ARENE FUNCTIONALIZATION BY COOPERATIVE CATALYSIS OF Pd(II) AND NORBORNENE

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INTRODUCTION

Ubiquitous in nature, arenes are a common feature of many organic compounds used today. Stabilized by aromaticity, they are unreactive under a wide range of conditions. This stability can cause functionalization of the ring system to be difficult. Since the 1860's, chemists have used electrophilic aromatic substitution (EAS) reactions to functionalize various sites on aromatic rings.[1] However, as the location of this substitution is guided by the electronic effects of other substituents, manipulating the site of modification can be difficult. Since the discovery of EAS reactions, chemists have endeavored to develop new methods with better selectivity and a larger diversity of functionality. One of the newest methods, the Catellani reaction, uses two catalysts, palladium and norbornene (NBE), to functionalize specific sites of aromatic rings.[2]

Numerous derivatives of the initial Catellani reaction have been developed to access different site-selective functionalities.[2] These methods follow the same general mechanism. Using the existing functionality of the arene, the Pd inserts into a C-X or C-H bond. The norbornene then inserts into the Pd-C bond, freeing the Pd to activate the adjacent carbon which is then functionalized. Both the Pd catalyst and the norbornene are then regenerated, allowing the cycle to continue.[3] Whereas early versions employed a Pd(0) catalyst, recent advances use Pd(II) catalysts. Often these catalysts can install different functionalities compared to their Pd(0) counterparts.

META-SELECTIVE FUNCTIONALIZATION

Inspired by *ortho*-functionalization strategies, Yu and coworkers developed a method to functionalize the *meta*-position of aryl rings. Using an aryl amide as the directing group, Yu was able to achieve *meta*-functionalization with aryl and alkyl substituents (Figure 1).[4] In a similar study, Dong and coworkers employed a benzylic tertiary amine as the directing group, but could only install aryl, but not alkyl, groups.[5] For both of these methods, substitution at the *meta*-position occurs unless the *meta* or adjacent *ortho*-position is substituted. Thus, the ring will be difunctionalized unless a blocking group is present.[5]

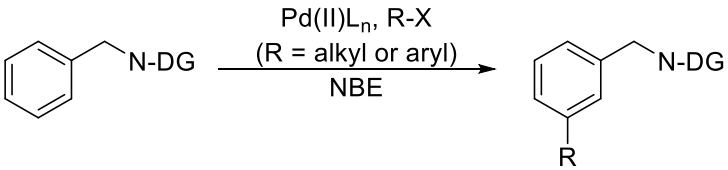

Figure 1. Generalized schematic of Yu's and Dong's *meta*-selective functionalization.

ORTHO-FUNCTIONALIZATION OF ARYLBORONS

Owing to the ubiquity of cross coupling reactions, arylborons are commonly employed by chemists to synthesize larger molecules. Simultaneous *ipso*-olefination and *ortho*-alkylation of these arylboronic acids can be achieved using Pd(II) and norbornene catalysts. First described by Zhang and coworkers, a variety of olefins and alkyl groups can be added to the arene.[3] This method requires stoichiometric amounts of an oxidant to regenerate the Pd(II) catalyst (Figure 2A). An alternative method of ortho-functionalization has been developed by Dong and coworkers.[6] In this method, the *ortho*-acylation and *ortho*-amination of boroxines requires a catalytic amount of base, but not an oxidant. The second electrophile is a proton which couples at the *ipso* position (Figure 2B).

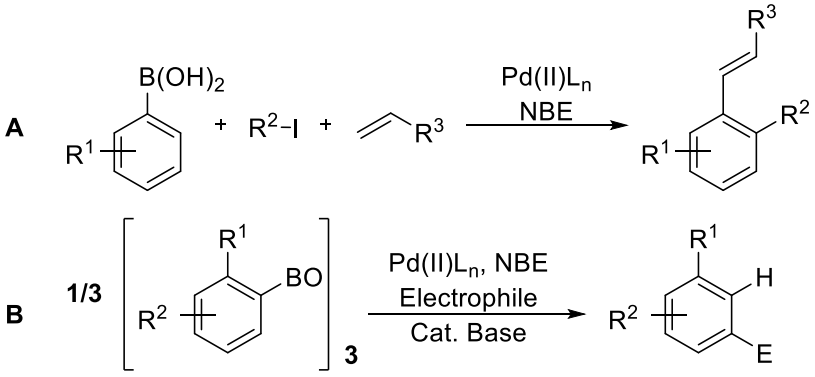

Figure 2. General schemes for Zhang's (A) and Dong's (B) arylboron functionalization methods.

2-FUNCTIONALIZATION OF INDOLES AND PYRROLES

The functionalization of heteroaromatic compounds through N-H activation with Pd(II)/NBE catalysis was first performed by Bach and coworkers.[7] With Pd(II), NBE, stoichiometric base, and an alkyl halide, the 2-position of indoles and pyrroles can be alkylated (Figure 3). Initially, the Pd catalyst was thought to first activate the C3-H bond, but mechanistic studies show that the Pd first activates the N-H bond. This method has been used to establish a new strategy for the synthesis of *Aspidosperma* alkaloids.[7] Additionally, a collaboration between the Xue and Jiang's laboratories developed a method to functionalize indoles with aryl aryl groups as well.[8] Collectively, these advances in arene chemistry expand the scope of Pd/norbornene catalysis, allowing for greater diversity and site-selectivity in functionalization strategies.

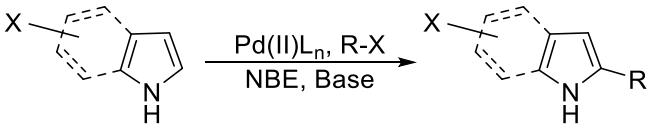

Figure 3. Bach's method for 2-functionalization of indoles and pyrroles.

References

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