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Letter

I(III)-Mediated Arene C−H Amination Using (Hetero)Aryl Nucleophiles

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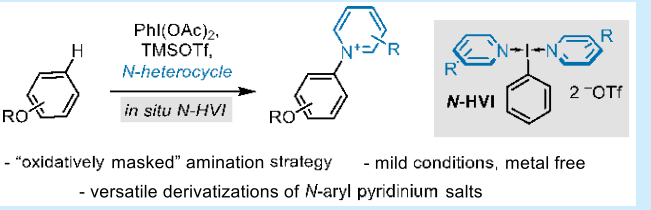
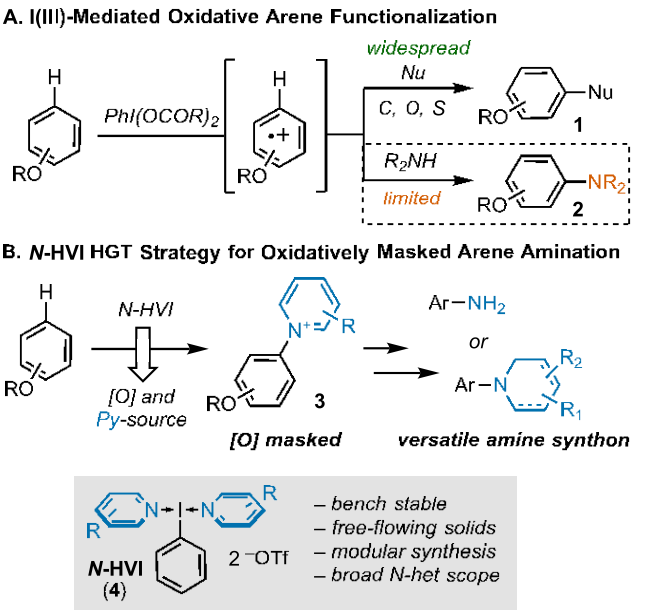
ABSTRACT: Herein, we report the metal-free oxidative C−H amination of arenes via a "heterocyclic group transfer" reaction from an I(III) *N*-HVI reagent. N-Heterocycles serve as oxidatively masked amine nucleophiles, and the resulting *N*-arylpyridinium salts are inert to further oxidation. The reaction proceeds under mild conditions, and mechanistic studies indicate the intermediacy of an arene radical cation. Derivatizations of the resulting pyridinium salts to diverse aryl amine scaffolds are demonstrated.



Aryl amines are among the most ubiquitous functional groups in natural products and small molecule drug scaffolds. As a result, strategies for accessing these motifs are widespread, with the most common approaches relying on transition metal cross coupling of aryl electrophiles or C−H functionalization.[1−5] Despite their utility, these methods are not without limitations, such as the need for prefunctionalized substrates, expensive precious metal catalysts, or directing groups. The oxidation and subsequent nucleophilic trapping of electron-rich aromatics offers a complementary and powerful strategy for direct arene functionalization.[6] Unfortunately, applications of this strategy to amination are limited due to competitive oxidation of the amine nucleophile and over-oxidation of the aminated product.[6−8] This challenge is particularly apparent in I(III)-mediated oxidative functionalizations, which have seen extensive development in C−C, C−O, and C−S bond formations (1), but aminations remain scarce and are limited to azide or phthalimide nucleophiles (2) (Scheme 1A).[9−12]

In recent years, our laboratory has developed the I(III) *N*-HVI reagent class (4); its members possess datively bound N-heterocyclic ligands (Scheme 1B, inset).[13−17] These reagents are bench stable, can be accessed in a single step from commercial materials, and are compatible with a broad range of heterocyclic ligands.[18] Recent work from our group has demonstrated their utility in "heterocyclic group transfer" (HGT) reactions with olefins as a novel means of accessing complex *N*-alkylpyridinium salts.[17] These salts then serve as a powerful platform for subsequent diversification, either via dearomative[19,20] or deaminative[21] functionalizations. In considering the extension of HGT reactions to C(sp^2)−N bond formation, we recognized that an *N*-HVI HGT strategy could serve as a convenient and potentially general approach to I(III)-mediated arene amination (Scheme 1B). The N-heterocycles would act as "oxidatively masked" nucleophilic amines, and the product would be shielded from overoxidation

Scheme 1. I(III) Oxidative Arene Functionalizations



as a cationic pyridinium salt (3).[8,22] Pioneering work by Yoshida[8] and recent reports by Carreira,[23] Ritter,[24] Morofuji,[25] and Sanford[26,27] have achieved oxidative arene amination via (hetero)aryl nucleophiles through the use of electrochemistry, photoredox catalysis, or EDA complexes, and we demonstrated

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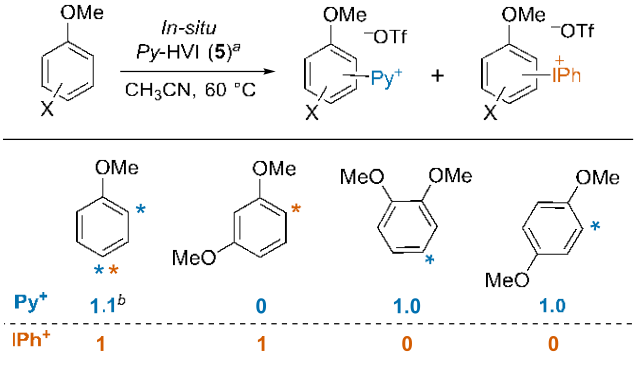
a complementary benzylic-selective C−H collidination,[28] demonstrating the utility of such an approach.

Herein, we report the metal-free oxidative amination of electron-rich aromatics via HGT with I(III) *N*-HVIs.[29] The reaction proceeds under mild, operationally simple conditions and was demonstrated on seven arene derivatives and nine electronically diverse N-heterocycles. The resulting *N*-aryl (hetero)arylonium salts can be subsequently functionalized, or we demonstrate eficient cleavage to reveal the free amine. There was a clear substituent effect on competitive SET and EAS reaction pathways, providing insights for future I(III)-mediated oxidative functionalizations. The demonstrated use of N-heterocycles as masked amines provides a potential general approach to the long-standing challenge of I(III)-mediated oxidative amination.

At the outset of our studies, while the use of both $PhI(OAc)_2$ and $PhI(OTFA)_2$ as SET oxidants had been demonstrated,[9] it was unclear if *N*-HVI reagents, with datively bound heterocyclic ligands,[30] would behave similarly or act predominantly as electrophiles to give diaryliodonium salt products. Dutton has previously reported that treatment of anisole with pyridine-ligated *N*-HVI (*Py*-HVI, 5) in chloroform gave almost exclusively diaryliodonium with only a trace of *N*-arylpyridinium; however, pyridinium salt formation was observed upon treatment of tellurophenes and select five-membered heterocycles.[31,32] Furthermore, a recent report by Lectka discussed the effect of dialkoxy arene substitution patterns on the reaction pathway upon treatment with Selectfluor; 1,2- and 1,4-substitution favored amination via initial SET, while 1,3-substition gave predominantly the expected electrophilic fluorination.[33] Thus, to begin, we benchmarked the reactivity of *in situ Py*-HVI (5) against anisole and all three regioisomers of dimethoxybenzene and found that both electronics and substitution pattern played a significant role in determining the reaction outcome (Scheme 2). Under our conditions, anisole gave quantitative conversion

Scheme 2. Substituent Effects on SET versus EAS Pathways

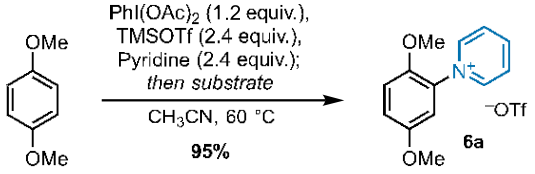


[a]*In situ Py*-HVI: $PhI(OAc)_2$ (1.2 equiv), TMSOTf (2.4 equiv); then pyridine (2.4 equiv); followed by addition of the substrate. [b]Py^+ salts formed in a 2.4:1 *ortho*:*para* ratio.

to a ⍰1:1 ratio of both *ortho* and *para* pyridinium salts to diaryliodonium. In the case of dimethoxybenzenes, similar to the findings of Lectka, 1,3-substitution gave exclusively the diaryliodonium salt, whereas both 1,2- and 1,4-derivatives gave exclusively the desired pyridinium salt, as single regioisomers as determined by ^1H NMR. This reactivity trend is also supported by an examination of redox potentials, as 1,4- and 1,2-dimethoxybenzenes undergo the most facile oxidation (1.30 and 1.43 V vs SCE, respectively), thus resulting in predominant SET-mediated reactivity.[34] It was therefore concluded that both EAS and SET pathways are accessible with *N*-HVI reagents and that careful attention would have to be paid to substrate electronics to achieve selectivity.

Further optimization of the desired amination reaction was conducted using 1,4-dimethoxybenzene as a model substrate (Table 1). Treatment with *in situ*-generated *Py*-HVI (5) in

Table 1. Optimization of *N*-HVI HGT Arene Amination



entry	deviation from standard conditions	yield (%)
1	run at 40 °C	81
2	run at rt	74
3	run at 80 °C	93
4	isolated *N*-HVI	68
5	$PhI(OTFA)_2$, pyridine, 80 °C	9
6	$PhI(OTFA)_2$, pyridine, HFIP, rt	trace
7	$PhI(OAc)_2$, pyridine, rt or 80 °C	0

CH_3CN at 60 °C, as described above, gave a 95% isolated yield of pyridinium 6a. Decreasing the temperature had a detrimental effect on conversion (entries 1 and 2), while increasing it to 80 °C had no effect (entry 3). Use of the isolated *Py*-HVI reagent under otherwise identical conditions gave a decreased 65% yield of 6a (entry 4). Control reactions using either $PhI(OAc)_2$ or $PhI(OTFA)_2$ in the presence of pyridine, in various solvents or at various temperatures, produced only trace amounts of the desired products (entries 5−7), indicating the need to leverage the *N*-HVI reagent as both an oxidant and a nucleophile source. It is noteworthy that this process does not require the addition of exogenous activators (e.g., $BF_3{\cdot}OEt_2$ or HFIP), which speaks to the enhanced reactivity of the *N*-HVI reagent class.[35]

With eficient conditions in hand, we examined the scope of the reaction with regard to arene (Scheme 3). In each case, the pyridinium salts resulting from *N*-HVI HGT were isolated, and these products were subjected to Zincke aminolysis to provide the anilines; yields of both steps as well as the overall yield (in parentheses) are provided. On the basis of our initial reactivity probe (see Scheme 2), we restricted the scope to 1,2- and 1,4-disubstituted arenes to suppress competitive EAS pathways. Both HGT amination and Zincke cleavage were highly eficient on 1,4-dimethoxybenzene, giving a 95% yield of 6a and an 86% yield of aniline 7a over two steps; this process could also be telescoped to give a nearly quantitative 97% yield of 7a. 1,2-Dimethoxybenzene gave exclusively C4-pyridinium 6b in 94% yield. Benzoyl substitution was well tolerated, giving 6c in 68% yield. We next examined the effect of differing heteroatom substitutions and found that a protected *p*-anisidine underwent HGT *ortho* to the methoxy group in excellent yield, giving 6d as a single regioisomer. We were pleased to find that π-extended aromatics, including biphenyl and naphthalene, were also competent in HGT amination. Biphenyl gave exclusively C4-pyridinium 6e in 82% yield, and naphthalene produced a 1:1 mixture of C1 (6f) and C2 (6f′) pyridinium salts in 87%

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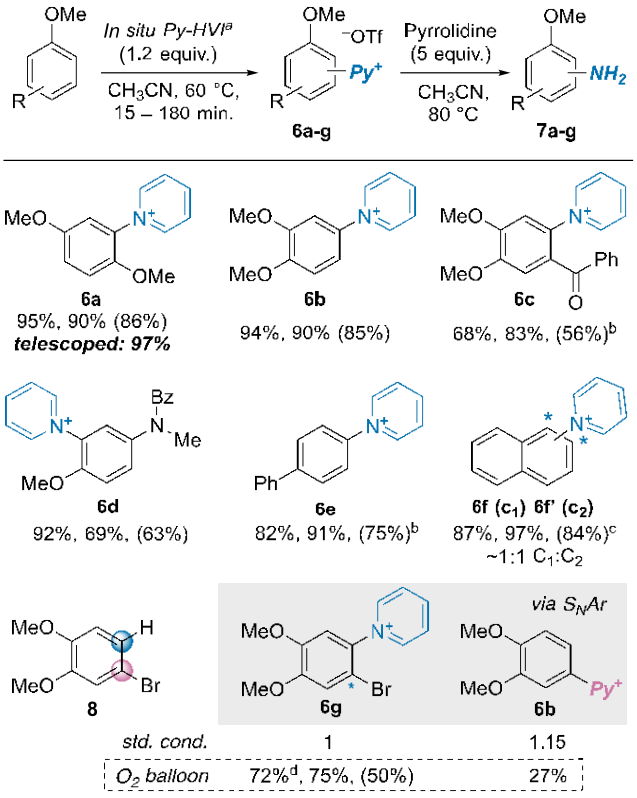
Scheme 3. Arene Scope of *N*-HVI HGT Amination[e]

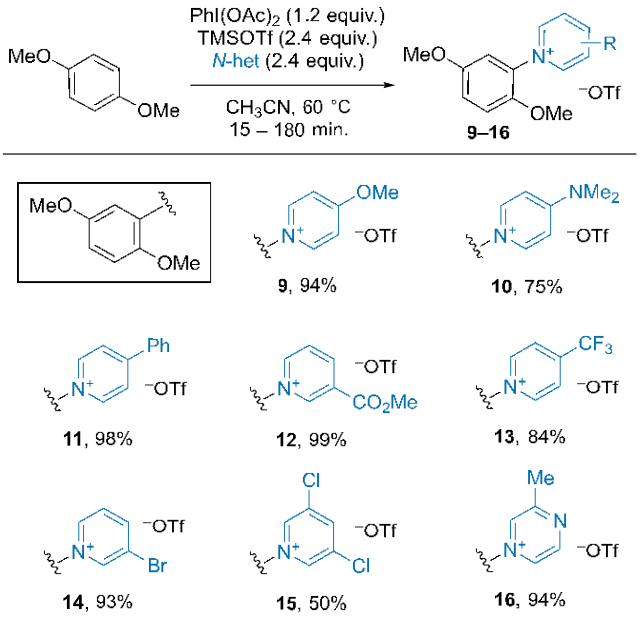


[a]*In situ Py*-HVI: PhI(OAc)$_2$ (1.2 equiv), TMSOTf (2.4 equiv); then pyridine (2.4 equiv); followed by addition of the substrate. [b]Reaction run with 3.6 equiv of *N*-HVI. [c]Combined yield of an inseperable mixture of C1 and C2 anilines. [d]^{1}H NMR internal standard yield from a mixture of 6g and 6b. [e]Yields are reported for each step, with the overall yield in parentheses.

combined yield. Finally, we examined brominated arene 8, and under standard conditions, we were surprised to find that we obtained a 1.0:1.15 ratio of expected C−H pyridinium product 6g to C4-pyridinium 6b, the latter resulting from an S$_N$Ar reaction on the aryl bromide. While similar S$_N$Ar reactivity was previously observed by both Sanford[26] and Nicewicz[36,37] under photoredox catalysis, with our conditions it is unclear what is serving as the reductant in this net redox netural process; ongoing studies seek to fully understand this reactivity. Nonetheless, running the reaction under a balloon of O_2[6,26] improved the ratio to 2.7:1.0 in favor of C−H amination, giving 6g in 72% yield.

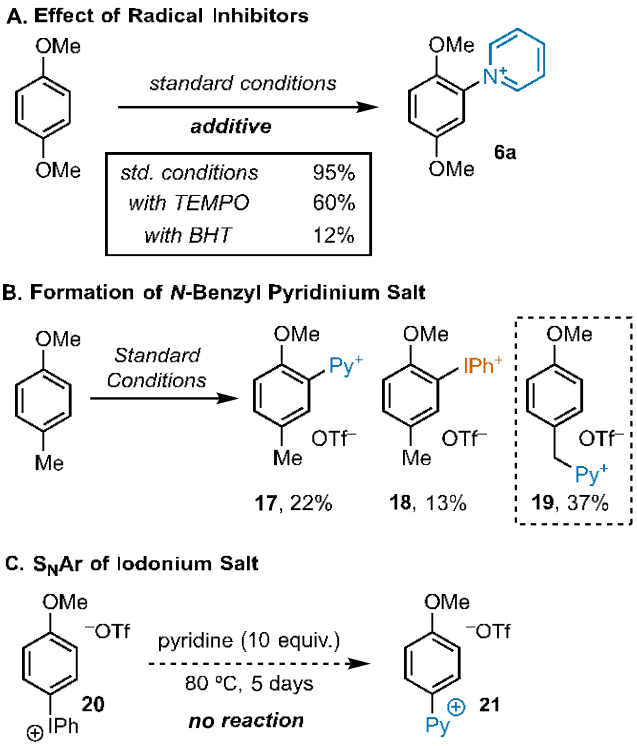
Given the versatility of the resulting pyridinium salts for the synthesis of diverse *N*-aryl piperidines via dearomative functionalizations,[19] we next examined the scope with regard to the N-heterocycle (Scheme 4). Electron-rich 4-OMe-, 4-NMe$_2$-, and 4-Ph-pyridine all gave the corresponding pyridiniums in high yields (9−11, respectively). Of particular interest was the incorporation of electron-deficient N-heterocycles, as these derivatives are challenging to access via S$_N$Ar pathways due to their reduced nucleophilicity.[38] We were pleased to find that pyridinium salts incorporating 3-carbomethoxy (12), 4-CF$_3$ (13), 3-Br (14), 3,5-dichloro (15), and 2-Me-pyrazine (16) groups were all formed in good to excellent yields. These examples also provide a complementary scope to prior photochemical methods as 13−15 could not be accessed.[27]

Scheme 4. N-Heterocycle Scope of *N*-HVI HGT Amination



On the basis of both initial reactivity profiling studies (see Scheme 2) and prior mechanistic studies of Kita,[9] we propose that *N*-HVI-mediated C−H pyridination is proceeding via single-electron transfer to give an intermediate radical cation. To further validate this hypothesis, we ran the reaction in the presence of TEMPO or BHT, each of which resulted in either moderate or near complete inhibition of reactivity (Scheme 5A). Further support was found in the reaction of 4-Me-anisole wherein, in addition to arylpyridinium 17 and diaryliodonium salt 18, benzylic pyridinium 19 was also observed (Scheme

Scheme 5. Mechanistic Investigations



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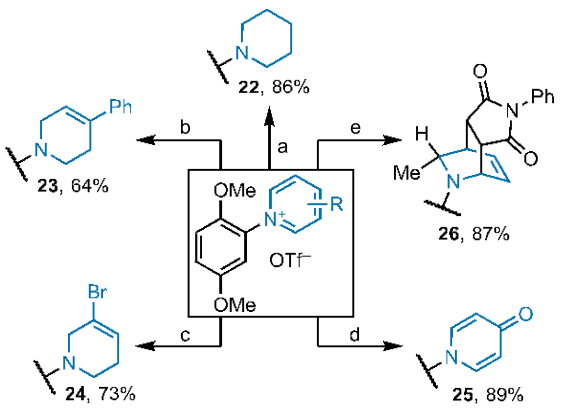
5B). Mechanistically, the formation of 19 can be explained via deprotonation of a radical cation intermediate to generate an electrophilic benzylic position, followed by nucleophilic trapping.[28,39−41] An alternative hypothesis was that an S_NAr reaction on an initially formed diaryliodonium salt could give the observed pyridinium products; however, this seemed unlikely as it would require nucleophilic attack on the more electron-rich aromatic.[42,43] This possibility was further discounted as prolonged heating of anisole-derived iodonium 19 with excess pyridine yielded none of the corresponding pyridinium (20) (Scheme 5C).

Finally, to demonstrate the utility of this strategy toward the synthesis of diverse *N*-aryl piperidine scaffolds, derivatizations were performed on a selection of *N*-arylpyridinium salts (Scheme 6). Hydrogenation of pyridinium 6a with Adam's

Scheme 6. Derivatizations of *N*-Aryl Pyridinium Salts[a]



[a]Reagents and conditions: (a) from 6a, H_2 (1 atm), PtO_2 (15 mol %), MeOH (0.1 M), 16 h; (b) from 11, $NaBH_4$ (5 equiv), MeOH (0.1 M), 0 °C to rt, 8 h; (c) from 14, $NaBH_3CN$ (6 equiv), MeOH (0.1 M), 0 °C to rt, 8 h; (d) from 9, NaI (2 equiv), MeCN (0.2 M), 80 °C, 24 h; (e) from 6a, MeMgBr (6 equiv), THF (0.02 M), 0 °C, 2 h; then *N*-phenylmaleimide (1.04 equiv), CH_2Cl_2 (0.1 M), 16 h.

catalyst gave fully reduced piperidine 22 in 86% yield. Partial reduction was achieved with borohydride reductants to give 23 and 24, now containing a styrenyl olefin and vinyl bromide, respectively. Cleavage of 4-methoxy-pyridinium 9 with NaI gave the corresponding 4-pyridone (25) in excellent yield. Lastly, a one-pot sequence involving Grignard addition and subsequent Diels−Alder cycloaddition of the resulting 1,2-dihydropyridine generated *N*-aryl isoquinuclidine 26 in 87% yield. The array of structural complexity generated via these derivatizations is representative of the power of pyridinium salts to serve as diverse platforms toward the synthesis of piperidine-containing small molecule analogues.

In conclusion, we report the oxidative C−H amination of electron-rich arenes via heterocyclic group transfer reaction of I(III) *N*-HVI reagents. The *N*-HVI reagents can be prepared *in situ* from commercial reagents and allow for modular incorporation of a broad range of heterocycles. The reaction has a good scope with regard to both arene and heterocycle and proceeds under mild conditions. Key to the success of this approach is the N-heterocyclic nucleophile, which addresses two long-standing challenges in this field. They first serve as "oxidatively masked" amines, and the resulting pyridinium salts shield the products from overoxidation. The pyridinium salts serve as a diverse platform for the synthesis of aryl amines, either via dearomative functionalizations to access piperidine derivatives or via Zincke cleavage to unveil the free aniline. We believe that this strategy could provide a general solution to I(III)-mediated amination, and further applications are ongoing in our laboratory.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

* Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c00809.

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

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Notes

The authors declare no competing financial interest.

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