THE PENNSYLVANIA STATE UNIVERSITY
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DEPARTMENT OF CHEMISTRY

Electrochemical Cross-Coupling of *N*-Heteroarenes

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ABSTRACT

The importance of nitrogen-containing heteroaromatic compounds is highlighted by their essential structural roles in pharmaceutical compounds. As a result, the need for rapid access to functionalized heteroaromatics plays a critical role in the drug discovery process.

Due to their abundance and low cost, ***unfunctionalized*** nitrogen-containing heteroaromatic compounds make for ideal coupling partners compared to their borated and halogenated counterparts, which currently represent the prevailing starting materials for C–C bond formation. Although attempts have been made to activate these simple staring materials, their inherent electronic diversity presents significant obstacles to strategies for their general activation.

Our project aims to leverage both Brønsted acid catalysis and electrocatalysis to develop a broad range of C–C and C–X forming technologies by temporarily accessing reduced, open-shell intermediates. If successful, such methods would represent a new and highly enabling catalytic mode to access these important heterocyclic structures.

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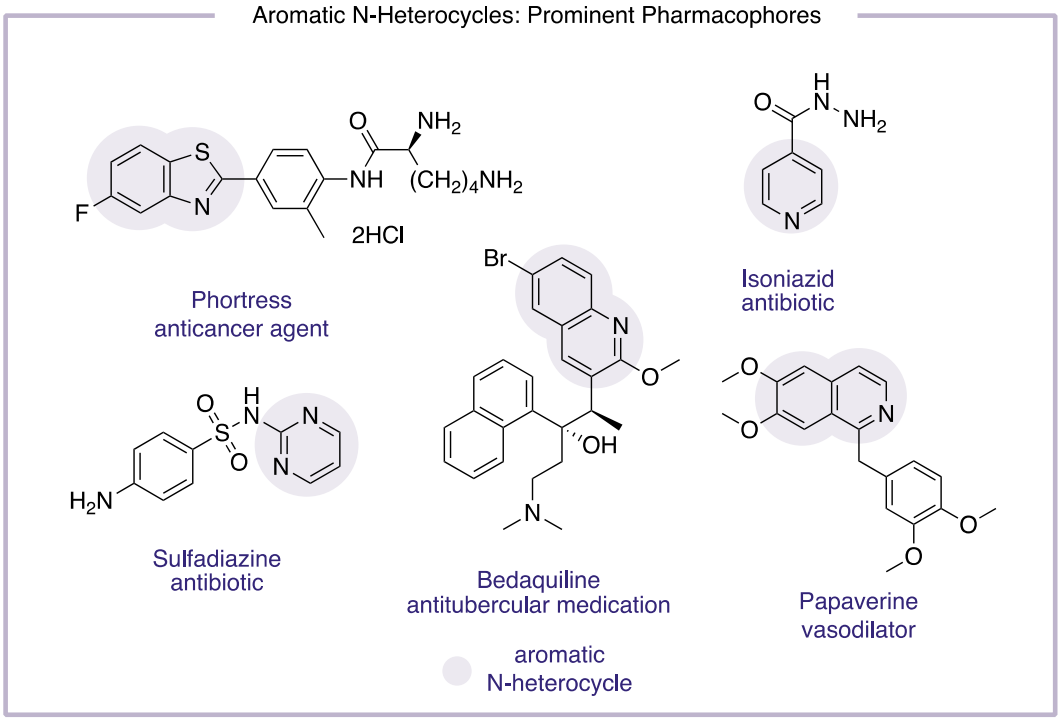
Chapter 1 *N*-Heteroarenes

N-heteroarenes refer to a group of aromatic compounds that contain nitrogen as part of the cyclic, conjugated π system. *N*-heteroarenes represent one of the most prevalent structural motifs in medicinal agents. An analysis of American FDA-approved pharmaceutical agents revealed that 25% of small-molecule drugs contain at least one such subunit (Figure 1)[1]. When present, these *N*-heteroaromatic motifs play essential roles in the drug's activity. For example, a recent article studying the structure and antitubercular activity relationship of Bedaquiline found that its quinoline moiety is necessary for it to maintain its activity[2]. In some cases, this *N*-heteroarene motif requirement has been shown to be due to its role in receptor binding. In addition, a 1994 study comparing papaverine to a nonaromatic analog found that the planarity of the isoquinoline ring facilitated the drug's interaction with receptor sites[3]. Along with the simple *N*-heteroarene motif, the bi(hetero)aryl motif has also been broadly represented in materials science, agrochemicals, natural products, and pharmaceuticals.

Figure 1.



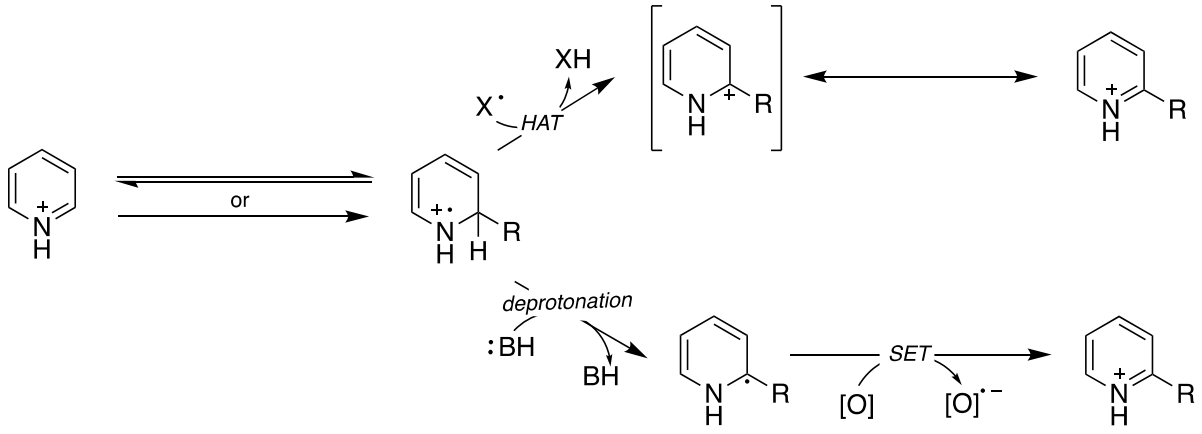
Electron-*deficient N*-heteroarenes are also more prevalent in medicinal agents compared to their electron-rich counterparts[1]. Correspondingly, a disproportionate amount of time and effort is typically dedicated to optimizing these electron-deficient structures in the drug-discovery process. Due to their electron-deficient nature, existing technologies to functionalize *N*-heteroarenes have largely depended greatly on their electrophilic reactivity, although de novo synthesis also remains a commonplace approach.

Chapter 2 Functionalizations of *N*-Heteroarenes

2.1 Minisci Radical Substitution

A Minisci-type reaction refers to a homolytic C–H substitution of protonated heteroarenes. The substitution renders products with the opposite selectivity and reactivity as would be expected from a Friedel-Crafts aromatic substitution, with more electron-deficient heteroarenes reacting faster[4]. The mechanism begins with the addition of the nucleophilic carbon-centered radical to the basic heteroarene. Stoichiometric amounts of acid are used to facilitate the addition of the radical to the protonated, cationic *N*-heteroarene, which has a consequently lower LUMO energy. Depending on the nature of the substrate and the radical, this addition may or may not be reversible[5]. After the addition of the radical, there are two possible pathways towards rearomatization. In one possible pathway, it is accomplished by a hydrogen-atom transfer from the radical-cation intermediate, followed by deprotonation. In another, the acidic α-proton of the radical cation is first removed. This event is followed by an oxidation of the neutral radical, which affords a non-conjugated 6π-intermediate, and forms the new C−C bond in place of the former C−H bond after oxidation and deprotonation.

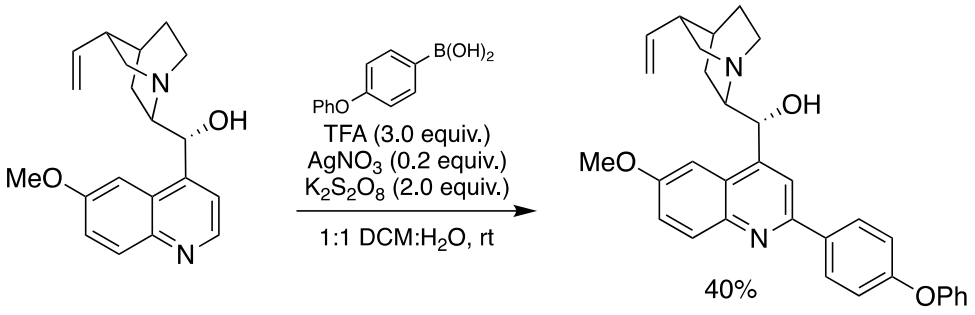
Scheme 1.



Minisci-type reactions provide versatile transformations that prove useful for medicinal chemists seeking to functionalize compounds with biological activity, or intermediates en route to the desired product. Although Minisci decarboxylation provides for a respectable scope for alkyl radical partners, it has been joined by a fresh array of new radical-generation strategies that allow for a wide range of new substrates to be utilized.

For example, in 2010, Baran and coworkers reported the direct C–H arylation of electron-deficient heterocycles through the use of arylboronic acids as aryl-radical precursors[6]. This feat could not be achieved through decarboxylation. The utility of this Minisci-type reaction was demonstrated in the functionalization of sensitive late-stage intermediates such as the direct arylation of quinine (Scheme 2), a transformation that would typically require multiple steps, the addition of protecting groups, and prefunctionalization of the heterocycle.

Scheme 2.



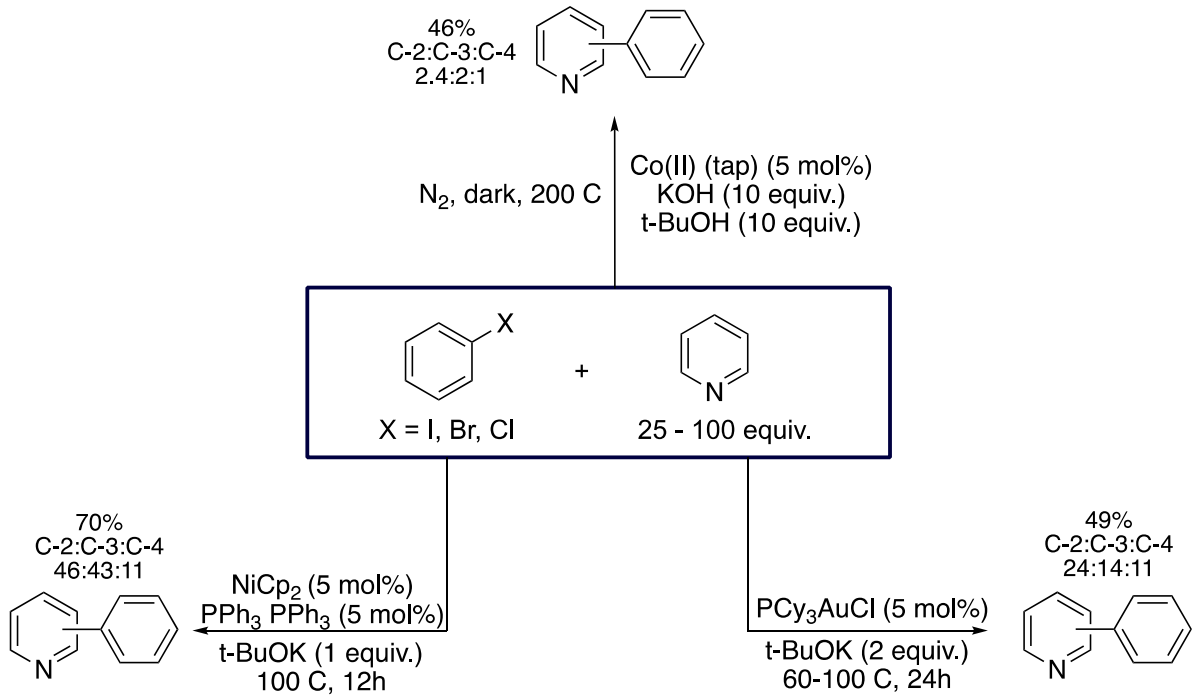
While useful, Baran's reported C–H arylation fails to include electron-*deficient* boronic acids.

2.2 Metal-Catalyzed Direct C-H Arylation of Heteroarenes

Transition-metal catalysts are attractive due to their low-cost stoichiometry. They still, however, require pre-functionalization of the *N*-heteroarene. For the most representative C(sp^2)-H arylations, the mechanism begins the oxidative addition of a metal onto an aromatic halide

followed by a metal-mediated C–H bond activation[7]. Various transition metals have been shown to mediate the *N*-Heteroarene C(sp^2)-H arylation, with a selection of reported transformations outlined in Scheme 3[7, 8, 9].

Scheme 3.

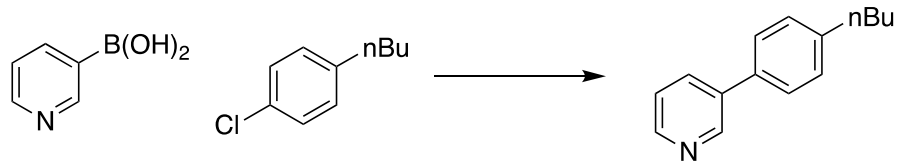


A significant drawback of the metal-catalyzed arylation reactions is that they have a relatively narrow *N*-heteroarene substrate scope. For example, among published arylations utilizing gold, nickel, or cobalt catalysts, pyridine, pyrazine, and pyrrole were the only heteroaromatics reported[789]. Some other limitations to the reaction include its poor regioselectivity and the requirements for high temperatures and large excesses of *N*-heteroarene starting materials. These limitations make the transformation unsuitable for the functionalization of sensitive late-stage intermediates.

2.3 Suzuki Cross Coupling Reactions

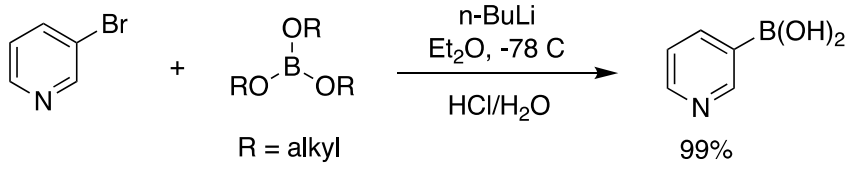
The Suzuki reaction is a cross-coupling reaction between an sp^2-hybridized organoboron compound and an sp^2-hybridized organic halide or triflate with a palladium(0) complex serving as the catalyst[4] (Scheme 4).

Scheme 4.



This highly versatile reaction has been applied to a variety of fields, ranging from materials science to medicinal chemistry[4]. Some favorable aspects of the reaction include its mild reaction conditions and the relative commercial availability of simple boronic acids. The major disadvantage is that even modestly complex boronic acids or halides must be prepared by multiple steps (Scheme 5)[4, 10]. Though inefficient compared to the previously outlined transformations, a 2014 study found that the Suzuki coupling was the fifth-most frequently occurring reaction in medicinal chemistry literature[11].

Scheme 5.

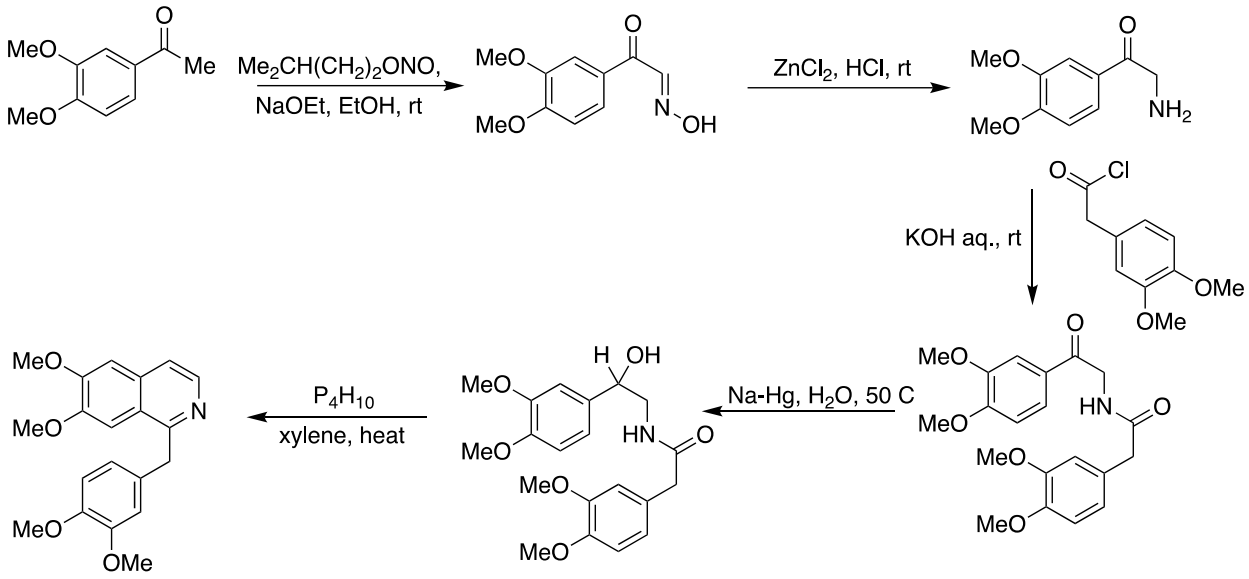


2.4 De Novo Synthesis

De novo synthesis refers to the formation of heterocycles from linear precursors via multistep synthetic pathways. This method accommodates many different functional groups in the

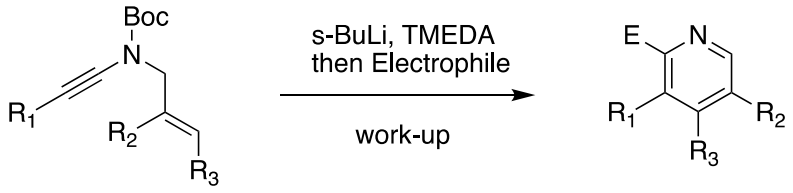
target molecule. It remains an approach for constructing highly specific structures, but the numerous synthetic steps required makes it tedious and inefficient. For example, a report on the de novo synthesis of the vasodilator (papaverine), from 3',4'-dimethoxyacetophenone required six steps (Scheme 6)[12].

Scheme 6.

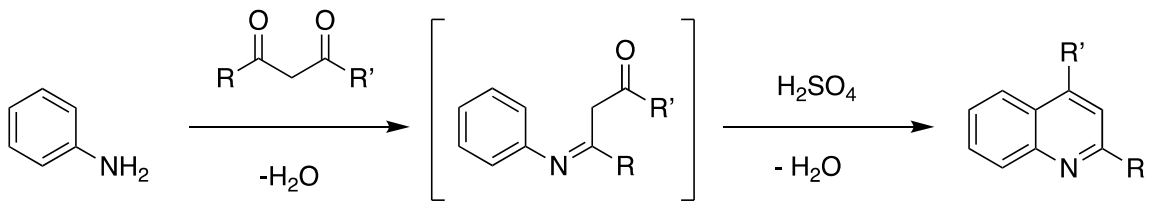


De novo synthesis also is not a general method. The steps and conditions required to form one product can be drastically different than forming another. In the case of *N*-heteroarenes, this can be shown by comparing the de novo syntheses of pyridine to that of quinolone (Schemes 7 & 8)[13, 14]. The starting materials for these sequences can also be challenging to access.

Scheme 7.



Scheme 8.



Chapter 3 Electrochemistry

Over the past decade, electrochemistry has emerged as a practical method for organic synthesis. Some of its advantages include using simple and inexpensive electricity as an oxidant/reductant, which is inherently safer and more readily available than the chemical oxidizing or reducing agents conventionally used to generate neutral radicals, radical cations, radical anions, and other reactive intermediates. Furthermore, many limitations associated with the exact redox potentials needed to generate these intermediates can be addressed by precisely tuning the applied potential. For example, if a certain substrate is difficult to reduce, one would normally require a stronger reductant. With electrochemistry, however, one can simply increase the potential between the two electrodes.

3.1 Electrochemistry Basics

There are several ways in which an electrochemical reaction differs from a conventional organic reaction. One obvious difference is that an electrochemical cell has a power source that is connected to electrodes constituting and "anode" and a "cathode," wherein the potentials have a fixed potential difference, or the potential of one electrode is set against a "reference" electrode. The movement of electrons in solution proceeds from cathode to anode, with compounds being reduced at the cathode and oxidations taking place at the anode. Both oxidative and reductive

processes must occur, with the reaction medium acting essentially as a circuit through which ionized species pass.

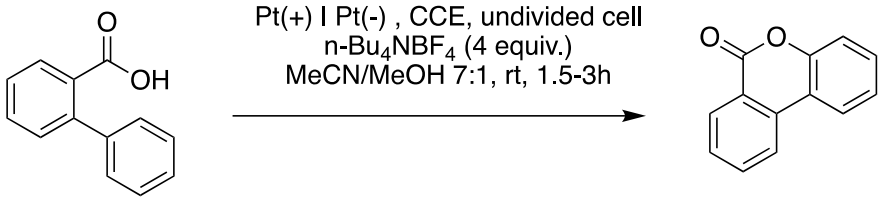
When developing methods using electro-organic synthesis, it is important to understand how each of the variables can be manipulated. For example, the external power source may work at either constant current or constant potential. In addition, the electrode materials may play crucial roles, as may their surface areas. Finally, as in conventional reactions, variables such as concentration and solvent can be manipulated to optimize the outcome.

Electrochemistry also offers excellent scalability. This potential is shown by the Monsanto adiponitrile process that is used for the production of Nylon 6,6[15]. This efficient electrochemical method for reductively coupling acrylonitrile to form adiponitrile, an important intermediate in the production of nylon, is performed on the scale of 100 million kilograms per year[15].

3.2 Redox-Neutral Electrochemistry

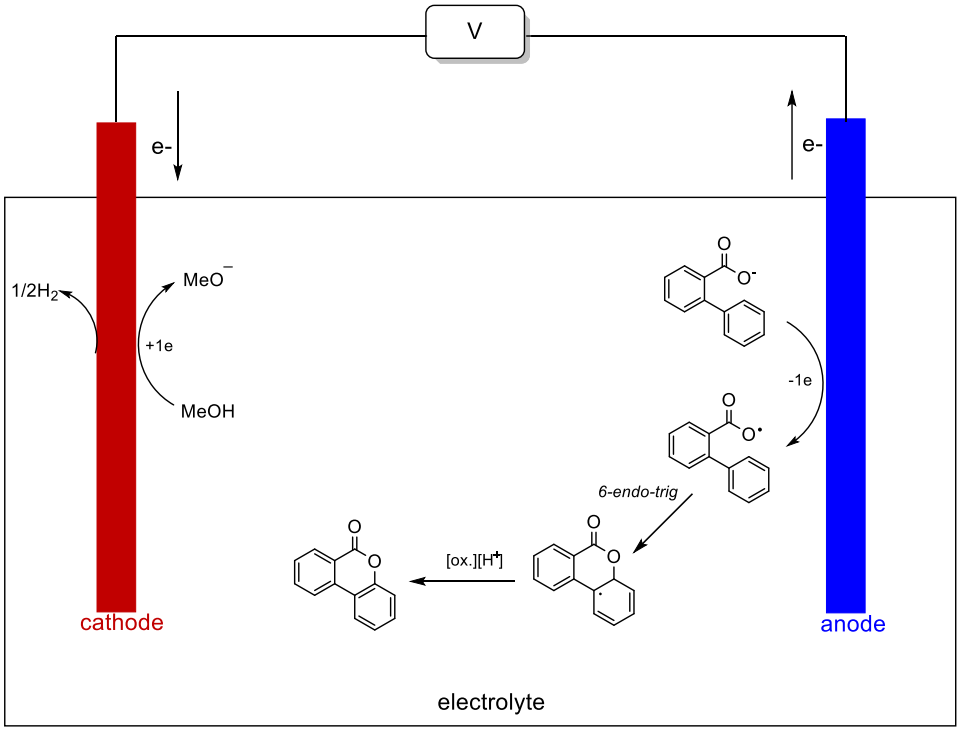
Differing from net oxidative reactions that demand a terminal oxidant, or net reductive reactions that demand a terminal reductant, redox-neutral transformations couple oxidation and reduction events in the same catalytic system. Redox neutrality has been shown to be a common feature of photoredox catalysis due to the generation of a complementary redox agent following an initial electron-transfer event. In contrast, most electrochemical transformations that have been reported are either net oxidative or net reductive since the anodic oxidations and cathodic reductions that take place occur at remotely distinct locations. With these more common electrochemical reactions, a sacrificial oxidant or reductant is required to be present in order to maintain the flow of electrons. One example of an electrochemical oxidation reaction is the lactonization of carboxylic acids (Scheme 9)[16].

Scheme 9.



In this reaction, single-electron oxidation of the carboxylate occurs at the anode, while reduction of the methanol solvent (the sacrificial oxidant) generates hydrogen gas at the cathode[16]. Following anodic generation of the carboxyl radical, C(sp2)-H lactonization occurs by 6-endo-trig cyclization, and rearomatization is carried out by a further single-electron oxidation (Figure 2).

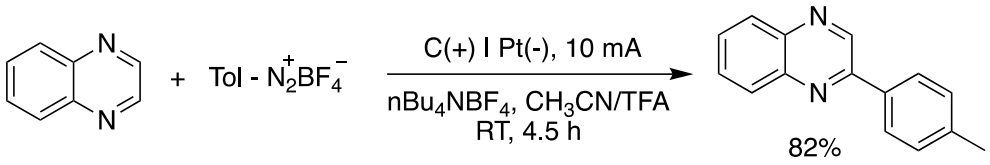
Figure 2.



While net redox-neutral electrosyntheses are rare, their ability to run without external oxidants or reductants makes them desirable in terms of atom economy and green chemistry. An example of a redox-neutral electrosynthesis can be shown by a 2019 paper when Wang, Lei, and

coworkers reported the electrochemical arylation of quinoxaline[17] (Scheme 10). The proposed mechanism for this reaction begins with the simultaneous single-electron reductions of quinoxaline and 4-methylbenzenediazonium tetrafluoroborate to generate the corresponding radical species. In this reaction, quinoxaline generates a ***persistent*** radical, whereas the diazonium salt leads to a transient aryl-radical species. After radical-radical coupling, the coupled product is generated after sequential oxidations and deprotonations at the anode.

Scheme 10.



Although this report demonstrates the viability of activating *N*-heteroarenes for novel bond-forming reactions by single-electron reduction, its requirement for highly electron-poor frameworks such as quinoxaline or heteroarenes bearing multiple electron-withdrawing groups significantly limits its scope.

Chapter 4

Results and Discussions

4.1 Goals

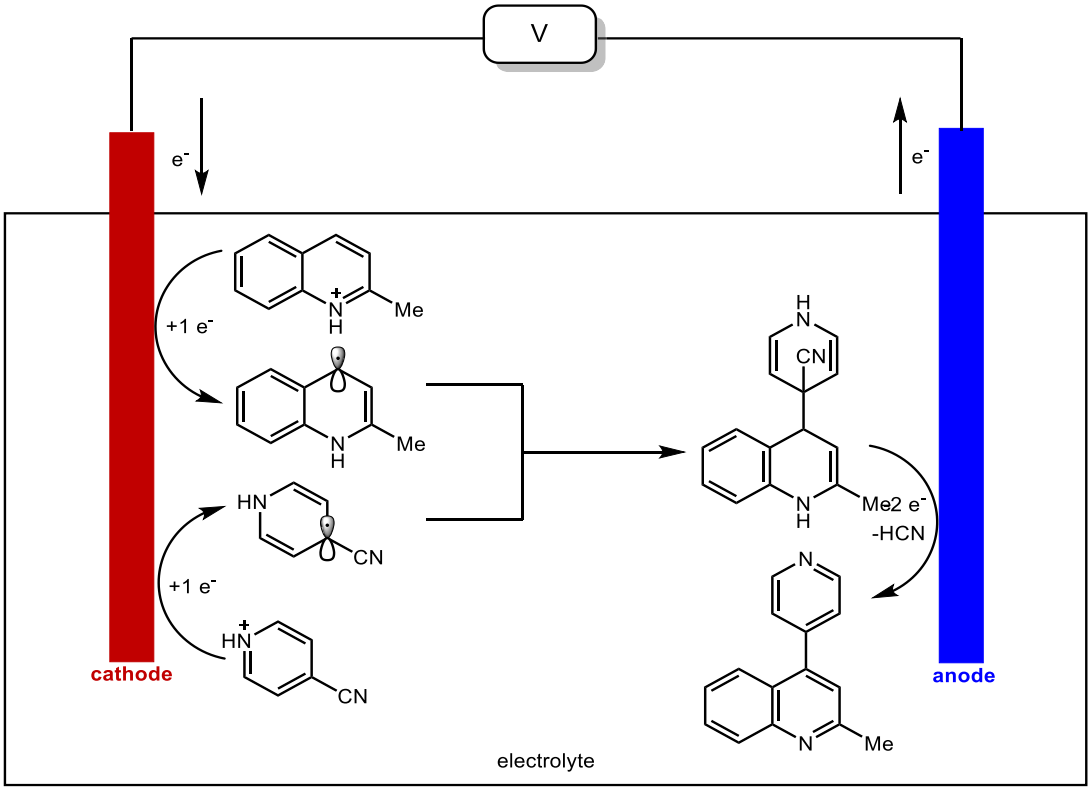
Analytical studies on the electrochemical reduction of *N*-heteroarenes have reported that these aromatic compounds are capable of undergoing single-electron reduction in the presence of acid. The resulting nucleophilic 7π intermediates have significant synthetic potential since they afford heterocycles the novel ability to engage as reactive groups, at least in principle. The

resulting capacity for these readily available species to react directly as coupling partners has the potential to effectively circumvent their previously outlined requirement for pre-functionalization as aryl halides or boronic acids. Although this approach is theoretically attractive for organic synthesis, however, synthetically enabling reactions involving these intermediates have yet to be explored.

4.2 Results and Discussion

Our group envisioned utilizing preparative, redox-neutral electrolysis as a lynchpin method for generating the aforementioned reactive intermediates due to their several advantages over classical methods (see Chapter 3). It is well-known that these key 7π-intermediates can be studied electroanalytically. To validate the *synthetic* potential of our hypothesis, however, the redox-neutral electrochemical coupling of quinaldine with 4-cyanopyridine was explored. 4-cyanopyridine was chosen as the coupling partner due to its engagement as a persistent radical following single-electron reduction that allows for its selective cross-coupling with the postulated transient 7π-intermediates derived from unfunctionalized *N*-heteroarenes.

Figure 3.



Initially, the reaction gave promising but inefficient yields of 10–13%. After several optimizations with respect to potential difference, electrolyte, and equivalence of acid we were pleased to obtain yields consistently upwards of ~70%. In light of these results, we decided to explore changing the cathode and anode materials in order to find the optimal electrolysis window.

Scheme 11.

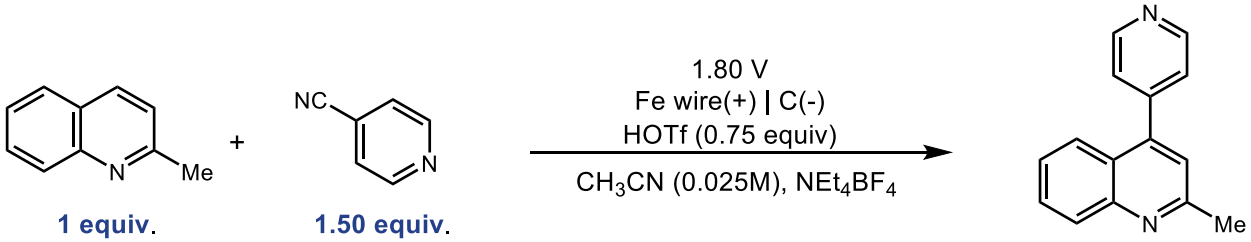


Table 1. Optimization of Cathode, Anode, and Potential

Entry	Anode	Cathode	Potential	% yield
1	Lead	Carbon	1.8 V	0%
2	Tin	Carbon	1.8 V	13%
3	Nickel Foam	Carbon	1.8 V	11%
4	Iron	Carbon	1.8 V	75%
5	Iron	Lead	1.8 V	8%
6	Iron	Tin	1.8 V	3%
7	Iron	Copper	1.8 V	2%
8	Iron	Iron	1.8 V	2%
9	Iron	Zinc	1.4 V	trace
10	Iron	Zinc	1.7 V	trace
11	Iron	Zinc	1.8 V	2%
12	Iron	Zinc	1.9 V	6%
13	Tin	Zinc	1.8 V	2%
14	Lead	Zinc	1.8 V	8%
15	Iron	Nickel Foam	1.5 V	0%
16	Iron	Nickel Foam	1.9 V	37%
17	Iron	Nickel Foam	2.1 V	18%
18	Iron	Nickel Foam	2.4 V	29%
19	Lead	Carbon	1.8 V	7%

As shown in Table 1, the reaction with the carbon cathode and iron anode produced the highest yield. Due to these high yields, we hypothesize that iron initially functions as a sacrificial anode which initializes the initial two-electron reduction process shown in Figure 3. The success of the carbon cathode may be attributed to the fact that the carbon felt has a high H^+ reduction overpotential. This would prevent the acid from being reduced to hydrogen gas. Carbon's effectiveness as a cathode could also be attributed to its high surface area compared to the other metal cathodes. Thankfully, carbon is inexpensive and its high-surface-area allotropes are commonly available. With the zinc and lead anodes mostly resulting in low yields, we hypothesize that these electrodes shorted the circuit since we observed this metal's precipitation on the cathode surface. This precipitation is most likely due to the fact that these zinc and lead are highly active

metals that have cations that are easily reduced after leaching into solution. Other heterocycles such as isoquinoline are also viable coupling partners based on our preliminary data.

Chapter 5 Conclusion

Looking forward, we are seeking to explore the potential for directly activating unfunctionalized heterocycles using electrochemistry, as well as possibility of utilizing these compounds for synthesizing biologically interesting molecules. Once the method being developed has been completely optimized, several more heterocycles will be evaluated. Further synthetically enabling reactions such as Giese additions and C–N or C–O bond formation will also be explored in the future.

Chapter 6

Methodology

Preparation of Isoquinolinium triflate:

Isoquinolinium trifluoromethanesulfonate was prepared from isoquinoline (156 mg, 1.21 mmol) and freshly distilled trifluoromethanesulfonic acid (200 mg, 1.3 mmol) in anhydrous diethyl ether (40 mL). The colorless solid, which precipitated immediately from the solution, was isolated by filtration, washed with dry diethyl ether (100 mL) and dried (20 C, 0:2 mbar, 3 h). Yield: 320 mg (95 %); ^{1}H NMR ($CDCl_3$): d = 8:04 – 8.05 (m, 1H),8.20 – 8.27 (m, 2H), 8.40 – 8.48 (m, 3H), 9.59 (s, 1H, 1-H),13.81 (broad, 1H, NH) ppm. – ^{13}C NMR ($CDCl_3$): d =121:78 (q, 1J(C,F) = 319:8 Hz, CF_3SO_3), 126.57 – 139.94 (8C, arom:), 147.85 (C-1) ppm.

Preparation of Quinaldinium triflate:

Quinaldinium triflate was prepared from quinaldine (173 mg, 1.21 mmol) and freshly distilled trifluoromethanesulfonic acid (200 mg, 1.3 mmol) in anhydrous diethyl ether (40 mL). The colorless solid, which precipitated immediately from the solution, was isolated by filtration, washed with dry diethyl ether (100 mL) and dried (20 ºC, 0:2 mbar, 3 h). Yield: 330 mg (93 %); ^{1}H NMR ($CDCl_3$): d = 2.76 (s, 3H), 7.30 (d, 1H), 7.47 (m, 1H), 7.63 (m, 1H), 7.78 (m, 1H), 8.02 (m, 1H), 8.06 (m, 1H) ppm.

Synthesis of 2-methyl-4-(pyridine-4-yl)quinoline:

All reactions were sparged with nitrogen gas and sealed in an 8-mL vial reaction vessel with a septa cap (Figure 4). Dry acetonitrile was obtained from a solvent dispensing system. Galvanized steel wire served as leads for the various cathode and anode materials. Power boxes were used as voltage sources for the experiments. Yields were determined through GC-MS analysis with a pyrene external standard. Reactions were stirred at 800–1000 rpm. Aliquots for GC-MS analyses were worked up via sodium bicarbonate and ethyl acetate. Ethyl acetate layer was diluted to a concentration of 0.01 mM.

Figure 4.

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Bacterial Cell Biology — **Fall 2017**

- Research Conducted with Dr. Meredith Ph.D. Biochemistry and Molecular Biology, at Penn State University, on the bacterial cell envelope, and in particular its formation through lipid metabolism.
- Ran experiments for the graduate student, Kelvin Kho, including PCRs, Gel Electrophoresis, along with using various lab equipment.

Center for Eukaryotic Gene Regulation — **Spring 2017** – **Summer 2019**

- Conducted Data Science on data provided from ChIP-seq experiments, along with conducting data formatting to run machine learning algorithms.
- Specifically, researched Histone Modifications in T-Cells under Dr. Kuzu in the Dr. Mahony Lab.

Chemistry Department — **Summer 2019 - Present**

- Conducted volunteer research under Dr. Nacsa with the problem of how do people make new C-C bonds to unfunctionalized aromatic heterocycles.
- Used various Electrochemical techniques along with the use of radical chemistry.

RESEARCH SKILLS

- Experienced in Cell Biology techniques, PCRs, Gel Electrophoresis, Data Formatting, Data Science, Galaxy (Bioinformatics Website), Nuclear Magnetic Resonance Instrumentations, Infrared Spectroscopy, Mass Spectrometry, Titration
- Proficient in Microsoft Excel, PowerPoint, Word, Python, R, and Linux

TEACHING EXPERIENCE

Learning Assistant for Mr. Pontius, General Chemistry 110, Penn State University — **Spring 2019**

- Assisted students with clicker questions during lecture
- Helped a small group of 20 students with questions during recitation
- Lead a Concept Review every Sunday that helped students who wanted extra help or review with the week's lecture material

Learning Assistant for Mr. Pontius, General Chemistry 112, Penn State University — **Summer 2019**

- Assisted students with clicker questions during lecture

- Held practice exam reviews prior to testing days

Learning Assistant for Dr. Maslak, Organic Chemistry 210, Penn State University **Fall 2019**

- Assisted students with clicker questions during lecture
- Held office hours twice a week

LEADERSHIP AND COMMUNITY SERVICE

Weekly Concept Review **Spring 2019**

- Lead a small group of Learning Assistants and Teaching Assistants during a concept review every Sunday at 6p.m.

Mathematics Tutor, YMWIC, West Chester, PA **Fall 2016-2017**

- Received a certificate of continued service by tutoring under-privileged students of various skill levels in mathematics.

Rustin Science Fair, West Chester Rustin High School **Spring 2016-2018**

- Aided in a Science Fair held annually by Rustin High School

WORK EXPERIENCE

Beach Lifeguard, Avalon, New Jersey **Summer 2016-Summer 2017**

- Trained and Passed Avalon Beach Lifeguard Test
  Completed CPR Certification