

C-H bond functionalization of Aromatics

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Functionalization of carbon-hydrogen bond is the hot topic in chemistry due to its enormous applications in synthetic organic chemistry. Since, the C-H bond is available ubiquitously in organic compounds, but offers limited reactivity; however, its functionalization is critical to make C-C bonds. Friedal-Crafts reactions have been historic to functionalize C-H bond, but that gives only alkyl or acyl-groups on the aromatic ring along with a wide influence of directing groups. To date, most C-H bond functionalization is achieved by the methods requiring transition metal catalysts, e.g. Suzuki, Mizoroki-Heck, Negishi, and Stille coupling. Unfortunately, majority of these methods requires prefunctionalization of either one or both coupling partners in order to be highly efficient and regioselective. Hence, the conventional methods involved the reactions of organometallic reagents using B, Sn, Si, Mg and Zn and the wide range of aryl halides, causing two major drawbacks, a) activation of the reagents, and b) the organic waste. Activation of the substrates requires installation of additional functional groups, *via* harsh reaction conditions including transition metal-catalysts, and then their removal after cross-coupling reactions.

Modern methods, preferred by most pharmaceutical industries, for the synthesis of such compounds are based on the C-H bond activation of either one or both aromatic coupling moieties. In single C-H bond activation, an activated substrate installed with halides or organometallic/carbonylative reagent undergoes cross-coupling reaction with unactivated arene in the presence of various metal-catalysts. Single C-H bond activation has been well developed in terms of regioselectivity and high efficiency; however it still has some disadvantages, for instance, installation/uninstallation of activating groups and purification waste etc. The other approach to construct biaryl is through oxidative C-C bond formation *via* activation of two C-H bonds with a net loss of two hydrogen atoms. Double C-H activation methodology significantly increases the efficiency of the reaction without requiring pre-activation of substrates; and is relatively greener and most atom economical approach. However, scientist are exploring the pathways to overcome these challenges by carefully selecting the reaction conditions to avoid undesired homocoupling products, and selecting marginally complex substates since the position of newly formed C-C bond is determined by the steric and electronic nature of the two substrates. Both single and double C-H bond activation are mostly carried out with the aid of transition metals, such as Pd, Rh, Ru, Cu and Fe, with or without ligands leading to aryl-aryl, aryl-alkyl and alkyl-alkyl bond formation; however palladium is the most preferred one. Most ligands are the phosphorus based soluble in organic solvents and are air and moisture sensitive, requiring extremely dry reaction conditions. These

ligands play an important role in cross-coupling reactions by the virtue of their electronic structure and their binding ability to the palladium metal, thereby influencing the oxidative as well as reductive elimination steps.

Further development in C-H bond functionalization is required in line with the use of common and economical metal catalyst, such as iron and copper, and environmentally benign methods such as ligand-free catalytic processes, to make the C-C bond formation efficient and environmentally friendly.^{1,2}

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