Direct C4- and C2 C–H Amination of Heteroarenes Using I(III) Reagents via a Cross Azine Coupling

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ABSTRACT: Aminated nitrogen heterocycles are valuable motifs across numerous chemical industries, perhaps most notably small molecule pharmaceuticals. While numerous strategies exist to install nitrogen atoms onto azaarenes, most require pre-functionalization and methods for direct C–H amination are almost entirely limited to the C2-position. Herein, we report a method for the direct C2 and C4 C–H amination of fused azaarenes via *in situ* activation with a bispyridine-ligated I(III)-reagent, $[(Py)_2IPh]2OTf$, or *Py*-HVI. Unlike commonly used *N*-oxide chemistry, the method requires no pre-oxidation of the azaarene and it provides unprecedented access to C4-amination products. The resulting *N*-heterocyclic pyridinium salts can be isolated via simple trituration, and the free amine can be liberated under mild Zincke aminolysis, or the amination and cleavage can be telescoped to a one-pot process. The scope of the method is broad, the conditions are mild and operationally simple, and the aminated products are produced in good to excellent yields. Computational studies provide insights into the mechanism of activation, which involves an unusual direct nucleophilic functionalization of an I(III)-ligand, as well as a kinetic basis for the observed C2 and C4 amination products.

Azaarenes are a ubiquitous heterocyclic motif found across pharmaceuticals, agrochemicals, and natural products.[1] C2- and C4–H aminated pyridines and quinolines represent particularly high value scaffolds, with diverse substitution patterns and applications across therapeutic areas such as anti-malarial (**1**), anti-anxiety (**2**) and chemotherapeutics (**3**) (Figure 1).

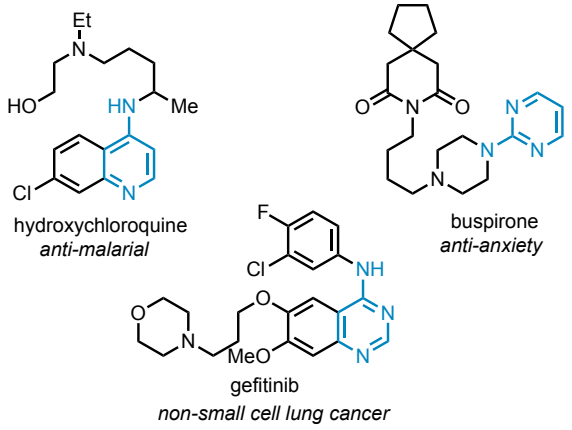
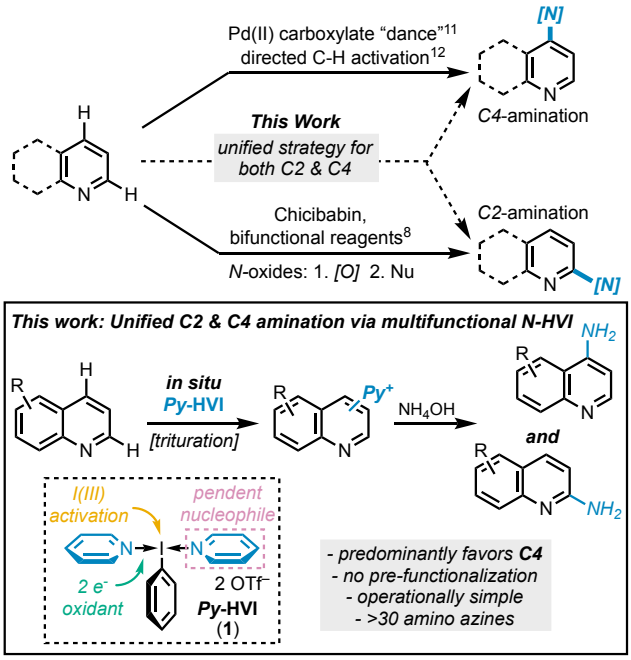


Figure 1. Small molecule pharmaceuticals containing C2- and C4-aminated azaarenes

Amination is typically achieved via the reaction of prefunctionalized halogenated arenes via S_NAr or transition metal cross couplings, with the regioselectivity of amination thus dictated by the initial halogenation step.[2] Alternatively, the direct C–H amination of azaarenes presents an atom- and step-economical alternative, but the scope and selectivities available via this approach remains narrow (Scheme 1). The classic Chichibabin reaction provides C2–H amination, however it requires forcing conditions and solvent quantities of ammonia, thus limiting its broader synthetic utility.[3] Perhaps the most common approach to C2–H functionalization has been the nucleophilic amination of azine *N*-oxides, with the ability to incorporate different amine nucleophiles under relatively mild conditions, however it necessitates pre-oxidation of the parent heterocycle.[4–7] In an elegant recent report, co-workers at Merck disclosed a designer reagent that obviates the need for pre-oxidation by serving as both the heterocyclic activator and amine source, however this only provides C2-aminopyridines.[8]



Scheme 1. Methods for C2- and C4- C–H amination, this work

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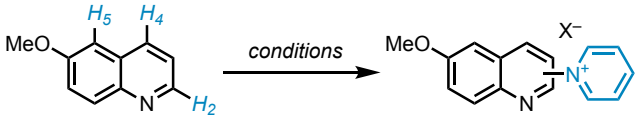
Notably absent from the above methods are examples providing C4–H amination. While the C4 position possesses similar innate electrophilic reactivity to that of C2, its direct functionalization has proven much more challenging to achieve. To date, no methods for the direct C4–H amination without the use of directing groups or functional group isomerization have been reported (Scheme 1, top arrow).[9–11]

Herein we report a method for direct C–H amination of fused *N*-heterocycles that requires no prefunctionalization or directing groups and provides access to both C2 and C4 isomers (Scheme 1, inset). The method leverages an *in situ* generated pyridine-ligated I(III) reagent (*Py*-HVI) as a multifunctional reagent that both activates the heterocycle and delivers a pendant heterocyclic nucleophile in a cross azine coupling event. The resulting *N*-heteroaryl pyridinium salts can be isolated via simple trituration or can be cleaved in a one-pot fashion to directly yield the free amines. Computational studies support a mechanism involving initial I(III) ligation to generate a mixed *Py,N*-HVI reagent and a kinetic model for the observed regioselectivities.

Table 1. Reaction Development



2 **3**

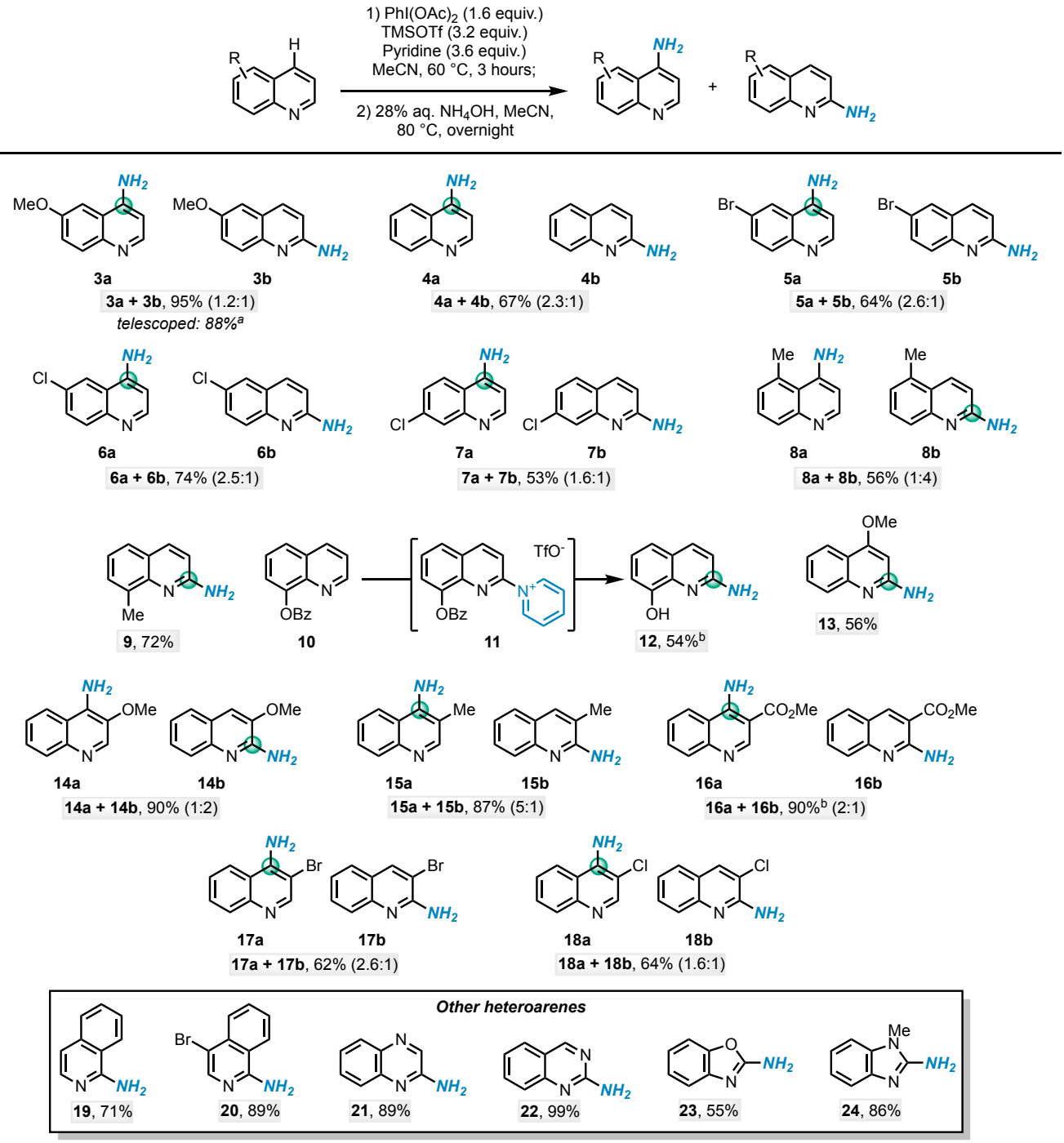
Entry	Conditions	C4:C2:C5	Yield (%)
1	$PhI(OAc)_2$, TMSOTf, pyridine, MeCN, 60 °C	1.2:1.0:0	98
2	$Py/PyHBF_4$ C(+) Pt(–), 15 mA, 2 F/mol	C5 only	47
3	1) *m*-CPBA 2) Tf_2O, then pyridine	C2 only	65
4	Tf_2O, pyridine, CH_2Cl_2	n.a.	0
5	Entry 1, no TMSOTf	n.a.	0
6	Entry 1, no $PhI(OAc)_2$	n.a.	0
7	Ph_2IOTf, pyridine, MeCN, 60 °C	n.a.	0
8	1) *m*CPBA 2) $PhI(OAc)_2$, TMSOTf, pyridine, MeCN, 60 °C	C2 only	32
9	1) CH_3I, MeCN 2) $PhI(OAc)_2$, TMSOTf, pyridine, MeCN, 60 °C	n.a.	0

Recently, the Wengryniuk and Dutton labs have both reported on the utility of the I(III) N-HVI reagent class to serve as "heterocyclic group transfer" (HGT) reagents to generate N-alkyl and N-aryl pyridinium salts from olefins and arenes.[12–16] The *N*-HVI reagents can be isolated or generated *in situ* from commercially available $PhI(OAc)_2$, providing a modular and practical platform for oxidative amination. In a recent report, we demonstrated that *in situ* generated *N*-HVI reagents could affect umpolung C–H amination of electron-rich arenes via the arene radical cations, giving rise to *N*-aryl pyridinium salts.[13] During the course of this study, it was found that 6-OMe-quinoline (**2**) did not give rise to any of the C5-amination product which would be expected following single-electron oxidation of the methoxyarene ring (Table 1, entry 1). Instead, a mixture of C4 (**3a**) and C2 (**3b**) amination was obtained, in a 1.2:1.0 ratio and 95% yield as the *N*-heteroaryl pyridinium salts. Not only was this indicative of an alternate reaction pathway being operative, it also provided unprecedented levels of C4-amination and required no pre-activation of the heteroarene. A brief examination of alternative conditions for heteroarene C–H amination found this result to be unique in both its efficiency, chemo- and site-selectivity. Electrochemical oxidation led to exclusive C5-amination, supportive of the aforementioned radical cation pathway (entry 2).[17,18] Pre-oxidation to the *N*-oxide followed by treatment with Tf_2O and pyridine gave exclusively C2-heteroarene amination, in agreement with a prior report by Xiong et al (entry 3).[19] Treatment with the McNally conditions[9] for C4-selective phosphonium ion generation, but using pyridine in place of PPh_3, gave no reaction (entry 4). Finally, various control reactions were conducted. When TMSOTf was excluded (entry 5) no conversion was detected, indicating the importance of *N*-HVI formation. Removing $PhI(OAc)_2$ from the reaction (entry 6) showed no reaction of starting material through silylium catalysis.[20] Using Ph_2IOTf as an alternate I(III) activator led to no conversion (entry 7). A working hypothesis of operative *N*-I(III) activation was then probed via functionalization on the quinoline nitrogen. Formation of *N*-oxide followed by standard conditions lead to only the C2-amination product in low yield (entry 8) while pre-formation of the *N*-methyl quinolinium resulted in no reaction (entry 9), supportive of N–I ligation.

The scope with regards to azaarene was then examined (Table 2). For the yields shown, the pyridinium salt resulting from C–H amination is isolated via simple trituration, and the resulting solid directly subjected to Zincke aminolysis. Extensive screening found that aqueous NH_4OH or ethanolamine proved optimal for aminolysis due to ease of work-up and purification. The resulting amino azine C4/C2 regioisomers can be readily separated using flash chromatography, and substrates that give only one isomer product only require a short silica plug to yield analytically pure material. The reaction can also be conducted in oven dried glassware without any precautions to exclude air or moisture.

In general, it was found that except in cases where significant steric bias was imparted, the amination favored C4, with subtle variations in ratio based on arene electronics. The model substrate 6-OMe-quinoline (**3**) gave a 1.2:1 ratio of C4:C2 (**3a, 3b**) and a combined yield of 95%. This reaction was also telescoped to give **3a**,**3b** directly in 88%, with no change in C4/C2 ratio. In contrast to our previous arene C–H amination which relied on a radical cation mechanism and thus required electron donating groups, this platform was amenable to a wide scope of electronic variation of the heteroarene.[13,21] With regards to benzoarene substitution, it was found that more electron-deficient substrates (relative to **3**) led to increased C4:C2 ratios. The reaction proceeded smoothly with quinoline, providing **4a**,**4b** in 2.6:1 ratio and 67% yield. Halogenated substrates worked well, with 6-Br, 6-Cl, and 7-Cl-quinolines giving amination favoring C4 in good yields (**5a**,**b**–**7a**,**b**). Notably in these cases, the reaction was completely selective for C–H

Table 2. Scope of *N*-HVI mediated Azine C–H Amination

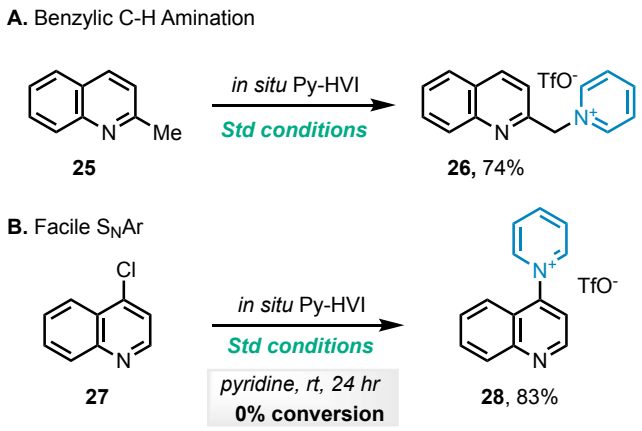


[a]Zincke aminolysis performed without isolation of *N*-heteroaryl pyridinium salt (see SI). [b]Zincke aminolysis performed with ethanolamine (5.0 equiv.), MeCN, rt.

amination of the heteroarene, with no S_NAr reactivity on the benzohalides observed. Substitution at C5- and C8- was found to have a dramatic effect on site-selectivity. A C5-methyl group led to a reversal in site-selectivity, favoring C2 in a 1:4 ratio (**8a**,**8b**), hypothesized to be due to steric blocking of C4. Similarly, installation of a methyl or OBz group at C8 led to exclusively C2-amination (**9a**,**b**, **10a**,**b**) in good yields. In the case of **10a**,**b**, the benzoyl group was also cleaved during aminolysis, directly giving 2-amino-8-quinolinol (**11**), an important molecule in both pharmaceuticals and materials science.[4] Moving to the azine ring, blocking of C4 with a methoxy group gave exclusively C2-amination in 56% yield (**13**). Substitution at C3 was found to have a divergent impact on site-selectivity depended on the nature of the group. 3-OMe-quinoline gave

14a,**b** in a 1:2 ratio favoring C2, likely due to resonance donation to the C4 position. In contrast, 3-Me or 3-CO_2Me-quinoline both favored C4, giving **15a**,**b** and **16a**,**b** in excellent yields and 2:1 and 5:1 ratios respectively. We were pleased to see that halogens on the heteroarene were also tolerated, with C3-Cl and C3-Br-quinolines undergoing smooth amination biased to C4 (**17a**,**b**, **18a**,**b**). Attempts to aminate pyridine under these conditions returned only starting material, indicating the importance of the benzofusion (not shown). We then expanded the scope to other fused heteroarenes. Isoquinolines proceeded well to give exclusively C2-amino azines (**19**, **20**). Examination of diazines found that quinazoline and quinoxaline underwent smooth amination to give **21** and **22** in 89% and 99% yield respectively. The amination was also applicable to 5-membered benzofused systems, with benzoxazole and *N*-methyl benzimidazole undergoing successful C–H amination in good to high yields (**23**, **24**).

Scheme 2. Alternate *Py*-HVI mediated aminations

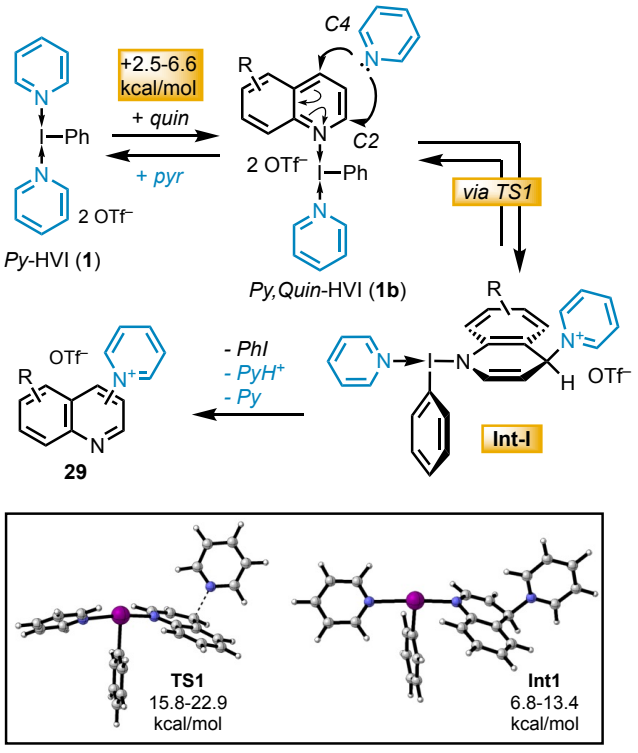


Beyond the C2/C4 functionalized products in Table 2, two additional aminations of note were observed (Scheme 2). The use of 2-Me-quinoline (**25**) led to exclusively benzylic C(sp^3)–H amination (**26**) in 74% yield, likely via a benzylic deprotonation/dearomatization sequence (Scheme 2A).[22,23] Finally, in contrast to the C–H amination of 3-Cl-quinoline (**18a**,**b**), treatment of 4-Cl-quinoline under the standard conditions led to an 83% yield of S_NAr on the chlorine to give C4-pyridinium **28** (Scheme 2B). I(III)-activation appears to be critical for the observed S_NAr under such mild conditions, as a control reaction using just pyridine gave no conversion after 24hrs and this reactivity is under further investigation in our laboratory.

To gain further insights into the mechanism and origins of the site-selectivity and substituent effects in this C–H amination, theoretical studies were then conducted on a select subset of quinoline substrates including quinoline, 3-OMe, 6-OMe, 6-Br, 7-Cl, and 8-Me derivatives. The reaction pathway was found to be consistent across all the derivatives studied with intermediates and transition states very close in energy. Prior work with *N*-HVI reagents,[24] as well as preliminary control experiments (see Table 1, entries 8-9) led us to propose a reaction coordinate based on initial heteroarene *N*-activation by I(III)-ligation and this was supported by computation (Scheme 3). Reversible ligand exchange[25] between the *in situ* formed *Py*-HVI (**1**) and the substrate heteroarene would give mixed *N*-HVI species *Py,Quin*-HVI **1b**.

In this case the mixed *Py,Quin*-HVI **1b** is calculated to be only 2.5-6.6 kcal/mol higher in energy than *Py*-HVI (**1**) across the different derivatives studied (DLPNO-CCSD(T), acetonitrile CPCM), consistent with facile ligand exchange and *Py,Quin*-HVI **1b** not being an observed species. A second ligand exchange to give a bis-quinoline *N*-HVI is a further 1.0-6.5 kcal/mol higher in energy, which is also accessible at room temperature, but *Py,Quin*-HVI **1b** should be higher in abundance as an intermediate (see Table S2).

Once ligated to the I(III) center, the quinoline would now be rendered highly electrophilic at both C4 and C2 and undergo nucleophilic attack by pyridine via **TS1** (Scheme 3, inset), to give Wheland-type **Int1** (Scheme 3, inset), albeit arising from a nucleophilic attack rather than an electrophilic process. For the experimentally observed C2 and C4 substitutions the barrier height (**TS1**) lies 15.8-22.9 kcal/mol above the reactants, with the subsequent intermediate (**Int1**) 6.8-13.4 kcal/mol above the reactant. In the intermediate for attack on C4 using an unsubstituted quinoline (**Int 1**) as a representative example, the quinoline unit is tilted out of plane, with the nitrogen bound to iodine gaining amide character (Scheme 3, inset). The I-N_{quin} bond distance in **Int1** shortens with respect to *Py*-HVI **1** from 2.29 Å to 2.13 Å (Mayer bond index increases from 0.64 to 0.81) and the opposite I-N_{pyr} bond elongates to 2.39 Å (Mayer bond index of 0.49). The final step in the mechanism was found to be barrierless and irreversible, with deprotonation by pyridine in the reaction triggering a reductive loss of IPh accompanied by rearomatization of newly formed heteroarene, analogous to classical *N*-oxide reactivity.



Scheme 3. Proposed mechanism of *N*-HVI mediated azine C–H amination

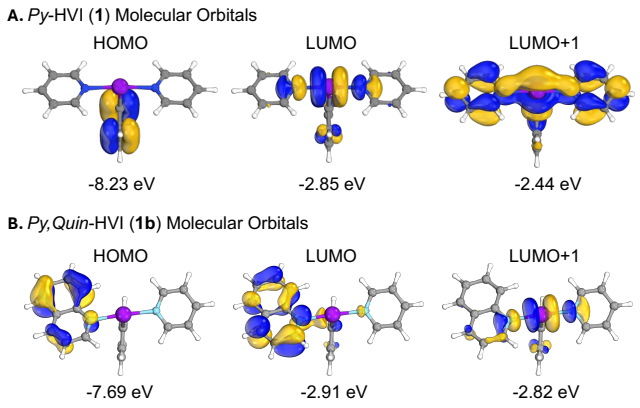


Figure 2. Frontier molecular orbitals of (A) *Py*-HVI (1) and (B) *Py,Quin*-HVI (1b).

As direct nucleophilic functionalization of an X-ligand on an I(III) reagent is atypical, with ligand exchange at the I(III) center predominating (as seen with *Py*-HVI **1**), we then examined the frontier molecular orbitals of both *Py*-HVI **1** and *Py,Quin*-HVI **1b**. In *Py*-HVI (**1**) the LUMO has sigma antibonding character along the N-I-N bond axis (Figure 2) and LUMO+1 lies on the pyridine rings, which is consistent with the observed nucleophilic attack at I(III) and ligand exchange to generate *Py,Quin*-HVI (**1b**). However, in *Py,Quin*-HVI (**1b**), the LUMO and LUMO+1 invert, with the LUMO primarily based on the quinoline unit and 0.47 eV lower than the corresponding LUMO+1 orbital in *Py*-HVI **1**, rendering the quinoline ring susceptible to nucleophilic attack (MOs for all species are presented in Table S5-S6). The LUMO of *Py,Quin*-HVI (**1b**) has the largest coefficients on the C2 and C4 positions of quinoline, which is also consistent with the experimentally observed preference for attack at C2 and C4.

The next question surrounded the observed site-selectivity of amination, which provided mixtures of C4 and C2 products, in contrast to the exclusive C2-selectivity of related, prior C-H amination approaches or the C-5 amination of radical cation methods.[17-19] Thermodynamically, amination was found to be competitive for all potential sites of C5, C4, and C2, with $\Delta\Delta G_{rxn}$ within 8 kcal/mol), however the barrier for C5 attack is significantly higher in energy (> 32.4 kcal/mol). The C5 intermediate (30.1-38.1 kcal/mol) is similarly much higher in energy than the intermediates for C2 or C4 attack (6.8-13.4 kcal/mol), and these values indicate this site is kinetically inaccessible.

When comparing C2 and C4, the two sites are competitive in all examined cases when considering both the thermodynamics ($\Delta\Delta G_{rxn}$ 1.39-5.36 kcal/mol) and kinetics (TS1 barrier height, 1.86-6.09 kcal/mol) of the reaction coordinate. The same holds true for intermediate **Int1** in almost all cases, where C4 vs C2 are nearly identical in energy (within 0.6 kcal/mol). The exception is 3-OMe-quinoline, wherein C2 is favored by 5.1 kcal/mol, likely due to electronic resonance donation to C4, and this is borne out experimentally as this substrate favors C2 in a 1:2 ratio (see **14a**,**b**, Table 2). Taken together the calculations indicate that site selectivity is kinetically controlled, with the relatively similar barriers for C2 and C4 attack for most derivatives accounting for the observed mixture of products obtained.

In conclusion, the direct C2 and C4 C–H amination of fused heteroarenes has been reported. The method relies on *in situ* activation by an I(III) *N*-HVI reagent, obviating the need for pre-oxidation or functionalization of the heterocycle. The unprecedented levels of C4-amination provide access to previously challenging substitution patterns for future structure-activity relationship studies and library synthesis. The conditions are mild and operationally simple and the initially formed *N*-heteroaryl pyridinium products can be isolated via simple trituration and cleaved under mild conditions to reveal the free amine. Computational studies provide insights into the unusual direct nucleophilic functionalization of an I(III) X-ligand and the observed mixture of C2 and C4 products is kinetic in origin. Additional amination processes observed, including benzylic C–H functionalization and facile S_NAr processes are under further study in our laboratory.

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Author Contributions

The manuscript was written through contributions of all authors and all authors have given approval to the final version of the manuscript.
BJM and AHQ conducted synthetic experiments, collected and analyzed associated data, and BJM compiled Supporting Information file.
SEW oversaw project direction and was involved in data analysis.
JLD and DJDW conducted all computational studies.

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Notes

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ABBREVIATIONS

HVI, hypervalent iodine; *N*-HVI, *N*-heterocyclic ligated hypervalent iodine; TS, transition state; Int, intermediate; Py, pyridine; Quin, quinoline; HOMO, Highest Occupied Molecular Orbital; LUMO, Lowest Unoccupied Molecular Orbital.

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