DISSERTATION

RING-CONVERSION AND FUNCTIONALIZATION OF NITROGEN-CONTAINING HETEROCYCLES

Submitted by

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ABSTRACT

RING-CONVERSION AND FUNCTIONALIZATION OF NITROGEN-CONTAINING HETEROCYCLES

Pyridines and related azines are ubiquitous in pharmaceuticals and agrochemicals development. Chemist rely on the development of new synthetic methods to modify these heterocycles. Described herein are the development of methods to functionalize azines and convert pyridines and diazines into new heterocycles. Novel hydrogenation and molecular editing strategies were designed and leveraged to accomplish this goal.

Chapter one introduces the importance of pyridines and related heterocycles in pharmaceuticals as well as methods to access and functionalize these molecules. Both classical and contemporary methods for functionalization and hydrogenation of pyridines are discussed to provide context for this work. Chapter two describes a novel method to selectively reduce pyridines to dihydropyridines, tetrahydropyridines, and piperidines. This method offers a complementary alternative to current hydrogenation or reduction methods, in which the degree of saturation cannot be controlled, and applies to complex azine starting materials.

Chapter three explains the importance of structure-activity relationship (SAR) studies and its implications on the drug-discovery process. It also describes classical and contemporary strategies that apply to SAR diversification including de novo heterocycle synthesis and molecular editing strategies. Finally, chapter four presents a novel method for SAR diversification of pyrimidine containing molecules using a deconstruction/reconstruction approach.

ACKNOWLEDGMENTS

No feat is ever accomplished without the empathy, kindness, and aid of other people. The work described in this dissertation is no exception. I would first like to thank my advisor, Andy. Coming into graduate school, I was not the best chemistry student by a wide-margin. You took a chance on me and fostered the skill-set I had at the time to its fullest potential in order to become the best chemist I could be at the end of this degree. It was no means an easy feat for either of us; however, you taught me to develop a hunger for knowledge, to find the problem first rather than blindly search for a solution, to thicken my skin in the face of adversity, and to sharpen my skills to the highest standard. You have also encouraged me to keep pushing forward when I was sure I didn't have what it took; I cannot express how much your belief in me meant in those moments. Thank you for showing me that with hard work, grit and dedication, even the underdog can succeed. I'd also like to thank my committee members, Jeff, Jean, and Brad, for witnessing my milestones in my graduate career. Thank you all for the incredible feedback and chemistry discussions over the years as well as the kindness you all have extended during my time here. Almost every graduate student dreads the major milestones, like candidacy exams, but because of you all my experience is remembered as a fun discussion of my research with three scientists I truly admire. Thank you all for the opportunity to get to know you and work with you during this time.

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your time, knowledge, and advice. Whenever I bothered him about chemistry, you handled it with empathy and grace taking time out of your busy schedule to explain chemistry concepts in detail and quizzing me randomly to make sure the information stuck. In addition, you was always there to lend a listening ear or make me laugh during difficult times. Thank you for showing me what a mentor should be. In addition, I would like to thank Chirag, Kyle, and Ben B. for all the helpful research discussions, hilarious memories, and interesting conversations over the years. I'd also like to thank Jake G. and Jeff L. for serving as excellent role-models for not only myself, but the lab in general. Jake G. offered me incredible advice over the years, in chemistry and in life. Jeff L. is an amazing chemist I always looked up to for his skills, creativity, and knowledge. In every lab, there is a clear divide between those senior and junior to your cohort. The people who came after me have been just as impactful as those who came before. I'd like to thank Marie for accompanying me on coffee runs whenever I needed it and for all the laughs, discussions, and friendship over the years. Like-wise, I'd like to thank Dane for accompanying me down chemistry rabbit holes and interesting conversations from everything to classical literature to the making of Melort sausages. I'd like to thank Ben U. for always being a great partner when we worked on a project together, giving expert advice on the weather, and sharing wild stories about his youth that always leave me amazed. Amanda is someone who always makes me laugh and understands my references when no one else does. Thank you for always lightening my mood. Jake S. allowed me the opportunity to serve as his de facto mentor over the past few years. It has been amazing to see you grow and thank you for the opportunity to help foster that, even in a small way. I will always cherish our lengthy chemistry discussions, gossiping about the daily JACS line-up, and joking around at our hoods. It has also been a privilege to watch our most junior members, Kalia and David, make exponential growth in first two years. I am grateful for you both allowing me the

opportunity to grow as a mentor and teach you new things, whether it's how to shoot NMR caps out of pipette bulbs or hints about problem sets. I have no doubts you all will be incredible chemists and I wish you all the absolute best in your graduate careers. Finally, I'd like to thank my fellow cohort members Hillary and Louis for accompanying me on my graduate journey. Spending time with you both is like spending time with siblings. I am incredibly privileged to have grown with you both. Thank you for all the experiences we have shared over the years.

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Growing up, higher education always seemed out of reach and something I thought I would never have the privilege of attending. However, my family always encouraged me to accomplish this goal even when they didn't have all the answers themselves. Words cannot express how thankful I am for my family's hard work and dedication to helping me achieving my goal, whether that was going without so that I could pay for academic endeavors, meeting with teachers to see what my options are for affordable education, or trusting me to take my education into my own

hands when they had their doubts. I would like to thank my parents, Tammy, Stan, and Dana for doing everything in their power to get me to this point. I'd also like to thank my siblings, Jared, Anthony, Allissa, and Andrew for making sure I didn't take life too seriously and took some time to have fun. Thank you all for everything.

Finally, I'd like to thank my partner, Bryce, for sticking by my side for the past five years. You were a key role in why I found undergraduate research so much fun. Working in the lab next to yours was an absolute delight and I always admired (and secretly envied) you as not only a scientist, but as a person. You always seemed to know what is going on and when you don't you are always trying to learn more or fill gaps in your understanding, which inspires me to be a better scientist. The conversations we had working in the stockroom, in between classes, or studying together in between our labs are some of my most treasured memories. Thank you for taking a leap of faith with me when you moved to Colorado from Wisconsin after spending a year apart. You have always been incredibly patient, kind, and optimistic during my graduate studies when I was struggling. Our conversations mean everything to me and you have an incredible ability to put things into perspective. Thank you for getting me out of my own head when I need it. Even when I am having a bad day, the thought of coming home and spending time with you, Lucy, and Stuart gets me through the day and up the next, ready to tackle problems head on. You are an integral reason why I have kept going. Talking about chemistry (and science in general) with you reminds me why I fell in love with this field. You have and continue to be an irreplaceable pillar of support and I cannot express how much I appreciate everything you are. I couldn't imagine anyone else in the role you serve in my life. Every moment I spend with you is cherished and thank you for being genuinely, unapologetically yourself.

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CHAPTER ONE

INTRODUCTION OF NITROGEN-CONTAINING HETEROCYCLES AND IMPLICATIONS IN DRUG-DISCOVERY

1.1 Nitrogen-Containing Heterocycles and Their Role in Pharmaceuticals

Six-membered nitrogen-containing heterocycles (N-heterocycles) have and continue to be long standing synthetic targets in drug development (**Figure 1.1**). In fact, the presence of N-heterocycles found in U.S. FDA-approved drugs accounts for 59% of total small molecule therapeutics developed, according to a 2014 study.[1] Of this unique subset of molecules, pyridine is the most frequently occurring N-heterocycle closely followed by its saturated form, piperidine. The frequency of these motifs cannot be underestimated; a 2022 report found that pyridine and piperidine rank as the second and third most commonly occurring ring-systems found in FDA-approved pharmaceuticals, respectively, following benzene.[2] Other related commonly occurring N-heterocycles include piperazine, pyrimidine, quinazoline, and 1,4-dihydropyridine. In 2021, eight of the ten top small molecule drugs in global sales contained one or more of these *N*-heterocycles and select examples are shown in **Figure 1.1**.

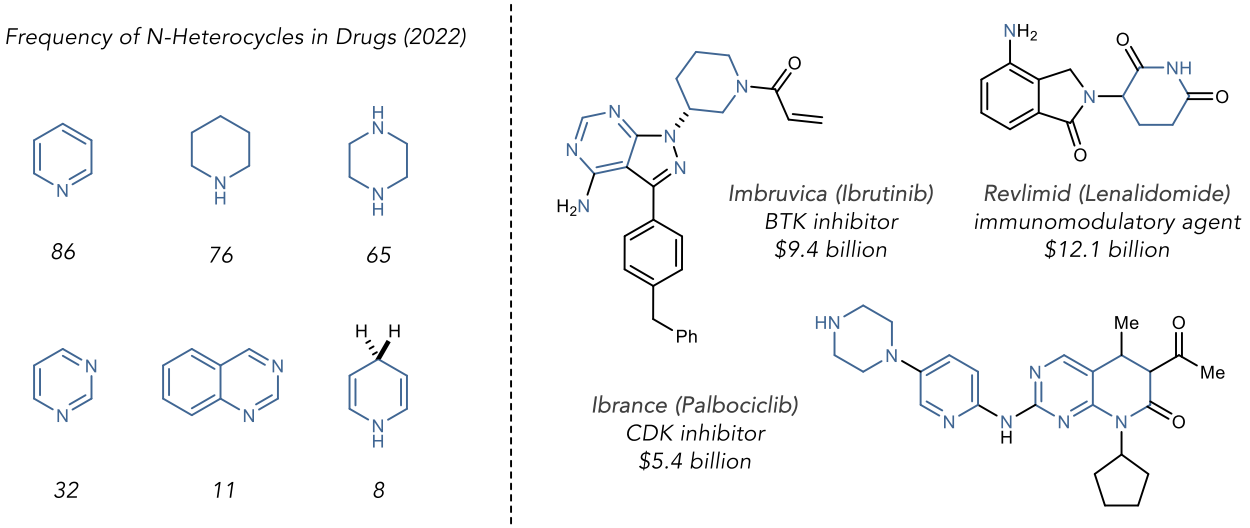

Figure 1.1. Most frequently occurring *N*-heterocycles and examples of top-selling drugs of 2021.

The continued prevalence of these motifs is a direct result of the pharmacokinetic properties the N-heterocycle imparts on the molecule in biological systems, including increased aqueous solubility and hydrogen-bonding (H-bonding) capabilities, due to the presence of the nitrogen-atom (N-atom) within these systems. These properties have a profound effect on a drug molecule's bioavailability and desired drug-target interactions. To illustrate these effects, Imatinib, an anti-cancer drug used to treat acute lymphoblastic leukemia, is shown in **Figure 1.2** H-bonding to amino acid residues present in mutant KIT^{S628N}.[3] Imatinib inhibits specific enzymes called tyrosine kinases. These kinases are responsible for numerous cell functions including cellular communication, growth, and division through transferring phosphates from ATP to tyrosine residues.[4] However, it can also transfer phosphates to other amino acid residues, such as serine (Ser) and threonine (Thr). Hindering this phosphorylation process inhibits the cellular functions described above. In terms of suppressing cancer growth, the N-heterocycles present on imatinib are key in preventing phosphorylation of the mutant Thr residue. The amide and pyrimidine lone pair participate in hydrogen bonding with Thr 670 preventing the lone pair of the alcohol group to effectively undergo phosphorylation. However, it is not just this H-bonding event

that contributes to inhibition. Other important H-bonding motifs affect how the molecule is orientated in the enzyme pocket allowing the key H-bonding to the alcohol functional group to occur. The pyridine motif binds to the amine hydrogen bond in cystine (cys) 673, the amide N–H bond binds to the carbonyl oxygen atom in glutamic acid (Glu) 640; finally, the piperazine and amide bond on imatib simultaneously bind to aspartic acid (Asp) 810. All of these H-bonding events work in tandem to prevent cancerous cellular growth and reproduction. In addition, the increased H-bonding of N-heterocycles through its nitrogen lone pair (N-lone pair) improves aqueous solubility compared to benzene derivatives resulting in a higher concentration of the drug present in the blood stream. This allows smaller dosages of the drug to be administered without sacrificing bioavailability.

Another biological benefit from the presence of N-heterocycles in pharmaceuticals is how they are metabolized in biological systems. For example, imatinib is metabolized by the body through oxidation with CYP3A4, an isoenzyme in the cytochrome P450 system.[5] In this process, multiple sites on the drug molecule are targeted for oxidation **(Figure 1.2)**.[6] The pyridine scaffold, methyl substituted benzene ring, benzylic methylene unit, and piperazine ring are oxidized breaking the molecule into two fragments. Electron-rich arenes, such as benzenes, readily undergo oxidation. However, aromatic N-heterocycles, such as pyridine, are oxidized much more slowly. Thus, incorporation of N-heterocycles in pharmaceutical drugs makes the molecule more resistant to metabolism, which is crucial in achieving desired metabolic stability.

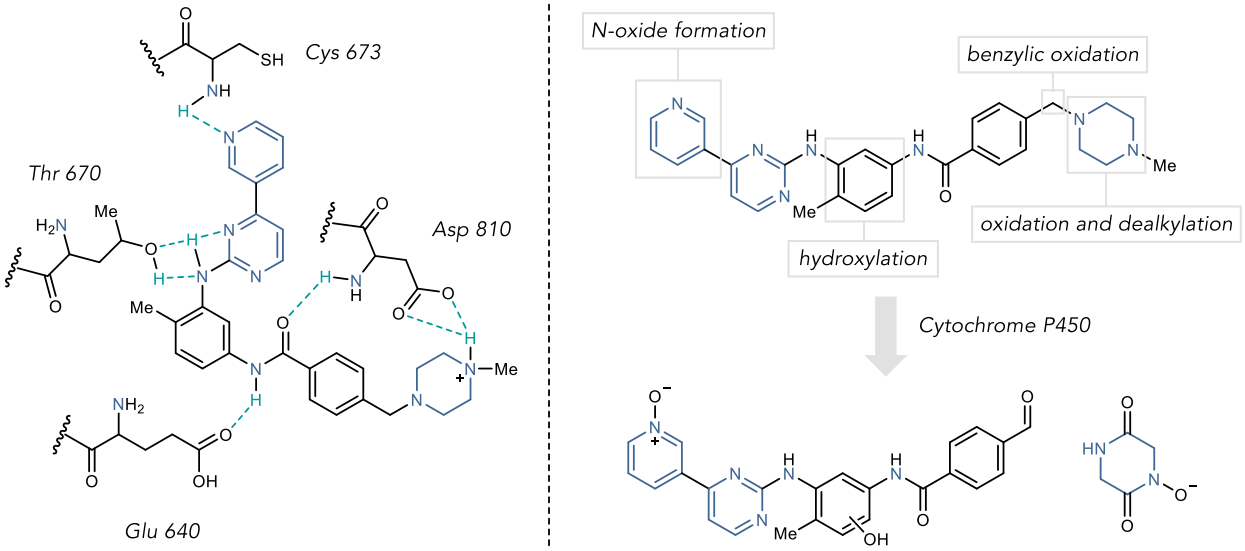

Figure 1.2. Inhibition of threonine amino acid residue and metabolic oxidation of imatinib.

1.2 Pyridine Functionalization Strategies

1.2.1 Classical Approaches

The efficacy and pharmacokinetic properties of N-heterocycles in drug molecules are not only reliant on the presence of the ring itself. It is also greatly affected by the identity of the substituents on the periphery of the ring. Thus, it is important for medicinal chemists to synthetically alter and install specific substituents onto N-heterocyclic ring-systems. Since pyridine is the second most common heterocycle found in FDA-approved drugs, it has received great attention in the synthetic community and methods to alter its aromatic system been studied extensively.

Due to the inherent properties of pyridines, classical reactions to install electrophiles onto the carbon framework, such as electrophilic aromatic substitution (EAS), are significantly more challenging compared to its benzene counterpart. The N-lone pair induces a dipole where electron

density is localized on the N-atom **(Figure 1.3)**. This decreases the overall π-nucleophilicity of the aromatic ring compared to benzene rings where electron density is shared evenly among the carbon atoms. The pyridine aromatic ring is electron deficient in nature. As a consequence, harsh reaction conditions are required to achieve conversion to a functionalized pyridine product. To illustrate this point, **Figure 1.3** shows EAS bromination reactions of benzene and pyridine. To achieve effective bromination, the pyridine starting material is subjected to elemental bromine in sulfuric acid at elevated temperature resulting in mixtures of 3-bromopyridine and 3,5-dibromopyridine as the major products.[7] Comparatively, benzene bromination is achieved with elemental bromine in the presence of an iron catalyst at room temperature. These harsh reactions and product mixtures limit the use of electrophilic bromination reactions conducted in this fashion to simple pyridine building-blocks without sensitive functionality.

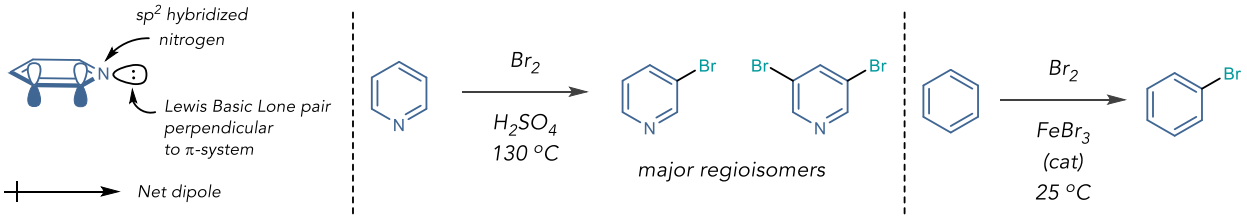

Figure 1.3. Electronic properties of pyridine and representative bromination conditions of pyridines and benzenes

Another method that installs electrophiles onto the pyridine framework is through directed lithiation. In this strategy, the aromatic C–H bond is deprotonated by lithium bases or Grignard reagents resulting in a pyridyl anion. The pyridyl anion then reacts with an electrophile to form a functionalized pyridine product. The regioselectivity of the deprotonation is dictated by an existing substituent on the aromatic ring which may guide the incoming base to a specific position.

Without a sufficient directing group, regiomeric mixtures form. Again, this strategy is limited to simple pyridines and base sensitive groups cannot be present on the pyridine starting material.

Although installing electrophiles with classical approaches requires harsh reactions conditions, nucleophiles readily add to pyridine rings. As mentioned previously, the pyridine ring contains a significant dipole where resting electronegativity is placed on the N-atom allowing for nucleophilic addition on the carbon framework. In these processes, nucleophiles add to the pyridines *ortho* (C2) or *para* (C4) positions forming a pyridyl anion, called a Meisenheimer intermediate. Subsequent elimination of a pyridyl hydride yields the functionalized pyridine product. A classical example of this reaction platform is the Chichibabin reaction yielding a 2-amino pyridine product using sodium amide in ammonia. The mechanism of the Chichibabin reaction is shown in **Figure 1.4** and represents a general mechanism for the described addition-elimination process. To obtain exclusive regioselectivity for the pyridines' 2-position, a 6-position substituent must be present. If this site is not blocked, regiomeric mixtures form.

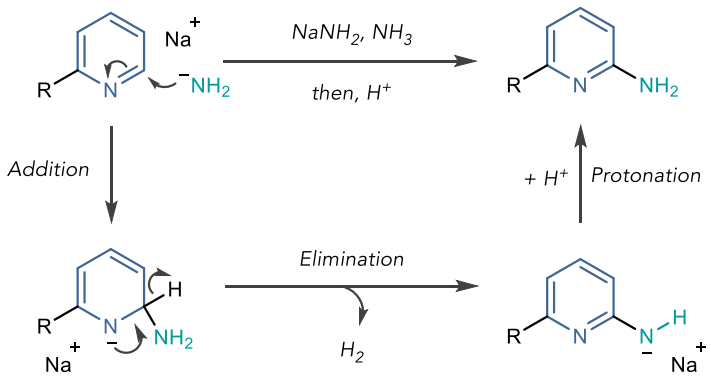

Figure 1.4. Chichibabin reaction and mechanism

Adding nucleophiles to unactivated pyridine species is an endothermic process. Thus, strong nucleophiles or increased reaction temperatures are required to achieve a productive

nucleophilic addition. To decrease the activation energy of the dearomatization step, the N-atom of the pyridine first reacts with a suitable electrophile producing a pyridinium salt.[8] This process places cationic character on the N-atom allowing for weaker nucleophile addition and decreased temperature for the nucleophilic addition step. However, high temperatures may be required for activation of the N-lone pair. The most common activator for pyridines is Brønsted-Lowry acids, but acyl chlorides, silyl groups, and alkyl or aryl halides are also amenable **(Figure 1.5)**. After nucleophilic addition, the resulting dihydropyridine intermediate undergoes oxidation rather than hydride elimination **(Figure 1.5)**. The regioselectivity of the addition step is controlled by various factors including pre-existing substituents on the pyridine ring, the identity of the activating group, and the electronic properties of the incoming nucleophile. [8] Common nucleophiles for this process include Grignard reagents, Gilman reagents, and cyanide salts.

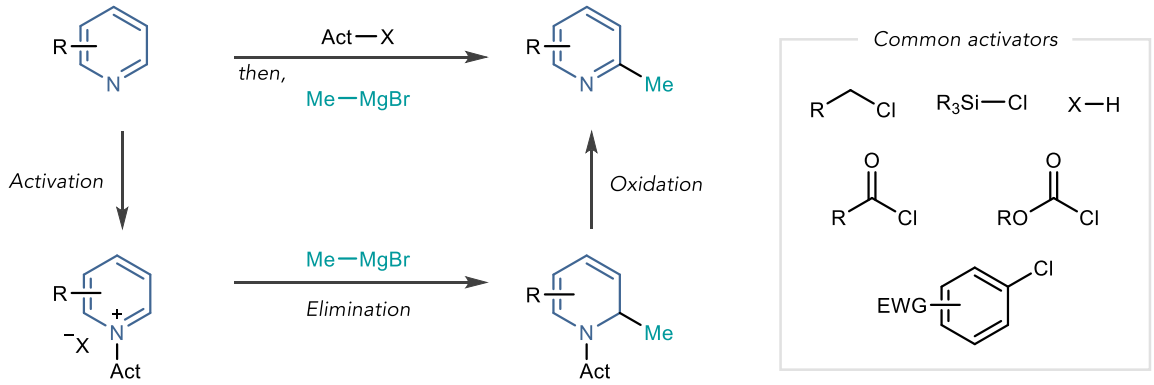

Figure 1.5. Pyridine N-activation strategy and common activators

The strategies described thus far are two-electron processes; however, one-electron processes also occur on pyridines. These processes occur through radical additions to protonated pyridinium salts and are typically known as Minisci reactions. In these reactions, an alkyl radical is generated from an alkyl halide, carboxylic acid, or boronic acid in the presence of a silver - catalyst. The radical then adds to the protonated pyridinium yielding a pyridyl radical cation. The

radical cation undergoes oxidation and deprotonation to furnish the functionalized pyridine product. In unbiased systems, radical addition is not selective and adds to each position on the pyridine ring. However, unlike other classical approaches for pyridine functionalization, these reactions apply to late-stage analogues containing sensitive functionalities **(Figure 1.6)**.[9]

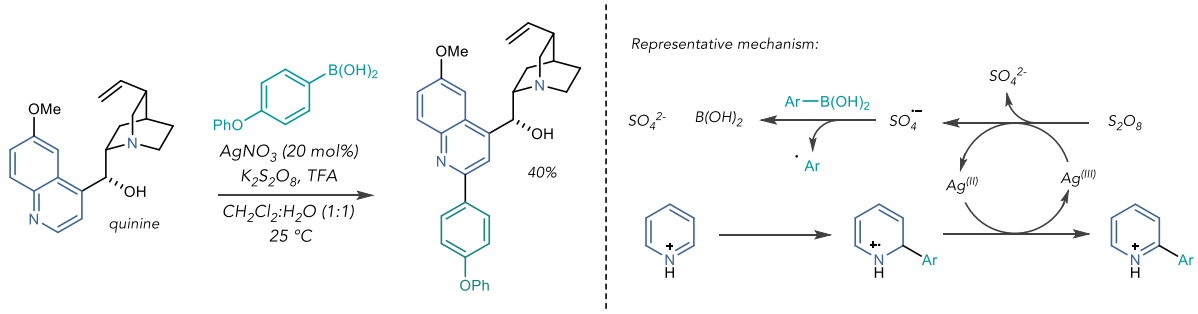

Figure 1.6. Late-stage Minisci reaction and representative mechanism

1.2.2 Modern Approaches

Modern approaches to pyridine functionalization build from the concepts and limitations of classical approaches. For example, the Minisci reaction has greatly improved its scope and cross-coupling partners with the advancement of photoredox catalysis. The MacMillan group developed a trifluoromethylation procedure for various arenes including pyridines **(Figure 1.7)**.[10] Rather than a chemically initiated radical generation, the trifluoromethyl radical is initiated through photoexcitation of a photocatalyst and a subsequent single-electron transfer (SET) reduction of triflyl chloride. The resulting radical adds to the corresponding pyridinium salt generating an aryl radical cation. Then, a SET oxidation of the radical cation by the oxidized photocatalyst and deprotonation liberates the product and completes the catalytic cycle. In this

report, regiomeric mixtures of the trifluoromethylated products form. However, using photoredox catalysis to produce radicals via visible light mediated photoexcitation of an iridium or ruthenium based photocatalyst allows for a variety of radical precursors to apply. Subsequent reports by MacMillan[11], Leonori[12], DiRocco[13], and Baran[14] show alcohols, aminoboranes, peroxides, and sulfinates also serve as radical precursors in and apply to late-stage compounds.

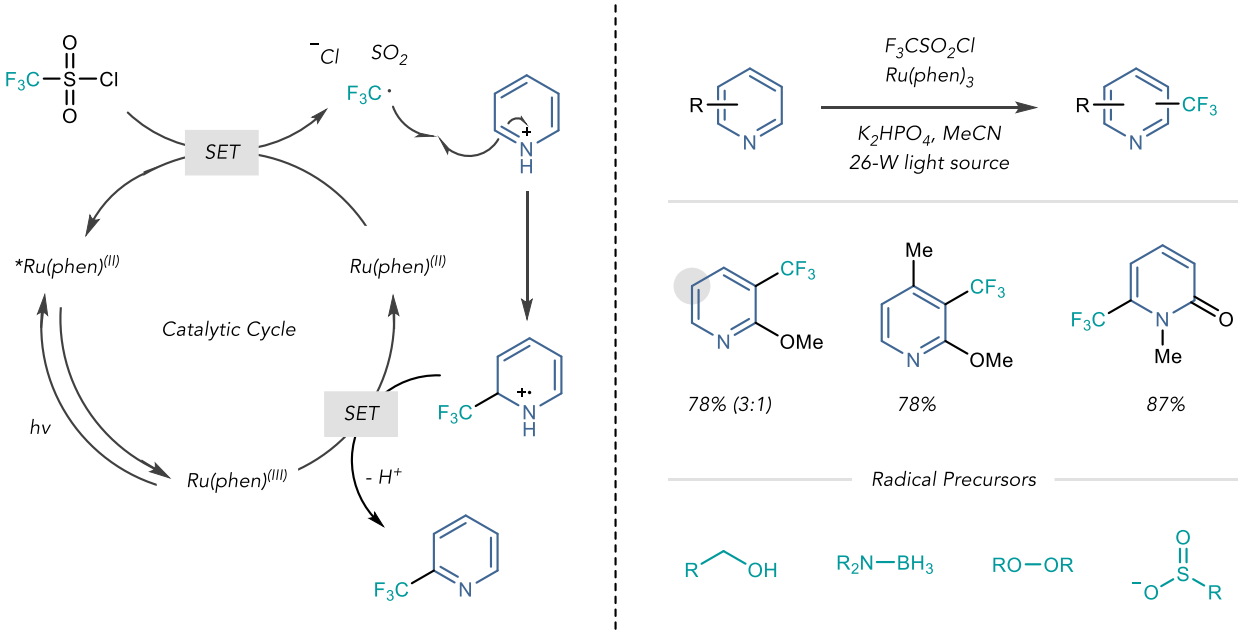

Figure 1.7. MacMillian's trifluoromethylation of arenes and other radical precursors

Ortho selective functionalization of pyridines, inspired by the Chichibabin reaction, have also received attention in recent literature. In 2013, Hartwig developed a method for *ortho* selective pyridine fluorination reaction **(Figure 1.8)**.[15] The mechanism of the fluorination process is similar to the mechanism of the Chichibabin reaction. First, the silver(II) fluoride (AgF_2) reagent coordinates to the pyridine starting material. Then, the Ag–F bond adds across the pyridine's π-system through a single electron process. Rather than hydride elimination, hydrogen-atom abstraction (HAT) by a second equivalent of the AgF_2 reagent aromatizes the pyridine ring

and eliminates silver(I) fluoride (AgF) producing hydrofluoric acid as a biproduct. The resulting 2-fluorinated product is a valuable because the C–F bond serves as a functional handle for nucleophilic aromatic substitution (S_NAr) reactions. A variety of nucleophiles are compatible for the S_NAr process including amines, alkoxides, and deprotonated nitriles, among others.

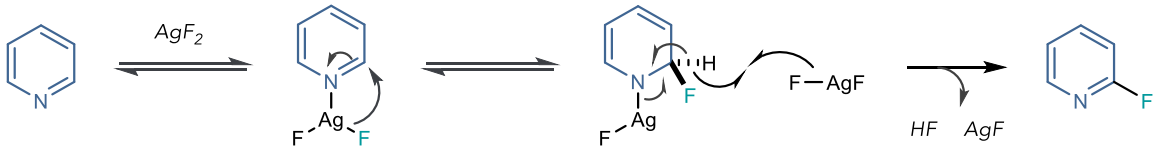

Figure 1.8. Mechanism of Hartwig *ortho* selective fluorination

Modern dearomatization strategies also achieve *ortho* selective functionalization of pyridine rings through careful synthetic design of novel activating groups. In 2017, Fier developed a novel chloro oxime activating group for *ortho* selective pyridine cyanation reactions **(Figure 1.9)**.[16] The chloro oxime activating group is derived from aldehyde oximes and an electrophilic chlorinating reagent, which allows access to a diversity of designed activating groups for pyridines. To achieve successful cyanation, the pyridine of interest is activated with the chloro oxime activator yielding a pyridinium salt. Cyanide salts then add to the pyridines *ortho* position forming a dihydropyridine intermediate. The intermediate is then oxidized via base mediated elimination of the activating group. The method applies to a variety of pyridines, including late-stage compounds, and nucleophiles such as alkoxides, Grignard reagents, alkylzincs, and malonate esters. In a follow-up paper published in 2020, *ortho* selective amination is demonstrated using a bifunctional reagent that activates the pyridine starting material and delivers the amine nucleophile **(Figure 1.9)**.[17]

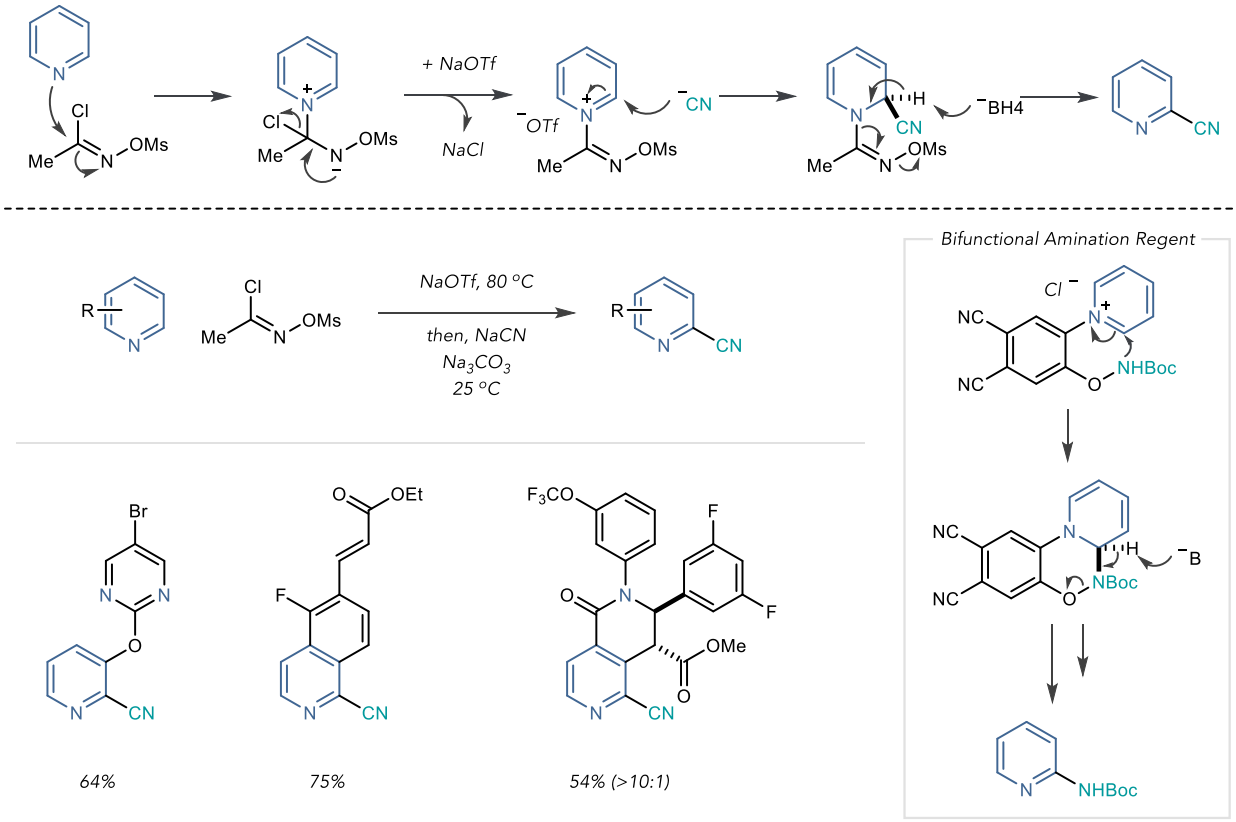

Figure 1.9. Fier cyanation and amination via designed activating groups

The methods described thus far are either unselective or *ortho* selective processes to functionalize pyridines. However, *meta* (C3) selective functionalization of pyridines has also received considerable attention. One strategy to achieve meta selective functionalization is selective C–H activation in which a transition metal catalyst inserts into the pyridine C–H bond. The regioselectivity of this process is either sterically or electronically controlled; the most electron-rich C–H bond or most sterically accessible site will undergo activation. One challenge for transition metal catalysis is avoiding catalyst poisoning by the Lewis basic nitrogen atom present on pyridine's aromatic ring. Despite this, transition metal C–H activation remains a viable strategy for *meta* selective functionalization. A notable example of this platform is Hartwig's C–H borylation of pyridines catalyzed by an iridium transition metal.[18] Following this report, Yu[19],

Hartwig[20], and Fagnou[21] developed methods to install alkenes, halides, and aryl groups using transition metal catalysis to access pyridines' *meta* position.

A unique strategy to achieve *meta* selective functionalization uses either stable dearomatized intermediates or ring-opened pyridines to alter the electronic nature of the aromatic ring system. In 2022, the McNally[22] and Studer[23] groups concurrently published *meta* selective halogenation reactions of pyridines. In the former case, *N*-trifyl (*N*-Tf) activation and use of collidine as a base allows dibenzylamine to add selectively to the *ortho* position. The resulting dihydropyridine intermediate then undergoes a polar ring opening step yielding an aza-triene system called "Zincke imine". The Zincke imine reacts with electrophilic halogenating reagents selectively at the pyridine's *meta* position. In a related report, the Studer lab leverages pyridine dearomatization to achieve a similar transformation. In this report, the pyridine of interest is activated with dimethyl acetylenedicarboxylate (DMAD) and methyl pyruvate (MP) to achieve a selective dearomatization. The dihydropyridine intermediate is stable under atmospheric conditions and undergoes a variety of transformations including halogenation, nitration, trifluoromethylation, and thiolation. A subsequent report by the Studer lab showed arylation is also amenable to this strategy.[24]

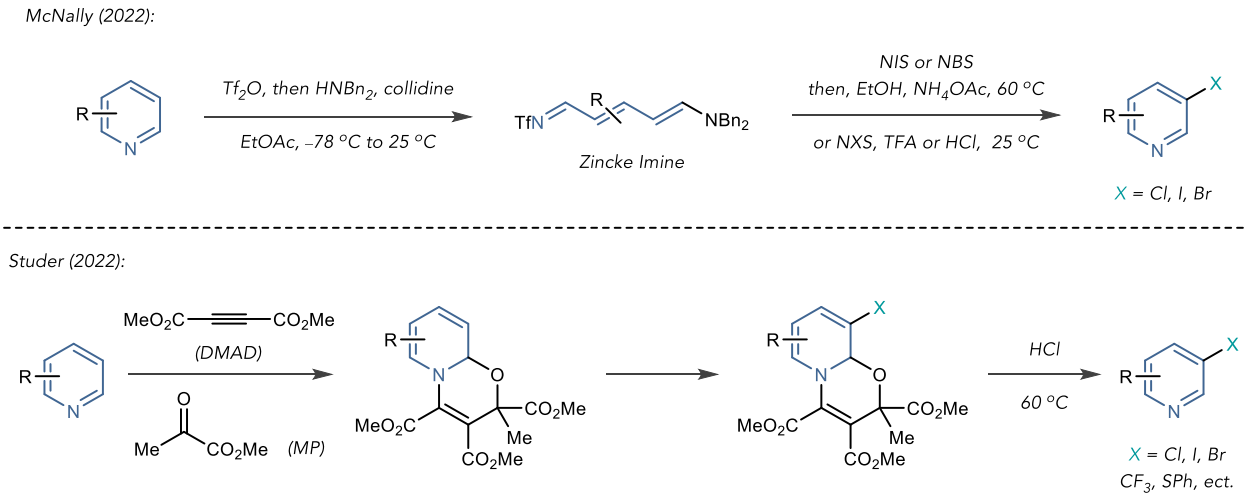

Figure 1.10. McNally's and Studer's *meta* selective functionalization of pyridines

Finally, *para* selective processes are also viable through a variety of strategies. One interesting method that is inspired by "halogen dance" strategies for arene functionalization is base catalyzed halogen transfer reactions. The Bandar lab refined this approach to arene functionalization in 2020.[25] In these reactions, a pre-installed halide at the pyridine *meta* position migrates to the corresponding *para* position upon deprotonation of the *para* position with an appropriate base. Then, an incoming nucleophile displaces the halide yielding a *para* functionalized product. In subsequent reports, a halogen transfer reagent is used instead, which transfers the halide from the transfer reagent to the deprotonated arene of choice. This avoids the need for a pre-installed halide on the pyridine of interest. Suitable nucleophiles for this process include amines and alcohols producing aminated[25], etherified[26], and hydroxylated[27] products.

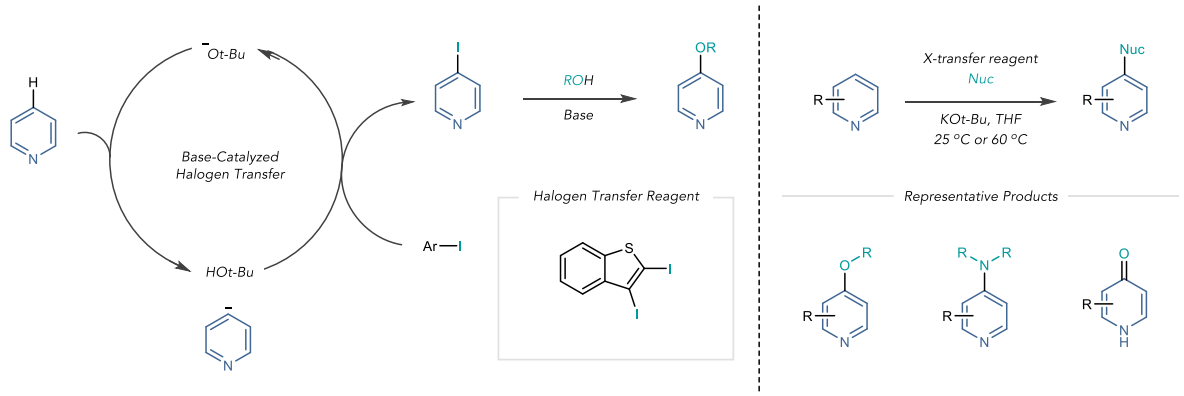

Figure 1.11. Bandar's base catalyzed halogen transfer and *para* selective functionalization of pyridines

Another strategy to functionalize the *para* position of pyridine is installing a versatile functional handle onto this position that can access a variety of bond transformations. The McNally group developed a reaction platform using this strategy by installing phosphonium salts selectivity at the *para* position of the azine ring (**Figure 1.12**). The phosphine is installed through *N*-Tf pyridinium formation and subsequent attack by the phosphine nucleophile yielding a dihydropyridine intermediate. The ring regains aromaticity through a base mediated oxidation process initiated by 1,8-Diazabicyclo [5.4.0]undec-7-ene (DBU). The resulting phosphonium salt undergoes a wide variety of reaction mechanisms including nucleophilic addition[28], metal

insertion[29], ligand coupling[30], radical processes[31], and fragmentation[32] reactions yielding a variety of products from the phosphonium intermediate (**Figure 1.12**).

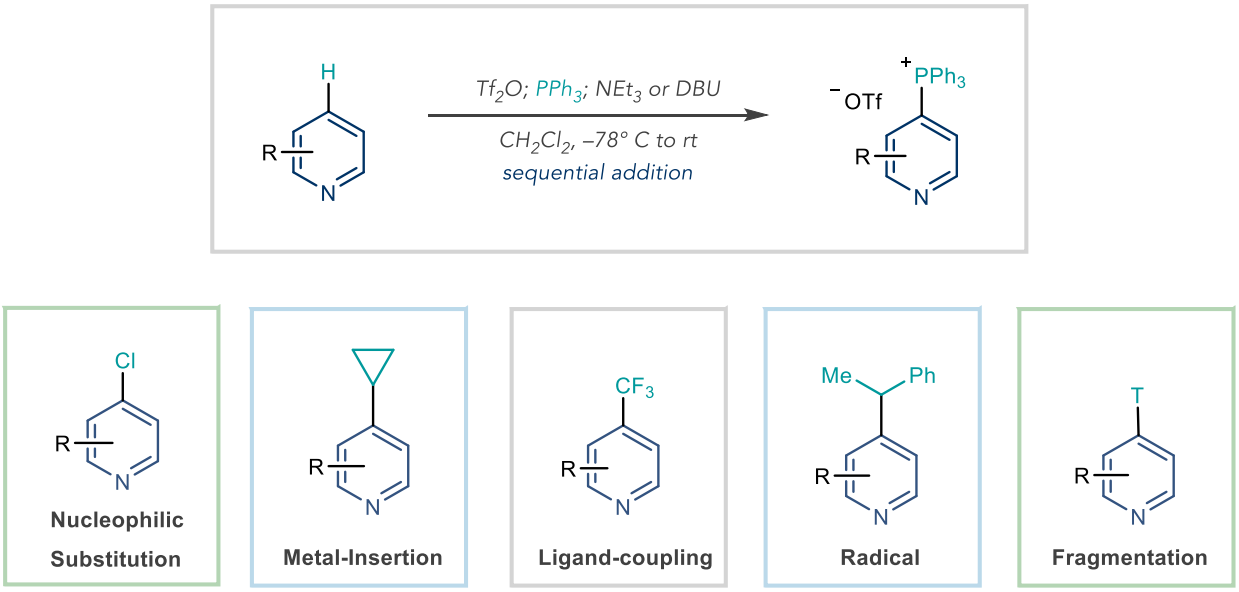

Figure 1.12. McNally's phosphonium salt formation and representative products

1.3 Pyridine Hydrogenation Strategies

1.3.1 Classical Approaches

Piperidine is the most common heterocycles in FDA approved drugs, as mentioned above. Since the piperidine carbon framework is sp^3 hybridized, incorporating this motif in drug molecules induces chirality, which projects substituents into three-dimensional space rather than a linear shape compared to pyridine molecules. Like pyridines, piperidines have inherent synthetic challenges for functionalization. The Lewis basic N-lone pair coordinates to transition metals and causes undesired ligation. In addition, its sp^3 carbon framework is much more inert than its aromatic counterpart. Piperidine synthesis through the hydrogenation of a pyridine precursor is an attractive strategy due to the wide breadth of pyridine functionalization reactions available

compared to its saturated counterpart as described in the previous section of this chapter. Thus, pyridine hydrogenation methods have a long history in synthetic chemistry and continue to be synthetic targets today.

Classical approaches for pyridine hydrogenation rely on heterogenous catalyst systems, which typically have poor functional group tolerance and are limited to simple pyridine building block compounds (**Figure 1.13**). The first reported hydrogenation of pyridine was developed by Koenig in 1915.[33] In this report 4-hydroxypyridine underwent hydrogenation with sodium metal in methanol, which are reaction conditions similar to a Birch reduction. To expand the chemoselectivity of the hydrogenation process, focus shifted to transition metal catalysis. In 1923, Adams developed a platinum-based catalytic system to hydrogenation biological relevant pyridines.[34] In the following years, nickel, ruthenium, rhodium, and palladium based catalysts successfully hydrogenated simple building-block pyridines. Although the synthetic community has adopted homogenous catalysts in recent years, heterogeneous catalysis for hydrogenation is still used today for alkene and heterocycle hydrogenation. For example, in 2020, the Glorius group used a palladium based heterogeneous catalyst to hydrogenate fluoropyridines to the corresponding piperidine without protodefluorination.[35]

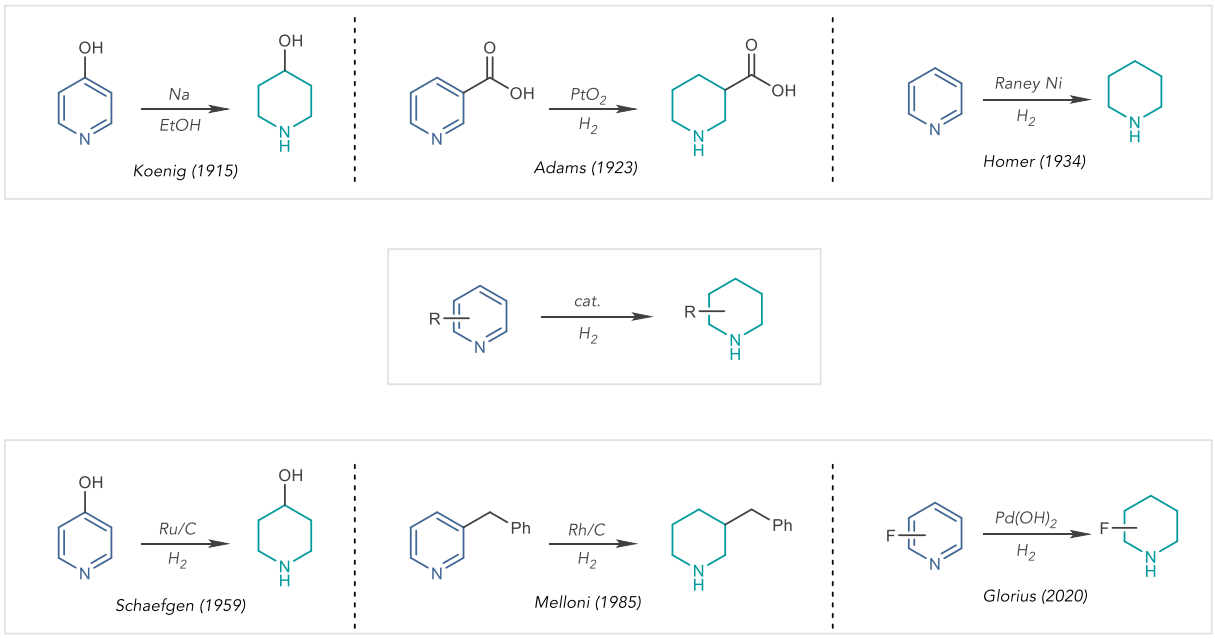

Figure 1.13. Classical approaches for pyridine hydrogenation

1.3.2 Modern Approaches

Modern approaches for pyridine hydrogenation typically undergo direct hydrogenation, in which the pyridine starting material transforms into its fully saturated form. However, step-wise reduction approaches, where intermediate oxidative forms are observed, are also widely applied and will be introduced in Chapter 2. In addition, modern approaches typically have a broader functional group tolerance and improved chemoselectivity compared to classical approaches. However, these methods are still limited to simple pyridine building blocks. Hydrogenation methods that apply to late-stage compounds are rare.

Direct hydrogenation approaches typically use rhodium (Rh) or iridium (Ir) homogeneous catalysis to achieve hydrogenation of a pyridine precursor.[36] In 2000, the Studer group developed a Rh based catalytic system for the hydrogenation of 2-, and 3-ester and carboxylic acid derived

pyridines under high pressures of hydrogen gas (**Figure 1.13**).[37] Pyridinium salts lower the enthalpy of hydrogenation and offer a means to milder reaction conditions and shorter rection times. In 2005, Charette developed an iridium catalyzed hydrogenation method for pyridine derivatives using *N*-benzoyliminopyridium ylides (**Figure 1.13**).[38] However, lithium in ammonia is necessary to remove the *N*-activator. Similar catalytic systems have been developed by Zhou[39] using high pressures of hydrogen gas without pre-activation of the pyridine starting material.

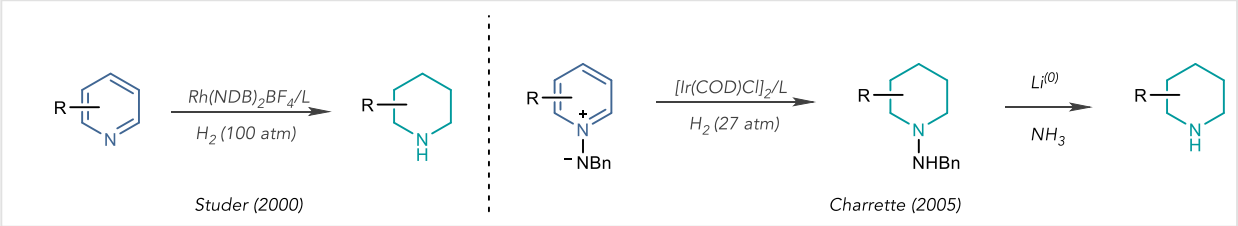

Figure 1.13. Homogeneous catalysis for pyridine hydrogenation

Hydrogenation of pyridines is also achieved without the use of a transition metal. Organocatalyzed transfer hydrogenation and frustrated Lewis-pairs (FLPs) have also received attention in the field of pyridine hydrogenation. The first organocatalyzed transfer hydrogenation was reported by Rueping in 2007.[40] Unlike transition metal mediated approaches, this report avoided the use of hydrogen gas by using Hantzch esters as the hydride source and a chiral phosphoric acid catalyst. In a related report, the Sun group also used a chiral phosphoric acid catalyst. In this case, hydrosilanes act as the hydride source for the reaction.[41]

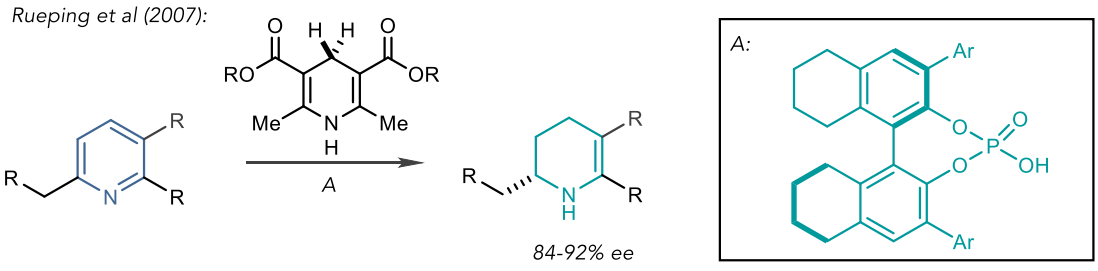

Figure 1.13. Rueping's organocatalyzed transfer hydrogenation

Building off the pioneering work in FLP hydrogenations by Stephan[42], the Du group reported a FLP catalyzed hydrogenation of pyridine using bis-pentafluorophenyl borane and an electron deficient alkene as the catalytic system (**Figure 1.14**).[43] The active catalyst is generated from a hydroboration reaction with an alkene. The basis of FLP chemistry relates to two sterically encumbered species that are polarity matched to react. In this case, the pyridine starting material acts as a Lewis base and the borane catalyst acts as a Lewis acid. Since these two species are sterically hindered, they cannot react with each other. Instead, they split hydrogen gas into a proton and a hydride equivalent, in this case a protonated pyridine species and a borohydride. The borohydride generated reduces the pyridine to the corresponding piperidine. However, pyridines that are sterically encumbered around the nitrogen atom are necessary for conversion.

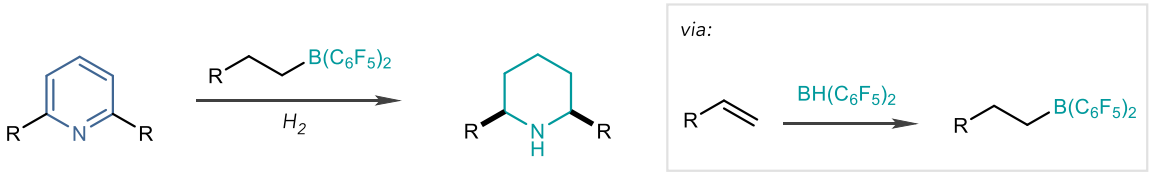

Figure 1.14. Frustrated Lewis-acid hydrogenation of pyridine

1.4 Conclusion

This chapter serves as an introduction to pyridine and piperidine and their importance in pharmaceuticals. Classical and modern approaches to pyridine functionalization are discussed to demonstrate the breadth of reactions available for these pyridines to serve as piperidine precursors. Additionally, classical and modern approaches for pyridine hydrogenation are discussed. Classical approaches are limited in functional group tolerance and are limited to simple pyridine building blocks. Recent advancements improve functional group tolerance, but hydrogenation of complex pyridines remains elusive.

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CHAPTER TWO

DEGREE OF SATURATION CONTROLLED HYDROGENATION OF COMPLEX PYRIDINES

2.1 Introduction to Pyridine Dearomatization via Hydride Addition

2.1.1 Importance and Synthesis of 1,4-Dihydropyridines via Hydroboration/Hydrosilylation

1,4-dihydropyridines (1,4-DHPs) are a prevalent motif in biochemistry and serve important cellular functions. For example, Nicotinamide adenine dinucleotide (NAD) is a coenzyme central to an array of biological processes including the Krebs cycle, the electron transport chain, and gluconeogenesis. In the majority of these processes, NAD is involved in redox reactions by shuttling electrons between molecules. It is found in two forms NAD^+, an oxidizing agent that accepts electrons from biological substrates, and NADH, a reducing agent that donates electrons **(Figure 2.1)**. **Figure 2.1** illustrates a step in the Krebs cycle in which NAD^+ is reduced to NADH and isocitrate is oxidized to α-ketoglutamate. Incorporating these motifs in pharmaceuticals would allow similar redox process to occur in biological systems. Thus, 1,4-DHPs represent an important synthetic target in medicinal chemistry.

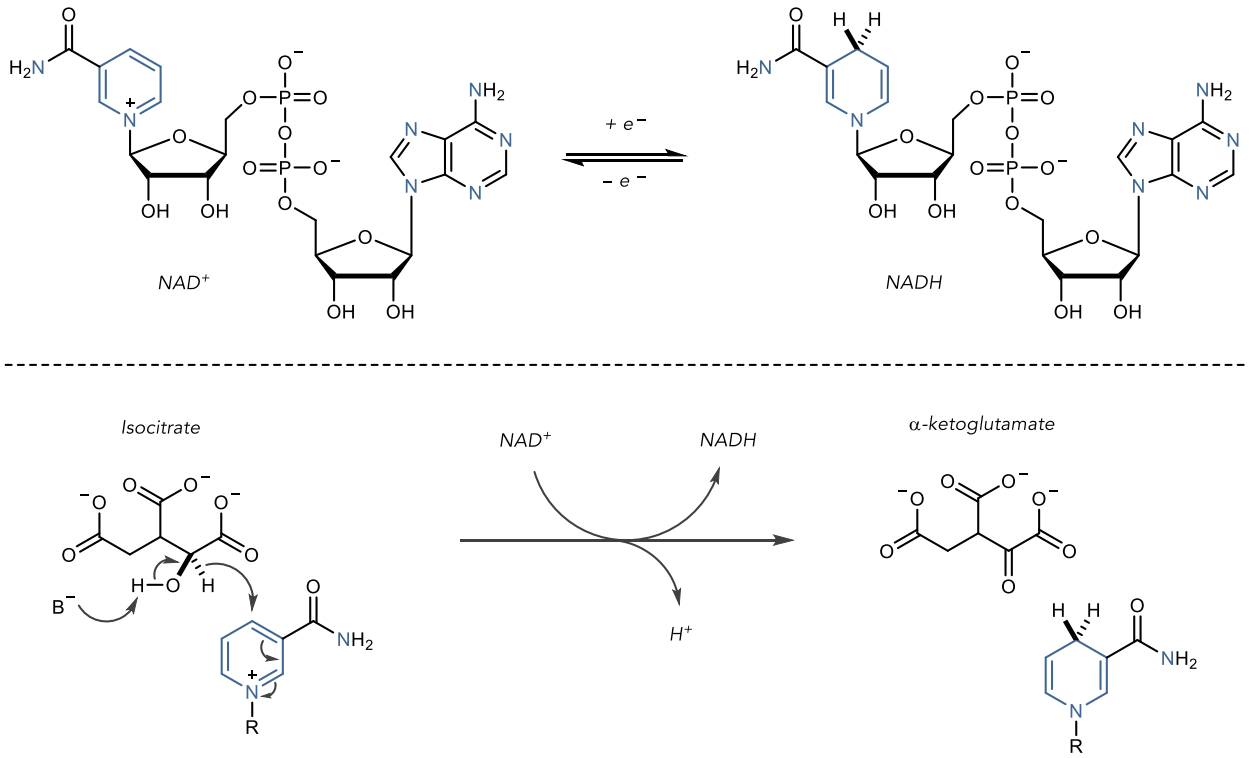


Figure 2.1. Structure and redox processes of nicotinamide adenine dinucleotide.

Synthetically, 1,4-DHP are prepared via hydroboration or hydrosilylation reactions with unactivated pyridines or activated pyridinium salts.[1] Dearomatization of unactivated pyridines allows the practitioner to install an *N*-substituent of their choice; however, harsh reaction conditions are often required. Alternatively, pyridinium salt dearomatization offers a milder approach while installing the *N*-substituent in a single step. The hydroboration/hydrosilylation process is typically transition metal or organocatalyzed. However, over-reduction of the 1,4-DHP intermediate is common and results in a mixture of reduced products.

In 1998, the Harrod group developed the first transition metal catalyzed hydrosilylation reaction of pyridines using a titanium-based catalyst.[2] Although the reaction successfully synthesized 1,4-DHPs, the reaction suffered from a lack of chemoselectivity resulting in mixtures

of the desired dihydropyridine and over-reduced tetrahydropyridine (THP). To remedy this, the Nikonov group developed a ruthenium catalyzed hydrosilylation reaction that applied to a variety of pyridine building-blocks (**Figure 2.2**).[3] However, the reaction is not amenable to 2-substituted pyridines and electron-withdrawing group is present at the 3-position form mixtures of reduced products. In addition, nitrile and acyl groups are not tolerated in the reaction procedure. Concurrently with this report, Oesteich reported a similar tethered ruthenium catalyzed hydrosilylation reaction with a broader substrate scope; however, 2-position substituents are still not tolerated (**Figure 2.2**).[4] Both reactions undergo similar mechanistic steps (**Figure 2.2**). First, the pyridine starting material binds to the silicon atom of the hydrosilane and transfers a hydride to the cationic ruthenium species. This results in a metal hydride and silicon activated pyridinium salt. Then, the metal hydride adds to the pyridinium selectively at the C4 position yielding the 1,4-DHP product. Similar metal catalyzed hydrosilylations were developed by Park and Chang[5], and Harder[6] using iridium and calcium catalysts, respectively. Hydroborations of this type have also been developed by Hill[7], Harder[8], Ohmura and Suginome[9], and Gunanathan.[10]

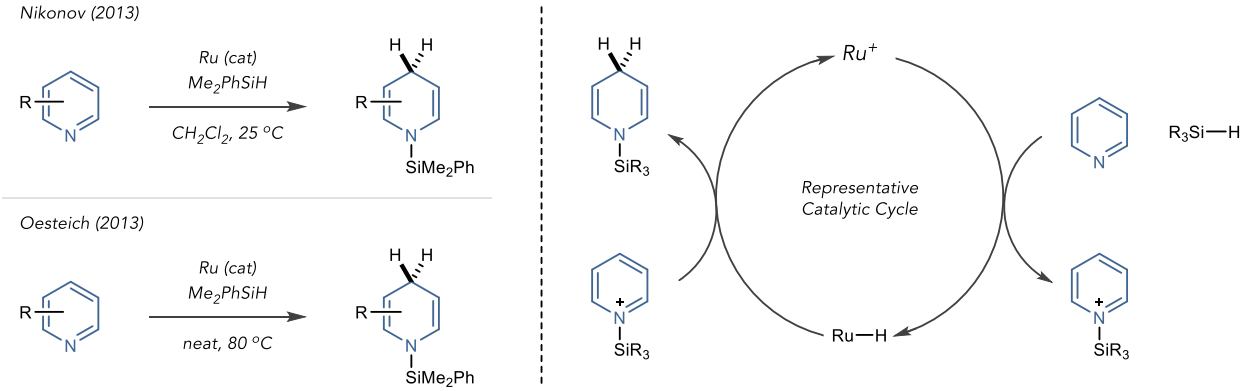


Figure 2.2. Nikonov's and Oesterich's ruthenium catalyzed hydrosilylation.

A major advancement in the field of pyridine hydrosilylation reactions used trispentafluorophenylborane ($B(C_6F_5)_3$) as the hydride transfer catalyst in place of transition metals. Following the pioneering work of Stephen[11], Chang developed a dearomative approach to pyridine reduction strategy using a combination of $(BC_6F_5)_3$ and hydrosilanes under mild conditions (**Figure 2.3**).[12] Unlike transition metal catalyzed reactions of this type, 2-position substituents are well tolerated and produced piperidine products. The regioselectivity of the hydride addition and product distribution is dependent on the substituents on the ring. 2-substituted and 3-substituted pyridines undergo 1,4-addition and produce piperidine and tetrahydropyridine (THP) products, respectively. On the other hand, 4-substituted pyridines undergo 1,2-addition and produce THP products. The reaction mechanism is similar to transition metal catalyzed processes (**Figure 2.3**). First, the pyridine binds to the silicon atom and transfers a hydride to the highly Lewis acidic $B(C_6F_5)_3$. Then, the resulting borohydride, generated in situ, adds to the pyridinium salt. Subsequent imine to enamine tautomerization via electrophilic capture of the silicon group and reduction with the borohydride yields the corresponding product. Subsequent reports have used this type of catalytic system for hydroboration reactions developed by Crudden[13] and Li and Wang.[14]

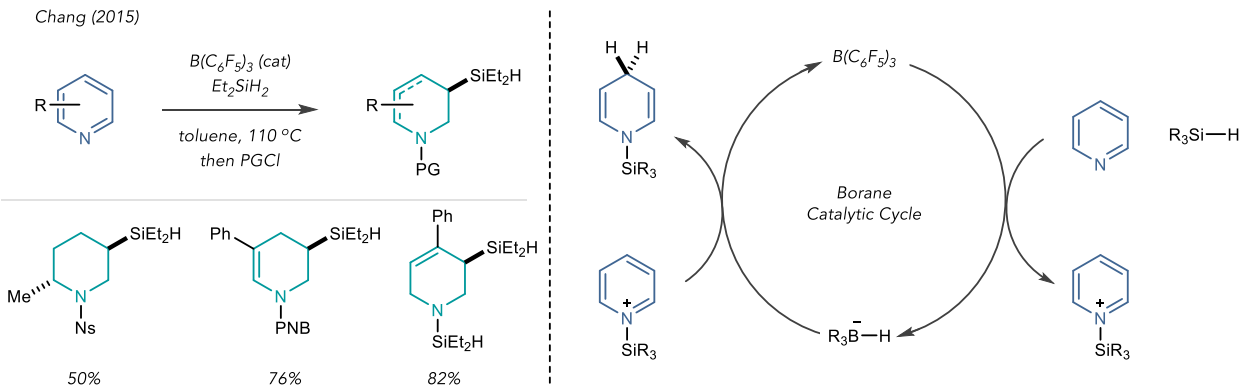


Figure 2.3. Chang's $(BC_6F_5)_3$ catalyzed reduction of pyridines.

Concurrently with the work presented in this chapter, the Glorius group reported a pyridine dearomatization strategy for *N*-trifyl (*N*-Tf) pyridinium salts using stochiometric ammonium borane as the hydride donor.[15] Due to the *N*-Tf activation of the pyridine N-atom, the reaction conditions are much milder than other reports discussed in this chapter. The reaction also demonstrates a wide functional group tolerance (**Figure 2.4**). However, the reaction is sensitive to steric interactions around the N-lone pair resulting in low conversion to the 1,4-DHP product for 2-substituted pyridines. Regiomeric mixtures of the 1,2- and 1,4-dihydropyridine also form. In addition, the method only applies to simple pyridine building-blocks. Thus, dearomatization and hydrogenation methods that apply to complex pyridines remains elusive.

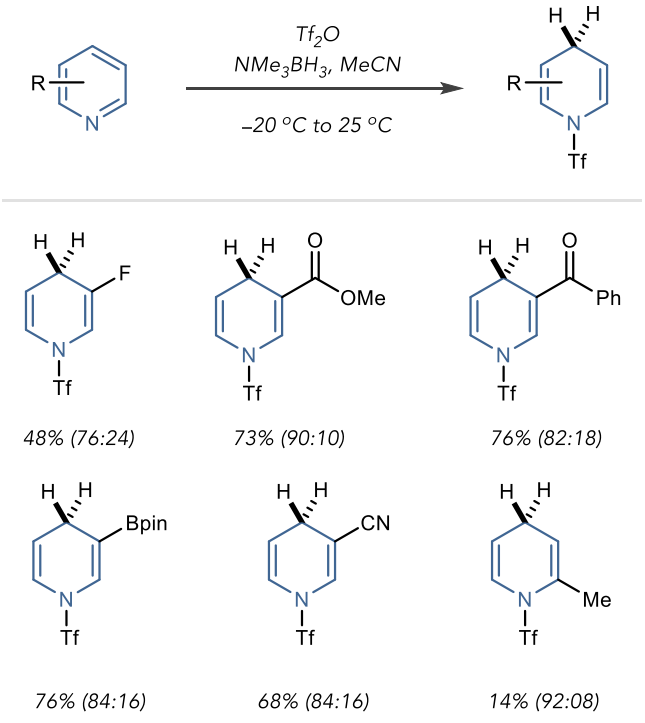


Figure 2.4. Glorius' pyridine dearomatization of *N*-Tf pyridiniums

2.2 Introduction to Degree of Unsaturation Controlled Hydrogenation of Complex Pyridines

Despite the growing reports of pyridine dearomatization and hydrogenation strategies, modern synthetic methods still cannot tolerate complex pyridine scaffolds typically encountered in drug development campaigns. As described in sections **1.1** and **2.1**, the reduced forms of pyridine molecules, such as dihydropyridines, tetrahydropyridines, and piperidines, are important motifs in pharmaceutical drugs; selected examples of these motifs are shown in **Figure 2.5**. Although a majority of pyridine reduction or hydrogenation methods typically generate these reduced forms as intermediates, it is difficult to chemoselectivity of these processes to generate each of these reduced forms exclusively.

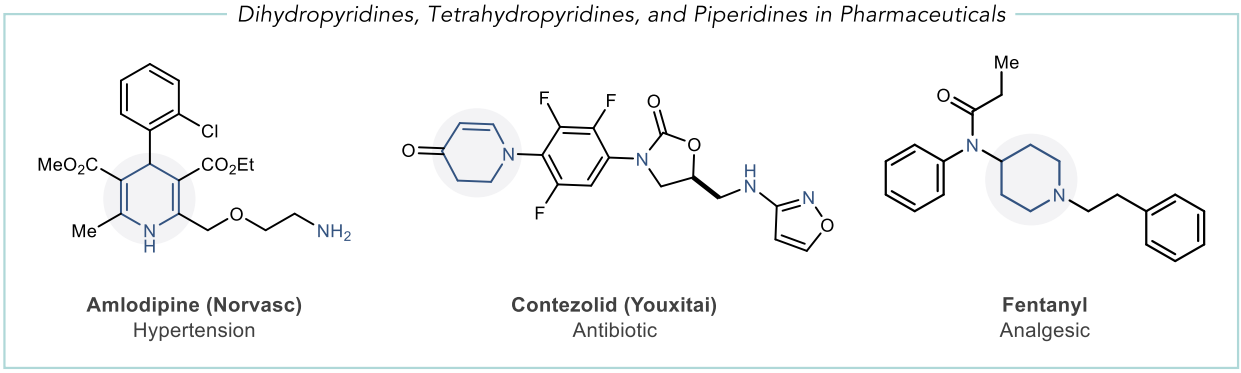


Figure 2.5. Dihydropyridines, tetrahydropyridines, and piperidines in pharmaceuticals

Achieving a step-wise dearomatization approach for pyridine reduction also has synthetic benefits. Accessing each stage of the reduction process enables functionalization of the carbon framework allowing practitioners the ability to install substituents around the periphery of the ring through the corresponding π-bonds (**Figure 2.6**). For example, practitioners can leverage the reactivity of dihydropyridines for difunctionalization reactions. Reacting the dihydropyridine with a suitable electrophile at C3 generates a reactive iminium species which is then intercepted

by a nucleophile at C2 generating a difunctionalized tetrahydropyridine core, which could undergo further derivatization or hydrogenation to access highly substituted piperidine cores.

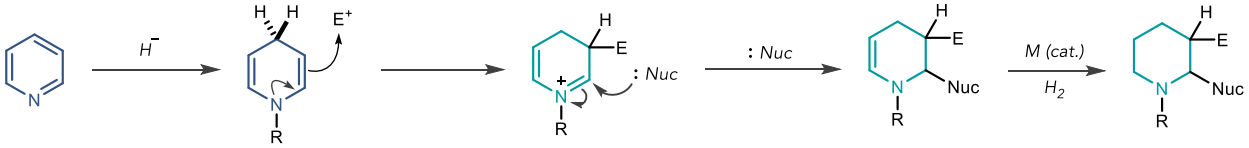


Figure 2.6. Derivatization of the dihydropyridine intermediate.

We hypothesized that triflic anhydride (Tf_2O) activation would yield a pyridinium salt that would undergo selective dearomatization with the appropriate reducing agent. From previous studies within our laboratory, Tf_2O activation applies to a wide variety of pyridines at each stage of the drug-discovery process including late-stage analogues.[16–18] After a dearomatization strategy is developed, the dihydropyridine intermediate is then reduced to the corresponding tetrahydropyridine or piperidine product depending on the catalytic system employed. To achieve our goal of a mild hydrogenation of pyridines via dearomatized intermediates, a successful dearomatization step must be realized. Thus, the hydride source must meet a few important criteria: (1) the hydride addition must be regioselective to avoid product mixtures (2) the dearomatization must extend to a variety of substituted pyridines with varying electronic and steric considerations, (3) the nucleophilic hydride must be chemoselective for the *N*-Tf pyridinium rather than reduction labile functionalities on the molecule.

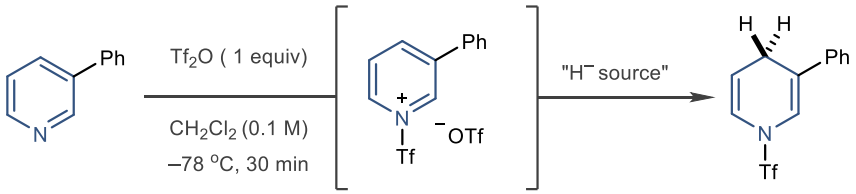
2.3 1,4-Selective Tris(pentafluoro)borane Catalyzed Dearomatization of Pyridines

With these goals in mind, we began investigating suitable hydride nucleophiles for the dearomatization process. To study these dearomatization processes, we chose 3-phenylpyridine as our model substrate, triflic anhydride (Tf_2O) as the pyridine activating group, and a series of common reducing agents for our dearomatization process at 60 °C (**Table 2.1**). Using hydrosilanes

as reducing agents resulted in encouraging yields for the 1,4-dihydropyridine intermediate (entries 1 and 2). Alternatively, using common borohydride reductants resulted in trace amounts of product formation potentially due poor solubility of these species in dichloromethane despite the higher reduction potential of borohydrides compared to hydrosilanes (entries 3-5).

Increasing the temperature, concentration, and equivalence of the hydrosilane did not lead to an increase in product formation. We hypothesized pyridinium salt decomposition outcompeted the reduction process inhibiting product formation. Tris(pentafluorophenyl)borane ($B(C_6F_5)_3$), a strong Lewis acid, is reported to activate Si–H bonds in hydride transfer reactions and has been used to promote the reduction of ketones, aldehydes, imines, and heterocycles. Indeed, when we employed a catalytic amount of $B(C_6F_5)_3$ to the reaction conditions, a significant increase in product formation was observed and proved to be a key additive in the dearomatization process (entry 6). The catalytic $B(C_6F_5)_3$ additive also allowed for milder reaction conditions since the temperature and time of the reaction could also be lowered to room temperature and one hour, respectively (entries 7). Further optimization studies showed –78 ℃ was the optimal temperature for the dearomatization process presumably due to the increased stability of the pyridinium species at this temperature (entry 8) and two equivalence of the hydrosilane was necessary for full conversion (entry 9).

Table 2.1. Optimization of 1,4-dihydropyridine formation



Entry	H^- source	Temperture (°C)	solvent	equiv H^-	yield
1	Ph_2SiH_2	60	CH_2Cl_2	1.1	28
2	Et_3SiH	60	CH_2Cl_2	1.1	43
3	$NaBH_4$	60	CH_2Cl_2	1.1	0
4	$NaBH_3CN$	60	CH_2Cl_2	1.1	3
5	$NaBH(OAc)_3$	60	CH_2Cl_2	1.1	0
6	$Et_3SiH/B(C_6F_5)_3$	60	CH_2Cl_2	1.1	45
7	$Et_3SiH/B(C_6F_5)_3$	25	CH_2Cl_2	1.1	71
8	$Et_3SiH/B(C_6F_5)_3$	–78	CH_2Cl_2	1.1	82
9	$Et_3SiH/B(C_6F_5)_3$	–78	CH_2Cl_2	2.0	95

a,Tf_2O (1 equiv), CH_2Cl_2 (0.1 M), –78 °C, 30 min, then, $B(C_6F_5)_3$ (10 mol%), Et_3SiH (2 equiv), –78 °C, 1 hr, then, 25 °C, 30 min

With the optimized conditions in hand, we then examined the scope of the dearomatization process (**Figure 2.7**). Monosubstituted building blocks with substituents at the 2-, 3-, and 4-positions are tolerated (**1-3**). In particular, sterically encumbering group at the C2-position, such as a phenyl substituent, represents major advancement in the field of pyridine dearomatization as this substitution is not typically tolerated. In addition, the electronics of the ring are altered without any depletion in yield. For example, **3** contains of a strong electron withdrawing group at the 4-position and **13** displays strong electron donating group at the 2-position. A series of poly substituted building blocks are also amenable in the reaction procedure (**4-7**). The reaction is tolerant of other heteroaromatics (**6**) and aryl halides (**4**) without any off-target reduction or proto-dehalogenation. Highly substituted pyridines are also amenable (**5**). Interestingly, high

regioselectivity for hydride addition is retained even when the 4-position is sterically encumbered (**5** & **7**). In fact, the 1,2-DHP regioisomer only forms when the 4-position is blocked by a substituent (**3**). In all other cases, the 1,4-DHP dominates and is the only regioisomer observed for pyridine dearomatization. We hypothesized that a steric interaction between incoming hydride nucleophile and the *N*-trifyl group guides reactivity to the C4 position selectively producing the 1,4-DHP product exclusively.

In addition to a broad scope of pyridine building blocks amenable to the dearomatization process, complex drug-like molecules and drugs themselves are well tolerated (**8-16**). These complex molecules contain functionalities that are susceptible to reduction, such as sulphones (**8**), sulphonamides (**10**), esters (**11**), amides, and aryl halides (**8**, **10**, **12**, & **14-16**). Other heteroaromatics with lower reduction potentials than pyridine, such as quinoline, undergo the dearomatization without overreduction (**9**). Another interesting feature of this dearomatization process is the ability to selectively dearomatize a single pyridine ring in a polyazine system (**4** & **16**). In these cases, exclusive dearomatization is observed for the 3-substituted pyridine (x) over the 2-substituted pyridine (y) due to selective trifyl activation of the 3-substituted pyridines over the more sterically hindered 2-subsituted pyridine. Finally, the dearomatization process applies to drug-molecules directly, showcasing the power of this method for medicinal applications (**12-16**).

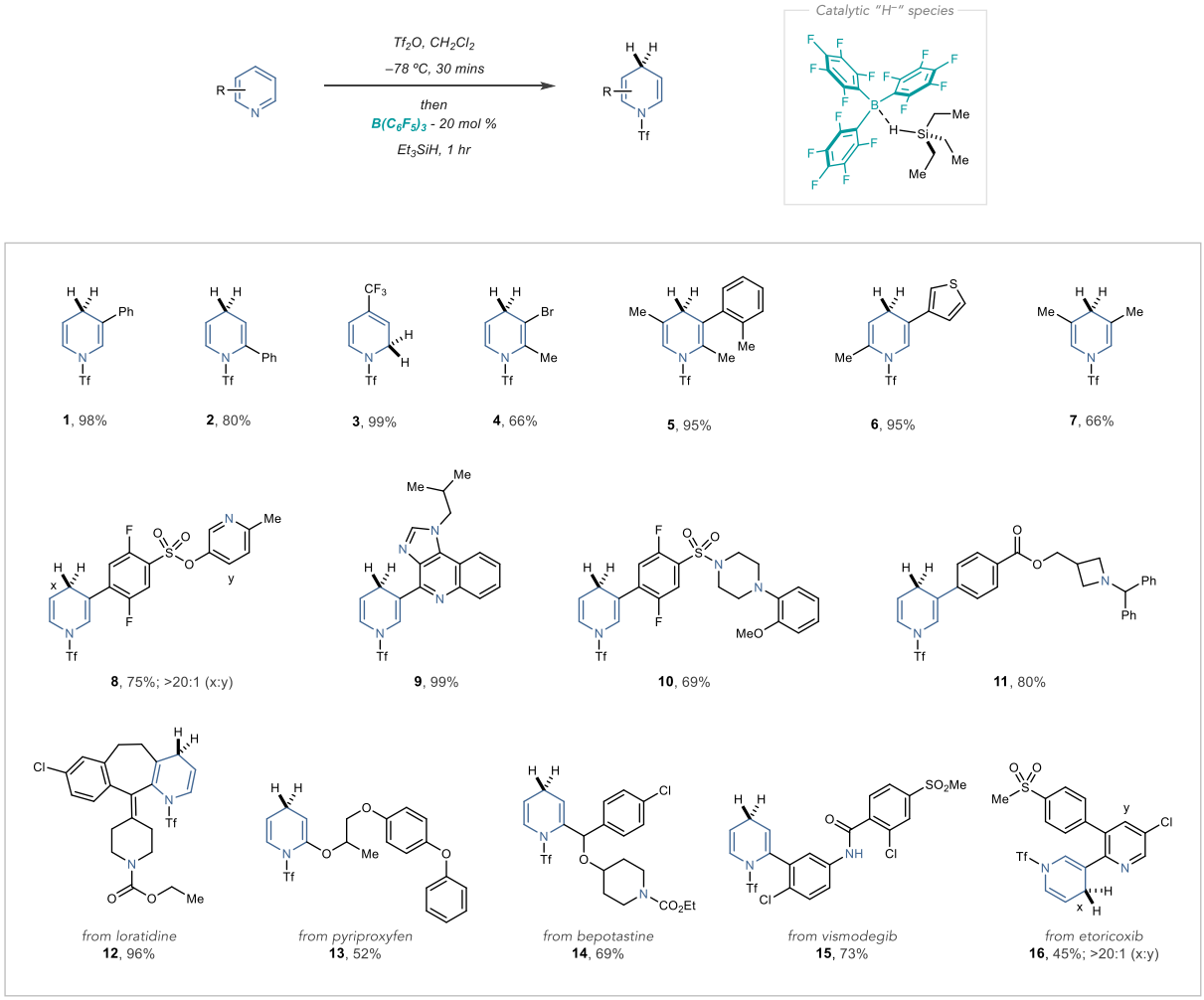


Figure 2.7. Scope of 1,4-dihydropyridine formation. Yields calculated by ^{1}H NMR using triphenylmethane as an internal standard

Although the dearomatization process applies to a wide-variety of pyridines at each stage of the drug-discovery process, a few distinct limitations are notable. First, the dearomatization process is not amenable to 2,6-disubstituted pyridines due to insufficient trifyl activation. Next, reactive functional groups, such as free amines, alcohols, and alkyl amides, outcompete the pyridine for trifyl activation resulting in low conversions to the 1,4-DHP. However, the expansive scope of this reaction is an advantage over other developed methods allowing for complex

pyridines and 2-substiuents to now be amenable. Due to the limited stability of theses dearomatized products, ^{1}H NMR yields are shown. Thus, the DHP intermediate must be either undergo derivatization or further hydrogenation to yield a stable product.

2.3.1 Preliminary Results for 1,4-Dihydropyridine Derivatization

As mentioned in **Section 2.2**, one of the benefits of a step-wise reduction/hydrogenation strategy is the potential for further derivatization to the carbon framework. The presented derivatizations undergo one of two strategies (**Figure 2.8**). The first is a pyridine functionalization strategy in which the enamine bond reacts with an electrophile forming an iminium species, which is then quenched by a suitable base. The functionalized dihydropyridine intermediate undergoes oxidation to produce a 3-functionalized pyridine product. The second is a difunctionalization strategy described in **Section 2.2** yielding a tetrahydropyridine product.

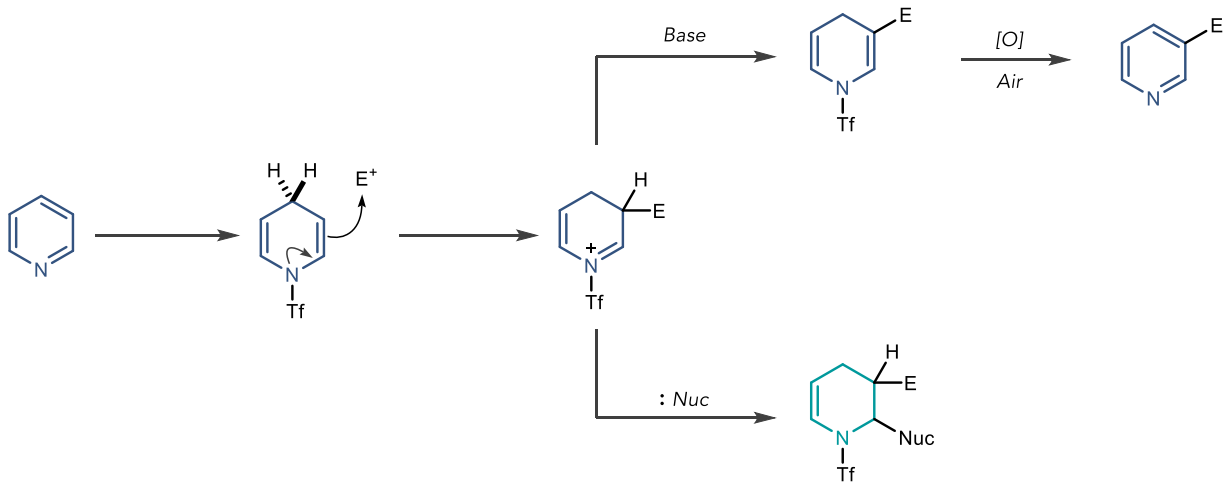


Figure 2.8. Strategies for 1,4-dihydropyridine functionalization

Preliminary results for the 3-selective functionalization strategy demonstrate trifluoromethylation is feasible (**Figure 2.9**). Exposing the 1,4-DHP intermediate of 3-octyl pyridine to Tongi II, a commercially available trifluoromethylation reagent, in dichloromethane at low temperatures results in a trifluoromethylated pyridine in 63% yield. Unlike other methods, this reaction does not require a photocatalyst to generate the trifluoromethyl radical for addition to the C3 position. Instead, we hypothesize a radical chain mechanism dominates by continuously generating trifluoromethyl radical via homolysis of the *N*-trifyl group. On the other hand, difunctionalization is also viable by exposing the DHP intermediate to halosuccinamides in a mixture of dichloromethane and methanol. In these cases, a halide is installed at the C3 position and a methoxy group is installed at the C2 position.

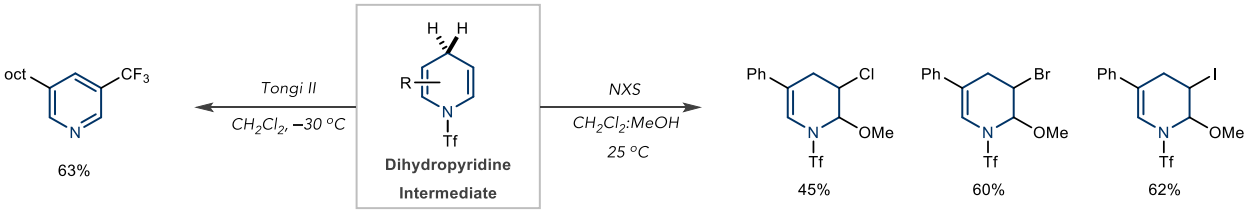


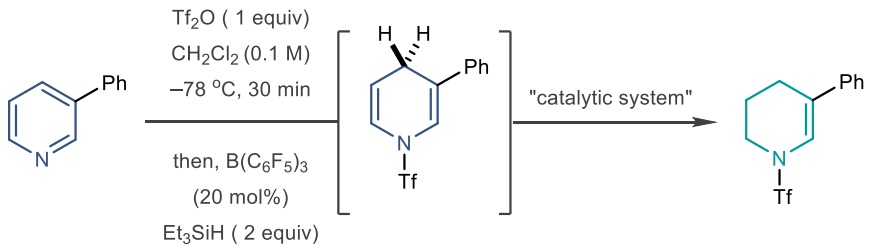
Figure 2.9. Derivatization of 1,4-dihydropyridine intermediate

2.4 Iridium Catalyzed Hydrogenation of the 1,4-Dihydropyridine Intermediate

After successful development of a chemoselective pyridine dearomatization strategy, we began exploring suitable hydrogenation systems to yield tetrahydropyridine products (**Table 2.2**). We prioritized reaction conditions that would be safe for the practitioner to conduct due explosive hazards associated with hydrogen gas. To minimize hazards, we limited the reaction pressure to 100 bar, did not exceed room temperature, and conducted the reactions with appropriate blast shielding. We then started our optimization campaign with a series of heterogeneous catalysts (entries 1 & 2). Palladium on carbon yielded no conversion to the dihydropyridine intermediate and platinum dioxide (Adam's catalyst) produced the corresponding piperidine product, but also reduced the phenyl substituent.

We hypothesized homogeneous catalysts would be better suited for the hydrogenation process to the corresponding tetrahydropyridine product since they are generally more selective than heterogeneous catalysts. Indeed, using homogeneous Ru- and Ir-based catalysts with a dppf ligand yielded the desired tetrahydropyridine product in 24% and 51% yield, respectively, while lowering the catalyst loading to 1 mol% (entries 3 & 5). Employing other ligands with the iridium pre-catalyst resulted in lower product yields (entries 6 & 7). Increasing the pressure of hydrogen gas and conducting the reaction in methanol produced the optimal conditions for tetrahydropyridine formation (entries 8 & 9).

Table 2.2. Optimization of tetrahydropyridine formation



Entry	Catalyst ID	Pressure H_2 (bar)	solvent	temperature (°C)	yield
1	Pd/C (10 mol%)	6	MeOH	25	0
2	PtO_2 (10 mol%)	6	MeOH	25	45 (phenyl reduced)
3	$Ru(acac)_3$/dppf (1 mol%)	55	CH_2Cl_2	25	24
4	$[Rh(nbd)_2]BF_4$/dppf (1 mol%)	55	CH_2Cl_2	25	0
5	$[Ir(cod)Cl]_2$/dppf (1 mol%)	55	CH_2Cl_2	25	51
6	$[Ir(cod)Cl]_2$/(R)-BINAP (1 mol%)	55	CH_2Cl_2	25	20
7	$[Ir(cod)Cl]_2$/(R)-SEGPhos (1 mol%)	55	CH_2Cl_2	25	20
8	$[Ir(cod)Cl]_2$/dppf (1 mol%)	69	CH_2Cl_2	25	74
9	$[Ir(cod)Cl]_2$/dppf (1 mol%)	69	MeOH	25	82

We next evaluated the scope of the hydrogenation process of the dihydropyridine intermediate to its corresponding tetrahydropyridine. 2- and 3-aryl substituted pyridines undergo the hydrogenation process in moderate to excellent yields (**17** & **18**). Alkyl groups are also amenable (**21**, **33** & **34**). Disubstituted pyridines perform well under the hydrogenation process and electron withdrawing groups at C3 are amenable (**23** & **24**).

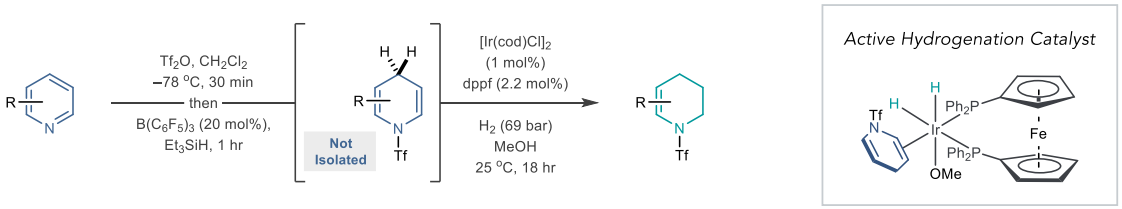
In addition, the hydrogenation procedure can accommodate functionalities that are prone to reduction, such as esters and aromatic nitro groups (**23** & **28**). Aryl fluorides are also tolerated on the pyridine ring without hydrodefluorination, which represents a synthetic challenge in azine hydrogenation processes (**24**). Other heterocyclic substituents are tolerated without undesired reduction of the more electron-rich heterocycle (**25** & **26**). Sulfur containing groups, such as thiophenes, react well under the reaction conditions without significant poisoning of the iridium

catalyst (**25**, **40** & **41**). Quinolines can also be converted to their corresponding tetrahydroquinoline without over-reduction (**27** & **28**).

A particularly challenging class of molecules for selective hydrogenation are polyazines; selectively distinguishing the two or more azine moieties are difficult even for modern methods. Often times compounds in drug-discovery programs have multiple azines; we demonstrated our method can be used for the regioselective hydrogenation of these polyazine systems while controlling chemoselectivity. Compounds **29**-**32** shows how one pyridine ring can be selectively hydrogenated over another pyridine moiety on the molecule. The site-selectivity in these cases is influenced by the steric environment around each N-atom during the trifylation process. The 3-substituted azine is more sterically available for the triflation process compared to its 2-subsituted counterpart. Thus, regioselective dearomatization and hydrogenation is achieved. Hydrogenation of both rings is also viable by doubling the equivalents of Tf_2O. Compounds **31** and **32** are molecules that exemplify this control of saturation where either one or both pyridines in this molecule can be reduced depending on the reaction conditions.

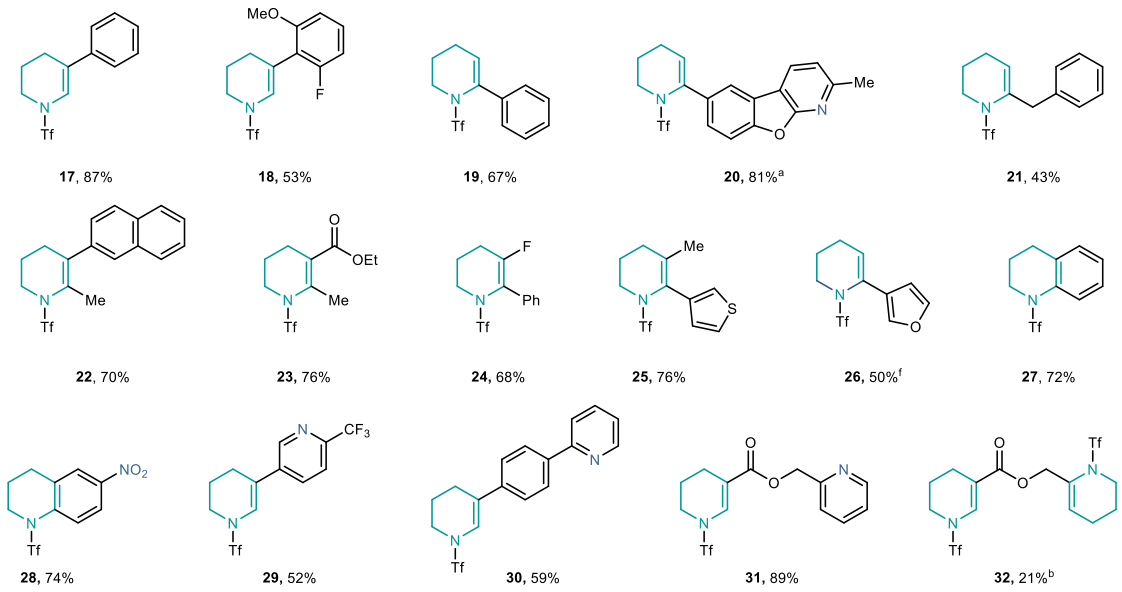
We then focused our attention on applying our hydrogenation method to a series of complex and drug molecules. Complex pharmaceutical fragments can contain polar functionalities, such as amides, sulphones, and sulphonamides (**35**, **37** & **32**). Notably, other saturated heterocycles, such as piperazines and piperidines, are tolerated without causing catalyst inhibition (**24**, **30** & **35**). Aryl chlorides and fluorides, motifs often found in drug-discovery campaigns, remain in-tact after the hydrogenation process (**28**-**31**); however, aryl bromides and iodides undergo protodehalogenation (**26**). Pleasingly, pharmaceuticals themselves undergo the hydrogenation process in encouraging to excellent yields (**27**-**28**, & **41**). Bisacodyl reacts well under the reaction conditions, although, deacylation was observed upon isolation (**36**). A

beptotastin precursor, **39**, delivers 51% of the desired tetrahydropyridine with an increase in catalyst loading from 1 mol% to 3 mol%. Loratadine and Vismodegib performed very well under the reaction conditions showcasing this platform's potential for late-stage hydrogenation of complex molecules (**44** & **37**).



Building Block Pyridines

a



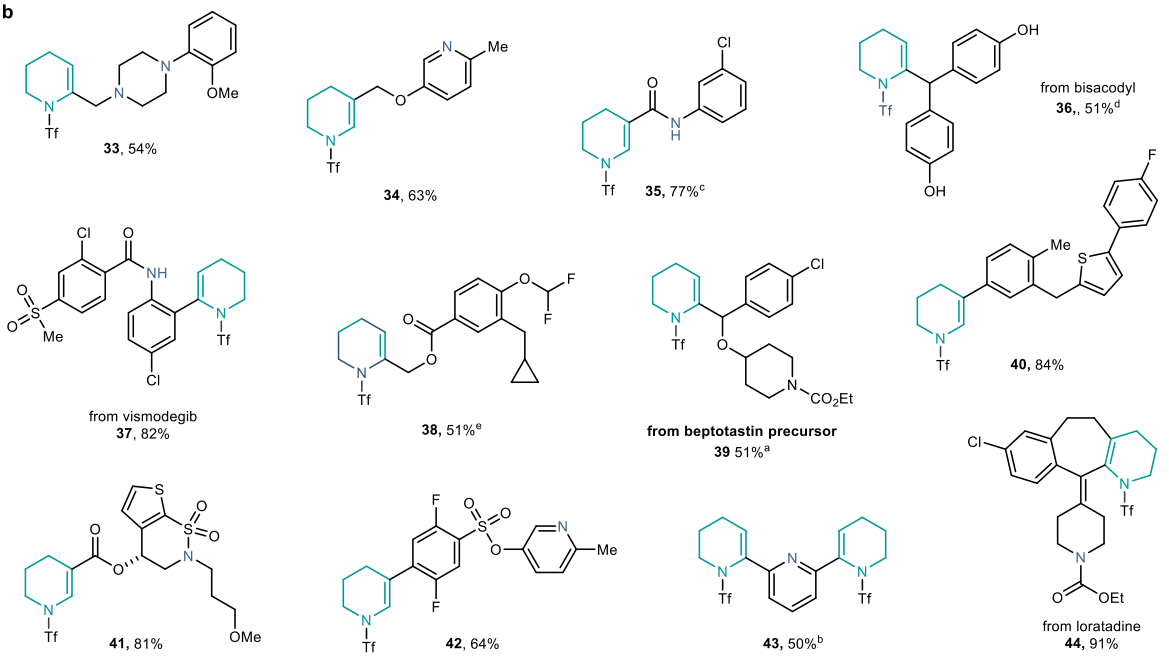
17, 87% | **18**, 53% | **19**, 67% | **20**, 81%[a] | **21**, 43%

22, 70% | **23**, 76% | **24**, 68% | **25**, 76% | **26**, 50%[f] | **27**, 72%

28, 74% | **29**, 52% | **30**, 59% | **31**, 89% | **32**, 21%[b]

Complex Pyridines, Drugs, and Agrochemicals

b



33, 54% | **34**, 63% | **35**, 77%[c] | from bisacodyl **36**,, 51%[d]

from vismodegib **37**, 82% | **38**, 51%[e] | **from beptotastin precursor** **39** 51%[a] | **40**, 84%

41, 81% | **42**, 64% | **43**, 50%[b] | from loratadine **44**, 91%

[a] $[Ir(cod)Cl]_2$ (3 mol%), dppf (6.6 mol%), H_2 (69 bar), MeOH (0.1 M), 25 °C, 18hr. [b] Tf_2O (2 equiv), CH_2Cl_2 (0.1 M), –78 °C, 30 min then, $B(C_6F_5)_3$ (20 mol%), Et_3SiH (4 equiv), –78 °C, 1 hr, then, 25 °C, 30 min, then, $[Ir(cod)Cl]_2$ (3 mol%), dppf (6.6 mol%), H_2 (69 bar) MeOH (0.1 M), 25 °C, 18hr. [c] Deiodinated product observed [d] Deacylated product observed [e]Isolated with 7% impuritiy [f]Isolated with 5% dihydropyridine

Figure 2.10. Scope of tetrahydropyridine formation

2.5 Hydrogenation of the 1,4-Dihydropyridine Intermediate to Piperidine Products

Finally, we showed the utility of the 1,4-dihydropyridine intermediate to synthesize piperidines. Selected examples of this hydrogenation process are shown in **Figure 2.11**. Using an alternative set of conditions yields the piperidine product as shown in **45** and **46**. It is important to note both of these substrates yield the tetrahydropyridine product using the iridium-catalyzed reaction conditions. However, by switching the catalyst to palladium on carbon and increasing the catalyst loading, the piperidine product can be realized from the same precursor. In addition, the reaction conditions are milder than the iridium-catalyzed hydrogenation; only an atmosphere of hydrogen is used for these reaction conditions. However, there are certain instances of the iridium-catalyzed hydrogenation that yield the corresponding piperidine product, such as **47** and **48**. With **47**, a potential directing group effect drives piperidine formation. Alkenes out of conjugation with the N-lone pair also yield the piperidine. This highlights the practitioner's ability to control the degree of saturation based on the reaction conditions implemented, which will be useful for late-stage hydrogenation of pyridine containing molecules. This approach to pyridine hydrogenation is likely amenable to numerous late-stage candidates and compliments other existing methods for pyridine hydrogenation that target simple building block pyridines.

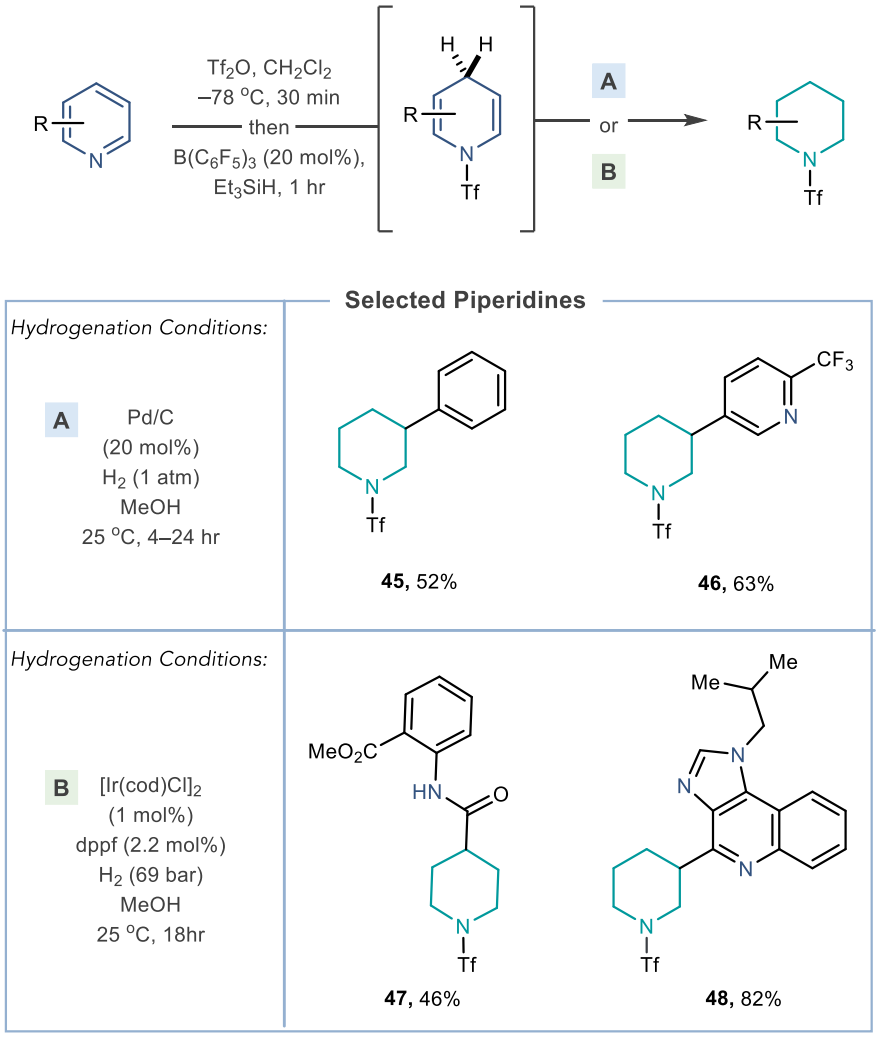


Figure 2.11. Scope of piperidine formation

2.6 Conclusion

In conclusion, numerous reports of direct pyridine hydrogenation and dearomatization strategies apply to simple pyridine building blocks; however, methods that apply to complex molecules are rare. Here, we report a method for complex pyridine hydrogenation via a step-wise dearomatization/hydrogenation strategy. In addition, the degree of saturation is controlled by the catalytic system applied. Catalytic borane yields 1,4-dihydropyridines, which is further reduced

to its corresponding tetrahydropyridine or piperidine. The 1,4-dihydropyridine intermediate is also used for derivatization showcasing the intermediate's synthetic utility.

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CHAPTER THREE

INTRODUCTION TO STRUCTURE-ACTIVITY RELATIONSHIP STUDIES AND CLASSICAL AND EMERGING STRATEGIES FOR DIVERSIFICATION

3.1 Structure-Activity Relationship Studies in Drug-Discovery

Structure-activity relationship (SAR) studies are critical in the drug-discovery process as it enables scientists to optimize the physicochemical properties of drug candidates in pharmaceutical development. In these studies, medicinal chemists use synthetic strategies to make small alterations in the chemical structure of a drug candidate and then test the new modifications for its biological effects.[1–3] SAR analysis enables the precise determination of key chemical motifs, such as those responsible for on-target binding. Thus, modifications of these key motifs are selected deliberately by medicinal chemists to alter the potency and overall bioavailability of a drug structure until the desired properties are observed.

Expedited access to new chemical analogs is paramount for getting new drug-compounds to market in a timely and cost-effective manner. Thus, SAR studies often rely on pre-installed functionalities or C–H functionalization strategies to install new functionalities on a targeted motif. To illustrate this, key SAR modifications of an anticancer drug, Dabrafenib, are shown in **Figure 3.1**. In 2013, a team of medicinal chemists at GlaxoSmithKline (GSK) were studying a promising drug-candidate that displayed B-Raf kinase inhibition, which slowed cancerous tumor growth.[4] A lead compound showed moderate potency in *in vitro* kinase inhibitory activity against $B\text{-}Raf^{V600E}$; however, the compounds potency inadequate for use as an active drug molecule for

human consumption. The amine motif at the pyrimidine's C2 position caused this insufficient potency. Thus, SAR studies focused on altering the amine group to increase the potency as well as display other desired biological properties. In this campaign, medicinal chemists synthesized twelve amine derivatives from a 2-chloropyrimidine starting material via aromatic substitution reactions (S_NAr) with nucleophilic amines. Alkyl amines provided increased the potency compared to the lead compound. However, a free amine at the C2 position yielded the optimal physicochemical properties and potency. This derivative later became the anti-cancer drug dabrafenib.

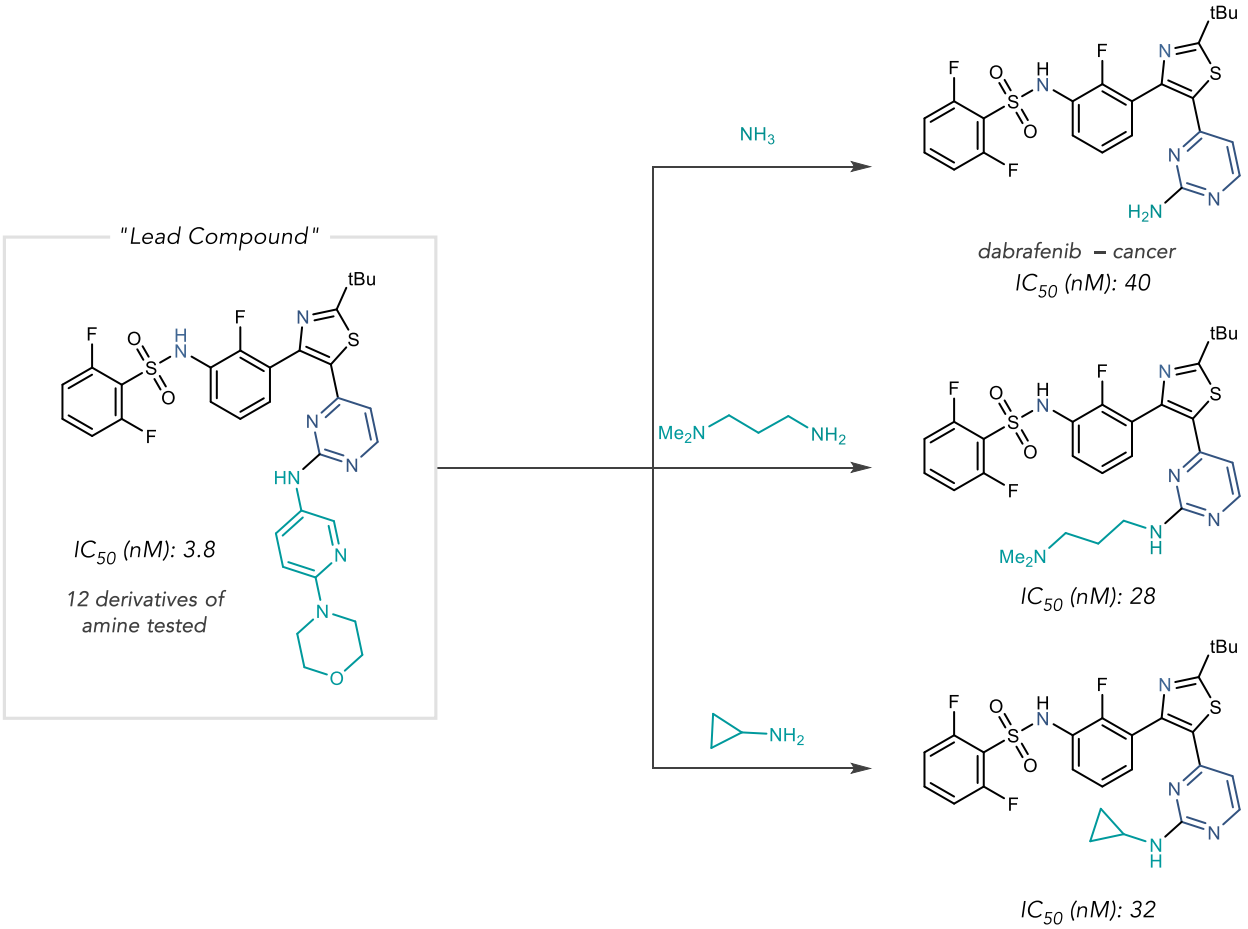

Figure 3.1. Structure-activity relationship studies of a lead compound to anti-cancer drug, dabrafenib.

The discovery of dabrafenib represents an idealized case for SAR studies. The installation of the key pyrimidine C2 chloride occurred late in the synthetic sequence. However, if the S_NAr active chlorine atom was instead installed early in the synthesis, it would likely not survive subsequent synthetic steps. Thus, a plethora of chemical reactions must be available to medicinal chemists that alter a drug-candidates periphery in a limited number steps, especially methods that apply to complex molecular structures. Commonly employed methods in SAR campaigns and emerging methods are discussed in this chapter.

3.2 Introduction to De Novo Nitrogen-Containing Heterocycle Synthesis

3.2.1 Synthesis of Five-Membered Azoles and Diazoles

De novo heterocycle synthesis represents a powerful method in which small chemical fragments, such as amines and carbonyl derivates, combine to form substituted rings. This type of heterocycle synthesis typically forms heterocycle building-blocks in early stages of SAR studies. However, convergent synthesis of drug fragments also uses de novo synthesis.[5] Due to the high reactivity of carbonyl precursors, de novo synthesis is typically unamenable to late-stage diversification. This strategy, however, is commonly employed for the synthesis of various azoles and diazoles, such as pyrroles (indoles), pyrazoles (indazoles), imidazoles (benzimidazoles), isoxazoles (benzoisoxazoles), and isothiazoles (benzoisothiazoles). For the purposes of this section, the benzo-fused heterocycle synthesis (i.e. indole) of various five-membered azoles and diazoles will be omitted as the synthetic strategy is typically similar to the unfused counterpart (i.e. pyrrole).[6]

Classical approaches for de novo five-membered heterocyclic ring synthesis typically rely on condensation reactions between dicarbonyls and amine coupling partners (**Figure 3.2**). For

examples, the Paal-Knoor pyrrole synthesis is a condensation reaction between a 1,3-dicarbonyl and a substituted amine (**Figure 3.2**).[7] In these reactions, the amine reacts with one of the carbonyls to form an imine, which generates water as a by-product. Imine to enamine isomerization occurs and the resulting amine reacts with the other carbonyl. Elimination of water aromatizes the ring and generates the pyrrole product. In similar reactions, 1,3-dicarbonyls combine with hydrazines or hydroxylamines to furnish pyrazoles and isoxazoles as mixtures of two regioisomers (**Figure 3.2**).[8,9] Alternatively, thioketones and thioesters in the presence of ammonium salts yield isothiazoles (**Figure 3.2**).[10]

The Van Leusen imidazole synthesis represents a classical method to synthesize imidazole as shown in **Figure 3.2**.[11] In this strategy, deprotonated tosylmethyl isocyanide (TosMIC) adds to a substituted imine producing an amine anion. The amine anion then cyclizes at the isocyano carbon atom forming a carbanion which is quenched immediately by a proton source. Elimination of the tosyl group completes the reaction mechanism and forms the imidazole product. Modern approaches for five-membered N-heterocycle synthesis builds on the core tenants of classical approaches and often undergo similar mechanistic steps or have similar carbonyl starting materials.

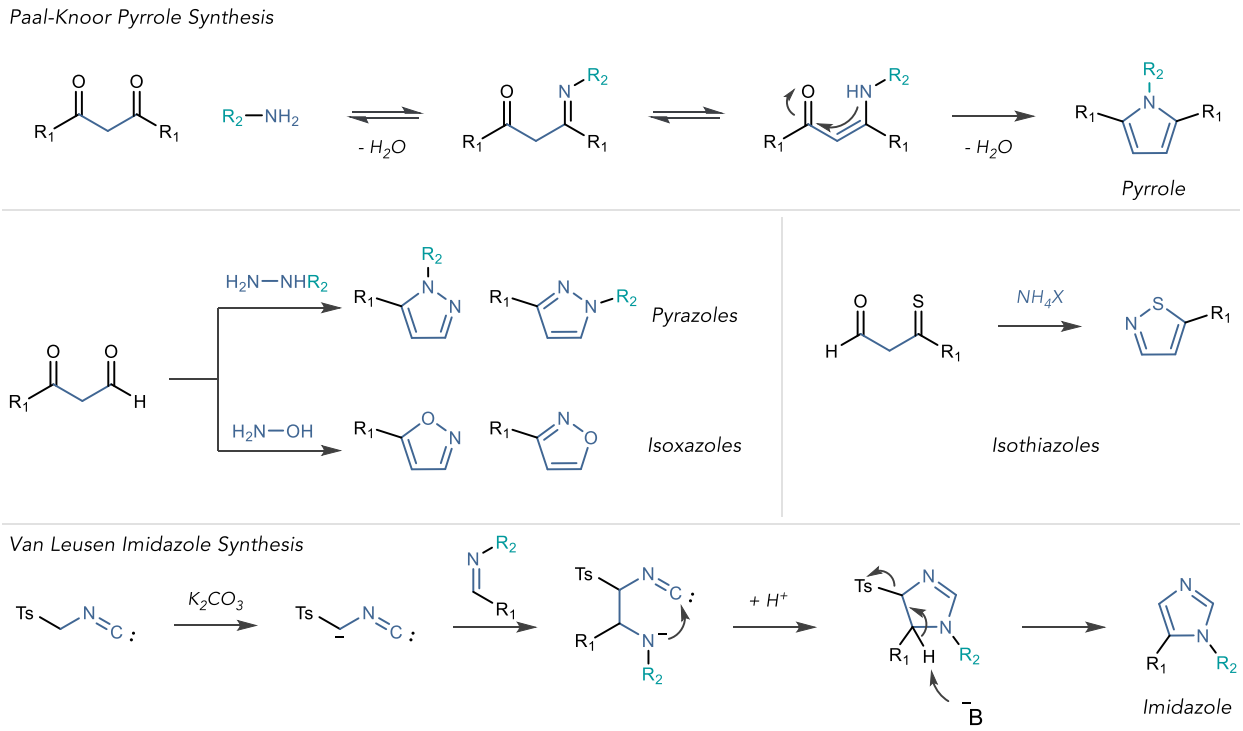

Figure 3.2. Classical approaches for de novo synthesis of five-membered azoles and diazoles

Modern approaches expand the array of coupling partners at the practitioner's disposal to make five-membered heterocycles. For example, alkynes and alkenes also form pyrroles through transition metal catalysis. These cyclization's typically fall into one of three categories: (1) gold-catalyzed, pendant nucleophilic π-acid chemistry, (2) based-induced allene formation and intramolecular cyclization, and (3) transition metal-catalyzed cyclization. In 2005, Toste reported a method for pyrrole synthesis through a gold-catalyzed intermolecular cyclization reaction between an azide and alkyne (**Figure 3.3**).[12] The gold-catalyst acts as a π-acid for the reaction which increases the electrophilicity of the alkyne. This allows the cyclization reaction to occur with the azide nucleophile. Gold-mediated nitrogen extrusion followed by isomerization yields the pyrrole product. Since the initial report, similar methods were developed by Krause and Lipshutz[13], Sugimoto and Tokuyama[14], and Ohno[15]; some of which also apply to isoxazole synthesis.

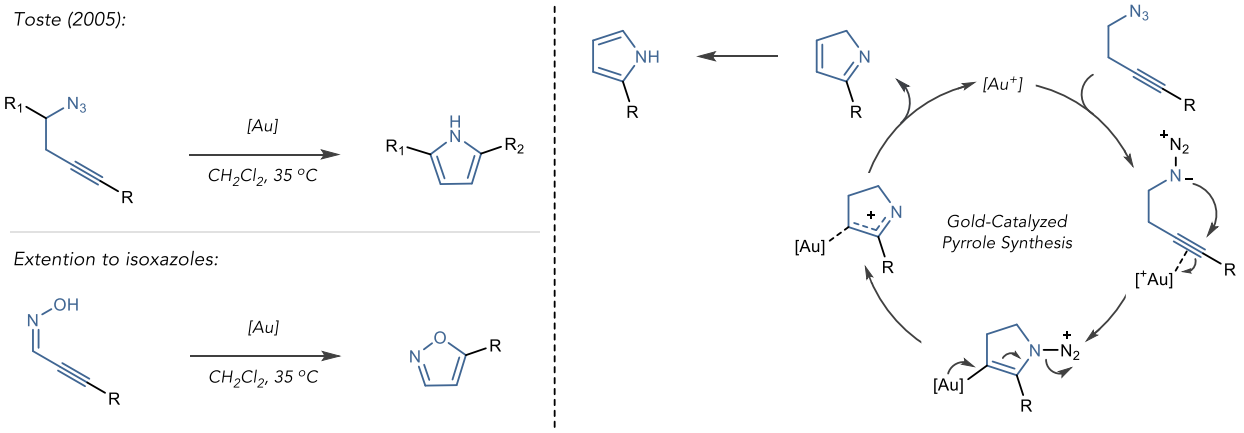

Figure 3.3. π-Acid catalyzed synthesis of pyrroles and isoxazoles

Base or transition metal-induced allene formation and cyclization is another common method for five-membered ring formation. In 2005, Gevorgyan reported a copper-catalyzed pyrrole synthesis of alkynyl imines.[16] In this reaction, the alkyne first undergoes a base-induced propargyl to allenyl isomerization. The copper-catalyst binds to the allene and is attacked by the pendant imine nucleophile forming a Zwitter-ionic species that rearranges to the pyrrole. Again, this reaction platform has received attention by numerous groups including Sakar[17], Fensterbank[18], and Kirsh[19] using gold and silver catalysis.

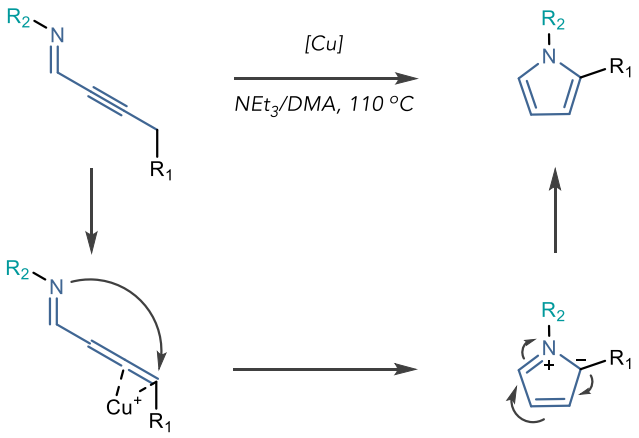

Figure 3.4. Gevorgyan's pyrrole synthesis via allene intermediate

Finally, transition metal-catalyzed cyclization as a de novo synthesis strategy applies to a wide array of five-membered rings. This type of cyclization is used to synthesize pyrroles[20–24], pyrazoles[25–27], isoxazoles[28–30], and isothiazoles.[31] Palladium, ruthenium, rhodium, and copper are common metals that mediate this process. In particular, Grubb's ring-closing metathesis is frequently employed.[32–34] However, a limitation that affects all of these strategies is the starting material must be synthesized prior to the cyclization, which limits the substrate scope to building-block heterocycles.

On the other hand, a majority of modern imidazole-forming reactions use 1,2-dicarbonyls and aldehyde-derived imines in the presence of an ammonium source.[35–38] Mechanistically, these reactions follow similar trends to 1,3-dicarbonyl condensation reactions to produce pyrroles. These reactions also offer more variety in scope compared to other methods due to the wide breadth of carbonyl starting materials available and proceed under mild conditions.

3.2.2 Synthesis of Six-Membered Azines and Diazines

Much like five-membered ring systems, de novo synthesis is employed to synthesize six-membered azines and diazines (**Figure 3.5**). Instead of using 1,3-dicarbonyl logic to synthesize the carbon framework, 1,5-dicarbonyl surrogates serve as de novo building-blocks. For example, the Bohlmann-Rahtz pyridine synthesis combines enamines with ethynylketones to produce trisubstituted pyridines.[39] In this reaction, the enamine adds to the terminal end of the ethnylketone through a Micheal-addition. Subsequent proton transfer yields the 1,5-dicarbonyl surrogate. At elevated temperatures, *Z/E* isomerization occurs and the amine adds to the carbonyl. Liberation of water aromatizes the ring and releases the pyridine product. Similarly, 1,3-dicarbonyls combine with substituted amidines to produce substituted pyrimidines.[40] Synthetic methods that produce pyridazines and pyrazines as a single regioisomer are more scarce compared to pyridines

and pyrimidines and typically use condensation reactions with uncommon starting materials[26,41,42] or Diels-Alder cyclization with tetrazines.[43] Using de novo synthesis to form six-membered ring systems is often less employed than forming five-membered ring systems. Instead, functionalization of existing six-membered rings is much more common due to the high commercial availability of azine and diazine starting materials and plethora of reactions available to functionalize these ring systems.[44]

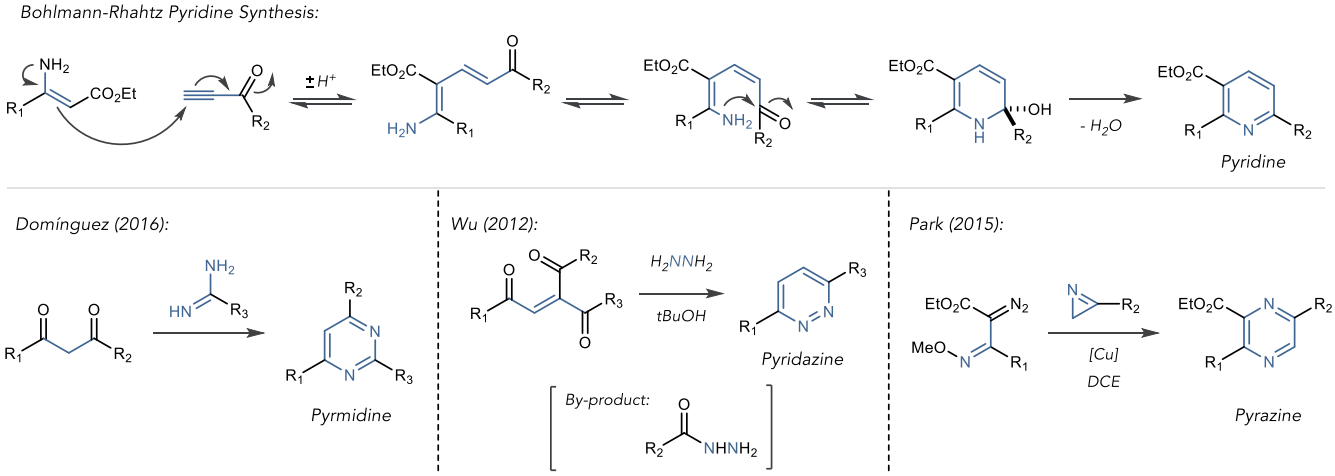

Figure 3.5. De novo synthesis of six-membered azines and diazines

3.3 Emerging Methods for Molecular Editing of Heteroaromatics

3.3.1 Carbon-Atom Ring-Expansion

Molecular editing, first coined by Campos in 2019[45], is described as "the insertion, deletion, or exchange of atoms in highly functionalized compounds at will and in a highly specific fashion" and represents an attractive, emerging strategy for potential SAR diversification. These editing strategies typically fall into one of three categories: (1) single-atom ring-expansion, (2) single-atom ring-contraction, and (3) single-atom exchange. Modern approaches to molecular

editing are also described as “skeletal editing”, which was coined by a landmark report by Levin in 2021.[46]

Contemporary methods for single-carbon ring-expansion strategies draw inspiration from the Ciamician-Dennstedt reaction, first published in 1881 (**Figure 3.6**).[47] In this reaction, a pyrrole nucleophile undergoes a single-carbon ring-expansion in the presence of sodium hydroxide and chloroform. Sodium hydroxide initiates dichlorocarbene formation upon deprotonation. The carbene adds to the aromatic ring producing a cyclopropane intermediate. Finally, the lone-pair on the nitrogen atom causes the ring-expansion to occur producing a 3-chloropyridine product from the corresponding pyrrole. A modified procedure using sodium trichloroacetate as the dichlorocarbene precursor synthesized lycodine upon tert-butoxycarbonyl (-Boc) deprotection and dehalogenation (**Figure 3.6**).[48] Similarly, rhodium-carbenes, also known as carbenoids, derived from halodiazoacetates participate in ring-expansion through a mechanism similar to the Ciamician-Dennstedt reaction (**Figure 3.6**). An electron-withdrawing substituent is necessary on the halodiazo starting material, which installs an ester at the 3-position of the quinoline product rather than a halogen. This strategy was applied in the synthesis of norfloxacin by Bonge-Hansen in 2019.[49]

A major advancement by Levin allows practitioners to install certain substituents of choice, such as benzenes and pyridines, onto pyrrole and indole frameworks (**Figure 3.6**).[50] Substituted amidines serve as the precursor for chlorodiazerines. Carbene generation from the chlorodiazerine is thermally promoted with loss of nitrogen gas. The carbene then adds to the pyrrole or indole and a mechanism similar to the Ciamician-Dennstedt reaction installs aryl groups onto the quinoline or pyridine product. The regioselectivity of carbene addition is sterically controlled; thus, atom insertion occurs adjacent to small substituents on the carbon framework. However,

atom insertion is guided adjacent to H-bond donors when one is present on the molecule even when these groups are more sterically encumbed. In 2022, Levin expanded this strategy to pyrazoles and indazoles to produce pyrimidines and quinazolines, respectively (**Figure 3.6**).[51] Unlike pyrroles and indoles, this reaction undergoes a distinct mechanism compared to the Ciamician-Dennstedt reaction. Instead of cyclopropantion, the carbene adds to the pyrazole nitrogen atom which produces a Zwitter-ionic species. This species undergoes electrocyclic ring-opening producing a diazahexatriene intermediate. A 6π-electrocyclic ring-closure liberates chloride and forms the protonated pyrimidine product. Unlike other methods, these strategies are amenable to complex structures.

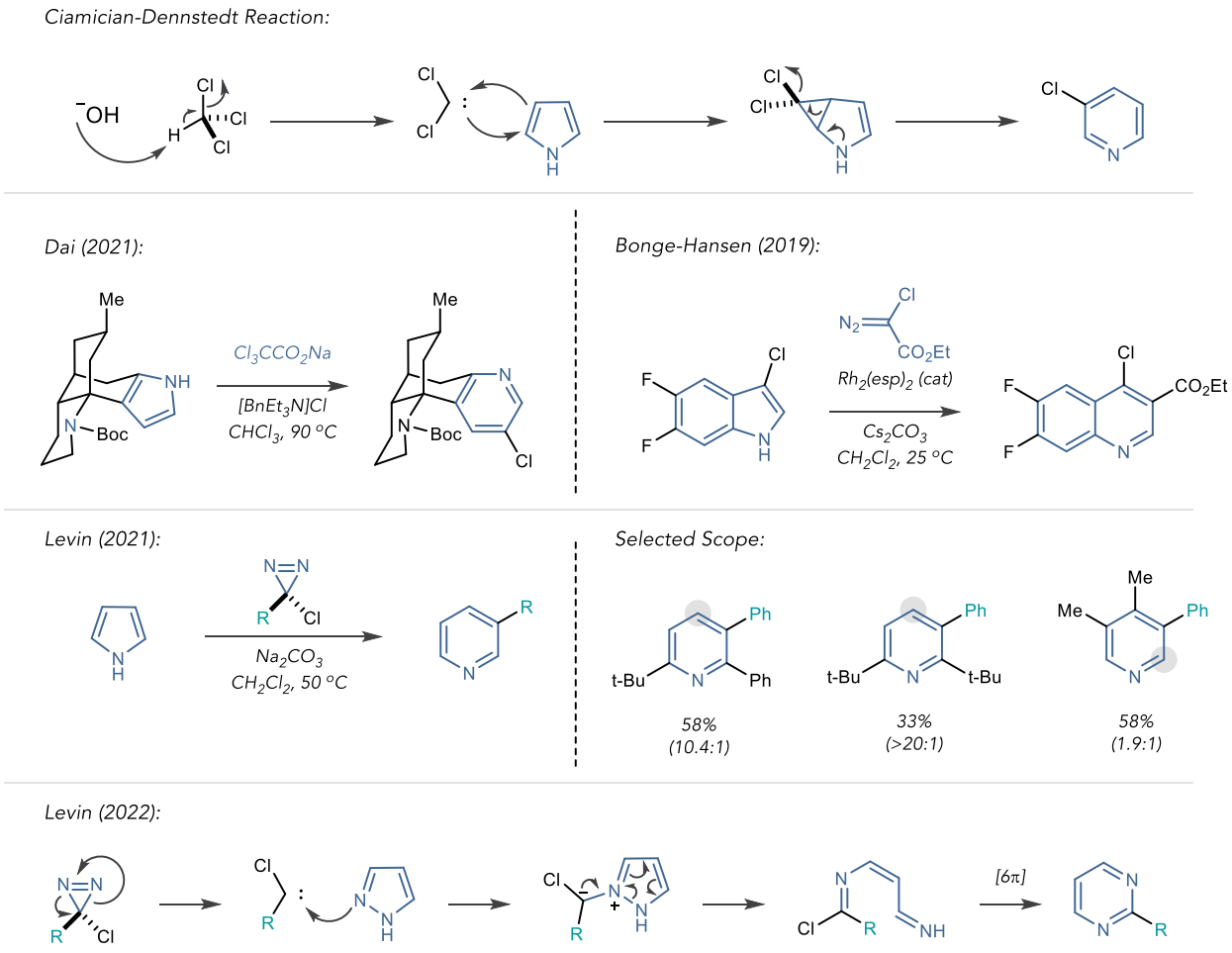

Figure 3.6. Strategies for carbon-atom ring-expansion.

3.3.2 Nitrogen-Atom Ring-Expansion

Rather than using a carbene or carbene surrogate to install a single carbon atom, nitrenes or nitrene surrogates install a single nitrogen atom. In 1987, Kumar showed this strategy is viable using N-aminophtamlimide in the presence of lead(IV) acetate to convert indoles into quinazolines (**Figure 3.7**).[52] In this procedure, N-acetoxyaminophthamlimide is generated in situ, which serves as the nitrene surrogate.[53] An aziridination step, reminiscent of the cyclopropanation mentioned above, occurs and a similar rearrangement yields the quinazoline product upon

deprotection of the intermediate. A more general approach that follows this synthetic strategy was developed by Morandi in 2022 (**Figure 3.7**).[54] This reaction uses an in situ generated iodonitrene to perform the aziridination step, which is formed from ammonium carbamate and (bis(trifluoroacetoxy)iodo)benzene (PIFA). Unlike the Kumar report, this method applies to late-stage compounds, although silyl protecting group on the indole starting material is necessary for the desired reactivity.

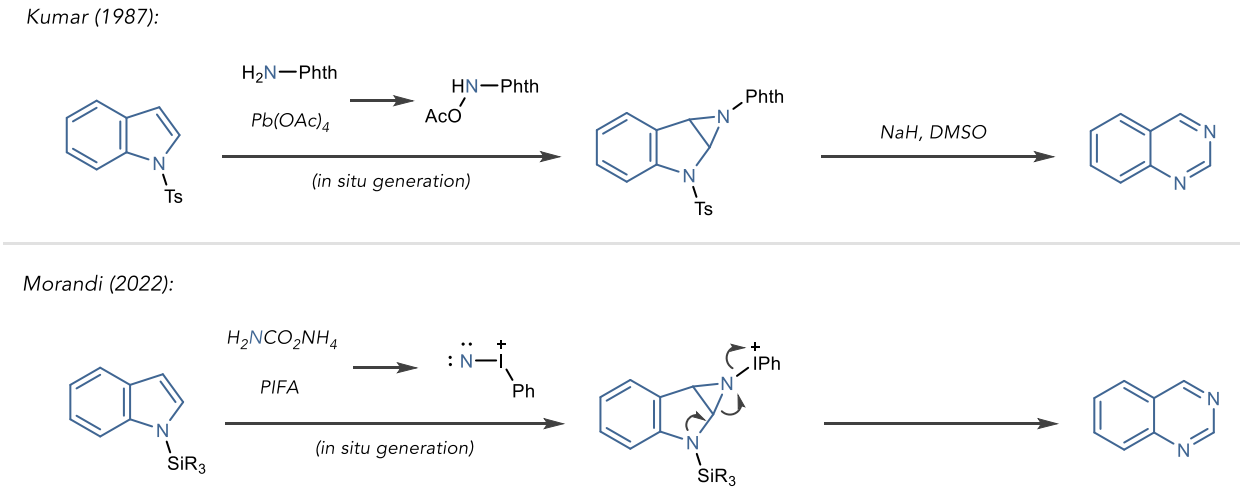

Figure 3.7. Strategies for nitrogen-atom ring-expansion.

3.3.3 Heterocycle Ring-Contraction

Another emerging method for molecular editing is ring-contraction reactions. In these reactions, rather than adding a single-atom to the heterocyclic framework, a single-atom is instead removed, known as atom deletion. Much like atom insertion, carbon atoms are usually targeted for deletion.

In terms of carbon deletion, *N*-oxide or *N*-amides are common precursors for carbon deletion, which was pioneered by Kaneko and Tscuchiya in the early 1980's (**Figure 3.8**).[55,56] In

these reactions, benzoxaepines or benzodiazepines are generated from the quinoline *N*-oxide or *N*-amide with high energy light. Either basic or acidic conditions trigger ring-opening. The ring-opened intermediate then undergoes ring-closure to the corresponding indazole product. Inspired by these reports, Levin developed a method for ring-contraction of quinoline *N*-oxides to indazoles that applies to late-stage compounds (**Figure 3.8**).[46] Much like Kaneko's report, the *N*-oxide starting material generates a benzoxaepine intermediate, which undergoes ring-opening under acidic conditions. The resulting amide attacks the carbon atom of the newly formed aldehyde and aromatizes to produce the carbon-deleted product. A mechanistically distinct method for carbon deletion of pyrimidines to pyrazoles was also reported in 2022 (**Figure 3.8**).[57] Following an initial report of *N*-Tf pyridinium and pyrimidinium ring-opening by McNally in the same year,[58] Sarpong found that *N*-Tf pyridinium salts undergo ring-opening in the presence of hydrazine nucleophiles producing an aza-Zincke intermediate. Tautomerization and ring-closure selectively produces the pyrazole framework. Finally, aromatization and amidine expulsion affords the pyrazole product. Like Levin's report, this method also applies to late-stage compounds.

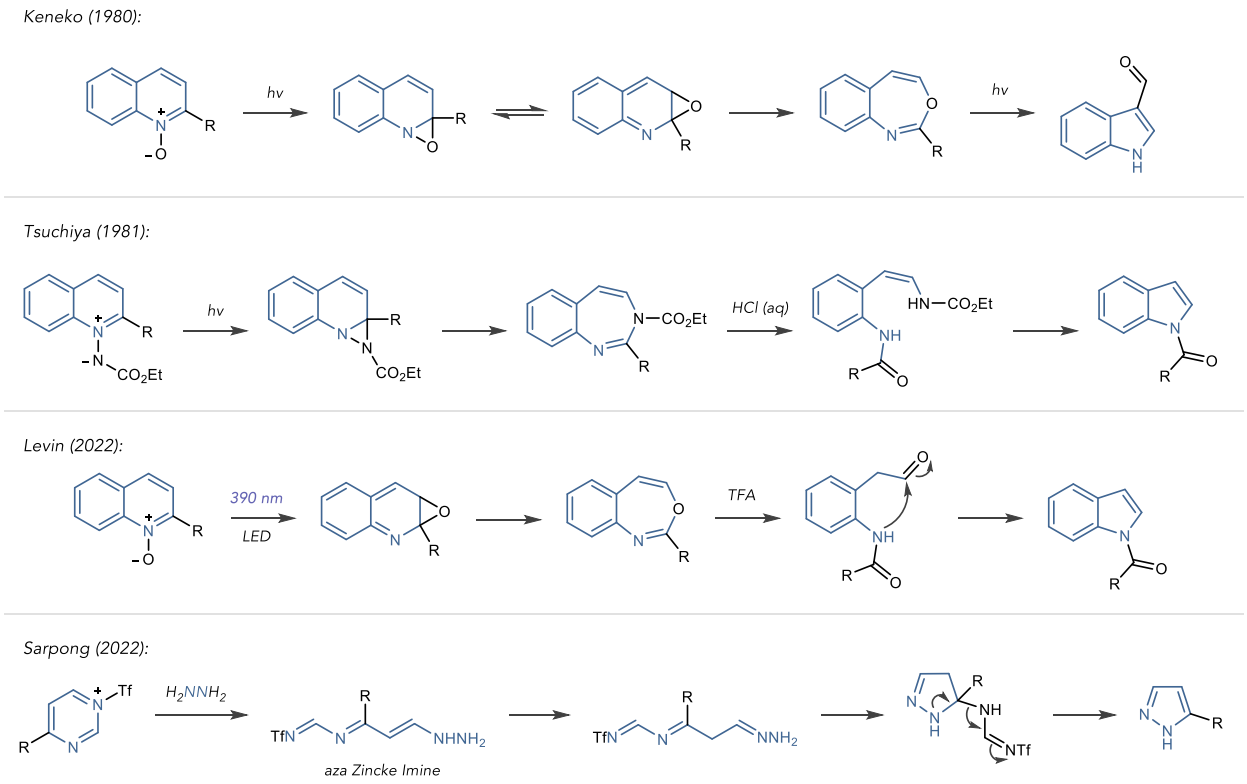

Figure 3.8. Strategies for heterocyclic ring-contraction

3.3.4 Single-Atom Exchange Strategies

Single-atom exchange describes the process in which an atom is replaced with a different atom without a ring-contraction or expansion occurring. Levin and Burns independently reported an aryl azide to pyridine transformation in which a carbon atom is replaced with a nitrogen atom within in the aromatic ring (**Figure 3.9**).[59,60] Both reaction platforms are initiated by photolysis of the aryl azide. This generates a nitrene intermediate that inserts into the benzene π-system and forms an azirine intermediate. Then, a thermally initiated 6π electrocyclic ring opening forms a cyclic ketenimine, which is subsequently attacked by an amine nucleophile. Tautomerization generates a stable 2-aminoazepine. From this step, the two mechanisms differ. In the Levin case,

2-aminoazepine is oxidized by an electrophilic brominating reagent and the alcohol on the 2-amino group forms a spirocycle. Thermal rearrangement aromatizes the ring and extrudes a carbene thus forming the pyridine product. In the Burns report, the 2-aminoazepine undergoes a [4+2] cycloaddition with singlet oxygen yielding a peroxy-bridged intermediate. Subsequent ring-opening yields an exocyclic peroxide that undergoes a 6π electrocyclization. This forms a Wheland intermediate transforms the product upon deformylation. In this case, a 2-amino group is installed on the pyridine product. These two reports also differ in the regioselectivity of the deletion. The Levin report undergoes *ipso* deletion while the Burns report undergoes *meta* deletion.[61] In a related report, Levin shows a carbon atom swaps with a nitrogen atom under oxidative conditions (**Figure 3.9**). The reaction occurs through a similar mechanism described in **Section 3.2.3** to form the benzoxaepine intermediate, which is subsequently oxidized. A nitrogen source is introduced and ring-closure occurs to form the quinazoline product. Finally, Morofuji and Kano described a nitrogen to carbon replacement of pyridines to anilines (**Figure 3.9**).[62] This reaction goes through Zincke activation and ring-opening with an amine. A nucleophilic methylene source is introduced which promotes ring-closure to the aniline product. A related report by Mindiola uses titanium metal to convert pyridines to substituted benzenes.[63]

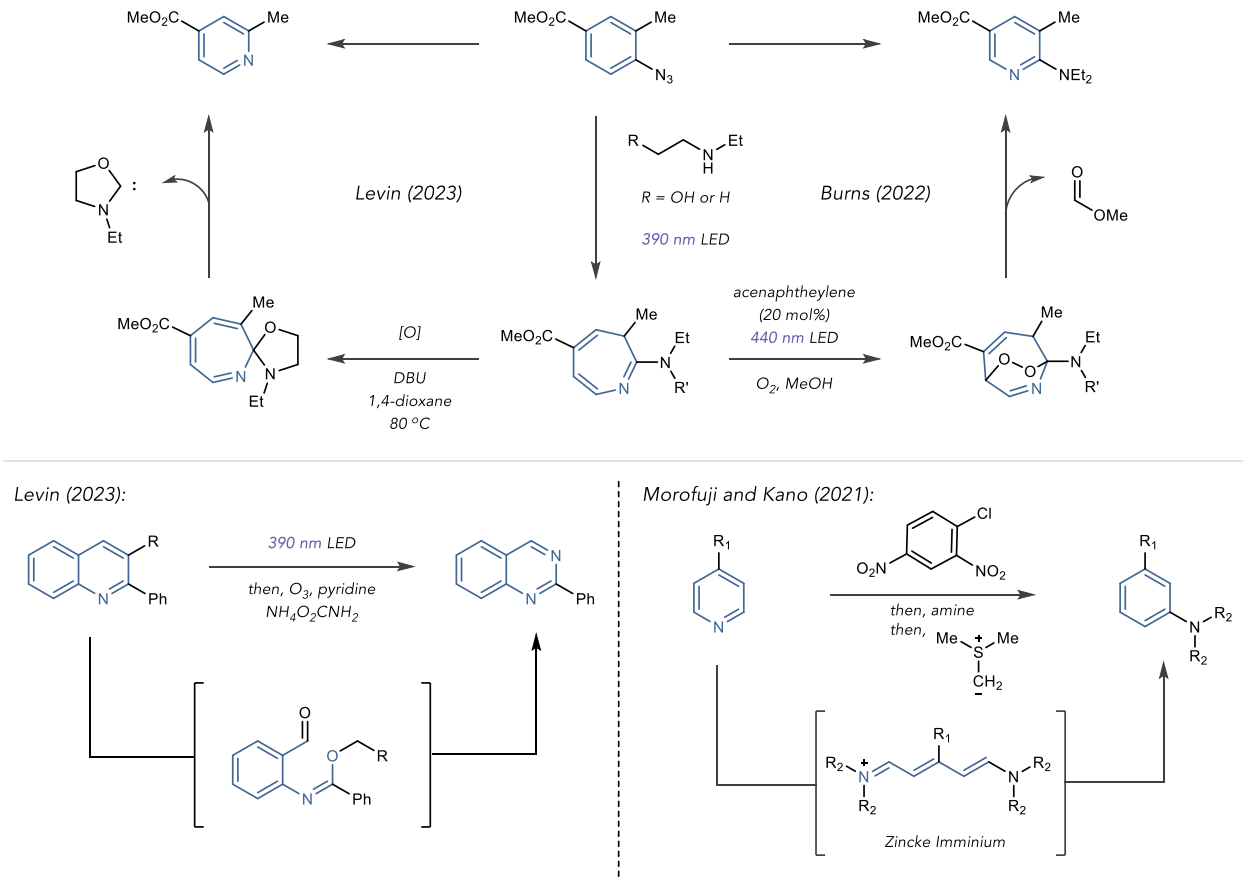

Figure 3.9. Strategies for heterocyclic single-atom replacement

3.4 Conclusion

This chapter serves as an introduction to SAR studies and outlines classical and modern approaches for diversification. Classical approaches for SAR diversification rely on de novo synthesis. Methods to build five- and six-membered nitrogen-containing heterocycles are discussed, as well as limitations. Molecular editing strategies represent a powerful, emerging strategy for potential SAR diversification. Three editing strategies are discussed including single-atom ring-expansion, single-atom ring-contraction, and single-atom exchange.

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CHAPTER FOUR

A DECONSTRUCTION-RECONSTRUCTION STRATEGY FOR PYRIMIDINE DIVERSIFICATION

4.1 Introduction to Pyrimidine Deconstruction-Reconstruction

Despite the growing reports of molecular editing strategies, methods in which a diverse set of products can be reached from a single intermediate or precursor remain elusive. This type of strategy would be useful in structure-activity relationship (SAR) studies as it allows for rapid library generation of a lead compound. As described in **Section 3.2**, current strategies for molecular editing typically change a single atom and generate a single class of heterocycles. We considered an alternate strategy in which we deconstruct a heterocyclic starting material into a versatile heterocycle building-block late into a synthetic campaign, such as a 1,3-dicarbonyl surrogate (**Figure 4.1**). The resulting intermediate then undergoes condensation reactions, such as those employed in de novo heterocycle synthesis, to reconstruct the intermediate into a variety of heterocyclic products.

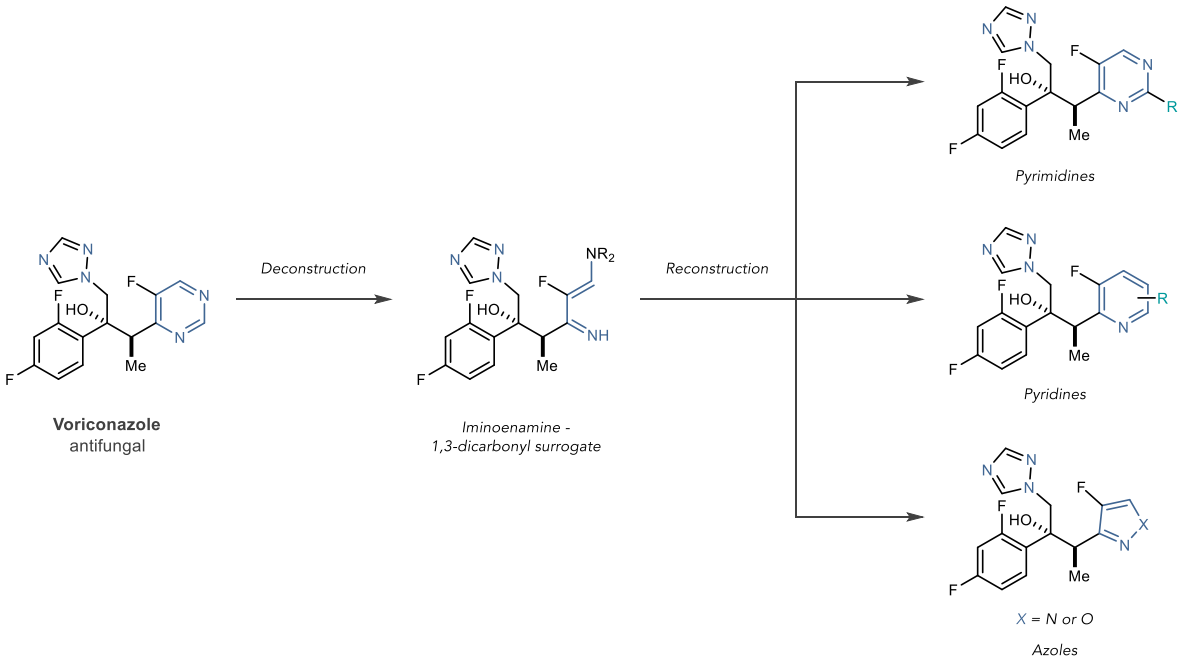


Figure 4.1. A deconstruction-reconstruction strategy for heterocyclic diversification

While studying ring-opening reactions of *N*-Tf pyrimidiniums with an aniline nucleophile, we observed an unusual result. Instead of the expected ring-opened aza-Zincke imine,[1,2] we observed rapid ring-closure to an *N*-aryl pyrimidinium salt in near quantitative yield in the case of 4-phenyl pyrimidine (**Figure 4.2**). We hypothesized the *N*-aryl pyrimindium is susceptible to C2 carbon cleavage with an ideal nucleophile. Indeed, implementing piperidine as the nucleophile in an ethanolic solution obtained an iminoenamine intermediate in 85% yield with 13% yield of a vinamidinium salt by ^{1}H NMR. We hypothesized the 1,3-dicarbonyl surrogate could successfully be recombined with amidines to produce C2-functionalized pyrimidines and hydrazines and hydroxylamines to produce pyrazoles and isoxazoles, respectively. In addition, we reasoned that addition of enolate nucleophiles could generate a 1,5-dicarbonyl surrogate in situ, which is used to produce pyridine products.

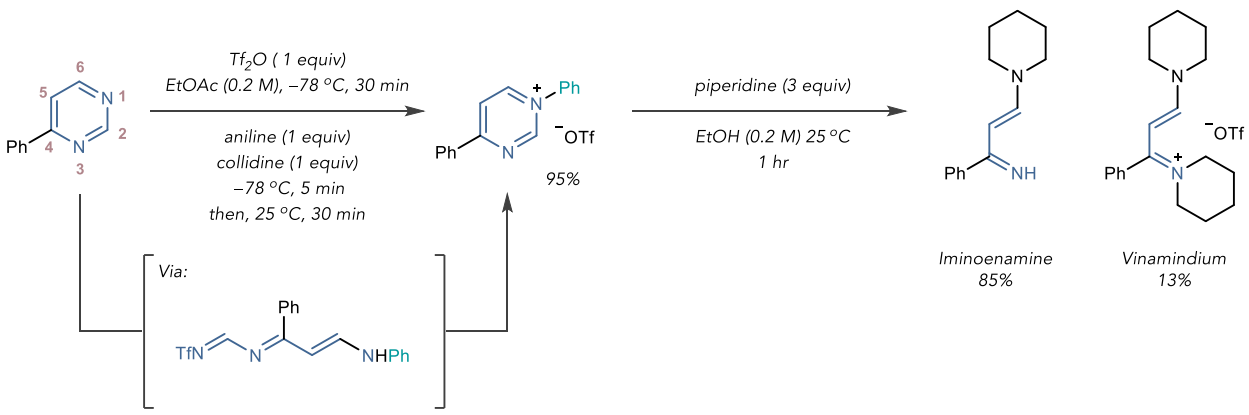


Figure 4.2. *N*-Aryl pyrimidinium formation and C2 carbon cleavage with piperidine.

4.2 Selected Scope of *N*-Aryl Pyrimidinium Formation

With these goals in mind, we first began our investigation of the substrate scope of *N*-aryl pyrimidinium formation. Selected examples are shown in **Figure 4.3**. In terms of monosubstituted building blocks, we were delighted to see that changing the identity of the aryl group at the C4 position to an indole-based fragment yielded the desired *N*-aryl pyrimidinium salt in 73% (**49**). In addition, the electronics at this position could be altered greatly where an electron-rich methoxy group (**50**) is converted to the product in 63% yield. An electron-deficient amide (**51**) also cleanly afforded the product using a modified procedure with 2,4,6-trimethylaniline. Di-substituted pyrimidines are also amenable (**52** & **54**). Lewis basic nitrogen atoms do not hinder reactivity of the *N*-aryl pyrimidinium salt formation as shown with **52** where the pyridine competes with the pyrimidine for trifylation. In addition, fused heterocycles (**53**) effectively undergo the ring-opening-ring-closing procedure.

In addition to simple pyrimidine building-blocks, complex pyrimidines also convert to the desired product (**54-58**). The reaction is tolerant of various functional groups often found in medicinal chemistry synthetic campaigns, such as benzylated amides (**55**), sulphonamides (**58**),

aryl halides (**55**, **56**, & **58**), and other heterocycles (**56** & **58**). Compound **57** represents a steroid derivative synthesized from pregnenolone, which cleanly converts to the product without undesired epimerization. In addition, compound **58** is a precursor to an anti-cancer drug, Dabrafenib, which shows *N*-aryl pyrimidinium formation occurs on late-stage compounds. Additional examples are shown in **Appendix A2.2**.[3]

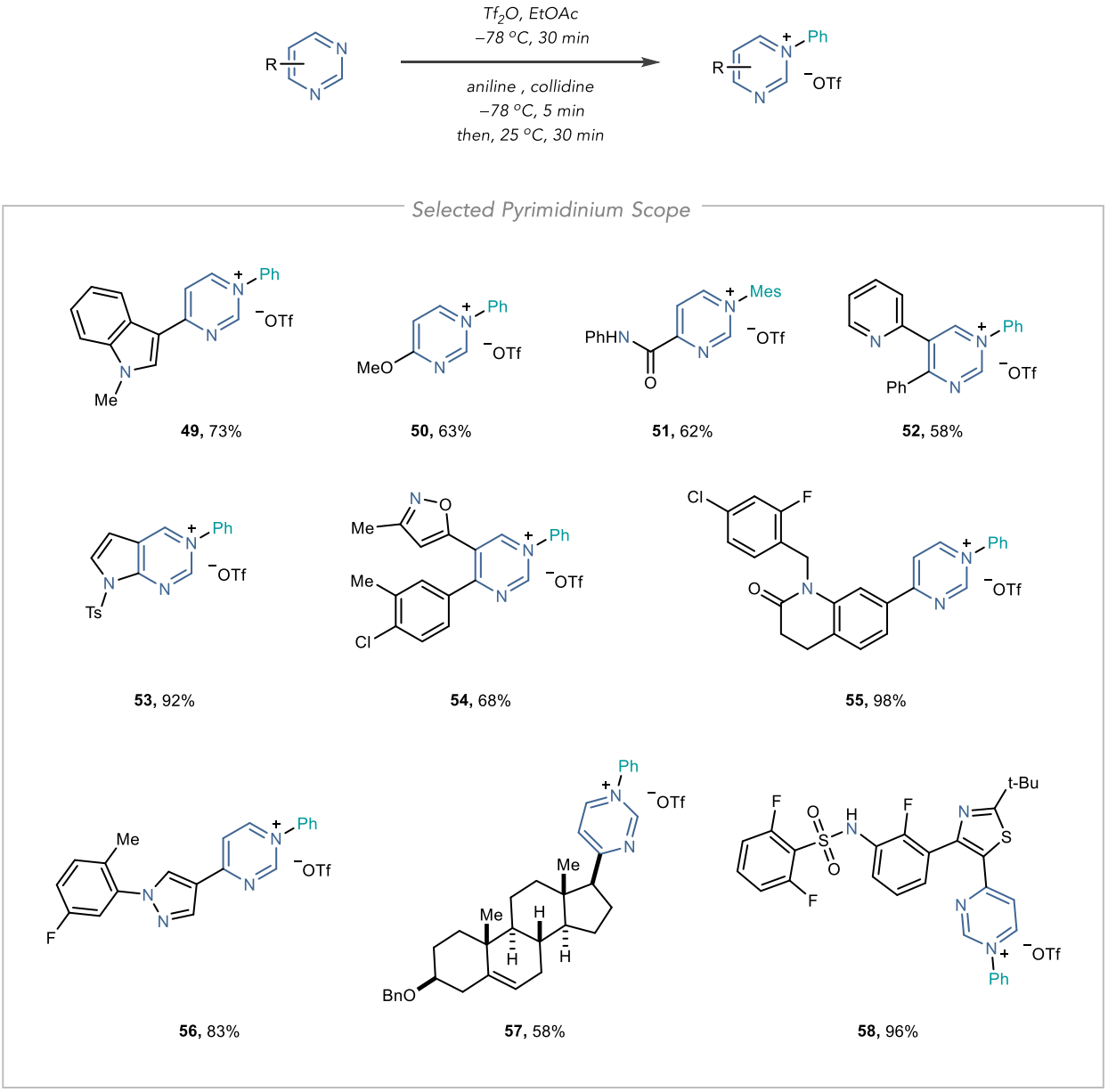
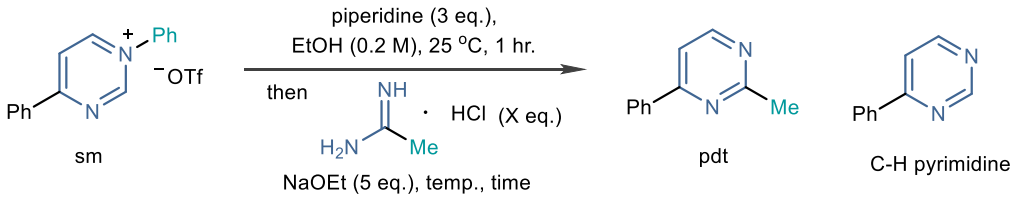


Figure 4.3. Selected scope of *N*-aryl pyrimidinium formation.

4.3 C2-Functionalization of Pyrimidines via Deconstruction/Reconstruction

Having established *N*-aryl pyrimidinium formation and cleavage using piperidine as the nucleophile, we next investigated the reconstruction phase of the reaction to produce C2-functionalized pyrimidines (**Table 4.1**). De novo synthesis commonly employs amidines with 1,3-dicarbonyls under basic conditions to form functionalized pyrimidines.[4] Thus, we began our investigation of the deconstruction/reconstruction process using 4-phenyl pyrimidinium triflate as our model substrate, and acetamidine hydrochloride as our amidine coupling partner with five equivalents of sodium ethoxide as a base in ethanol. Using one and a half equivalents of the amidine coupling partner at 90 ºC yielded 32% of the desired C2-methylated product (entry 1). Increasing the amidine equivalents to three improved the yield to 72% and are optimal for the recombination step (entry 2). A large excess of the amidine coupling partner lowers the yield to 65% and increases the amount of undesired C–H pyrimidine compared to three equivalences (entry 3). In addition, lowering the temperature and reaction time also negatively affects conversation to the C2-functionalized product (entries 4-7).

Table 4.1. Optimization of C2-functionalization of pyrimidines. Yields determined by ^{1}H NMR using mesitylene as internal standard.

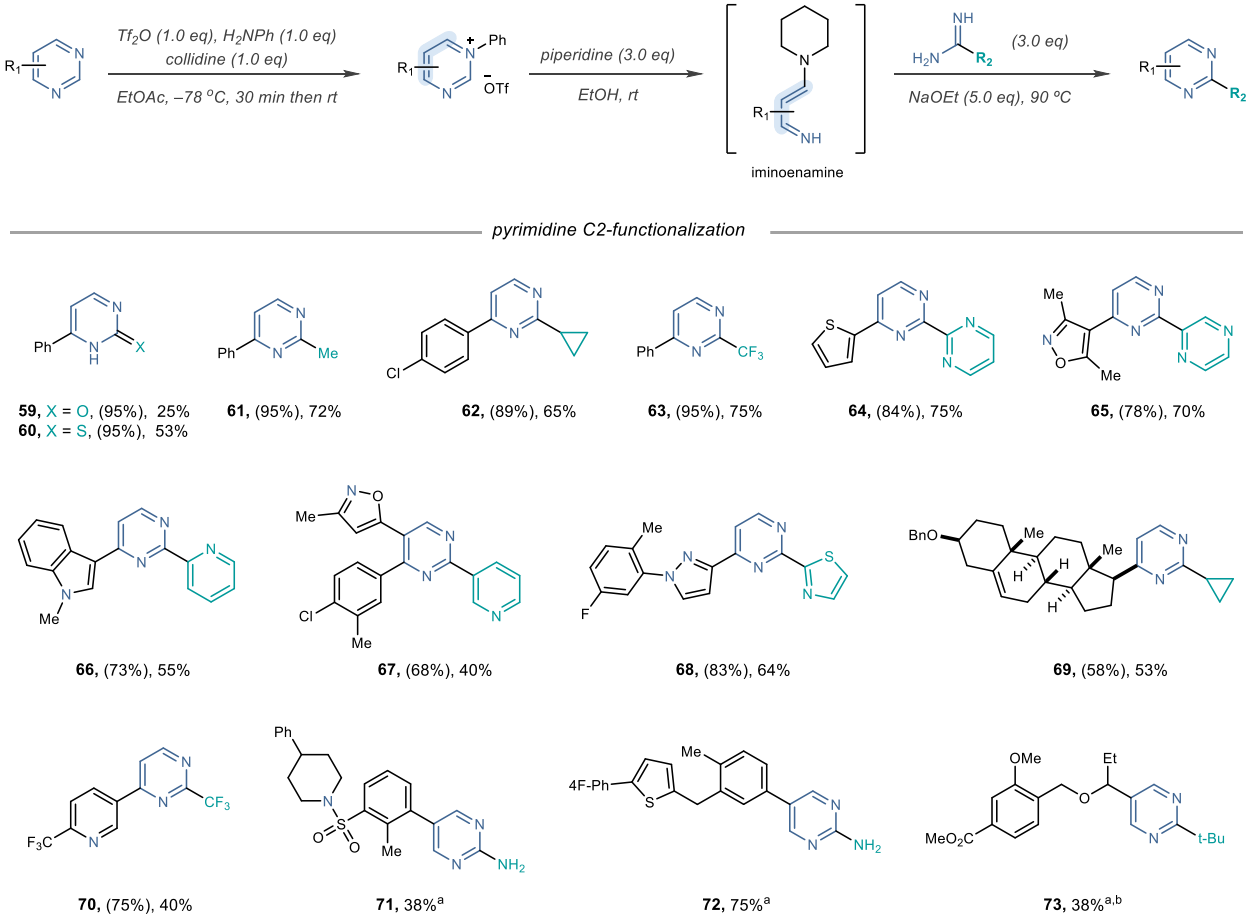


entry	amidine equiv	temperature (°C)	time (hr.)	C-H pyrimidine	pdt
1	1.5	90	18	03	32
2	3	90	18	06	72
3	5	90	18	16	65
4	3	50	18	05	38
5	3	70	18	05	54
6	3	90	1	04	38
7	3	90	5	04	51

With our optimized conditions in hand, we next examined the substrate and amidine scope for the C2-functionalization of pyrimidines (**Figure 4.4**). Urea (**59**), thiourea (**60**), and guanidine (**71** & **72**) serve as compatible amidine coupling partners for heterocycle recombination allowing for the installation of heteroatoms at the C2 position without a pre-installed functional group. In addition, cyclopropyl groups are readily installed in a single step in 65% yield in the case of **62** which typically required multiple synthetic steps to install. Deficient amidine coupling partners are also amenable, enabling a net trifluoromethylation reaction at the C2 carbon (**63**). Aromatic substituted amidines install heterocycles at C2 without relying on a pre-installed halide. Compound **64** represents a challenging C2-C2 pyrimidine coupling that typically cannot be reached using transition metal catalysis. The deconstruction/reconstruction strategy also allows for pyrazine (**65**), pyridine (**66** & **67**), and thiazole (**68**) installation. In terms of pyrimidines, simple (**59-66**) and complex (**67-73**) pyrimidines effectively undergo C2-functionalization.

Although C5-substituted pyrimidinium salts cannot be isolated, this substitution pattern undergoes C2-functionalization under a modified set of conditions using 4-nitroaniline and an

excess of the amidine coupling partner (**71-73**). Again, functionalities typically encountered in drug-discovery campaigns are also well tolerated including other heteroaromatics (**66-68**, **70** & **72**), aryl halides (**67** & **68**), esters (**73**), sulphonamides (**71**), stereocenters (**69**), and ethers (**73**) without undesired reactivity. More examples are shown in **Appendix A2.2**.



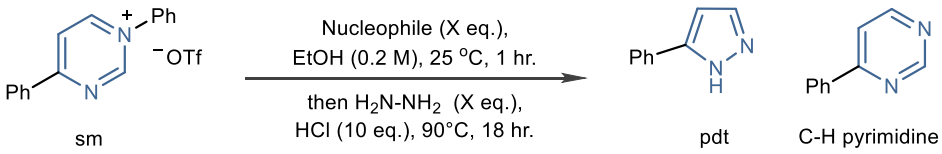
[a] one-pot procedure: 4-nitroaniline used instead of aniline. Then, solvent was exchanged for EtOH. In ring-closing step 10-20 equiv amidine were used.
[b] NaOMe and MeOH used instead of NaOEt and EtOH

Figure 4.4. Selected scope of C2-functionalized pyrimidines. Yields in parenthesis yields of *N*-aryl pyrimidinium formation.

4.4 Pyrimidine Ring-Contraction via Deconstruction/Reconstruction

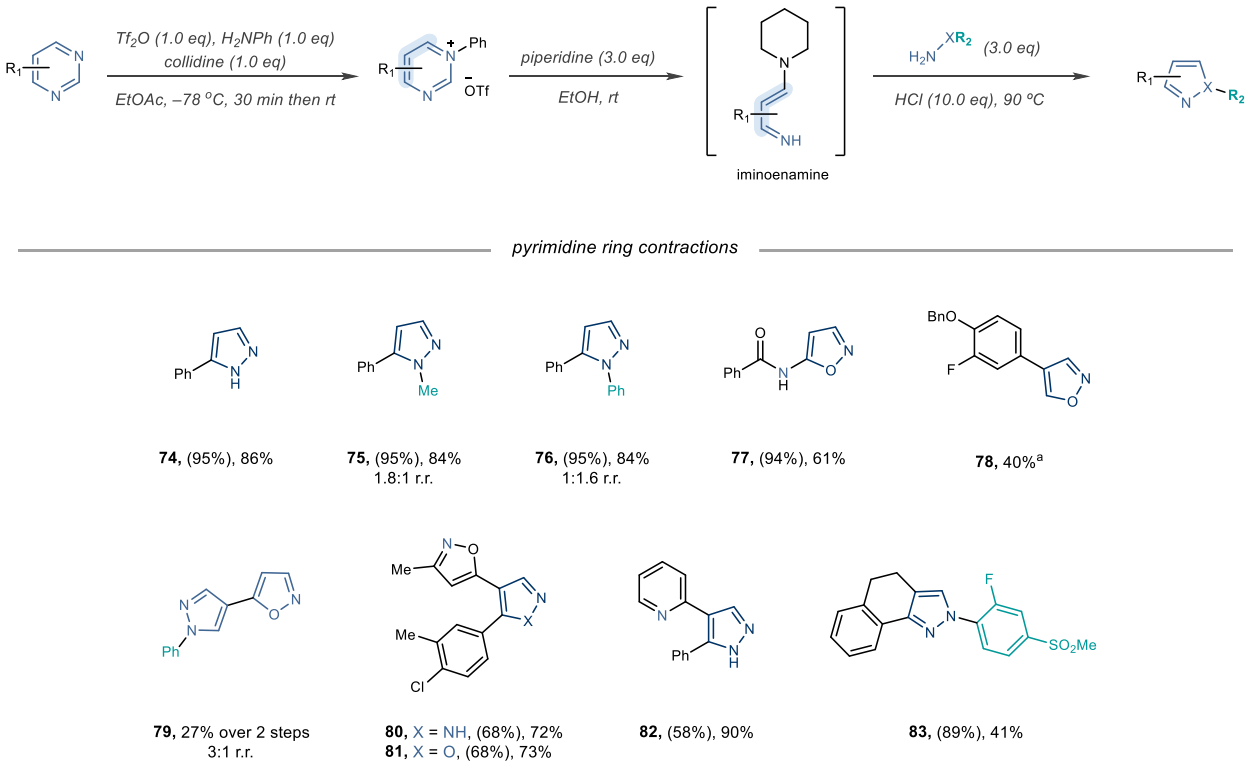
Since the iminoenamine intermediate serves as a 1,3-dicarbonyl surrogate, we hypothesized other heterocycles could be accessed from this intermediate that are typically synthesized from 1,3-dicarbonyls. Azoles, such as pyrazole and isoxazole, fit this criterion.[5,6] Thus, we began our investigation of the deconstruction/reconstruction process using 4-phenyl pyrimidinium triflate as our model substrate and hydrazine as the recombination nucleophile under acidic conditions (**Table 4.2**). Using sodium hydroxide as the nucleophile and three equivalents of the hydrazine nucleophile generated the desired pyrazole product in 83% yield (entry 1). Increasing the equivalents of sodium hydroxide and hydrazine increased the yield of the reaction (entries 2-4). However, some functional groups, such as esters, are sensitive to sodium hydroxide and could undergo undesired reactivity. To increase the functional group tolerance, piperidine was employed as the cleavage nucleophile and gave similar yields to the sodium hydroxide nucleophile (entries 5 & 6). Optimal conditions are presented in entry 5. In addition, hydroxylamine gives similar yields to the hydrazine product to form isoxazole products.

Table 4.2. Optimization of pyrimidines ring-contraction to pyrazoles. Yields determined by ^{1}H NMR using mesitylene as internal standard.



entry	nucleophile ID	nucleophile equiv	hydrazine equiv	C-H pyrimidine	pdt
1	NaOH	3	3	n.d.	83
2	NaOH	5	3	n.d.	88
3	NaOH	3	5	n.d.	92
4	NaOH	5	5	n.d.	87
5	piperidine	3	3	01	92
6	piperidine	3	5	01	88

We next examined the substrate scope for the ring-contraction process to yield pyrazoles and isoxazoles (**Figure 4.5**). Unsubstituted alkyl and aryl substituted hydrazines are amenable coupling partners to produce N–H, N–alkyl, and N–aryl substituted pyrazoles (**74-76**). Like typical de novo synthesis,[5] a mixture of regioisomers form when implementing substituted hydrazines. In addition, electron-withdrawing groups at the C4-position readily convert to the 1,2-isoxazole product (**76**). C5-substituted pyrimidines undergo ring-contraction as well using a modified, one-pot procedure (**77**). Compound **79** shows that a bipyrimidine starting material undergoes two consecutive ring-contractions to synthesize a biazole product with precise regiocontrol throughout the cleavages and recombination steps. Complex pyrimidines also convert to pyrazoles and isoxazoles (**80-83**). Compounds **80** and **81** show two different azole products are produced from a single starting material simply by changing the identity of the nucleophile. In addition, compound **83** shows complex hydrazines install N-substituents on pyrazole products in a single step.



[a] one-pot procedure: 4-nitroaniline used instead of aniline. Then, solvent was exchanged for EtOH. In ring-closing step 10-20 equiv hydroxylamine used

Figure 4.5. Scope of pyrimidine ring-contraction to pyrazoles and isoxazoles. Yields in parentheses yields of *N*-aryl pyrimidinium formation.

4.5 Formal N-Atom to C-Atom Replacement Converting Pyrimidines to Pyridines

Next, we leveraged our ability to form vinamidinium salts to transform pyrimidines into pyridines using our deconstruction-reconstruction approach. As mentioned in **Section 4.1**, when preforming the ring-cleavage with piperidine, a mixture of two products form; the iminoenamine and a vinamidinium salt. Using six equivalents of a pyrrolidine nucleophile for the cleavage favors formation of the vinamidinum salt in 97% yield in the case of 4-phenyl pyridine. Previous reports have shown these vinamidnium salts combine with ketone derived enolates to form a 1,5-dicarbonyl surrogate in situ.[7] Subsequent tautomerization and cyclization with ammonium salts form the pyridine product. We hypothesized an acyl silane derived enolate would undergo similar

reactivity to ketone derived enolates and perform a formal N- to C-atom replacement upon cleavage of the silyl group (**Figure 4.6**). This procedure, if successful, would transform pyrimidines to pyridines via single-atom replacement, which would be a useful maneuver in SAR campaigns.

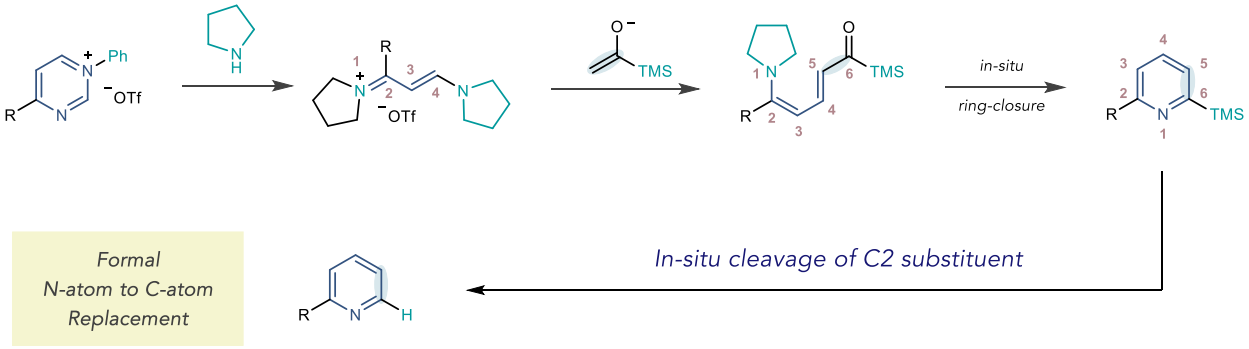


Figure 4.6. Strategy for formal N- to C-atom replacement

Indeed, by adapting a procedure from Marcoux[7] using three equivalents of the lithium enolate of a commercially available acetyltrimethylsilane followed by a mixture of ammonium acetate and acetic acid at 95 ºC, we successfully achieved single-atom conversion of pyrimidines to pyridines (**Figure 4.6**). In **Figure 4.6**, we show four complex examples that are reminiscent of pyrimidines typically found in drug-discovery campaigns where the pyrimidine is converted to its corresponding pyridine. The single atom replacement is tolerant of electron-rich aromatics, such as pyrazoles (**84** & **85**). In addition, benzylic amides (**85**), aryl halides (**84-86**), and piperidine rings (**87**) were also tolerated. We hypothesize the silyl group is cleaved after heterocycle formation under the reaction conditions.

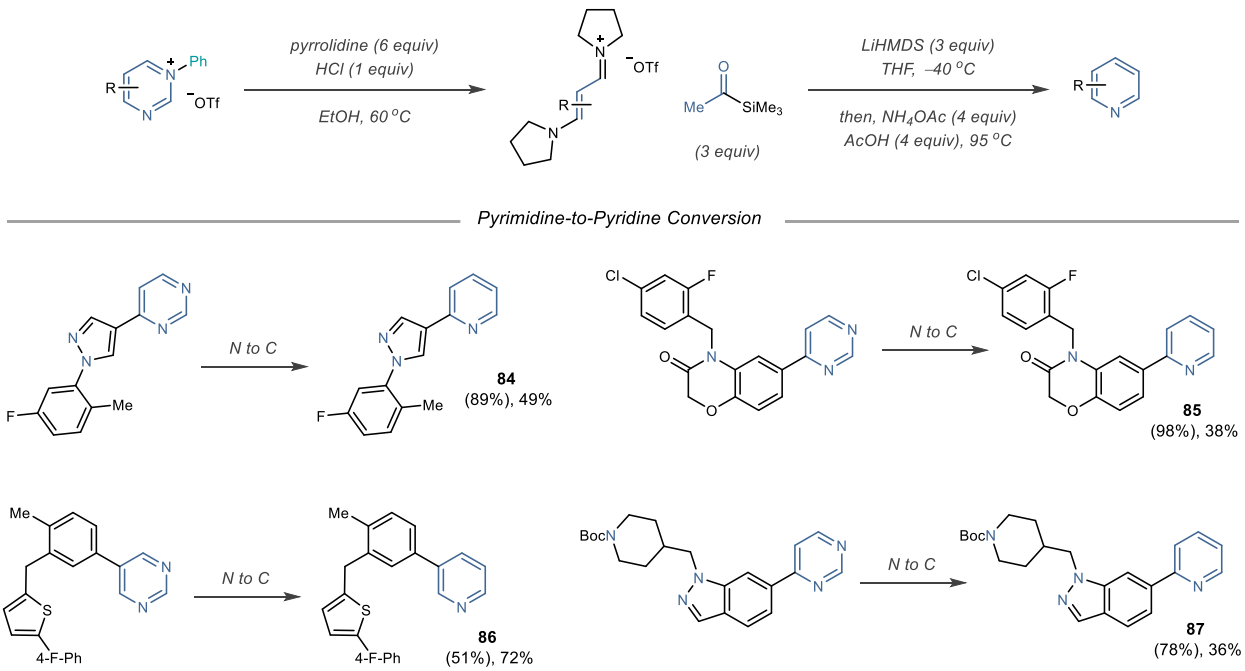


Figure 4.6. Pyrimidine-to-pyridine conversion via deconstruction-reconstruction. Yield in parenthesis yield of vinamidium salt formation.

In addition to formal N-atom to C-atom replacement, we also showed the pyridine ring undergoes functionalization at C2 or C5 using ketone and hydrazone derived enolates rather than acylsilane derived enolates (**Figure 4.7**). Compounds **88** and **89** show that employing acylsilanes or hydrazone enolates result in either unfunctionalized pyridine products or C5-ethylated pyridines. By choosing which enolate derivative is used, practitioners choose which product is formed. This would allow for rapid generation of chemical libraries. To exemplify this, four different pyridine derivatives are produced from a single precursor simply by changing the identity of the ketone to install a methyl, cyclopropyl, pyridyl, and thiophenyl group at the C2-position of the pyridine product (**90-93**).

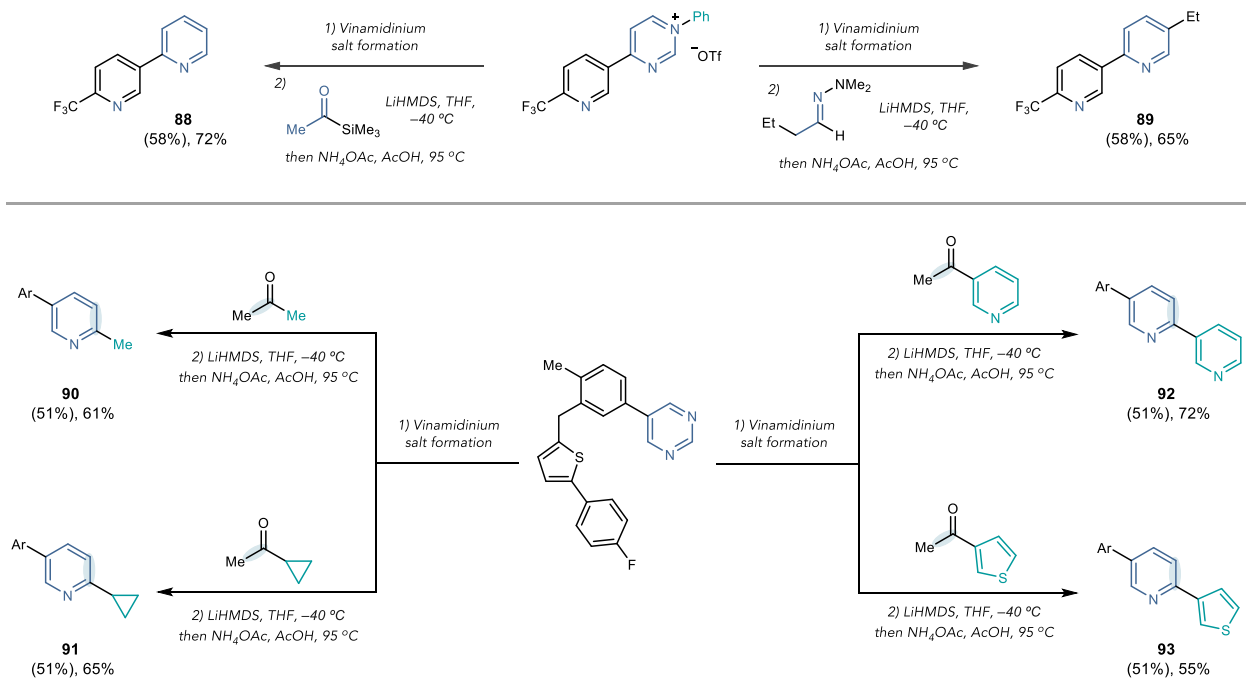


Figure 4.7. Pyrimidine-to-pyridine conversion and functionalization via deconstruction-reconstruction. Yield in parenthesis yield of vinamidinium salt formation.

4.6 Deconstruction-Reconstruction Approach for Structure-Activity Relationship Diversification

Rapidly modifying the structure of a lead compound is a paramount goal in SAR studies which enables optimization of key physiochemical properties. Using our deconstruction-reconstruction approach gives practitioners the ability to rapidly decorate the periphery of pyrimidine molecules with a variety of adorning substituents from a single precursor. In addition, our ability to leverage de novo synthesis late into a synthetic campaign allows for "scaffold-hopping", a process that coverts the pyrimidine into other heterocycles, such as azoles. **Figure 4.8** shows the deconstruction-reconstruction process applied to biologically active compounds, fenarimol, an anti-fungal agent, and a precursor to dabrafenib, an anti-cancer drug. In the

fenarimol case, we performed a one-pot procedure to deconstruct the pyrimidine to the iminoenamine and reconstruct it to three derivatives installing a free-amine (**94**), cyclopropyl group (**95**), and phenyl (**96**) substituent at the C2-position of the azine periphery. In addition, we applied the deconstruction-reconstruction process to a precursor of dabrafenib. Using guanidine as the amidine coupling partner allowed for the synthesis of the active drug form (**97**) without a pre-installed chlorine atom at C2, which was previously required to synthesize the drug. To show rapid diversification of other derivatives, we also prepared two separate C2-funtionalized derivatives, a cyclopropanated and trifluoromethylated form (**98** & **99**). Finally, we showed "scaffold-hopping" to pyrazoles and isoxazoles (**101-103**), including a derivative with a complex pyrimidine containing *N*-group, which could undergo further derivatization, and represents a convergent coupling process of two complex fragments.

Another benefit of the deconstruction-reconstruction process is the ambiphilic nature of the iminoenamine intermediate. Due to each side of the iminoenamine containing a nitrogen group, electrons flow freely throughout the conjugated π-system. This "push-pull" system places a δ-negative charge on the iminoenamine C3 position; thus, this site on the iminoenamine system allows for reactions with electrophiles, which translates to the pyrimidine's C3 position upon recyclization. We exploit this electronic bias to capture an electrophilic chlorine atom at the C5 position of the pyrimidine backbone forming intermediate **103** (**Figure 4.8**). Recombining this intermediate with a substituted amidine nucleophile allows for a difunctionalized product at the C5 and C2 positions. We combined the chlorinated iminoenamine with a cyclopropylamindine coupling partner to yield difunctionalized compound **104** in a single step from the corresponding pyrimidinium triflate salt.

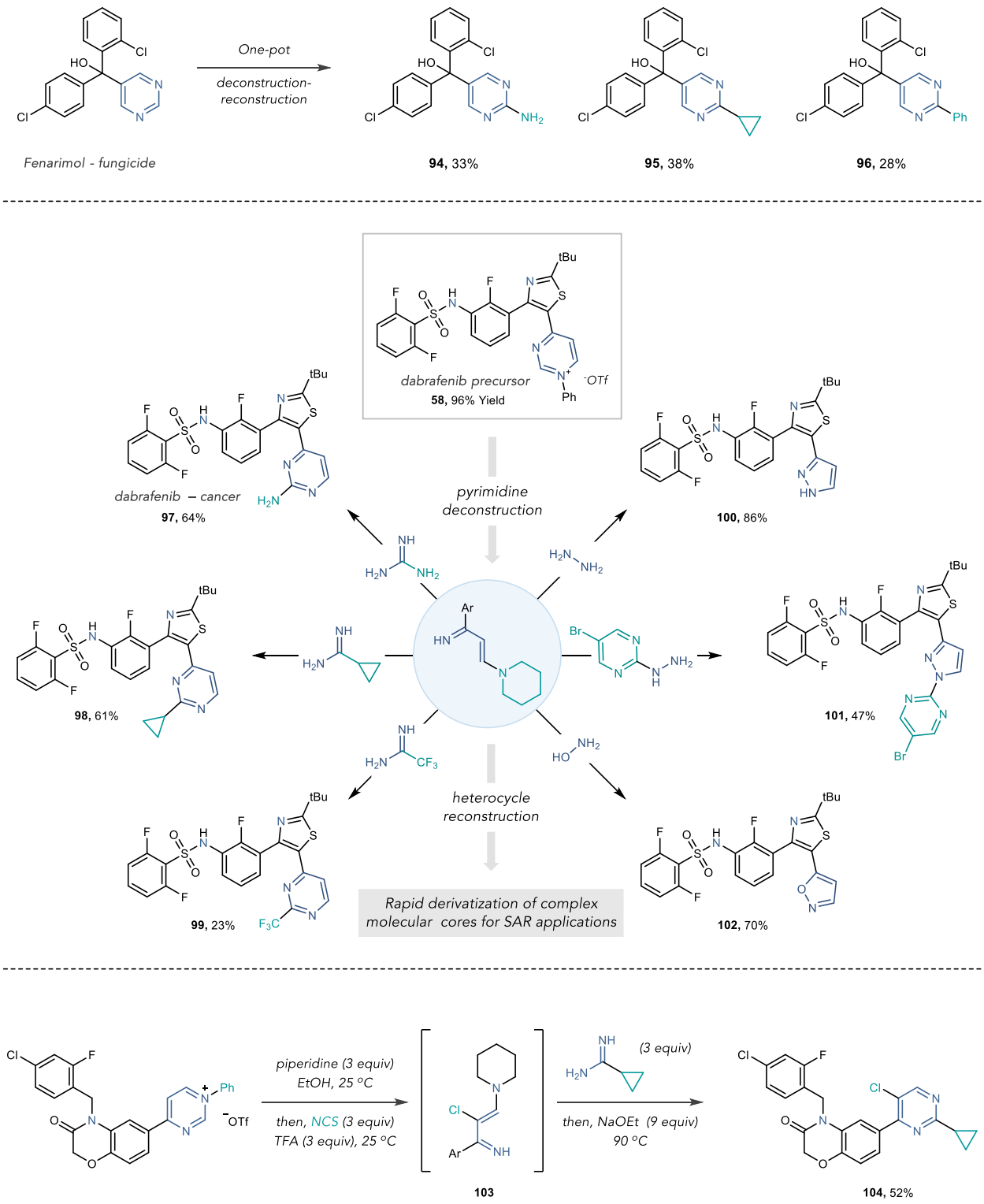


Figure 4.8. Application of deconstruction-reconstruction process for structure-activity relationship diversification and pyrimidine difunctionalization of iminoenamine intermediate.

4.7 Mechanistic Studies of Pyrimidinium Salt Formation

In the final part of this study, we studied the mechanism of pyridine ring-opening/ring-closing in collaboration with the Paton group at Colorado State University. Mechanistic studies were conducted computationally by performing quantum chemical calculations at the ωB97X-D/def2-TZVP// Q13 ωB97X-D/6-31+G(d,p) level in ethyl acetate (**Figure 4.9A**). In the first step of the reaction mechanism, 4-phenyl pyrimidine undergoes an exergonic trifylation process with triflic anhydride forming **Int-Act**. From this intermediate, attack of the nucleophilic aniline occurs at either the C2 or the C6 position. We found attack at the C6-position ($\Delta G^{\ddagger}$=15.1 kcal mol^{-1}) is kinetically favored over the C2-position ($\Delta G^{\ddagger}$=15.9 kcal mol^{-1}) at −78 °C. Subsequent deprotonation by collidine yields **Int-I** as a dihydropyrimidine. Although attack of the aniline nucleophile is an endergonic process, deprotonation of collidine is energetically barrierless driving the formation of **Int-I** forward.

Next, **Int-I** undergoes ring-opening to the aza-triene intermediate (aza-Zincke imine) through an endergonic process. Then, the aza-Zincke imine tautomerizes to **Int-II** before ring-closing via a polar mechanism to dihydropyrimidine, **Int IV**. Ring-closure represents the highest barrier across the reaction profile making this step rate-limiting. Finally, extrusion of the triflimide counterion and counterion exchange with the collidine triflate salt completes the reaction mechanism yielding the pyrimidinium product.

We also found the steric and electronic properties of substituents at the C4-position of the pyrimidine substituents have an impact on the energy barriers for pyrimidinium formation (**Figure 4.9B**). In the ring-closure step, substituents at the C4-position experience destabilizing allylic strain ($A^{1,3}$) with its neighboring allylic hydrogens in **TS-IV**. Increasing the allylic strain with sterically encumbering substituents also increases ground state destabilization; thus, the energetic

barriers for ring-closure decrease. This is exemplified by comparing the energetic barriers of ring-closure among various substituents. Phenyl groups and methyl groups ($\Delta G^{\ddagger}$=18.1 and 18.0 kcal mol^{-1}, respectively) at the C4 position have lower barriers for ring-closure compared to hydrogen groups ($\Delta G^{\ddagger}$=22.7 kcal mol^{-1}). Electron-withdrawing groups at C4 also destabilize Int-II and lower the cyclization barrier by affecting the electronic properties of aza-Zincke imine. Although the barrier for cyclization is much lower than sterically encumbering groups, the yield of *N*-aryl pyrimidinium formation is much lower. We hypothesize electronic-deficient pyrimidines do not effectively react with triflic anhydride (**Figure 4.9C**). Thus, competitive trifylation with the aniline nucleophile hinders product formation. However, employing sterically encumbered aniline nucleophiles, such as 2,4,6-trimethylanine, to prevent competitive trifylation increases the yield of the pyrimidinium product.

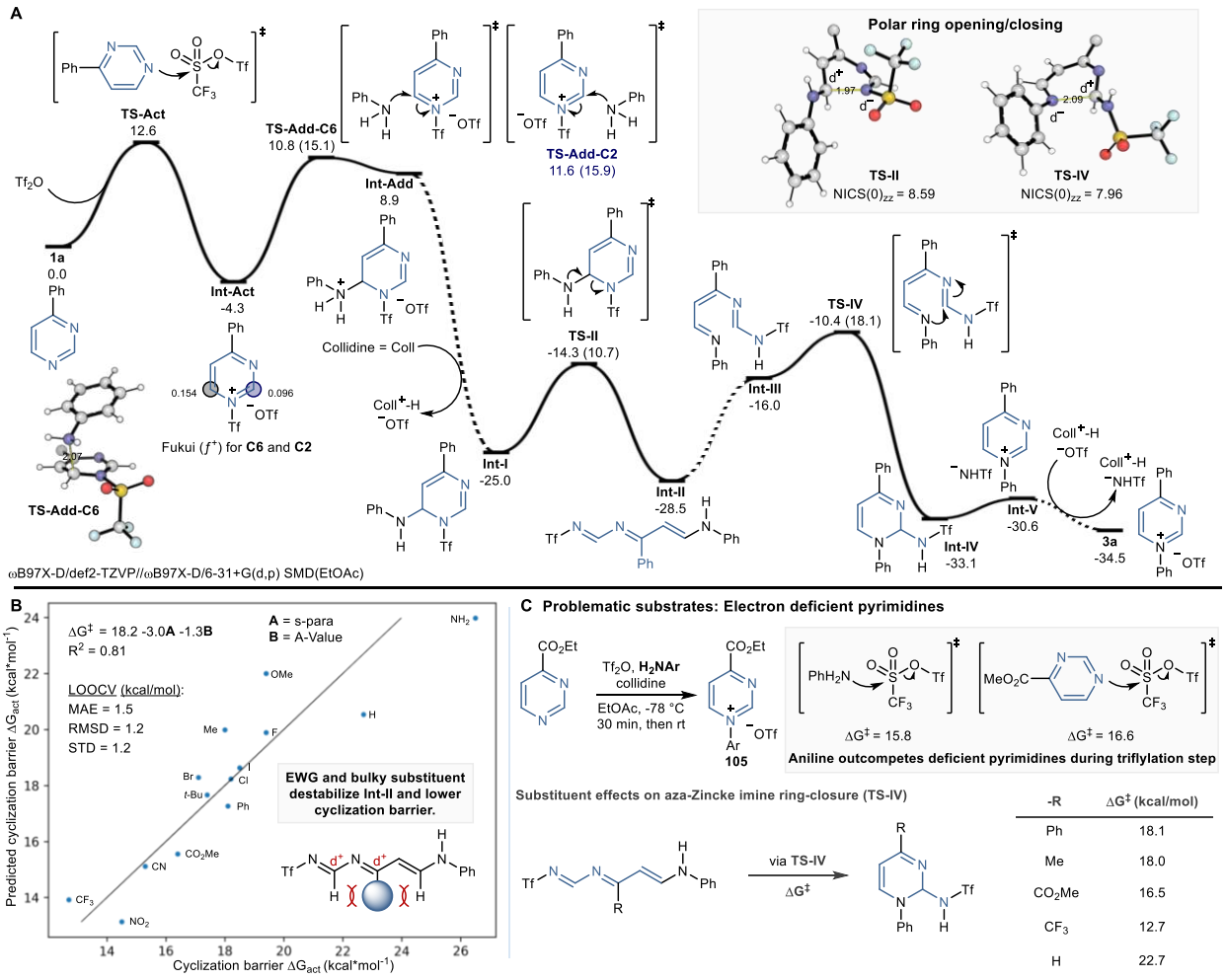


Figure 4.9. Mechanistic Studies of Pyrimidine Ring-Opening/Ring-Closing.

4.8 Preliminary Results on Thiol-Ring-Opening of C2-substituted Pyrimidines

One limitation in the deconstruction-reconstruction process is C2-substituted pyrimidines do not undergo ring-opening to the aza-Zincke imine. Instead, full recovery of the pyrimidine starting material is observed by ^{1}H NMR or decomposition. However, by changing the amine nucleophile to a thiol, near quantitative ring-opening is observed in the case of 2-piperidine-4-phenyl-pyrimidine. Unlike the pyrimidine aza-Zincke imines opened with an aniline or amine

nucleophile, the thiol aza-Zincke imines allow for isolation of the ring-opened intermediate. This isolation procedure as well as experimental information for opening is outlined in **Appendix A2.3**. **Figure 4.10** shows a preliminary scope of thiol ring-opening and cleavage of the thiol-ring-opened product is currently under investigation within our laboratory. This cleavage reaction would enable swapping the C2-substitutent with a different substituent via recombination with an amidine coupling partner will allow a new editing approach through "substituent exchange" processes.

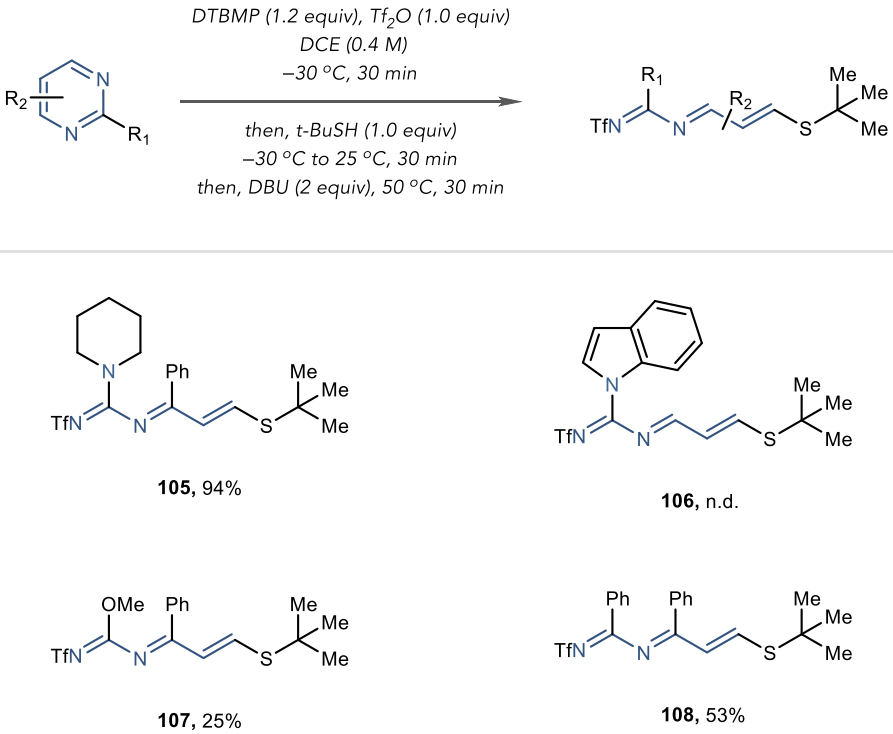


Figure 4.10. Preliminary scope of thiol ring-opening of pyrimidines.

4.9 Conclusion

In conclusion, SAR diversification relies on the synthetic strategies available to medicinal chemists to make molecules; however, methods that apply to complex molecules without a pre-installed functional group are rare. Here we report a method for complex SAR diversification by

deconstructing pyrimidine containing molecules to an iminoenamine, which serves as a 1,3-dicarbonyl surrogates. We then reconstruct this intermediate with substituted amidines, hydroxylamines, and hydrazines to produce substituted pyrimidines, isoxazoles, and pyrazoles. In addition, using pyrrolidine rather than piperidine for *N*-aryl pyrimidinium cleavage allows for the formation of vinamidinium salts, which combine with enolate nucleophiles to produce pyridines. Finally, current investigations on thiol ring-opening are on-going to achieve substituent exchange reactions.

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