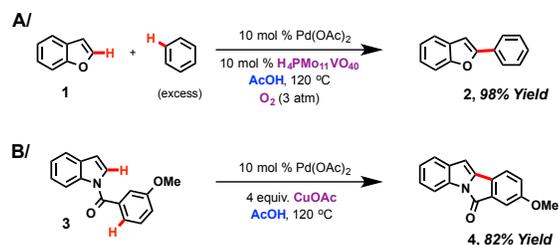


Development of New Reactions Using C–H Functionalization

We are developing new methods by which strong carbon-hydrogen (C–H) bonds can be selectively transformed into new carbon-carbon (C–C) or carbon-nitrogen (C–N) bonds. We have discovered novel processes by which arenes and heteroarenes can be oxidatively coupled to form new biaryl and aniline moieties. Most of the work involves precious metal catalysts; however, we are now expanding our work to study to use non-toxic and readily available iron catalysts and even metal-free conditions. This work is generally considered to be a part of the field of Green Chemistry. In 2011, I received the Pfizer Green Chemistry Award for my work in this field. Our work in this field has been supported by both the National Science Foundation (NSF), the Petroleum Research Fund (PRF) and the National Institutes of Health (NIH).

Organic synthesis via C–H activation is a relatively young field, but it is expanding at a blistering pace. In fact, green coupling reactions involving C–H activation were declared the highest-priority “aspirational” research area for new reaction development by a consortium of process chemists from major pharmaceutical companies.¹ Our work in the field of oxidative coupling for the formation of heterocoupled biaryls has resulted in high-impact publications (>1250 citations, to date). Our patent in 2006 represents the seminal example of the synthesis of arylated heterocycles via catalytic oxidative cross-coupling, and our initial work in the field with benzofuran substrates is the “greenest” synthesis of a cross-coupled biaryl molecule that has been published: It employed simple arene substrates and molecular oxygen as the terminal oxidant (Scheme 1).²



Scheme 1. Early catalytic oxidative arylations from the DeBoef laboratory.

With funding from the NSF, NIH and PRF we discovered five new oxidative coupling reactions that form C–C or C–N bonds via C–H activation (Scheme 2). Additionally, we have performed careful mechanistic studies of these oxidative coupling processes. Using the insight gained from some of these mechanistic studies, we developed a method for regioselectively arylating *N*-alkylindoles (Scheme 2A),³ and we demonstrated the utility of this oxidative coupling reaction in the synthesis of one of the best inhibitors of botulinum neurotoxin.⁴

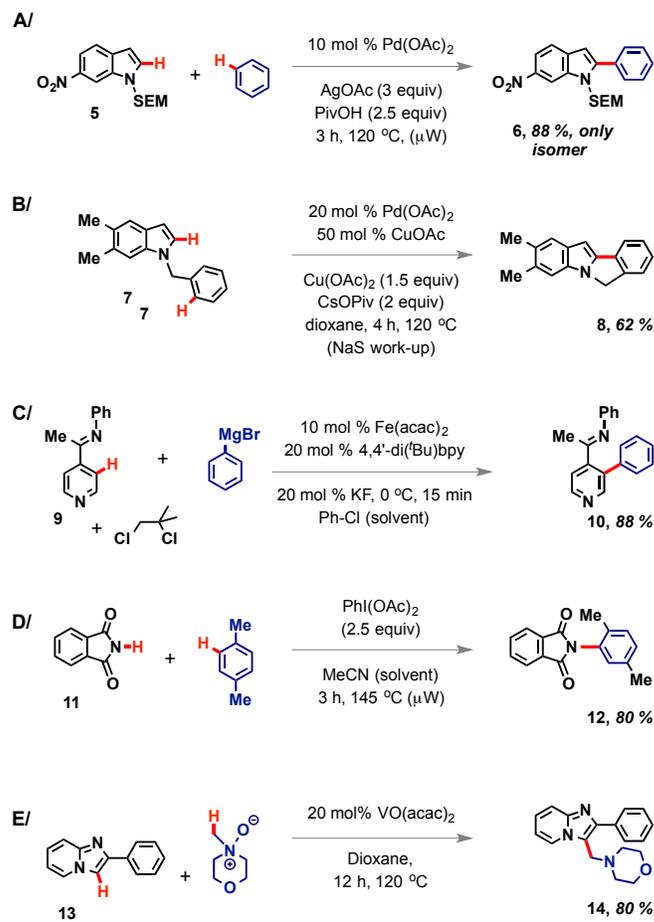
Subsequently, we studied the relationship between the oxidant and the mechanism of the Pd-catalyzed oxidative cross-coupling reactions. Through an extensive study of reaction kinetics and competition reactions, we demonstrated that oxidative coupling conditions employing heteropoly acids and O₂ (e.g. Scheme 1A),² proceed via a Pd(II)/Pd(IV) mechanism. To the best of our knowledge, this is the first example of a Pd(IV)-mediated oxidative coupling reaction.⁵

Though the majority of work in the field of oxidative coupling has involved the use of electron-rich heteroarenes, we have recently discovered that electron-poor heteroarenes can also participate in intramolecular oxidative coupling reactions (Scheme 2B). The two-fold C–H functionalization was achieved using a combination of Cu(I) and Pd(II) to metallate the two C–H bonds.⁶

Having established that biaryl C–C bonds could be readily synthesized by oxidative C–H bond coupling, we recently expanded our research focus to include the synthesis of C–N bonds, and we quickly discovered a novel method for oxidatively forming the C–N bonds of *N*-arylphthalimides using phenyliododiacetate (PIDA) as the only reagent (Scheme 2D).⁷ Additionally, we recently developed a method for tethering an amine to a heteroarene by constructing the C–C bond that is adjacent to the nitrogen atom via an oxidative aminomethylation reaction (Scheme 2E).⁸

While the majority of our work to date has focused on creating green catalytic reactions by employing substrates that are not pre-functionalized, an alternative method for creating a green reaction would be to develop new catalysts based on earth-abundant and non-toxic elements such as iron. Iron-catalyzed cross-couplings have been known for decades, but their popularity has increased dramatically in recent years.⁹ One of the most notable recent developments is the facile coupling of aryl halides with aryl Grignard reagents to form biaryls.¹⁰ These reactions are green, in that they proceed at low temperatures and employ simple, nitrogen-based ligands, if they need any formal ligands at all. The mechanisms of these reactions appear to be complicated, involving low-valent iron intermediates, possibly even intermediates in negative oxidation states, but the potential utility of these reactions is clear. Consequently, in addition to developing palladium, copper or gold catalyzed arylation and amination reactions, we have begun to focus our research on iron-catalyzed coupling reactions that involve C–H activation (Scheme 2C).¹¹

Our recent NSF grant, which was awarded in July 2016, will be used fund our efforts to further develop a gold-catalyzed C–H amination methodology that we have recently discovered and to further explore the mechanism of iron-catalyzed C–H activation reactions.



Scheme 2. New reactions developed with prior NSF funding.

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