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## Introduction

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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

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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 pseudohalides 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 phenylnorbornenylpalladium(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(sp<sup>2</sup>)-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 heteroarene with broad functional group tolerance. An exemplified discussion of such non-directed distal arene functionalization is made by van Gemeren 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 *para*-C–H functionalizations. Distinction of energetically comparable C–H bonds to achieve regioselective 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 *para*-selective functionalization. Although electronic controlled Friedel–Crafts reaction being the early examples to promote *para*-C–H functionalization but this strategy is severely restricted with certain substrates and produced *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 *para*-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 *para*-functionalizations to enlighten the scope of *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 C–H functionalization of heterocycles is of paramount importance as the derivatization of these heterocyclic cores can alter their inherent properties. However, C–H functionalizations of heteroarenes are predominantly achieved at electronically biased positions. Therefore, standing against the innate inertness to attain selective 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 C–H functionalization of apparently inert C–H bonds present in heteroarenes. Hirano and Miura have elucidated these recent reports in Chapter 9. Recent progress on C–H functionalization of important heterocycles, namely, indole, (benzo)thiazole, pyrrole, pyridine, quinoline, and others is concisely recapitulated in Chapter 9.

Unlike arene C(sp<sup>2</sup>)-H functionalization, aliphatic C(sp<sup>3</sup>)-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 C–H bonds adjacent to electron-withdrawing functional group or allylic and benzylic C–H bonds was exploited with electrophile, reciprocating such reactivity is impossible for remote 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<sup>3</sup>)-H functionalizations. Intramolecular hydrogen atom transfer process has provided a synthetically useful tool to promote regioselective functionalization of aliphatic substrates. Hofmann-Löffler-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.

