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Site-Selective C–H Functionalization of (Hetero)Arenes via Transient, Non-Symmetric Iodanes

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SUMMARY

A strategy for C–H functionalization of arenes and heteroarenes has been developed to allow site-selective incorporation of various anions, including Cl, Br, OMs, OTs, and OTf. This approach is enabled by *in situ* generation of reactive, non-symmetric iodanes by combining anions and bench-stable $PhI(OAc)_2$. The utility of this mechanism is demonstrated via *para*-selective chlorination of medicinally relevant arenes, as well as site-selective C–H chlorination of heteroarenes. Spectroscopic, computational, and competition experiments describe the unique nature, reactivity, and selectivity of these transient, unsymmetrical iodanes.

INTRODUCTION

In the realm of medicinal chemistry, synthetic methods for the replacement of C–H bonds within complex molecules are of significant value.[1] Among various approaches that enable aryl C–H functionalization,[2-5] we are most interested in the suitability of hypervalent iodine-mediated chemistry[6] to enable post-synthetic modification of medicinal agents. Since the pioneering contributions of Kita *et al.*, λ^3-iodanes have been known to substitute electron-rich arenes with certain nucleophiles (e.g. N_3, CN, OAc).[7,8] With the goal of expanding the scope of arenes and nucleophiles that may be coupled by this mechanism, we sought to develop a new, *in situ* iodane activation strategy (Figure 1).

Although it is generally understood that bench-stable iodanes, like $PhI(OAc)_2$, may be activated with Lewis (e.g. BF_3, Me_3Si^+)[8] or Brønsted acids (e.g. TsOH, TfOH, Ts_2NH),[9] the precise nature of this acid-activation remains unclear. Recent investigations by Shafir and co-workers revealed it entails transient formation of a non-symmetric iodane (e.g. BF_3 coordination to one of the ligands of $PhI(OAc)_2$).[10] This model for increased reactivity via iodane desymmetrization may also explain the novel reactivity of Koser's reagent, PhI(OH)OTs,[9a] and other hybrid iodanes.[11,12] With this hypothesis in mind, we proposed that while unsymmetrical iodanes typically require preformation, their *in situ* generation may provide the dual benefits of (i) employing bench-stable precursors, and (ii) harnessing greater reactivity, including towards heteroarenes. Furthermore, we anticipated that *in situ* generation of non-symmetric iodanes with anions may enable the use of a wide range of nucleophiles for aryl C–H functionalization.

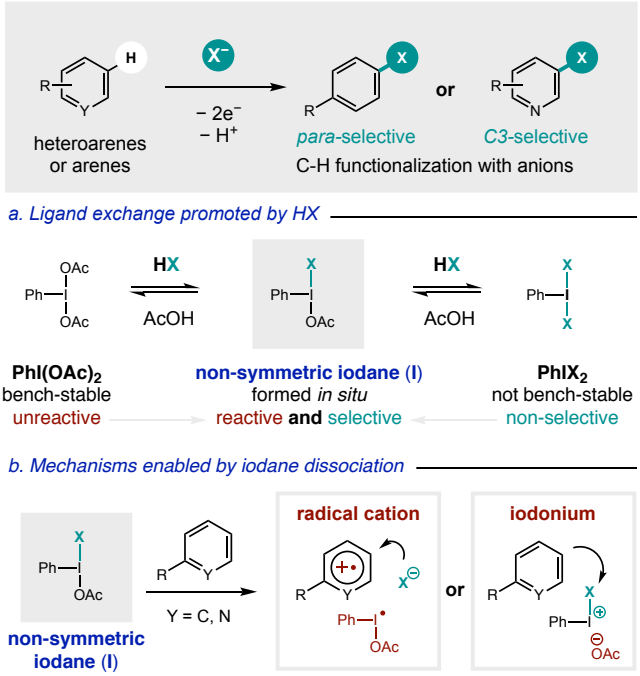


Figure 1. Selective C–H functionalization of arenes and heteroarenes with anions, enabled by *in situ* activation of an iodane

In designing a unified strategy for site-selective, aryl C-H functionalization via non-symmetric iodanes, we expected these reactive intermediates could be readily accessed through ligand exchange[13] of bench-stable iodanes by anions (Figure 1a). As a simple and versatile source of anions, we proposed addition of acids, HX, to $PhI(OAc)_2$ may promote ligand substitution to form $PhIX_2$ – in analogy to acid-mediated formation of PhI(OH)OTs and Ph_2IOTf.[14] Moreover, we anticipated any acids stronger than AcOH should drive this acid/base equilibrium toward $PhIX_2$ – an unstable reagent class associated with non-selective, homolytic reactivity.[6] Essentially, however, we noted this process must proceed via an unsymmetrical iodane intermediate (**I**). We postulated this highly reactive species – having an elongated I-X bond and low-lying LUMO[10] – could react *selectively* with arenes through either of two, transient-iodonium-based mechanisms (Figure 1b).[15] First, anionic dissociation of X^- affords cationic $PhI(OAc)^+$, which may participate in single-electron transfer (SET) to oxidize an arene.[7] The resulting radical cation is then prone to nucleophilic attack by the dissociated anion (X^-). After net loss of H•, this mechanism can enable *para*-selective reactivity through the site-specific electrophilicity of an aryl radical cation.[16] Alternatively, AcO^- dissociation from non-symmetric iodane **I** affords a net polarity-reversal of X^- via an electrophilic $PhI(X)^+$ iodonium species. Attack by the (hetero)arene nucleophile at its most nucleophilic position, and subsequent deprotonation would afford the X-substituted product. Thus, site-selective C–H functionalization may also be accessed by a closed-shell mechanism.

RESULTS & DISCUSSION

To test our hypothesis of the generalizability of this *in situ* iodane activation strategy, a series of acids was combined with N-Piv-*o*-toluidine and $PhI(OAc)_2$ in DCE at 50 ° C (Figure 2a). Surprisingly, several acids (spanning a range of >10 pKa units) afforded *para*-selective C–H functionalization by incorporation of their

conjugate bases into the arene. Notably, TfOH alone facilitates iodane-mediated C–H oxytriflation to afford aryl triflate **1**, without the need for stoichiometric AgOTf.[17] Similarly, C–H oxy-sulfonylations are observed with TsOH and MsOH, which afford tosylate **2** and mesylate **3**, also without additional promoters (e.g. BF_3).[18] Importantly, aqueous mineral acids, HBr and HCl, afford halogenated arenes, **4** and **5**, with high efficiency (up to 88% yield) and *para*-selectivity (>20:1).

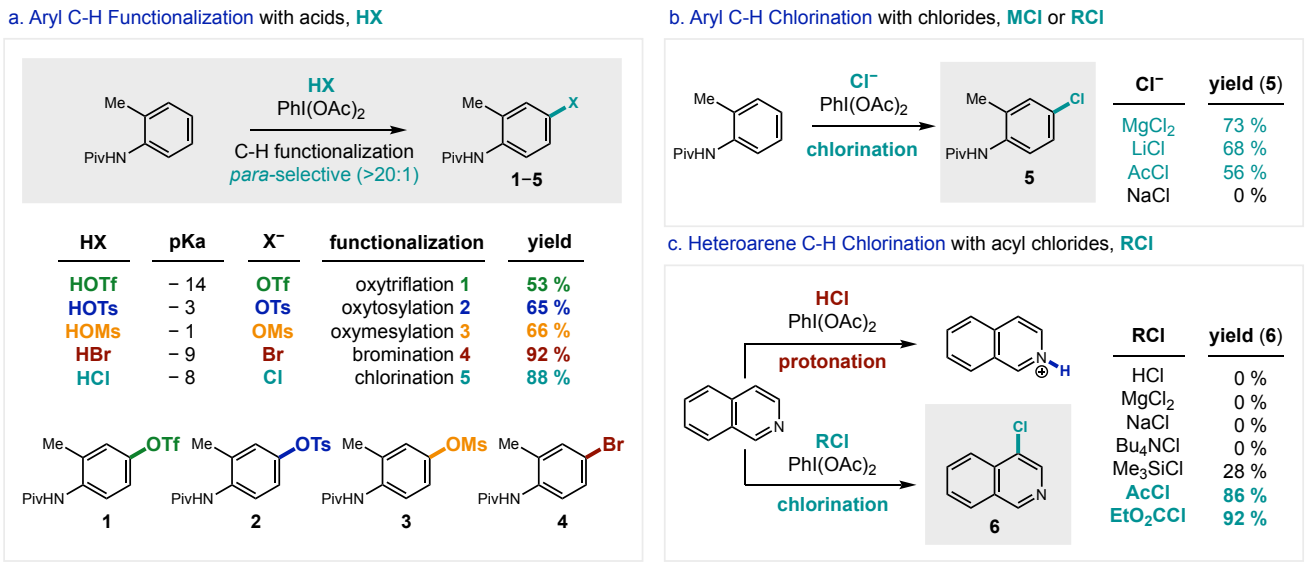


Figure 2. Site-selective C–H functionalization incorporates the anions of acids, salts, and acyl halides.

With a highly, *para*-selective C–H functionalization observed for each of these halides and pseudo-halides, we chose to focus further studies on the most valuable of these reactions: chlorination. The post-synthetic halogenation of a medicinal candidate has two-fold utility: (i) improving biological properties by enhancing binding affinity, cellular membrane permeability, or metabolic stability,[2] and (ii) enabling further synthetic manipulation. As a prototypical halide, the chloride is ubiquitous in medicines, with Cl ranking as the sixth most common element found in approved pharmaceuticals (after H, C, N, O, S),[19] especially as a *para*-aryl substituent.[20] Yet, although direct, post-synthetic modification by aryl C–H functionalization offers streamlined access to libraries of chlorinated medicinal candidates, such analogs are typically prepared by iterative synthesis with pre-halogenated arenes. In the case of chloride, the challenge arises from the traditional reliance on harsh reagents and non-selective methods for aryl chlorination, which are often not applicable to complex, drug-like molecules. An explanation is that aryl chlorination reagents either require (i) overly reactive reagents (e.g. Cl_2, SO_2Cl_2, ^tBuOCl), or (ii) milder, more practically handled reagents that are sometimes not sufficiently reactive (e.g. NCS). This challenge has been addressed in recent years by the development of novel chlorination methods with reagents, such as Palau'chlor and IBA-Cl.[21] Nonetheless, we noted that the "mild reagent vs sufficient reactivity" paradox remains unsolved in the realm of aryl C–H chlorination.[22]

Encouraged by the simple use of dilute, mineral acids (e.g. 1M HCl in water) to enable this C–H functionalization, we questioned whether other chloride reagents might also promote this ligand exchange to access this unique iodane reactivity

from $PhI(OAc)_2$ (Figure 2b). Indeed, we observed that several chlorides afford aryl chlorination, including Lewis acids (e.g. $MgCl_2$), salts (e.g. LiCl), and acyl halides (e.g. AcCl).

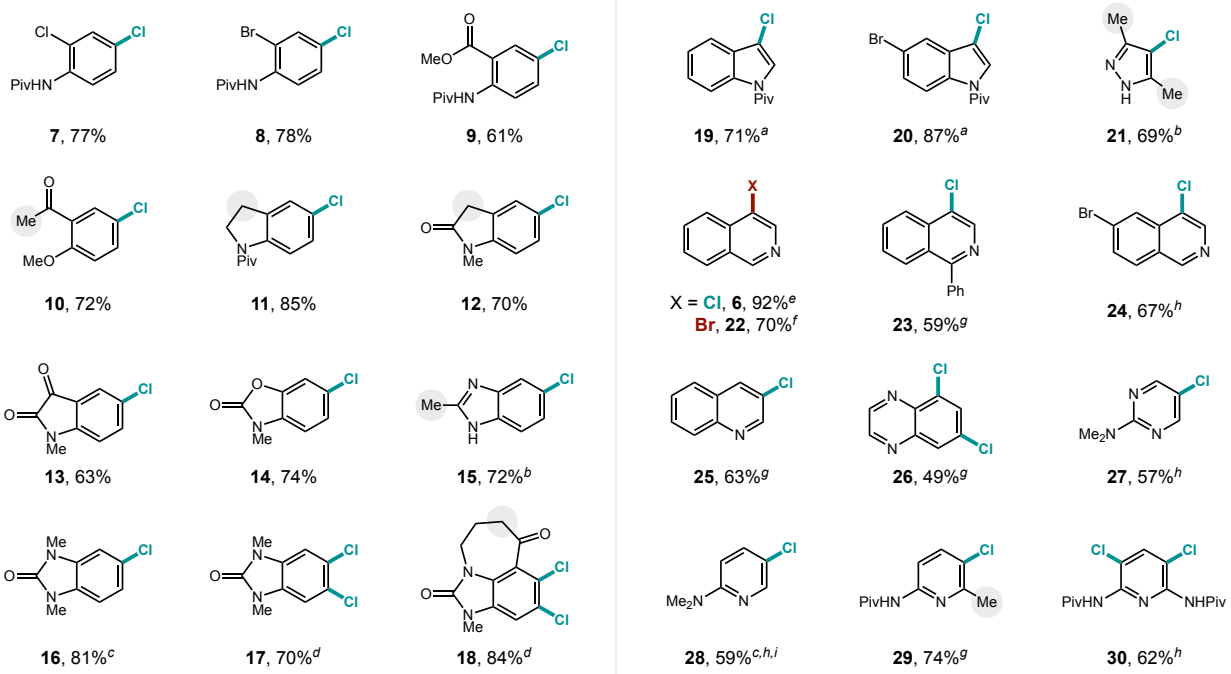
Finally, cognizant of the privileged role of N-containing heterocycles in medicine,[23] we focused our attention on the C–H chlorination of heteroarenes (Figure 2c). Notably, there are few ways to prepare chloro-(iso)quinolines – each analog requiring its own multi-step synthesis.[24] With this in mind, we subjected isoquinoline to the HCl-mediated conditions. Although this acidic protocol did not afford chlorination, we observed complete protonation by ^{1}H NMR, which likely renders the heteroarene significantly less nucleophilic. We therefore investigated other chloride reagents for aryl chlorination. While many of these chloride reagents were also ineffective (e.g. $MgCl_2$), we found that acyl chlorides promote this reaction efficiently (up to 92% yield). We suspect these anhydrous sources of chloride anion, which may also function as desiccants, lack the acidity to deactivate the isoquinoline nucleophile. Interestingly, the observed selectivity in this case (for nucleophilic C4) is orthogonal to most heteroarene functionalizations (for electrophilic C1 or C3) via polar[25] or radical mechanisms.[26]

With robust conditions in hand for the selective C–H chlorination of either arenes or heteroarenes, we sought to investigate the generality and utility of this transformation (Figure 3). In the case of HCl-mediated aryl chlorination, various drug-like scaffolds are amenable to this reaction, including those containing halides, amides, esters, ketones, and imides (**7**–**18**). Notably, exclusive *para*-regioselectivity is observed in all cases. Additionally, this iodane-mediated reaction is chemo-selective, affording only sp^2 C-H chlorination – with neither benzylic nor α-carbonyl oxidation (positions highlighted in grey), as typically observed via homolysis of $PhICl_2$.[27] In the case of heteroarenes, aryl chlorination of both five-membered heterocycles (e.g. indoles, pyrazoles, **19**–**21**) and six-membered heterocycles (e.g. isoquinoline, quinoline, pyrimidine, pyridine, **6**, **23**–**30**, via acyl chlorides) are also possible (up to 92%).

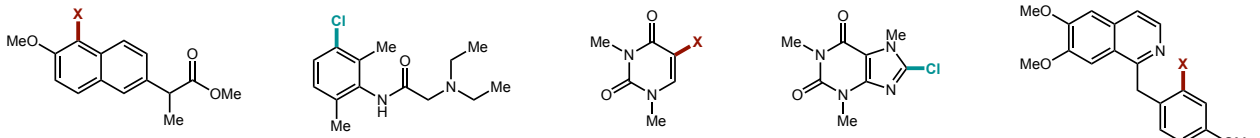
With our ultimate goal of medicinal application in mind, we then subjected a series of pharmaceuticals and natural products to this post-synthetic C−H chlorination strategy. Remarkably, a wide range of functionality is tolerated, including esters, amides, amines, imides, enamides, pyrroles, and dimethoxyarenes. As shown in Figure 3, the chlorinated analogs of naproxen, lidocaine, uracil, caffeine, and papaverine (**31**–**38**) were each accessed in a single-step using this protocol. Notably, the tertiary amine of lidocaine **33** remains intact, despite its oxidant-sensitivity, likely due to protection by protonation under these acidic conditions. As expected, bromination is also possible for both arenes (**4**) and heteroarenes (**22**), including within more complex drug-like scaffolds (**32**, **35**, **38**).

Figure 3. C−H Chlorination of arenes and heteroarenes via an *in situ* generated, non-symmetric iodane strategy.

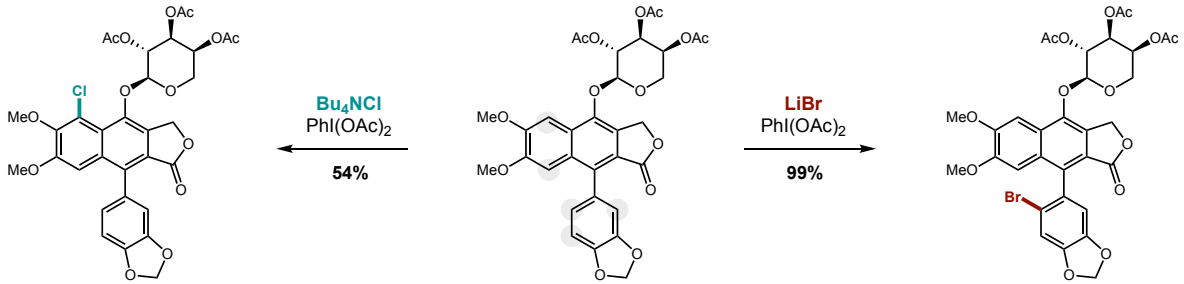
arene chlorination[a] | *heteroarene chlorination*



halogenation of pharmaceuticals and natural products



application to a medicinal chemistry program



Site-selective (hetero)aryl C–H chlorination: Arene (0.4 mmol), chloride reagent (5 equiv), $PhI(OAc)_2$ (1.5 equiv), DCE (0.2 M), 50°C, 45 min – 24 hr. Isolated yields. No regioisomeric chlorination observed

(susceptible positions highlighted with grey circles). **Chloride reagents**: [a] 1M HCl, [b] Bu_4NCl, [c] $PhI(OAc)_2$ (0.9 equiv), [d] 1M HCl (10 equiv), $PhI(OAc)_2$ (2.5 equiv), [e] EtO_2CCl, [f] KBr, [g] C_6F_5COCl, [h] AcCl, [i] 3:1 *para:ortho*, [j] 48% HBr, [k] 2M HCl in Et_2O.

Finally, we sought to test this iodane-based strategy within the context of an active medicinal chemistry program. In particular, we have shown that analogs of phyllanthusmin D exhibit potent, anti-cancer activity against HT-29 human colon cancer cells.[28] Although this natural product is structurally related to the DNA topoisomerase IIα inhibitor, etoposide, it appears to exhibit biological activity via a distinct mechanism of action. Notably, when non-natural sugars are affixed to the aglycone core of phyllanthusmin, especially potent analogs have been identified (IC_{50} < 10 nM).[29] In order to streamline our exploration of the structure-activity relationship for substitution of the aryl core, we pursued a C−H functionalization strategy to rapidly generate a library of medicinal analogs. To this end, we subjected Ac-phyllanthusmin D to our HCl-mediated protocol. Unfortunately, the critical sugar was rapidly hydrolyzed off under these acidic conditions, affording the biologically inactive agylcone. On the other hand, employing Bu_4NCl as the chloride reagent yields the C−H chlorinated derivative (**39**) in a single step. Similarly, LiBr affords direct C−H bromination (**40**). Interestingly, divergent regioselectivity is observed for these two reactions, with the smaller Cl atom substituting the more electron-rich naphthalene and the larger Br atom adding to the less-hindered, axially rotatable benzene. Importantly, in both cases, the sugar substituent is unperturbed, allowing us to access a family of potent derivatives from a single advanced intermediate.

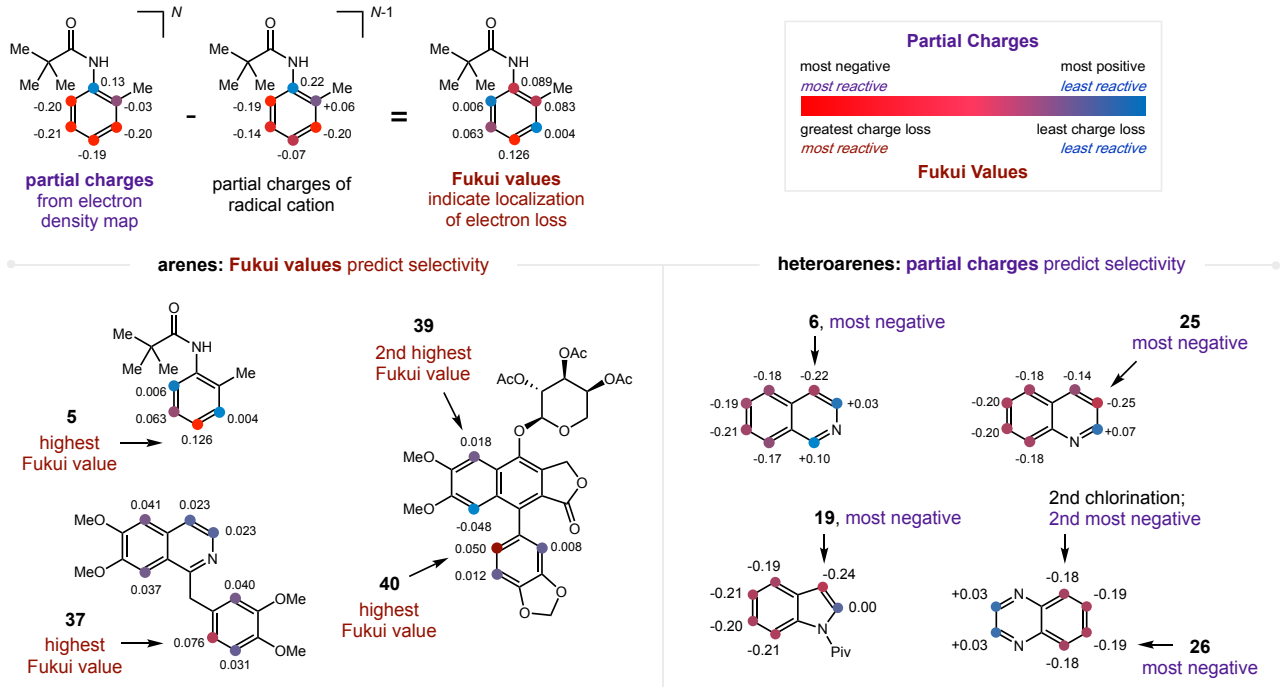


Figure 4. Computational experiments predict regioselectivity.

In order to better understand the excellent regioselectivity observed in the C-H halogenations of various arenes in Figure 3, we conducted DFT experiments according to Ritter's procedure.[4b] Specifically, we determined Fukui index values for several (hetero)arenes by computing a population analysis for each arene and its

corresponding N-1 ionization state – and then subtracting the charge densities of the latter from the former in each case (see SI for details). As shown in Figure 4, employing this Fukui analysis correctly predicts the most reactive positions of several complex molecules from Figure 3.

In particular, this analysis predicts and explains the results obtained for anilide, as well as the medicinally relevant natural products, papaverine and phyllanthusmin. Each example contains polyaromatic rings with multiple possible sites of reactivity. Yet, Fukui analysis predicts the most reactive atom in the case of papaverine (**37**) and the two most reactive positions for phyllanthusmin (i.e. sites of chlorination **39** and bromination **40**).

On the other hand, we noted that a simple electron-density map of partial charges provides a more accurate predictor of the site-selectivity observed for heteroarene C-H functionalization. For example, the most negative position by natural population analysis correlates to the most reactive position for quinoline (**25**), isoquinoline (**6**), indole (**19**), and quinoxaline (**26**). Interestingly, for three of these four classes of heteroarene, Fukui analysis predicts alternate regioselectivity, suggesting divergent mechanisms between the arene and heteroarene reactions.

Thus, given the correct prediction of site-selectivity by these DFT calculations, we propose the mechanisms shown in Figure 1 are both viable. As shown in Figure 5, given the strong correlation of the Fukui analysis, which is dependent on radical cation character, to predict regioselectivity for the arenes, we suggest the 'radical cation' mechanism is likely more relevant for the electron-rich arenes. In this case, the transient, non-symmetric iodane intermediate likely promotes single-electron oxidation to afford a radical cation with electrophilicity (and nucleophilic attack) localized at the predicted *para* position. Alternatively, for less-electron-rich heteroarenes, the iodane likely combines directly with the heteroarene via the 'iodonium' mechanism. This pathway is supported by the *C3* regioselectivity of the products, which are correctly (and exclusively) predicted via partial charge analysis as correlating to the most negative, or electron-dense, sites.

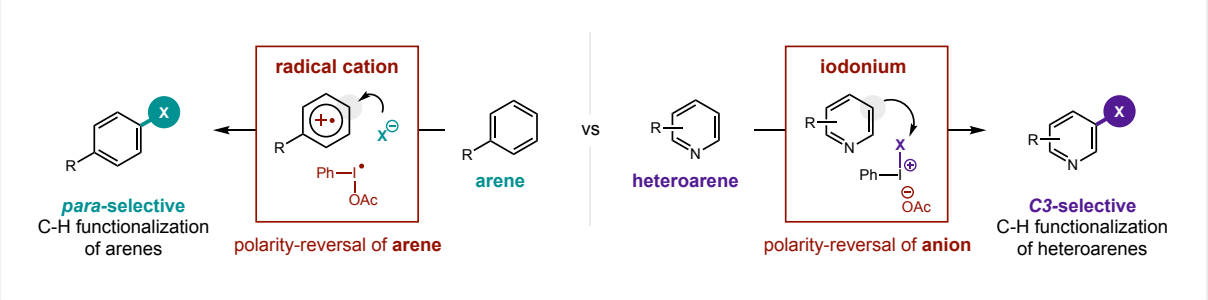


Figure 5. Computationally supported divergent mechanisms explain predicted and observed regioselectivities for arenes versus heteroarenes.

The chemoselectivity observed among the various arenes in Figure 3 also led us to question the possibility of developing methods to enable reagent-based control over selectivity. To this end, we subjected a 1:1 mixture of heteroarene and arene to a series of competition experiments (Figure 6). Indeed, when heteroaryl conditions are employed (e.g. EtO_2CCl), isoquinoline chlorination is exclusively observed, even in the presence of electron-rich anisoles. Yet, under acidic, aryl conditions (e.g. HCl), isoquinoline is presumably protonated, affording exclusive anisole chlorination (**41**).

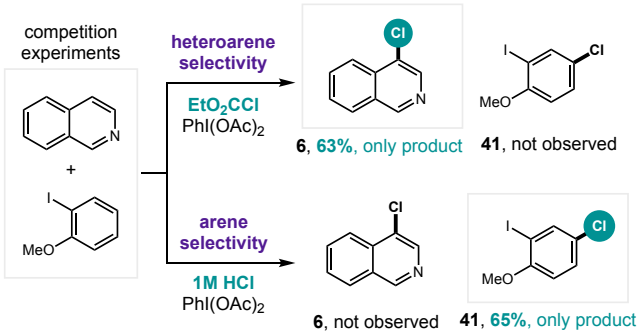


Figure 6. Competition experiments demonstrate chemoselectivity.

We were also interested in further probing the unique C–H chlorination of heteroarenes, especially given the importance of these motifs in medicine. To the best of our knowledge, this *in situ* iodane activation strategy comprises the mildest and most efficient protocol for C–H chlorination of (iso)quinolines,[30] affording regioselective substitution of the most nucleophilic carbon (e.g. 4-Cl-isoquinoline or 3-Cl-quinoline). To test this hypothesis, we investigated the chlorination of both isoquinoline and quinoline by common aryl chlorination methods, as shown in Figure 7. Surprisingly, no chlorinated products were detected for either class of heteroarene (**6** or **25**) – even in the presence of state-of-the-art chlorinating reagents, Palau'chlor and IBA-Cl. Similarly, several other arenes in Figure 3 are not efficiently halogenated using alternate literature methods, such as $PhICl_2$ (e.g. 10, 15, 33, 39; see SI).

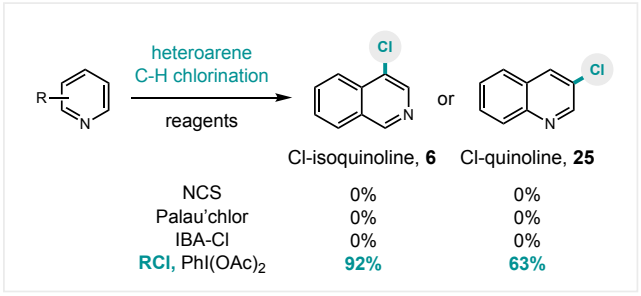


Figure 7. Reactivity comparison with other chlorinating reagents.

Noting a distinct difference in reactivity between our postulated, transient non-symmetric iodane and cyclic IBA-Cl in particular, we sought to investigate the precise nature of the *in situ* generated iodane. We first probed if a diaryliodonium pathway could promote this unprecedented heteroaryl chlorination (Figure 8a). To examine the viability of such a mechanism, we prepared 3-pyridyl-diaryliodonium and heated it in the presence of acyl chloride, both with and without $PhI(OAc)_2$. In both cases, we did not observe any chlorination (aryl or heteroaryl) thereby precluding this type of mechanism. Similarly, $Ph_2I^+Cl^-$ does not afford PhCl, when heated with or without HCl. Additionally, bis-N-substituted di(hetero)aryl iodonium was prepared and subjected to various acyl chlorides (Figure 8b). In this mechanistic probe, no chloroarene was obtained, neither with nor without $PhI(OAc)_2$, further suggesting such iodoniums are not likely intermediates in this mechanism.

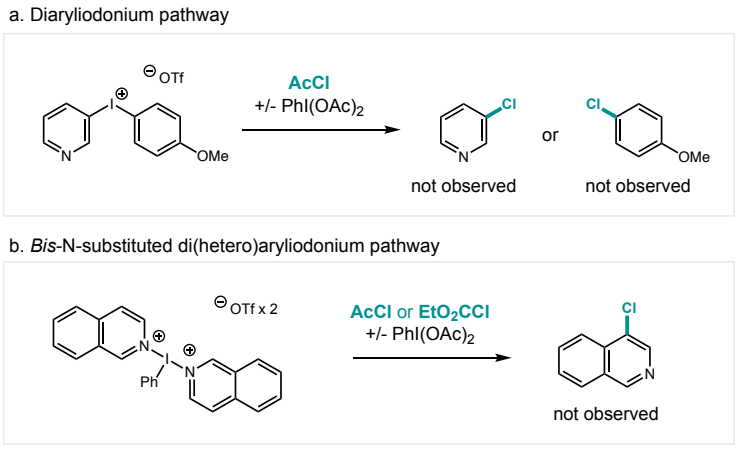


Figure 8. Mechanistic probes suggest alternate iodonium pathways are not viable.

To obtain further support for our proposed mechanism (*c.f.* Figure 1), we sought to spectroscopically observe the transient, non-symmetric iodane intermediate. Several representative NMR experiments from this investigation are shown in Figure 9. After identifying diagnostic, aromatic ^{1}H NMR signals for the *homo*-di-substituted iodanes, PhI(OAc)$_2$ and PhICl$_2$, we subjected PhI(OAc)$_2$ to varying stoichiometries of HCl and observed a new signal, which we ascribe to the non-symmetric iodane, PhI(OAc)Cl. Notably, this signal is also observed when AcCl is used as the chloride reagent. And interestingly, the same signal is observed upon combination of PhICl$_2$ with Ac$_2$O, which serves as an anhydrous source of acetate.

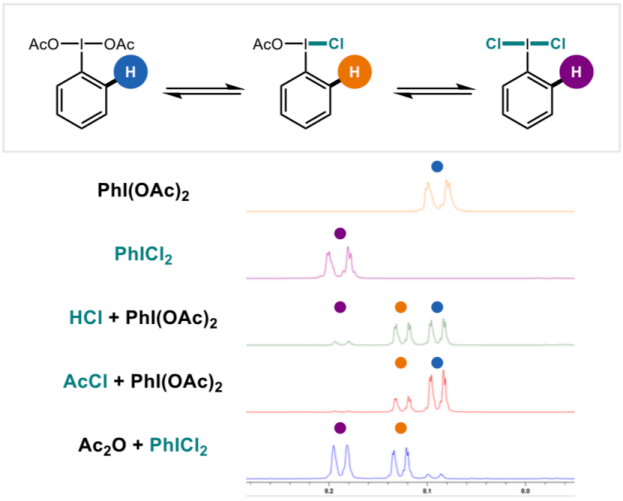


Figure 9. ^{1}H NMR experiments indicate the intermediacy of a non-symmetric iodane intermediate.

In order to examine the role of this observed species as a possible intermediate, we then subjected isoquinoline to chlorination under various conditions (Figure 10). As expected, Willgerodt's reagent, PhICl$_2$, does not afford appreciable quantities of chlorination (**6**). However, a combination of PhICl$_2$ and Ac$_2$O, which also generates the unsymmetrical iodane *in situ*, recapitulates the reactivity of PhI(OAc)Cl that is not observed for PhICl$_2$ alone. Additionally, a mixture of AcCl and PhI(OAc)$_2$, which more selectively forms PhI(OAc)Cl over PhICl$_2$, affords the desired heteroaryl chloride in high yield (86%; similar to EtO$_2$CCl, 92%).

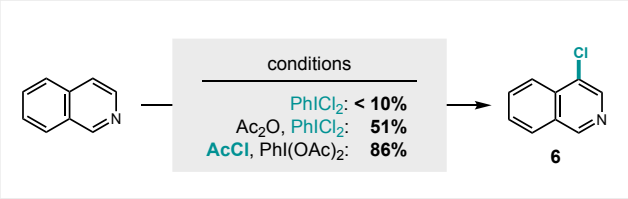


Figure 10. Heteroarene chlorination by orthogonal reagents; recapitulation of reactivity supports mono-chloro-iodane hypothesis.

In summary, a site-selective hetero(aryl) C−H functionalization strategy has been developed. This practical method is enabled by *in situ* generation of non-symmetric iodanes from $PhI(OAc)_2$ and the anions of acids, salts, and acyl halides. These mild conditions afford access to new types of reactivity and selectivity, as illustrated in the chemo- and regio-selective C−H halogenation of a range of medicinally relevant (hetero)arenes. Importantly, spectroscopic, computational, and experimental support for *in situ* generation of unsymmetrical iodanes under such conditions provides mechanistic validation to enable further development of new iodane reactivity.

SUPPLEMENTAL INFORMATION

Supplemental Information includes:
Experimental procedures and characterization for all new compounds (PDF)
^{1}H and ^{13}C NMR spectral data (PDF)
Figures S1-S157
Tables S1-S33
Schemes S1-S4

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AUTHOR CONTRIBUTIONS

SCF and DAN designed the strategy. SCF and CMH designed, performed, and analyzed all chemical experiments. ADC performed computational experiments. All authors contributed to writing this manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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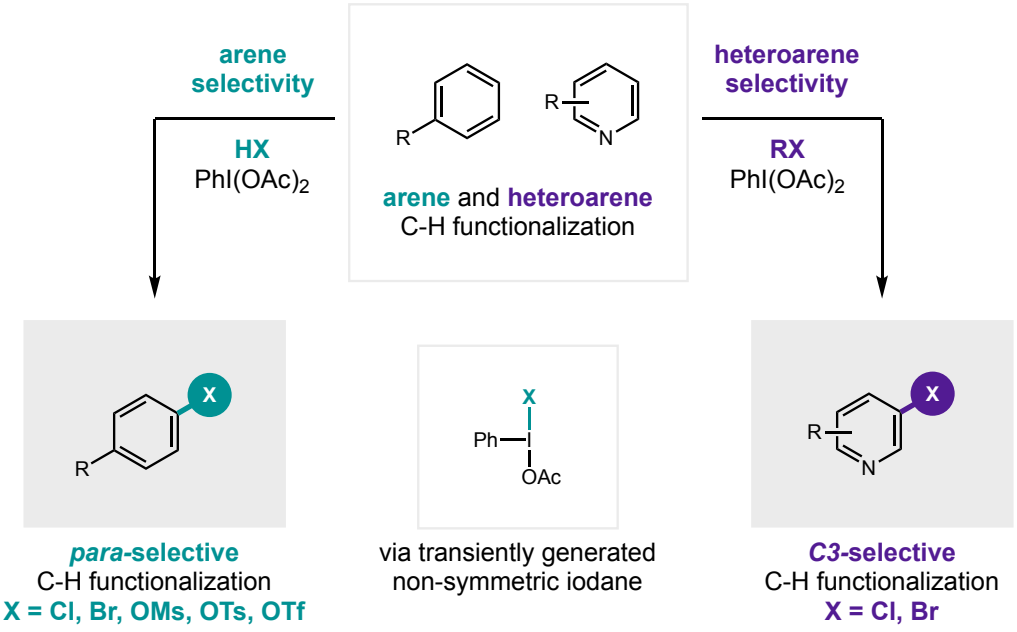

***para*-selective**
C-H functionalization
X = Cl, Br, OMs, OTs, OTf

via transiently generated
non-symmetric iodane

***C3*-selective**
C-H functionalization
X = Cl, Br