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Digest paper

# C–H activation reactions as useful tools for medicinal chemists

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ABSTRACT

In recent years, there has been an exponential rise in the number of reports describing synthetic methods that utilize catalytic $sp^3$ and $sp^2$ C–H bond activation. Many have emerged as powerful synthetic tools for accessing biologically active motifs. Indeed, application to C–C and C–heteroatom bond formation, provides new directives for the construction of new pharmaceutical entities. Herein, we highlight some recent novel C–H activation processes that exemplify the utility of these transformations in medicinal chemistry.



In recent years, C–H activation reactions have emerged as powerful tools for C–C bond formation[1] and provide an efficient synthetic alternative to conventional cross-coupling reactions. C–H transformations are particularly useful for shortening multi-step syntheses since they do not require the installation of activated functional groups such as halogens or triflates. In addition, C–H halogenation and C–H borylation provide a synthetic tool to access challenging substrates that can be subsequently converted to a wide range of motifs through more traditional Pd-catalyzed coupling reactions (Scheme 1).

Even though great advances in the field of C–H activation have been achieved, many challenges still remain. In addition to the low reactivity of C–H bonds (due to their high bond strength, ca. 110 kcal/mol), controlling regio-selectivity of C–H transformations has proven difficult since substrates usually display multiple C–H bonds with close dissociation energies. Also, chemoselectivity in the presence of sensitive functional groups still presents a challenge. Herein, we will highlight the application of C–H functionalization for the construction of pharmaceutically relevant scaffolds and describe the latest advances made to overcome these issues, thus rendering C–H activation a powerful tool for medicinal chemists.

Medicinal chemists heavily rely on C–C bond-forming reactions in the design of small molecules libraries. Among these reactions, arylations play an important role and, if regioselectivity can be controlled and predicted, arylations via C–H activation methods can represent a powerful synthetic tool. One of the most commonly applied strategies to achieve regioselectivity involves chelation assistance by a proximal Lewis-basic directing group (DG) which leads to *ortho*-selective C–H functionalization.[2] Su and co-workers recently developed a Pd(II)-catalyzed *ortho*-C–H arylation (Scheme 2) in which variously substituted benzoic acids as well as 3-chlorophenyl acetic acid smoothly underwent C–H arylation with aryl iodides.[3] However, the reaction did not work with *ortho*-substituted aryl iodides or those bearing strong electron-withdrawing groups (e.g., $NO_2$, $CF_3$). Even so, this method provides the first example of C–H functionalization of electron-deficient benzoic acids under mild conditions.

Along these lines, Miura and co-workers developed an environmentally benign copper-catalyzed intermolecular biaryl cross-coupling (Scheme 3) of indoles/pyrroles and 1,3-azoles.[4] Notably, the cross-coupling proceeded exclusively at the indole/pyrrole C2-position, thus providing a selectivity outcome complementary to prior Pd-based methodologies. In parallel, an *ortho*-selective Cu-mediated intermolecular direct biaryl coupling was also described for arylazines and azoles (Scheme 3).[5]

Pd-catalyzed C–H arylations of heterocycles typically produce a mixture of regioisomers or favor the inherently reactive position (Scheme 4). In the absence of DGs, regioselectivity can be achieved through a Pd-catalyzed protocol using a chlorine activating/blocking group (Scheme 5).[6] A chlorine atom was installed on a reactive site: (1) to selectively arylate C2 or C5 of substituted thiophenes (Scheme 5, a and b); (2) to obtain exclusively C2- or C3-arylated indoles (Scheme 5, c and d); (3) to divert typical selectivity outcome of C–H arylation of thiazoles or oxazoles from C5 to C4 (Scheme 5, e); (4) to divert the arylation of benzothiophenes or benzoxazoles from C2 to C3 (Scheme 5, f). Additionally, the chlorine atom acted as an activating group to improve the yield of C–

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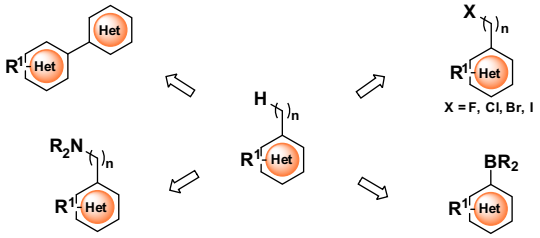
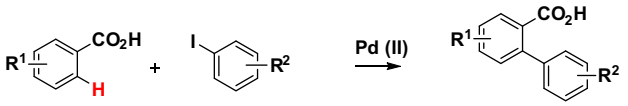
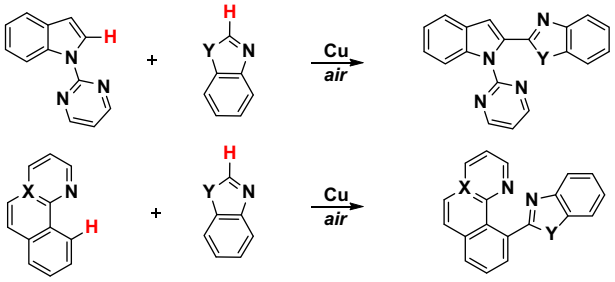



**Scheme 1.** C–H activation reactions provide diverse functionalization of aromatic and heteroaromatic motiffs.




**Scheme 2.** Pd-catalyzed *ortho*-C–H arylation of benzoic acids.

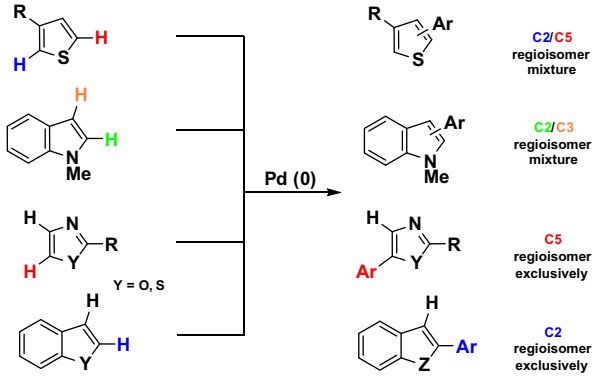



**Scheme 3.** Cu-catalyzed biaryl cross-coupling via C–H activation.

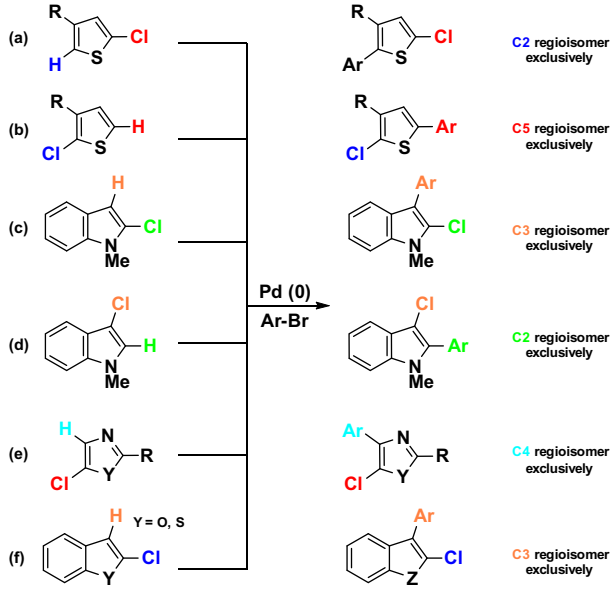
H arylation of imidazoles at C2. This protocol has valuable synthetic utility since it enables selective access to regioisomers that are difficult to synthesize with conventional metal-catalyzed cross-couplings (e.g., formation of C4-biaryl bond in thiazoles/oxazoles in the presence of C5 C–H bonds). It is worth noting that chlorine can be easily introduced on aromatic rings and may be easily removed or exploited for further transformations. Similar halogen-blocking strategies have been published for pyrazoles and are not limited to Cl.[7]

Selectivity towards other substitution patterns on aromatic rings is also possible via C–H activation methods. Interestingly, recent methods have been reported on selective activation of C–H bonds that are in remote *meta* position from the DG.[8–10] A *meta*-selective C–H arylation (Scheme 6) via Pd/norbornene catalysis has been recently described[8] for variously substituted benzylamines with aryl iodides bearing an electron-withdrawing substituent (e.g., $CO_2Me$, COMe, $CONMe_2$, $NO_2$) in *ortho*-position.[3] As highlighted by the authors, the use of a benzyl dimethyl amino DG gives the opportunity to access versatile synthetic precursors (e.g., benzaldehydes, benzyl chlorides) and can also be readily removed under standard hydrogenolysis conditions.

Yu and co-workers have developed a method for *meta*-C–H alkylation of phenylacetic amides that in turn was applied to *meta*-C–H arylation[11] (Scheme 7). The substrate scope is limited since the desired biaryl compounds were obtained only when using aryl iodides bearing an *ortho*-coordinating group (e.g., $CO_2$-Me, COMe) or highly electron withdrawing functionalities. Even so, this approach has interesting applications for the late stage arylation of heterocycles such as dihydrobenzofuran and indolines. Copper has also been proven to be useful in selective *meta*-arylation of pivalanides.[12]




**Scheme 4.** Typical regioselectivity of Pd-catalyzed arylation of heteroaromatics.




**Scheme 5.** Chlorine induce and diverted regioselectivity of C–H direct arylation.

Another commonly employed transformation utilized in the construction of pharmaceuticals is transition metal mediated $sp^2$ alkylation reactions. Traditionally, these reactions are performed through standard Pd-catalysis requiring a variety of reactive groups (e.g., –OTf, –Br, –I) to be pre-installed on the substrate. For this precise reason, the field of C–H activation has begun to address these limitations.

Several reports have been published on metal-catalyzed alkylation of $C(sp^2)$–H and $C(sp^3)$–H bonds. Rhodium has been reported to catalyze the oxidative *ortho*-directed C–H alkylation of arenes (Scheme 8) using potassium alkyltrifluoroborates.[13] This protocol is compatible with functionalizable groups (e.g., oximes) as well as other DGs including pyridines and pyrimidines, and is applicable to variously substituted indoles. An alternative protocol for *ortho*-C–H alkylation was developed for phenylacetic and benzoic acids (Scheme 9) using Pd(II)-catalysis and alkylboron reagents.[14] This protocol has important applications in medicinal chemistry considering the opportunity to chemically manipulate carboxylic acids and the prevalence of phenylacetic/benzoic acids as scaffolds. Rh-catalyzed $C(sp^3)$–H alkylation, using triarylboroxines as alkylation agents, has been described for various 2-ethyl pyridines and quinolines in the presence of $Ag_2O$.[15]