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Cross-Coupling of Heteroatomic Electrophiles

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Abstract

At the advent of cross-coupling chemistry, carbon electrophiles based on halides or pseudohalides were the only suitable electrophilic coupling partners. Almost two decades passed before the first cross-coupling reaction of heteroatom-based electrophiles was reported. Early work by Murai and Tanaka initiated investigations into silicon electrophiles. Narasaka and Johnson pioneered the way in the use of nitrogen electrophiles; while Suginome began the exploration of boron electrophiles. The chemistry reviewed within provides prospective on the use of heteroatomic electrophiles specifically silicon-, nitrogen-, boron-, oxygen- and phosphorus-based electrophiles in transition-metal catalyzed cross-coupling. For the purposes of this review, a loose definition of cross-coupling is utilized; all reactions minimally proceed via an oxidative addition event. Although not cross-coupling in a traditional sense, we have also included catalyzed reactions that join a heteroatomic electrophile with an *in situ* generated nucleophile. However, for brevity, those involving hydroamination or C–H activation as a key step are largely excluded. This work includes primary references published up to and including October 2018.

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1. Introduction

The importance of cross-coupling reaction is difficult to understate. Since early studies by Heck were disclosed the late 1960s, the development and application of cross-coupling chemistry has had an immense impact on the field of organic chemistry.^{1–7} In the nearly 50 years since those initial reports, an explosion of diversity in metals, ligands, and coupling partners has led to thousands of publications in this field, and many reviews and books have been published cataloging the advancements.^{8–44} This has led to cross-coupling reactions being a cornerstone technology in vastly diverse research industries, including pharmaceuticals,^{34–35} agrochemicals,³⁷ polymers,^{45–47} and electronics⁴⁸ – among others. Indeed, the importance of this general area was recognized by the award of the 2010 Nobel Prize in Chemistry to Professors Heck, Suzuki, and Negishi for their development of palladium-catalyzed cross-coupling.

As outlined below, the vast majority of cross-coupling reactions have focused on the use of carbon-based electrophiles. And, until recently, most of those have focused exclusively on sp^2 -hybridized carbon ($C-sp^2$) electrophiles. The reasons for this stem both from the mechanistic aspects of early catalytic cross-coupling reactions, as well as a traditional focus on carbon-carbon ($C-C$) bond formation in organic reaction method development. However, in parallel to the development of these “traditional” carbon-electrophile based cross-coupling reactions, non-traditional cross-coupling reactions involving non-carbon-based electrophiles have also been explored. Until recently, however, work in this area has progressed at a much slower pace. In the past few years, increased interest in transition-metal catalyzed reactions of these heteroatomic electrophiles has demonstrated that cross-couplings protocols cannot only utilize these reagents, but that interesting and useful chemistry can emerge from them. And in many cases, these “heteroatomic” cross-coupling reactions lead to more efficient access to heteroatom-containing organic molecules than their “traditional” cross-coupling counterparts. Although certain classes of cross-coupling reactions have been described in highly-focused reviews,^{8, 10–14, 18–20, 26–27, 36, 38} to date there has been no comprehensive review of cross-coupling reactions that employ heteroatomic electrophiles. The chemistry reviewed within provides prospective on the use of heteroatomic electrophiles specifically silicon-, nitrogen-, boron-, oxygen- and phosphorus-based electrophiles in transition-metal catalyzed cross-coupling.

For the purposes of this review, a loose definition of cross-coupling is utilized to include all reactions that minimally proceed via an oxidative addition event of a transition-metal catalyst to a non-carbon-based electrophile. Because, in most cases, the details are not yet known, we have made no attempt to define or limit the mechanism by which this “oxidative addition event” occurs. Although not considered cross-couplings in a traditional sense, we have also included catalyzed reactions that join a heteroatomic electrophile with an *in situ* generated nucleophile. This work includes references published up to and including October 2018. Finally, we also note that heteroatomic electrophiles (particularly those of nitrogen) have been used in a range of other important reactions, including hydroamination and C-H functionalization. We have not included those here, as they are beyond the scope of cross-coupling and are expansive in their own right, but it is important to note the key contributions in these closely related areas.^{49–77}

1.1 Traditional Cross-Coupling Reactions

To contrast cross-couplings of heteroatomic electrophiles, it is important to briefly discuss the chemistry of more “traditional” cross-coupling reactions. Going back to the work of Heck, the earliest examples of catalytic cross-coupling reactions (Heck,^{1–5} Kumada-Corriu,^{78–79} Sonogashira,⁸⁰ Negishi,⁸¹ Stille,^{82–83} Suzuki,^{84–85} etc.) focused on the formation of carbon-carbon bonds. Over the years, a vast number of related reactions have been developed. While a comprehensive cataloging of these transformation is not possible here, rough mechanistic outlines for several key reactions are shown in Figure 1.⁸⁶ Prototypically, all of these reactions involve the cross-coupling of a C-sp² electrophile (typically an aryl or vinyl halide or pseudohalide) to a variety of carbon-based nucleophiles. All of the reactions involve the oxidative addition of a low-valent metal complex into the electrophilic center. The resultant electrophilic organometallic complex, featuring a now oxidized metal center, then reacts with the nucleophile to generate an organometallic complex bearing two carbon centers. In the case of the Heck reaction, the nucleophilic component is an alkene that reacts via migratory insertion.⁸⁷ In most other cases, the nucleophile is a metalated organic compound that undergoes transmetalation. Although the mechanistic details of these later steps vary considerably by reaction, in all cases, the formation of a new carbon-carbon (C–C) bond ultimately results, and the metal center is returned to the catalytic cycle via a reductive process (often concurrently with C–C bond formation). Reactions of this type have been employed countless times in industrial applications, and have been instrumental in the construction of unsaturated organic molecules.

Historically, cross-coupling reactions had been limited to the use of C-sp² electrophiles both because of the relative ease of oxidative addition and relative stability of the organometallic intermediates that resulted. For example, for many years, reactions involving C-sp³ electrophiles suffered both from slow oxidative addition and rapid β-hydride elimination from the resulting organometallic intermediates. However, more than two decades ago, early examples from Tamura^{88–90} and Miyaura⁹¹ paved the way for Knochel,^{92–94} Fu,^{95–97} and others^{25, 98–100} to understand how to control reactions involving C-sp³ electrophiles, and pioneered their development as useful agents in cross coupling reactions (see Figure 2 for an example). Today, a wide variety of C-sp³ electrophiles are broadly useful in Csp³–C cross-couplings to make saturated organic compounds, and more recently have been shown to also be compatible in related reductive cross-couplings processes.^{101–102}

At about the same time C-sp³ electrophiles began to be explored in cross-coupling reactions, Buchwald and Hartwig (following earlier independent work from Migita¹⁰³ and Boger¹⁰⁴) recognized that heteroatomic *nucleophiles* could also be used in cross-coupling processes. The resultant amination reaction, now known as Buchwald-Hartwig amination, successfully coupled C-sp² electrophiles with a range of nitrogen nucleophiles, and has become a critical reaction in the development of pharmaceutical agents and other amine containing materials. Over the intervening years, a number of related heteroatomic nucleophiles, and ranges of catalysts have also been shown to be compatible with this general process.^{8, 105–116} Mechanistically, studies have shown that these processes are closely related to the more classical C–C bond forming reactions, and proceed via initial oxidative addition of the low-valent metal catalyst to the C-sp² electrophile, which undergoes exchange of anionic ligands,

and ultimately reductive elimination provides the observed products (Figure 3).^{117–118} Additionally, during this time, catalytic protocols for cross-coupling aryl halides to heteroatomic nucleophiles based on classical Goldberg reactions were developed,^{119–120} as well as oxidative protocols to cross-couple nucleophilic C-sp² nucleophiles (e.g. aryl boronic acids) to heteroatomic nucleophiles.^{121–124} Not only are all of these protocols important means of accessing heteroatom-containing organic molecules, they also highlight the compatibility of heteroatoms in cross-coupling reactions.

Common to all of the examples outlined above is the use of carbon-based electrophiles in the cross-coupling reaction.

1.2 Introduction to Heteroatomic Electrophiles

Beyond carbon, electrophilic species of many of the main group elements exist, and provide interesting opportunities to explore their use in cross-coupling reactions. From a fundamental standpoint, understanding which types of electrophiles are compatible with cross-coupling reactions and what types of nucleophiles they can be combined with in catalyst-controlled reactions provides an exciting intellectual arena for discovery. From a practical standpoint, as elaborated on below, the controlled introduction of heteroatoms into organic structures remains a key challenge in organic synthesis, as heteroatoms impart function and reactivity to most organic molecules. Cross-coupling of heteroatomic electrophiles presents an underexplored, yet highly promising means to accomplish those goals. And, in principle, by rendering compounds with different types of heteroatoms electrophilic, similar synthetic strategies can emerge for introducing disparate types of heteroatomic structures.

Through the lens of “traditional” cross-coupling reactions involving carbon electrophiles, there are two main classes of heteroatomic electrophiles to be considered for cross-coupling; those with electrophilic elements less electronegative than carbon (i.e. Si, B, P, etc), and those elements more electronegative than carbon (i.e. N and O). Each class presents unique challenges and opportunities.

Elements that are less electronegative than carbon are naturally electropositive and easily rendered into electrophiles. In contrast, in most cases, preparing nucleophiles of electropositive elements - such as would be required in “traditional” cross-couplings - is often challenging and frequently requires highly reducing conditions, which limits the scope of the reagents that can be prepared. The ready availability of these classes of electrophiles make exploration of their cross-coupling reactions particularly attractive.

In contrast, for elements more electronegative than carbon, preparation of electrophilic species is often less straightforward than for their nucleophilic counterparts. As detailed below, however, in many cases, access to these heteroatomic electrophiles is still readily accomplished, and in many cases, the reagents are remarkably easy to handle once prepared. The slight synthetic cost of preparing these reagents, however, is vastly off-set by the opportunities these reagents provide for developing new classes of heteroatom-installing reactions. Indeed, because the polarity of disconnections is reversed (umpoled) compared to

traditional approaches, new coupling partners, new mechanistic paradigms, and new opportunities for control of reactivity present themselves.

As is cataloged in this review, regardless of the electronegativity of the heteroatomic electrophile, new, exciting, and efficient synthetic pathways have emerged by leveraging the reactivity of these reagents in cross-coupling reactions.

As mentioned above, in addition to the new strategies and efficiencies that can be gained by the use of heteroatomic electrophiles in cross-coupling reactions, all of these methods lead directly to the installation of heteroatoms into organic molecules. And the construction of carbon-heteroatom bonds (particularly carbon-silicon, carbon-boron, carbon-nitrogen, carbon-oxygen and carbon-phosphorus bonds, which are the focuses of this review) are of significant importance.

For example, organic compounds bearing silicon^{125–126} have increasing been used not only as coupling partners in allylation, Hiyama, and related cross-couplings,^{127–133} but also as masked alcohols or carbonyls through the Fleming-Tamao oxidation.^{134–135} Organosilicon compounds have also found extensive use in industrial and aerospace applications as lubricants or cryogenic fluids.¹³⁶ Silicon atoms are also found in the structures of a number of small-molecule agrochemicals including the silylmethyltriazole fungicide Flusilazole (DPX-H6573) (**4**, Figure 4).^{137–140} Organosilicon compounds also appear in medicinal chemistry applications as bioisosteres because of their subtle structural and electronic differences compared to carbon and their non-toxicity.^{141–143}

Like silicon, boron has also found use as an atypical element in pharmaceutical agents,¹⁴⁴ most notably with boronic acid-bearing chemotherapeutic agent bortezomib (VELACDE®) (**5**, Figure 4) being approved by the FDA in 2003.¹⁴⁵ More notably, boronic acids, boronates, boroximes, and trifluoroborates can serve as functional group handles for further elaboration. The Suzuki-Miyaura coupling, arguably the most commonly employed cross-coupling reaction, pairs these organoboron species with carbon electrophiles to generate new C–C bonds.^{22, 146–149} Organoboronic acids or boronates are also employed in Chan-Lam-Evans coupling reactions^{110, 150–151} and Liebeskind-Srogl couplings.¹⁵² Also, boronic acids are employed in a variety of other transformations including homologations, conjugate additions, and allyl transfer reactions.¹⁵³

The importance of nitrogen- and oxygen-containing molecules is hard to overstate given the prevalence of these atoms in natural products, pharmaceutical agents, agrochemicals, and the fundamental building blocks of life, proteins and DNA. Both the construction of C–N bonds and the use of C–N bonds as cross-coupling handles in metal-catalyzed processes has become a flourishing area of research.¹⁵⁴ Key metal-mediated processes for the construction of C–N bonds will be discussed in section 3.1.^{155–156} As for the activation of carbon-nitrogen bonds in cross-coupling, a number of prominent examples and reviews can be found in the following references.^{157–161} There are a myriad of ways to install oxygen atoms in organic frameworks ranging from simple oxidations with peroxides or ozone to asymmetric processes like using Davis oxaziridine.¹⁶² Consequently, the number of cross-

coupling-type methods for the introduction of oxygen is dwarfed in comparison with only a few examples of electrophilic oxygen cross-coupling detailed in Section 5.

Although C–P bonds are less prevalent in biologically relevant organic compounds, organophosphorus compounds serve important roles. Phosphorus atoms are commonly found in agrochemicals, with glyphosate (**7**, Figure 4), a phosphonate sold under the name Roundup, being one of the most widely used herbicides.¹⁶³ Organophosphorus compounds also serve as synthetic intermediates in the commonly employed Wittig,^{164–165} Horner-Wadsworth-Emmons,^{166–167} and Seyferth-Gilbert reactions.¹⁶⁸ The use of organophosphines, phosphites, phosphonites, and phosphoramidites as ligands is critical in many cross-coupling transformations,^{169–170} and they can even serve as organocatalysts in Morita-Baylis-Hilman^{171–172} and related Rauhut-Currier reactions.¹⁷³

2 Silicon Cross-Coupling

Chronologically, the earliest studies related to the cross-coupling of heteroatomic electrophiles focused on silicon electrophiles. Initial studies focused on examining the stoichiometric addition of transition metals to silyl halides, which eventually gave way to the development of catalytic processes to prepare unsaturated organosilanes.

2.1 Early Stoichiometric Studies of Silicon-Halide Oxidative Addition

Silicon-halide bonds have been activated by transition metals beginning in the late 1970's. The first report comes from Kuyper.¹⁷⁴ This initial report explored the synthesis of platinum complexes derived from the activation of germanium-chloride bonds. Analogous reactions using chlorosilanes were attempted, although direct oxidative addition complexes could not be isolated or observed by NMR. However, platinum chloride complexes observed in the reaction were hypothesized to come from a transient silyl-platinum intermediate.

In 1988, Tanaka reported the first transition-metal complex from the oxidative addition of a trimethylsilylbromide (**9**) and the platinum(0) complex $\text{Pt}(\text{PEt}_3)_3$ (**8**, Figure 5).¹⁷⁵ The resulting *trans*- $\text{Me}_3\text{SiPtBr}(\text{PEt}_3)_3$ complex (**10**) was isolated as pale yellow needles and was characterized by single-crystal X-ray diffraction. Tanaka also found that the similar platinum(0) complex $\text{Pt}(\text{PEt}_3)_4$ could also be reacted with trimethylsilylbromide to give **10**, albeit at a slower rate. Trimethylsilyliodide could also react with $\text{Pt}(\text{PEt}_3)_4$, but the analogous silylchloride was unreactive, likely due to the higher bond strength of the Si–Cl bond (98 kcal/mol) compared to that of Si–Br (76 kcal/mol).

This same platinum(0) precursor **8** was used again by Tanaka in 1990 for studies on the reactivity of halodisilanes at either the silylhalide bond or the disilyl bond in metal complex formation.¹⁷⁶ Tanaka also reported on halogen-exchange reactions of rhodium and iridium complexes where the halide source is a trimethylsilylhalide.¹⁷⁷ He suggests that two mechanisms may be possible. One of his proposed mechanisms involves the oxidative addition of the silylhalide followed by reductive elimination to produce the observed metal complex; however, his observed trends in reactivity disfavor this mechanism. Typically iridium complexes are more reactive than rhodium complexes in oxidative addition reactions but the opposite trend was observed in his system. The second proposed mechanism involves

a four center σ -bond metathesis interaction, however, he could not conclusively determine a mechanism.

In 1989, Milstein synthesized and obtained a crystal structure for the oxidative addition product of methyltrichlorosilane (**11**) with iridium complex **12** (Figure 6).¹⁷⁸ Reaction of the same iridium complex **12** with trimethylsilylchloride (**14**) did not provide the oxidative addition complex; rather, he proposes that it generates silene **16** and hydridocomplex **15**, most likely arising from a β -hydride elimination.

Tanaka also investigated iridium complexes in the oxidative addition of halo(methyl)silanes including trichloromethylsilane, dichlorodimethylsilane, and trimethylsilyliodide.¹⁷⁹ He also investigated the β -hydride elimination proposed by Milstein, and found NMR evidence to support the proposed pathway. When subjecting complexes of type **17** (Figure 7) to neohexene and silyl halides at 120 °C in a sealed NMR tube, he observed signals corresponding to the dihydrido complex, which would reasonably arise from β -hydride elimination, appear, and starting material peaks disappear. However, he could not completely rule out a disproportion reaction mechanism. More recent work on the activation of Si–Cl, Ge–Cl, and Ge–F bonds by iridium using computations has been completed by Kameo.^{180–181}

Use of platinum in the activation of silyl–halide bonds was revisited by Puddephatt in 1994 and 1996.^{182–183} His initial investigation studied the enthalpy differences between chloro-, bromo-, and iodotrimethylsilane in the oxidative addition step with a platinum(II) complex. It was found that the softer, larger iodide gave the most facile oxidative addition. He was able to isolate and crystallize the oxidative addition complex **21** of trimethylsilyliodide and platinum(II) precursor **20** (Figure 8).

The syntheses of additional platinum complexes were explored in his 1996 publication while platinum in the activation of silicon–chloride bonds was explored by Turculet.¹⁸⁴ More recently, Ozerov has found that rhodium bearing a pincer ligand can be utilized in the activation of silicon–halide bonds, including less reactive silicon–chloride bonds (Figure 9).¹⁸⁵ To our knowledge, this is the only trialkyl chlorosilane oxidative addition complex that has been characterized, and the authors argue that the reaction is driven by irreversible reductive elimination of the alkane from **22**. In addition, NHC-ligated palladium complexes have been investigated for their silyliodide bond activation.¹⁸⁶

2.2 Cross-Coupling of Silicon Electrophiles

2.2.1 Palladium-Catalyzed Silyl-Heck Reactions—In a seminal study on the cross-coupling of heteroatomic electrophiles, Tanaka also explored the formation of silicon–carbon bonds via a cross-coupling catalytic cycle initiated by his well-studied oxidative addition. In 1991, he reported a Heck-type reaction of trimethylsilyliodide with styrene derivatives in the presence of triethylamine base and catalytic $\text{PdCl}_2(\text{P}(\text{Et}_3)_2)$.¹⁸⁷ Only three simple styrene derivatives were examined, and modest yields ranging from 42–45% were observed. Although limited in scope and efficiency, this constitutes the first report of a silyl-Heck reaction. The trans product **26** was favored over the cis (>100:1) (Figure 10). A cumulative publication on Tanaka's work with platinum(O) and silyl–halide bond activation including an

example of platinum-mediated silyl-Heck reaction (providing only trace yield) was published in 1997.¹⁸⁸

In 2012, an improved palladium-catalyzed silyl-Heck reaction of styrenes and isolated terminal alkenes with silyliodides to generate silyl styrenes and allyl silanes respectively was reported by our group.^{189–190} The key to the improved catalytic system was the use of the ligand *tert*-butyl diphenylphosphine. This ligand was rationalized to provide the optimal balance of steric and electronic factors while being both electron rich to support low-valent palladium and small enough to accommodate the bulky trimethylsilyl moiety. A variety of styrenes including those bearing heterocycles were coupled with iodotrimethylsilane giving exclusively the *E*-products (e.g. **29–31**, Figure 11).

A slight adjustment in the reaction conditions - lowering the catalyst loading and temperature as well as switching the solvent from toluene to trifluorotoluene - allowed for the synthesis of allyl silanes from isolated terminal alkenes. Yields, however, were modest due to starting material isomerization. Good selectivity for the *E*-product was observed for many of the substrates although some substrates did exhibit minor amounts of the vinylsilane product (Figure 12). The synthetic use of these silanes by subsequent functionalization of these products including their participation in allyl transfer and crotylation reactions was also reported.

This reaction was further improved by the development of a second-generation ligand for the catalytic system.¹⁹¹ In the pursuit of improving the yields of the allyl silane products, additional phosphine ligands were synthesized and examined in the silyl-Heck reaction. Ligand **38** was designed with electron-donating groups on the aryl rings which leads to a more electron-rich phosphine center than the previous ligand. A more electron rich ligand promotes oxidative addition and consequently improves the overall reactivity of the catalyst. With the use of ligand **38**, greatly improved yields were seen with an expanded allyl silane scope although the *E:Z* selectivity was comparable to the original ligand (Figure 13).

In a second publication exploring the utility of ligand **38**, the necessity of using a thermally sensitive palladium precatalyst and the limited scope in regards to the silane was addressed.¹⁹² It was found that ligand **38** accommodated the use of Pd₂(dba)₃ as the precatalyst and, with slight modifications to the catalyst loading and solvent, comparable yields of the vinylsilane products could be obtained. Also, for the first time, bulkier silanes could participate in the reaction, and also provided high yields for vinyl silanes. However, iodotriethylsilane failed to give more than traces of the desired product (Figure 14). In addition, only limited yields for allyl silanes were observed with the use of **38** and Pd₂(dba)₃, making the earlier protocol involving (COD)Pd(CH₂SiMe₃)₂ still more advantageous for their synthesis.

A third variation on this silyl-Heck reaction was reported in 2011.¹⁹³ A single-component, bench-stable palladium precatalyst [(**38**)PdI₂]₂ (Figure 15) was synthesized in one step from ligand **38** and palladium(II) iodide. The advantage of a single component catalyst is ease in reaction setup, the fact that the precatalyst is stable to long-term storage under ambient

conditions, and it provides the allyl and vinylsilane products in uniformly high yield (Figure 16).

In addition to targeting trialkylsilylhalides as coupling partners, we have also explored the use of silyl ditriflates to generate vinylsilyl ethers (**45**) and disiloxanes (**46**) from styrenes (Figure 17).¹⁹⁴ Using the same strategy as was developed for coupling trimethylsilylchlorides,¹⁸⁹ we found that the addition of an iodide additive allowed the *in situ* generation of si-lyliodide, which readily undergoes oxidative addition. Only catalytic amounts of sodium iodide were required to achieve quantitative yield of the coupled product. Quenching the reaction with various alcohols led to a variety of substituted vinylsilylethers (e.g. **47–53**) and quenching with water provided the disiloxane (e.g. **54**). The product vinylsilylethers were also shown to be excellent substrates for Hiyama-Denmark coupling providing isomerically pure product over two steps in superior yields to the related direct Heck approach.

2.2.2 Nickel-Catalyzed Silyl-Heck Reactions—In addition to our interest in palladium-catalyzed silyl-Heck reactions, we have also developed a nickel-catalyzed variant on this reaction for the direct activation of silyltriflates.¹⁹⁵ We found that we were able to couple trimethylsilyltriflate with styrenes without the addition of an iodide additive using Ni(COD)₂ as the precatalyst. A number of ligands were investigated, and unlike with palladium, large trialkyl phosphines provided the best yields. The nickel variant was also able to tolerate bulkier silanes such as triethylsilane (Figure 18) which proved problematic in the second-generation palladium conditions with iodotriethylsilane (see Figure 10). The yields in many of these cases are modest due to steric bulk, and the reaction fails with triisopropylsilyltriflate. One downside is that a larger excess of the silyl halide is required, 3.0 equivalents compared to 1.4 equivalents used in most palladium catalyzed processes.

In 2018, in a major advance in silyl-Heck reactions, Shimada and Nakajima reported on the use of nickel catalysis in the direct activation of Si–Cl bonds of mono-, di-, and tri-chlorosilanes and subsequent silyl-Heck reaction (Figure 19).¹⁹⁶ By use of an electron-rich nickel catalyst and an added Lewis acid (AlMe₃), styrenal-derived alkenes could easily be converted to the silylated alkene. Monochlorosilanes were sluggish with their initially optimized conditions, but by increasing the equivalents of silylchloride, catalyst loading, and temperature while also changing the base, high yields were observed.

2.2.3 Multicomponent Couplings of Silyl Electrophiles—Murai was also interested in cross-coupling reactions initiated by the oxidative addition of palladium across silyl-halide bonds. Contemporaneously to the catalytic reaction reported by Tanaka, his initial report in 1991 detailed a multicomponent coupling of silyliodides, terminal alkynes and tin reagents to generate vinylsilane products.¹⁹⁷ The proposed mechanism (Figure 20) begins with the oxidative addition of palladium(0) across the Si–I bond generating intermediate **58** which then inserts into acetylene **59** to give vinylpalladium **60**. This vinylpalladium undergoes transmetalation with the tin reagent **61** and then releases the product **62** by reductive elimination.

Murai followed up this report in 1995 with a cross-coupling similar to his previous report, but utilizing organozinc reagents instead of alkynyl stannanes.¹⁹⁸ This multicomponent reaction featured an expanded substrate scope in regards to the terminal alkyne and the dialkyl organozinc reagent. Additional silyl groups could be introduced both on alkyne or zinc reagent. However, the reaction was still limited to terminal alkynes and arylzinc reagents were not explored in this multicomponent coupling.

2.2.4 Silyl-Negishi and Silyl-Kumada–Tamao–Corriu Reactions—Our group has also applied palladium catalysis to the cross-coupling of silyl halides in other classes of cross-coupling reactions. In 2017, we reported the palladium-catalyzed silyl-Negishi reaction of alkylsilyliodide electrophiles and alkyl zinc halides.¹⁹⁹ An initial ligand screen identified triarylphosphine ligand **65** as the optimal ligand for this reaction. Given success using single-component precatalysts in electrophilic silicon coupling (see section 2.2.1), (**65**)₂PdI₂ was prepared and used as catalyst, and showed excellent performance at even 1 mol % palladium loading. A variety of primary and secondary zinc bromides or iodides were competent coupling partners in the reaction and several trialkylsilyliodides could be utilized although the bulkier triethylsilyliodide provided diminished yield (Figure 21). One attractive feature of this reaction is that it can be run without rigorous exclusion of oxygen or water. A reaction run on the benchtop in a capped vial provided the product in 88% yield compared to 98% yield when run under rigorous anaerobic conditions.

Later in 2017, we reported a silyl-Kumada–Tamao–Corriu reaction of silylchloride electrophiles and organomagnesium reagents.²⁰⁰ Although both this and the silyl-Negishi reaction use the same catalyst ((**65**)₂PdI₂) and can provide identical products, the developed silyl-Kumada–Tamao–Corriu reaction utilizes less reactive chlorosilanes, which are much more tolerant of air and moisture than their iodide counterparts. More importantly, an immense array of silylchloride coupling partners are commercially available, yielding a diversified product library (Figure 22). This constituted the first time that chlorosilanes were used in a cross-coupling reaction. These conditions are also tolerant of bulky silylchlorides with triethylsilylchloride providing a near quantitative yield of **78**. Again, these reactions can be run at room temperature but the optimal solvent is diethyl ether. Although in the standard reaction conditions heavier halides are present, the reaction can also run with (**65**)₂PdCl₂ and *i*PrMgCl with the silylchloride, suggesting that direct activation of the silicon chloride bond may be at play in the reactions.

3 Nitrogen Cross-Coupling

3.1 Introduction

New methods for the formation of nitrogen-carbon bonds have been of interest since the advent of synthetic organic chemistry due to the prevalence of nitrogen atoms in biologically relevant molecules. Traditional methods for the generation of carbon–nitrogen bonds include the Gabriel amine synthesis (1887),²⁰¹ the Ritter reaction (1948),^{202–203} and reductive amination.²⁰⁴ Metal-mediated or metal-catalyzed methods have more recently been developed to complement traditional approaches and greatly extend the accessible chemical space.²⁰⁵ Examples of these metal-mediated reactions include the related Ullmann coupling,

²⁰⁶ Goldberg reaction,^{120, 207–209} and Chan–Lam–Evans coupling,^{110, 150, 210–212} as well as the prototypical cross-coupling reaction for the generation of $\text{sp}^2\text{C–N}$ bonds, the Buchwald–Hartwig amination.^{213–218} Another metal-mediated reaction, the aza-Wacker reaction, reported by Hegedus beginning in 1976,^{219–222} generates $\text{sp}^3\text{C–N}$ bonds. Asymmetric variants^{223–224} have been developed and detailed mechanistic studies of the aza-Wacker reaction have been conducted.^{225–227}

One feature common to the mechanisms of all the aforementioned metal-mediated C–N bond forming reactions is that the nitrogen coupling partner acts as the nucleophile. In general, reactions in which nitrogen acts as a nucleophile are very common; reactions involving electrophilic amination are less common and have been atopic of recent interest.^{228–233} Reactions combining both metals and electrophilic nitrogen in cross-coupling^{234–235} will be detailed in the following sections.

3.2 Cross-Coupling of Nitrogen Electrophiles

3.2.1 Oxime Ester Electrophiles with Palladium—Early studies by Narasaka investigated the activation of oxime N–O sulfonyl bonds with copper²³⁶ and in 1999 he found that a stoichiometric reaction of palladium(0) with *O*-sulfonyloxime **82**, followed by aqueous quench, resulted in the formation of imine **84** (Figure 23). This result suggests the reaction proceeds through oxidative addition of palladium into the N–O bond followed by protodepalladation.²³⁷

Further support for the proposed oxidative addition of palladium across N–O bonds of oximes to generate species of type **83** was disclosed by Hartwig twenty years after Narasaka's initial investigation. Hartwig isolated and characterized by single X-ray diffraction complex **86**, the direct oxidative addition complex of **85** and palladium(0) (Figure 24).²³⁸

Following his initial report, in 2001, Narasaka exploited this reactivity in the development of novel N–C bond forming reactions, specifically to the cyclization of alkene-tethered *O*-pentafluorobenzoyloxime **87**. He attributed this to a Heck-like pathway. The product **88**, which under the reaction conditions or with the addition of trimethylsilylchlorides, isomerizes to pyrrole **89** (Figure 25). This work was further extended to sequential Heck reactions resulting in spiro-imines.^{239–240} During this study he also examined aldoximes as potential precursors. However, the cyclized product was not isolated but rather the nitrile, which he suggested results from Beckmann fragmentation of the aldoxime.

The framework of other complex aza-heterocycles could be synthesized via this Heck reaction.²⁴¹ 5-*Exo* cyclization and subsequent isomerization allowed access to substituted pyrroles (Figure 25).²⁴² Pyridines could also be accessed via a 6-*endo* cyclization of **90**²⁴³ while isoquinolines **93** could be accessed following isomerization of a 6-*exo* cyclized product derived from **92** (Figure 26).²⁴⁴ Sequential Heck cyclization followed by chemical oxidation allowed access to azaazulenes.^{245–246} This methodology, specifically the use of oxime esters in Heck cyclizations to generate nitrogen heterocycles, is now commonly referred to as a Narasaka–Heck reaction.²⁴⁷

O-Pentafluorobenzoyloximes were also utilized in a 5-*endo* Heck cyclization by Ichikawa to synthesize difluormethylene-substituted pyrrolines or fluorinated pyrroles after isomerization from appropriate substrates.^{248–249} In a related reaction, Abell found use of *O*-pentafluoroben-zoylamidoximes such as **94** in the synthesis of imidazoles (Figure 27).²⁵⁰

Notably, a Narasaka-Heck reaction was utilized by Fürstner in his total synthesis of butylcycloheptylprodigiosin **98** (Figure 28).^{251–252}

Bower has done extensive work extending the Narasaka–Heck reaction to the formation of stereogenic heterocycles. In 2012, he reported the formation of heterobicyclic structures via the 5-*exo* Narasaka–Heck cyclization from cyclohexene-tethered pentafluorobenzoyloxime esters (e.g. **99**, Figure 29).²⁵³ His optimized conditions utilized a catalytic palladium(0) source (loadings as low as 2.5 mol %) with the electron-deficient phosphine ligand P(3,5-(CF₃)₂C₆H₃)₃. He hypothesize that the electron-deficient ligand serves to improve the stability of the iminio–Pd(II) intermediate by reducing the electron density around palladium and consequently increasing the strength of the iminio–Pd bond, which limits protodepalladation. Electron-deficient phosphine ligands have been shown by Hartwig to accelerate the migratory insertion of alkenes into Pd–N bonds.²⁵⁴

Good yields were seen for aryl-substituted products such as **100**, and many could proceed efficiently at 60 °C; conversion could even be seen at ambient temperature. Alkyl substituted products such as **101** were more challenging to access as appreciable amounts of hydrolyzed ketone byproduct were formed in addition to the desired cyclized product. The alkyl-substituted substrates also required higher temperatures (up to 120 °C) to proceed efficiently. Ald-oximes failed to give the desired cyclized product **102**, and instead underwent Beckman rearrangement²⁵⁵ to give the nitrile. This undesired reactivity of ald-oximes was previously noted by Narasaka. For products bearing more than one stereocenter such as **103**, good diastereoselectivities were observed, and Bower attributes this to base-mediated equilibrium post-cyclization, since he observed that poor diastereomeric product mixtures could be subjected to the 120 °C conditions to improve the diastereomeric ratio (Figure 30).

Bower followed up this work a year later with a report of the Narasaka–Heck reaction of pentafluorobenzoyloxime esters with tethered 1,2-disubstituted alkenes to give unconjugated, stereogenic dihydropyrroles bearing an *E*-alkene (Figure 31a).²⁵⁶ The yields of some of the substrates such as **111**, were reduced due to isomerization to the pyrrole. Bower suggests that formation of the pyrrole is a kinetic phenomenon, as resubjection of the desired product **111** to the reaction conditions did not result in isomerization to the pyrrole. He also utilized oximetethered 1,1-disubstituted alkenes to construct fully substituted nitrogen-bearing stereogenic centers which cannot undergo isomerization to the pyrrole (Figure 31b).²⁵⁷ In a subsequent report Bower further explores the mechanism of these reactions and notes that two mechanistic pathways are possible depending on the choice of ligand.²⁵⁸

Electron-rich phosphines promote the generation of iminyl radicals through an interrupted one electron oxidative addition, whereas electron-poor phosphines promote a two-electron pathway more similar to that of conventional cross-coupling reactions (Figure 32).

In 2017, Bower reported the first asymmetric Narasaka–Heck cyclization to form fully-substituted nitrogen-bearing stereogenic centers in a selective fashion.²⁵⁹ The key to his asymmetric induction was the use of a SIPHOX ligand (**116**) along with a palladium(0) precatalyst and triethylamine in DMF at elevated temperatures. A range of alkyl and aryl substitutions were well tolerated (Figure 33). Bower has also published a review on the use of aza-Heck reactions in the asymmetric synthesis of nitrogen-containing heterocycles.²⁶⁰

The Narasaka–Heck reaction has also been extended beyond alkenes to alkyne-tethered pentafluorobenzoyloxime esters as reported by Abell in 2007.²⁶¹ Following migratory insertion of the iminio-palladium(II) species **122** into the alkyne, reaction of the resulting vinylpalladium species **123** with carbon monoxide occurs yielding an acylpalladium(II) intermediate **124**. This further reacts with ethanol to furnish the ethyl ester product **125** (Figure 34). Subsequent isomerization of the unconjugated diene yields the ester-substituted pyrrole **126**. Unfortunately, this domino reaction results in mixtures of the desired ethyl ester pyrrole **126** and the unsubstituted pyrrole **129** which results due to the generation of vinylpalladium hydride **127**.

Kitamura took advantage of a similar domino reaction of alkyne-tethered pentafluorobenzoyloximes (**130**) in the creation of substituted isoindoles (**131**).²⁶² In this domino reaction the vinylpalladium species undergoes transmetalation with an arylboronic acid followed by reductive elimination of the arylated product (**131**, Figure 35).

Several other groups have also taken advantage of domino reactions involving interrupted Narasaka–Heck reactions. Bower has reported a carboamination reaction utilizing his Narasaka–Heck conditions in which the migratory insertion intermediate undergoes further reaction to generate one or more C–C bonds.²⁶³ Due to deliberate substrate design, there are no β -hydrogens present, prohibiting β -hydride elimination from occurring. Several variants were explored including the transmetalation of the migratory insertion product with an aryl-, alkenyl-, or alkynylboronate or stannane followed by reductive elimination to generate a $\text{Csp}^3\text{--Csp}^2$ or a $\text{Csp}^3\text{--Csp}$ bond. The authors also successfully intercepted the migratory insertion intermediate with carbon monoxide followed by a transmetalation with a boronate or tetraarylborate, and then reductive elimination to generate the ketone product (Figure 36).

The formation of carbon-halogen bonds via intercepted Narasaka–Heck cyclization was developed by Tong in 2015.²⁶⁴ This iminohalogenation requires the use of four equivalents of either NaI, LiBr, or LiCl as the halide source, along with a palladium(II) precatalyst and an electron-deficient arylphosphine ligand. Mechanistic investigation ruled out a radical pathway as TEMPO did not interfere in the chlorination and bromination reactions. Deuteration studies found no erosion or scrambling when the vinyldeuteride **138** was subjected to the reaction, suggesting a stereospecific migratory insertion. Additional stereochemical data (see Figure 37) also suggests that the carbon-halogen bond formation occurs via an $\text{S}_{\text{N}}2$ -type reductive elimination mechanism.

An enantioselective variant of an intercepted Narasaka–Heck cyclization was more recently reported by Zhu (Figure 38).²⁶⁵ He found that with the commercially available bidentate phosphine ligand SYNPHOS, a palladium(II) precatalyst, and base at elevated temperatures

the cyclized and coupled products could be obtained in modest to good enantioselectivities (as high as 83% ee) when both substituents (R^1 and R^2) are aryl groups. Alkyl substitution on the oxadiazole (R^2) resulted in diminished enantioselectivity, typically around 75% ee.

Initial studies found that the solvent can play an immense role in the reaction mechanism. A reaction run in toluene in the presence of TEMPO yielded the TEMPO-trapped adduct suggesting a radical mechanism. Switching the solvent to DMF yielded the product with no formation of the TEMPO-trapped adduct. The optimal conditions utilize DMSO as the solvent, and TEMPO experiments resulted in the formation of small amounts of TEMPO adduct, however, the high levels of enantioselectivity observed seems to suggest against a solely radical mechanism. Two competing mechanisms were proposed (Figure 39).

In the first two electron process mechanism, oxidative addition of palladium into the N–O bond followed by migratory insertion generates the alkylpalladium intermediate **148**, which is intercepted by transmetalation with an oxadiazole anion generated *in situ*. The palladium(II) species **149** then undergoes reductive elimination releasing the product **146** and regenerating the catalyst. The second mechanism is a single-electron process in which iminyl radical **150** is generated and undergoes cyclization. The alkyl radical **151** recombines with the Pd(I), generating the same alkylpalladium **148** as described in the two-electron mechanism.

3.2.2 Oxime Ester Electrophiles with Copper—Copper has also been found competent in the activation of N–O bonds of oximes. In 2007, Liebeskind reported the *N*-iminium of boronic acids and organostannanes using copper and *O*-acylketoximes (Figure 40).²⁶⁶ The proposed mechanism suggests oxidative addition of copper(I) into the N–O bond to generate a copper(III) intermediate which then undergoes transmetalation with the boronic acid or organostannane. Reductive elimination of the product and regeneration of the copper(I) catalyst then follows. When switching from the ketoximes to the aldoximes (**152** $R^1 = H$), the desired product was not isolated. Rather, as seen in Narasaka's work with palladium (section 3.2.1), the nitrile was formed, which he suggests results from β -elimination of the oxidative addition intermediate. This work was extended to the synthesis of substituted pyridines via coupling of *O*-pentafluorobenzoylketoximes (**160**) with vinylboronic acids (**161**) followed by air oxidation (Figure 41).²⁶⁷

Liebeskind also extended his copper-mediated coupling of boronic acids or organostannanes beyond oximes to *O*-acetylhydroxamic acids (**163**) yielding *N*-amidyl products with the use of stoichiometric or superstoichiometric copper (Figure 42).²⁶⁸ Different conditions were required to couple either the boronic acid or the stannane. Boronic acid coupling utilized one equivalent of copper(I) thiophene-2-carboxylate (CuTC), while the stannanes required two equivalents of copper(I) diphenylphosphinate (CuDPP) (Figure 42). He hypothesized that stoichiometric copper was required in the coupling of *O*-acetylhydroxamic acids (as opposed to catalytic copper with *O*-acyloximes) because the oxidative addition complex can form bridging amido-dimers, which are less susceptible to transmetalation.

Liu and Xi also used copper in their stoichiometric cross-coupling of *O*-benzoylketoximes and aldoximes with alkenylzirconocenes to generate 2-azadienes.²⁶⁹ This is the first example

of a successful coupling of an aldoxime, as previous attempts by Narasaka, Liebeskind, and others resulted in undesired nitrile formation. In Liu and Xi's proposed mechanism (Figure 43), an initial transmetalation from zirconium (**166**) to copper generates an alkenylcopper intermediate (**167**) which undergoes oxidative addition into the N–O bond of oxime **168**. This is followed by reductive elimination of the product (**170**). One limitation of this reaction is the necessity to pre-generate the alkenylzirconocene from alkynes, resulting in diminished functional group tolerance.

In 2014, Bower reported a copper-catalyzed cyclization of *O*-pivaloyl oximes to yield unsaturated pyrrolidines in a transformation similar to that of Narasaka.²⁷⁰ However, mechanistic studies revealed that the copper-catalyzed reaction does not proceed via migratory insertion of the M–N bond like in Heck reactions, but rather proceeds through addition of an iminyl radical or iminio–Cu(III) species. A similar transformation using stoichiometric copper was reported by Zard using alkene-tethered *O*-acetylketo oximes.²⁷¹

3.2.3 Other Oxime-Derived Electrophiles—*O*-Phosphinyloximes (e.g. **171**) have also been utilized in aza-Heck cyclizations by Zhu.^{272–273} Under differing sets of conditions, either the 5-*exo* isomerized pyrrole or the 6-*endo* dehydrogenated pyridine (e.g. **172**) could be obtained in modest yields from the linear substrate. The authors also examined fused substrates in a subsequent publication. They found that the *trans*-disposed substrates as shown in Figure 44 could cyclize and dehydrogenate under the reaction conditions to form the fused pyridine product.²⁷⁴

3.2.4 Aza-Heck Reactions of Other Electrophiles—More recently, research efforts have extended the aza-Heck reaction beyond oxime substrates to electrophilic nitrogen centers bearing three different substituents. Bower, who made many advancements to the Narasaka–Heck reaction, has investigated (pentafluorobenzoyloxy)sulfonamide substrates allowing access to stereogenic sulfonamide-containing heterocycles in a 5-*exo* cyclization.²⁷⁵ The proposed mechanism follows similarly to that of the Narasaka–Heck reaction (Figure 45). First, an oxidative addition of palladium(0) into the N–O bond followed by a proposed dissociation of the pentafluorobenzoate gives cationic intermediate **175** which undergoes syn-migratory insertion^{254, 276–277} to give alkyl palladium intermediate **176**. To complete the cycle, β -hydride elimination releases the product **177** and generates palladium hydride, which undergoes base-induced reductive elimination to regenerate the palladium(0) catalyst. Bower proposes that the catalytic cycle is driven by protodecarboxylation (corroborated by ¹⁹F NMR analysis) of the pentafluorobenzoate leaving group.

A variety of alkyl-substituted substrates could be cyclized to give the pyrrolidene products in modest to good yields; however, unified conditions were not utilized. Bower notes that solvent effects are pronounced, and combinations of THF, DMF, *n*BuCN, or toluene were utilized for optimal yields of many of the substrates. The sulfonamide protecting group on the nitrogen was also varied, some bearing tosyl while others, mesyl.

In addition to the 5-*exo* cyclization that was a hallmark of Narasaka–Heck cyclizations, he also briefly investigated a 6-*exo* cyclization with his catalytic conditions. The only 6-*exo*

substrate that is reported (**178**) features a conformationally-restricting phenyl group and cyclizes to **179** in 42% yield (Figure 46).

Although this reaction produces products similar to that of the aza-Wacker reaction, the advantage of the aza-Heck approach is that it exhibits a wider tolerance of functional groups. Aza-Wacker reactions do not tolerate large α -substituents and electron-deficient alkenes susceptible to conjugate addition. Bower's aza-Heck approach can accommodate both of these limitations and provides the additional advantage of potential domino processes.

Another unique solution to the aza-Heck reaction was developed by our group in 2016.²⁷⁸ This aza-Heck reaction eliminates the need to use the large pentafluorobenzoyl group, and like the Bower chemistry described above, moves beyond the oxime substrates of the Narasaka-Heck reaction.²⁷⁹ Like the Liebeskind work described in section 3.2.2, this approach uses hydroxamate derivatives. However, unlike the earlier chemistry, *O*-acyl activation proved incompatible, and *O*-phenylhydroxamate ethers were identified as the key to success. These reactions proceed via 5-*exo* cyclization to form γ -lactams (Figure 47). For the first time, protection or full substitution on the nitrogen is not required and free N-H products are isolated directly from an aza-Heck reaction. It is noteworthy that the N-O bonds of *O*-arylhydroxylamines have previously been broken in metal-free electrophilic amination of aryl boronic acids.²⁸⁰

Although this may seem like a significant departure from the previously discussed Narasaka-Heck and aza-Heck reactions, preliminary mechanistic data suggests a palladium-catalyzed heteroatomic Heck reaction mechanism rather than an aza-Wacker reaction. An aza-Wacker mechanism would involve the activation of the N-H bond by Pd(II), whereas the aza-Heck mechanism would involve direct activation of the N-O bond by Pd(0). Optimized reaction conditions involved the use of a Pd(II) precatalyst (COD)Pd(CH₂SiMe₃)₂²⁸¹ which typically reduces *in situ* to Pd(0).²⁸² To probe whether or not Pd(II) is the active catalyst (suggesting an aza-Wacker mechanism), Pd[P(OEt)₃]₄²⁸³ was synthesized and used as a single-component catalyst in the reaction. The reaction was high yielding of the desired product indicating that the Pd(0) catalyst is sufficient and Pd(II) is not the active catalyst, suggesting against an aza-Wacker mechanism.

We demonstrated a wide substrate scope including compatibility with other heteroatoms, aryl bromides (**189**), and a pyridine-derived substrate (**188**, Figure 47). The reaction provides good diastereoselectivity for vicinal stereocenter-containing compounds **184**. Distal stereocenters fail to impart any selectivity. Interestingly, even tetrasubstituted alkenes could participate in the reaction resulting in **187**, which remains a rare class of alkenes in aza-Heck reactions. It is also noteworthy that the products (**183** and **190**) of this aza-Heck reaction are isolated as single olefin isomers. It is hypothesized that phenoxide produced during this reaction mitigates the formation of palladium-hydride, which has plagued other related transformations with unwanted olefin scrambling.

Similar to Bower, we were also interested in expanding the scope of the reaction to include 6-*exo* cyclizations. We found that in this reaction, conformationally restricted substrates (**191**) are required for 6-*exo* cyclization to proceed in good yield (**192**, Figure 48).

In 2018, Bower reported an aza-Heck cyclization of *N*-pentafluorobenzoyl carbamates that accommodates both 5-*exo* and 6-*exo* cyclizations.²⁸⁴ This reaction takes advantage of a Pd(0) precatalyst, bulky phosphadamantyl ligands, and elevated temperatures. For more challenging substrates the electronic properties of the ligand could be tuned by varying the aryl substituent on the phosphorus with ligands **196** and **197** performing the best in both challenging 5-*exo* cyclizations and in the 6-*exo* cyclizations (Figure 43). Even a 7-*exo* cyclization could be accomplished to provide **203** using this method, although in modest yield. Bower found that the substituent on the carbamate (R¹ in Figure 49) could be varied with the 5-*exo* substrates (e.g. **198–200**). However, for the 6-*exo* and 7-*exo* substrates (**201–203**) only the *tert*-butyl substituent on the carbamate provided the optimal yields.

Another recent development in aza-Heck chemistry reported by our group is the expansion of the hydroxamate-type electrophiles to more complex urea-derived electrophiles (**204**) generating imidazolidinones (**205**, Figure 50).²⁸⁵ To move away from (COD)Pd(CH₂SiMe₃)₂, we found that [(cinnamyl)PdCl]₂ could be used as the precatalyst with PhMgBr as a cocatalytic reductant. Like our earlier study, P(OCH₂CF₃)₃ remained the optimal ligand. In some cases, addition of silver(I) tosylate boosted the yield of product by suppressing undesired alkene isomerization. In contrast, this alkene isomerization could be harnessed for the selective formation of dihydroimidazolones (**206**) by addition of iodide additives. A variety of substitution was well tolerated including when R¹ = H (Figure 50), allowing for the synthesis of doubly unprotected products, a challenge not previously met in other metal-mediated methods for the synthesis of imidazolidinones.

In addition to the activation of N–O bonds in aza-Heck type cyclizations, N–Cl bonds have also been utilized. In 2000, Gottlich reported the activation of N–Cl bonds by copper in a radical cyclization reaction.²⁸⁶ In 2002, he followed up with the development of a palladium-catalyzed hetero-Heck-type reaction of alkene-tethered chloramines (**207**) to access a limited scope of cyclized alkyl chlorides (**208**) in modest to good yields (Figure 51).²⁸⁷

The authors propose that following the oxidative addition and migratory insertion, reductive elimination forming a C–Cl bond proceeds rather than the typical β-hydride elimination observed in the Heck reaction (Figure 52). Although a radical mechanism seems possible, Gottlich argues that the addition of acid or base, which normally affects aminyl-radical reactions, has no effect on this reaction. He also suggests that the diastereoselectivity seen with **210** would not be possible in a radical mechanism.

3.2.5 Nitrogen Electrophiles in Arylation and Alkylation

3.2.5.1 *N*-Acyl Electrophiles in Arylation and Alkylation: In addition to Naraska, one of the early pioneers in the activation of N–O bonds using metals was Johnson. In 2004, he reported the copper-catalyzed coupling of diorganozinc reagents and *O*-benzoylhydroxylamine derivatives (Figure 53), an aza-version of the Negishi reaction.²⁸⁸ These *O*-benzoylhydroxylamines have become a very commonly used source of electrophilic nitrogen, which has recently been reviewed.²³⁵ In Johnson's initial report a variety of *O*-benzoylhydroxylamine derivatives bearing *N,N*-dialkyl substitution could be

efficiently coupled with dialkyl- or diarylzinc reagents at room temperature. Several copper sources were competent in the reaction. Even *ortho*-substitution on the diarylzinc reagent or diheteroarylzinc reagents could be accommodated with only slight drop in yield (**222** and **223** respectively). The scope of diarylzinc reagents was expanded in a subsequent full paper.
289

In addition to using copper to activate N–O bonds, Johnson concurrently reported a nickelcatalyzed variant of the C–N cross-coupling reaction of *O*-benzoylhydroxylamines with arylzinc halides (Figure 54).²⁹⁰ In the previous copper-catalyzed method, arylzinc halides (**234**) were not well tolerated, however this complementary method uses aryl- or alkylzinc halides that are generated *in situ* from transmetalation of the corresponding Grignard reagent. The reaction also takes advantage of the commercially available and air stable bis(tri-phenylphosphine)-nickel(II) dichloride as the catalyst. The substrate scope in regards to the organozinc species was limited to aryl-(such as **222**) or primary alkyl zincs (such as **224**); secondary and tertiary alkylzinc halides failed to give the cross coupled product. Only *N,N*-dialkyl *O*-benzoylhydroxylamines were tested, but varied substitution on the arylzinc was well tolerated. For comparable products synthesized via the two methods, the yields using the copper-catalyzed method were typically higher and later investigations further explored the copper chemistry.

In 2006, Johnson greatly expanded the scope of his copper-catalyzed cross-coupling method.²⁹¹ This work highlights a simple method to prepare the *O*-benzoylhydroxylamines that improves upon the previously utilized method developed by Ganem.²⁹² Shorter reaction times, lower reaction temperature, and limited side product formation could be achieved via a simple oxidation of the amine using a combination of benzoyl peroxide and an inorganic base in DMF. This method allowed expedient syntheses of a host of mono- and disubstituted *O*-benzoylhydroxylamines (**219**). Good to excellent yields were obtained when coupling with organozinc reagents for over twenty different coupled products including the sterically demanding coupling to form **245**, albeit in modest yield (Figure 55). Even *ortho*-substituted diarylzincs, obtained from directed *ortho*-lithiation and metalation, could be coupled to morpholine-derived *O*-benzoylhydroxylamine.

Mechanistic investigations by Johnson eliminated a radical pathway due to retention of stereochemistry in endo- and exonorbornyl substrates (Figure 56).²⁹³

By using an isotope labeling cross-over study with conformationally restricted substrate **248** (Figure 57), Johnson was able to gain insight into the mechanism of the reaction. In this experiment, a pathway involving oxidative addition to the N–O bond, followed by transmetalation and reductive elimination (traditional cross-coupling) would be expected to proceed via an intramolecular pathway. In this case, no cross-over of isotopic labels should be observed. In contrast, because of the constrained geometry, an intramolecular mechanism involving transmetalation followed by S_N2 displacement at nitrogen would have to proceed through a strain-forbidden 6-*endo-tet* cyclization. In such a case, a similar intermolecular pathway would be expected to dominate, and cross-over of the isotope labels would be expected. In the event, subjecting a mixture of **248** and **248-d**₁₄ to the reaction conditions

resulted in a statistical mixture of all four possible isotopic products (d_0 , d_4 , d_{10} , and d_{14} Figure 57). This result supports a N-O cleavage occurring via an S_N2 -like pathway.

In 2012, Miura utilized *O*-benzoyl hydroxyl amines in a cross-coupling with arylboronates.²⁹⁴ The optimized conditions utilized arylboronic acid neopentylglycol esters (**250**), monohydrated copper(II) acetate catalyst, 1,2-bis(diphenylphosphino)-benzene ligand (**252**), and super-stoichiometric lithium *tert*-butoxide in tetrahydrofuran, along with *N,N*-dialkyl *O*-benzoylhydroxylamines (**219**, Figure 58). A variety of aryl groups could be coupled to the *N,N*-dibenzyl-*O*-benzoyl hydroxyl amine in yields ranging from 53–93%. Diminished yields were observed upon changing the alkyl substituents on the *O*-benzoyl hydroxyl amine from benzyl, as noted by **257–259**.

Concurrently, efforts by Lalic expanded the substrate scope of the coupling of arylboronates and *O*-benzoyl hydroxyl amines.²⁹⁵ His optimized conditions also utilized arylboronic acid neopentylglycol esters (**250**), but the catalyst was derived from copper(I) *tert*-butoxide and Xantphos (Figure 59). An impressive array of highly substituted *N,N*-dialkyl *O*-benzoylhydroxylamines could be coupled, including even the highly sterically congested 2,2,6,6-tetramethylpiperidine with an *ortho*-substituted arylboronic ester to give **268** in 60% yield.

In 2013, Miura published a copper-catalyzed amination of arylsilanes using *O*-benzoylhydroxylamines (**219**) to generate anilines.²⁹⁶ The optimized arylsilane was [(2-hydroxymethyl)-phenyl]dimethylphenylsilane (**269**), originally developed by Nakao and Hiyama, which forms the pentacoordinated arylsilicate *in situ*.²⁹⁷ A screen of ligands found that the combination of JohnPhos (**270**) and copper(I) iodide gave the best yields of the cross-coupled product. A variety of *N,N*-dialkyl substituted *O*-benzoylhydroxylamines performed well in this chemistry, but the aryl group was limited due to the requirement of the silane substitution (Figure 60).

A similar amination of *O*-benzoyl hydroxyl amines using silicon-based nucleophile was reported by Smith also in 2013.²⁹⁸ He takes advantage of a siloxane transfer reagent **274** which *in situ* reacts with an aryllithium such as phenyllithium (**273**) generating a species **275** suited to transmetalate the aryl group (in this case phenyl) from silicon to copper giving **276** which can subsequently react with the electrophilic nitrogen species in the cross-coupling event (Figure 61).

Another adaptation on the arylation of *O*-benzoyl hydroxyl amines was reported by Zhou and Wang in 2015.²⁹⁹ Similar to Johnson's work with arylzincs and copper catalysis, this report details the use of aryl or heteroarylaluminum species with a copper catalyst (Figure 62). The high reactivity of organoalanes allows for full completion in an hour at room temperature.

In addition to organoalanes, other organometallic nucleophiles have been coupled with *O*-benzoylhydroxylamines. Similar to the work of Liu and Xi who cross-coupled *O*-benzoylketoximes and aldioximes with alkenylzirconocenes (see section 3.2.2), Xi reports a cross-coupling of *O*-benzoylhydroxylamines with alkenylzirconocenes.³⁰⁰ Sterically

demanding amines could be coupled giving products such as **286**. Though in general, the scope in regards to the alkenylzirconocene (R^2 , R^3 , R^4 in Figure 63) is limited to those with simple alkyl or aryl substituents.

Knochel has built upon Gosmini's precedence (see section 3.2.5.2) with a cobalt-catalyzed coupling of arylzincs with *O*-benzoylhydroxylamines as the electrophilic nitrogen source instead of chloramines as used by Gosmini.³⁰¹ Using aryl zinc pivalates **289**, accessed through initial halide-magnesium exchange, he is able to couple an assortment of functionalized arenes (both carbocyclic and heterocyclic) with a variety of both *N,N*-dialkyl *O*-benzoylhydroxylamines and *N*-alkyl,*N*-aryl *O*-benzoylhydroxylamines (Figure 64). This allows access to diarylalkylamines **290** which could not be accessed in the previously described copper- and nickel-catalyzed methods.

3.2.5.2 *N*-Acyl Electrophiles in Diaminations and Oxyaminations: *O*-

benzoylhydroxylamines have also found use as one nitrogen component in diamination and oxyamination reactions. Wang first reported a copper-catalyzed diamination of alkenes with tethered *N*-methoxyamides ($X = C$ in Figure 65a) or *N*-methoxyureas ($X = C$ in Figure 65b) and *O*-benzoylhydroxylamines.³⁰² This report was followed more recently by Wolfe who used palladium catalysis in the diamination of alkenes with tethered *N*-allylguanidines ($X = N$ in Figure 65b) or *N*-allylureas ($X = O$ in Figure 65b) and *O*-benzoylhydroxylamines.³⁰³ Variations of interrupted Wacker-type mechanism were proposed in both accounts.

Wang has also studied the use of *O*-benzoylhydroxylamines in the oxyamination of alkenes. Her two reports detail both three-component coupling and two-component couplings in which the alkene is tethered to the carboxylic acid (Figure 65c).^{304–305} There have been many examples of oxyaminations utilizing *O*-benzoylhydroxylamines or other N–O bond-bearing species; however, the mechanisms invoked are often radical-based or involve iron-nitrenoid species rather than an oxidative addition event, and they will not be described in detail here.³⁰⁶

3.2.5.3 Chloramines in Arylation: In 2008, Lei investigated the coupling of boronic acids with aniline-derived chloramines using copper catalysis (Figure 66).³⁰⁷ The author was able to rule out a radical mechanism because a reaction containing radical scavenger 1,1-diphenylethylene proceeded without inhibition. He also found that preforming the [PhCu] species resulted in no formation of coupled product. With this information, Lei's proposed mechanism involves an initial oxidative addition of copper into the N–Cl bond. However, the details of the reaction mechanism post oxidative addition, including the key N–C bond forming step with the boronic acid remain unclear.

Significant work in the field of N–Cl bond activation by metal catalysts has been done by Jarvo beginning with her publication in 2009. She reports a nickel-catalyzed amination of diorganozinc reagents using preformed *N,N*-dialkylchloramines (**300**).³⁰⁸

A variety of chloramines were coupled in good yields, including several bearing additional heteroatomic substitution (**310**), and in one case an unprotected primary amide (**311**) (Figure 67). However, the reaction is sensitive to substitution directly adjacent to the amine, as

evidenced by α -branched amine product **312**. Jarvo also demonstrated a one-pot chlorination/arylation protocol, which greatly improves the utility of this synthetic method by eliminating the need to isolate sensitive chloramine intermediates.

The one-pot chlorination and cross-coupling is featured again in her titanium-mediated reaction of primary chloramines and Grignard reagents (Figure 68).³⁰⁹ While she found that a nickel catalyst could direct the coupling with Grignard reagents, the yields were modest. Switching to titanium boosted the yields, and a ligand was not required. Unlike the previous method, substitution next to the nitrogen was well tolerated (e.g. **316**). It is likely that this does not proceed through a traditional oxidative addition mechanism.

The cross-coupling of chloramines and arylzincs has also been investigated by Gosmini using a cobalt catalyst (Figure 69).³¹⁰ This two-step procedure utilizes cobalt(II) bromide and zinc powder to generate arylzinc species **321**. Upon full conversion of the arylbromide, the zinc dust is filtered off and the solution is added directly to freshly prepared chloramine **283**, bearing one or two alkyl substituents (R^1 and R^2 in Figure 69), and triethylamine in acetonitrile at 0 °C. A variety of aryl groups could be incorporated, including those bearing carbonates, tri-fluoromethyl groups, chlorides (**322**), fluorides (**324**), nitriles, thiols (**323**), and methoxy groups (**325**). Sterically encumbered chloramines could also be coupled but with slightly diminished yields as noted by **324**.

3.2.5.4 N-Alkoxy Electrophiles in Arylation: In 2016, an interesting arylation of electrophilic nitrogen was reported by Sato.³¹¹ He utilized a novel source of electrophilic nitrogen, *N*-methoxyamines. He notes that, due to the poor leaving group ability of methoxy compared to the more commonly used benzoyl, the reaction requires additional activation of the methoxy by a Lewis acidic group. Modest coupling was seen between **326** and aryl boroxines using a copper catalyst (Figure 70).

To access aminated arenes bearing primary amines several strategies have been employed involving different nitrogen electrophiles. In 2010, oxime derived electrophiles were employed by Da kapan which upon hydrolysis gave rise to primary amines.^{312–313} Kürti has employed the use of unsubstituted oxaziridines.³¹⁴ Oxaziridines had been used previously by Vidal in transition-metal free electrophilic amination.³¹⁵ This unsubstituted oxaziridine **330** in the presence of stoichiometric copper could aminate aryl lithiums, aryl Grignards, and aryl zinc reagents which, upon aqueous workup, yields the primary arylamine (e.g. **331**) products in modest to good yields (Figure 71). He also can access secondary amine products when using *N*-alkyl-*O*-benzoyl hydroxylamines (BzONHR) as the electrophilic nitrogen source. Two mechanistic pathways for this oxaziridine chemistry were proposed. In one proposal there is direct nucleophilic attack of the aryl cuprate on the oxaziridine. However, the mechanism favored involves oxidative addition of the arylcopper(I) across the N–O bond forming a metal-lacycle which reductively eliminates, and upon workup, hydrolyses to give the observed product.

3.2.6 Amination of Silyl Ketene Acetals with Nitrogen Electrophiles—T. Miura and Murakami have utilized chloramines to aminate silyl ketene acetals (**332**) and generate amino acid derivatives (**334**) using copper (Figure 72).³¹⁶ Mechanistically the authors

invokes oxidative addition of copper(I) to the chloramine to generate an amino copper(III) intermediate. Subsequent transmetalation with the silyl ketene acetal generates a copper(III) enolate, which reductively eliminates to form the new C–N bond and regenerate the catalyst. The substrate scope in regards to the chloramine is diverse, however the silyl ketene acetal was limited to those derived from triisopropylsilylchloride (TIPSCl) and methyl arylacetates.

Similar to T. Miura and Murakami's work using chloramines to aminate silyl ketene acetals using copper,³¹⁶ M. Miura developed a method to aminate silyl ketene acetals using *O*-benzoylhydroxylamines and a copper catalyst.³¹⁷ The new method boasted a greatly expanded sub-strate scope in regards to the silyl ketene acetal. The method using chloramines was largely limited to aryl acetate-derived substrates, whereas a variety of alkyl and even unsubstituted acetates could be utilized as the silyl ketene acetal with *O*-benzoyl hydroxyl amines in good to excellent yields (Figure 73). Sterically hindered amines (**343**) could be coupled as well. Though he did not have enough data to propose an exact mechanism, Miura was able to rule out a radical pathway by conducting a TEMPO addition study and finding no inhibition.

Similar products as those described above could be obtained by Wang directly from the ester or amide using *in situ* generated zinc enolates rather than preformed silyl ketene acetals.³¹⁸ In the presence of copper(II) chloride and bipyridine ligand the zinc enolate **345** could be converted to the aminated product **346** using *O*-benzoylhydroxylamine (Figure 74). In the absence of copper and ligand and at elevated temperatures, the zinc enolate reacts with the *O*-benzoylhydroxylamine to preferentially give the acylated product **347**, suggesting that an oxidative addition event between copper and *O*-benzoylhydroxylamine is necessary to achieve the aminated product. Good yields were seen for a variety of ester and amide substrates as well as for a variety of differentially substituted hydroxylamines including one bearing a free N–H bond such as R² = H in Figure 74. Wang reported another variant on this amination chemistry from phosphonates or phosphine oxides instead of esters.³¹⁹

3.2.7 Nitrogen Electrophiles in Nontraditional Alkylations—Lalic also developed a one-pot sequential hydroboration to generate primary alkyl boronates followed by transmetalation and a copper-catalyzed electrophilic amination to generate *anti*-Markovnikov tertiary amine products in a formal hydroamination via *in situ* generated boronates.³²⁰ The optimized conditions involve treating the terminal alkene substrate to a stoichiometric copper NHC complex in toluene along 9-borabicyclo(3.3.1)nonane, and an *N,N*-dialkyl-substituted *O*-benzoylhydroxylamine. The reaction affords access to sterically demanding amines, including adamantyl-substituted **351** and 2,2,6,6-tetramethylpiperidine-derived **353** (Figure 75).

3.2.8 Nontraditional Arylations of *N*-Acyl Electrophiles—Another approach to the formation of aryl–N bonds utilizes *in situ* generated organometallic reagents as the nucleophile. One example comes from Wang. His net C–H amination of arenes, an adaptation of his work on the amination of organozinc reagents derived from esters and amides (see section 3.2.6), proceeds through *in situ* generation of aryl zinc species.³²¹ Initial formation of the metalated arene (e.g. **355**) is followed by addition of a symmetrical or

unsymmetrical *N,N*-dialkyl-substituted *O*-benzoyl hydroxyl amine along with a copper(II) acetate catalyst, generating the coupled product (e.g. **356**, Figure 76).

A similar strategy was reported by Lee in 2017 on the coupling of *in situ* generated aryl alanes and *N,N*-dialkyl *O*-benzoyl hydroxyl amines using copper catalysis.³²² The aryl ring is initially deprotonated, and the resulting anion is converted to the aryl alane (**358**). The copper catalyst and electrophile then are added (Figure 77). Good yields were obtained for the coupling of a variety of different heteroaryl starting materials and other electronically-biased arenes. The reaction could even be run effectively on gram scale.

Another related transformation was reported by Wang.³²³ In this reaction the nucleophile, an arylzinc (**361**), is generated *in situ* from an electronically-biased arene or with the assistance of a directing group. This nucleophile couples to the nitrogen electrophile with a copper catalyst (Figure 78).

A number of *ortho*-directing groups were suitable for phenyl rings, while biased heteroarenes were found to not require a directing group (Figure 79). A diverse array of aminated products were obtained using this method, and naturally occurring compounds like nicotine could be aminated giving **368** under the reaction conditions. This method was successfully extended by Wang to include azidation using azidoiodinane as the electrophilic nitrogen source in the same publication.

3.2.9 N–N Bond Electrophiles

3.2.9.1 Hydrazonium Electrophiles: In addition to the traditional pentafluorobenzoyloxime ester substrates that are a hallmark of the Narasaka–Heck reaction (see section 3.2.1), Narasaka also found that *N,N,N*-trialkylhydrazonium salts can also react with palladium(0) in a similar transformation.³²⁴ When the benzophenone derived hydrazonium **369** was subjected to a Pd(0) source in deuterated DMF, the trimethylamine signal of the starting material disappeared and a new signal appeared up-field. He suggests that the shift of this upfield signal is more indicative of either free trimethylamine, the trimethylamine hydrochloride salt, or a trimethylamine bound to a palladium(II) species rather than a hydrazine species. Either of these three possibilities would result from the cleavage of the N–N bond supporting the proposed oxidative addition of palladium into the N–N bond (Figure 80).

When Narasaka subjected *N,N,N*-trialkylhydrazoniums bearing terminal or internal pendant alkenes he noted the formation of both 5-*exo* cyclization products (the unconjugated pyrrolidine and pyrrole (**372**) in varying amounts depending on the conditions used (Figure 81).

3.2.9.2 Diaziridinone Electrophiles: Shi has also activated the N–N bonds of diaziridinones and the related thiadiaziridines^{325–327} in a host of copper- or palladium-catalyzed diaminations of mono-, di-, and trienes as well as esters and ketones.^{328–342} From his work in palladium-catalyzed asymmetric diamination, Shi found that Pd-NHC complex **376** was found to be the optimal catalyst, but only diaziridinone **374** was utilized in the substrate scope in which moderate enantioselectivities were obtained (Figure 82). The

mechanism of this transformation has been studied³⁴³ and this chemistry was detailed in an account in 2014.³⁴⁴

Shi has also applied the use of diaziridinone **374** in the synthesis of spirocyclic indolines. In 2013, he reported a polyamination of α -methylstyrenes with diaziridinone **374** via an oxidative addition of palladium across the N–N bond followed by sequential C–H animations.³⁴⁵ He built on this methodology in 2014 to synthesize mono-aminated norbornane-fused indolines **382** (Figure 83).³⁴⁶ In the reaction, a cascade Heck reaction with norbornene (**378**) was followed by C–H activation of the pendant arene. This generates palladium(II) palladacycle **380** which adds oxidatively across the N–N bond of the diaziridinone **374** to form palladium (IV) species **381** which releases the indoline product **382** and *tert*-butyl isocyanate (**383**).

3.2.10 N–CN Electrophiles: Recent work in the field of electrophilic nitrogen cross-coupling by Nakao has identified a novel class of compounds suitable for oxidative addition by a metal catalyst. Instead of activating a N–O bond or an N–N bond he is able to activate the N–CN bond of cyanamides (e.g. **384**).³⁴⁷ A review detailing the construction of cyanamides has been reported.³⁴⁸ The initial report details the palladium-catalyzed aminocyanation of alkenes in the presence of an addition Lewis acid catalyst which likely serves to coordinate the nitrile nitrogen, further activating the N–C bond for oxidative addition by palladium(0). This is corroborated by the isolation and crystal structure of an oxidative addition complex. A variety of 5-*exo* cyclized and cyanated products of type **385** could be obtained, and modest enantioselectivity could be seen when using SKP ligands (e.g. **390**, Figure 84). Similar to efforts in the field of aza-Heck chemistry, 6-*exo* cyclization was possible with conformationally restricted substrate giving product **388** in modest yield, though more challenging substrates were not reported.

Concurrently to this publication, a similar reaction was reported by Douglas in which the same transformation could be accomplished in the absence of a metal catalyst, albeit with sulfonamide-derived cyanamides instead of the carbamate-derived cyanamides (**384**) used by Nakao.³⁴⁹ Computational work investigating this metal-free variant have been conducted.³⁵⁰ An interesting variant on Nakao's chemistry was reported by Shi in 2016 in which methylenecyclopropanes were oxycyanated by carbamate-derived cyanamides to give structurally complex products (Figure 85).³⁵¹

In 2018, Douglas reported another similar aminocyanation of alkenes using cooperative palladium and Lewis-acid catalysis that allowed access to a diversified product library. He also explored downstream functionalization of the products and further explored the mechanism of this transformation, finding evidence to support an interrupted aza-Heck-type mechanism (Figure 86).³⁵² First, the Lewis acid **B** (usually a BR3 species) coordinates to the terminal nitrogen and palladium(0) undergoes oxidative addition across the N–CN bond. Coordination of the alkene to the Pd(II) intermediate gives rise to **394** (Figure 86). Then *syn*-migratory insertion occurs giving cyclized **395**, which then undergoes reductive elimination with the nitrile to yield the product **396** and regenerate the Pd(0) catalyst.

4 Boron Cross-Coupling

Organoboron compounds have long been utilized as nucleophiles in traditional crosscoupling especially with palladium catalysis, and they have been lauded for their stability, low toxicity, and ready availability.^{22,353} In addition to metal catalyzed cross-coupling of organoborons, there has been a long standing interest in metal catalyzed hydroboration.³⁵⁴ Early interest in metal-boryl complexes stemming from hydroboration by Marder, Norman, Merola, Hartwig, Suzuki, and Miyaura in the 1990s found that metals can add oxidatively across B–H and B–B bonds.^{355–360} Typically, these reagents are associated with reductive borylation processes. In contrast, the more electrophilic boryl halides, which do not typically provide reductive byproducts in reactions with organic molecules, have also recently begun to be explored as a means to introduce boron centers via cross-coupling reactions.

4.1 Introduction

In 1998, Marder and Norman began to investigate the oxidative addition of boron-chlorine and boron-bromine bonds with platinum.³⁶¹ In 2001, Tanaka reported the construction of a palladium complex derived from the oxidative addition of a B–Cl bond (see section 4.2).³⁶² In the late 2000s, Braunschweig again investigated the oxidative addition of palladium into boron-halide bonds. First, complexes derived from the oxidative addition of palladium across B–Br were crystallized (Figure 87).³⁶³

The oxidative addition of B–Br bonds would later be studied computationally by Sakaki.³⁶⁴ Then in 2009 Braunschweig investigated the oxidative addition of boryl chlorides with platinum.³⁶⁵ And lastly in 2011, Braunschweig also showed that platinum was able to activate B–F bonds.³⁶⁶

In 2001, Marder proposed a boron variant of a Heck reaction to give the same products as dehydrogenative borylation.³⁶⁷ However, in order for this reaction to be successful, he needed to determine if the chosen electrophilic boron source, chlorocatechol borane (catBCl, **400**), was compatible with the phosphine ligand and base that are necessary in the Heck reaction and many other cross-couplings. In the presence of triethylamine or phosphines, adducts (**399** and **401**) were formed at ambient temperature according to NMR analysis (¹¹B shift information in Figure 88) and crystal structures were obtained for catBCl adducts including for the trimethylphosphine adduct **399** and the triethylamine adduct **401**. He concluded that undesirable side reactivity of the catBCl, in which ring opening and dimerization of the catBCl can occur, would be prohibitive of the use of labile phosphine ligands. Also, he concluded that the oxidative addition of the B–Cl bond in amine adducts by transition metals is unprecedented and would need to be explored.

4.2 Preliminary Efforts Towards Cross-Coupling

The first reported metal-mediated reaction of a boron electrophile and an alkyne nucleophile was published in 2001 by Tanaka.³⁶² He previously had an interest in the activation of other chloro-heteroatom bonds specifically silyl–chloride bonds (see section 2.2.1). In his 2001 report, Tanaka found that oxidative addition of palladium across the B–Cl bond of **403**

generates complex **404** which can insert into an alkyne **405** to give products of type **406** (Figure 89).

4.3 Intramolecular Cross-Coupling of Boron Electrophiles

The first report of a catalytic coupling of a B–Cl species, (diisopropylamino)chloroboryl ether, and an alkyne was reported in 2005 by Suginome,³⁶⁸ who has subsequently done extensive work on the intramolecular coupling of boron electrophiles. The initial reaction was intramolecular, forming the 5-*exo* product, and utilized a nickel catalyst and triphenylphosphine ligand. By using the amine-substituted borylchloride (e.g. **407**), which is more electron-rich than ClBcat, he was evidently able to avoid the undesirable phosphine-boron adduct formation that was reported by Marder (section 4.1).

Following oxidative addition across the B–Cl bond and insertion into the alkyne, the generated intermediate vinylnickel species **409** undergoes cis-to-trans isomerization to the sterically favored trans isomer **410** (Figure 90). This then undergoes transmetalation with an alkynylstannane **411** to yield **412**. Reductive elimination yields the direct product of the coupling **413**, which - due to its sensitivity to moisture - is transformed to the acetate-protected pinacol boronate **414** before isolation. Suginome was able to isolate and obtain a crystal structure of the cyclized vinylnickel intermediate of type **410**, supporting the proposed cis-to-trans isomerization step.

In 2008, Suginome reported another intramolecular borylation reaction using similar starting materials. In this case, palladium was used instead of nickel, and an organozirconium reagent was used in place of the stannane.³⁶⁹ What is remarkable about this transformation is that the cis/trans selectivity could be controlled by the choice of phosphine ligand (Figure 91). When using trimethylphosphine as the ligand, the cis product **416** was obtained in greater than 99:1 selectivity for most substrates tested. Switching to a bulkier phosphine ligand such as tri-*tert*-butylphosphine or tricyclohexylphosphine inverted the selectivity to favor the trans product **417** again in greater than 99:1 selectivity for most substrates tested. The proposed mechanism is nearly identical to that of Figure 90. Suginome attributes the observed selectivity to the influence the ligand has on the cis-to-trans isomerization step. With a small ligand, the steric clash with the dialkylamino group is less significant and transmetalation proceeds faster than cis-to-trans isomerization resulting in the cis product **416**. With a large ligand, the steric clash with the dialkylamino group is significant and cis-to-trans isomerization proceeds faster than transmetalation resulting in the trans product **417**.

Suginome and Daini later extended this method from alkynes to tethered alkenes generating products with a stereogenic center (Figure 92).³⁷⁰ The use of trimethylphosphine in a 2:1 ratio with palladium was crucial to obtaining a high yield of the trans product as was found in their previous work. However, unlike their previous work, only alkenylzirconiums were reactive; arylzirconiums and alkylzirconiums did not participate in the coupling reaction. 1,2-Disubstituted alkenes also failed to participate in the reaction and only 5-*exo* cyclizations were possible.

In 2013, Suginome further extended this methodology to a tandem boration of an internal alkyne followed by a Heck reaction.³⁷¹ Again PdCp(allyl) was found to be the optimal

palladium source, but triphenylphosphine was the optimal ligand and triethylamine base was needed to turn over the palladium catalyst. The formation of unreactive triethylamine adducts as described by Marder (Section 4.1) was inconsequential - perhaps due to the use of an electron-rich aminoborylchloride (e.g. **420**). Higher yields could be obtained in acetonitrile than toluene; however, this limited the temperature to 80 °C and many of the substrates were sluggish. Aryl- and heteroaryl-substituted alkenes gave modest yields while alkyl-substituted alkenes provided diminished yields of coupled product (Figure 93). Yields could be increased by the addition of geminal substitution and taking advantage of the Thorpe-Ingold effect.^{372–374}

4.4 Intermolecular Cross-Coupling of Boron Electrophiles

In addition to doing extensive work on intramolecular borylation reactions using electrophilic boron, Suginome also developed an intermolecular multicomponent coupling of alkynes, chloroborane **403**, and vinylzirconocenes (**423**) or arylzirconocenes.³⁷⁵ Like his previous work his optimal conditions were a catalyst derived from PdCp(allyl) and trimethylphosphine and toluene solvent at elevated temperatures. As before, the direct products of the coupling were converted to the Bpin esters prior to isolation. Symmetrical, unsymmetrical, and terminal alkenes were all competent coupling partners with R¹ (Figure 94) being the smaller of the two alkyne substituents.

In 2016, our group reported an intermolecular boryl-Heck reaction of catBCl and terminal alkenes.³⁷⁶ To overcome the issue of triethylamine sequestering the chloroborane (see section 4.1), a number of bases were investigated and it was found that large, sterically encumbered amine bases such as *N,N*-dicyclohexylmethanamine (Cy₂NMe) provided the desired coupled product **429** with minimal starting material isomerization. ¹¹B NMR experiments revealed that Cy₂NMe binds less strongly to catBCl than does triethylamine. In a competition experiment, the triethylamine adduct was formed preferentially over the Cy₂NMe adduct (Figure 95c). The broader, further downfield peak seen for the Cy₂NMe adduct (Figure 95b) is also indicative that the exchange between free Cy₂NMe and its adduct is more fluxional than that with triethylamine. This suggests that the oxidative addition of catBCl occurs via the equilibrium concentration of free catBCl.

Further optimization of the reaction explored alternative catalysts and we found that a single-component catalyst derived from the optimal phosphine ligand **38** simplified reaction setup and gave better and more consistent yields of the vinylboronate products. Styrenyl substrates could also be coupled with slightly modified conditions. In these cases, catalytic lithium iodide is added which accelerates the reaction rate which allowed the reaction temperature to be decreased from 90 °C to a milder 70 °C and improved yields. A variety of boron acid derivatives could be obtained if alternative reagents were added at the end of the reaction (Figure 96).

In the case of linear α -olefins, alkene isomerization proved problematic in initial studies. The addition of lithium iodide was not helpful here, and instead only increased starting material isomerization. Instead, it was found that the addition of stoichiometric lithium triflate (LiOTf) suppressed the starting material isomerization (Figure 97). The exact role of LiOTf is not well understood, though we hypothesize that the insolubility of LiCl in the

reaction solvent may shift equilibria involving the palladium hydrides - which are likely the cause of starting material isomerization. The direct products of the coupling bearing catechol can be converted to the pinacol ester for ease of isolation simply by the addition of pinacol at the end of the reaction. A variety of linear products could be obtained (Figure 97) using the LiOTf conditions.

More recent work in the field of boryl-Heck chemistry from our group has identified modified conditions for the coupling of 1,1-disubstituted and 1,2-disubstituted alkenes (Figure 98).³⁷⁷ These second generation conditions utilize a different electrophilic boron source *B*-bromocatecholborane (catBBr), and a more active catalyst, [(**38**)PdI₂]₂. Coupling with 1,1-disubstituted alkenes results in the trisubstituted vinyl boronate with high selectivity for the *E*-isomer (e.g. **439** in Figure 98). For styrenyl-derived 1,2-disubstituted alkenes, high selectivity for the *Z*-isomer (e.g. **441**) was obtained when starting from the *E*-starting material (e.g. **440**).

5 Cross-Coupling of Oxygen Electrophiles

Given the breadth of uncatalyzed ways to install oxygen in organic compounds, there have been comparatively few examples of the use of oxygen electrophiles in cross-coupling. The known examples, reviewed below, arise from the activation of C–O bonds in esters or oxyacyanated species, and result in intermediates that have the character of electrophilic oxygen centers.³⁷⁸ These reactions are distinct from a much larger class of reactions in which C–O bonds are activated to generate electrophilic carbon species in cross-coupling reaction, 154, 379–381 which fall into mold of “traditional” cross-couplings and are not reviewed here.

5.1 Activation of C–O Bonds of Esters

The first report comes from Ohe in 2009 in which he proposes oxidative addition of palladium across the C–O bond of an ester (facilitated by the addition of zinc powder) followed by addition into a pendant nitrile ultimately leading to the formation of an aminobenzofuran (**443**, Figure 99).³⁸²

This work was followed up by Douglas in 2011 who used rhodium to activate the C–O bond of an ester (**444**).³⁸³ A strategically placed quinoline group both directs the metal center to the acyl C–O bond and serves as a chelating ligand to support complex **445**. Following oxidative addition, complex **445** undergoes C–O bond forming migratory insertion and reductive elimination to form product **447** (Figure 100). Both five- and six-membered rings could be formed and the reaction was tolerant of substitution on the backbone aryl ring. Douglas returned to his initial rhodium-catalyzed oxyacylation conditions in 2017 and further explored the mechanism and expanded the substrate scope.³⁸⁴ Additional DFT studies on the mechanism were completed by Cavallo in 2015.³⁸⁵

Douglas followed this initial report up with another in 2014.³⁸⁶ Instead of using rhodium to activate the C–O bond, he uses iridium which allows the use of a simpler directing group handle, an easily functionalized phenol. Use of an iridium precatalyst with added MOP ligand (**452**) at elevated temperatures allowed for the formation of five- (**451**) or six-membered (**450**) ring products in good to modest yields (Figure 101). Although a chiral

ligand **452** was used, no enantioselectivity was observed. A similar mechanism for the cyclization as to the prior rhodium report was proposed.

5.2 Activation of NC–O Bonds

While the activation of NC–N bonds in cross-coupling was discussed in 3.2.10, analogous chemistry on the activation of NC–O bonds was described concurrently.³⁸⁷ Nakao, similar to his reported work on cyanamides (section 3.2.10), reported a palladium-catalyzed oxycyanation reaction to form both five- and six-membered rings. Using a Pd(0) precatalyst and Xantphos ligand in conjunction with triphenylborane Lewis acid cocatalyst, a variety of substituted products could be synthesized (Figure 102).

6. Cross-Coupling of Phosphorus Electrophiles

The sole example of a cross-coupling involving a phosphorus electrophile was reported by Beletskaya in 2003. The reaction, a heteroanalog of a Sonogashira reaction, couples a terminal alkyne to a diaryl- or dialkylchlorophosphane using a nickel catalyst and triethylamine base.³⁸⁸ The proposed mechanism follows that of a traditional Sonogashira reaction (Figure 103).

In addition to nickel, palladium could also catalyze the reaction but was found to be less active than the nickel catalysts. A number of solvents were compatible in the reaction ranging from nonpolar solvents like benzene and toluene to more polar solvents such as dichloromethane and acetonitrile. The reaction is very fast at 80 °C, reaching completion in many cases in under thirty minutes. Bulky substituents like *tert*-butyl groups on the chlorophosphane greatly slowed the reaction to the point of impracticability with **471** being obtained in only 25% NMR yield after fourteen days at 120 °C. However, the bis-isopropylchlorophosphane reacted to give **468** in only ten minutes (Figure 104). Substitution on the phenyl rings of the diarylchlorophosphane was not tolerated, resulting in complex mixtures.

7 Conclusion

Although couplings utilizing carbon electrophiles have been the gold standard in cross-coupling chemistry, the development of couplings utilizing heteroatomic electrophiles is an ever-expanding area of research. Since Tanaka's seminal initial report of the use of silicon electrophiles in coupling, the overall field has expanded to the creation of C–Si, C–N, C–B, C–O and C–P bonds. The umpolung strategy of enlisting these heteroatoms as electrophiles, rather than more traditionally as nucleophiles, has allowed access to complementary structural diversity that would be hard to access using traditional cross-coupling. Although the past 10–15 years has seen an immense expansion of the cross-coupling reactions using heteroatomic electrophiles, the field remains in its infancy. Of the main group elements, only a handful have been explored as electrophilic centers in these reactions. Likewise, the classes of reaction that have been investigated, particularly outside of nitrogen electrophiles, is very limited. Many opportunities for the development of new reactions, and in particular asymmetric reactions, using these general strategies remain.

Finally, as compared to traditional cross-coupling reactions using carbon electrophiles, very little is known about the mechanistic details of many of the reactions in this arena. Deeper understanding of the mechanism and pathways of these reactions will do doubt lead to further expansions of the scope and importance of this class of reactions. Future directions in the field will likely further explore the utility of the existing sources of electrophilic silicon, boron, oxygen, and nitrogen in cross-coupling chemistry with a variety of nucleophiles and metal catalysts, as well as identify new ways to activate heteroatoms as electrophiles. Likewise, as the field matures, heteroatomic electrophile cross-couplings will continue to find applications in more complex settings. Use of heteroatomic electrophile cross-coupling for the installation of heteroatoms has been scarcely utilized in total synthesis and industrial applications, though many opportunities exist given the host of high-yielding, robust processes in these contexts. We expect to see many developments in this area over the next decade and look forward to the exciting ways in which this field will advance.

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Donald A. Watson received his B.S. in chemistry from UC San Diego in 1998, and his Ph.D. in chemistry from UC Irvine in 2004. After completing postdoctoral studies at UC Berkeley and MIT, he was appointed as an Assistant Professor in the Department of Chemistry and Biochemistry at the University of Delaware in 2009. He was promoted to Associate Professor with tenure in 2015, and to Professor in 2018. His laboratory is focused on the invention of new chemical transformations and the synthesis of complex molecules.

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Figure 1.

a) General Mechanism of Traditional Cross-Coupling Reactions (Suzuki Y=B, Kumada Y=Mg, Hiyama Y=Si, Sonogashira Y=Cu, Negishi Y=Zn, Stille Y=Sn) b) Mechanism of the Heck Reaction.

Figure 2.
Example of C-sp³ Cross-Coupling of a Primary Alkyl Chloride with a Primary Alkyl 9-BBN
Reagent from Fu.⁹⁷

Figure 3.
Mechanism of the Buchwald-Hartwig Reaction.

Figure 4.
Relevant Structures Containing Silicon, Boron, Nitrogen, or Phosphorus Atoms.

Figure 5.
Tanaka's Formation of a Platinum Oxidative Addition Complex from a Si–Br Bond.

Figure 6.
Milstein's Iridium Oxidative Addition Complexes with Chlorosilanes.

Figure 7. Tanaka's Synthesis of Complexes to Probe Silene Formation by β -Hydride Elimination.

Figure 8.
Puddephatt's Platinum Oxidative Addition Complex with Trimethylsilyliodide.

Figure 9.
Ozerov's Me_3SiCl Oxidative Addition Complex with Rhodium.

Figure 10.

First Report of a Silyl-Heck Reaction of Styrenes and Silyliodides by Tanaka.

Figure 11.
Scope of Watson's Initial Silyl-Heck Reaction of Styrenes.

Figure 12.
Scope of Watson's Initial Silyl-Heck Reaction of Terminal Alkenes.

Figure 13.
Scope of Watson's Second-Generation Silyl-Heck Reaction of Terminal Alkenes.

Figure 14. Watson's Improved Silane Scope with Second-Generation Catalytic System for Silyl-Heck of Styrenes.

Figure 15.
Crystal Structure of Watson's Single-Component Precatalyst [(38)PdI₂]₂ for Palladium-Catalyzed Silyl-Heck Reaction.

Figure 16. Scope of Watson's Silyl-Heck Reaction of Terminal Alkenes and Styrenes Using Single-Component Precatalyst 35.

Figure 17.

Scope of Watson's Silyl-Heck Reaction of Silylditriflates with Styrenes Yielding Vinylsilylethers or Disiloxanes.

SiR_3	Yield
$SiMe_2Bn$	67%
$SiMe_2Ph$	70%
$SiEt_3$	65%
$SiPh_2Me$	74%
$Si(iPr)_3$	0%

Figure 18.

Scope of Watson's Nickel-Catalyzed Silyl-Heck Reaction Using Silyltriflates.

Figure 19. Shimada and Nakajima's Silyl-Heck Reaction of Styrenes by Direct Si-Cl Bond Activation with Nickel.

Figure 20.
Proposed Catalytic Cycle of Murai's Multicomponent Coupling of Trimethylsilyliodides.

Figure 21.
Scope of Watson's Silyl-Negishi Reaction.

Figure 22.
Scope of Watson's Silyl-Kumada-Tamao-Corriu Reaction.

Figure 23.
Narasaka's Initial Discovery of Palladium Oxidative Addition into N–O Bonds.

Figure 24.
Hartwig's Oxidative Addition Complex Derived from *O*-pentafluorobenzoyloxime and Palladium(0).

Figure 25.
Narasaka's Palladium-Catalyzed Intramolecular Heck Reaction of Alkene-Tethered *O*-pentafluorobenzoyloximes to Pyrroles.

Figure 26.
Narasaka's Construction of Complex Aza-Heterocycles via Heck-type Cyclization.

Figure 27.

Abell's Use of *O*-Pentafluorobenzoylamidoximes in the Synthesis of Imidazoles by Heck-type Cyclization.

Figure 28.

Fürstner's Use of a Narasaka–Heck Reaction in the Total Synthesis of Butyl-cycloheptylprodigiosin (98).

Figure 29.

Bower's Narasaka-Heck Reaction To Generate Stereogenic Bicyclic Imines From Pentafluorobenzoyloxime Esters.

Figure 30.
Bower's Diastereoselective Narasaka-Heck Reaction of Cyclohexene-Tethered
Pentafluorobenzoyloxime Esters.

Figure 31.

a) Bower's Narasaka-Heck Reaction of 1,2-Disubstituted Alkenes b) Bower's Narasaka-Heck Reaction of 1,1-Disubstituted Alkenes.

Figure 32.

Bower's Proposed Divergent Mechanism for Narasaka-Heck Cyclization.

Figure 33.
Scope of Bower's Asymmetric Narasaka-Heck Reaction.

Figure 34.
Proposed Catalytic Cycle of Abell's Domino Narasaka–Heck Reaction and Carbonylation.

Figure 35.
Kitamura's Domino Reaction of Alkyne-Tethered Pentafluorobenzoyloximes to Form Isoindole Products.

Figure 36.
Scope of Bower's Tandem Narasaka-Heck and Carbonylation.

Figure 37.

Tong's Deuterium Studies of the Iminohalogenation Reaction that Suggest an S_N2-Type Reductive Elimination of the Product.

Figure 38.
Zhu's Tandem Asymmetric Narasaka–Heck Reaction and Arylation with Oxadiazole.

Figure 39. Proposed Two Electron and Single Electron Pathways for Zhu's Enantioselective Interrupted Narasaka-Heck Reaction.

Figure 40.
Scope of Liebeskind's *N*-Imination of Boronic Acids.

Figure 41.
Liebeskind's Synthesis of Substituted Pyridines via Coupling of Vinylboronic Acids and O-Pentafluoroenzoylketoximes.

Figure 42.
Liebeskind's Copper-Mediated Coupling of *O*-Acyl Hydroxamic Acids with Boronic Acids and Stannanes.

Figure 43.
Proposed Mechanism of Liu and Xi's Copper-Mediated Coupling of Alkenylzirconocenes and *O*-Benzoyloximes.

Figure 44.
Zhu's Aza-Heck Cyclization of *O*-Phosphinyloximes and Subsequent Dehydrogenation to Fused Pyridines.

Figure 45.
Proposed Catalytic Cycle for Bower's Sulfonamide Aza-Heck Cyclization.

Figure 46.
Bower's 6-*exo* Sulfonamide Aza-Heck Cyclization.

Figure 47.
Scope of Watson's 5-*exo* Aza-Heck Reaction of *O*-Phenylhydroxamates.

Figure 48.
Watson's 6-*exo* Aza-Heck Reaction of an *O*-Phenylhydroxamate.

Figure 49. Scope of Bower's Aza-Heck 5-*exo* and 6-*exo* Cyclizations of Carbamates.

Figure 50.

Watson's Aza-Heck reaction of Urea-derived Electrophiles to Generate Imidazolidinones or Dihydroimidazolones.

Figure 51.
Scope of Gottlich's Hetero-Heck-Type Reaction of Chloramines.

Figure 52.
Proposed Catalytic Cycle of Gottlich's Chloramine Heck-Type Cyclization.

Figure 53.

Scope of Johnson's Copper-Catalyzed Coupling of Diorganozincs and *O*-Benzoylhydroxylamines.

Figure 54.

Scope of Johnson's Nickel-Catalyzed Variant of Coupling of *O*-Benzoylhydroxylamines and Zinc Reagents.

Figure 55. Scope of Johnson's Copper-Catalyzed Coupling Utilizing an Improved *O*-Benzoylhydroxylamine Synthesis.

Figure 56.
Retention of *Endo*-Stereochemistry In Johnson's Copper-Catalyzed Cross-Coupling of
Organozincs and *O*-Benzoylhydroxylamines.

Figure 57.
Johnson's Deuteration Study Resulting In Statistical Mixture of Crossover And Non-Crossover Products Supporting An Intermolecular Reaction Mechanism.

Figure 58. Scope of Miura's Copper-Catalyzed Coupling of Arylboronates with *O*-Benzoylhydroxylamines.

Figure 59. Scope of Lalic's Coupling of Arylboronates and *O*-Benzoylhydroxylamines.

Figure 60.
Scope of Miura's Amination of Arylsilanes with *O*-Benzoylhydroxylamines.

Figure 61.
Proposed Mechanism of Smith's Arylation Using Siloxane Transfer Reagents.

Figure 62.
Zhou and Wang's Cross-Coupling of Electrophilic Nitrogen with Organoalanes.

Figure 63.

Scope of Xi's Copper-Catalyzed Electrophilic Amination of Alkenylzirconocenes.

Figure 64.
Scope of Knochel's Cobalt-Catalyzed Coupling of Aryl-Substituted Hydroxylamine Electrophiles.

Figure 65

. Wang's (A) and Wolfe's (B) Diamination Reactions of *O*-Benzoylhydroxylamines and Wang's (C) Aminolactonization Reaction.

Figure 66.
Scope of Lei's Coupling of Chloramines with Aryl Boronic Acids.

Figure 67.
Scope of Jarvo's First-Generation Nickel-Catalyzed Coupling of Chloramines and Diphenylzinc.

Figure 68.

Scope of Jarvo's Titanium-Mediated Coupling of *in situ* Generated Chloramines and Aryl Grignard Reagents.

Figure 69.

Scope of Gosmini's Cobalt-Catalyzed Amination of Arylzincs with Chloramines.

Figure 70. Scope of Sato's Arylation of *N*-Methoxyamines with Copper Catalysis.

Figure 71.

Example of Kürti's Amination Using Oxaziridines to get Primary Arylamines.

Figure 72.

T. Miura and Murakami's Amination of Silyl Ketene Acetals Using Chloramines.

Figure 73.
 Scope of M. Miura's Amination of Silyl Ketene Acetals Using *O*-Benzoylhydroxylamines.

Figure 74. Wang's Coupling of *in situ* Generated Organozincs with Electrophilic Nitrogen.

Figure 75.

Scope of Lalic's One-Pot Hydroboration and Copper-Catalyzed Electrophilic Amination.

Figure 76.

Wang's C–H Zincation Followed by Electrophilic Amination with Copper.

Figure 77.

Lee's *in situ* Generation of Organoalane for Cross-Coupling with Electrophilic nitrogen.

Figure 78.

Strategy of Wang's Directed Zincation of Arenes Followed by Copper-Catalyzed Electrophilic Amination.

Figure 79.
Scope of Wang's Amination of *in situ* Generated Arylzincs with Electrophilic Nitrogen.

Figure 80.

Narasaka's NMR Studies of Proposed Oxidative Addition Intermediate of *N,N,N*-Trialkylhydrazone Salts.

Figure 81.
Narasaka's 5-*exo* Cyclization of *N,N,N*-Trialkylhydrazone Bearing Pendant Alkene.

Figure 82.
Shi's Diamination using Diaziridinones and a Palladium-NHC Catalyst.

Figure 83.
Proposed Catalytic Cycle of Shi's Indoline Synthesis via C-H Activation and Electrophilic Amination.

Figure 84.
Scope of Nakao's Aminocyanation of Alkene-Tethered Cyanamides.

Figure 85.
Shi's Cyclopropyl Variant on Nakao's Chemistry

Figure 86.
Proposed Mechanism of Douglas' Aminocyanation Reaction.

Figure 87.

Braunschweig's Substituted Catecholboronate Oxidative Addition Complex.

Figure 88.
Marder's NMR Studies and ^{11}B Shift Information for Phosphine and Triethylamine
Adducts in CDCl_3 .

Figure 89.

Tanaka's Preliminary Efforts Towards Cross-Coupling of Boron Electrophiles.

Figure 90.
Proposed Catalytic Cycle of Suginome's Nickel-Catalyzed Intramolecular Borylation/Stille Coupling.

Figure 91.
Suginome's Observed Reversal of Selectivity in the Intramolecular Borylation and Coupling with Organozirconium Species.

Figure 92.
Suginome's Borylation of Alkenes and Subsequent Cross-Coupling with Organozirconium Species.

Figure 93.
Suginome's Tandem Electrophilic Borylation Followed by Heck Reaction.

Figure 94.
Scope of Suginome's Intramolecular Carboboration Reaction.

Figure 95.

Watson's ^{11}B NMR Studies on Amine Adduct Formation with catBCl in CDCl_3 .

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Figure 96.

Scope of Boronic Derivatives Derived from Watson's Boryl-Heck Reaction.

Figure 97.
Scope of Linear α -Olefin Products in Watson's Boryl-Heck Reaction.

Figure 99.
Example of Ohe's Formation of Aminobenzofurans.

Figure 100.
Proposed Mechanism of Douglas' Intramolecular Oxyacylation Reaction.

Figure 101.
Substrate Scope of Douglas' Iridium-Catalyzed Oxyacylation.

Figure 102.
Products Synthesized by Nakao's Oxycyanation Reaction.

Figure 103.
Proposed Mechanism of Belatskaya's Coupling of Terminal Alkynes and Chlorophosphanes.

466
95% yield

467
86% yield

468
79% yield

469
96% yield

470
78% yield

471
25% yield

Figure 104.

Scope of Beletskaya's Cross-coupling of Chlorophosphanes and Terminal Alkynes.