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# Beyond the Zincke reaction: Modern advancements in the synthesis and applications of *N*-aryl pyridinium salts

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ABSTRACT

In this review, we highlight recent advances in the synthesis of *N*-aryl pyridinium salts, which have moved beyond the classical Zincke $S_NAr$ reaction to focus on strategies reliant on C–N bond formation using an ever expanding array of reaction manifolds. This expansion to include C–N bond forming approaches, as well as enabling an unprecedented breadth of both arene and *N*-heterocyclic coupling partners, has led to a shift in perception of *N*-aryl pyrdinium salts to now serving as a platform for aryl amine synthesis. As a result, new synthetic applications of these salts have begun to emerge, both utilizing classic (nucleophilic additions, radical reactions, cycloadditions, etc) and emergent transformations such as deaminative transformations, isotopic labeling, and molecular editing. This review provides a timely synopsis of novel *N*-aryl pyridinium salt syntheses from the last 10 years (2013 to present). These strategies are separated into the two main classes, radical cation and non-radical cation methods. Highlights of recent transformations and applications of the resultant *N*-aryl pyridinium salts are also discussed to demonstrate the untapped synthetic potential of these scaffolds and highlight areas of continued interest.

## 1. Introduction

Pyridine and related *N*-heteroarenes are ubiquitous motifs in synthetic chemistry, serving as ligand scaffolds, versatile scaffolds for heterocyclic synthesis, as well as appearing in almost 60 % of U.S. FDA approved drugs [1]. Quaternization of the pyridine nitrogen to generate the corresponding *N*-alkyl, *N*-acyl or *N*-aryl pyridinium salts provides a new class of charged molecules with applications across synthesis, biology, and materials science [2]. As synthetic intermediates, these cationic species possess increased electrophilicity relative to their neutral counterparts, enabling more facile reactions with nucleophiles, reducing agents, cycloaddition partners, radicals, etc. Of this sub-class, *N*-aryl amines have long held an untapped potential to leverage the above transformations and serve as a diversity platform for aryl amine synthesis, a potential which has been restricted due to limited means of synthesis.

The classical method for preparation of *N*-aryl pyridinium salts was reported by Zincke in 1903 [3–5]. Treatment of 2,4-dinitro-chlorobenzene with pyridine leads to an *N*-aryl pyridinium "Zincke" salt (Scheme 1A). This Zincke salt can then be treated with anilines in what amounts to an "*N*-aryl pyridinium salt metathesis", exchanging the *N*-aryl moiety via ring opening/closing sequence. The synthetic interest in the Zincke salt has primarily been focused not on the resultant new *N*-aryl pyridinium motif, but rather intercepting the ring open form, or "Zincke imine", which is isolable when a secondary amine nucleophile is used. While elegant applications of these Zincke imines have been made in synthesis [6], this neglects the aforementioned potential of *N*-aryl pyridinium salts to serve as precusors to diverse aryl amines. When considered through this lens, the Zincke salt approach suffers from the limitations of requiring a preexisting aryl C–N bond on the aniline nucleophile and thus it does not readily compete with modern cross-coupling amination approaches. As broad interest in *N*-aryl pyridiniums has continued to grow in the last decade, new methods have emerged to fill this gap and enable the synthesis *N*-aryl pyridinium salts through C–N bond formation.

This review will cover new synthetic approaches to *N*-aryl pyridinium salts from 2013 to present via arene amination of C–H, C–X (X = halogen), and C–B bonds with pyridine and related aromatic heteroarenes (Scheme 1B). Strategies ranging from electrochemistry to transition metal catalysis have been developed and will be divided into two general categories of discussion: radical cation and non-radical cation methods. New strategies for the downstream manipulation of *N*-aryl

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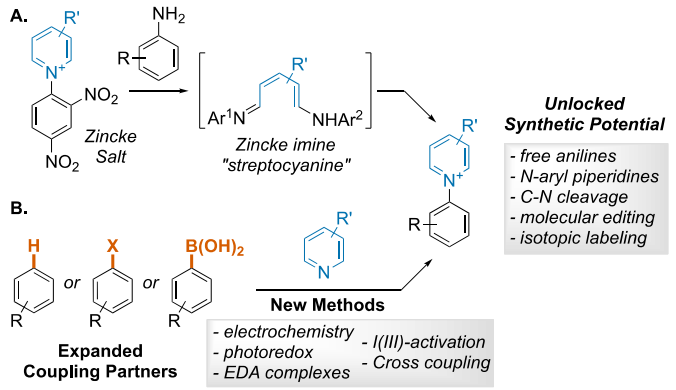



**Scheme 1.** (A) Classical synthesis of *N*-aryl pyridinium salts from Zincke salts. (B) Recent advances in synthesis and applications of *N*-aryl pyridinium salts (this review).

pyridinium salts will also be discussed, including deaminative functionalization, molecular editing, and isotopic labeling to capture emerging opportunities.

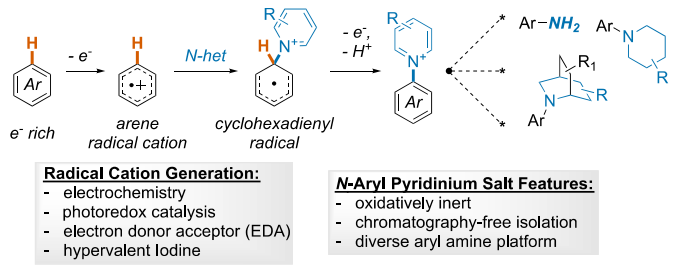
## 2. Radical cation methods

Transformations of aromatic C–H bonds directly into C–N bonds represents a step- and atom-economical amination strategy [7]. For the synthesis of *N*-aryl pyridinium salts directly from C–H bonds, arene radical cation pathways have emerged as the dominant approach. Diverse methods including electrochemistry, photoredox catalysis, and electron donor-acceptor complexes have been leveraged as single-electron oxidants in these methods. Mechanistically, single electron oxidation is followed by attack of the resulting radical cation by pyridine to generate a cyclohexadienyl intermediate, followed by loss of a second electron and deprotonation to generate the rearomatized *N*-aryl pyridinium salt (Scheme 2).

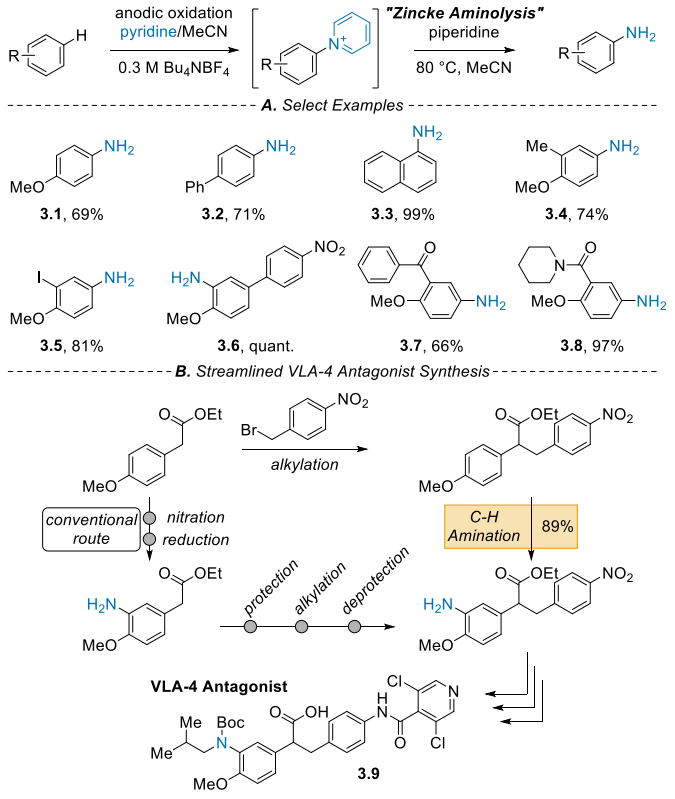
In general, oxidative arene amination is challenging due to competitive nucleophile and product degradation. The use of pyridine nucleophiles provides several strategic advantages that overcome these barriers: (1) the high oxidation potential of pyridine allows for selective oxidation of the arene scaffold (2) the nucleophilicity of pyridine enables attack on the resultant arene radical cation to produce *N*-aryl pyridinium salts and (3) the resulting cationic *N*-aryl pyridinium salts prevent product over-oxidation. The following reports serve to highlight the utility of intermediacy of *N*-aryl pyridinium salts as an enabling approach to oxidative arene amination.

### 2.1. Electrochemical methods

In 2013, Yoshida and Morofuji reported an electrochemical synthesis of *N*-aryl pyridinium salts directly from C–H bonds and demonstrated that these molecules could be smoothly converted to anilines through a Zincke aminolysis reaction in one pot (Scheme 3) [8]. Electrochemistry




**Scheme 2.** Mechanistic pathway for oxidative C–H amination via arene radical cations.



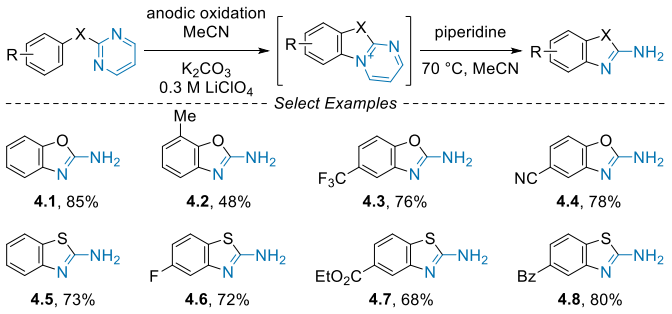

**Scheme 3.** Yoshida and Morofuji's intermolecular electrochemical arene C–H amination via *N*-aryl pyridinium salts. (A) Select examples of aniline synthesis. (B) Demonstration in small molecule drug synthesis.

had previously been used as a tool used to study the nature of arene radical cations, however there reports were not explored for their synthetic utility [9–12]. The work from the Yoshida lab in 2013 could be considered the starting point for inspiring modern interest in new methods for *N*-aryl pyridinium salts synthesis. Their work elegantly demonstrated that *N*-aryl pyridinium salts could serve as aniline precursors with powerful applications in medicinal chemistry and late-stage functionalization.

The electrochemical C–H amination displays excellent functional group compatibility with electron rich (**3.1**) and π-extended aromatic compounds (**3.2, 3.3**). Benzylic C–H bonds *ortho* to the position of the electron donating group remained untouched (**3.4**). Notably, this reaction works in the presence of aryl halides to give iodoaniline derivative (**3.5**) containing a functional handle for further derivatization. The reaction can also proceed in the presence of highly electron-withdrawing nitro groups (**3.6**). Taken together, these examples (**3.5, 3.6**) would be synthetically challenging to access via traditional cross-coupling reactions or nitration/reduction sequences. The reaction proceeds with high regioselectivity in the presence of molecules with alternative sites of C–H oxidation such as amides or unsymmetric biaryls (**3.6–3.8**).

Amination occurred with high regioselectivity *para* to the electron-donating group and this was explained through DFT calculations that showed the lowest unoccupied molecular orbital (LUMO) coefficients of the radical cation were predictive for the site of nucleophilic attack by pyridine. This predictable selectivity was used in a streamlined VLA-4 antagonist synthesis (**3.9**). The electrochemical C–H amination could eliminate a nitration/reduction and protection/deprotection sequence, enabling a more step-economic synthesis.

In 2015, Morofuji and Yoshida expanded upon their first report, again leveraging *N*-aryl pyridinium salts to achieve a complementary ortho-selective C–H amination (Scheme 4) [13]. To override the high *para* selectivity of their prior method, they utilized a tethered amine nucleophile to give amination *ortho* to C–O and C–S bonds. Through



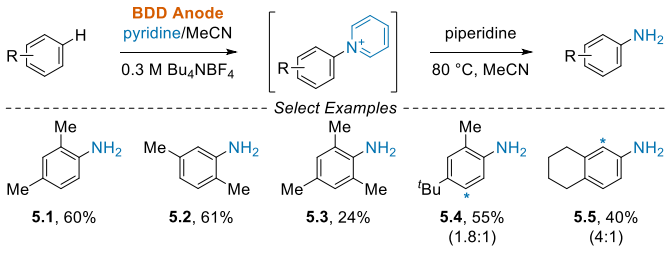

**Scheme 4.** Yoshida and Morofuji's intramolecular electrochemical arene C–H amination.

anodic oxidation of 2-pyrimidyloxybenzenes and 2-pyrimidylthiobenzenes, *N*-aryl pyridinium salts could be generated and were again directly subjected to Zincke aminolysis to give 2-aminobenzoxazoles (**4.1**) and 2-aminobenzothiazoles (**4.5**). This intramolecular C–H amination was compatible with benzylic C–H bonds (**4.2**) as well as a variety of substituted and unsubstituted electron deficient phenol derivatives (**4.3, 4.4**). This chemistry also worked well with thiophenol derivatives (**4.5**–**4.8**) to produce 2-aminobenzothiazoles, important motifs in medicinal chemistry. Prior syntheses of these compounds relied on C–O or C–S bond formation from aniline derivatives, and so this electrochemical method provides a complimentary disconnection via C–N bond formation.

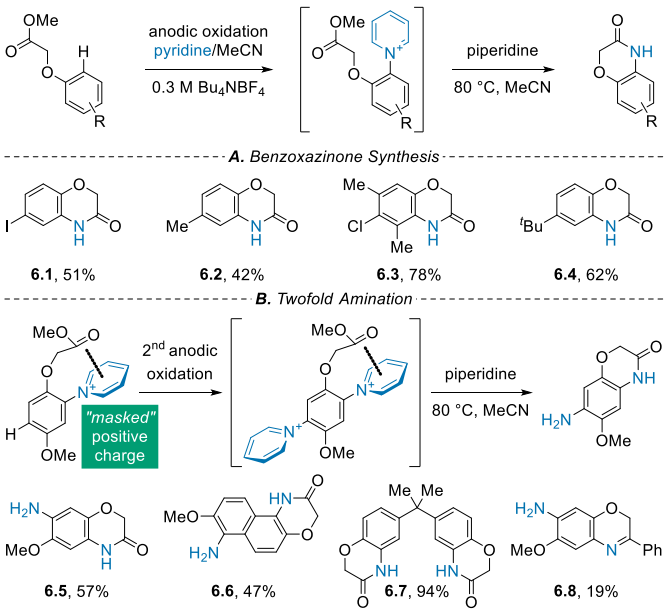
A persistent limitation of electrochemical C–H aminations is that all substrates required an electron-donating group for efficient oxidation. In 2016, Waldvogel showed that switching electrode material from carbon fleece or graphite to a boron doped diamond (BDD) electrode material would allow for the synthesis of *N*-aryl pyridinium salts from arenes lacking an electron-donating group (Scheme 5) [14]. BDD is an anode material based on $sp^3$-carbons, which tends to show a higher performance at more positive potentials than $sp^2$-carbon based electrodes, enabling anodic oxidation of less-activated arenes without electrode fouling that is observed when using these substrates with graphite anodes. It was also found that when tetrafluoroborate anion was used as electrolyte, radical cation intermediates were stabilized and yields were increased when electrolyte concentration was higher. The reaction was demonstrated on a scope of alkylarenes (**5.1**–**5.5**) without any competitive benzylic C–H amination detected.

Yoshida and Waldvogel would then team up in 2017 to develop two electrochemical methods for the synthesis of 1,4-benzoxazin-3-ones via *N*-aryl pyridinium salts (Scheme 6) [15,16]. Using para-substituted phenoxyacetates as starting materials leads to formation of *N*-aryl pyridinium salts which undergo a concomitant Zincke aminolysis and intramolecular cyclization to furnish the bicyclic benzoxazinones (Scheme 6A) [15]. This method shows good compatibility with halides that could serve as functional handles in subsequent reactions as well as good tolerance of steric effects (**6.1**–**6.4**).

Up until this point, all electrochemical methods for *N*-aryl pyridinium salt synthesis stop after the first C–H amination, a generally




**Scheme 5.** Waldvogel's use of BDD anodes to enable oxidative C–H amination of less-activated arenes via *N*-aryl pyridinium salts.




**Scheme 6.** (A) Waldvogel and Yoshida's first collaboration for benzoxazinone synthesis. (B) Waldvogel and Yoshida's *N*-aryl pyridinium diamination strategy via an ester "masking group".

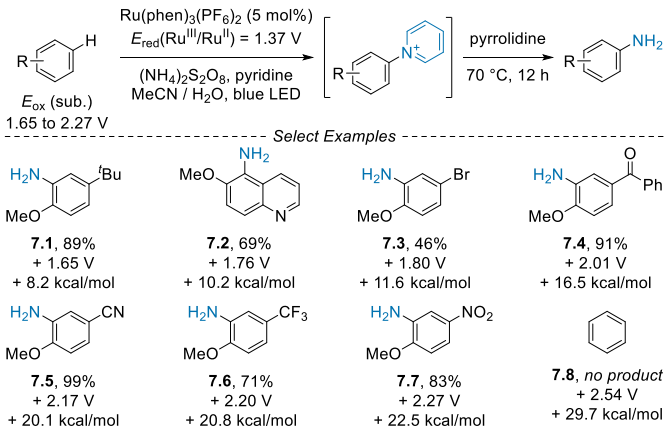
advantageous feature of the oxidatively inert pyridinium salts. However, in their subsequent collaboration, Yoshida and Waldvogel found that replacing one alkyl group with a pendent ester in a dialkoxy arene unlocked a strategic second amination reaction (Scheme 6B) [16]. The second amination can occur due to the ability of the pendent ester to mask the electron-withdrawing effect of the cationic *N*-aryl pyridinium salt intermediate via pi-coordination. This allowed for the first oxidative synthesis of bis-*N*-aryl pyridinium salts which can be converted to highly substituted and electron-rich anilines. Waldvogel and Yoshida were able to diaminate various 1,4-activated phenoxy systems (**6.5**–**6.8**), generating high value, medicinally relevant compounds.

### 2.2. Photoredox methods

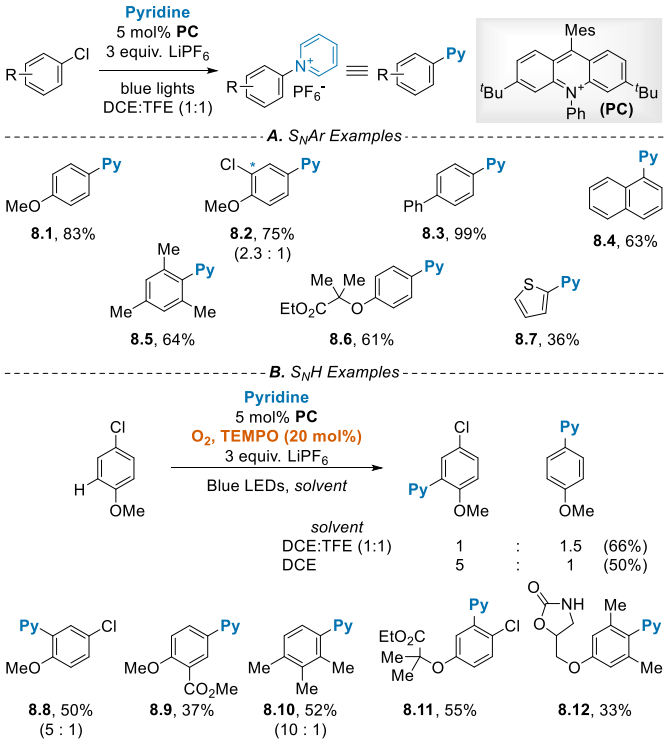
Photoredox catalysis has emerged as an alternative approach to electrochemistry for the synthesis of *N*-aryl pyridinium salts through radical cation pathways. Numerous research groups have demonstrated that photoredox catalysis can be used to further expand the scope of oxidative *N*-aryl pyridinium synthesis via aminations of less-activated arenes, heteroarenes, phenols, and aryl halides as well as not requiring the specialized equipment necessary for an electrochemical setup.

In 2020, Morofuji and Kano demonstrated the first examples of photoredox-mediated *N*-aryl pyridinium salt synthesis, via oxidative C–H amination (Scheme 7) [17]. Typically in photoredox catalysis, arene radical cations are generated from arenes with oxidation potentials lower than the reduction potential of the photocatalysts excited state. Morofuji was able to show that a thermodynamically disfavored electron transfer was not a prerequisite to C–H amination, meaning that *N*-aryl pyridinium salts could be generated and converted to anilines from molecules with high oxidation potentials. Electron-deficient anisole derivatives were compatible (**7.1**–**7.6**) including 4-nitroanisole (**7.7**) which has a 22.5 kcal/mol uphill electron transfer to Ru $(phen)_3(PF_6)_2$. However, there is a limit to this chemistry as benzene, a nearly 30 kcal/mol uphill electron transfer, displayed no reaction (**7.8**).

Moving beyond C–H amination, in 2021, Sanford used photoredox catalysis for an $S_NAr$ reaction of aryl halides leading to *N*-aryl pyridinium salts (Scheme 8) [18]. $S_NAr$ reactions typically use electron-deficient aryl halides due to the requirement for nucleophilic




**Scheme 7.** Morofuji and Kano's photoredox C–H amination.




**Scheme 8.** Sanford's $S_NAr$ and C–H amination approaches to *N*-aryl pyridiniums. (A) Umpoled $S_NAr$ amination using acridinium photoredox catalysis. (B) Oxidative C–H amination under aerobic conditions.

attack on the arene, but under photoredox conditions an umpoled version of the reaction is possible. Using acridinium photoredox catalysis to generate arene radical cations from electron-rich aryl halides, Sanford was able to show that pyridine attacks *ipso* to halide substituents on the aromatic rings, forming a cyclohexadienyl radical intermediate. Single electron reduction by the reduced acridinium catalyst is followed by elimination of halide anion to generate *N*-aryl pyridinium salt. This chemistry is analogous to previous work reported by Nicewicz [19] using imidazole nucleophiles, but due to the fact that pyridine nucleophiles lack an N–H bond, the halide leaving group becomes the charge balancing anion for the pyridinium product. Adding $LiPF6_6$ results in significantly increased yields through sequestration of the chloride anion leaving group.

The reaction displayed good selectivity and was able to generate *N*-aryl pyridinium salts from numerous chloroanisole derivatives (**8.1**). In the presence of multiple aryl-chloride bonds, the reaction favored substitution at the *para* position to the methoxy group (**8.2**). The requirement for a methoxy group could be alleviated in highly conjugated aromatic systems (**8.3, 8.4**), or when using sufficiently activated xylene derivatives (**8.5**). The reaction was also demonstrated to work on medicinally relevant molecules such as clofibrate (**8.6**) or heteroaryl halides (**8.7**).

In addition to an umpoled $S_NAr$ reaction, this method could be modified with aerobic conditions and removal of fluorinated alcohol solvent, leading to a C–H amination method to *N*-aryl pyridinium salts (**8.8-8.12**).

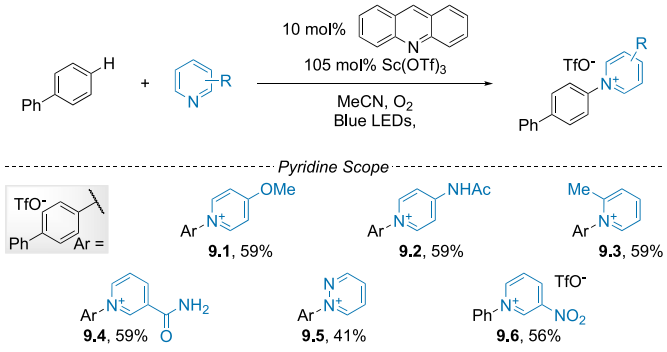
In 2024, Sanford developed a potent photooxidation system using acridine and Lewis acids [20]. This system enables the amination of less-activated arenes without requiring pre-assembled catalysts that are expensive to purchase or require multiple steps to synthesize.

Sanford was able to demonstrate the success of this reaction on biphenyl with a range of pyridine derivatives (Scheme 9). The pyridine scope proved very general, with electron-rich pyridines (**9.1, 9.2**), eletron-deficient ((**9.4, 9.5**), and even sterically hindered 2-picoline (**9.3**) was compatible with the reaction conditions. The remarkable utility of this potent photooxidant system was demonstrated via the challenging oxidative C–H amination of benzene with electron-deficient 3-nitropyridine (**9.6**).

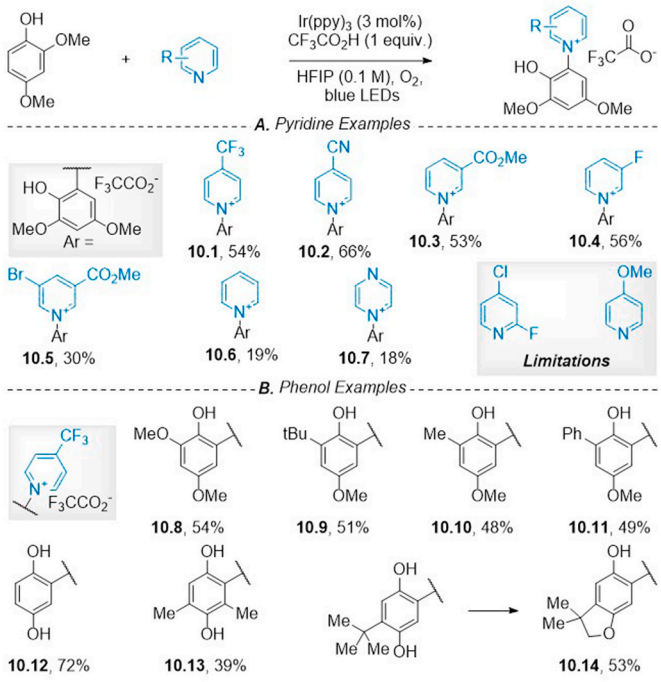
In 2024 the Kozlowski lab developed a C–H amination reaction through merging photoredox catalysis and electron donor-acceptor complexation to synthesize *N*-aryl pyridinium salts from unprotected phenols, a substrate class that had not been successful in previously described methods (Scheme 10) [21]. Under oxidizing conditions, it was found that pyridine could successfully trap phenoxy radical cations to form the desired *N*-aryl pyridinium salt products.

Noteworthy in the Kozlowski group's work is the broad scope of electron-deficient pyridine derivatives (10.**1**–10.**5**) leading to products that can be further diversified into substituted *N*-aryl piperidines containing fluorinated moieties (10.**1, 10.4**), functional handles for further derivatization (10.**2, 10.3, 10.5**), or aryl bromides for cross-coupling (10.**5**). Neutral pyridine (10.**6**) and pyrazine (10.**7**) gave lower yields while electron rich pyridines were incompatible in their reaction conditions, likely due to being poor acceptors in the EDA complex with electron donating phenols. The phenol scope was able to tolerate *ortho*-substitution (10.**8**-10.**11**) and notably benzylic C–H bonds did not display competitive C–H amination (10.**10, 10.13**). Hydroquinones (10.**12**–10.**14**) were also successfully aminated, with an intramolecular cyclization reaction taking place with *tert*-butylhydroquinone. Unlike previous methods, anisole derivatives were not compatible in the reaction conditions.

Rigorous mechanistic studies led the authors to propose a dual-catalytic cycle with iridium photocatalyst and EDA complexation. Both cycles can produce the key phenoxy radical cation intermediate which can react with pyridine to form the key C–N bond. It was found that removal of photocatalyst from the reaction gave diminished yields,




**Scheme 9.** Sanford's potent photooxidation system for oxidative C–H amination of unactivated arenes to generate *N*-aryl pyridinium salts.

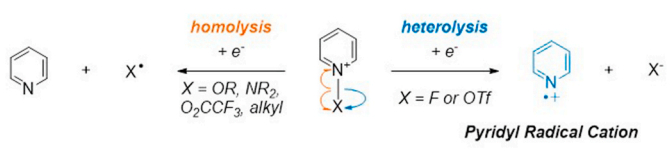



**Scheme 10.** Kozlowski's tandem EDA-photoredox C–H amination. (A) Selected pyridine scope. (B) Selected phenol scope.

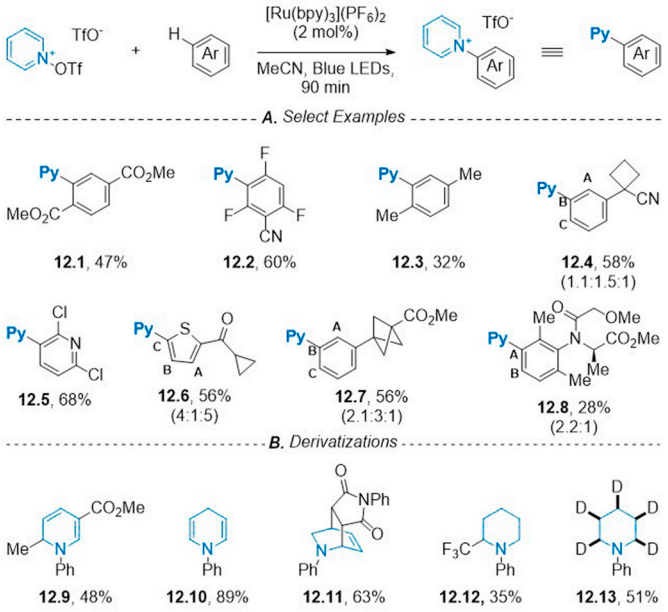
indicating both photocatalysis and EDA complexation are necessary.

All the previously mentioned C–H functionalization methods to *N*-aryl pyridiniums have relied on single electron oxidation of the arene coupling partner to generate a reactive radical cation. In 2019, an orthogonal strategy was concurrently developed by a collaboration between Carreira and Togni and a separate report from the Ritter lab, wherein pyridyl *N*-centered radical cations are reductively generated and trapped by neutral arenes [22–24]. This strategy utilizes single electron reduction of highly reactive N-X pyridinium salt derivatives (Scheme 11) [25]. Upon reduction, the N-X pyridinium salts can undergo either homolytic or heterolytic bond cleavage depending on the nature of the N–X bond. It was found that highly electronegative X-groups such as fluorine or triflate will favor heterolytic cleavage to generate the corresponding X-anion and desired N-centered pyridyl radical cation. These strategies offer a complementary approach to the previously described methods as the pyridyl radical cation intermediate can be viewed as highly electrophilic toward arene trapping and thus increase functional group compatibility and substrate scope.

Carreira's report utilized pyridine *N*-oxides which could be activated with trifluoromethane sulfonic anhydride to give triflyloxy pyridinium salts, serving as isolable precursors to the *N*-centered pyridyl radical cations (Scheme 12) [22]. Exposure of these salts to blue LEDs in the presence of a $[Ru(bpy)]_3PF_6$ catalyst led to the heterolytic N-X cleavage In this reaction, highly electron-deficient arenes could be used (**12.1**–**12.3**), expanding the scope far beyond anisole derivatives. One key difference between this strategy and the oxidative strategies previously described is that pyridyl radical cations do not lead to high levels of regioselectivity, with steric hindrance having little effect (**12.4, 12.6**–**12.8**). Carreira also showed that heteroarenes (**12.5, 12.6**) could form *N*-aryl pyridinium salts, which had yet to be demonstrated in prior C–H functionalization strategies. The reaction in the presence of the increasingly popular bicyclopentante building block proceeded smoothly (**12.7**) and the fungicide Metalaxyl was able to be pyridinated (**12.8**) illustrating the potential for late-stage functionalization strategies using pyridyl radical cations. Carreira and Togni also showed examples of *N*-aryl pyridinium salt derivatization beyond simple Zincke aminolysis. Grignard addition followed by methoxycarbonylation can provide 1,2-dihydropyridine (**12.9**). Sodium amalgam reduction can lead to the 1,4-dihydropyridine product (**12.10**) while sodium borohydride reduction followed by Diels-Alder reaction gave isoquinuclidine (**12.11**). Trifluoromethylation followed by hydrogenation can give *N*-aryl piperidine (**12.12**), or deuterated (**12.13**) can be generated under similar hydrogenation conditions. This derivatization panel by Carreira represented one of the first cases wherein the potential of the resulting *N*-aryl pyridinium salts to access diverse *N*-aryl amine scaffolds was highlighted, as opposed to direct Zincke cleavage to the anilines.



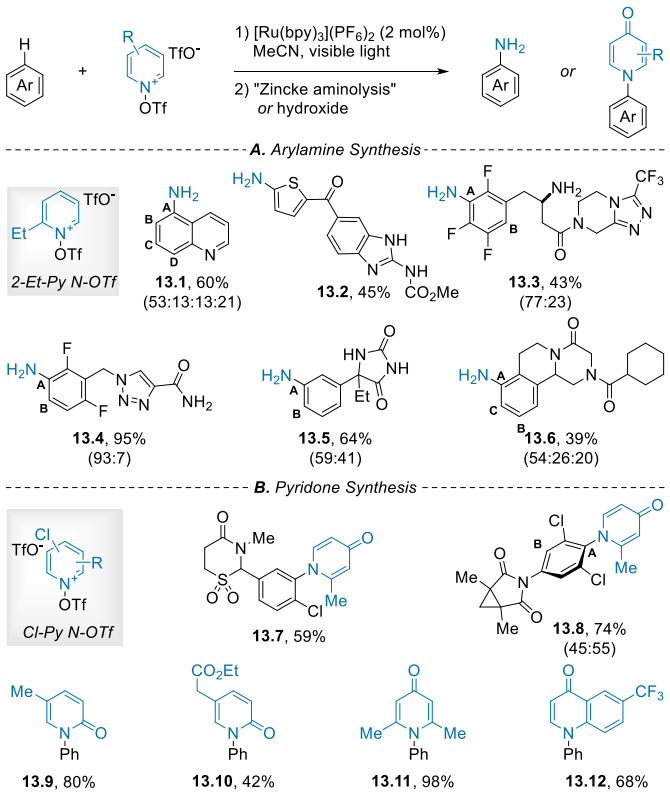

**Scheme 11.** Pyridinium N–X cleavage pathways: homolytic vs heterolytic determined by identity of X-group.




**Scheme 12.** Carreira and Togni's collaborative report on *N*-aryl pyridiniums via pyridinium radical cation amination (A) Scope of arene coupling partners (B) Derivatizations of *N*-aryl pyridinium salts to diverse cyclic *N*-aryl amine scaffolds.

In a back to back report, Ritter group also reported on this strategy, in their case finding the use of a 2-ethyl-pyridinium salt led to increased reagent stability and thus improved yields (Scheme 13) [23]. Like the Carreira report, the amination was not site-selective, leading to statistical mixtures of regioisomers (**13.1**). The amination strategy was also demonstrated to be compatible with complex molecules and marketed drugs (**13.2**–**13.6**) in a late-stage fashion. A follow-up method was published where chlorinated pyridine *N*-oxides derivatives were used, leading to *N*-aryl pyridinium salts that could be smoothly converted to pyridones upon hydrolysis [24]. This method showed similar functional group compatibility to the first report from Ritter (**13.7, 13.8**). The pyridinium *N*-oxide could have a chloride substituent at the C2 or C4 position, leading to 2- or 4-pyridones (**13.9-13.11**) and it was shown that a quinoline *N*-oxide was also capable in engaging in this pyridyl radical cation pathway, leading to quinolone (**13.12**).

Taken together, the works of Carreira, Togni and Ritter show the potential of leveraging *N*-centered pyridyl radical cations as C–H amination reagents via *N*-aryl pyridinium salts. These seminal reports set the stage for future exploration and applications of the underexplored reactivity of *N*-centered pyridyl radical cations.



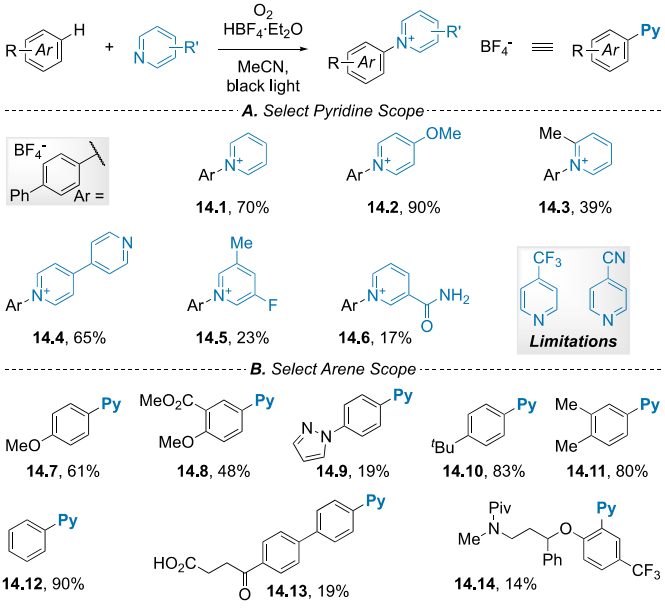

**Scheme 13.** Ritter's C–H amination to *N*-aryl pyridiniumds with pyridine *N*-OTf salts (A) Anline synthesis via 2-Et-*N*-OTf pyridinium salts. (B) Pyridone synthesis using 2-Cl or 4-Cl pyridine *N*-OTf salts.

### 2.3. Other radical cation methods

In addition to electrochemistry and photoredox catalysis, there have been a few reports of using electron donor-acceptor (EDA) complexes and hypervalent iodine chemistry to generate arene radical cations towards the synthesis of *N*-aryl pyridinium salts, obviating the need for expensive catalysts or electrochemical equipment. It is worth noting that radical cation generation from pyridine-arene EDA complexes and using hypervalent iodine reagents have both been methods known for decades [26–28], but only recently have their potential for pyridinium salt synthesis been realized.

In 2022, Sanford provided a follow-up to their 2021 report [18], this time using EDA complexes and black light under catalyst-free, aerobic conditions (Scheme 14) [29]. Inspired by seminal work of Bargon and Gardini who studied the EDA complex of naphthalene and pyridinium acetate [26], Sanford hypothesized that black-light irradiation of a pyridinium EDA complex could form a radical cation which could be trapped by pyridine free base and rearomatize in the presence of a terminal oxidant. The success of this reaction would mean that *N*-aryl pyridinium salts could be synthesized from C–H bonds without needing a photocatalyst.

A variety of substituted pyridines were compatible in the reaction, providing functional handles that can be precursors to substituted piperidines. Electron-rich and neutral pyridines (**14.1, 14.2**) and 2-substitution on the pyridine (**14.3**) were all well tolerated, the latter being a noteworthy limitation of many of the aforementioned methods. Using less nucleophilic heterocycles (**14.4**) or pyridines containing electron-withdrawing groups (**14.5, 14.6**) resulted in lower yields. When switching to pyridines with strong electron-withdrawing groups like trifluoromethyl or cyanopyridine, the reaction returns less than 5 % yield of product. With respect to arene scope, this method is compatible with anisole (**14.7**) and other electron-rich arenes (**14.8, 14.9**), as well as less-activated alkylarenes (**14.10,14.11**), and can even form *N*-phenyl pyridinium salt when benzene was used (**14.12**). The potential for late-stage functionalization was also demonstrated on drug molecules, albeit in low yields (**14.13, 14.14**).

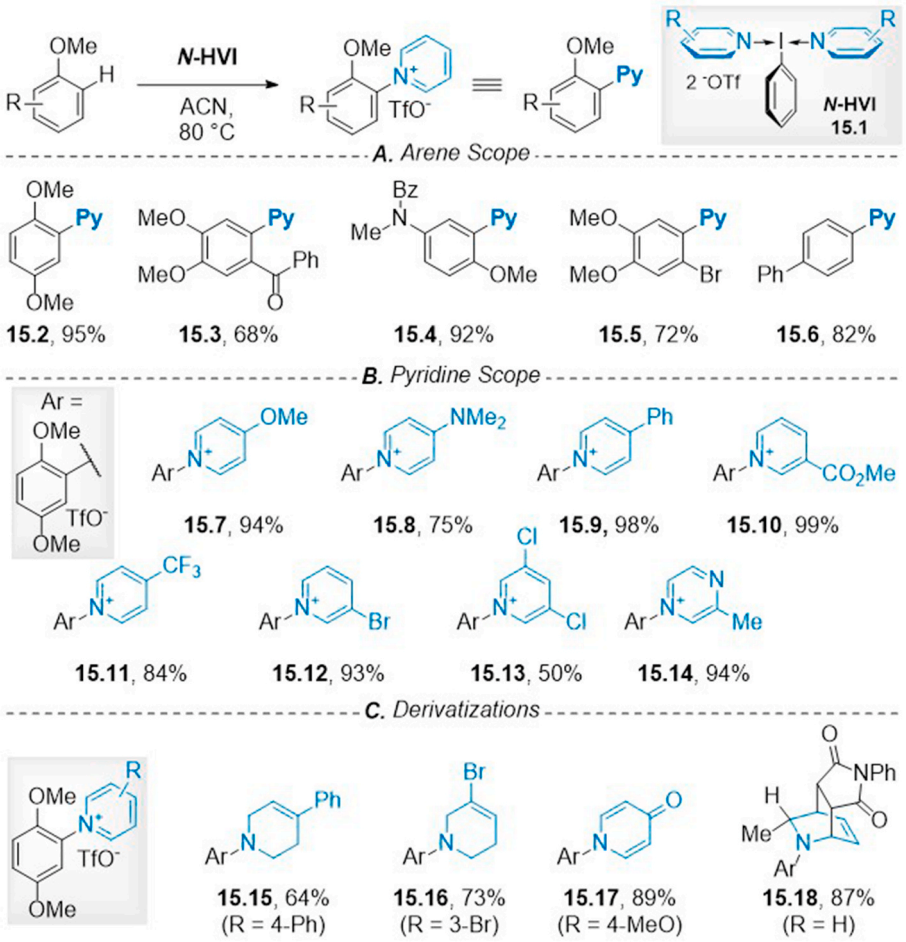



**Scheme 14.** Sanford's EDA mediated C–H amination to *N*-aryl pyridinium salts (A) Representative scope of pyridine coupling partners. (B) Representative scope of arene coupling partners.

Mechanistically, this reaction is successful due to the reversible nature of pyridine protonation, allowing it to engage in the EDA complex while protonated, and to serve as a nucleophile to trap radical cations while in its free-base form. Black light irradiation triggers single electron transfer, generating the key arene radical cation intermediate, which is then trapped by pyridine before back electron transfer can occur. With oxygen serving as terminal oxidant, *N*-aryl pyridinium salts can be successfully generated from arene C–H bonds without the need for an exogenous photocatalyst.

In 2023, the Wengryniuk lab reported that hypervalent iodine reagents (HVI) could be used to form arene radical cations, generating *N*-aryl pyridinium salts (Scheme 15) [30]. Seminal work from the Kita group [27,28] showed that hypervalent iodine reagents could serve as competent single electron oxidants to generate arene radical cations in the presence of fluorinated alcohols However it was found that when pyridine was used in these classical reaction conditions, no desired *N*-aryl pyridinium salt product was detected likely due to competitive hydrogen bonding with the fluorinated alcohol solvent. The Wengryniuk group found that *N*-aryl pyridinium salts could be generated using a unique class of (bis)cationic *N*-heterocyclic ligated I(III) reagents known as *N*-HVIs (**15.1**). The *N*-HVI reagents are shown to act as both single-electron oxidant and heterocyclic group transfer reagents through incorporation of one of the heterocyclic X-ligands. Notable of this chemistry is the use of pyridine ligands enables facile oxidative amination chemistry with I(III) reagents, an area that has limited development due to the incompatibility of typical amine nucleophiles with I(III) oxidants [31,32].

It was found that substitution pattern on the arene ring had a significant effect reaction outcome, with arenes possessing 1,2- and 1,4-disubstitued electron-donating groups giving *N*-aryl pyridinium salts, all in high site-selectivity. Dialkoxyarenes (**15.2, 15.3**) gave aminated products in high yields. Excellent site-selectivity was observed with methoxy anilides (**15.4**), giving amination *ortho* to the methoxy group. Interestingly, dimethoxy aryl bromide gave a mixture of C–H amination (**15.5**), as well as an unexpected redox neutral $S_NAr$ of the C–Br bond analogous to the Sanford report (see Scheme 8). This unusual redox-neutral




**Scheme 15.** Wengryniuk's I(III) *N*-HVI mediated synthesis of *N*-aryl pyridinium salts (A) Selected scope of arene derivatives. (B) Selected scope of pyridine derivatives (C) Derivatizations of *N*-aryl pyridinium salts to diverse *N*-aryl cyclic amines.

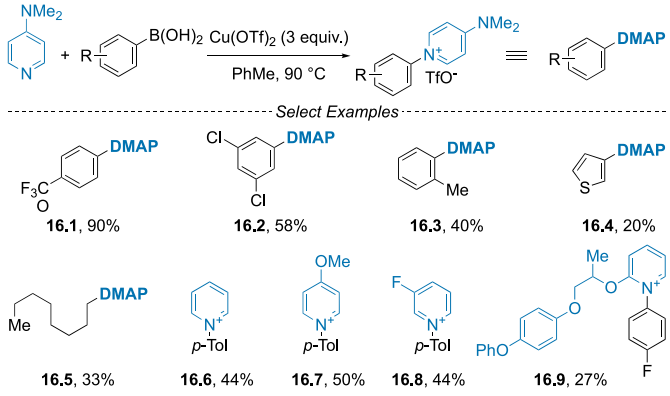
transformation under oxidizing conditions is the subject of ongoing investigation within the Wengryniuk lab. Polyaromatic systems were also tolerated (**15.6**) providing amination products without the need for multiple electron-donating groups. The modular synthesis of the *N*-HVI reagent (**15.1**) allows a broad scope of pyridines to be used in the reaction, with both electron-rich (**15.7**–**15.9**) and electron-deficient (**15.10**–**15.14**) pyridines being highly successful. This broad heterocycle scope was demonstrated to give a variety of substituted *N*-aryl piperidine derivatives through downstream functionalization. Borohydride reduction gave partially reduced 3,4-dehydropiperidines with either phenyl (**15.15**) or bromide (**15.6**) substitution on the alkene which would be challenging to access through typical C–N cross-coupling methods. Methoxy pyridinium salts can be converted to pyridones (**15.17**) through nucleophilic demethylation. A sequential Grignard reaction followed by Diels-Alder reaction also provided isoquinuclidine (**15.18**) in excellent yield. It is worth noting that while some of the "classical" reactions of *N*-phenyl pyridinium salts have proven to be general in these studies, variation in both the arene and pyridine substiution has revealed surprising outcomes and unexpected challenges. These observations have only been made possible through the increasing diversity of substrates available via the discussed methods, showing the continued need for further exploration in this area.

## 3. Non-radical cation methods

While the single-electron redox strategies described above have dominated much of the developments in *N*-aryl pyridinium synthesis, complimentary approaches using transition metal catalysis or *N*-activation of an azine have also been developed.

In 2021, Allan Watson's group developed a copper mediated cross-coupling method using pyridines and aryl boronic acids for the synthesis of *N*-aryl pyridinium salts (Scheme 16) [33]. Typically in transition metal C–N bond forming reactions, the nitrogen coupling partner bears at least one N–H bond. Watson found that neutral N-ligands can also engage in cross-coupling reactions with a variety of aryl boronic acids, leading to *N*-aryl pyridinium products.

The reaction works best with electron-rich pyridine derivatives,




**Scheme 16.** Watson's copper catalyzed *N*-aryl pyridinium synthesis via coupling of pyridine and aryl or alkyl boronic acids.

likely due to the oxidative nature of the coupling process. The scope of aryl boronic acids includes both electron-rich (**16.1**) and electron-deficient (**16.2**) arenes, all giving good yields. For *ortho*-substituted aryl boronic acids (**15.3**) and heterocycles (**16.4**), the reaction proceeded, albeit in slightly lower yields. Alkyl boronic acids could also engage in this reaction (**16.5**), leading to formation of *N*-alkyl pyridinium salts. A small heterocycle scope was also demonstrated to be successful (**16.6**–**16.8**) offering options for further derivatizations. The agrochemical Pyriproxyfen could also engage in the *N*-arylation reaction (**16.9**), demonstrating potential for late-stage functionalization applications.

The reaction proceeds analogously to a Chan-Lam coupling. HRMS data provided me chanistic support that suggested transmetalation of arylboronic acid followed by disproportionation to give Cu(III) intermediates which can then undergo reductive elimination to form the desired C–N bond. This is the first example of the synthesis of pyridinium salts via cross-coupling, and will hopefully inspire new methodologies and approaches to pyridinium salts using transition metal catalysis.

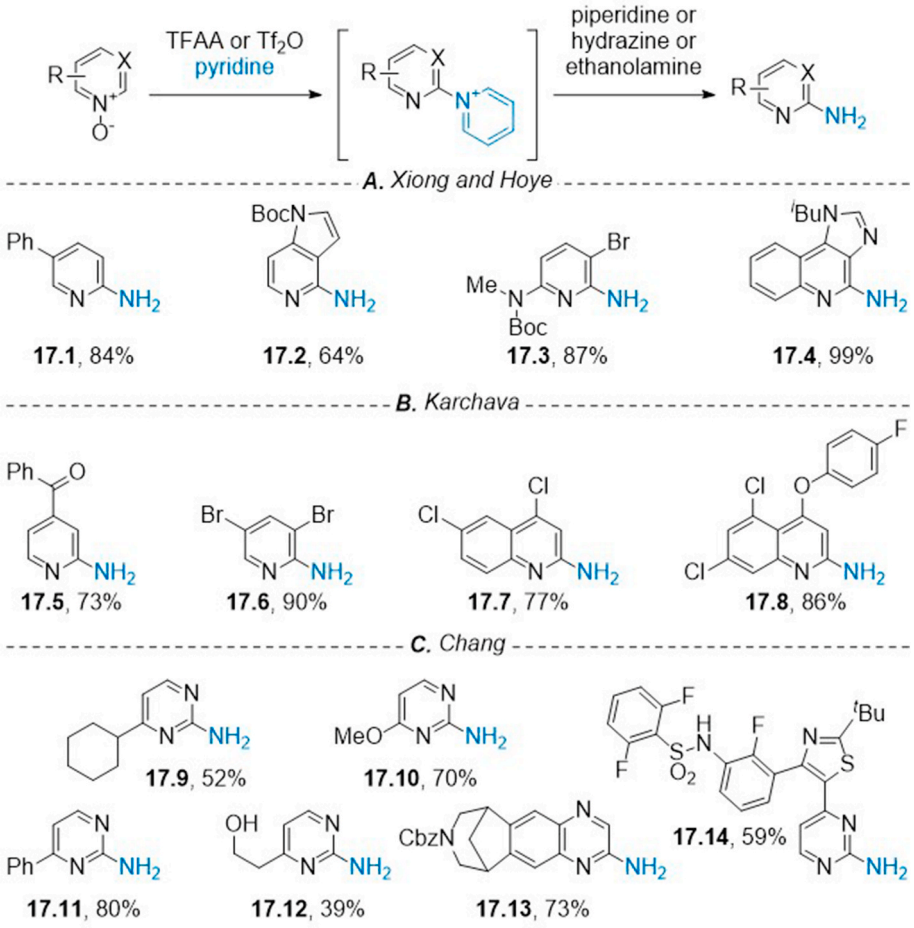
A series of reports from Xiong and Hoye [34], Karchava [35], and Chang [36] utilized azine *N*-oxides for the synthesis of *N*-heteroaryl pyridinium salts (Scheme 17). All three reports proceed via the two-step oxidation/activation sequence typical of *N*-oxide chemistry, wherein the *N*-oxide species is then activated and subjected to nucleophilic attack with pyridine derivatives. Despite being electrophilic at both C2 and C4, amination of pyridine or quinoline derivatives (Scheme 17A, B) occurs selectively at the C2-position of the *N*-oxide, which aligns with prior reports of *N*-oxide amination in the literature. Conversely, pyridination of pyrimidines (Scheme 17C), shows site-selectivity that is dependent on the electronics of the pyridine nucleophile.

In their ongoing efforts to fluorinate pyridine *N*-oxides [37], Xiong and Hoye serendipitously discovered that they could generate *N*-aryl pyridinium salts and smoothly convert them to 2-aminoazine products through Zincke aminolysis (Scheme 17A) [34]. This chemistry was applied to a variety of medicinally relevant molecules. The conditions were also demonstrated to be highly effective for late-stage amination as well as a useful strategy for isotopic labeling.

The Karchava group utilized their methodology to make *N*-heteroaryl pyridinium salts as precursors for hybrid NHC-containing ligands (Scheme 17B) [35]. The nature of the pyridinium salt imparts several attractive features as a ligand: strong σ-donating and π-accepting ability, increased stability, and potential hemilability which provides easy generation of vacant coordination sites in catalytically active transition metal complexes.

The Chang group developed a C2-amination of pyrimidines using an *N*-oxide activation strategy (Scheme 17C) [36]. The presence of an additional nitrogen within the pyrimidine heterocycle led to the formation of regioisomeric mixtures of pyridinium products at either C2 or C4/C6 position Using the Bell-Evans-Polanyi principle, the Chang group showed that electron-rich pyridine derivatives produced mixtures of C2 and C4 products and electron-deficient pyridines strongly favored C2 amination. This strategy was successfully demonstrated on a variety of pyrimidines containing benzylic C – H bonds (**17.9**) and in late-stage functionalization reactions (**17.14**) using electron-deficient trifluoromethyl pyridine derivatives as amine source.

In 2024, the Chang lab explored the origin of C4-selectivty in pyridine C–H amination [38]. It was found that when subjecting pyridine




**Scheme 17.** Synthesis of *N*-heteroaryl pyridinium salts from azine *N*-oxides. (A) Xiong and Hoye's azine C–H amination. (B) Karchava's azine C–H amination (C) Chang's C2 selective pyrimidine C–H amination.

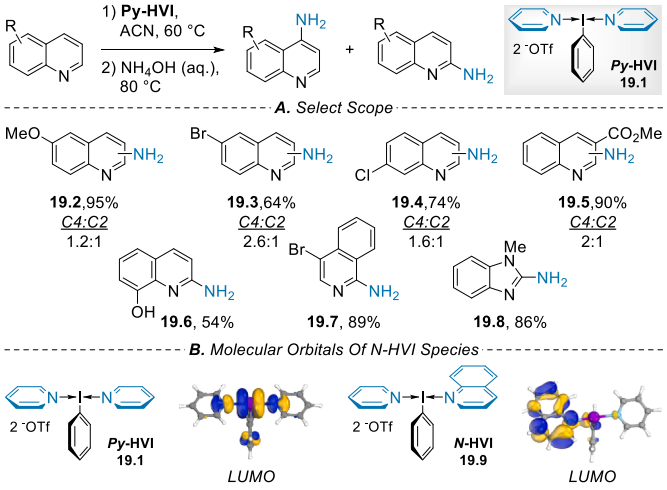
*N*-oxides to a triflyloxy-activating group in polar solvents with electron-deficient pyridine derivatives, the typical C2-amination pathway was no longer favored, instead providing C4 aminated products (Scheme 18). Detailed mechanistic investigations revealed that strong polarizability in the proton elimination step is what is ultimately responsible for the C4-selective addition.

This operationally simple and robust procedure displayed phenomenal functional group compatibility including halogenated pyridines (**18.1**), pyridines containing Michael acceptors (**18.2**), and could be used in late stage functionalization of Loratadine (**18.5**). This methodology was also expanded to demonstrate C4-amination of benzofused pyridines (**18.3**), and complex diazines (**18.4**). All pyridinium salts could be smoothly converted to the corresponding amines via Zincke aminolysis. This work represents the first C4-selectvie C–H amination of pyridines, a previously underdeveloped and understudied reaction.

In 2024, the Wengryniuk lab demonstrated a method for the direct synthesis of *N*-heteroaryl pyridinium salts that obviated the need for pre-oxidation to the *N*-oxides (Scheme 19) [39]. Once again utilizing the *N*-heterocyclic ligated I(III) *N*-HVI reagents, this time with an *in situ* generated pyridine-based reagent, *Py*-HVI (**19.1**), mixtures of C4 and C2 amination products were generated. It should be noted that the high degree of C4-amination is in contract to the C2-selective *N*-oxide methods shown in Scheme 16. Similarly to Chang's C4-selective amination (see Scheme 18), this work demonstrates another possible avenue for the elusive C4–H amination.

The substrate scope was tolerant of both electron-rich (**19.2**) and electron-poor (**19.3**–**19.5**) quinoline derivatives with substitution on both the benzo portion and azine portion tolerated. The reaction generates mixtures of C2 and C4 *N*-heteroaryl pyridinium salts except for cases where the C8 position is substituted (**19.6**). The pyridinium salt intermediates can be easily converted to aminoquinolines via Zincke aminolysis, either via a trituration/cleavage sequence or in a telescoped one-pot process. In addition to quinolines, isoquinolines (**19.7**) and 5-membered benzo-fused heterocycles (**19.8**) were also compatible with this chemistry.

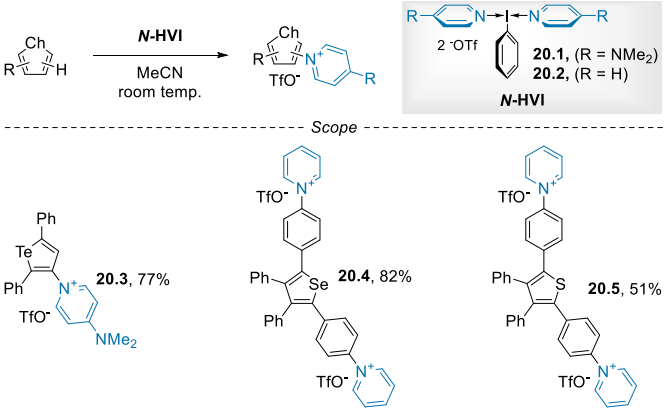
Computational studies conducted by Dutton and Wilson supported a mechanism where *Py*-HVI (**19.1**) served as a multifunctional reagent. First, the benzofused azine displaces a pyridine ligand, generating an unsymmetric hypervalent iodine intermediate (**19.9**). The LUMO of this species is then localized to the benzofused azine, rendering the C2 and C4 position of the positions to become highly electrophilic. Pyridine can then attack at either C2 or C4, followed by elimination of phenyl iodine and rearomatizing the azine leading to the mixture of *N*-heteroaryl pyridinium salts. Kinetic barriers to attack at either C2- or C4- were found to be very close in energy, explaining the regioisomeric mixtures of products. Not only does this method avoid the additional oxidation step of N-oxides, but the high levels of C4-amination provide



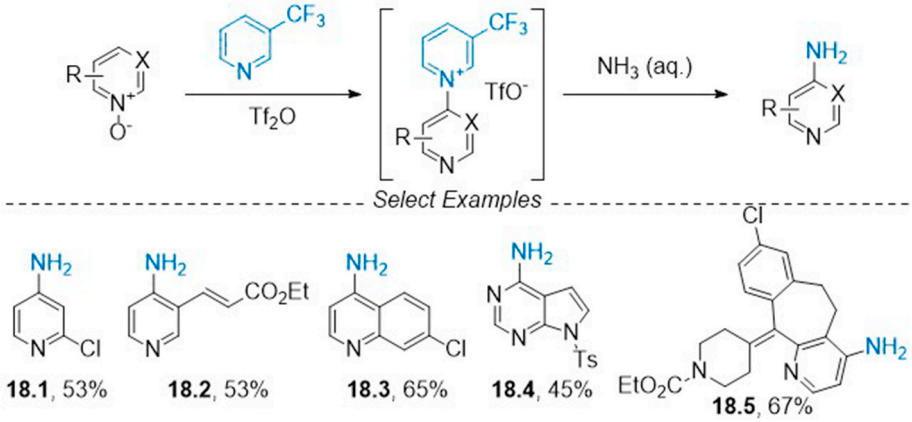

**Scheme 19.** Wengryniuk's benzofused direct C2/C4 azine C–H amination via I(III) *N*-HVI activation. (A) Select scope of heteroarene coupling partners. (B) Computationally predicted LUMOs of *N*-HVI reagents.

complementary product distributions, providing a valuable new tool in heteroarene amination.

In 2015, Dutton and Wilson previously had explored if chalcogen containing heterocycles could have their optical absorption properties tuned through oxidation of the chalcogen atom (Scheme 20) [40]. When combined with *N*-HVI reagent (**20.1**), unexpected C–H functionalization




**Scheme 20.** Dutton and Wilson's I(III) *N*-HVI mediated synthesis of *N*-aryl pyridinium salts from chalcogen containing heterocycles.




**Scheme 18.** Chang's C4-selective amination of pyridine *N*-oxides.

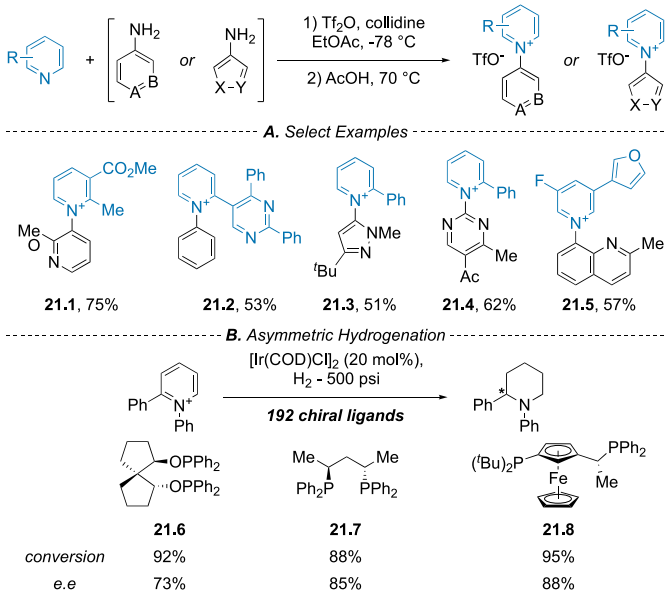
took place, providing a unique *N*-aryl pyridinium salt (**20.3**) with unique electronic properties. Followup studies extended this chemistry to include oxidation of the lighter chalcogens with (**20.2**), providing dicationic bis *N*-aryl pyridinium salts (**20.4, 20.5**) [41].

The McNally group, in collaboration with Merck Sharp and Dohme LLC developed a new method to prepare *N*-heteroaryl pyridinium salts from heteroaryl amines (Scheme 21). The strategy uses the triflic anhydride activation strategy pioneered by the McNally group to activate pyridine derivatives, which in this case are attacked by aminated azines in a modern interpretation of the Zincke reaction (see Scheme 1). This method generates diverse substituted *N*-heteroaryl pyridinium salts which can then be hydrogenated to provide substituted piperidines. The scope of the reaction was examined using high throughput experimentation (HTE) consisting of pharmaceutically relevant compounds. HTE revealed trends and enabled discovery of successful reactions which may not have been considered possible using chemical intuition, including 2-substitited pyridines (**21.1**–**21.4**), and complex, electron-deficient heteroaryl amines (**21.3**–**21.5**).

While hydrogenation of pyridinium salts to produce piperidines is a well-established reaction, a general asymmetric version had not yet been reported. Using HTE, McNally and the Merck collaborators were able to screen nearly 200 chiral phosphine ligands and iridium pre-catalysts in asymmetric hydrogenation reactions. They found success with multiple chiral ligands (**21.6**–**21.8**) indicating that a general approach for asymmetric catalysis is viable, noting that future studies are ongoing to identify ligand scaffolds capable of reducing a broader scope of pyridinium derivatives.

## 4. Novel reactions of *N*-aryl pyridinium salts

The synthetic advances outlined in the prior sections represent important advancements towards the ability of *N*-aryl pyridinium salts to be viewed as general amine precursors. As the focus of these efforts lie in the new methods of accessing the pyridinium compounds, any downstream functionalizations were limited to established methods from the literature. It was repeatedly demonstrated that *N*-aryl pyridinium salts are useful as masked aniline precursors, with the free amine readily unvield via Zincke aminolysis. Furthermore, hydrogenations, borohydride reductions, nucleophilic functionalizations and cycloadditions all demonstrated access to functionalized lower oxidation state *N*-heterocycles or pyridones. The following section will highlight recent advances in *N*-aryl pyridinium salt derivatizations, with applications ranging from molecular editing to isotopic labeling, that highlight the frontiers of this research area.

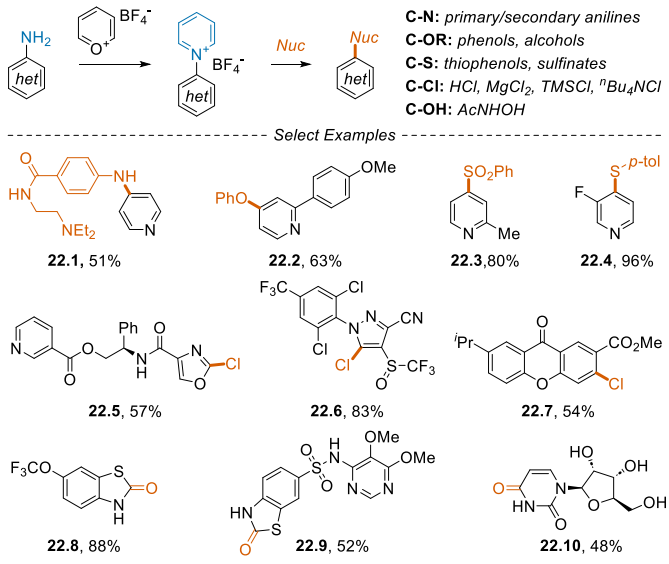



**Scheme 21.** McNally and Merck's *N*-heteroaryl pyridinium salt synthesis via triflate activation. (A) Selected scope from HTE study. (B) Asymmetric hydrogenation of an *N*-aryl pyridinium salt enabled by HTE catalyst and ligand screening.

### 4.1. Deaminative functionalizations of *N*-heteroaryl pyridinium salts

The preparation of highly functionalized heterocycles by $S_NAr$ reactions using heteroaryl halides is one of the most ubiquitous reactions in industrial chemistry. An analogous substitution strategy but starting from heteroaryl amines would represent a highly coveted orthogonal transformation as it would enable aryl C–N bonds, prevalent in many pharmaceuticals, to be transformed in $S_NAr$ fashion. The Cornella lab conceived of such a strategy via the activation of the aryl C–N bond by conversion to the corresponding aryl pyridinium upon condensation with an oxopyrylium (Scheme 22) [42]. The resultant *N*-heteroaryl pyridinium salts can then undergo facile $S_NAr$ reactions leading to a variety of new functionalized heteroarenes through the net substitution of an aryl amine [43–45].

Cornella has demonstrated that *N*-heteroaryl pyridinium salts can engage in efficient $S_NAr$ reactions with a broad range of nucleophiles, providing new C–N, C–O, C–S, and C–$SO_2$R bonds [43]. This method offers incredible safety and chemoselectivity and was demonstrated successfully for late-stage functionalization of pharmaceutically relevant molecules (**22.1**–**22.4**). Certain nucleophiles such as primary alkylamines, and carbon centered nucleophiles were incompatible with the desired $S_NAr$ reaction. To increase the scope, a single flask preparation of heteroaryl chlorides from aminoheterocycles was developed [44]. Similar to the Sandmeyer reaction but with broader functional group compatibility, this method avoids the use of explosive diazo intermediates and strongly oxidizing reagents, allowing for a mild deaminative chlorination reaction. High functional group tolerance enables access to heteroaryl chlorides which could be used in further cross coupling reactions that can form new C–N and C–C bonds in late-stage functionalization strategies (**22.5**–**22.7**). Deaminative hydroxylation was also developed to reverse hydrogen bonding ability via an inverted tautomer [45]. Using hydroxamic acid to cause a mild, bio-inspired Lossen rearrangement enabled a deaminative hydroxylation of *N*-heteroaryl pyridinium salts. This method was applicable to biorelevant molecules with broad functional group tolerance and was also able to convert electron deficient anilines to the corresponding




**Scheme 22.** Cornella's deaminative functionalization strategy: C–N bond activation via pyridinium salt formation.

phenols (**22.8-22.10**).

In addition to deaminative $S_NAr$ reactions, the Cornella lab developed a novel deaminative borylation reaction which proceeds through a homolytic bond cleavage (see Scheme 11) to form an aryl radical which can undergo C–B bond formation (Scheme 23) [46]. In recent years, pyridinium salts have been used to generate carbon centered radicals, but this has seen success almost exclusively on alkyl N–C($sp^3$) pyridinium salts [25,42,47–49]. The Cornella lab was able to demonstrate that a designer pyrylium reagent (**23.1**) which forms an *N*-aryl pyridinium salt capable of generating aryl radicals upon single electron reduction from a borane-amide complex. Mechanistically, the designer pyrylium reagent (**23.1**) forms an *N*-aryl pyridinium salt which contains constrained ethane bridges, leading to a heavily strained polyaromatic system. The release of this bond angle torsion allows the *N*-aryl pyridinium salt to overcome the thermodynamic barrier associated with homolytic C–N cleavage in the putative mechanism.

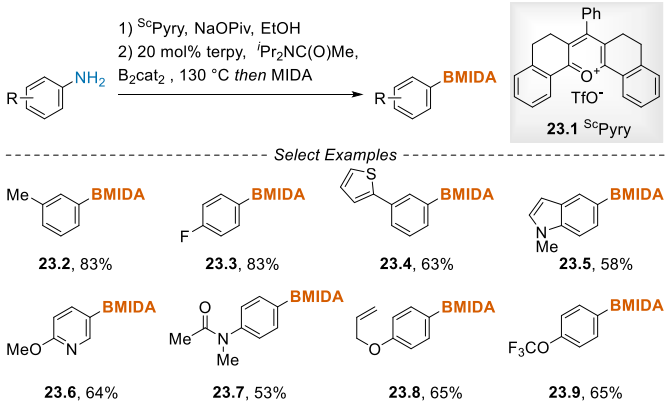
This borylation reaction is compatible with a range of functional groups, tolerating benzylic C–H bonds (**23.2**) as well as aryl halides (**23.3**) which provide products with orthogonal cross-coupling handles for future reactions. Heterocyclic aryl radical can be generated without competitive Minisci-type reactions (**23.4**–**23.6**) and electron-rich anilines can also be used as starting materials (**23.7**–**23.9**).

### 4.2. Reactions with Zincke salts

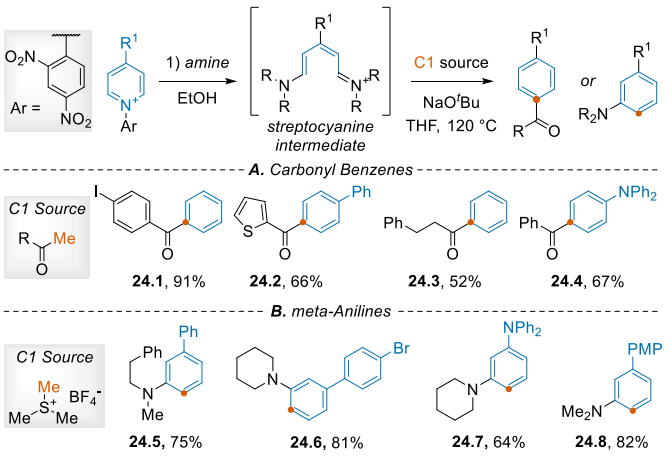
The reaction of the Zincke salt with primary and secondary amines to produce either new *N*-aryl pyridinium salts or cyanine dyes has been known for over a century [50–52]. These reactions utilize an "addition of the nucleophile, ring opening, and ring closing" (ANRORC mechanism) used to make *N*-aryl pyridinium salts from Zincke salts (see Scheme 1). In recent years, there have been creative advances for the synthetic utility of this reaction through the addition of nucleophiles which unlock new reaction pathways. There have been several examples of molecular editing and isotopic labeling which combine the ANRORC reaction of Zincke salts with novel nucleophiles, expanding the synthetic utility of the classic *N*-aryl pyridinium salts.

Morofuji and Kano have explored molecular editing of Zincke salts to convert pyridines to benzenes through a formal nitrogen to carbon exchange enabled by the reactivity of streptocyanines (Scheme 24). The overall strategy can be thought of as a (5 + 1) strategy for the synthesis of benzene rings. These two strategies lead to either 1,4-substituted carbonyl benzenes [53] or 1,3-substituted anilines [54] depending on choice of C1 nucleophile.

When methyl ketones were used as nucleophilic C1 source, the carbonyl benzene derivatives were all formed in excellent yield with good functional group compatibility (Scheme 24A) [53]. The reaction is tolerant of aryl halides (**24.1**), providing functional handles for future




**Scheme 23.** Cornella's deaminative borylation using a designer pyrylium reagent.



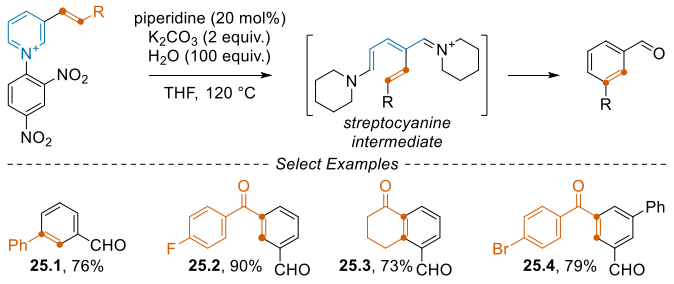

**Scheme 24.** Morofuji and Kano's formal 5 + 1 molecular editing strategy. (A) Examples of carbonyl bene derivatives (B) Synthesis of 1,3-disubstituted anilines.

reactions, heterocycles (**24.2**), non-aromatic methyl ketones (**24.3**), and substituted pyridine derivatives (**24.4**). This method represents and orthogonal approach to the typical cross-coupling or Friedel-Crafts reactions used to form these compounds.

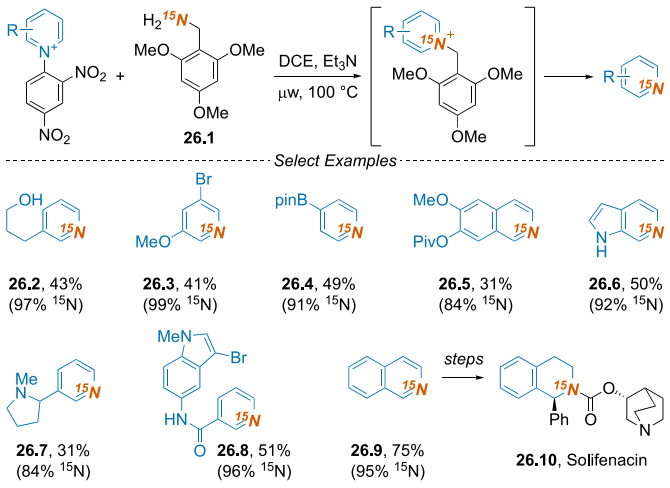
Switching to dimethylsulfonium methylide as a nucleophilic C1 source combines C–H amination with molecular editing for the synthesis of 1,3-substituted anilines from 4-substituted pyridines (Scheme 24B) [54]. This completely regioselective reaction is noteworthy as this substitution pattern is incompatible with electrophilic aromatic substitution chemistry and it does not require directing groups typically used to make 1,3-substituted aryl amines. The scope of the reaction was good with unsymmetric secondary amines being compatible in the reaction (**24.5**), as were electron-poor biphenyl pyridines which even contained bromo substitution, proving a handle for further transformation (**24.6**). Pyridines with diphenyl amine at the C4 position provide 1,3-diamino arenes (**24.7**), and the electron-rich 4-methoxyphenyl group was also tolerant of the reaction (**24.8**).

A third strategy that Morofuji and Kano developed used 3-vinyl pyridines to synthesize benzaldehyde derivatives using amine catalysis (Scheme 25) [55]. Using 3-alkenyl pyridines to make Zincke salts, a catalytic amount of piperidine will form streptocyanine intermediates which then undergo ring closing followed by elimination of piperidine to provide 3-substituted benzaldehydes upon work up. The tolerance for alkene substitution is high with styryl pyridines (**25.1**) and benzoylvinyl substituted pyridines (**25.2**) working in the reaction. More complex cyclohexanone moieties were able to form tetralones (**25.3**) as a single regioisomer. The starting pyridine could also be substituted at positions besides C3 to provide tri substituted benzaldehyde derivatives (**25.4**).

In 2024, the lab of Joel Smith used Zincke salts to label azines with $^{15}N$ (Scheme 26) using a designer $^{15}N$-labeled reagent (**26.1**) produced from commercial materials and an inexpensive $^{15}N$ source [56]. This




**Scheme 25.** Morofuji and Kano's amine catalyzed synthesis of benzaldehydes through a ring-closing reaction.




**Scheme 26.** Smith's Zincke salt $^{15}N$ azine labeling strategy.

reaction goes through a classic Zincke reaction to generate a highly reactive *N*-benzyl pyridinium salt. The highly electron rich trimethoxy arene putatively weakens the benzylic C–N bond which causes the ejection of the $^{15}N$ labeled pyridine derivatives with, on average, >95 % $^{15}N$ incorporation. This labeling strategy was compatible with simple pyridine derivatives (**26.2**–**26.4**) as well as more elaborate azines such as isoquinolines (**26.5, 26.9**), azaindoles (**26.6**), nicotine (**26.7**), and more complex pyridines (**26.8**). To show that this strategy could be incorporated into synthesis of bioactive compounds, a short formal synthesis of $^{15}N$ labeled Solifenacin (**26.10**) was carried out.

## 5. Conclusion

In conclusion, the diverse number of strategies to access *N*-aryl pyridinium salts has grown considerably in the last decade. Building on the pioneering work of Zincke, new methods now leverage a much broader range of coupling partners, transforming C–H and C-X bonds to *N*-aryl pyridinium salts. Many of the methods utilize oxidative strategies to activate either the arene or pyridine as radical cations, but complementary N-activation or cross coupling methods have also been reported. This ever expanding toolkit is fueling innovation in the downstream application of pyridinium salts, an area that will undoubtedly see continued growth in the years to come. We hope that this review serves as a useful overview of emerging methods, strategies, and opportunities in the synthesis and reactivity of *N*-aryl pyridinium salts.

## CRediT authorship contribution statement

**Bill J. Motsch:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Sarah E. Wengryniuk:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

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