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Site-Selective Synthesis of N-Benzyl 2,4,6-Collidinium Salts by Electrooxidative C−H Functionalization

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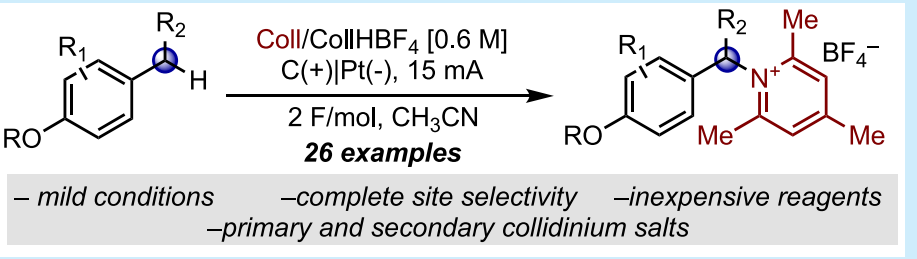

ABSTRACT: *N*-alkylpyridinium salts are versatile pseudohalides for SET-mediated cross couplings. However, the common 2,4,6-triphenylpyridinium salt is plagued by poor atom economy and high cost of synthesis. Thus, there is a growing need for more practical scaffolds and innovative strategies for pyridinium salt formation. Herein, we report the synthesis of benzylic 2,4,6-collidinium salts via electrooxidative C−H functionalization. This method provides a complementary approach to tradtional strategies relying on substitution and condensation of prefunctionalized substrates.

N-alkylpyridinium salts are scaffolds of diverse biological and synthetic importance.[1] In organic chemistry, they serve as oxidants,[2] ionic liquids,[3] and phase transfer catalysts,[4] as well as versatile synthetic intermediates en route to functionalized nitrogen heterocycles.[1] The pyridinium core can also be found in marine sponge secondary metabolites,[5] as well as a cellular cofactor in the NAD^+/NADH electron transport chain.[6] Their role as electron acceptors also formed the basis of the recent pioneering work of Watson, who, in 2017, first reported deaminative radical couplings via single electron transfer (SET) to a 2,4,6-triphenylpyridinium (**2**), or "Katritzky salt", using low-valent nickel catalysis (Scheme 1A).[7] Since Watson's seminal reports, this area has seen tremendous growth and now also includes diverse examples employing nickel catalysis,[8] photoredox catalysis,[9] electrocatalysis,[10] and photoexcited electron donor−acceptor complexes,[11] with these strategies allowing formation of diverse carbon−carbon and carbon-heteroatom bonds from amine precursors.[12] However, a persistent limitation in this chemistry is the need for the 2,4,6-triphenylpyridinium salt. Formed via condensation of an amine with 2,4,6-triphenylpyrylium tetrafluoroborate (**1**), this scaffold suffers from poor atom economy and the high cost of the oxopyrylium ($2000 mol^{-1}), making process and other large-scale applications impractical. Furthermore, this constrains the application of pyridinium-based radical couplings to the presence of a substrate amine.

A recent report from Weaver posited that the utility of pyridinium salts may extend beyond deaminative processes, serving as a useful class of redox active pseudohalides with more normalized redox potentials than their halogen counterparts.[13] The potential for such broad utility further magnifies the need to develop more practical pyridinium scaffolds for SET coupling processes,[14] as well as methods for their incorporation that move beyond amine-pyrylium condensation. In a key advance, the Weaver report utilizes benzylic 2,4,6-collidinium salts (**5**) in iridium-mediated radical Giese reactions, providing the first evidence that this scaffold is competent in SET coupling processes (Scheme 1B). The collidinium scaffold is attractive as it is more atom economical than the Katritzky salt and cost-effective as the salts can be generated using inexpensive 2,4,6-collidine ($30 mol^{-1}). Unfortunately, the steric hindrance of the collidine nucleophile means the required substitution reactions require forcing conditions, are restricted to primary leaving groups, and still rely on prefunctionalized halides (**4**), leaving significant opportunity for improvement.[13]

Our laboratory has a growing interest in developing novel oxidative strategies for the conversion of alkenes and C−H bonds directly to *N*-alkyl and *N*-arylpyridinium salts.[15] Inspired by the Weaver report, we felt that a method enabling the direct synthesis of benzylic pyridinium salts via oxidative C−H amination would be of high value. Such a method could

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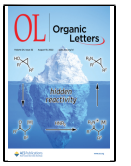

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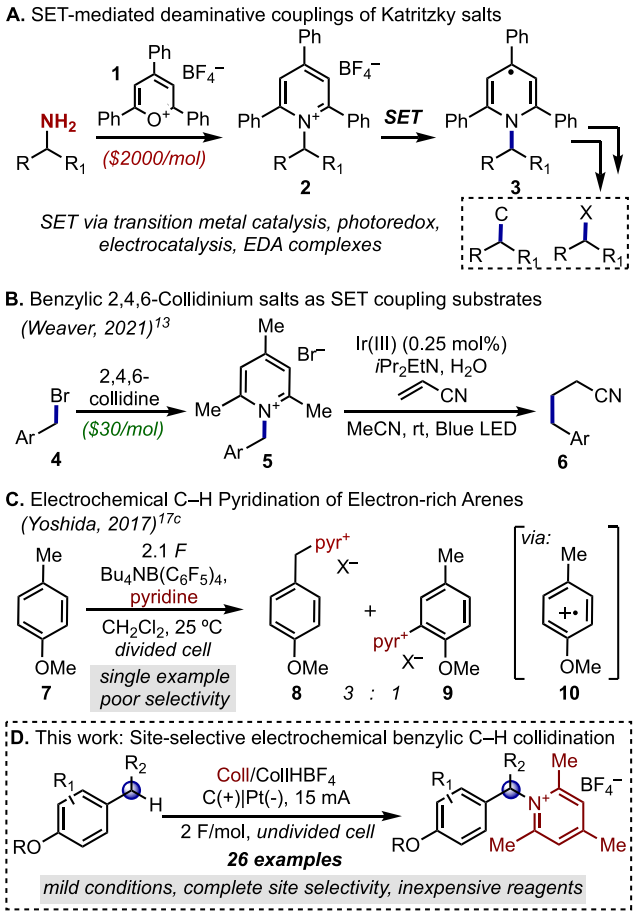
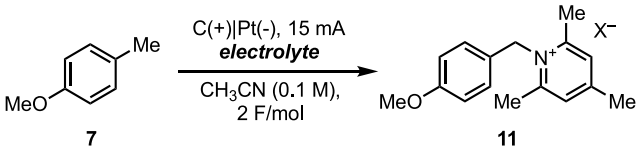
Scheme 1. *N*-Alkyl 2,4,6-Trisubstituted Pyridinium Salts



broaden the scope of accessible pyridinium scaffolds, as well as obviate the need for prefunctionalized benzylic halides and potentially proceed under more mild conditions. Electrochemical oxidation has been demonstrated as an effective means of achieving benzylic C−H functionalization via single electron transfer,[16,17] and offers the advantages of being mild, green, and precisely tunable.[18] A 2017 report from Yoshida provided a single example of an electrochemical benzylic C−H pyridination of electron-rich arenes; however, the reaction proceeded with poor site-selectivity for benzylic versus arene amination, and no further studies were reported (Scheme 1C).[17c] It has been shown that site-selectivity in arene radical cation reactions can be modulated based on sterics of the nucleophile,[19] and we hypothesized that use of 2,4,6-substituted pyridines could lead to a benzylic selective methodology. Herein, we report the synthesis of benzylic 2,4,6-collidinium salts via site-selective electrooxidative C−H functionalization of activated arenes (Scheme 1D). The reaction proceeds under mild conditions, has a broad scope, and features an inexpensive and recyclable collidinium electrolyte system, making it attractive for large scale applications. Furthermore, secondary collidinium salts are accessible in good yields, compounds not readily amenable to synthesis via nucleophilic substitution.

Using 4-Me-anisole (**7**) as a model substrate, we began our study by using slightly modified Yoshida's conditions and replacing pyridine with 2,4,6-collidine (Table 1, entry 1). Encouragingly, the use of the more sterically hindered collidine nucleophile did result in complete selectivity for the benzylic

Table 1. Reaction Optimization



7 **11**

entry	conditions/electrolyte	yield[a]
1	$TBABF_4$ (0.1 M, CH_2Cl_2), collidine (10 equiv)[b,c]	77%
2	Coll/Coll·$HClO_4$ (0.6 M)	70%
3	Coll/Coll·HBF_4 (0.6 M)	88% (82%)[d]
4	Coll/Coll·HBF_4 (0.3 M)	73%
5	Coll/Coll·HBF_4 (0.1 M)	59%
6	recycled Coll/Coll·HBF_4 (0.6 M), precaution-free[e,f]	82% (80%)[d]

[a]Yields via ^1H NMR with CH_2Br_2 internal standard. [b]Modification of Yoshida procedure: $TBABF_4$ used in place of $TBAB(C_6F_5)_3$. [c]C(+)|| Pt(−), 3 mA. [d]Isolated yield. [e]Use of nonanhydrous solvent and no inert atmosphere [f]1 mmol scale.

position to give collidinium **11** in good yield. Unfortunately, separation of **11** from the tetrabutylammonium electrolyte proved extremely challenging, and using our electrochemical setup,[20] we were only able to achieve constant current up to 3 mA under these conditions. In considering alternative electrolytes, we turned to collidine/collidine·H^+, which would serve as both electrolyte and source of nucleophile.[21] We also hypothesized that switching to a protic system would allow us to run the reaction in an undivided cell as facile cathodic H_2 production would suppress any competitive reduction of the collidinium product. The use of 0.6 M collidine/collidine·$HClO_4$ at 15 mA constant current gave a 70% yield of **11** (entry 2), which was now readily isolable via simple Et_2O trituration. A switch to the Coll·HBF_4 salt gave an improved 88% yield and also avoided use of potentially explosive perchlorates (entry 3). Notably, the Coll·HBF_4 salt can be readily prepared on multigram scale and isolated as a free-flowing white powder, and the 0.6 M electrolyte solution can be prepared in batches and stored for several months on the benchtop. Lower electrolyte concentrations led to reduction in yields (entries 4, 5), along with formation of 4-anisaldehyde, believed to be from addition of adventitious water or oxygen to the intermediate cation or radical, respectively.[22] The higher concentrations of electrolyte also allowed the use of higher current, reducing reaction times, and the excess collidine can be recovered in high yield and reused.[23] The scalability and robustness of the reaction is demonstrated as a 1 mmol scale reaction using recycled electrolyte under "precaution-free" conditions (no care to exclude air or moisture), gave **11** in a comparable 82% yield (entry 6).

With optimized conditions in hand, the scope of the collidination reaction was examined, beginning with electronic variation about the anisole ring (Scheme 2). Additional heteroatom substitution at the *meta*-position was well tolerated, with 2-methoxy and 2-phthalimide substitution giving collidinium salts **12** and **13** in 89% and 77% yield, respectively. The reaction was compatible with an aryl bromide, giving **14** in 76% yield, which possesses complementary functional handles for subsequent cross coupling. Moving to electron-withdrawing groups, ketone, ester, and amide substitution all gave collidinium salts in high yield (**15**−**17**). Notably the amide was completely selective for collidination of the benzylic C−H bond, with no Shono-type

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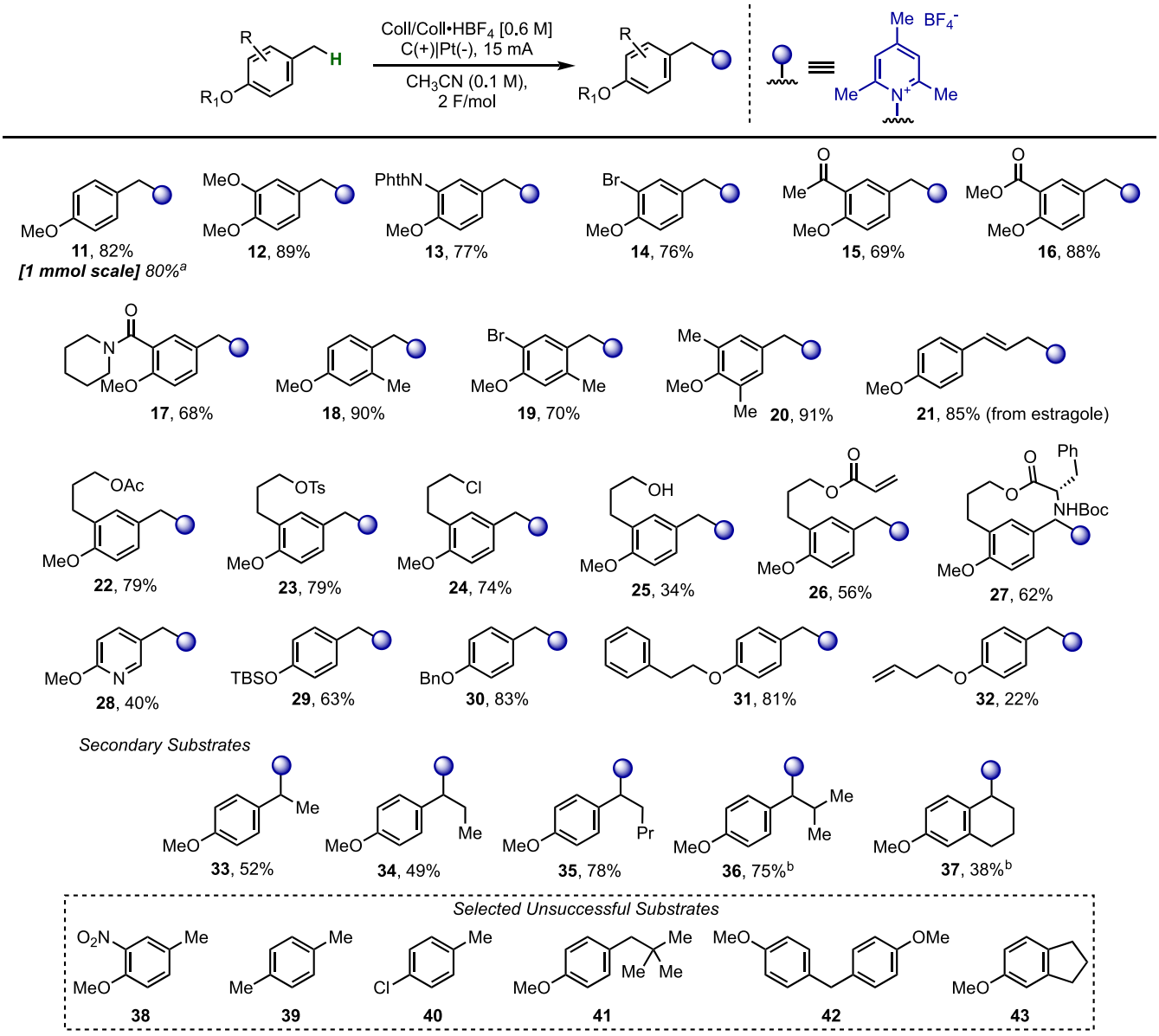
Scheme 2. Scope of Benzylic C−H 2,4,6-Collidination[a]



[a]All reactions run on 0.3 mmol scale using an IKA ElectraSyn 2.0. Products isolated via trituration with Et_2O. [b]Yield via ^1H NMR with CH_2Br_2 internal standard due to contamination with inseparable protonated collidine.

oxidation products detected. A more electron-withdrawing nitro-substitution shut down reactivity (see **38**, inset). Site- and chemoselectivity were then probed in substrates containing competing sites of reactivity or sensitive functional groups. Substrates with multiple benzylic positions were examined, as these would be challenging substrates for complementary processes for benzylic functionalization, such as those relying on radical C−H abstraction. The reaction was found to be completely selective for *para*-collidination over both *meta*- (**18**, **19**) and *ortho*-Me (**20**) groups relative to the methoxy substituent. The use of estragole gave terminal collidinium salt **21** in 85% yield, via isomerization of the putative intermediate allylic cation. Primary −OAc, −OTs, and −Cl groups all gave clean conversion to the benzylic collidinium salts **22**−**24** with no observation of competitive S_N2 displacement. Reactive functional groups including a nucleophilic alcohol (**25**), reducible acrylate (**26**), and an N-Boc-phenylalanine (**27**) containing an N−H bond and an additional benzylic methylene all gave desired salts in moderate to good yields, demonstrating the utility of mild and selective electrochemical oxidation. It was also found that nitrogen heterocycles were compatible substrates, with 2-OMe-5-Me-pyridine undergoing smooth oxidation to give **28** in 40% yield. While a *para*-oxygen substituent was found to be required (see **39**, **40**, inset), the methyl ether could be varied to include silyl (**29**), benzyl, homobenzyl (**30**, **31**), or homoallyl ethers (**32**).

We then, examined the synthesis of secondary collidinium salts, products that would be exceptionally challenging to access via traditional nucleophilic substitution. Beginning with extended linear alkyl chains, we were pleased to find the reaction still gave moderate to good yields of salts **33**−**35**. Perhaps surprisingly, the sterically hindered isobutyl substrate gave high yields of collidinium **36**, which we hypothesize is due to the sterically hindered methine β C−H bond inhibiting

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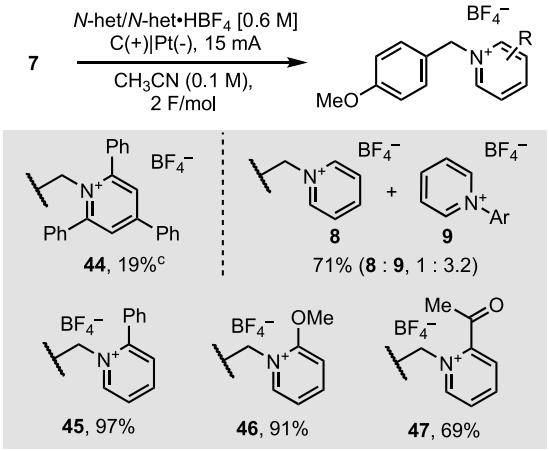
elimination pathways of either cationic intermediates or product. In support of this hypothesis, tetralin-derived collidinium **37** was obtained in decreased yield, along with styrenyl byproducts, as restricted rotational freedom allowed for more facile elimination. The limits of the secondary scope included a more hindered *t*-butyl group (**41**) and the diarylmethane (**42**), both of which returned exclusively starting material and indane **43** which provided product that rapidly decomposed during isolation.

Having established a broad arene scope, we revisited those examples that were unsuccessful on the basis of arene electronics (**38**−**40**, inset). The requirement of a *para*-oxygen substituent is consistent with prior reports of oxidative arene radical cation functionalization.[17a,24] A study from Waldvogel[25] indicated that under our conditions, the presence of an *N*-heterocycle may be suppressing arene oxidation in less activated substrates. CV measurements on **7**, **38**, **39**, and **40** in 0.1 M $TBABF_4$ compared with 0.1 M Coll·HBF_4 with 15 mM collidine found that while the oxidation peak of **7** was still present, those of **38**−**40**, with oxidation onset >∼2.0 V, were completely suppressed in the presence of collidine (see SI for details). While we currently can not explain this effect, it does provide a simple tool for preliminary assessment of potential substrates.

As the high level of site-selectivity was attributed to steric modulation of the pyridine nucleophile, we then examined the use of differentially substituted pyridines, in the interest of establishing a steric limit for achieiving high levels of benzylic selectivity (Scheme 3). To probe the upper limits of steric

Scheme 3. Steric Effects on Benzylic Site-Selectivity[a,b]

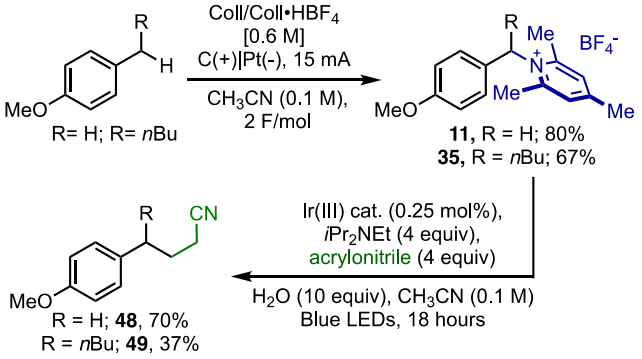


[a]In each case the electrolyte solution was generated using the corresponding *N*-heterocycle/*N*-heterocycle·HBF_4 salt. [b]Reactions run on 0.3 mmol scale. [c]Modifications to standard conditions: 2,4,6-Ph-pyr (2.0 equiv), 2,4,6-Ph-pyr·HBF_4 (1.0 equiv), CH_2Cl_2 (0.05 M).

tolerance, 2,4,6-collidine was exchanged for 2,4,6-Ph-pyridine, which would give rise to the Katritzky pyridinium salt currently used in deaminative couplings.[12] Using slightly modified conditions, primarily due to the low solubility of the 2,4,6-Ph-pyridine electrolyte system, benzylic pyridination could be achieved to give **44** in a modest 19% yield. The use of simple pyridine gave 71% yield of a 1:3.2 mixture of benzylic to arene pyridination (**8**:**9**, Scheme 3); interestingly, the ratio obtained under our conditions is the inverse of that observed in Yoshida's prior report (*vide supra*).[17c] However, it was found that a single substituent at C2 of the pyridine ring was sufficient to completely suppress arene amination, and 2-phenyl, 2-methoxy, and 2-acyl-pyridine were all found to give exclusively the benzylic pyridinium salts (**45**−**47**) in excellent to high yields. This methodology could therefore also be applied to the direct electrochemical synthesis of oxidatively masked 2-substituted piperidines[26] via subsequent derivatization of the pyridinium salts.[1]

Finally, we wished to demonstrate that the electrochemically generated collidinium salts were effective in subsequent coupling reactions (Scheme 4). To this end, both primary

Scheme 4. 2,4,6-Collidinium Salts in Iridium-Catalyzed Giese Reaction



[a]Electrochemical collidination run on 1 mmol scale.

(**11**, R = H) and secondary (**35**, R = *n*Bu) collidinium salts were synthesized via the standard method and, with no purification beyond simple trituration, subjected to conditions of Weaver for iridium-catalyzed Giese reaction with acrylonitrile.[13] 4-Me-anisole derived salt **11** gave **48** in 70% yield, on par with that reported by Weaver for the corresponding chloride salt. Due to synthetic limitations, no secondary collidinium salts were included in the prior scope;[27] however, utilizing our methodology, we were able to access 4-pentyl-anisole salt **35** and demonstrate that it successfully gave **49** in a moderate 37% yield without optimization.

In conclusion, we report the synthesis of benzylic 2,4,6-collidinium salts via the electrooxidative C−H functionalization of electron-rich arenes. The reaction proceeds with complete site-selectivity, proceeds under mild conditions, uses a cheap and recoverable 2,4,6-collidine electrolyte system, and does not require chromatography. The broad scope includes both primary and secondary collidinium salts, the latter being effectively inaccessible via traditional nucleophilic substitution. The resulting 2,4,6-collidinium salts represent an emerging scaffold for SET-mediated pyridinium cross couplings, offering improved atom economy, cost, and versatility in synthesis over the established Katrizky salts. This method represents the first synthesis of alkylpyridinium salts via a net C−H functionalization, providing a complementary approach to traditional substitution and condensation reactions of prefunctionalized substrates. Future studies aim to extend this platform to additional heterocycles and alkyl positions to provide a general oxidative strategy to access these motifs, as well as to examine the utility of diverse pyridinium scaffolds as functional replacements for the 2,4,6-triphenyl Katritzky salt in reductive cross couplings.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02376.

Experimental procedures, full characterization data for all new compounds, NMR spectra, and cyclic voltammetry (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

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