Synthesis of Bench-stable *N*-Quaternized Ketene *N*,*O*-Acetals and Preliminary Evaluation as Reagents in Organic Synthesis

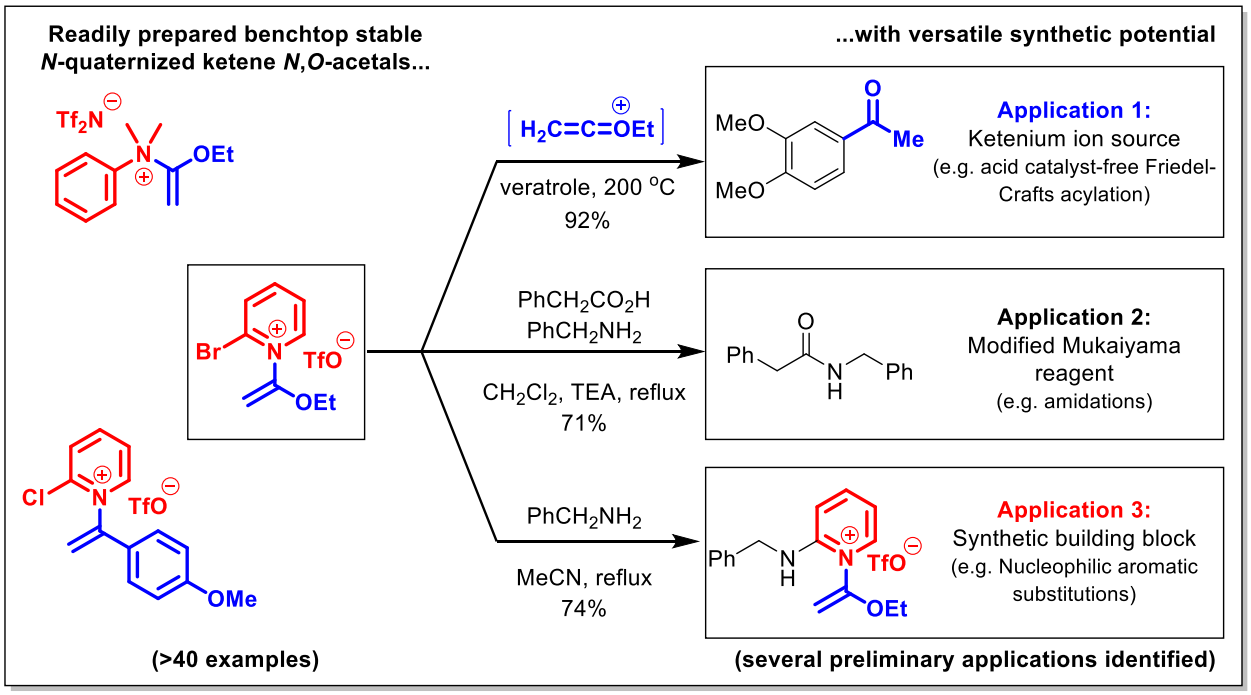
Danielle L. McConnell, Alisha M. Blades, Danielle Gomes Rodrigues, Phoebe V. Keyes, Justin C. Sonberg, Caitlin E. Anthony, Sofia Rachad, Olivia M. Simone, Caroline F. Sullivan, Jonathan D. Shapiro, Christopher C. Williams, Benjamin C. Schafer, Amy M. Glanzer, Holly L. Hutchinson, Ashley B. Thayaparan, Zoe A. Krevlin, Isabella C. Bote, Yasin A. Haffary, Sambat Bhandari, Jack A. Goodman, and Max M. Majireck*

Chemistry Department, Hamilton College, 198 College Hill Rd., Clinton, NY 13323

*Corresponding author: mmajirec@hamilton.edu; Tel.: +1 315-859-4742

Abstract: *N*-Quaternized ketene *N*,*O*-acetals are typically an unstable, transient class of compounds most commonly observed as reactive intermediates. In this report, we describe a general synthetic approach to a variety of bench-stable *N*-quaternized ketene *N*,*O*-acetals via treatment of pyridine or aniline bases with acetylenic ethers and an appropriate Brønsted or Lewis acid (triflic acid, triflimide, or scandium(III) triflate). The resulting pyridinium and anilinium salts can be used as reagents or synthetic intermediates in multiple reaction types. For example, *N*-(1-ethoxyvinyl)pyridinium or anilinium salts can thermally release highly reactive *O*-ethyl ketenium ions for use in acid catalyst-free electrophilic aromatic substitutions. *N*-(1-Ethoxyvinyl)-2-halopyridinium salts can be employed in peptide couplings as a derivative of Mukaiyama reagents or react with amines in nucleophilic aromatic substitutions under mild conditions. These preliminary reactions illustrate the broad potential of these currently understudied compounds in organic synthesis.

Graphical Abstract:



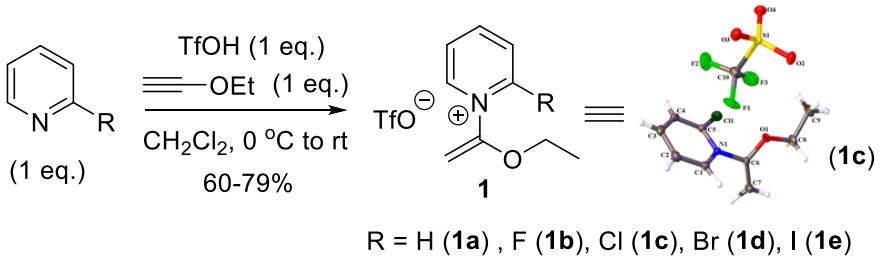
Keywords: Pyridinium salt, anilinium salt, *N*-quaternized ketene *N*,*O*-acetal, *N*-(1-alkoxyvinyl) ammonium, ketenium ion, ketene hemiaminal, electrophilic aromatic substitution, nucleophilic aromatic substitution, amidation, peptide coupling.

Introduction:

The discovery of reagents and their corresponding methodologies drive the advancement of chemical synthesis along with its many applications, such as complex organic synthesis[1] and drug discovery.[2] Of the myriad reagents available to the modern chemist, pyridinium salts are among the most frequently employed due to their ready availability, broad synthetic versatility, and solubility in a wide range of nonpolar to polar solvents.[3] For example, 2-halo-*N*-alkylpyridinium salts (Mukaiyama reagents[4]), first reported in 1964 by Sutherland and Widdowson,[5] then vastly expanded upon by Mukaiyama and others,[6] have become an indispensable class of reagents for inter- and intramolecular peptide or ester couplings, ketene generation, dehydrations, rearrangements, and numerous other transformations.[7] Owing to their accessibility and ease of use, many other pyridinium and related onium salts have been developed for a range of synthetically valuable transformations. For example, Dudley's reagent is a bench-stable pyridinium salt for O- and N-benzylation under neutral conditions.[8] *N*-Alkyl,[9] *N*-acyl,[10] *N*-fluoro,[11] *N*-oxo,[12]

N-amino,[13] and other *N*-activated pyridinium salts[14] promote a broad range of valuable transformations or act as building blocks for cycloadditions, rearrangements, reductions, oxidations, transition metal couplings, and nucleophilic additions.[15] Protonated pyridinium salts such as pyridinium *p*-toluenesulfonate (PPTS),[16] a mild organic soluble acid, and pyridinium chlorochromate (PCC),[17] a mild organic soluble oxidant, represent two mainstay reagents in organic synthesis. In addition to synthetic applications, pyridinium salts have been exploited for their physicochemical properties as surfactants, phase transfer agents, optoelectronics, and dyes, and for their biological activities as antimicrobial agents.[18] Considering the exceptionally broad use of pyridinium salts as reagents, synthetic intermediates, functional materials, and bioactives, it is clear that this compound class will continue to maintain its high value across a variety of chemical fields.

Recently, our laboratory discovered a new class of pyridinium salts that contain unusually stable *N*-quaternized ketene-*N*,*O*-acetals and, consequently, have the potential of engaging in a variety of useful synthetic transformations.[19] Such compounds are simple to prepare by direct treatment of a pyridine with ethoxyacetylene and triflic acid (Scheme 1). Most of the resulting *N*-(1-ethoxyvinyl) pyridinium triflate complexes **1** are remarkably stable, amenable to column chromatography, and able to be stored long-term under ambient, dry conditions. While an isolable *N*-(1-alkoxyvinyl)pyridinium salt is, to the best of our knowledge, unprecedented,[20] there are a few previous reports of presumably isolable *N*-(1-alkoxyvinyl)ammonium salts.[21] Nevertheless, despite the first structure in this broader class being reported over eight decades ago,[21a] there has been little attempt to study their reactivity despite their potentially broad range of synthetic applications.

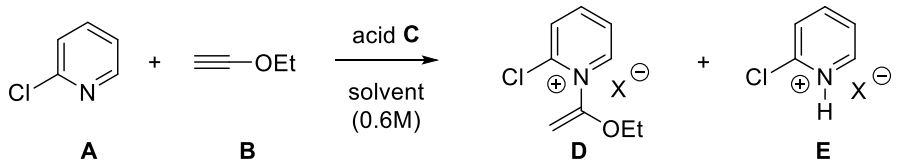


Scheme 1 – Previous work on synthesis of *N*-(1-ethoxyvinyl) pyridinium triflates[19]

Results and Discussion:

Following our initial report,[19] which primarily focused on extensive characterization of these unusual complexes, we desired to broaden the scope and efficiency of *N*-(1-alkoxyvinyl)ammonium salt synthesis while simultaneously examining their innate reactivity in useful synthetic transformations. To begin, we revisited our original protocol for synthesizing *N*-(1-alkoxyvinyl)pyridinium salts with the aim of systematically evaluating critical parameters including: time, temperature, stoichiometry, acid source, solvent, order of reagent addition, and method of purification. Our first procedure involved adding triflic acid (1 equiv) directly to a stirring 0 °C solution of pyridine (1 equiv), ethoxyacetylene (1 equiv), and dichloromethane (0.6 M), followed by gradual warming to room temperature over 18h (Table 1, entry 1). Purification by silica gel column chromatography[22] using a 0-100% chloroform/isopropanol gradient cleanly provided product **D** in 72% yield when using 2-chloropyridine (**A**). Analysis of the crude product mixture by ^{1}H NMR prior to purification revealed the presence of NH-salt side product **E** as the main impurity. This compound is easily separated via chromatography; however, since N-protonation is the major side reaction we hoped to suppress, we opted to use short silica plug filtration in subsequent optimization trials so that we could quickly and effectively assess ratios of **D**:**E** in each experiment. Thus, repeating our original procedure but with silica plug filtration (dichloromethane to elute nonpolar impurities, followed by MeOH to elute **D** and **E**) allowed us to obtain the full mass balance of products as a 5:1 mixture of **D**:**E** (entry 2).

Table 1 – Evaluation of reaction parameters for the synthesis of *N*-(1-ethoxyvinyl) 2-chloropyridinium salts **D**.



A **B** **D** **E**

Entry	Equiv. **A** / **B**[a] / **C**	Acid	Mix[e]	Solvent	Time/Temperature	Yield (Ratio **D**:**E**)[b]
1	1 / 1 / 1	TfOH	**I**	CH_2Cl_2	18h, 0 °C to rt	72% **D**[c]
2	1 / 1 / 1	TfOH	**I**	CH_2Cl_2	18h, 0 °C to rt	100% (5:1)
3	1 / 1 / 1	TfOH	**I**	CH_2Cl_2	5 min, 0 °C	88% (1.8:1)
4	1 / 1 / 1	TfOH	**I**	CH_2Cl_2	60 min, -78 °C	66% (1.8:1)
5	1 / 1 / 1	TfOH	**I**	CH_2Cl_2	30 min, 0 °C to rt	81% (4.2:1)
6	1 / 1 / 1	TfOH	**I**	CH_2Cl_2	30 min, 0 °C to rt	78% (9.1:1)[d]
7	2 / 1 / 1	TfOH	**I**	CH_2Cl_2	30 min, 0 °C to rt	100% (5.9:1)
8	1 / 2 / 1	TfOH	**I**	CH_2Cl_2	30 min, 0 °C to rt	75% (4.3:1)
9	1 / 1 / 1	TfOH	**I**	CH_2Cl_2	60 min, 0 °C	100% (6.7:1)
10	1 / 1 / 1	TfOH	II	CH_2Cl_2	60 min, 0 °C	100% (4.8:1)
11	1 / 1 / 1	TfOH	III	CH_2Cl_2	60 min, 0 °C	66% (42:1)
12	1 / 1 / 1	TfOH	IV	CH_2Cl_2	60 min, 0 °C	100% (13:1)
13	1 / 1 / 1	TfOH	IV	1,2-DCE	60 min, 0 °C	78% (5.9:1)
14	1 / 1 / 1	TfOH	IV	$CHCl_3$	60 min, 0 °C	58% (6.7:1)
15	1 / 1 / 1	TfOH	IV	CCl_4	60 min, 0 °C	70% (10:1)
16	1 / 1 / 1	TfOH	IV	PhH	60 min, 0 °C	97% (3.8:1)
17	1 / 1 / 1	TfOH	IV	hexanes	60 min, 0 °C	83% (4.3:1)
18	1 / 1 / 1	Tf_2O	IV	CH_2Cl_2	60 min, 0 °C	0%
19	1 / 1 / 1	MsOH	IV	CH_2Cl_2	60 min, 0 °C	9% (1:3)
20	1 / 1 / 1	Tf_2NH	IV	CH_2Cl_2	60 min, 0 °C	84% **D**
21	1 / 1 / 1	TFA	IV	CH_2Cl_2	60 min, 0 °C	0%
22	1 / 1 / 1	$Sc(OTf)_3$	IV	CH_2Cl_2	60 min, 0 °C	83% **D**
23	1 / 1 / 1	HCl	IV	CH_2Cl_2	60 min, 0 °C	19% (1:2.1)
24	1 / 1 / 1	H_2SO_4	IV	CH_2Cl_2	60 min, 0 °C	0%

a - 40 wt. % in hexanes

b - Total combined yield of **D** and **E**; Ratios based on ^{1}H NMR of filtered product mixture, all obtained via short silica gel plug filtration with CH_2Cl_2 then MeOH (except for entries 1 and 6)

c - Pure product obtained via column chromatography

d - Product mixture obtained via short silica plug filtration with CH_2Cl_2 followed by iPrOH

e - Mix methods: **I -** Acid added to pyridine/alkyne/solvent; **II -** Acid added to alkyne/solvent; pyridine added last; **III -** Acid added to pyridine/solvent; alkyne added last; **IV -** Alkyne/pyridine/solvent added to acid/solvent

Since warmer temperatures and/or longer periods of stirring might lead to product degradation, we first examined the impact of time and temperature. Both an inferior yield and **D**:**E** ratio was observed when halting the

reaction at 5 min, or stirring at -78 °C for 60 min (entries 3-4). Compared to these trials, a modest improvement in yield and product ratio was observed when running the reaction from 0 °C to room temperature over 30 min (entries 5-6); notably, use of isopropanol in place of methanol during the silica plug filtration provides a better product ratio with only slightly lower yield. Maintaining a temperature of 0 °C for 60 min once again yielded a full mass balance of products, but with a somewhat better **D**:**E** ratio compared to stirring overnight (cf. entries 2 and 9).

Two experiments on the stoichiometry of pyridine **A** and alkyne **B** were conducted (entries 7-8). Using an excess of 2-chloropyridine provided **D**:**E** in an acceptable yield and ratio, but complicates purification due to leftover starting material. In comparison, an excess of alkyne led to substantially lower yield, potentially due to ynol ether-ketenium condensation side reactions.[23]

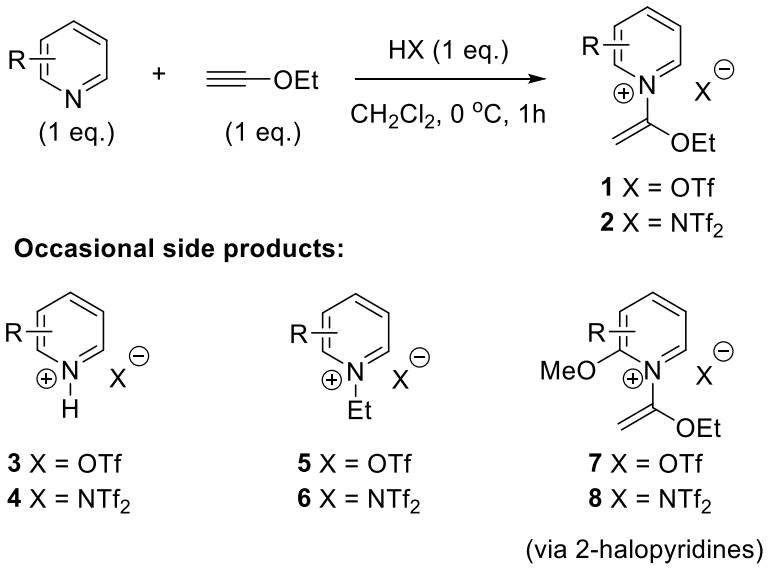
An interesting factor to examine was the order in which the pyridine **A**, alkyne **B**, and acid **C** were mixed, since this likely impacts the product ratio. Compared to standard conditions (acid added to a solution of pyridine/alkyne, Mix Method I), we observed more of side product **E** when the pyridine was added to a solution of alkyne/acid (Mix Method II, cf. entries 9 and 10). Surprisingly, adding alkyne to a solution of pyridine/acid (i.e. pre-forming the NH salt **E**; Mix Method III) led to a modest yield of desired product but with an excellent 42:1 ratio of **D**:**E** (entry 11). Finally, for the best balance between yield and purity, we found that adding a solution of pyridine/alkyne/dichloromethane dropwise over 5 min to a triflic acid/dichloromethane solution at 0 °C led to a high yield of **D** with only a small fraction of **E** (entry 12, Mix Method IV).

The effect of several alternative solvents on the **D**:**E** product ratio was examined, but none performed as well as dichloromethane (cf. entries 9, 13-17). Nevertheless, moderate to good yields of product can be obtained in both halogenated and nonpolar solvents.

A brief study was also conducted on the scope of acids (**C**) capable of producing *N*-(1-ethoxyvinyl)pyridinium salts **D**. As a control we tested triflic anhydride, which would produce TfOH during the purification step,[19] however no product was formed (entry 18). The strong mineral acid HCl favored N-protonation, whereas H_2SO_4 led to a complex mixture (entries 23 and 24). We did find, however, that the super-acid triflimide (Tf_2NH)[24] is a superior, albeit expensive, Brønsted acid for formation of desired adduct **D**, as no traces of **E** were observed by ^{1}H NMR

analysis of the filtered product (entry 20). Similarly, the Lewis acid scandium(III) triflate produces **D** with high purity and no detectable NH side product **E** (entry 22). However, despite leading to exceptional product purity, Tf_2NH and $Sc(OTf)_3$ are both highly hygroscopic and require rigorously anhydrous manipulation and storage. Therefore, we view TfOH as being the most practical in terms of availability, ease of use, and cost.

Following extensive evaluation of reaction parameters, we examined the scope of pyridines that could participate in Brønsted acid-promoted formation of stable pyridinium ketene-*N*,*O*-acetals (Scheme 2 and Tables 2-6). In addition to testing the generality of this procedure, we aimed to create a broad range of products that could serve as reagents in a variety of synthetically useful transformations. Triflic acid was used as the acid promotor on all substrates examined and select reactions were tested using triflimide for comparison. In all but a few noted cases, yields are based on purified product following column chromatography. Additionally, we observed that Mix Methods I or IV (vide supra, Table 1) were both amenable to synthesis of the desired *N*-quaternized ketene *N*,*O*-acetals; however, no single mix method was found to be universally superior for all substrates.



Scheme 2 – Standard procedure for synthesis of *N*-(1-ethoxyvinyl) pyridinium salts. See Tables 2-6 for results.

As previously disclosed,[19] 2-chloro-, 2-bromo-, and 2-iodopyridine are among the most efficient substrates in the formation of stable pyridinium ketene *N*,*O*-acetals (Table 2, **1c-e**, **2c-e**). Therefore, we began by surveying a broader range of halopyridines. 2-Fluoropyridinium salts **1b** and **2b** are both unstable; however, when either

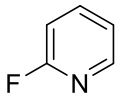
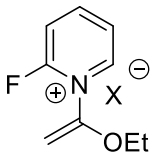
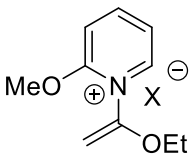
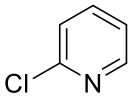
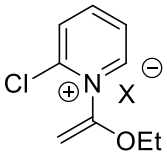
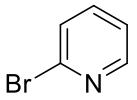
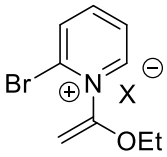
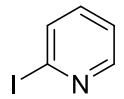
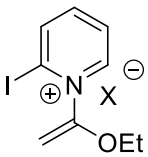
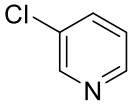
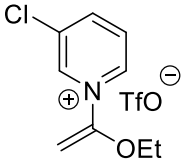
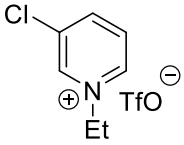
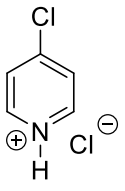
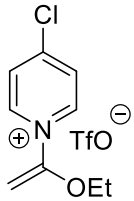
compound is subjected to methanol and silica gel during chromatographic purification, an S_NAr reaction occurs to yield the stable 2-methoxypyridinium salts **7b** and **8b**. Notably, this provides an expedient method for generation of pyridinium ketene *N*,*O*-acetals bearing an electron-donating group at the 2-position of the pyridine, which cannot be synthesized directly (e.g. using 2-methoxypyridine as starting material; vide infra Table 6). Use of 3-chloropyridine provided only a low yield of desired pyridinium ketene *N*,*O*-acetal **1f**, suggesting that 3-chloro substitution is electronically disfavored compared to 2-chloro. Additionally, an unexpected *N*-ethyl side product **5f** was isolated, presumably originating from an S_N2 attack by the pyridine's nucleophilic *N*-atom on the methylene carbon of the *N*-ethylketenium ion intermediate. Similar *N*-ethyl pyridinium salt byproducts were observed in other scenarios in which formation of a pyridinium ketene *N*,*O*-acetal is sterically or electronically disfavored (vide infra). Finally, we were interested in examining the effect of 4-chloro substitution on the pyridine ring, but since the free base of 4-chloropyridine is less stable than its regioisomers, it was generated in situ from its corresponding hydrochloride salt. Using this unoptimized protocol, the desired complex **1g** can be obtained, albeit in low yield.

All analogues of dichloropyridine were evaluated for comparison amongst each other, as well as the monochloropyridine series (Table 3). Of all dichloro substrates, the 2,3-dichloropyridinium triflate **1h** was the only product obtained with good yield and purity using our standard procedures. Other dichloropyridines gave either low yields, side products, or no desired product at all. Owing to its greater electrophilicity toward S_NAr processes, the 1,4-dichloro analogue **1i** and 1,6-dichloro analogue **1k** could not be obtained via chromatography, but instead yielded their corresponding methoxy-substituted S_NAr products within complex mixtures. However, products **1k**/**1i** were found to be stable in non-nucleophilic solvents such as CH_2Cl_2 or MeCN, and could be isolated in crude form along with variable amounts of their corresponding *NH*-pyridinium salts. The less electrophilic 2,6-dibromopyridine provided its corresponding pyridinium ketene *N*,*O*-acetal as a single, pure product **1l**, albeit in low yield, following column chromatography.

We next investigated pyridines containing strong electron-withdrawing groups in order to survey whether these significantly less nucleophilic/basic analogues would be capable of forming isolable pyridinium ketene *N*,*O*-acetals (Table 4). Among the substrates tested, only 2-acyl and 2-cyano substitution were tolerated (**1m-o** and **2m-n**). The

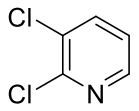
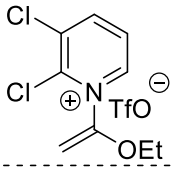
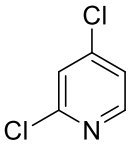
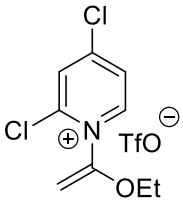
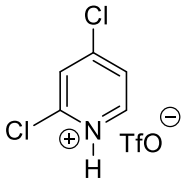
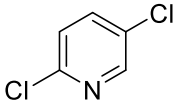
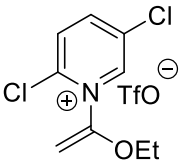
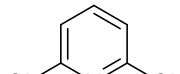
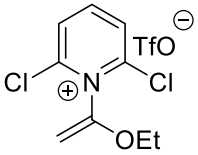
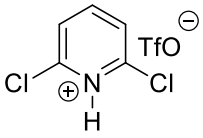
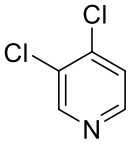
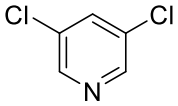
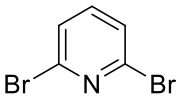
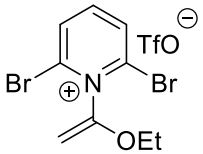
adduct of 2-acetylpyridine was isolated from a complex mixture in very low yield, most likely due to side reactions promoted by this enolizable substituent, whereas the 2-benzoyl analogue was produced in substantially better yield and purity (cf. **1m**/**2m** and **1n**/**2n**). Interestingly, when the cyano group is located on the 3- or 4-position of pyridine, no detectable adducts were formed.

Table 2 – Halopyridine substrate scope in the direct synthesis of pyridinium ketene *N*,*O*-acetals

Starting Pyridine	Isolated Product(s)	
		**1b**, 79%[a] (X = OTf) **2b**, 67%[a] (X = NTf_2)
		**7b**, 52%[b] (X = OTf) **8b**, 46%[b] (X = NTf_2)
		**1c**, 93% (X = OTf) **2c**, 84% (X = NTf_2)
		**1d**, 71% (X = OTf) **2d**, 52% (X = NTf_2)
		**1e**, 60% (X = OTf) **2e**, 45% (X = NTf_2)
		**1f**, 37%
		**5f**, 14%
		**1g**, 18%[c]

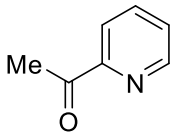
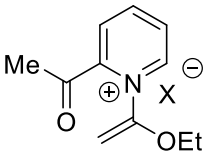
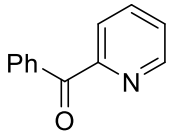
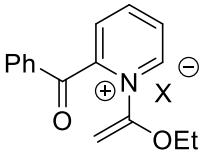
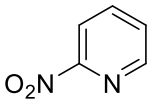
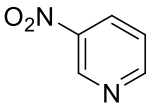
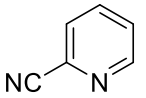
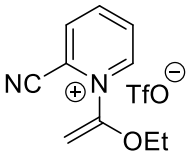
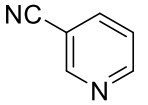
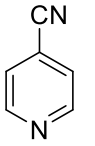
a - Crude yield due to instability on silica gel
b - S_NAr product following silica gel column chromatography with methanol/chloroform.
c - Via in situ free basing of 4-chloropyridinium hydrochloride with NaH (unoptimized)

Table 3 – Dihalopyridine substrate scope in the direct synthesis of pyridinium ketene *N*,*O*-acetals

Starting Pyridine	Isolated Product(s)
	 **1h**, 81%
	 **1i**, 78%[a]  **3i**, 16%[a]
	 **1j**, 27%
	 **1k**, 39%[a]  **3k**, 43%[a]
	no desired product[b]
	no desired product[b]
	 **1l**, 16%

a - Crude yield due presence of inseparable impurities
b - Following column chromotagraphy; crude product isolation was not attempted

Table 4 – Substrate scope of pyridines with an electron-withdrawing group in the direct synthesis of pyridinium ketene *N*,*O*-acetals

Starting Pyridine	Isolated Product(s)
	 **1m**, 8%[a] (X = OTf) **2m**, 27% (X = NTf_2)
	 **1n**, 54% (X = OTf) **2n**, 30% (X = NTf_2)
	no desired product
	no desired product
	 **1o**, 34%[a]
	no desired product
	no desired product

a - Approximate yield due to presence of minor impurities

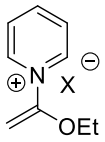
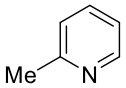
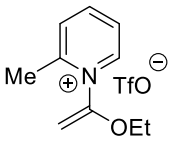
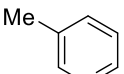
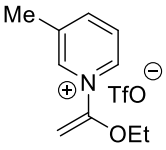
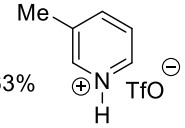
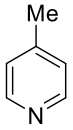
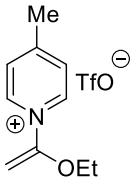
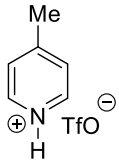
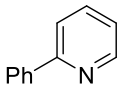
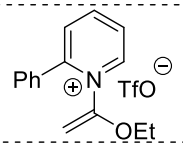
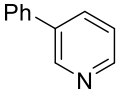
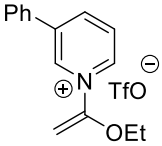
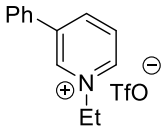
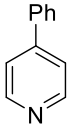
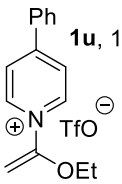
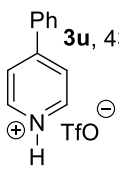
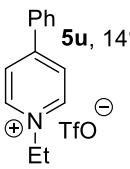
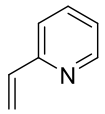
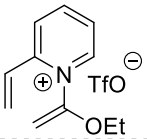
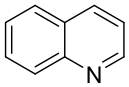
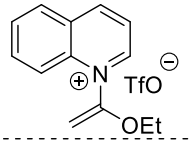
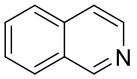
The influence of alkyl, aryl, and vinyl substituents on the pyridine ring was also studied (Table 5). As a baseline comparison, simple pyridine readily forms its corresponding pyridinium ketene *N*,*O*-acetals (**1a** and **2a**). We were unable to form substantial amounts of the desired adduct derived from 2-picoline (**1p**). The less sterically hindered 4-picoline performed somewhat better to form **1r** in low yield, but surprisingly 3-picoline generates its corresponding adduct **1q** with much greater efficiency. This, and other examples, underscore an interesting but not

yet fully understood interplay between the steric and electronic effects of pyridine substituents in formation of pyridinium ketene *N*,*O*-acetals, which merits further study.

As for the aryl and vinylpyridines, multiple adducts could be formed in moderate to good yields but were, in general, more difficult to purify and occasionally were isolated with unknown side products. We speculate that electrocyclization or cycloaddition pathways within these systems might be competing with formation of the desired products. Nevertheless, conjugated alkene and carbocyclic aromatic rings were demonstrated to be feasible substituents for this protocol (**1t**-**w**).

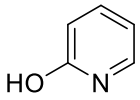
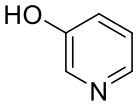
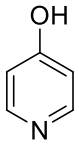
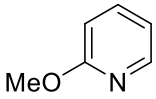
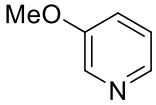
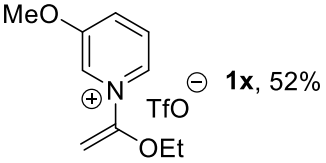
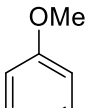
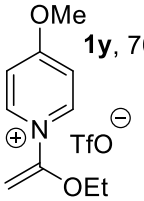
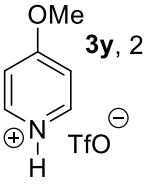
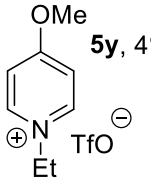
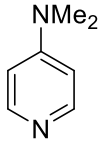
Of the examples tested, only a few pyridines containing strongly electron-donating groups were found to participate in this protocol for direct pyridinium ketene *N*,*O*-acetal synthesis (Table 6). For example, use of 2-methoxypyridine or *N*,*N*-dimethylaminopyridine (DMAP) did not yield their corresponding adducts, but both 3- and 4-methoxy substitution were found to be compatible in the formation of complexes **1x** and **1y**. Not surprisingly, the protic hydroxypyridines are incompatible with this procedure; however, neutral pyridone ketene *N*,*O*-acetals derived from hydroxypyridines have been synthesized under different conditions.[25] Though direct use of pyridines with an electron-donating group at C2 was unsuccessful, it should be noted here that both alkoxy- and amino-substitution are possible within *N*-(1-ethoxyvinyl)pyridinium triflate systems, but they must be prepared via an S_NAr reaction (vide supra, Table 2 and vide infra, Scheme 7).[19]

Table 5 – Alkyl-, aryl-, and vinyl-pyridine scope in the direct synthesis of pyridinium ketene *N*,*O*-acetals

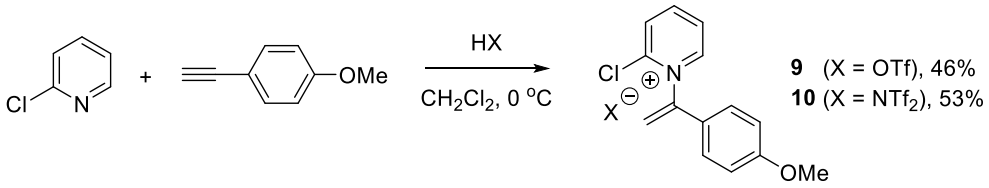
Starting Pyridine	Isolated Product(s)
	 **1a**, 79% (X = OTf) **2a**, 53% (X = NTf_2)
	 **1p**, trace
	 **1q**, 63%  **3q**, 35%
	 **1r**, 16%  **3r**, 78%
	 **1s**, trace
	 **1t**, 35%[a]  **5t**, 21%
	 **1u**, 17%  **3u**, 43%  **5u**, 14%
	 **1v**, 51%
	 **1w**, 37%
	no desired product

a - Approximate yield due to presence of minor impurities

Table 6 – Scope of pyridines with an electron-donating group in the direct synthesis of pyridinium ketene *N*,*O*-acetals

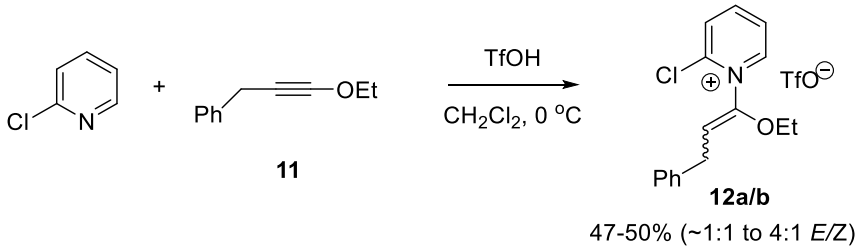
Starting Pyridine	Isolated Product(s)
	no desired product
	no desired product
	no desired product
	no desired product
	 **1x**, 52%
	 **1y**, 70%  **3y**, 21%  **5y**, 4%
	no desired product

We next briefly examined use of alternative alkynes and amine nucleophiles. The conjugated aryloxy alkyne 4-ethynylanisole readily forms complexes **9** and **10** with 2-chloropyridine when treated with either TfOH or Tf_2NH (Scheme 3). However, when phenylacetylene, cyclohexylacetylene, 1-pentyne, and 1-hexyne were tested, none of the corresponding *N*-vinylpyridinium salt adducts were observed despite the ability of TfOH and Tf_2NH to form vinyl carbocations from unactivated alkynes.[26] Taken together, these results highlight the stabilizing nature of conjugated alkoxyvinyl or aryloxyvinyl *O*-atoms within this family of complexes.



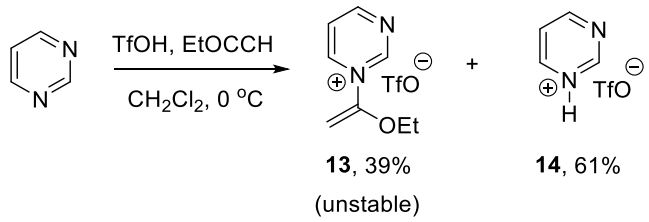
Scheme 3 – Synthesis of *N*-(1-aryloxyvinyl)pyridinium salts

One *N*-quaternized ketene-*N*,*O*-acetal derived from an internal alkyne was also synthesized. Treating known alkyne **11**[27] with 2-chloropyridine and triflic acid yielded the stable adducts **12a/b** as mixture of geometric isomers, which can be separated by column chromatography (Scheme 4). Interestingly, this procedure reliably produced about 50% yield of **12a/b** when run on a 2, 4, or 9 mmol scale, but the *E/Z* ratio varied between approximately 4:1 and 1:1.



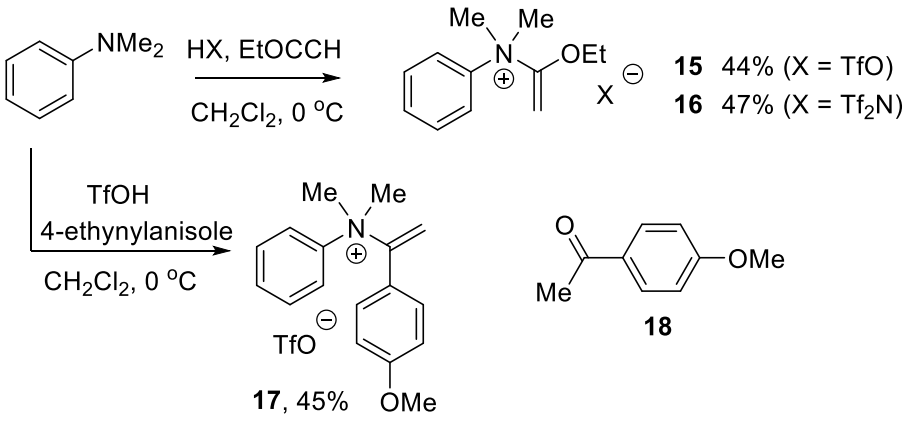
Scheme 4 – Synthesis of pyridinium ketene *N*,*O*-acetals derived from internal alkynes

Following a small screen of alkyl and aryl amines, we found that harder amine nucleophiles such as quinuclidine or triethylamine are incompatible with our standard procedures. Of all three permutations of the pyridine-like diazine family, only 1,3-diazine (pyrimidine) led to an isolable adduct **13**, along with protonation side product **14** (Scheme 5). Full characterization of this adduct proved to be challenging, since diazinium salt **13** decomposes in a matter of hours (in either solid form or in solution), and rapidly hydrolyzes upon treatment with silica gel.



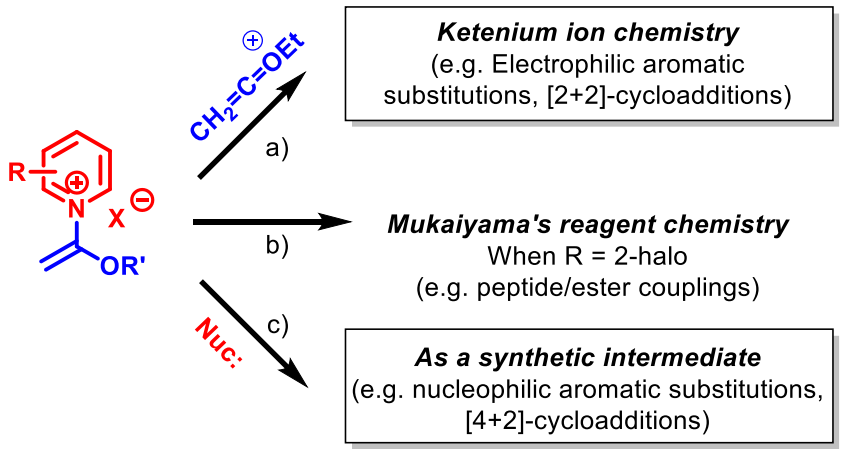
Scheme 5 – Synthesis of diazinium ketene *N*,*O*-acetals

A small survey of softer *N*-nucleophiles revealed that *N*,*N*-dimethylaniline forms the relatively stable complexes **15**-**16** upon treatment with ethoxyacetylene and either triflic acid or triflimide (Scheme 5). In a similar manner anilinium ketene *N*,*O*-acetal **17** was generated using 4-ethynylanisole and triflic acid. In this reaction, hydrolysis product **18** was occasionally isolated, which suggests that the overall lower yields in these systems may be due, in part, to the hydrolytic sensitivity of anilinium ketene *N*,*O*-acetals.



Scheme 6 – Synthesis of anilinium ketene *N*,*O*-acetals

With a variety of bench-stable *N*-quaternized ketene-*N*,*O*-acetals now in hand, we have begun to explore their unique and potentially valuable applications in synthetic chemistry. We considered three broad categories as illustrated in Scheme 7: a) as a bench-stable reagent for thermal release of ketenium ion, b) as a dehydrative and/or coupling agent when using 2-halopyridinium salts that resemble Mukaiyama's reagent, and c) as a "building block" for heterocycles (e.g. as electrophiles in nucleophilic additions/substitutions).

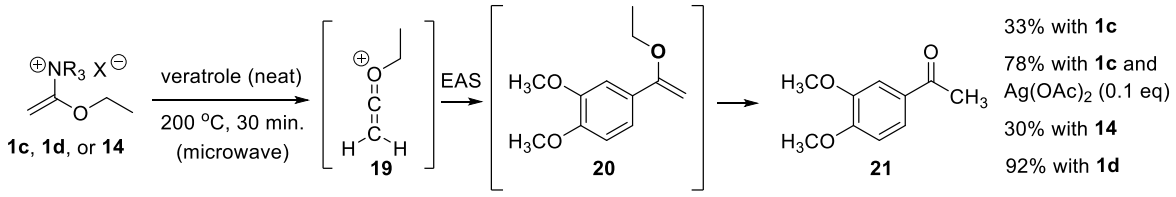


Scheme 7 – Potential modes of reactivity for *N*-quaternized ketene-*N*,*O*-acetals

Due to the previous rarity of isolable *N*-quaternized ketene-*N*,*O*-acetals, we envision a broad range of new applications can be discovered and encourage other research groups to explore the fertile grounds of their synthetic potential. Notably, these unusual compounds bear structural similarities with well-studied and synthetically valuable species such as neutral ketene-*N*,*O*-acetals[28] and ammonium enolates.[29] Moreover, the highly electrophilic *O*-alkyl ketenium ion intermediates may react analogously to keteniminium ions, the latter of which is a well-established yet rapidly expanding field.[30] To date, comparatively few reports on the use of *O*-alkyl or *O*-aryl ketenium ions in synthetic applications have been reported, despite their apparently broad utility. [23f,g,31] We reason that this is largely due to the lack of bench-stable ketenium ion precursors (in contrast to, for example, the abundant number of ynamides analogues for generation of structurally similar keteniminium ions).[30]

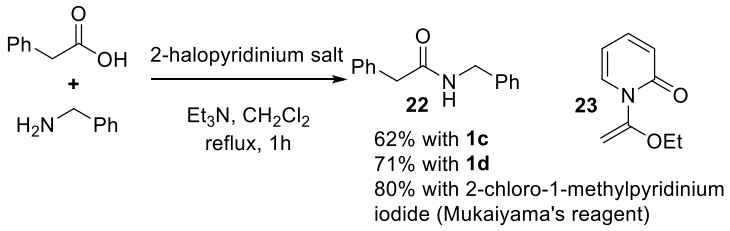
First we examined the use of *N*-quaternized ketene-*N*,*O*-acetals as bench-top stable sources of ketenium ion (i.e. "trapped ketenium ions"). Using veratrole (1,2-dimethoxybenzene) as a test substrate, we found that several pyridinium and anilinium salts are capable of generating *O*-ethyl ketenium ion **19** at elevated temperature, which initiates an electrophilic aromatic substitution, ultimately leading to aryl methyl ketone **21** via hydrolysis of enol ether **20** (Scheme 8). Notably, this constitutes a rare example of an acid catalyst-free Friedel Crafts acylation.[31,32,33d] Nevertheless, the activation energy for release of electrophile **19** appears to be relatively high, underscoring the unusual stability of these salts. If optimized, this approach has a high potential for application given the strong acids

required in conventional Friedel-Crafts acylations,[33] but the obvious current limitation is the requisite high heat (only trace product is observed at 190 °C) and unbalanced stoichiometry. Preliminary efforts to address this limitation through use of alternative salts and/or catalysts have been partially successful. For example, bromopyridinium salt **1d** performs substantially better than chloro-analogue **1c** and anilinium salt **14**, yet all reagents require high heat. A screen of Lewis acid catalysts in combination with chloropyridinium salt **1c** has revealed the potential of silver salts to increase the efficiency of this reaction. For example, 10 mol.% of silver acetate in combination with **1c** significantly improves the yield of product **21**, albeit still at high temperature. Therefore, future research will attempt to discover milder reaction conditions as well as expand scope of participating aromatics.



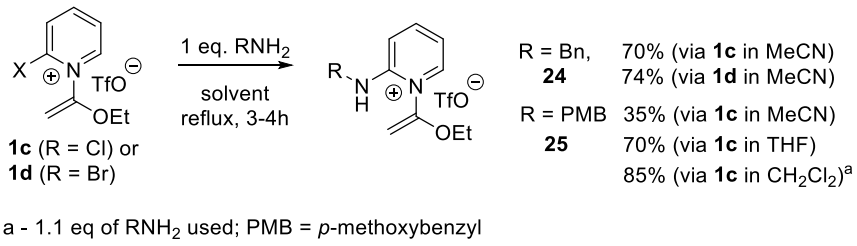
Scheme 8 – Acid-catalysis free elecrophilic aromatic substitution via thermal release of ketenium ion

Because the *N*-(1-ethoxyvinyl)-2-halopyridinium salts contain both a stable *N*-quaternized ketene *N*,*O*-acetal with a more common, but broadly useful 2-halopyridinium ring, we decided to run several baseline experiments to compare our compound with Mukaiyama's reagent in amide synthesis.[4-7] Indeed, when following Mukaiyama's protocol using **1c** or **1d**, we are able to promote the coupling of phenylacetic acid and benzylamine to produce amide **22** in acceptable yield (62-71%) compared to 80% using Mukaiyama's salt (2-chloro-1-methylpyridinium iodide) (Scheme 8). When using either **1c** or **1d**, the somewhat unstable ketene *N*,*O*-acetal byproduct **23** can be isolated by chromatography. Although little attempt was made to optimize these conditions, given the wide variety of existing options available for amidation,[6c-d] this reaction illustrates the potential of *N*-(1-ethoxyvinyl)-2-halopyridinium salts to react similarly to Mukaiyama reagents. However, future work could attempt to make use of the unique *N*,*O*-ketene acetal functionality of **1c-d** (or byproduct **23**) in tandem synthetic processes.



Scheme 9 – Comparison of 2-halopyridinium salts in amidation reactions

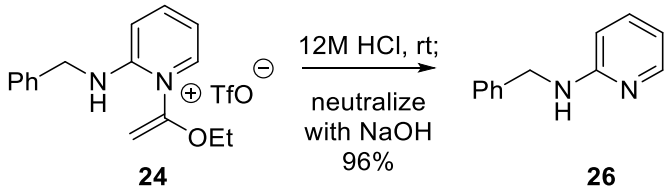
As mentioned above, pyridines with strong electron-donating groups at C2 do not add directly to ethoxyacetylene in the presence of TfOH or Tf_2NH. However, by use of S_NAr substitution, adducts bearing an alkoxy group can be readily obtained via treatment of 2-fluoropyridinium salts **1b** or **2b** with MeOH or iPrOH[19] and silica gel (Table 2 **7b** and **8b**). Building off this observation, we briefly examined use of amine nucleophiles in S_NAr reactions with *N*-(1-ethoxyvinyl)-2-halopyridinium salts and have discovered several promising conditions (Scheme 10). For example, both benzylamine and *p*-methoxybenzylamine add efficiently to pyridinium salts **1c** or **1d** to yield 2-amino complexes **24** or **25** with the *N*-quaternized ketene *N,O*-acetal still intact. Notably, 2-aminopyridines are well-represented among neuroactive small molecules,[34] and this approach provides a new entry into this product class that can complement existing methods.[14b,35] The stable *N*-(1-ethoxyvinyl) moiety may serve as a protecting group for the basic *N*-atom of pyridines, or it may be exploited as an unusual functional group in further transformations.



Scheme 10 – Synthesis of *N*-(1-ethoxyvinyl)-2-aminopyridinium salts

Surprisingly, the *N*-(1-ethoxyvinyl) group of **24** was largely unaffected when stirred overnight in 6M HCl, or heated 100 °C in water, CH_2Cl_2/AcOH, or CH_2Cl_2/TFA. Likewise, treatment under strongly basic conditions such as 6M NaOH or KOH for two weeks, and concentrated aqueous ammonium hydroxide overnight, yielded primarily returned starting material. A more forcing thermal procedure in water/MeCN at 200 °C provided 2-

benzylaminopyridine **26**, albeit in low yield. To date, the most efficient procedure to remove this unusually stable *N*-(1-ethoxyvinyl) group is to stir in 12M aqueous hydrochloric acid overnight, which following neutralization gives 2-benzylaminopyridine (**26**) in excellent yield (Scheme 11). Future research will explore alternative methods for removal of the *N*-(1-ethoxyvinyl) substituent, which serves both as an activating group for the aromatic ring in S_NAr reactions, and as a protecting group for the basic pyridine *N*-atom.



24 **26**

Scheme 11 – Removal of the *N*-(1-ethoxyvinyl) functional group

Conclusion

In summary, we have identified a straightforward protocol for the direct synthesis of a broad array of bench-stable *N*-quaternized ketene *N*,*O*-acetals, significantly adding to the repertoire of these rare species for use in reagent and/or synthetic building block applications. Several preliminary applications including a "trapped ketenium ion" reagent for acid catalyst-free Friedel-Crafts acylation, a unique Mukaiyama salt in peptide couplings, and an electrophilic substrate in mild S_NAr reactions provide an early view into the broad synthetic versatility of this underexplored compound class.

Experimental Section

General Experimental Methods: All commercially available chemicals were used as obtained, without further purification. NMR Spectra were obtained on Bruker Avance 400 or 500 MHz NMRs. For compounds containing known impurities or present in mixtures, ^{1}H NMR integrations were used to calculate accurate yields of the desired and/or side product(s). Both nominal and high-resolution mass spectra were obtained on a Waters Micromass 70-

VSE. For all *N*-quaternized ketene *N*,*O*-acetals, only the pyridinium or anilinium cation was detected and analyzed by mass spectrometry due to weak coordination by the triflate or bistriflimide anions.

Column chromatography was performed using new RediSep Rf Gold normal phase silica columns (20–40 micron) with a Teledyne Isco CombiFlash Rf200 purification system. We found automated chromatography to be most convenient, but not essential. Standard column chromatography may be employed, but high grade silica is recommended (e.g. fine spherical silica, 20-40 μM) in order to avoid contamination of broken off silica in the product while using polar alcohol solvents (e.g. methanol or isopropanol). Multiple control experiments involving extensive washing of RediSep Rf Gold normal phase silica columns with pure methanol or isopropanol showed that little (<1 mg) to no silica was eluted.

General procedures for synthesis of *N*-quaternized ketene *N*,*O*-acetals:

A. Mix Method I: Ethoxyacetylene (479 μL, 2 mmol, ~40 wt % in hexanes) and the appropriate pyridine (2 mmol) were dissolved in dichloromethane (3.5 mL) at 0 °C and then the appropriate acid (2 mmol) was slowly added. Following an additional 60 min. of stirring at 0 °C, the reaction mixture was concentrated in vacuo to provide a crude residue which was purified by silica gel column chromatography with a 0–50% chloroform/methanol gradient.

B. Mix Method II: Ethoxyacetylene (479 μL, 2 mmol, ~40 wt % in hexanes) and the appropriate acid (2 mmol) were dissolved in dichloromethane (3.5 mL) at 0 °C and then the appropriate pyridine (2 mmol) was slowly added. Following an additional 60 min. of stirring at 0 °C, the reaction mixture was concentrated in vacuo to provide a crude residue which was purified by silica gel column chromatography with a 0–50% chloroform/methanol gradient.

C. Mix Method III: The appropriate pyridine (2 mmol) was dissolved in dichloromethane (3.5 mL) at 0 °C and then the appropriate acid (2 mmol) was slowly added. The resulting solution was stirred for 5 min before adding ethoxyacetylene (479 μL, 2 mmol, ~40 wt % in hexanes) and stirring for an additional 60 min. at 0 °C. Following this, the reaction mixture was concentrated in vacuo to provide a crude residue which was purified by silica gel column chromatography with a 0–50% chloroform/methanol gradient.

D. Mix Method IV: Ethoxyacetylene (479 μL, 2 mmol, ~40 wt % in hexanes) and the appropriate pyridine (2 mmol) were dissolved in dichloromethane (1 mL). The resulting solution was added dropwise to a 0 °C solution of acid (2 mmol) in dichloromethane (2.5 mL). Following an additional 60 min. of stirring at 0 °C, the reaction mixture was concentrated in vacuo to provide a crude residue which was purified by silica gel column chromatography with a 0–50% chloroform/methanol gradient.

1-(1-Ethoxyvinyl)-2-fluoropyridin-1-ium trifluoromethanesulfonate (**1b**). Synthesized via modified General Procedure A, without column chromatography, and obtained crude as a brown residue (501 mg, 79%). Spectral data matched those previously reported.[19]

1-(1-Ethoxyvinyl)-2-fluoropyridin-1-ium bis((trifluoromethyl)sulfonyl)amide (**2b**). Synthesized via modified General Procedure D, without column chromatography, and obtained crude as a brown residue (600 mg, 59%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (dddd, J = 8.7, 7.6, 5.6, 1.9 Hz, 1H), 8.68 (ddd, J = 6.1, 4.0, 1.9 Hz, 1H), 7.96 (ddd, J = 7.6, 6.2, 1.2 Hz, 1H), 7.86 (ddd, J = 8.7, 4.0, 1.2 Hz, 1H), 4.86 (d, J = 5.5 Hz, 1H), 4.70 (d, J = 5.5 Hz, 1H), 4.06 (q, J = 7.0 Hz, 2H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4 (d, $^{1}J_{CF}$ = 284 Hz), 154.2 (d, $^{3}J_{CF}$ = 12.5 Hz), 149.3, 143.5 (d, $^{3}J_{CF}$ = 8.8 Hz), 124.8 (d, $^{4}J_{CF}$ = 3.8 Hz), 120.3 (q, $^{1}J_{CF}$ = 318 Hz, CF_3), 115.1 (d, $^{2}J_{CF}$ = 18.8 Hz), 87.5, 67.7, 13.5; Mass spectrometry analysis was unsuccessful due to decomposition.

1-(1-Ethoxyvinyl)-2-methoxypyridin-1-ium trifluoromethanesulfonate (**7b**). Synthesized via General Procedure A and obtained as a light yellow amorphous solid (340 mg, 52%). ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.75 (ddd, J =

9.1, 7.4, 1.8 Hz, 1H), 8.69 (dd, *J* = 6.4, 1.8 Hz, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.74 (ddd, *J* = 7.5, 6.4, 1.1 Hz, 1H), 4.86 (app d, *J* = 1.4 Hz, 2H), 4.45 (s, 3H), 4.21 (q, *J* = 7.0 Hz, 2H), 1.39 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 160.47, 151.48, 150.80, 142.57, 121.2 (q, $^{1}J_{CF}$ = 319 Hz, *C*F_3), 118.95, 112.16, 86.23, 66.88, 59.73, 29.53, 29.47, 29.37, 29.22, 29.07, 28.91, 28.76, 28.60, 13.30; LRMS-ES+ *m/z* (relative intensity) 180.1 ($C_{10}H_{14}NO_2$ M+, 100); HRMS-ES+ ($C_{10}H_{14}NO_2$) calcd 180.1025 (M+), found 180.1026.

1-(1-Ethoxyvinyl)-2-methoxypyridin-1-ium bis((trifluoromethyl)sulfonyl)amide (**8b**). Synthesized via General Procedure D and obtained as a light yellow amorphous solid (420 mg, 46%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (ddd, *J* = 9.1, 7.4, 1.9 Hz, 1H), 8.25 (ddd, *J* = 6.4, 1.9, 0.6 Hz, 1H), 7.66 (dt, *J* = 9.0, 0.8 Hz, 1H), 7.55 (ddd, *J* = 7.4, 6.4, 1.1 Hz, 1H), 4.65 (d, *J* = 5.0 Hz, 1H), 4.61 (d, *J* = 5.0 Hz, 1H), 4.32 (s, 3H), 4.09 (q, *J* = 7.0 Hz, 2H), 3.47 (s, 1H), 1.39 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 151.1, 151.0, 141.8, 119.7 (q, $^{1}J_{CF}$ = 319 Hz, *C*F_3), 118.9, 112.0, 86.5, 67.0, 59.9, 13.9; LRMS-ES+ *m/z* (relative intensity) 180.1 ($C_{10}H_{14}NO_2$ M+, 100); HRMS-ES+ ($C_{10}H_4NO_2$) calcd 180.1025 (M+), found 180.1016.

2-Chloro-1-(1-ethoxyvinyl)pyridin-1-ium trifluoromethanesulfonate (**1c**) – Synthesized via General Procedure D and obtained as a light brownish orange amorphous solid (630 mg, 93%). Spectral data matched those previously reported.[19]

2-Chloro-1-(1-ethoxyvinyl)pyridin-1-ium bis((trifluoromethyl)sulfonyl)amide (**2c**). Synthesized via General Procedure D and obtained as a light brownish orange amorphous solid (781 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (ddd, *J* = 6.1, 1.8, 0.6 Hz, 1H), 8.68 (ddd, *J* = 8.3, 7.8, 1.8 Hz, 1H), 8.18 (ddd, *J* = 8.3, 1.4, 0.5 Hz, 1H), 8.15 (ddd, *J* = 7.6, 6.2, 1.3 Hz, 1H), 4.87 (d, *J* = 5.5 Hz, 1H), 4.79 (d, *J* = 5.5 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 1.45 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 150.0, 147.6, 146.7, 130.3, 127.0, 119.7 (q, $^{1}J_{CF}$ = 319 Hz, *C*F_3) 87.5, 67.7, 13.7; LRMS-ES+ *m/z* (relative intensity) 184.0 ($C_9H_{11}NOCl$ M+, 100 (Cl-35 isotope)), 186.0 ($C_9H_{11}NOCl$ M+, 32 (Cl-37 isotope)); HRMS-ES+ ($C_9H_{11}NOCl$) calcd 184.0529 (M+), found 184.0531.

2-Bromo-1-(1-ethoxyvinyl)pyridin-1-ium trifluoromethanesulfonate (**1d**) – Synthesized via General Procedure A and obtained as a light brown amorphous solid (536 mg, 71%). Spectral data matched those previously reported.[19]

2-Bromo-1-(1-ethoxyvinyl)pyridin-1-ium bis((trifluoromethyl)sulfonyl)amide (**2d**). Synthesized via General Procedure D and obtained as a light brown amorphous solid (458 mg, 52%). ^{1}H NMR (500 MHz, D_2O) δ 9.04 (dd, *J* = 6.2, 1.7 Hz, 1H), 8.49 (td, *J* = 8.0, 1.7 Hz, 1H), 8.40 (d, *J* = 8.2 Hz, 1H), 8.08 (ddd, *J* = 7.6, 6.2, 1.4 Hz, 1H), 4.85 (d, *J* = 5.3 Hz, 1H), 4.74 (dd, *J* = 5.2, 1.2 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 149.0, 148.0, 137.6, 134.3, 127.3, 119.8 (q, $^{1}J_{CF}$ = 319 Hz, *C*F_3), 87.1, 67.7, 13.7; LRMS-ES+ *m/z* (relative intensity) 184.0 ($C_9H_{11}NOBr$ M+, 100 (Br-79 isotope)), 186.0 ($C_9H_{11}NOBr$ M+, 99 (Br-81 isotope)); HRMS-ES+ ($C_9H_{11}NOBr$) calcd 228.0024 (M+), found 228.0020.

1-(1-Ethoxyvinyl)-2-iodopyridin-1-ium trifluoromethanesulfonate (**1e**). Synthesized via General Procedure A and obtained as a light yellow amorphous solid (510 mg, 60%).

1-(1-Ethoxyvinyl)-2-iodopyridin-1-ium bis((trifluoromethyl)sulfonyl)amide (**2e**). Synthesized via General Procedure D and obtained as a light brown amorphous solid (500 mg, 45%). ^{1}H NMR (500 MHz, $CDCl_3$ + 1 drop CD_3OD) δ 8.95 (dd, *J* = 6.1, 1.7 Hz, 1H), 8.48 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.12 (td, *J* = 8.0, 1.7 Hz, 1H), 8.01 (ddd, *J* = 7.7, 6.1, 1.4 Hz, 1H), 4.62 (d, *J* = 1.6 Hz, 2H), 4.08 (q, *J* = 7.0 Hz, 2H), 1.35 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$ + 1 drop CD_3OD) δ 156.9, 147.6, 146.4, 141.3, 127.3, 119.5 (q, $^{1}J_{CF}$ = 319 Hz, *C*F_3), 115.6, 86.39, 67.27, 13.37; LRMS-ES+ *m/z* (relative intensity) 276.0 ($C_9H_{11}INO$ M+, 95); HRMS-ES+ ($C_9H_{11}INO$) calcd 275.9885 (M+), found 275.9886.

3-Chloro-1-(1-ethoxyvinyl)pyridin-1-ium trifluoromethanesulfonate (**1f**). Synthesized via General Procedure D and obtained as a brownish orange amorphous solid (247 mg, 37%). ^{1}H NMR (500 MHz, $CDCl_3$ + 1 drop CD_3OD) δ 9.19 (dt, *J* = 6.3, 1.3 Hz, 1H), 9.05 (t, *J* = 1.8 Hz, 1H), 8.65 (ddd, *J* = 8.6, 2.1, 1.1 Hz, 1H), 8.27 (dd, *J* = 8.5, 6.2 Hz, 1H), 5.17 (d, *J* = 6.2 Hz, 1H), 4.67 (d, *J* = 6.2 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 1.49 (t, *J* = 7.0 Hz, 3H; ^{13}C-

NMR (125 MHz, $CDCl_3$ + 1 drop CD_3OD) δ 153.6, 147.9, 141.4, 140.7, 136.1, 129.4, 120.2 (q, $^1J_{CF}$ = 316 Hz, *C*F_3), 84.4, 68.2, 13.9; LRMS-ES+ *m/z* (relative intensity) 184.1 ($C_9H_{11}NOCl$ M+, 100 (Cl-35 isotope)), 186.0 ($C_9H_{11}NOCl$ M+, 42 (Cl-37 isotope)); HRMS-ES+ ($C_9H_{11}NOCl$) calcd 184.0529 (M+), found 184.0525.

3-Chloro-1-ethylpyridin-1-ium trifluoromethanesulfonate (**5f**). Synthesized via General Procedure D and obtained as a light yellow amorphous solid (82 mg, 14%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (d, *J* = 6.0 Hz, 1H), 8.95 (t, *J* = 1.6 Hz, 1H), 8.43 (ddd, *J* = 8.5, 2.1, 1.1 Hz, 1H), 8.11 (dd, *J* = 7.7, 6.8 Hz, 1H), 4.86 (q, *J* = 7.4 Hz, 2H), 1.75 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$ + 1 drop CD_3OD) δ 145.0, 143.7, 143.2, 136.3, 129.3, 120.4 (app q, $^1J_{CF}$ = 320 Hz, *C*F_3), 58.6, 16.6; LRMS-ES+ *m/z* (relative intensity) 142.0 (C_7H_9ClN M+, 100 (Cl-35 isotope)), 144.0 (C_7H_9ClN M+, 36 (Cl-37 isotope)); HRMS-ES+ (C_7H_9ClN) calcd 142.0424 (M+), found 142.0424.

4-Chloro-1-(1-ethoxyvinyl)pyridin-1-ium trifluoromethanesulfonate (**1g**). Sodium hydride (80 mg, 60% dispersion in mineral oil, 2 mmol) was added to mixture of 4-chloropyridine hydrochloride (300 mg, 2 mmol) and dichloromethane at 0 °C. After 30 min, ethoxyacetylene (484 μL, 2 mmol, ~40 wt % in hexanes) then triflic acid (177 mL, 2 mmol) were added and the reaction was stirred for an additional 45 min at 0 °C. The resulting reaction mixture was concentrated in vacuo to provide a crude residue which was purified by silica gel column chromatography with a 0–50% chloroform/methanol gradient. Compound **1g** was obtained as a light yellow amorphous solid (120 mg, 18%). ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.37 (d, *J* = 6.6 Hz, 2H), 8.42 (d, *J* = 6.6 Hz, 2H), 5.19 (d, *J* = 5.8 Hz, 1H), 4.86 (d, *J* = 5.8 Hz, 1H), 4.31 (q, *J* = 6.9 Hz, 2H), 1.49 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 156.33, 154.18, 143.48, 128.67, 121.0 (app q, $^1J_{CF}$ = 319 Hz, *C*F_3), 83.27, 67.98, 13.27; LRMS-ES+ *m/z* (relative intensity) 184.0 ($C_9H_{11}NOCl$ M+, 20 (Cl-35 isotope)), 186.0 ($C_9H_{11}NOCl$ M+, 6 (Cl-37 isotope)); HRMS-ES+ ($C_9H_{11}NOCl$) calcd 184.0529 (M+), found 184.0529.

2,3-Dichloro-1-(1-ethoxyvinyl)pyridin-1-ium trifluoromethanesulfonate (**1h**). Synthesized via General Procedure A and obtained as a reddish brown amorphous solid (596 mg, 81%). ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.34 (dd, *J* = 6.1, 1.6 Hz, 1H), 9.09 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.33 (dd, *J* = 8.5, 6.1 Hz, 1H), 5.12 (d, *J* = 5.1 Hz, 1H), 5.06 (d,

J = 5.1 Hz, 1H), 4.31 (q, *J* = 7.0 Hz, 2H), 1.43 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 153.8, 149.6, 147.2, 146.1, 136.0, 127.1, 121.1 (q, $^{1}J_{CF}$ = 319 Hz, *C*F_3), 87.4, 67.8, 13.3; LRMS-ES+ *m/z* (relative intensity) 218.0 ($C_9H_{10}Cl_2NO$ M+, 20 (Cl-35 isotopes)), 220.0 ($C_9H_{10}Cl_2NO$ M+, 17 (Cl-35/37 isotopes)), 222.0 ($C_9H_{10}Cl_2NO$ M+, 2 (Cl-37 isotopes)); HRMS-ES+ ($C_9H_{10}Cl_2NO$) calcd 218.0139 (M+), found 218.0139.

2,4-Dichloro-1-(1-ethoxyvinyl)pyridin-1-ium trifluoromethanesulfonate (**1i**) and 2,4-dichloropyridin-1-ium trifluoromethanesulfonate (**3i**). Synthesized via General Procedure A, but without chromatography, and obtained as a reddish brown amorphous solid in a ~1:0.2 molar ratio of **1i**/**3i** (**1i**: 574 mg, 78%; **3i**: 95 mg, 16%). Spectral data of **3i** matched those previously reported.[36] **1i** (for clarity, only the desired product signals are reported): ^{1}H NMR (500 MHz, CD_3CN) δ 8.86 (d, *J* = 6.8 Hz, 1H), 8.37 (d, *J* = 2.3 Hz, 1H), 8.15 (dd, *J* = 6.7, 2.3 Hz, 1H), 4.88 (d, *J* = 5.2 Hz, 1H), 4.85 (d, *J* = 5.2 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 1.41 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 158.3, 153.3, 148.2, 148.1, 131.1, 128.0, 121.6 (q, $^{1}J_{CF}$ = 319 Hz, *C*F_3), 88.1, 68.4, 13.7; LRMS-ES+ *m/z* (relative intensity) 218.0 ($C_9H_{10}Cl_2NO$ M+, 100 (Cl-35 isotopes)), 220.0 ($C_9H_{10}Cl_2NO$ M+, 66 (Cl-35/37 isotopes)), 222.0 ($C_9H_{10}Cl_2NO$ M+, 12 (Cl-37 isotopes)); HRMS-ES+ ($C_9H_{10}Cl_2NO$) calcd 218.0139 (M+), found 218.0138.

2,5-Dichloro-1-(1-ethoxyvinyl)pyridin-1-ium trifluoromethanesulfonate (**1j**). Synthesized via General Procedure D and obtained as brown amorphous solid (200 mg, 27%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.64 (d, *J* = 8.0 Hz, 1H), 8.22 (d, *J* = 8.3 Hz, 1H), 5.16 (d, *J* = 5.1 Hz, 1H), 4.80 (d, *J* = 4.5 Hz, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 1.43 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 149.6, 146.1, 145.7, 134.8, 131.0, 120.5 (app q, $^{1}J_{CF}$ = 316 Hz, *C*F_3), 88.3, 67.8, 13.9. LRMS-ES+ *m/z* (relative intensity) 218.0 ($C_9H_{10}Cl_2NO$ M+, 20 (Cl-35 isotopes)), 220.0 ($C_9H_{10}Cl_2NO$ M+, 12 (Cl-35/37 isotopes)), 222.0 ($C_9H_{10}Cl_2NO$ M+, 2 (Cl-37 isotopes)); HRMS-ES+ ($C_9H_{10}Cl_2NO$) calcd 218.0139 (M+), found 218.0131.

2,6-Dichloro-1-(1-ethoxyvinyl)pyridin-1-ium trifluoromethanesulfonate (**1k**) and 2,6-dichloropyridin-1-ium trifluoromethanesulfonate (**3k**). Synthesized via General Procedure A, but without chromatography, and obtained as a brown amorphous solid in a ~1:1.1 molar ratio of **1k**/**3k** (**1k**: 287 mg, 39%; **3k**: 256 mg, 43%). Proton and mass

spectral data is reported separately for clarity. **1k**: ^{1}H NMR (500 MHz, CD_3CN) δ 8.61 (t, *J* = 8.4 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 2H), 5.01 (d, *J* = 5.4 Hz, 1H), 4.92 (d, *J* = 5.4 Hz, 1H), 4.24 (q, *J* = 7.0 Hz, 2H), 1.41 (t, *J* = 7.0 Hz, 3H); HRMS-ES+ ($C_9H_{10}Cl_2NO$) calcd 218.0139 (M+), found 218.0142; **3k**: ^{1}H NMR (500 MHz, CD_3CN) δ 7.81 (t, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 2H), 6.55 (s, 1H); LRMS-ES+ *m/z* (relative intensity) 148.0 ($C_5H_4Cl_2N$ M+, 100 (Cl-35 isotopes)), 150.0 ($C_5H_4Cl_2N$ M+, 63 (Cl-35/37 isotopes)), 152.0 ($C_5H_4Cl_2N$ M+, 10 (Cl-37 isotopes)); HRMS-ES+ ($C_9H_{10}Cl_2NO$) calcd 147.9721 (M+), found 147.9726; **1k**/**3k**: ^{13}C NMR (100 MHz, CD_3CN) δ 150.9, 150.6, 150.5, 149.8, 142.7, 129.4, 123.9, 121.6 (q, $^{1}J_{CF}$ = 319 Hz, CF_3 for both compounds), 89.2, 68.3, 13.7.

2,6-Dibromo-1-(1-ethoxyvinyl)pyridin-1-ium trifluoromethanesulfonate (**1l**). Synthesized via General Procedure A and obtained as a light brown amorphous solid (145 mg, 16%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 9.1, 7.2 Hz, 1H), 8.40 – 8.34 (m, 2H), 5.14 (d, *J* = 5.5 Hz, 1H), 4.82 (d, *J* = 5.5 Hz, 1H), 4.18 (q, *J* = 7.0 Hz, 2H), 1.46 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 149.2, 140.2, 133.4, 120.6 (q, $^{1}J_{CF}$ = 318 Hz, CF_3), 88.9, 67.4, 13.9; LRMS-ES+ *m/z* (relative intensity) 305.9 ($C_9H_{10}Br_2NO$ M+, 10 (Br-79 isotopes)), 307.9 ($C_9H_{10}Br_2NO$ M+, 20 (Br-79/81 isotopes)), 309.9 ($C_9H_{10}Br_2NO$ M+, 10 (Br-81 isotopes)); HRMS-ES+ ($C_9H_{11}NOCl$) calcd 305.9129 (M+), found 305.9125.

2-Acetyl-1-(1-ethoxyvinyl)pyridin-1-ium trifluoromethanesulfonate (**1m**). Synthesized via General Procedure D and obtained as a light brown amorphous solid (57 mg, 8%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.13 (dd, *J* = 6.1, 1.3 Hz, 1H), 8.89 (td, *J* = 7.8, 1.3 Hz, 1H), 8.47 (dd, *J* = 7.9, 1.4 Hz, 1H), 8.37 (ddd, *J* = 7.7, 6.1, 1.4 Hz, 1H), 5.07 (d, *J* = 5.7 Hz, 1H), 4.67 (d, *J* = 5.7 Hz, 1H), 4.08 (q, *J* = 7.0 Hz, 2H), 2.79 (s, 3H), 1.38 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 154.2, 150.2, 147.7, 146.6, 130.3, 127.7, 127.6, 119.20 (*CF_3), 86.4, 67.8, 28.8, 13.7, *full quartet of CF_3 indiscernible due to low sample size; LRMS-ES+ *m/z* (relative intensity) 192.1 ($C_{11}H_{14}NO_2$ M+, 100); HRMS-ES+ ($C_{11}H_{14}NO_2$) calcd 192.1025 (M+), found 192.1024.

2-Acetyl-1-(1-ethoxyvinyl)pyridin-1-ium bis((trifluoromethyl)sulfonyl)amide (**2m**). Synthesized via General Procedure D and obtained as a light brown amorphous solid (258 mg, 27%). ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.37 (ddd, *J* = 6.1, 1.4, 0.6 Hz, 1H), 9.07 (td, *J* = 7.9, 1.4 Hz, 1H), 8.66 (dt, *J* = 7.8, 0.9 Hz, 1H), 8.48 (ddd, *J* = 7.8, 6.1, 1.5 Hz, 1H), 5.13 (d, *J* = 5.4 Hz, 1H), 4.92 (d, *J* = 5.5 Hz, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 2.87 (s, 3H), 1.40 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 192.6, 154.6, 150.2, 148.3, 146.6, 129.7, 127.6, 120.1 (q, $^{1}J_{CF}$ = 320 Hz, *C*F_3), 85.9, 67.9, 28.4, 13.1; LRMS-ES+ *m/z* (relative intensity) 192.1 ($C_{11}H_{14}NO_2$ M+, 100); HRMS-ES+ ($C_{11}H_{14}NO_2$) calcd 192.1025 (M+), found 192.1031.

2-Benzoyl-1-(1-ethoxyvinyl)pyridin-1-ium trifluoromethanesulfonate (**1n**). Synthesized via General Procedure D and obtained as a light brown amorphous solid (435 mg, 54%). ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.54 (dd, *J* = 6.3, 1.4 Hz, 1H), 9.12 (td, *J* = 7.9, 1.4 Hz, 1H), 8.58 (ddd, *J* = 7.8, 6.2, 1.5 Hz, 1H), 8.52 (dd, *J* = 7.7, 1.5 Hz, 1H), 8.05 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.87 (tt, *J* = 7.3, 1.3 Hz, 1H), 7.69 (app dd, *J* = 8.4, 7.4 Hz, 2H), 5.24 (d, *J* = 5.5 Hz, 1H), 4.84 (d, *J* = 5.5 Hz, 1H), 3.88 (q, *J* = 7.0 Hz, 2H), 0.94 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 186.5, 154.0, 149.9, 148.3, 146.7, 135.7, 133.7, 130.4, 129.8, 129.5, 129.3, 128.2, 121.3 (q, $^{1}J_{CF}$ = 319 Hz, *C*F_3), 86.7, 67.7, 12.5; LRMS-ES+ *m/z* (relative intensity) 254.1 ($C_{16}H_{16}NO_2$ M+, 40); HRMS-ES+ ($C_{16}H_{16}NO_2$) calcd 254.1181 (M+), found 254.1171.

2-Benzoyl-1-(1-ethoxyvinyl)pyridin-1-ium bis((trifluoromethyl)sulfonyl)amide (**2n**). Synthesized via General Procedure D and obtained as a light brown amorphous solid (320 mg, 30%). ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.53 (dd, *J* = 6.2, 1.5 Hz, 1H), 9.13 (td, *J* = 7.9, 1.4 Hz, 1H), 8.63 – 8.52 (m, 2H), 8.10 – 8.00 (m, 2H), 7.88 (tt, *J* = 7.3, 1.3 Hz, 1H), 7.76 – 7.65 (m, 2H), 5.21 (d, *J* = 5.5 Hz, 1H), 4.86 (d, *J* = 5.5 Hz, 1H), 3.89 (q, *J* = 7.0 Hz, 2H), 0.94 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 186.4, 154.0, 149.8, 148.5, 146.5, 135.8, 133.7, 130.4, 129.6, 129.3, 128.2, 120.1 (q, $^{1}J_{CF}$ = 320 Hz, *C*F_3), 86.6, 67.7, 12.5; LRMS-ES+ *m/z* (relative intensity) 254.1 ($C_{16}H_{16}NO_2$ M+, 95); HRMS-ES+ ($C_{16}H_{16}NO_2$) calcd 254.1181 (M+), found 254.1184.

2-Cyano-1-(1-ethoxyvinyl)pyridin-1-ium trifluoromethanesulfonate (**1o**). Synthesized via General Procedure A and obtained as a light brown amorphous solid (220 mg, 34%). ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.65 (dd, J = 6.2, 1.9 Hz, 1H), 9.17 (tt, J = 8.4, 3.2 Hz, 1H), 9.00 (dd, J = 7.9, 1.8 Hz, 1H), 8.72 (tt, J = 6.1, 1.7 Hz, 1H), 5.30 (d, J = 5.3 Hz, 1H), 5.16 (d, J = 5.5 Hz, 1H), 4.38 (q, J = 7.0 Hz, 2H), 1.49 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 153.8, 149.7, 149.0, 134.9, 132.3, 125.7, 121.2 (q, $^{1}J_{CF}$ = 318 Hz, CF$_3$), 110.46, 87.9, 68.4, 13.2; LRMS-ES+ *m/z* (relative intensity) 175.1 ($C_{10}H_{11}N_2O$ M+, 25); HRMS-ES+ ($C_{10}H_{11}N_2O$) calcd 175.0871 (M+), found 175.0871.

1-(1-Ethoxyvinyl)pyridin-1-ium trifluoromethanesulfonate (**1a**). Synthesized via General Procedure D and obtained as a light brown residue (470 mg, 79%). Spectral data matched those previously reported.[19]

1-(1-Ethoxyvinyl)pyridin-1-ium bis((trifluoromethyl)sulfonyl)amide (**2a**). Synthesized via General Procedure, but on a 1 mmol scale for all reagents, and obtained as a light brown residue (230 mg, 53%). ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.40 – 9.36 (m, 1H), 8.93 (tt, J = 7.8, 1.3 Hz, 1H), 8.38 (t, J = 7.5 Hz, 1H), 5.17 (d, J = 5.6 Hz, 1H), 4.88 (d, J = 5.6 Hz, 1H), 4.33 (q, J = 7.0 Hz, 1H), 1.50 (t, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 155.0, 148.8, 142.6, 128.3, 120.1 (q, $^{1}J_{CF}$ = 320 Hz, CF$_3$), 83.2, 67.8, 13.3; LRMS-ES+ *m/z* (relative intensity) 150.1 ($C_9H_{12}NO$ M+, 58); HRMS-ES+ ($C_9H_{12}NO$) calcd 150.0919 (M+), found 150.0915.

1-(1-Ethoxyvinyl)-3-methylpyridin-1-ium trifluoromethanesulfonate (**1q**) and 4-methylpyridin-1-ium trifluoromethanesulfonate (**3q**). Synthesized via General Procedure A. Product **1q** was obtained as a light brown amorphous solid (390 mg, 63%) and **3q** as a white amorphous solid (270 mg, 35%). Spectral data of **3q** matched those previously reported.[37] **1q**: ^{1}H-NMR (500 MHz, Acetone-d_6) δ 9.27 (td, J = 1.7, 0.9 Hz, 1H), 9.21 (ddt, J = 6.6, 1.8, 0.9 Hz, 1H), 8.74 (ddt, J = 8.0, 1.9, 0.9 Hz, 1H), 8.24 (dd, J = 8.0, 6.3 Hz, 1H), 5.17 (d, J = 5.5 Hz, 1H), 4.84 (d, J = 5.5 Hz, 1H), 4.31 (q, J = 7.0 Hz, 2H), 2.70 (d, J = 0.8 Hz, 3H), 1.49 (t, J = 7.0 Hz, 3H); ^{13}C-NMR (125 MHz, Acetone-d_6) δ 154.9, 149.1, 142.2, 139.89, 139.85, 127.5, 121.4 (q, $^{1}J_{CF}$ = 320 Hz, CF$_3$), 83.2, 67.8, 17.6, 13.3;

LRMS-ES+ *m/z* (relative intensity) 164.1 ($C_{10}H_{14}NO$ M+, 100); HRMS-ES+ ($C_{10}H_{14}NO$) calcd 164.1075 (M+), found 164.1081.

1-(1-Ethoxyvinyl)-4-methylpyridin-1-ium trifluoromethanesulfonate (**1r**) and 4-Methylpyridin-1-ium trifluoromethanesulfonate (**3r**). Synthesized via General Procedure A. Compound **1r** co-eluted with a portion of inseparable **3**r in a ~1.6:1 molar ratio (150 mg) as a light brown residue, and a second fraction of pure **3r** was collected as a light brown amorphous solid (330 mg), providing an overall yield of 16% for **1r** and 78% for **3r**. **1r**: ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.22 (d, J = 6.9 Hz, 2H), 8.19 (d, J = 6.5 Hz, 2H), 5.13 (d, J = 5.5 Hz, 1H), 4.81 (d, J = 5.5 Hz, 1H), 4.30 (q, J = 7.0 Hz, 2H), 2.82 (s, 3H), 1.49 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 163.4, 141.4, 128.6, 128.3, 121.3 (q, $^{1}J_{CF}$ = 320 Hz, CF$_3$), 82.5, 67.7, 21.6, 13.3; LRMS-ES+ *m/z* (relative intensity) 164.1 ($C_{10}H_{14}NO$ M+, 100); HRMS-ES+ ($C_{10}H_{14}NO$) calcd 164.1075 (M+), found 164.1081. **3r**: ^{1}H NMR (500 MHz, Acetone-d_6) δ 11.86 (s, 1H), 8.88 (d, J = 6.8 Hz, 2H), 8.10 (d, J = 6.1 Hz, 2H), 2.76 (s, 3H); ^{13}C NMR (125 MHz, Acetone-d_6)) δ 161.6, 140.9, 128.3, 120.9 (q, $^{1}J_{CF}$ = 319 Hz, CF$_3$), 21.6; LRMS-ES+ *m/z* (relative intensity) 94.1 (C_6H_8N M+, 100); HRMS-ES+ (C_6H_8N) calcd 94.0657 (M+), found 94.0654.

1-(1-Ethoxyvinyl)-3-phenylpyridin-1-ium trifluoromethanesulfonate (**1t**) and 1-Ethyl-3-phenylpyridin-1-ium trifluoromethanesulfonate (**5t**). Synthesized via General Procedure A. Both **1t** (260 mg, 35%) and **5t** (140 mg, 21%) were obtained as a light brown amorphous solids. **1t**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (dt, J = 6.2, 1.4 Hz, 1H), 9.05 (t, J = 1.7 Hz, 1H), 8.79 (ddd, J = 8.2, 2.0, 1.2 Hz, 1H), 8.31 (dd, J = 8.2, 6.2 Hz, 1H), 7.76 – 7.71 (m, 2H), 7.59 – 7.52 (m, 3H), 5.18 (d, J = 6.0 Hz, 1H), 4.66 (d, J = 6.0 Hz, 1H), 4.24 (q, J = 7.0 Hz, 2H), 1.51 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 145.9, 141.6, 140.9, 138.9, 132.6, 130.8, 129.9, 128.9, 127.7, 120.7 (q, $^{1}J_{CF}$ = 319 Hz, CF$_3$), 84.2, 67.9, 14.0; LRMS-ES+ *m/z* (relative intensity) 226.1 ($C_{15}H_{16}NO$ M+, 45); HRMS-ES+ ($C_{15}H_{16}NO$) calcd 226.1232 (M+), found 226.1235. **5t**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (d, J = 1.6 Hz, 1H), 8.95 (dd, J = 6.0, 1.4 Hz, 1H), 8.57 (dt, J = 8.2, 1.5 Hz, 1H), 8.09 (dd, J = 8.2, 6.0 Hz, 1H), 7.77 – 7.71 (m, 2H), 7.59 – 7.48 (m, 3H), 4.85 (q, J = 7.4 Hz, 2H), 1.71 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.6, 142.4, 142.0,

141.9, 132.6, 130.6, 129.8, 128.7, 127.5, 120.7 (q, $^{1}J_{CF}$ = 319 Hz, *C*F_3), 57.9, 16.8; LRMS-ES+ *m/z* (relative intensity) 184.1 ($C_{13}H_{14}N$ M+, 10); HRMS-ES+ ($C_{13}H_{14}N$) calcd 184.1126 (M+), found 184.1126.

1-(1-Ethoxyvinyl)-4-phenylpyridin-1-ium trifluoromethanesulfonate (**1u**), 4-phenylpyridin-1-ium trifluoromethanesulfonate (**3u**), and 1-ethyl-4-phenylpyridin-1-ium trifluoromethanesulfonate (**5u**). Synthesized via General Procedure A. Products **1u** and **3u** co-eluted and were obtained as light brown residue as a ~1:2.5 molar mixture of **1u** (129 mg, 17%) and **3u** (261 mg, 43%). Product **5u** was isolated as an amorphous light brown solid (90 mg, 14%). Spectral data for a ~2.5:1 mixture of **3u**/**1u** : ^{1}H NMR (500 MHz, Acetone-d_6, signals of **1u** and **3u** are reported separately for clarity) **1u**: δ 9.34 (d, *J* = 7.1 Hz, 2H), 8.63 (d, *J* = 7.2 Hz, 2H), 8.14 (d, *J* = 6.8 Hz, 2H), 7.77 – 7.68 (m, 3H), 5.20 (d, *J* = 5.6 Hz, 1H), 4.84 (d, *J* = 5.6 Hz, 1H), 4.33 (q, *J* = 7.0 Hz, 2H), 1.51 (t, *J* = 7.0 Hz, 3H); **3v**: δ 9.63 (br s, 1H), 9.12 – 9.02 (m, 2H), 8.55 (d, *J* = 5.6 Hz, 2H), 8.10 – 8.05 (m, 2H), 7.76 – 7.57 (m, 3H); ^{13}C NMR (Acetone-d_6, signals of **1u** and **3u** are reported together) δ 158.5, 157.7, 154.5, 142.2, 134.6, 133.6, 132.9, 132.1, 129.9, 129.8, 128.5, 128.2, 124.60, 124.56, 121.2 (q, $^{1}J_{CF}$ = 318 Hz, *C*F_3), 82.7, 67.7, 13.4; LRMS-ES+ *m/z* (relative intensity) **1u**: 226.1 ($C_{15}H_{16}NO$ M+, 45); **3u**: 156.1 ($C_{11}H_{10}N$ M+, 20); HRMS-ES+ **1u**: ($C_{15}H_{16}NO$) calcd 226.1232 (M+), found 226.1233; **3u**: ($C_{11}H_{10}N$) calcd 156.0813 (M+), found 156.0814. Spectral data for **5u**: ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.21 (d, *J* = 7.0 Hz, 2H), 8.56 (d, *J* = 7.0 Hz, 2H), 8.10 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.72 – 7.65 (m, 3H), 4.89 (q, *J* = 7.3 Hz, 2H), 1.77 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 156.1, 144.7, 134.1, 132.1, 129.8, 128.1, 125.1, 121.4 (app q, $^{1}J_{CF}$ = 320 Hz, *C*F_3), 56.5, 15.9; LRMS-ES+ *m/z* (relative intensity) 184.1 ($C_{13}H_{14}N$ M+, 100); HRMS-ES+ ($C_{13}H_{14}N$) calcd 184.1126 (M+), found 184.1127.

1-(1-Ethoxyvinyl)-2-vinylpyridin-1-ium trifluoromethanesulfonate (**1v**). Synthesized via General Procedure A and obtained as a light brown amorphous solid (390 mg, 60%). ^{1}H NMR (500 MHz, D_2O) δ 8.76 (d, *J* = 6.3 Hz, 1H), 8.55 (t, *J* = 8.0 Hz, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 7.92 (t, *J* = 7.1 Hz, 1H), 6.99 (dd, *J* = 17.2, 11.3 Hz, 1H), 6.48 (d, *J* = 17.2 Hz, 1H), 6.08 (d, *J* = 11.2 Hz, 1H), 4.83 (d, *J* = 5.0 Hz, 1H), 4.71 (app d obscured by residual water signal, *J* = 5.0 Hz, 1H), 4.16 (d, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, D_2O) δ 152.7, 151.9, 147.6,

144.4, 129.6, 126.7, 125.9, 125.2, 119.7 (q, $^1J_{CF}$ = 315 Hz, *C*F_3), 87.0, 67.3, 13.1; LRMS-ES+ *m/z* (relative intensity) 226.1 ($C_{11}H_{14}NO$ M+, 12); HRMS-ES+ ($C_{11}H_{14}NO$) calcd 176.1075 (M+), found 176.1080.

1-(1-Ethoxyvinyl)quinolin-1-ium trifluoromethanesulfonate (**1w**). Synthesized via General Procedure A and obtained as a light brown amorphous solid (272 mg, 37%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (dd, *J* = 5.8, 1.5 Hz, 1H), 9.30 (dt, *J* = 8.4, 1.1 Hz, 1H), 8.41 (dd, *J* = 8.3, 1.4 Hz, 1H), 8.32 (dd, *J* = 8.4, 5.8 Hz, 1H), 8.29 – 8.16 (m, 2H), 8.01 (ddd, *J* = 8.2, 6.7, 1.3 Hz, 1H), 5.02 (d, *J* = 5.0 Hz, 1H), 4.96 (d, *J* = 5.1 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 150.2, 149.4, 137.6, 136.7, 130.7, 130.7, 129.7, 122.7, 120.8 (q, $^1J_{CF}$ = 318 Hz, *C*F_3), 119.2, 88.0, 67.4, 13.9; LRMS-ES+ *m/z* (relative intensity) 200.1 ($C_{13}H_{14}NO$ M+, 100); HRMS-ES+ ($C_{13}H_{14}NO$) calcd 200.1075 (M+), found 200.1080.

1-(1-Ethoxyvinyl)-3-methoxypyridin-1-ium trifluoromethanesulfonate (**1x**). Synthesized via General Procedure A and obtained as an off-white amorphous solid (xx mg, XX%). ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.00 (d, *J* = 6.0 Hz, 1H), 8.49 (dt, *J* = 9.0, 1.8 Hz, 1H), 8.24-8.28 (m, 2H), 5.19 (d, *J* = 5.6 Hz, 1H), 4.85 (d, *J* = 5.5 Hz, 1H), 4.31 (q, *J* = 7.0 Hz, 2H), 4.20 (s, 3H), 1.49 (t, *J* = 7.0 Hz, 3H); 13C NMR (125 MHz, Acetone-d_6, mixture of rotamers or tautomers; only major peaks reported) δ 158.7, 154.8, 135.2, 133.5, 130.0, 128.6, 120.9 (q, $^1J_{CF}$ = 319 Hz, *C*F_3), 83.4, 67.9, 57.5, 13.3; LRMS-ES+ *m/z* (relative intensity) 180.1 ($C_{10}H_{14}NO_2$ M+, 100); HRMS-ES+ ($C_{10}H_{14}NO_2$) calcd 180.1025 (M+), found 180.1025.

Synthesized via General Procedure A. Products **1y** and **3y** co-eluted and were obtained as light brown residue as a ~3.3:1 molar mixture of **1y** (464 mg, 71%) and **3y** (111 mg, 21%). Product **5y** eluted separately and was obtained as a clear residue (25 mg, 4%). ^{1}H NMR (500 MHz, Acetone-d_6, 3.3:1 mixture with NH salt **3y**, only major product peaks reported) δ 9.13 (d, *J* = 6.2 Hz, 2H), 7.77 (d, *J* = 6.2 Hz, 2H), 5.00 (d, *J* = 5.2 Hz, 1H), 4.71 (d, *J* = 5.3 Hz, 1H), 4.33 (s, 3H), 4.28 (app q, *J* = 10 Hz, 2H) 1.48 (t, *J* = 7.0 Hz, 3H; ^{13}C NMR (125 MHz, Acetone-d_6) δ 173.6, 154.3, 143.8, 121.4 (q, $^1J_{CF}$ = 320 Hz, *C*F_3), 113.4, 81.3, 67.4, 58.4, 13.3; LRMS-ES+ *m/z* (relative intensity) 180.1 ($C_{10}H_{14}NO_2$ M+, 90); HRMS-ES+ ($C_{10}H_{14}NO_2$) calcd 180.1025 (M+), found 180.1026. **5y**: ^{1}H NMR (500 MHz,

Acetone-d_6) δ 8.96 (d, J = 7.4 Hz, 2H), 7.69 (d, J = 7.5 Hz, 2H), 4.70 (q, J = 7.3 Hz, 2H), 4.24 (s, 3H), 1.66 (t, J = 7.3 Hz, 3H); ^{13}C NMR (12 MHz, Acetone-d_6) δ 171.3, 145.9, 121.4 (q, $^1J_{CF}$ = 319 Hz, CF$_3$), 113.7, 57.7, 55.3, 15.7; LRMS-ES+ *m/z* (relative intensity) 138.1 ($C_8H_{12}NO$ M+, 100); HRMS-ES+ ($C_8H_{12}NO$) calcd 138.0919 (M+), found 138.0920.

2-Chloro-1-(1-(4-methoxyphenyl)vinyl)pyridin-1-ium trifluoromethanesulfonate (**9**). Synthesized via General Procedure A and obtained as a light brown amorphous solid (364 mg, 46%). ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.31 (dd, J = 6.1, 1.7 Hz, 1H), 8.96 (td, J = 8.1, 1.8 Hz, 1H), 8.57 (dd, J = 8.4, 1.3 Hz, 1H), 8.44 (ddd, J = 7.6, 6.1, 1.3 Hz, 1H), 7.46 – 7.30 (m, 2H), 7.13 – 6.98 (m, 2H), 6.53 (d, J = 2.9 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 161.6, 149.7, 148.6, 147.5, 146.9, 131.1, 127.6, 127.0, 124.3, 121.4 (q, $^1J_{CF}$ = 319 Hz, CF$_3$), 115.2, 114.8, 55.1; LRMS-ES+ *m/z* (relative intensity) 246.1 ($C_{14}H_{13}NOCl$ M+, 10 (Cl-35 isotope), 248.1 ($C_{14}H_{13}NOCl$ M+, 3 (Cl-37 isotope) HRMS-ES+ ($C_{14}H_{13}NOCl$) calcd 246.0686 (M+), found 246.0688.

2-Chloro-1-(1-(4-methoxyphenyl)vinyl)pyridin-1-ium bis((trifluoromethyl)sulfonyl)amide (**10**). Synthesized via General Procedure D and obtained as a light brown amorphous solid (558 mg, 53%). ^{1}H NMR (500 MHz, Acetone-d_6) δ 9.37 (dd, J = 6.1, 1.7 Hz, 1H), 9.01 (td, J = 8.1, 1.8 Hz, 1H), 8.62 (dd, J = 8.4, 1.4 Hz, 1H), 8.49 (ddd, J = 7.6, 6.1, 1.4 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.09 – 7.02 (m, 2H), 6.56 (d, J = 2.9 Hz, 1H), 6.02 (d, J = 2.9 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 161.7, 149.6, 148.5, 147.6, 147.2, 131.1, 127.4, 127.0, 124.2, 120.2 (q, $^1J_{CF}$ = 319 Hz, CF$_3$), 115.0, 114.8, 55.1; LRMS-ES+ *m/z* (relative intensity) 246.1 ($C_{14}H_{13}NOCl$ M+, 100 (Cl-35 isotope), 248.1 ($C_{14}H_{13}NOCl$ M+, 32 (Cl-37 isotope) HRMS-ES+ ($C_{14}H_{13}NOCl$) calcd 246.0686 (M+), found 246.0694.

(*Z*)-2-chloro-1-(1-ethoxy-3-phenylprop-1-en-1-yl)pyridin-1-ium (**12a**) and (*E*)-2-chloro-1-(1-ethoxy-3-phenylprop-1-en-1-yl)pyridin-1-ium (**12b**). Synthesized via modified General Procedure A, using alkyne **11** in place of ethoxyacetylene and with all reagents at a 9 mmol scale, compound **12a** (960 mg, 25%) and **12b** (900 mg, 24%) were isolated separately, both as light brown oils. For clarity, NMR spectra are reported separately; mass

spectral data was obtained as a mixture. **12a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (d, *J* = 6.1 Hz, 1H), 8.64 (t, *J* = 8.1 Hz, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 8.11 (t, *J* = 7.0 Hz, 1H), 7.33 – 7.13 (m, 5H), 5.67 (t, *J* = 7.8 Hz, 1H), 3.85 (q, *J* = 7.0 Hz, 2H), 3.66 (d, *J* = 7.8 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 148.2, 147.2, 146.5, 137.8, 130.7, 128.8, 128.4, 127.1, 126.7, 120.6 (q, $^{1}J_{CF}$ = 319 Hz, *C*F_3), 116.4, 69.1, 31.2, 14.7. **12b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (dd, *J* = 6.2, 1.7 Hz, 1H), 8.77 (td, *J* = 8.1, 1.8 Hz, 1H), 8.30 (ddd, *J* = 7.6, 6.1, 1.3 Hz, 1H), 8.19 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.26 – 7.13 (m, 3H), 7.07 – 7.03 (m, 2H), 5.35 (dd, *J* = 8.1, 6.9 Hz, 1H), 4.19 (dq, *J* = 9.2, 7.0 Hz, 1H), 4.08 (dq, *J* = 9.2, 7.0 Hz, 1H), 3.28 (dd, *J* = 16.3, 6.9 Hz, 1H), 3.04 (dd, *J* = 16.3, 8.1 Hz, 1H), 1.39 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 148.8, 147.74, 146.5, 137.4, 130.3, 128.9, 128.2, 128.0, 127.0, 120.7 (q, $^{1}J_{CF}$ = 318 Hz, *C*F_3), 101.2, 67.4, 31.4, 14.0. **12a**/**12b**: ; LRMS-ES+ *m/z* (relative intensity) 274.1 ($C_{16}H_{17}NOCl$ M+, 30 (Cl-35 isotope), 276.1 ($C_{14}H_{13}NOCl$ M+, 10 (Cl-37 isotope) HRMS-ES+ ($C_{16}H_{17}NOCl$) calcd 274.0999 (M+), found 274.0999.

1-(1-Ethoxyvinyl)pyrimidin-1-ium trifluoromethanesulfonate (**13**). Synthesized via modified General Procedure A, without purification by chromatography, and obtained as a brown residue in a 1:2.7 mixture of desired product **13** (179 mg, ~39%) and pyrimidin-1-ium trifluoromethanesulfonate (**14**) (370 mg, ~61%). Spectral data for each compound are reported separately for clarity. **13**: ^{1}H NMR (500 MHz, CD_3CN) δ 9.78 (t, *J* = 1.5 Hz, 1H), 9.51 (dd, *J* = 5.0, 1.9 Hz, 1H), 9.35 (dt, *J* = 6.5, 1.9 Hz, 1H), 8.27 (ddd, *J* = 6.3, 4.9, 1.2 Hz, 1H), 5.07 (d, *J* = 6.0 Hz, 1H), 4.82 (d, *J* = 6.0 Hz, 1H), 4.25 (q, *J* = 7.0 Hz, 2H), 1.47 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 171.7, 167.9, 151.6, 150.1, 124.7, 121.5 (q, $^{1}J_{CF}$ = 319 Hz, *C*F_3) 85.3, 69.0, 15.8; Mass spectrometry analysis was unsuccessful due to decomposition. **14**: ^{1}H NMR (500 MHz, CD_3CN) δ 14.41 (s, 1H), 9.56 (s, 1H), 9.30 (d, *J* = 5.6 Hz, 2H), 8.19 (td, *J* = 5.6, 1.3 Hz, 1H); ^{13}C NMR (125 MHz, Acetonitrile-d_3) δ 158.8, 152.4, 124.8, 121.5 (q, $^{1}J_{CF}$ = 319 Hz, *C*F_3). LRMS-ES+ *m/z* (relative intensity) 81.0 ($C_4H_5N_2$ M+, 100); HRMS-ES+ ($C_4H_5N_2$) calcd 81.0453 (M+), found 81.0451.

N-(1-Ethoxyvinyl)-*N*,*N*-dimethylbenzenaminium trifluoromethanesulfonate (**15**). Synthesized via General Procedure A and obtained as a light brown amorphous solid (300 mg, 44%).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 –

7.61 (m, 2H), 7.56 – 7.46 (m, 4H), 5.08 (d, *J* = 6.9 Hz, 1H), 4.58 (d, *J* = 7.0 Hz, 1H), 3.96 (q, *J* = 7.0 Hz, 2H), 3.77 (s, 6H), 1.17 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, Acetone-*d6*) δ 158.1, 145.9, 130.4, 129.2, 121.7, 121.3 (q, $^{1}J_{CF}$ = 319 Hz, *C*F_3), 120.5, 80.9, 67.9, 54.9, 13.0; LRMS-ES+ *m/z* (relative intensity) 192.1 ($C_{12}H_{18}NO$ M+, 100); HRMS-ES+ ($C_{12}H_{18}NO$) calcd 192.1388 (M+), found 192.1394.

N-(1-Ethoxyvinyl)-*N*,*N*-dimethylbenzenaminium bis((trifluoromethyl)sulfonyl)amide (**16**). Synthesized via General Procedure D and obtained as a light brown amorphous solid (440 mg, 47%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.52 (m, 5H), 5.00 (d, *J* = 7.0 Hz, 1H), 4.61 (d, *J* = 7.0 Hz, 1H), 4.00 (q, *J* = 7.0 Hz, 2H), 3.75 (s, 6H), 1.22 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 145.2, 130.9, 130.8, 119.9 (q, $^{1}J_{CF}$ = 315 Hz, *C*F_3), 119.7, 81.1, 68.1, 55.4, 13.5; LRMS-ES+ *m/z* (relative intensity) 192.1 ($C_{12}H_{18}NO$ M+, 100); HRMS-ES+ ($C_{12}H_{18}NO$) calcd 192.1388 (M+), found 192.1388.

N-(1-(4-methoxyphenyl)vinyl)-*N*,*N*-dimethylbenzenaminium trifluoromethanesulfonate (**17**). Synthesized via General Procedure A and obtained as a light brown residue (363 mg, 45%). ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.07 – 7.96 (m, 2H), 7.79 – 7.68 (m, 3H), 6.95 – 6.81 (m, 4H), 6.46 (d, *J* = 4.1 Hz, 1H), 5.76 (d, *J* = 4.1 Hz, 1H), 4.02 (s, 6H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 161.1, 152.6, 145.0, 132.0, 130.9, 130.6, 123.6, 121.8, 121.4 (q, $^{1}J_{CF}$ = 320 Hz, *C*F_3), 115.1, 113.8, 55.3, 54.9; LRMS-ES+ *m/z* (relative intensity) 254.2 ($C_{17}H_{20}NO$ M+, 100); HRMS-ES+ ($C_{17}H_{20}NO$) calcd 254.1545 (M+), found 254.1538. Hydrolysis side product 4'-methoxyacetophenone (**18**) was obtained in variable yields during purification **17** by column chromatography. Spectral data matched those previously reported.[38]

1-(3,4-dimethylphenyl)ethan-1-one (**21**). Compound **1d** (251 mg, 0.66 mmol) was added to veratrole (1 mL, 7.8 mmol) in a microwave vial. The vial was sealed and heated to 200 °C with stirring for 30 min, then air-cooled to room temperature. The resulting brown liquid was purified by silica gel column chromatography; first by eluting all veratrole with pure hexanes, then eluting product **21** as a clear oil with a 0-40% EtOAc/hexanes gradient (110 mg, 92%). Spectral data of product **21** match those previously reported.[39]

N-Benzyl-2-phenylacetamide (**22**) and *N*-(1-ethoxyvinyl)-2-pyridone (**23**). Following a modification of Mukaiyama's seminal protocol[6a] – A flask was charged with phenylacetic acid (136 mg, 1 mmol), CH_2Cl_2 (10 mL), benzylamine (109 μL, 1.0 mmol), and trimethylamine (334 μL, 2.4 mmol). The resulting mixture was added to a separate flask containing compound **1d** (454 mg, 1.2 mmol) and the combined reaction mixture was refluxed in an oil-bath for 1h. After cooling to room temperature, the reaction mixture was diluted with Et_2O (75 mL) and washed with 1M HCl (3x10 mL) then water (10 mL). The organic layer was dried over Na_2SO_4 then concentrated *in vacuo* to provide *N*-benzyl-2-phenylacetamide (**22**) as a white solid in good purity (160 mg, 71%). Spectral data of **22** match those previously reported.[40] The byproduct **23** was also obtained as a light yellow oil in variable yields when using **1c** or **1d** as the coupling agent. Spectral analysis of **23** was similar to those previously reported,[25a] but higher resolution NMR data is provided here for more detail. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (ddd, *J* = 9.3, 6.5, 2.1 Hz, 1H), 7.27 (ddd, *J* = 6.9, 2.2, 0.8 Hz, 1H), 6.56 (ddd, *J* = 9.3, 1.3, 0.8 Hz, 1H), 6.13 (td, *J* = 6.7, 1.3 Hz, 1H), 4.36 (ABq, *J* = 4.6, 1.4 Hz, 2H), 3.99 (q, *J* = 7.0 Hz, 2H), 1.38 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 154.2, 140.0, 137.1, 122.0, 105.2, 83.6, 65.1, 14.1.

2-(Benzylamino)-1-(1-ethoxyvinyl)pyridin-1-ium trifluoromethanesulfonate (**24**). Benzylamine (73 μL, 0.66 mmol) was added to a solution of compound **1d** (250 mg, 0.66 mmol) in acetonitrile (5 mL). The resulting mixture was placed in a pre-heated oil bath and refluxed for 3h. The reaction mixture was concentrated in vacuo to provide a crude residue, which was purified by silica gel column chromatography with a 0–50% chloroform/methanol gradient to provide compound **25** as a light brown amorphous solid (320 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.78 (t, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 6.6 Hz, 1H), 7.45-7.25 (m, 5H), 6.91 (d, *J* = 9.3 Hz, 1H), 6.83 (t, *J* = 6.9 Hz, 1H), 4.81 (d, *J* = 4.8 Hz, 1H), 4.74 (s, 2H), 4.67 (d, *J* = 4.8 Hz, 1H), 4.27 (q, *J* = 7.0 Hz, 2H), 1.43 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 150.7, 144.5, 139.4, 135.5, 129.0, 128.0, 127.1, 118.0 (q, $^1J_{CF}$ = 320 Hz, *C*F_3), 112.7, 112.0, 87.6, 66.8, 46.4, 13.8; LRMS-ES+ *m/z* (relative intensity) 255.2 ($C_{16}H_{19}N_2O$ M+, 100); HRMS-ES+ ($C_{16}H_{19}N_2O$) calcd 255.1497 (M+), found 255.1502.

1-(1-Ethoxyvinyl)-2-((4-methoxybenzyl)amino)pyridin-1-ium trifluoromethanesulfonate (**25**). 4-Methoxybenzylamine (95 μL, 0.73 mmol) was added to a solution of compound **1c** (220 mg, 0.66 mmol) in CH_2Cl_2 (5 mL). The resulting mixture was placed in a pre-heated oil bath and refluxed for 4h. The reaction mixture was concentrated in vacuo to provide a crude residue, which was purified by silica gel column chromatography with a 0–50% chloroform/methanol gradient to provide compound **25** as a light brown amorphous solid (370 mg, 85%). ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.63 (s, 1H), 8.17 (ddd, J = 6.7, 1.7, 0.7 Hz, 1H), 8.11 (ddd, J = 9.3, 7.1, 1.7 Hz, 1H), 7.43 (d, J = 8.9 Hz, 2H), 7.34 (dt, J = 9.2, 1.0 Hz, 1H), 7.09 (td, J = 6.9, 1.1 Hz, 1H), 6.94 (d, J = 8.7 Hz, 2H), 4.93 (d, J = 4.4 Hz, 1H), 4.90 (d, J = 4.4 Hz, 1H), 4.78 (s, 2H), 4.24 (q, J = 7.0 Hz, 2H), 3.79 (s, 3H), 1.41 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, Acetone-d_6) δ 159.45, 152.30, 151.19, 145.09, 140.19, 128.61, 128.18, 121.3 (q, $^1J_{CF}$ = 319 Hz, CF_3), 114.14, 112.99, 112.09, 87.14, 66.42, 54.72, 45.22, 13.35; LRMS-ES+ *m/z* (relative intensity) 285.2 ($C_{17}H_{21}N_2O_2$ M+, 100); HRMS-ES+ ($C_{17}H_{21}N_2O_2$) calcd 285.1603 (M+), found 285.1610.

N-Benzylpyridin-2-amine (**26**). Pyridinium salt **24** (113 mg, 0.28 mmol) was dissolved in 1 mL of 12M $HCl_{(aq)}$ and stirred for 18 h at room temperature. Following this, the reaction mixture was neutralized with 12 mL of 1M $NaOH_{(aq)}$, and the resulting aqueous solution was extracted with ethyl acetate (3 x 15 mL), dried with Na_2SO_4, and concentrated *in vacuo* to yield 2-aminopyridine **26** without need for further purification (50 mg, 96%). Spectral data of **26** matched those previously reported.[41]

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