directing group was employed for initial ortho-C–H activation and subsequent palladium relay was realized in presence of NBE to accomplish meta-selective arene-C–H functionalizations. While the directing group (DG) assisted C–H functionalization was extensively studied for ortho-functionalization, aforementioned seminal reports opened up a new horizon in distal meta-C–H functionalization. Cheng and Zhou discussed about the recent advancements on directing group assisted meta-selective functionalization of arenes relying on NBE mediated Catellani type reaction. A detailed discussion was made on various functionalizations including alkylation, arylation, alkynylation, chlorination, and amination, which were achieved by anchoring different ortho-directing groups such as amides, amines, pyridine, or even free carboxylic acid.

In Chapter 5, a comprehensive summary on ruthenium catalyzed distal meta- and para-C–H functionalization was provided by Ackermann and coworkers. In last decades a number of handful synthetic protocols were developed to accomplish remote arene C–H functionalization by Ru-catalysis. Ru-catalyzed ortho-C–H ruthenation and subsequent ortho-functionalization were known in literature over few decades. In a sharp contrast, a unique catalytic reactivity to furnish meta-functionalized product from such ortho-ruthenated arenes was first observed by Frost and Ackermann in 2011 and 2013, respectively. In later years, Ackermann, Frost, Greaney, Zhang, and others successfully demonstrated a number of useful meta-functionalization methods relying on similar strategy. Ru-catalyzed para-selective functionalization was also included in Chapter 5 to retrospect the entire spectrum of Ru-catalyzed remote C–H functionalization.

While Chapters 2–5 of this book were focused on discussing various approaches for distal arene C(sp²)–H functionalization based on directing group assisted protocols, Catellani reactions, or via arene cyclo-ruthenation methods, in Chapter 6 Phipps and coworkers devoted their efforts in summarizing a complementary strategy for remote arene functionalization harnessing the non-covalent interactions. Although non-covalent interactions are prevalent in enzymatic reactions but translating such interaction in regioselective functionalization of small molecule in synthetic scale is rare. Despite the several challenges associated in controlling the site selectivity of arene functionalization, in recent years a number of elegant methods were developed by Smith, Kanai, Phipps, Chattopadhyay, and others. Phipps and his co-authors illuminated about the emergence of non-covalent interaction in distal arene-C–H functionalization in Chapter 6.

Although use of directing group, transient mediator or non-covalent interactions have been popularized in recent years to harness the regioselective transformation of arenes. However, transition metal-catalyzed functionalization governed by the steric and/or electronic factors was cultivated over the century to mitigate the issues pertaining to the site-selectivity. Intrinsic biasness derived from the substituted functionality present in arenes or heteroarenes is considered to be the key component in defining the selectivity. While such strategy, precludes preinstallation of directing group or circumvent the complicated catalytic path involved in NBE mediated process, but were largely limited by the nature of substrate as well as usage of excess amount of arenes. However, prudent combination of catalyst, ligand, and reagent
designing has been realized in recent years to enable regioselective functionalization of arenes or heteroarenes with broad functional group tolerance. An exemplified discussion of such non-directed distal arene functionalization is made by van Gemmeren et al. in Chapter 7. The prime attention was paid in depicting the recent progresses on non-directed distal arene functionalization, where arenes were used as limiting reagent.

In Chapter 8, Dutta and Maiti discussed about the recent progresses in the realm of distal arene \( \text{para}-\text{C–H} \) functionalizations. Distinction of energetically comparable \( \text{C—H} \) bonds to achieve regioselective \( \text{C–H} \) functionalization is one of prime focus of modern synthesis. In this regard, a number of strategies are known in the literature to perpetrate \( \text{para} \)-selective functionalization. Although electronic controlled Friedel–Crafts reaction being the early examples to promote \( \text{para}-\text{C–H} \) functionalization but this strategy is severely restricted with certain substrates and produced \( \text{ortho} \)-functionalized product as an unavoidable side product. Thus, the propulsive thrust in establishing strategies exists, which are not dependent on the electronic properties of the targeted substrate. The use of directing group, steric governance, non-covalent interactions, and radical initiation is cultivated to expand the scope of arene \( \text{para}-\text{C–H} \) functionalization. Chapter 8 is aimed to provide a comprehensive and exemplified discussion on directing group assisted, steric controlled, and non-covalent interactions promoted \( \text{para} \)-functionalizations to enlighten the scope of \( \text{para} \)-selective functionalizations beyond electronic control.

Chapter 9 deals with heterocycle functionalizations at unusual positions. Heterocycles are prevalent structural core in pharmaceuticals, natural products, and agrochemicals. Regioselective \( \text{C–H} \) functionalization of heterocycles is of paramount importance as the derivatization of these heterocyclic cores can alter their inherent properties. However, \( \text{C–H} \) functionalizations of hetero-arenes are predominantly achieved at electronically biased positions. Therefore, standing against the innate inertness to attain selective \( \text{C–H} \) functionalization at unusual positions is of paramount importance in order to enrich the repertoire of heterocyclic compounds. The ever-expanding inquisitive minds have dedicated their efforts in finding and devising suitable methodology to promote site selective \( \text{C–H} \) functionalization of apparently inert \( \text{C—H} \) bonds present in heteroarenes. Hirano and Miura have elucidated these recent reports in Chapter 9. Recent progress on \( \text{C–H} \) functionalization of important heterocycles, namely, indole, (benzo)thiazole, pyrrole, pyridine, quinoline, and others is concisely recapitulated in Chapter 9.

Unlike arene \( \text{C(sp}^2\text{)}–\text{H} \) functionalization, aliphatic \( \text{C(sp}^3\text{)}–\text{H} \) functionalization is relatively challenging due to its inherent inertness, low acidity, and overabundance with flexible long chain. Additionally, control over stereoselectivity is another important aspect to take care. Although functionalization of acidic \( \text{C—H} \) bonds adjacent to electron-withdrawing functional group or allylic and benzylic \( \text{C—H} \) bonds was exploited with electrophile, reciprocating such reactivity is impossible for remote \( \text{C–H} \) functionalization of long chain aliphatic substrates. However, the assistance from directing group enabled the delivery of functional groups at a desired position with uncompromised yield and selectivity. A vivid exemplification about the recent
reports on directing group assisted remote functionalization of aliphatic substrates was presented by Li, Zhang, and Shi in Chapter 10.

Chapter 11 by Li and Zhu articulates the recent progresses on radical initiated distal C(sp\(^3\))–H functionalizations. Intramolecular hydrogen atom transfer process has provided a synthetically useful tool to promote regioselective functionalization of aliphatic substrates. Hofmann–Loffler–Freytag (HLF) reaction was considered as the pioneering invention in this realm. Although the potential of this strategy was realized lately in 2010, when a rapid growth was witnessed to promote radical initiated distal aliphatic functionalization via hydrogen atom transfer. In Chapter 11, comprehensive summary on different methods, synthetic applicability, and mechanistic intricacies are discussed from 2010 onwards.

Chapter 12 is devoted in discussing non-directed functionalizations of aliphatic compounds, governed by innate reactivity. Although several challenges associated with the site selective functionalization of aliphatic substrates, constant up-search in finding suitable protocols either by tuning the innate reactivity of particular C—H bond present in the substrate or by controlling the reagent and catalyst has led to revolutionize the modern era of aliphatic C–H functionalization. Sambiagio and Maes have summarized the recent progress on non-directed aliphatic C–H functionalization at the remote position. Although a major part of aliphatic C–H activation was accomplished by directing group assisted strategy, Chapter 12 includes only non-directed aspect of aliphatic distal C–H functionalization. Chapter 12 was broadly divided into two parts: (i) the reaction involving distinct formation of metal–carbon bond and (ii) the reactions occurring without the metal–carbon bond formation.

While the sojourn through transition metal-catalyzed distal C–H functionalization goes on in Chapters 2–12, in Chapter 13, Costas introduces to the territory of remote aliphatic C–H oxidation by bioinspired catalysis. Selective C–H oxidation is a routine task in biological system. The selectivity in enzymatic process is governed by the virtue of several interactions that enable the proper substrate trajectory and geometric orientation. Imitating such reactivity in laboratory synthesis is relatively challenging yet worthy to explore. Therefore, a persistent attempt to comprehend the mechanistic insight of biological reactivity and catalyst or ligand design was pronounced to furnish site selective functionalization of aliphatic substrate. A comprehensive survey on aliphatic C–H oxidation imparted by the bio-inspired catalysis is outlined by Costas in Chapter 13.

The endless curiosities of human mind are the key to the technological advancements and evolution. This eternal truth has remained the essence for every piece of advancement since ancient times and will continue to remain persistent till times eternity. Modernization of scientific research in organic chemistry genre has shaped up in the form of C–H activation based protocols that has fostered a novel dimension in synthetic prospects and restructured the temperament of the scientific fraternity accordingly. This book besides providing a comprehensive scenario on the field of distal C–H activation also aims to inculcate cognizance among researchers of present and future generations to streamline and channelize their scientific understanding for the welfare of human civilization.
2

Transition Metal-Catalyzed Remote meta-C–H Functionalization of Arenes Assisted by meta-Directing Templates

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2.1 Introduction

Site-selective C–H functionalization has emerged as an important synthetic methodology in organic synthesis in the past two decades [1–10]. For such synthetic methodology to be synthetically useful, precise control of the site-selectivity of C–H functionalization reactions is one of the most important issues required to be resolved due to the presence of several C—H bonds with similar reactivity in an organic molecule. Notably, meta-selectivity in C–H functionalization of arenes is one of the intriguing site selectivities that have been intensely studied in recent years [1–10]. Although thousands of methods for ortho-C–H functionalizations of arenes via proximity-induced cyclometallation have been reported, only a limited number of approaches have been disclosed in meta-C–H functionalizations of arenes. One of the representative approaches of meta-C–H functionalization of arenes is the directing template assisted remote meta-C–H functionalizations of arenes via geometry-induced metalation (Scheme 2.1a) [5–10].

ortho-C–H functionalization has been usually promoted by σ-chelation of the directing template. However, applying this chelation to meta-C–H functionalization is much more challenging since a strained cyclophane-like metallacycle might be involved in this transformation [11]. In 2012, the group of Yu and coworkers disclosed the first geometry-induced remote meta-C–H activation of toluenes and hydrocinnamic acids with a Pd(II) catalyst, which is assisted by two types of rationally designed nitrile-based templates that are covalently linked with toluenes or hydrocinnamic acids through an ether or amide bond (Scheme 2.1b) [11]. The presumable linear coordination mode of the nitrile-based chelating functionality (CF) in the U-shaped template that weakly coordinates to the palladium center in an end-on fashion is important for securing a possible less strained cyclophane-like pre-transition state. However, a more likely catalytic scenario is the weakly chelating template may “catch and release” the Pd(II) catalyst closely to the target meta-C—H bond, leading to a high effective concentration of the Pd(II)
catalyst at the target meta-C—H bond without forming an 11- or 12-membered cyclophane-like palladacycle.

(a) **Template assisted** meta-C—H activation

(b) **Seminal report**'s examples

(c) **Substrate types**: toluenes, acids, amines and N-heterocyclic arenes, sulfonic acids, phenols, alcohols, silanes, phosphonates

(d) **Dominant length** from chelating atom to target C—H bond: 10–12 atoms, 9–11 bonds

**Scheme 2.1** Directing template assisted meta-C—H bond functionalization. Related reviews: (a) Li et al. [5], Yang [6], Chattopadhyay and Bisht [7], Dey et al. [8], Ghosh and De Sarkar [9], and Dey et al. [10]; Source: (b) Modified from Leow et al. [11].

Inspired by this pioneering work, a series of directing template assisted remote meta-C—H activation reactions have been realized for a list of substrates including acids, amines, sulfonic acids, and so on (Scheme 2.1c). Notably, one of the key features of these reactions is the target C—H bond is usually 10–12 atoms away from the chelating atom of the template (Scheme 2.1b,d), although longer length was also possible. To date, three categories of CFs have been engineered including two nitrogen-based CN-containing (Scheme 2.2a) or heteroarene-containing (Scheme 2.2b) CFs and one oxygen-based CO₂H-containing CF (Scheme 2.2c). It should be noted that besides these three CFs that covalently attached to the substrate, two catalytic bifunctional templates that reversibly coordinate to the substrate were also reported recently and they are not classified in these categories [12, 13]. Another key feature of these reactions is that hexafluoroisopropanol (HFIP), which could also be used as an additive, appears to be the privileged solvent. Finally, N-acetyl glycine (Ac-Gly-OH), a mono-N-protected amino acid (MPAA), is often the ligand of choice for many of these reactions, although other MPAA ligands could also be utilized in some cases.

Herein, we summarize important achievements that were disclosed until October 2019 in the field of directing template assisted meta-C—H functionalization of arenes with Pd or Rh catalysts since 2012. Different aspects of this type of methodology will be covered while discussing the works that are categorized by the substrate type.
2.2 Template-Assisted meta-C–H Functionalization

2.2.1 Toluene Derivatives

In 2012, Yu and coworkers devised the first effective U-shaped nitrile-based directing template that was covalently linked to the toluene derivatives via a removable benzyl ether linkage (Scheme 2.3) [11]. Notably, the directing ability of the template was improved by installing two isobutyl templates at the α-position adjacent to the linearly chelating nitrile template due to the Thorpe–Ingold effect. This directing template efficiently enabled the meta-C–H olefination of a broad range of toluene derivatives using Pd(OPiv)₂ as the catalyst and AgOPiv as the oxidant. It is worth mentioning that such remote C–H activation that possibly demanded a cyclophane-like 11-membered palladacycle was first ever disclosed. Remarkably, the intrinsic electronic and steric biases of the substrates were successfully overridden. Finally, the directing template was readily cleaved through hydrogenolysis with a Pd/C catalyst.

Scheme 2.2 Three categories of chelating functionality (CF). (a) N-Based CN-containing CF; (b) N-based heteroarene-containing CF; (c) O-based CO₂H-containing CF.

Important mechanistic studies on this methodology will also be included. It is hoped that the reader will learn the key points, especially structural features, for rationally designing a feasible template for new substrates as well as developing new types of meta-C–H transformation after reading this chapter.

2.2 Template-Assisted meta-C–H Functionalization
2 Remote meta-C–H Functionalization

Scheme 2.3 meta-C–H activation of toluene derivatives. Source: Modified from Leow et al. [11].

2.2.2 Acid Derivatives

2.2.2.1 Hydrocinnamic Acid Derivatives

In Yu’s seminal report, meta-C–H olefination of hydrocinnamic acid derivatives was also achieved using an easily synthesized and recyclable 2,2′-azanediyldibenzonitrile directing template, which is now available from Sigma–Aldrich as the Yu–Li auxiliary [11]. This template was attached to several hydrocinnamic acids via a readily cleavable amide linkage (Scheme 2.4). It is worth mentioning that hydrocinnamic acids are core motifs of many drug molecules such as Baclofen. Notably, it was discovered that the MPAA ligand Ac-Gly-OH from the simplest amino acid significantly improved the yield of the reaction and improved the selectivity as well with the optimal HFIP solvent that was crucial for the full conversion of the substrate. It was found in subsequent reports that this set of novel reaction conditions was also highly effective for many of the directing templated assisted meta-C–H transformations. In this transformation, not only the intrinsic electronic biases of the substrate were overridden (9, 10), but also challenging steric hindrance was overcome by the template (11). Intriguingly, biaryl acid substrate that has the same length between the chelating nitrile group and the target meta-C—H bond as hydrocinnamic acid...
could also undergo meta-selective C–H olefination of the remote aryl ring (12). Finally, the directing template could be easily removed by hydrolysis under basic conditions at room temperature, leading to the meta-olefinated hydrocinnamic acids and the recycled directing template.

In 2016, Maiti and coworkers disclosed a 2-hydroxybenzonitrile template for mono meta-selective olefination of hydrocinnamic acids via an ester linkage (Scheme 2.5a) [14]. Due to the less statistical availability of the coordinating nitrile group compared with the original 2,2′-azanediyldibenzonitrile directing template, high mono-/di-selectivity could be obtained with this new template at lower reaction temperature using 1,2-dichloroethane (DCE) as the major solvent and HFIP as the minor solvent. Notably, hetero-di-olefination product could be afforded with a second meta-C–H olefination under similar reaction conditions using HFIP as the sole solvent (Scheme 2.5b).

Most recently, Li and coworkers developed the first example of carboxy group assisted, remote meta-selective C(sp²)–H activation with a PdII-catalyst via potential κ² coordination of the carboxyl, suppressing the ortho-C–H activation via the κ¹ coordination (Scheme 2.6a) [15]. Unlike the previous nitrogen-based CN-containing or heteroarene-containing templates, this is the first oxygen-based carboxyl-containing template, whose coordination geometry could be considered as a pseudo-linear coordination along the aryl–CO₂M bond similar to the nitrile-coordination geometry. Notably, hydrocinnamic acids could be meta-olefinated in a remote selective fashion, leaving the C—H bond ortho to the carboxy group on the same aryl intact, although carboxy group is well-known to be a good ortho-directing group (Scheme 2.6b). Moreover, tuning the electronic and
stERIC properties of the carboxy group by switching the hydrogen atom ortho to the carboxy group with a fluorine atom, the yield as well as the site selectivity could be improved to some extent (Scheme 2.6c). The possible presence of κ^2 coordination in assisting remote-selective C–H activation may inspire the exploration of novel site-selectivity of the carboxyl assisted C–H activation reactions.

Besides Pd-catalysts, Rh-catalyst could also be used for olefination of hydrocinnamic acids. In 2017, Lu, Sun, Yu, and coworkers reported the first example of Rh(III)-catalyzed, directing template assisted remote meta-C–H olefination of hydrocinnamic acids via a postulated 12-membered macrocyclic intermediate (Scheme 2.7a) [16]. The directing template bearing a single nitrile group was slightly different from Yu’s seminal template. Moreover, molecular oxygen could be used as the terminal oxidant for this reaction. Subsequently, meta-C–H alkenylation of hydrocinnamic acids was also realized using alkynes, which are significantly less reactive than the polarized and reactive acrylate (Scheme 2.7b) [17]. Notably, transition metal-catalyzed meta-alkenylation using alkynes has not been successful with Pd catalysts in previous reports on the directing template strategy.

In addition to meta-C–H olefination, meta-C–H arylation of hydrocinnamic acids was made possible using the directing template strategy. In 2013, Yu and coworkers reported the first example of Pd-catalyzed cross-coupling of meta-C—H bonds with arylboronic esters to afford meta-arylated hydrocinnamic acids derivatives.
2.2 Template-Assisted meta-C–H Functionalization

The working model

(a) Proposed remote-selective C–H activation via $\kappa^2$ coordination of the carboxyl. (b) Remote-selective meta-C–H olefination of hydrocinnamic acids. (c) Improved site-selectivity and reactivity with a modified carboxyl-containing template. Source: (a) Modified from Li et al. [15].
Scheme 2.7  (a) Rh(III)-catalyzed directing template assisted remote meta-C–H olefination of hydrocinnamic acids. (b) Rh(III)-catalyzed meta-C–H alkenylation of hydrocinnamic acids using alkynes. Source: (a) Modified from Xu et al. [16]; (b) Modified from Xu et al. [17].
2.2 Template-Assisted meta-C–H Functionalization

Scheme 2.8  meta-C–H arylation of hydrocinnamic acids with arylboronic esters. Source: Modified from Wan et al. [18].

Scheme 2.9  meta-C–H arylation of hydrocinnamic acids with aryl iodides. Source: Modified from Li et al. [15].

arylation of hydrocinnamic acid derivatives with aryl iodides assisted by the carboxyl-based template (Scheme 2.9) [15]. Notably, the site-selectivity is generally excellent with moderate to good yields. Moreover, aryl halides bearing an ortho-electron-withdrawing group (o-EWG) such as a methyl ester group were found to be most suitable with the reaction, which is possibly because that the combined electronic as well as weak coordinating effect of the o-EWG could facilitate oxidative addition with these aryl iodides.
Finally, C–H deuteration and alkylation of hydrocinnamic acid derivatives were also possible using N-based heteroarene-containing templates, but only isolated examples were disclosed [19]. In short, the notable meta-C–H activation hydrocinnamic acid derivatives includes olefination and arylation with Pd(II) or Rh(III) catalysts, using nitrile-based or carboxyl-based templates.

2.2.2.2 Phenylacetic Acid Derivatives

The generality of the template strategy in accommodating potential macrocyclopalladation processes with smaller ring sizes was also investigated with phenylacetic acid derivatives. Notably, the Fujiiwara–Moritani-type olefination is often used as the effective model reaction to test feasibility of a new substrate design of meta-C–H activation relation. In 2014, the Maiti group introduced a new category of nitrile-based phenolic directing template, which is now available from Sigma Aldrich as the Maiti–Bera–Modak (MBM) auxiliary, for meta-C–H olefination of phenylacetic acid derivatives via an ester linkage (Scheme 2.10) [20]. In this new class of substrates, a smaller 12-membered cyclic transition state was proposed for the palladation step than hydrocinnamic acid derivatives. With this easily synthesized and removable 2-hydroxybenzonitrile template, a broad range of phenylacetates were olefinated in a highly mono-selective as well as meta-selective fashion. Moreover, this protocol was also applied to drug molecules such as ibuprofen in a moderate yield and selectivity, products of which are difficult to access using conventional methods of diversification.

Simultaneously, Yu and coworker disclosed a protocol of the commercially available dibenzonitrile directing template assisted meta-C–H olefination of phenylacetic acid derivatives via an amide linkage [21]. Notably, N-formyl-protected glycine
(Formyl-Gly-OH) was identified as the new ligand for this new class of substrate. Unlike previous protocols, weak base KH$_2$PO$_4$ was required to use as the crucial additive. This reaction further demonstrates the good versatility of the template approach in accommodating potentially necessary macrocyclcopalladation processes with different ring size for different classes of substrates (Scheme 2.11) [21].

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\begin{align*}
\text{R}^1 & \quad \begin{array}{c} \text{H} \\ \text{Pd(OAc)}_2 (10 \text{ mol\%}) \\ \text{Formyl-Gly-OH (20 mol\%)} \\ \text{KH}_2\text{PO}_4 (50 \text{ mol\%}) \\ \text{AgOAc (3 equiv)} \\ \text{HFIP, 90 °C, 24 h} \\ \text{R}^1 \text{R}^2 \text{T} \end{array} \\
\text{R}^3 & \\
\text{T} = \begin{array}{c} \text{NC} \\ \text{Me} \end{array}
\end{align*}
\]

Scheme 2.11 meta-C–H olefination of phenylacetic acid derivatives. Source: Modified from Deng et al. [21].

In 2017, the Maiti group developed the first rhodium-catalyzed meta-C–H olefination of phenylacetic acid frameworks with the assistance of 2-hydroxy-4-methoxy benzonitrile template (Scheme 2.12) [22]. The XPhos (2,4',6'-diisopropyl-1,1'-bip

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\begin{align*}
\text{R}^1 & \quad \begin{array}{c} \text{H} \\ \text{[(Rh(COD)Cl)]}_2 (5 \text{ mol\%}) \\ \text{XPhos (10 mol\%)} \\ \text{Cu(CO}_2\text{CF}_3)_2 \cdot \text{xH}_2\text{O (1 equiv)} \\ \text{V}_2\text{O}_5 (1 \text{ equiv}) \\ \text{DCE, 120 °C, 36 h} \\
\text{R}^1 \text{R}^2 \text{T} \end{array} \\
\text{R}^2 & \\
\text{T} = \begin{array}{c} \text{NC} \\ \text{Me} \end{array}
\end{align*}
\]

Scheme 2.12 Rh-catalyzed meta-C–H olefination of phenylacetic acid derivatives. Source: Modified from Bera et al. [22].
henyl-2-yldicyclohexylphosphine) was identified as the crucial ligand for this reaction. Substituents of phenylacetic acid esters at all positions of the arene ring were found to be tolerated. Synthetic application of this protocol was also expanded to the diversification of ketoprofen, a drug molecule containing a secondary α-methyl substituent.

Besides nitrile-based templates, N-containing heteroarene-based templates also proved to be applicable for the phenylacetic acid frameworks (Scheme 2.13) [23]. In 2017, Yu and coworkers reported the a Pd-catalyzed meta-C–H olefination of phenylacetic acid scaffolds using a pyridine-based template via an amide linkage. A variety of phenylacetic acids, including cyclic and heterocyclic substrates, were efficiently meta-C–H olefinated in HFIP solvent without using additional ligand, opening new avenues for potential utility in C–H functionalization of advanced intermediates and late-stage modifications. Notably, the template could be used to extend the reaction scope to cross-coupling and iodination reactions (vide infra).

Scheme 2.13  Pyridine-based template assisted meta-C–H olefination of phenylacetic acid derivatives. Source: Modified from Jin et al. [23].

A novel N-containing pyrimidine-based template was also utilized to enable meta-C–H perfluoroalkenylation of phenylacetic acid derivatives by Werz, Zanoni, Maiti, and coworkers for the synthesis of organofluorine compounds (Scheme 2.14a) [24]. Notably, perfluoroalkenylation of drug molecule Ibuprofen was also possible with this protocol and the cleavage of the template is facile.

Meanwhile, Wang, Zhou, and coworkers also reported a close protocol using olefin coupling partners other than perfluoroolefins such as acrylates (Scheme 2.14b) [25].

As mentioned earlier, pyridine-based template has been devised for meta-C–H olefination of phenylacetic acid scaffolds by the Yu group [23]. In the same report, it was also demonstrated that the meta-C–H activation with this template could be extended to meta-C–H cross-coupling with potassium trifluoroborate and