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Article

A General Strategy for N-(Hetero)arylpiperidine Synthesis Using Zincke Imine Intermediates

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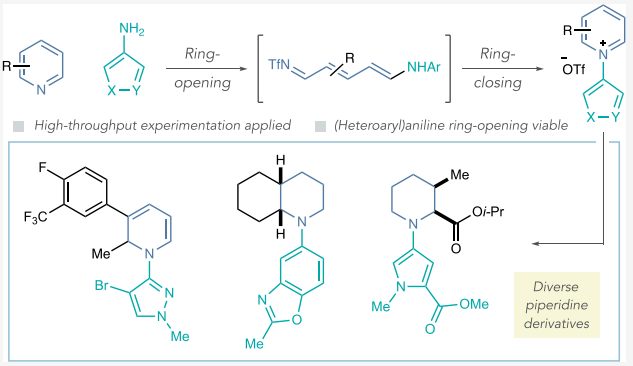
ABSTRACT: Methods to synthesize diverse collections of substituted piperidines are valuable due to the prevalence of this heterocycle in pharmaceutical compounds. Here, we present a general strategy to access *N*-(hetero)arylpiperidines using a pyridine ring-opening and ring-closing approach via Zincke imine intermediates. This process generates pyridinium salts from a wide variety of substituted pyridines and (heteroaryl)anilines; hydrogenation reactions and nucleophilic additions then access the *N*-(hetero)arylpiperidine derivatives. We successfully applied high-throughput experimentation (HTE) using pharmaceutically relevant pyridines and (heteroaryl)anilines as inputs and developed a one-pot process using anilines as nucleophiles in the pyridinium salt-forming processes. This strategy is viable for generating piperidine libraries and applications such as the convergent coupling of complex fragments.



INTRODUCTION

The importance of piperidines in pharmaceutical compounds is at odds with the capacity to easily modify their structure during structure−activity relationship (SAR) studies.[1−6] This dichotomy arises because piperidines are complex three-dimensional scaffolds that can vary substantially in their *C*- and *N*-substitution and stereochemistry, making synthetic alterations of these heterocycles challenging for even the most modern methods.[7−11] Furthermore, the pool of piperidine building blocks and predictable transformations of the ring system is limited compared to that of their aromatic pyridine counterparts. Here, we report a general approach to synthesizing *N*-(hetero)arylpiperidines, a common motif found in existing drugs and emerging candidates (Figure 1A). The strategy uses new versions of Zincke ring-opening and ring-closing chemistry to provide broad access to *N*-(hetero)-arylpyridinium salts from diverse sets of pyridines and (heteroaryl)anilines.[12,13] Numerous downstream reactions can access a multitude of piperidine derivatives. The strategy can generate compound libraries and enable strategic applications such as convergent couplings of complex substrates. Furthermore, this platform is suitable for high-throughput experimentation (HTE) to rapidly assess the compatibility of medicinally relevant pyridines with (heteroaryl)anilines.

There are several ways of forming *N*-(hetero)arylpiperidines, including de novo synthesis from acyclic precursors,[14,15] S_NAr reactions,[16] and metal-catalyzed C−N cross-couplings.[17] Practitioners must be aware of the capabilities and limitations of each reaction type during SAR studies. S_NAr reactions require electron-deficient (hetero)aryl halides with specific substitution patterns. Buchwald−Hartwig and Chan-Lam cross-couplings are significantly broader as the respective C−Hal and C−B coupling handles have fewer positional restrictions within (hetero)arenes.[17,18] However, piperidines with 2-position substituents can require specific phosphine ligands or can fail in these processes,[19,20] and Buchwald and Sather only recently reported a catalyst and base system for C−N coupling with five-membered heteroaryl halides.[21] Leonori reported that in situ-generated *N*-chloropiperidines can couple directly with arene C−H bonds in electron-neutral and electron-rich arenes using $Ru(bpy)_3Cl_2$ as a photocatalyst.[22]

An established way of synthesizing *N*-(hetero)-arylpiperidines is via their corresponding pyridinium salts,[23−27] with Zincke ring-opening and ring-closing chemistry being closely associated with this strategy (Figure 1B). In the first stage, pyridines react with 2,4-dinitro chlorobenzene to form *N*-arylpyrdinium salts; subsequent reactions with anilines

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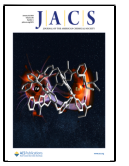

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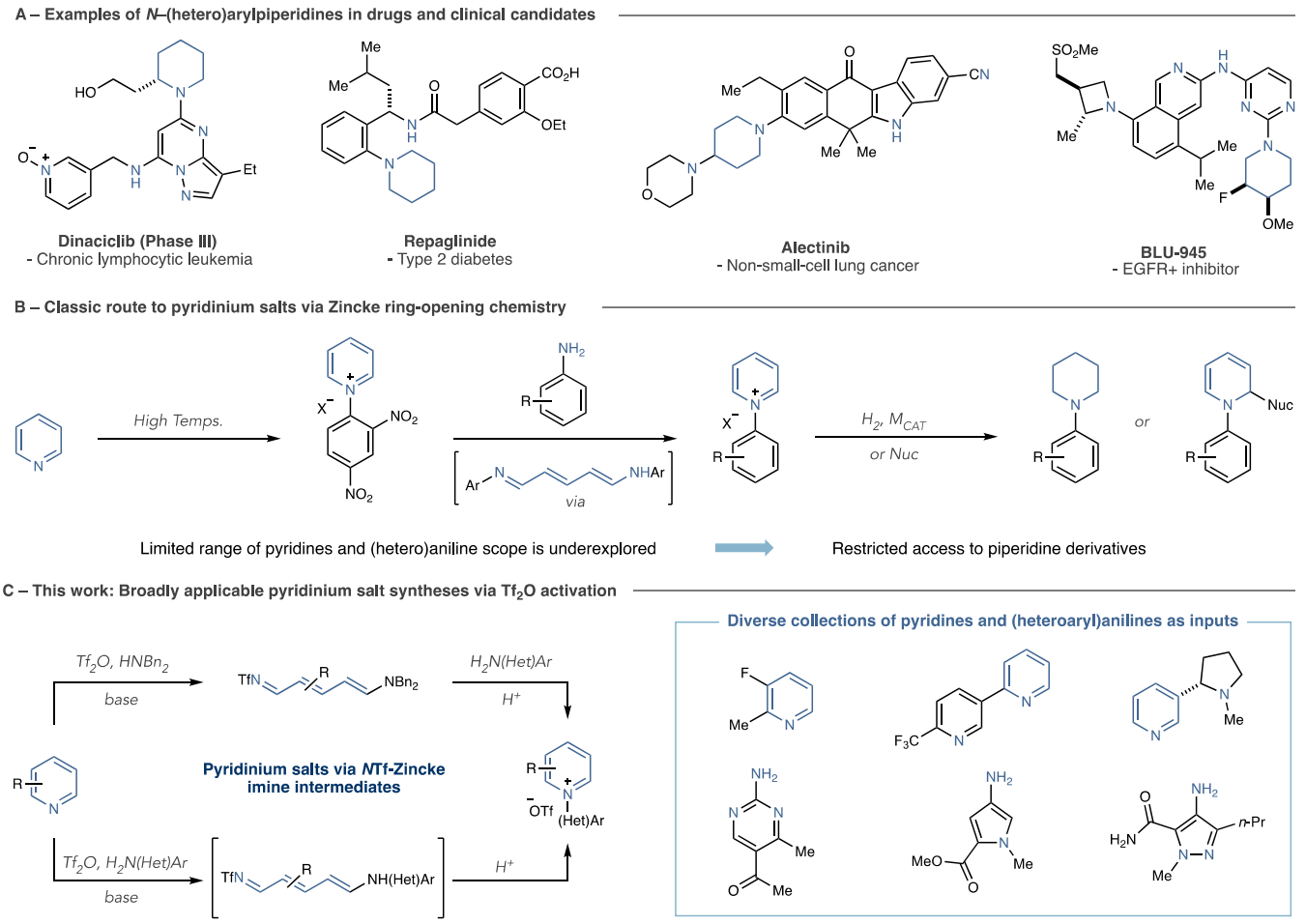


Figure 1. (A) Examples of pharmaceuticals and clinical candidates containing *N*-(hetero)arylpiperidines. (B) Classic Zincke approach using *N*-arylpyridinium salts and subsequent derivatizations. (C) New approach to *N*-(heteroaryl)pyridinium salts via *N*-Tf pyridinium salts that encompasses medicinally relevant pyridines and *N*-(heteroaryl)anilines.

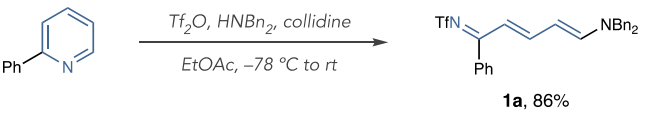
form the target pyridinium ion through ring-opened azatriene intermediates.[28,29] Metal-catalyzed hydrogenation reactions can provide access to piperidines and influence the stereochemical outcome.[30,31] Furthermore, pyridinium salts are reactive electrophiles and undergo addition reactions that substitute the carbon framework of the heterocycle. For example, nucleophiles selectively add to the 2- or 4-positions, and the resulting olefins in the dihydropyridine intermediates are amenable to further functionalization.[32] This flexible approach to piperidines is appealing for drug discovery, but the poor scope of pyridines that can function in the initial step to form the *N*-2,4-dinitroarylpyridinium salts effectively precludes routine use of this chemistry. Also, there has yet to be a thorough examination of the (heteroaryl)aniline scope in this reaction sequence. Direct approaches that form *N*-arylpyridiniumsvia radical ions or ionic cross-coupling reactions are highly promising. Controlling regioselectivity and expanding the scope of the pyridine partner are the remaining challenges for those processes.[23−27]

We disclosed a protocol for Zincke ring-opening chemistry via *N*Tf-pyridinium ion intermediates and dibenzylamine that functions on a broad range of substituted pyridines, including medicinally relevant structures (Figure 1C).[12] As a subsequent pyridinium salt-forming step proceeds via simple condensation and cyclization reactions, we hypothesized that many types of (heteroaryl)anilines could apply, and the overall ring-opening and ring-closing sequence would permit significant variation of the *C*- and *N*-substituents. Furthermore, given the pharmaceutical relevance of these building blocks and the general benefits of academic-industrial collaborations, we formed a partnership with Merck Sharp and Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD). This collaboration ensured that we could use resources such as MSD's HTE capabilities and extensive collection of (heteroaryl)anilines as well as pooling distinct expertise from each collection of scientists. During this study, we also discovered that (heteroaryl)anilines could be used directly in the ring-opening and ring-closing protocol to streamline this process.

RESULTS AND DISCUSSION

To begin our optimization study, we synthesized Zincke imine **1a** from 2-phenylpyridine in a good yield (Scheme 1). In Table 1, we tested reaction conditions to form *N*-phenylpyridinium salt **3a** using three equiv of aniline (**2a**) as a nucleophile in

Scheme 1. Pyridine Ring-Opening Protocol



1a, 86%

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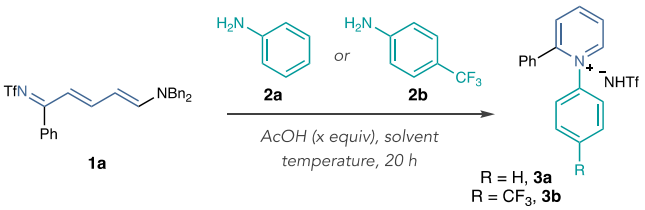
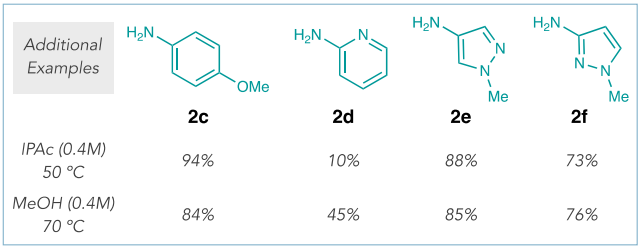
Table 1. Ring-Closing Optimization Study[a]



entry	aniline (equiv)	equiv. AcOH	solvent (M)	temp. (°C)	% **3a** or **3b**
1	**2a** (3.0)	0	IPAc (0.1)	50	trace
2	**2a** (3.0)	1	IPAc (0.1)	50	28
3	**2a** (3.0)	5	IPAc (0.1)	50	47
4	**2a** (3.0)	10	IPAc (0.1)	50	92
5	**2a** (1.5)	10	IPAc (0.1)	50	44
6	**2a** (1.5)	10	IPAc (0.2)	50	67
7	**2a** (1.5)	10	IPAc (0.4)	50	94
8	**2b** (1.5)	10	IPAc (0.4)	50	50
9	**2b** (1.5)	10	IPAc (0.4)	70	54
10	**2b** (1.5)	10	MeOH (0.4)	50	61
11	**2b** (1.5)	10	MeOH (0.4)	70	74



[a]Yields calculated by ^{1}H NMR spectroscopy using Ph_3CH as an internal standard.

isopropyl acetate (IPAc) as a solvent. We did not observe any product when we heated the two reactants at 50 °C (entry 1), and the reaction requires ten equivalents of AcOH to obtain a high yield of **3a** (entries 2−4). Lowering the equivalents of **2a** to 1.5 decreases the yield considerably, but increasing the reaction concentration restores efficient cyclization (entries 5−7). When we tested electron-deficient aniline **2b** under the same conditions as entry 7, we observed a 50% yield of **3b** (entry 8). Changing the solvent to MeOH and conducting the reaction at 70 °C resulted in a good yield of product **3b** (entries 9−11).

We suspected the aniline's electronic disposition might dictate the appropriate reaction conditions and tested four additional examples with a range of nucleophilicities. For *p*-anisidine (**2c**), using IPAc at 50 °C is more effective, whereas MeOH at 70 °C resulted in a higher yield for 2-aminopyridine (**2d**). This data indicates that the IPAc system could be more suitable for electron-neutral to electron-rich anilines and the MeOH system for electron-deficient anilines. When we tested 3- and 4-aminopyrazoles **2e** and **2f**, we saw that **2f** performed better, likely because the exocyclic NH_2 group is not conjugated with the ring sp^2-N atom and, therefore, more nucleophilic. However, we did not observe a significant difference between the two reaction conditions in each case. As we intended to vary the structures of the Zincke imine and aniline considerably and Table 1 is a relatively small dataset, we were cognizant of testing both solvents in the subsequent phase of the study.

With these sets of reaction conditions in hand, we explored the scope of the Zincke imine and (heteroaryl)aniline partners using HTE (Table 2).[33,34] In the first round of screening, we used Zincke imine **1a** with 24 (heteroaryl)anilines (**2b** and **2g**−**2ac**). The anilines include (hetero)aryl groups that are more likely to occur in drug discovery programs, despite the likelihood that the recyclization process may be challenging due to either steric congestion around the NH_2 group or electronic effects that would significantly reduce its nucleophilicity. We reasoned that it is more instructive for users to understand the limitations of this process, and a range of experimental results would help future studies in machine learning. Given our previous observations on the potential effect of temperature and solvent on the reaction outcome, we tested IPAc or MeOH at 50 or 70 °C, and we assembled the plates by dosing 5 μmol of imine **1a** and using 1.5 equiv of aniline and AcOH in each well. Reaction analysis used ultra performance liquid chromatography-charged aerosol detection (UPLC-CAD) with follow-up confirmation on select wells on a laboratory scale using quantitative ^{1}H NMR analysis.[35,36]

As shown in Table 2, we observed conversion to the desired pyridinium products for most cases, showing that a range of (heteroaryl)anilines with widely different steric and electronic characteristics are compatible. Exceptions include pyrimidine **2g**, 1,2-benzothiazole **2l**, 1,2-oxazoles **2u** and **2ab**, and furan **2x**, which produced no desired pyridinium products. However, these heterocycles should be competent for traditional S_NAr or C−N cross-coupling reactions when forming N-(hetero)-arylpiperidines, highlighting the complementarity of this approach. Although we anticipated that steric hindrance around the aniline NH_2 group could deter pyridinium salt formation, we were delighted to find that aminopyrazole **2i** worked reasonably well. In this screen, the reaction was largely invariant with solvent and temperature. Only aniline **2h** preferred MeOH at 70 °C, and anilines **2v** and **2w** improved significantly in IPAc at 50 °C. From these observations, we narrowed the reaction conditions to IPAc at 50 °C and MeOH at 70 °C in subsequent screens.

After we evaluated the (hetero)arylaniline component of the ring-closing process with our initial screen, we used HTE to broaden the scope of Zincke imine beyond imine **1a**. In Table 3, we synthesized 12-substituted Zincke imines (**1b**−**1m**, see Supporting Information for full details) and ran two 12 × 24 plates with the anilines **2b** and **2g**−**2ac** from Table 2. We ran the first plate in IPAc at 50 °C and the second in MeOH at 70 °C. In these larger screens, we reduced the amount of each imine needed to 2.5 μmol while running the plates at 0.18 M concentration with three equivalents of aniline to ensure the cyclizations could reach high yields (*cf.* Table 1, entry 4). In general, the two plates mostly overlap, regarding the outcome of the aniline−imine combinations. Anilines **2g**, **2d**, **2m**, **2q**, and **2v** gave the most appreciable yields of pyridinium salts across the Zincke imines tested, while anilines **2g**, **2l**, **2r**, **2u**, **2w**, and **2ab** gave little or no products under either set condition. As expected, the recyclization process proved to be challenging for aminopyrimidine **2g**, given its poor nucleophilicity. The lack of reactivity for the 1,2-azoles **2l**, **2u**, and **2ab** is surprising since the electronically comparable aminopyrazoles **2i**, **2o**, **2y**, and **2z** performed reasonably well. As in Table 2, pyrazole **2i** works well despite the exocyclic NH_2

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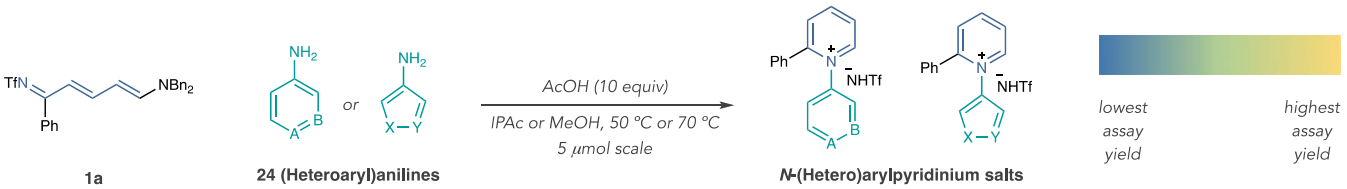
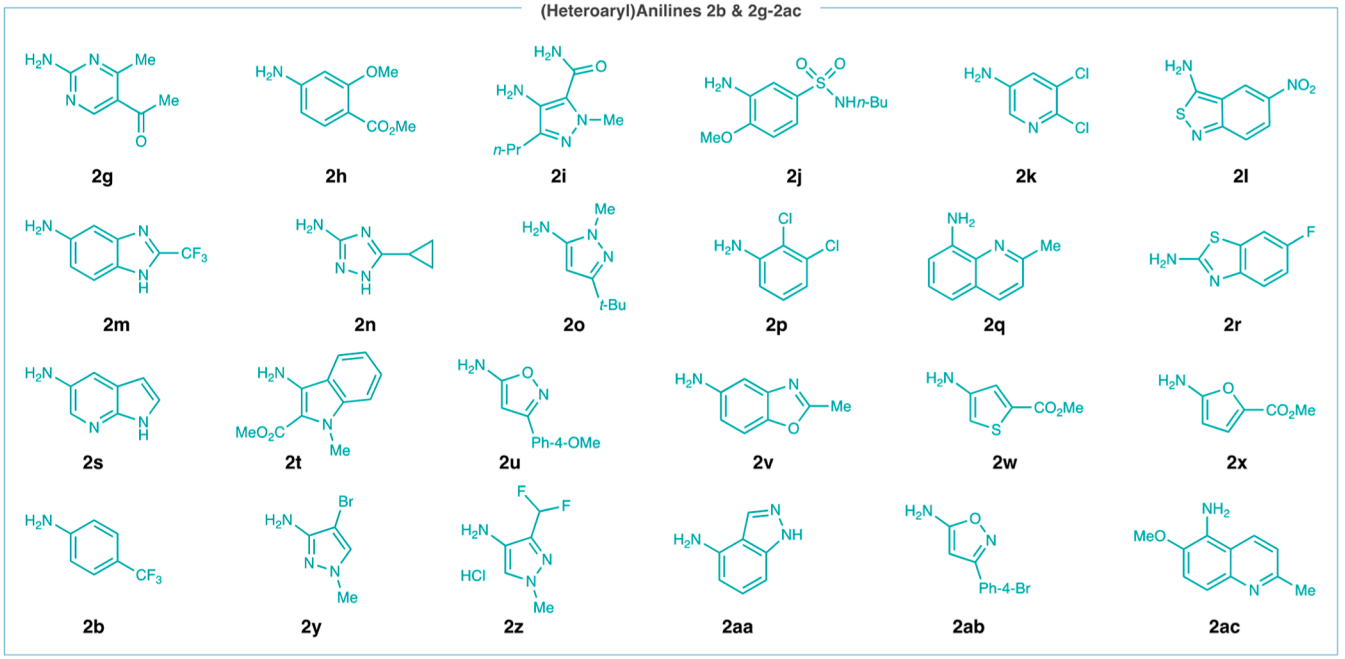
Table 2. High-Throughput Experimentation for Pyridinium Salt Formation: (Heteroaryl)aniline Evaluation[a,b]





	2g		2h		2i		2j		2k		2l		2m		2n		2o		2p		2q		2r	
	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH	IPAc	
50 °C	0	0	12	10	49	48	18	18	10	16	0	0	45	21	11	6	16	14	13	13	61	60	2	0
70 °C	0	0	19	42	41	43	15	17	24	30	0	0	43	40	3	7	9	12	2	7	50	30	0	0
NMR AY															16		24						Trace	

	2s		2t		2u		2v		2w		2x		2b		2y		2z		2aa		2ab		2ac	
	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH	IPAc	MeOH
50 °C	64	68	23	9	0	0	75	51	76	58	0	0	28	21	24	27	49	40	22	15	0	0	0	3
70 °C	66	50	21	16	0	0	51	35	39	37	0	0	8	10	23	30	47	27	34	27	0	0	3	13
NMR AY	29						61				0						72							

[a]24-(Heteroaryl)aniline screen: 5 μmol **1a**, 7.5 μmol (hetero)aryl aniline, 50 μmol AcOH, μmol, 0.39 M. [b]Yields calculated by UPLC-CAD analysis.

group being sterically hindered and in conjugation with the adjacent amide.

Although the data is primarily consistent between the two reaction conditions, Table 3 has several cases where pyridiniums form in IPAc at 50 °C but not in MeOH at 70 °C and vice versa. We show selected examples where a 10% yield of the product or more forms in one plate only.[37] These cases are particularly compelling as practitioners would obtain useful amounts of material for further studies. Furthermore, these results show that a typical optimization study, such as in Table 1, can be insufficient when reactants deviate significantly beyond simple systems and highlight the benefits of this HTE approach. While yields can vary considerably in Table 3, it is important to reiterate that the substrate combinations also vary extensively, and the range of pyridinium salts from this single approach is large. At this stage, it is difficult to provide definitive rules to predict successful pyridinium salt formation beyond simple nucleophilicity arguments. The structural and electronic variety in the (heteroaryl)anilines means that their reactivity is not straightforward to interpret using chemical intuition. We will use parametrization approaches and machine learning techniques in future studies to understand this cyclization reaction and develop predictive models.[38]

We then extended the scope of pyridinium salts on a preparative scale (Table 4). During this study, it was critical to develop purification methods that removed the reaction byproducts and functioned across this broad range of substrates. Exchanging the counterion from triflamide to triflate switches the pyridinium salts from aqueous to organic solvent soluble and enables isolation via simple extractions in most cases (see Supporting Information Section S5 for details). The first three entries **3c**−**3e** replicate Zincke imine and (heteroaryl)aniline combinations from Tables 2 and 3, which validates those data points. Salt **3f** further varied the pyridinium 2- and *N*-substituents. We obtained **3g** from nicotine and aminopyrazole **2i**, and **3h** is another example of a 3-substituted salt. We next examined a series of disubstituted salts; examples **3i**−**3l** contain carbon-bearing groups and halides on the pyridinium portion. Additionally, **3m** and **3n** show that the recyclization process tolerates esters at the 2-

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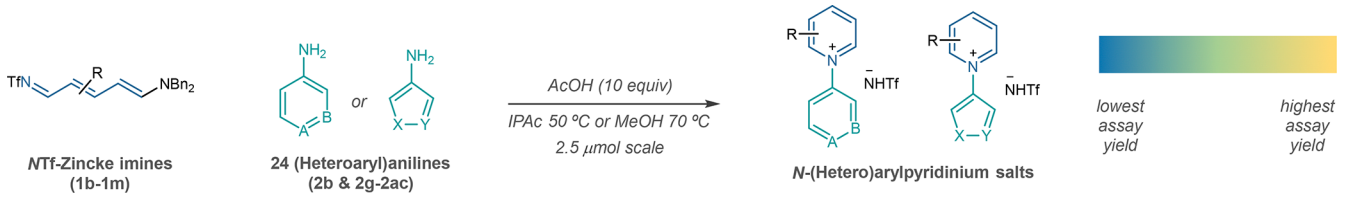
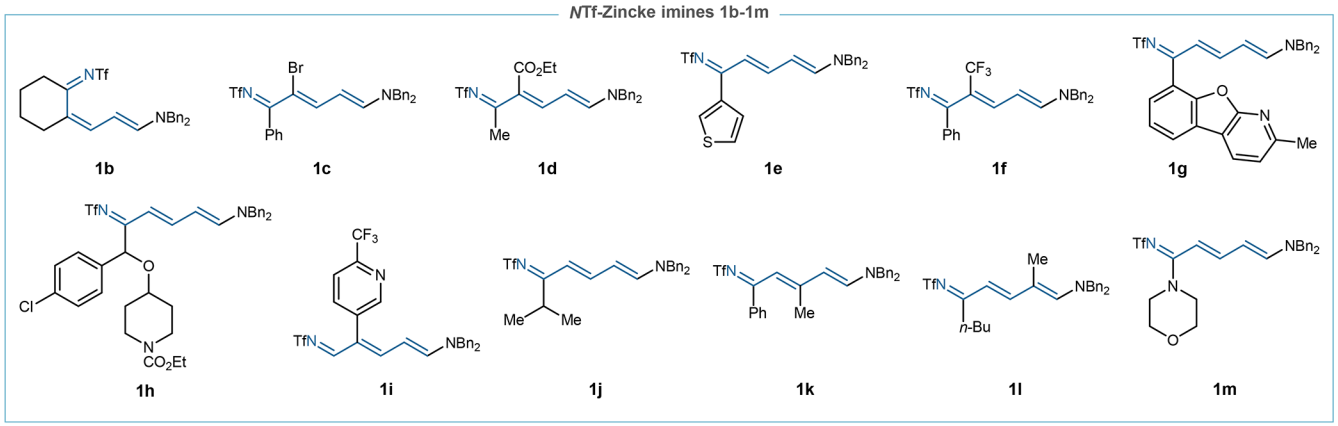
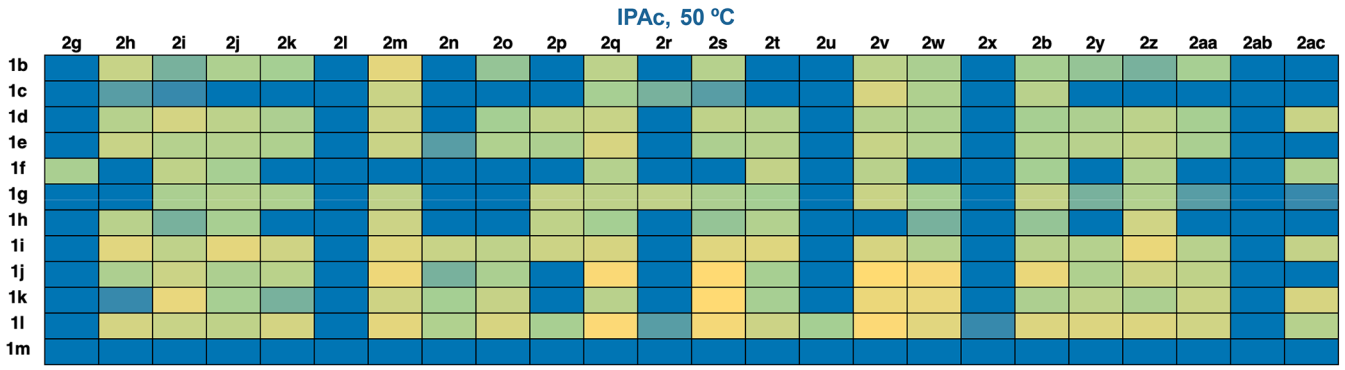
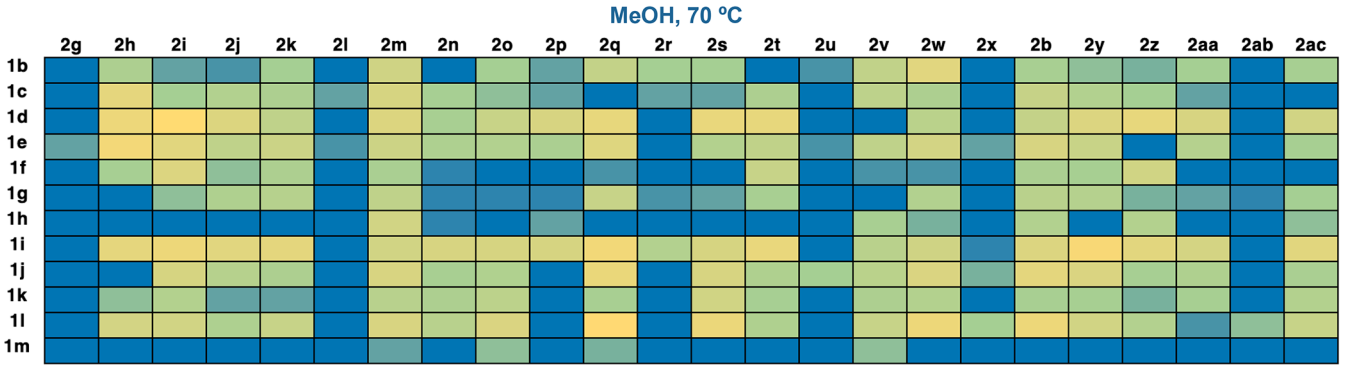
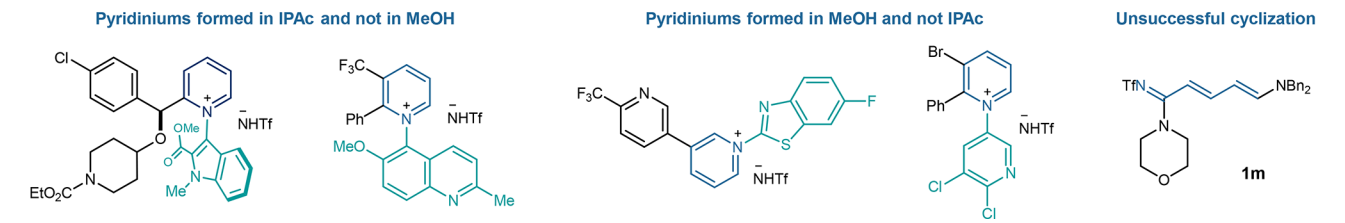
Table 3. High-Throughput Experimentation for Pyridinium Salt Formation: Simultaneous Zincke Imine and (Heteroaryl)aniline Screening[a,b]











[a]12 × 24 screen: 2.5 μmol **1b−1m**, 7.5 μmol (hetero)aryl aniline, 25 μmol AcOH, μmol, 0.18 M. [b]Yields calculated by UPLC-CAD analysis.

and 3-positions of the pyridinium ring. Notably, the (heteroaryl)aniline can vary substantially across **3c−3n**.

In the next part of the study, we attempted to streamline pyridinium salt formation by using (heteroaryl)anilines directly in a one-pot ring-opening-ring-closing process (Table 5). Here,

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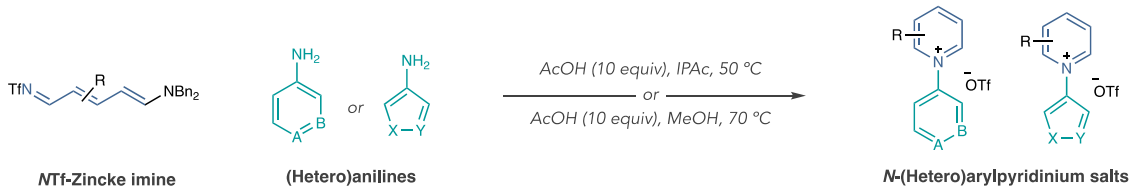
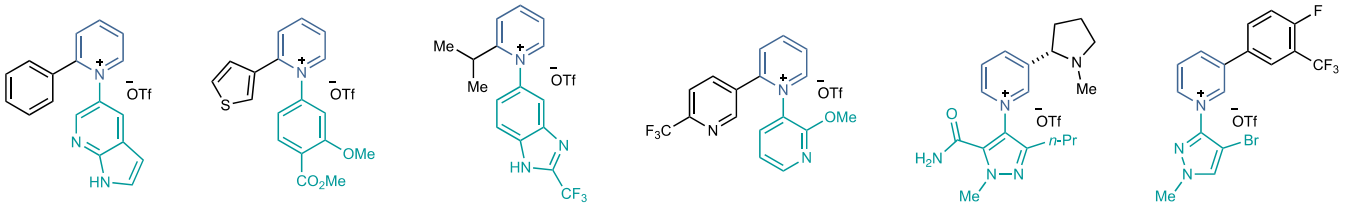
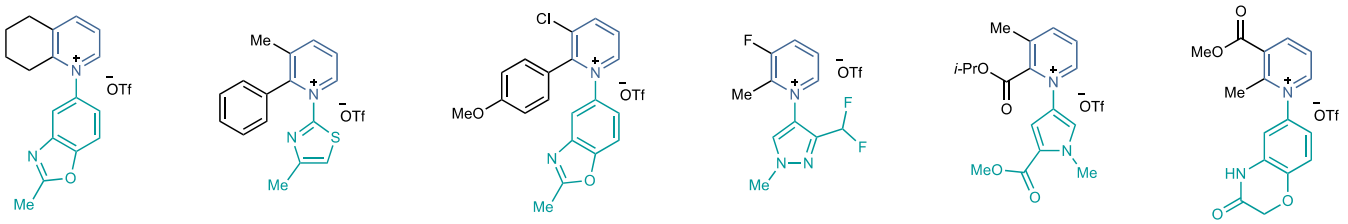
Table 4. Preparative Scale Pyridinium Salt-Forming Reactions[a,b,c,d]



*N*Tf-Zincke imine (Hetero)anilines *N*-(Hetero)arylpyridinium salts



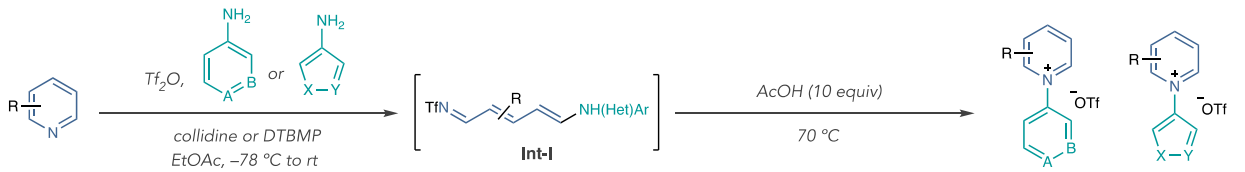
3c, 90% **3d**, 66% **3e**, 45% **3f**, 43% **3g**, 63%[c] **3h**, 88%



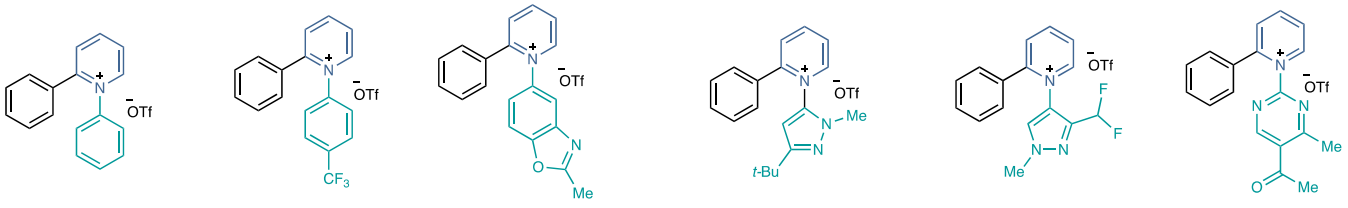
3i, 78% **3j**, 51%[d] **3k**, 68% **3l**, 66% **3m**, 69% **3n**, 78%

[a]Isolated yields are shown. [b]Reaction stoichiometry: Zincke imine (1.0 equiv), (heteroaryl)aniline (1.5 equiv), AcOH (10 equiv). [c]Isolated as a 10:1 mixture with an unknown impurity. [d]Isolated as a 12:1 mixture with an unknown impurity.

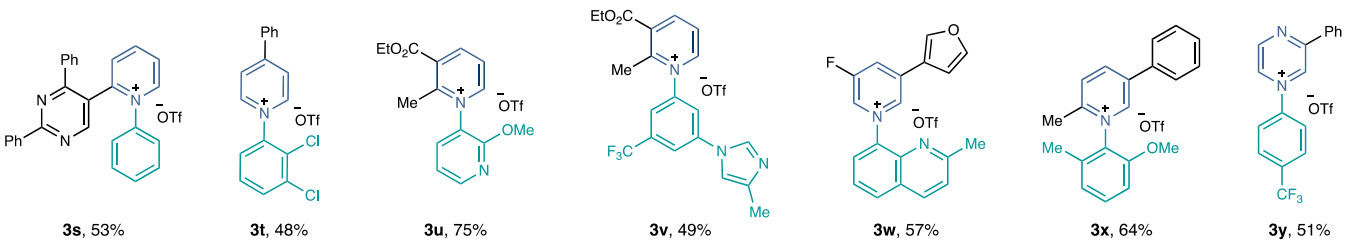
Table 5. One-Pot Pyridinium Salt Formation Using (Heteroaryl)anilines as Nucleophiles[a,b]



Pyridine *N*Tf-Zincke imine (not isolated) *N*-(Hetero)arylpyridinium salts



3a, 83% **3b**, 57% **3o**, 58% **3p**, 51% **3q**, 55% **3r**, 62%



3s, 53% **3t**, 48% **3u**, 75% **3v**, 49% **3w**, 57% **3x**, 64% **3y**, 51%

[a]Isolated yields are shown. [b]Reaction stoichiometry: pyridine (1.0 equiv), (heteroaryl)aniline (1.5 equiv), collidine or 2,6-di-tert-butyl-4-methylpyridine (DTBMP), (1.0 equiv), AcOH (10 equiv).

the anilines would replace dibenzylamine as the nucleophile in the ring-opening process and reside in the ring-opened adduct (Int-I). We reasoned that less nucleophilic (heteroaryl)anilines may function using this protocol as they do not need to

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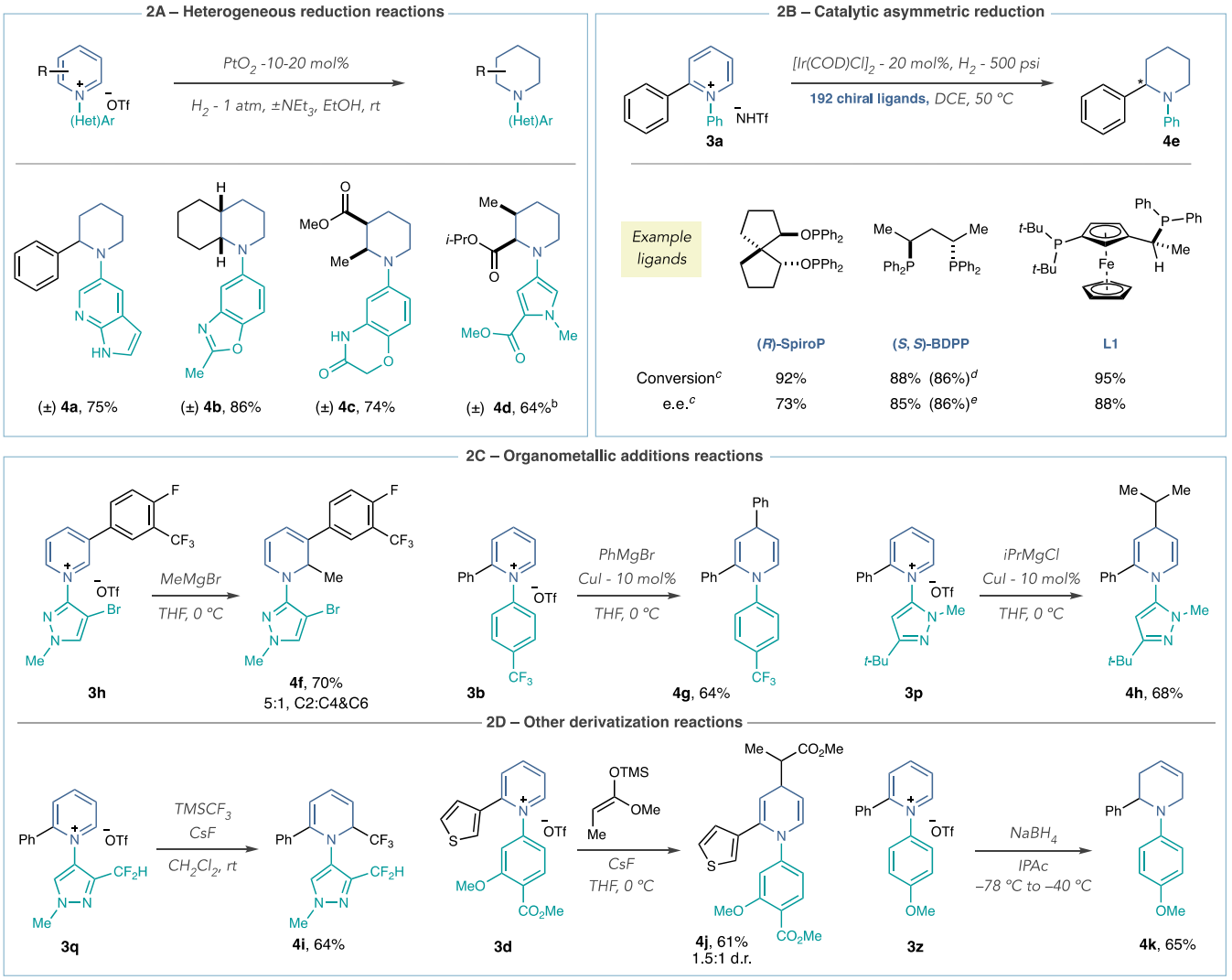
Scheme 2. Derivatizations of Pyridinium Salts: Catalytic Reductions, Organometallics, and Nucleophile Additions[a,b,c,d]



[a]Isolated yields are shown. [b]Conducted at 500 psi of H_2. [c]Screen of 192 chiral phosphine ligands was performed using 1 μmol of **3a**. [d]Isolated yield on a 400 μmol scale. [e]Enantiomeric excess measured on a 400 μmol scale.

substitute dibenzylamine from the Zincke imines used in Tables 2–4, and this approach could expand the scope of pyridinium *N*-substituents. However, the anilines must still be competent nucleophiles for the ring-opening process and avoid side reactions, such as reactions with the Tf portion of the *N*Tf-pyridinium salt intermediate. Using 2-phenylpyridine and anilines **2a** and **2b**, we performed the ring-opening process, added 10 equiv of AcOH, and heated the reaction to 70 °C. Using this protocol, model pyridinium salts **3a** and **3b** were formed in good yield.

Other (heteroaryl)anilines that were successful in Table 2 translated to this one-pot process (**3o**–**3r**). Pyridinium salt **3r** is notable because the aminopyrimidine **2g** failed to form any product in Table 2 and in only one case in Table 3, suggesting that a greater diversity of *N*-substituents is possible via this approach. In examples **3s**–**3w**, we varied both the (heteroaryl)aniline and pyridine substituents. Salt **3x** shows that this method can tolerate steric hindrance around the C–N axis, raising the possibility of controlling atropisomerism. Finally, we also obtained a preliminary result showing that the reaction can function on pyrazines (**3y**). We will investigate this direct aniline coupling reaction to establish its scope and limitations in future studies.

Next, we obtained a series of piperidine derivatives by performing reduction and nucleophilic addition reactions to pyridinium salts (Scheme 2).[30,39] Scheme 2A shows four examples of PtO_2 hydrogenation reactions forming racemic piperidines. We found that the purity of the pyridinium salt can significantly impact the yield of these processes; attempts to use crude cyclized material were only successful in simple cases, such as **3a** (not shown). However, using the simple purification procedures developed in Tables 4 and 5, we obtained piperidines **4b**–**4d** as single diastereomers in good yield. In Scheme 2B, we used asymmetric catalysis to reduce *N*-phenylpyridinium salt **3a**. Surprisingly, to the best of our knowledge, there are no examples of catalytic asymmetric reductions of *N*-(hetero)arylpyridinium salts.

We performed a HTE screen of 192 chiral phosphine ligands to identify a selective and efficient catalyst and chose an iridium precatalyst based on an analogy to enantioselective reductions of *N*-alkylpyridinium salts.[40–44] We ran the plate in 1,2-DCE at 50 °C under 500 psi of H_2 gas and saw that several

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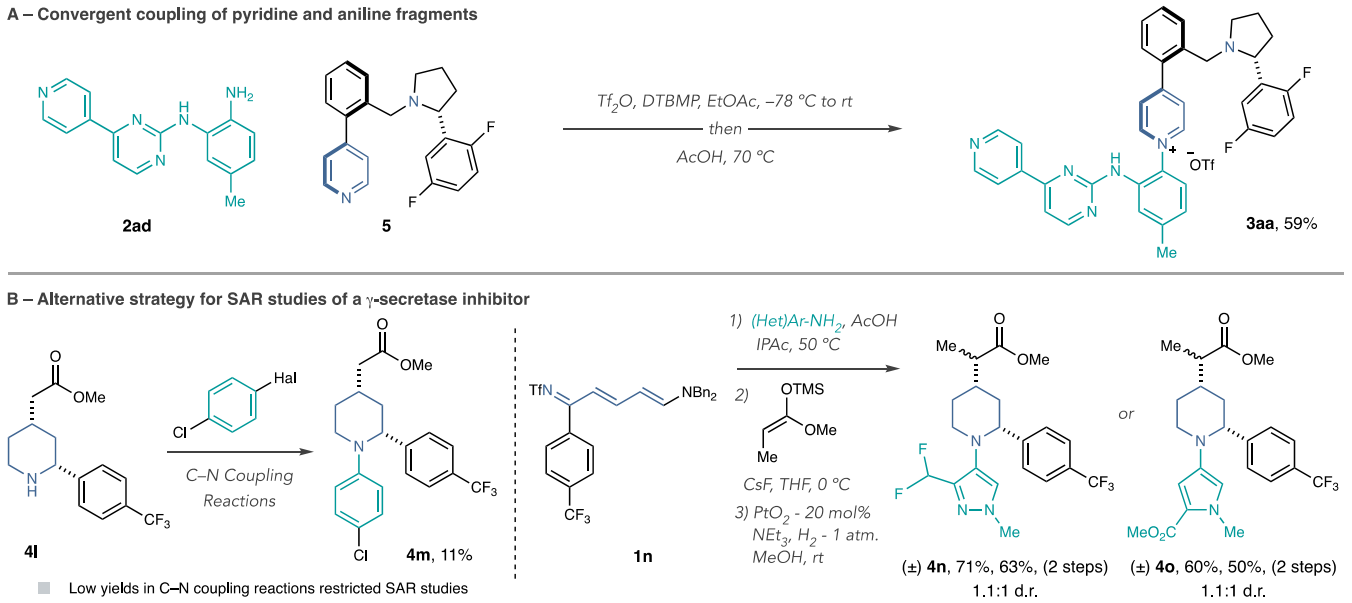
Scheme 3. Application of Pyridinium Salt Formation for Complex Molecule Synthesis and Analogue Development[a]



[a]Isolated yields are shown.

ligand classes gave good to high levels of enantioselectivity with high conversion (see Supporting Information for full details). Scheme 2B shows three examples of bisphosphines from the screen, with L1 proving optimal. These results indicate that a general platform for asymmetric catalysis is viable, and future studies will explore the effect of ligand structure across more diverse pyridinium structures.

Scheme 2C shows organometallic addition reactions to the pyridinium salts generated in this study. Adding a Grignard reagent to **3h** resulted in the dihydropyridine derivative **4f** with good 2-position selectivity.[24] Cuprates are known to add to the 4-position of pyridinium salts,[30] and when we added phenyl cuprate to **3b**, we isolated the dihydropyridine derivative **4g**, and similarly formed **4h** using isopropyl cuprate. Scheme 2D shows examples of other nucleophiles; adding trifluoromethyl anions is 2-selective (**4i**),[24] whereas a silyl enol ether added to the 4-position of **3d** forms **4j** as a 1.5:1 mixture of diastereomers.[45] Finally, we subjected the crude reaction mixture that formed pyridinium salt **3z** to sodium borohydride and obtained 3,4-dihydropyridine **4k** as a single regioisomer.[46]

Scheme 3 shows other strategic applications of this pyridinium salt-forming reaction. First, we tested its viability as a convergent coupling tactic involving complex pyridine and aniline partners. In Scheme 3A, we used aniline **2ad**, a component of the drug Gleevec, and pyridine 5 in the direct aniline coupling protocol from Table 5 to form pyridinium salt **3aa**. The process tolerates several challenging features in these reaction partners, including additional azaarenes and a pyrrolidine ring. It also implies that practitioners could design syntheses where a robust pyridine progresses through most steps before the piperidine is revealed at a late stage. Second, we applied this chemistry to a piperidine-containing γ-secretase inhibitor. During SAR studies, attempts to vary the *N*-substituent were troublesome as Pd-catalyzed C−N coupling with (hetero)aryl halides resulted in a limited number of *N*-arylpiperidines in poor yields.[47] For example, a MSD team prepared piperidine **4l** in three steps from commercial material and obtained an 11% yield of **4m** via C−N coupling. Our alternative strategy starts with Zincke imine **1n**. Pyridinium salt formation followed by silyl enol ether addition and hydrogenation provided piperidines **4n** and **4o**, where diversification of the *N*-substituent arises through the choice of (heteroaryl)-aniline, and the silyl enol ether substituent also allows variation of the exocyclic acetate group.

CONCLUSIONS

In summary, we have developed a pyridine ring-opening and ring-closing process that accesses *N*-(heteroaryl)pyridinium salts that provides broad access to substituted piperidine derivatives. We used HTE to evaluate diverse collections of ring-opened Zincke imines and (heteroaryl)anilines that demonstrated that both *C*- and *N*-substituents could vary significantly. The reactions translate well to the preparative scale, and (heteroaryl)anilines can be used directly in a one-pot pyridine ring-opening and ring-closing sequence. The pyridinium salts are amenable to reduction processes, including asymmetric variants, to form substituted piperidines. We also demonstrated a series of nucleophilic additions that add further substituents to the heterocyclic ring. The strategy is capable of convergent coupling of complex pyridine and aniline fragments as well as generating libraries for SAR studies. We anticipate that this chemistry will be immediately useful for medicinal chemists.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c11504.

Experimental procedures and characterization data; protocols for HTE; photographs of reaction blocks; and descriptions of analysis methods (PDF)

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Author Contributions

[▽]J.D.S. and J.W.G. contributed equally (match statement to author names with a symbol). The manuscript was written through the contributions of all authors. All authors have given their approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

SAR	structure−activity relationship
HTE	high-throughput experimentation
IPAc	isopropyl acetate
UPLC-CAD	ultra performance liquid chromatography-charged aerosol detection
NMR	nuclear magnetic resonance

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