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Halogen Bond–Assisted Electron–Catalyzed Atom Economic Iodination of Heteroarenes at Room Temperature

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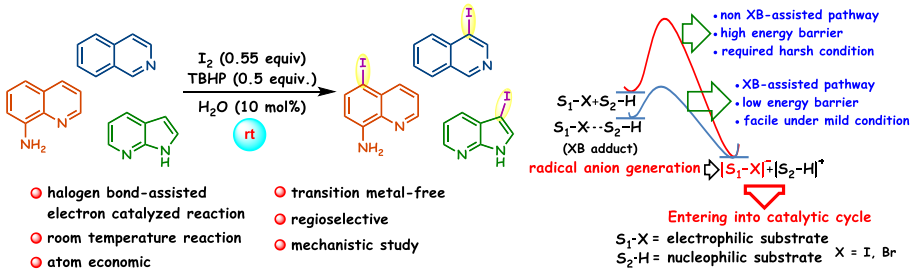
ABSTRACT



A halogen bond–assisted electron–catalyzed iodination of heteroarenes has been developed for the first time under atom economic conditions at room temperature. The iodination is successful with just 0.55 equivalent of iodine and 0.50 equivalent of peroxide. The kinetic study indicates that the reaction is elusive in absence of halogen bond between the substrate and iodine. The formation of halogen bond, its importance in lowering the activation barrier for this reaction, the presence of radical intermediates in reaction mixture and the regioselectivity of the reaction have been demonstrated with several control experiments, spectroscopic analysis and quantum chemical calculations. Allowing the formation of halogen bond may offer a new strategy to generate the reactive radical intermediates and to enable the otherwise elusive electron–catalyzed reactions under mild reaction conditions.

INTRODUCTION

Halogen bond (XB) refers to the attractive noncovalent interaction between an electrophilic halogen atom (XB donor) and a Lewis base (XB acceptor).[1] Several studies on XB were related to solid state chemistry but recently, its application has been realized in the field of crystal engineering,[2a] medicinal chemistry,[2b] self-assembly[2c] and supramolecular chemistry.[2d,e] In

addition to this, XB has emerged as an important tool in the field of organic synthesis. In the last few years, XB has been employed for activation of functional groups,[3a,b] synthesis of recyclable catalysts,[3c] photoactivation of halides to generate radical intermediates[3d] and transformation of gaseous compounds to easily–handleable condensed–phase liquid reagents.[3e]

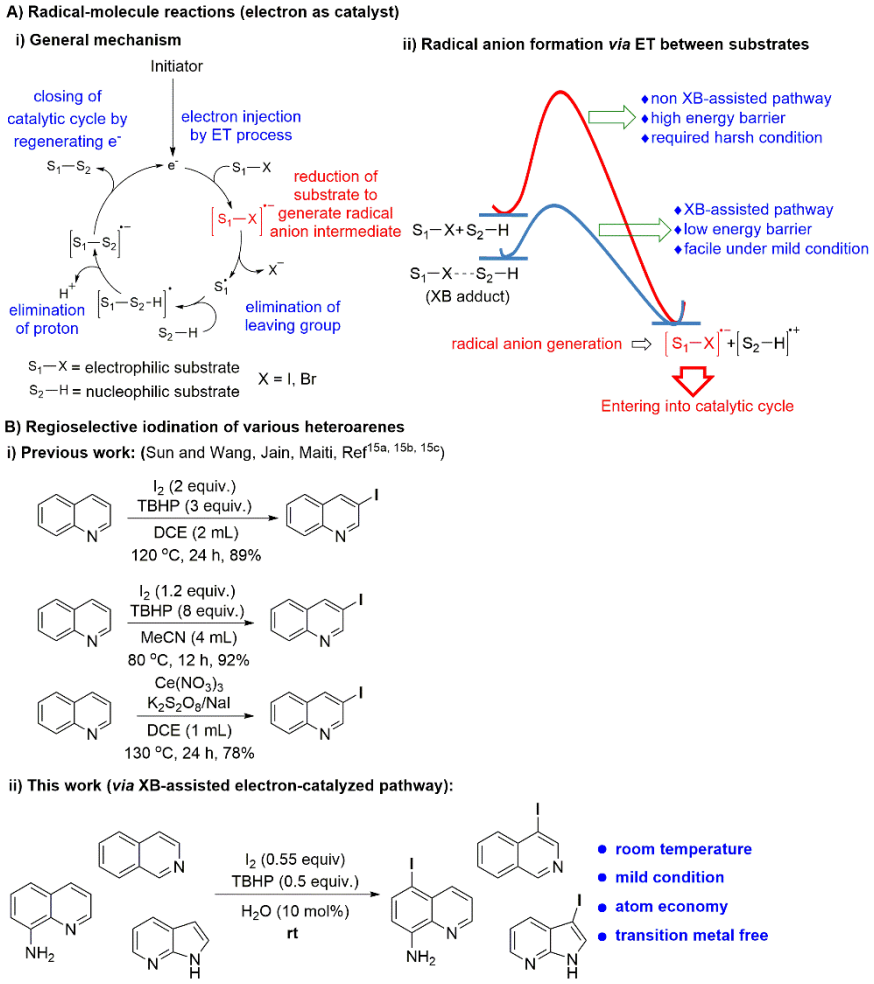


Figure 1. Concept of employing XB–assisted electron–catalyzed reaction for regioselective iodination of various heteroarenes under mild condition.

As the part of our on–going research on the effect of halogen bonds on the reactivity of halogen(I) reagents and in situ–generated halogen(I) intermediates,[4] we have observed that the XB between the Lewis base and halogen(I) center assists the electron transfer (ET) from the former to the latter to generate radical species.[4c] This observation was also reported by Roshokha and coworkers in 2014.[5] They demonstrated that XB significantly lowers the activation barrier for the electron transfer (ET) from donor (Lewis base) to acceptor (halogen(I) center). Thus, we envisaged that XB can be an efficient tool to modulate the electron transfer processes in organic synthesis.

The electron transfer (ET) process is the crucial initiation step for synthetically important radical–molecule reactions. The radical–molecule reaction is a reaction between radicals and close–shell molecules such as unimolecular radical substitution reactions ($S_{RN}1$),[6] base-promoted homolytic aromatic substitutions (BHAS),[7] transition-metal-free Heck-type reactions,[8] radical cross-dehydrogenative coupling reactions via BHAS[9] and alkoxy carbonylation of aryl halides.[10] According to Studer and Curran, these reactions can be mechanistically generalized as 'electron- catalyzed reactions'.[11] A general and simplified mechanistic pathway for an electron-catalyzed reaction is depicted in Figure 1A ('electron as catalyst' view).

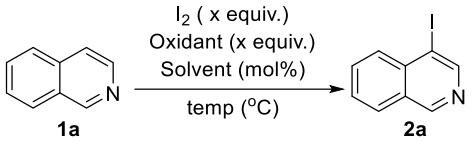
As the radicals are very reactive species, these reactions generally proceed smoothly (chain reaction) once the radical and radical anion intermediates are formed in the reaction mixture. The main challenge for these reactions is to initiate the generation of radical anion by ET process and to control the selectivity of the reaction (favoring one pathway among several other competitive pathways). In general, to initiate this ET process, harsh conditions such as high temperature, stoichiometric amount of base (such as KO^tBu), or stoichiometric amount of peroxide are required.[11] We hypothesized that the XB–assisted ET might be employed to generate the reactive radical intermediates and to initiate an electron–catalyzed radical–molecule reaction under mild reaction conditions. Moreover, this radical molecule reactions are helpful for radical C–H activation or radical cross coupling reaction.[12] Herein, for the first time, we demonstrate how halogen bond enables the electron–catalyzed iodination of hetero arenes at room temperature utilizing only semi-stoichiometric amount of iodine and peroxide as oxidant. The reaction is elusive under the same reaction conditions when halogen bond is absent between the substrate and iodine.

Due to the presence of weak carbon–iodine bond, heteroaryl halides are one of the most important structural precursors in synthetic organic chemistry and often used as starting materials for transition metal-catalyzed cross-coupling reactions[13] and nucleophilic aromatic substitution.[14] Recently, few procedures have reported the regioselective iodination of quinolines with I_2/TBHP[15a,b] and $K_2S_2O_8$/$Ce(NO_3)_3$/NaI.[15c] Unfortunately, in both the cases the reactions were carried out under harsh conditions and in presence of costly metal catalysts.

RESULTS AND DISCUSSION

To initiate our study, we have chosen isoquinoline **1a** as a model substrate in the presence of molecular iodine. The initial reaction was carried out by 1 equiv. of isoquinoline **1a** and 1.1

Table 1. Optimization for regioselective iodination of isoquinoline[a]



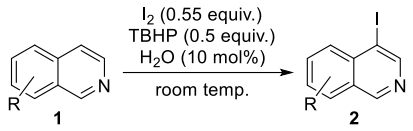
Entry	I_2 (equiv.)	Oxidant (equiv.)[b]	Solvent (mol %)	Temp (°C)	Time (h)	Yield (%)[c]
1	1.1	-	Py[d]	130	36	64[e]
2	1.1	-	-	rt	36	35
3	1.1	TBHP (1.0)	-	rt	24	73
4	0.60	TBHP (1.0)	-	rt	23	74
5	0.55	TBHP (1.0)	-	rt	24	73
6	0.50	TBHP (1.0)	-	rt	30	70
7	0.55	TBHP (0.6)	-	rt	23	73
8	0.55	TBHP (0.5)	-	rt	23	74
9	0.55	TBHP (0.3)	-	rt	24	42
10	0.55	TBHP (0.5)	AcOH (10)	rt	21	92
11	0.55	TBHP (0.5)	HCO_2H (10)	rt	24	85
12	0.55	TBHP (0.5)	$EtCO_2H$ (10)	rt	24	75
13	0.55	TBHP (0.5)	CF_3CO_2H (10)	rt	24	73
14	0.55	TBHP (0.5)	MeOH (10)	rt	22	78
15	0.55	TBHP (0.5)	EtOH (10)	rt	22	79
16	**0.55**	**TBHP (0.5)**	**H_2O (10)**	**rt**	**18**	**94**
17	0.55	H_2O_2 (0.5)	H_2O (10)	rt	24	63
18	0.55	DTBP (0.5)	H_2O (10)	rt	24	16

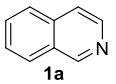
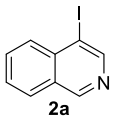
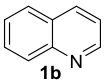
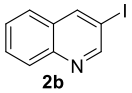
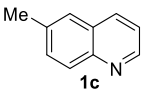
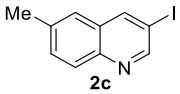
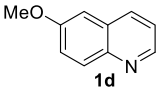
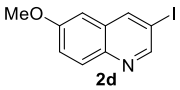
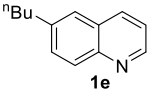
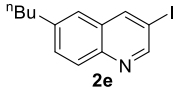
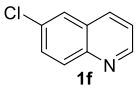
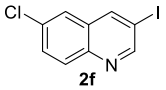
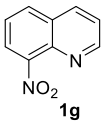
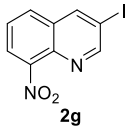
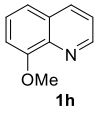
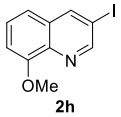
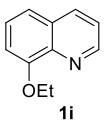
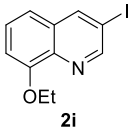
[a]Reaction conducted in 1 mmol scale. [b]TBHP in decane used. [c]Isolated yield. [d]3 equiv. of pyridine was used. [e]Oxygen balloon was used.

equiv. of molecular iodine in the presence of 3 equiv. of pyridine as a solvent under oxygen atmosphere yielded 64% of 4-iodoisoquinoline **2a** at 130 °C in 36 h (Table 1, entry 1). The reaction provided 35% yield of iodinated product at room temperature in absence of solvent (Entry 2). When the reaction was performed in the presence of 1.0 equiv. of TBHP in decane, 73% of product was isolated at room temperature (Entry 3). We did not observe any reduced yield of iodinated product by decreasing the loading of iodine from 1.1 equiv. to 0.55 equiv.

(Entry 4–6). Similarly, by screening the amount of TBHP, it was inferred that 0.50 equiv. of TBHP was adequate for the reaction (Entry 7–9). Further, a range of solvent were examined to improve the yield of **2a** (Entry 10–16) and the results are summarized in Table 1. Finally, it was observed that 10 mol% of H_2O gave the best yield of 94% of the isolated product (Entry 16).[16a] To improve the efficiency of the reaction, various oxidants were screened (Entry 17–18). In case of H_2O_2, the yield of C-3 iodinated isoquinoline was reduced to 63% (entry 17). The reaction provided very poor yield when DTBP (Di-tertbutyl peroxide) was used as an oxidant (Entry 18).

Table 2. Scope of the iodination of quinoline derivatives.[a]

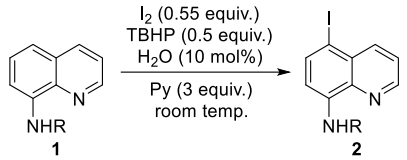


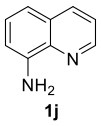
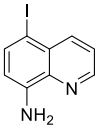
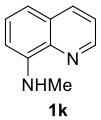
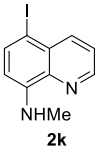
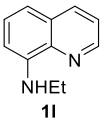
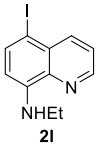
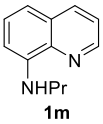
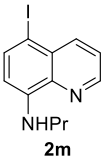
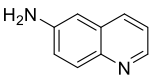
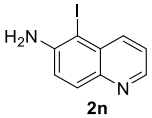
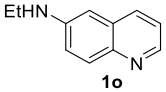
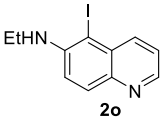
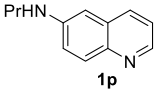
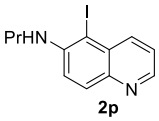
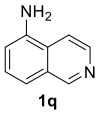
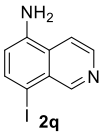
Entry	Substrate	Product	Time (h)	Yield (%)
1	 1a	 2a	18	94
2	 1b	 2b	33	90
3	 1c	 2c	30	74
4	 1d	 2d	48	65[b]
5	 1e	 2e	36	71[b]
6	 1f	 2f	72	62[b]
7	 1g	 2g	72	48[b]
8	 1h	 2h	72	54[b]
9	 1i	 2i	72	46[b]

[a]Isolated yield. [b]2 equiv. of pyridine was used.[16b]

With the optimized reaction conditions (Table 1, entry 16) in hand, the scope of regioselective iodination of various quinoline derivatives and 7-azaindoles were investigated. Substrates with both electron–donating and electron–withdrawing groups were well tolerated during the iodination reaction. Unsubstituted Isoquinoline and quinoline moieties were regioselectively iodinated in excellent yields (Table 2, **2a**–**b**). Good to excellent yields were observed with quinoline moiety having electron-donating groups (**2c**–**2e**). In contrast, the presence of

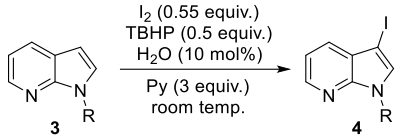
Table 3. Scope of the iodination of amino-quinoline.[a]

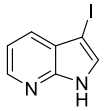
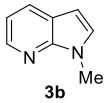
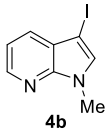
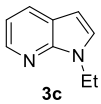
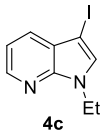
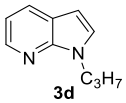
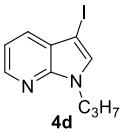
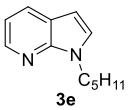
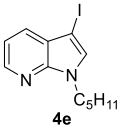
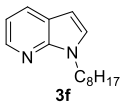
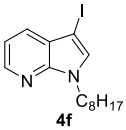
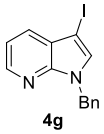
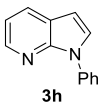
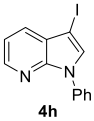
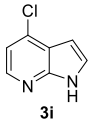
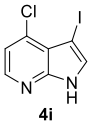
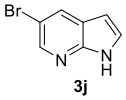
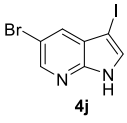
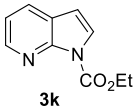
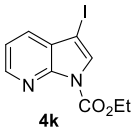


Entry	Substrate	Product	Time (h)	Yield (%)
1	 1j	 2j	4	92[b]
2	 1k	 2k	3	78
3	 1l	 2l	1.5	82
4	 1m	 2m	1.5	83
5	 1n	 2n	6	85
6	 1o	 2o	10	84
7	 1p	 2p	12	82
8	 1q	 2q	13	81

[a]Isolated yield. [b]5 equiv. of pyridine was used.[16b]

Table 4. Scope of the iodination of substituted 7-azaindoles.[a]



Entry	Substrate	Product	Time (h)	Yield (%)
1	 3a	 4a	6	91
2	 3b	 4b	3.5	86
3	 3c	 4c	3	82
4	 3d	 4d	1.5	81
5	 3e	 4e	4	81
6	 3f	 4f	4	80
7	 3g	 4g	5	73
8	 3h	 4h	22	75
9	 3i	 4i	9	86
10	 3j	 4j	10	81
11	 3k	 4k	26	0

[a]Isolated yield.[16b]

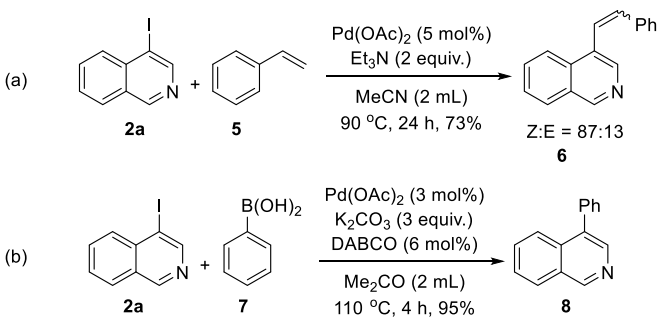
electron- withdrawing group at the quinoline ring decreased the yield of the product (**2f**–**2g**). For 8-substituted quinoline molecule, a decrease in the yield was observed owing to the steric hindrance near the donor nitrogen atom (**2h** and **2i**).

Quinoline moiety bearing amino functional group underwent iodination and generated the desired products in very good yields under the optimized reaction conditions (Table 3). The 8-aminoquinolines gave the corresponding C-5 iodinated products in good to excellent yields (**2j**–**2m**). The structure of the productwas established by single-crystal XRD analysis of **2j** (CCDC no. 1871694).[17a] The 6-aminoquinolines and 5-aminoisoquinolines were also transformed to C-5 and C-8 iodinated products respectively in high yield under the optimized reaction conditions (**2n**–**2q**).

The substrate scope of the reaction with various substituted 7-azaindoles was examined under the optimized conditions and the results have been described in Table 4. Generally, 7-azaindole containing electron-donating groups on the pyrrole ring were well tolerated and delivered the corresponding C-3 iodinated products in good to excellent yields (**4a**–**4f**). A slight decrease in the yield was observed for N-benzyl and N-phenyl 7-azaindole (**4g** and **4h**). The electron-withdrawing group containing 7-azaindoles were well tolerated and provided the corresponding C-3 iodinated products in good yields (**4i** and **4j**).When ethyl carboxylate containing group was subjected to the reaction condition even trace amount of product was not observed (**4k**).

Further, the synthetic application of 4-iodoisoquinoline has been manifested by the carbon-carbon bond formation reaction with styrene to give **6** which acts as an important precursor in organic synthesis (Scheme 1a).[18a] Similarly, when 4-iodoisoquinoline was treated with phenylboronic acid it was readily converted to **8** in presence of $Pd(OAc)_2$/DABCO system (Scheme 1b).[18b]

Scheme 1. Synthetic transformation of 4-iodoisoquinoline.



The exceptional mild conditions of this new iodination process propelled us to do the well–thought–out mechanistic investigations and to check our hypothesis on halogen bond–assisted electron–catalyzed pathway. To verify the presence of halogen-bonding interaction between isoquinoline and molecular iodine, UV-Vis experiment was performed in hexane (Figure 2A).[19] An absorption band corresponding to the free iodine in hexane was observed near 522 nm. When UV-Vis absorption spectrum of **1a** (40 equivalents) and iodine (1 equivalent) was

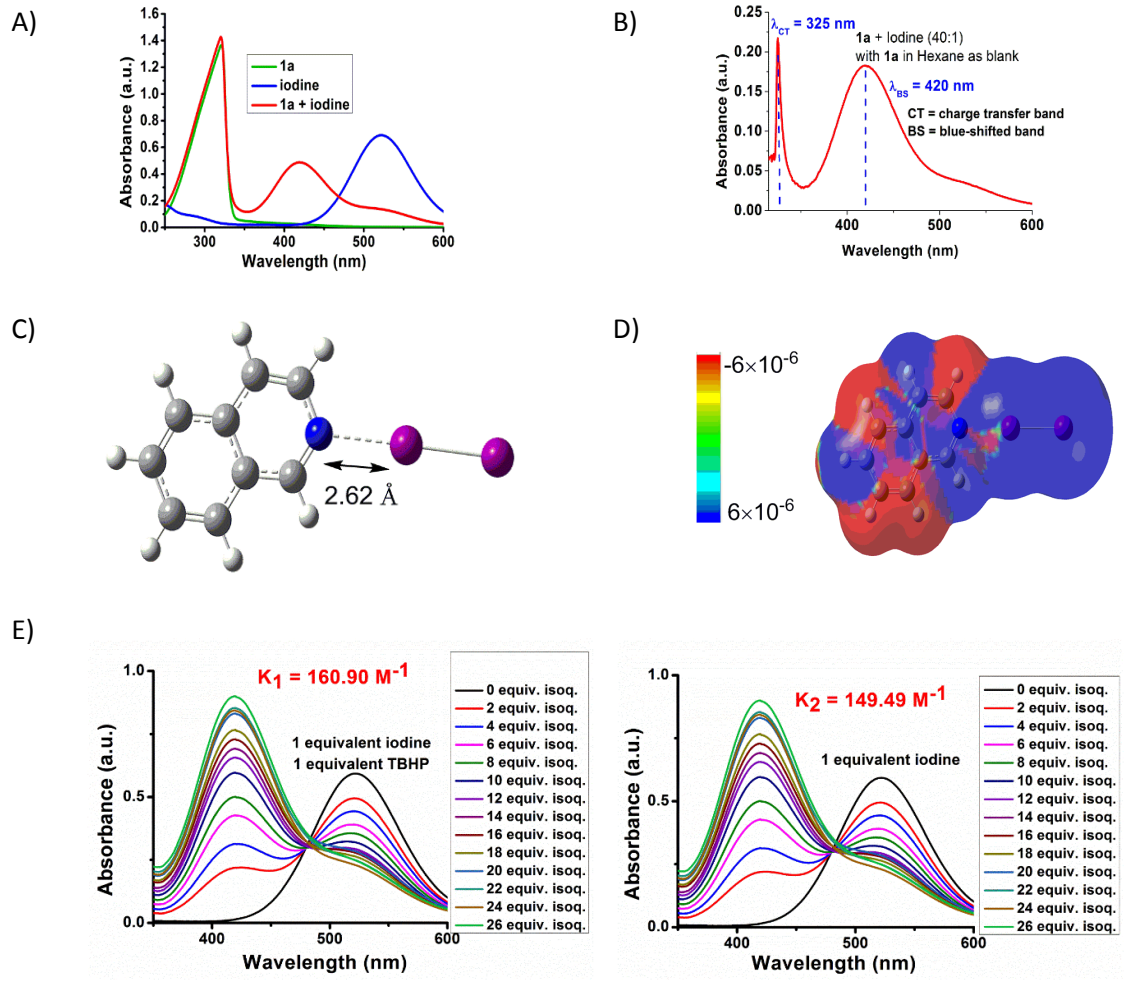


Figure 2. A) UV-Vis experiment of **1a** (green line), iodine (blue line) and **1a**+iodine (red line) in hexane at 40 equivalents for **1a** and 1 equivalent for iodine (path length = 1 cm). B) UV-Vis spectra of **1a** (40 equivalents) + iodine (1 equivalent) in hexane (path length = 1 cm) where 40 equivalents isoquinoline in hexane as blank. C) Optimized structure with DFT using ωB97X-D functional and 6-311G(d,p) for C,H; 6-311+G(d,p) for N; aug-cc-pVTZ-PP for I in hexane (IEFPCM). D) Difference in total electron density between the excited state (corresponding to λ=312 nm) and ground state mapped with electrostatic potential (isovalue = 0.0001). E) UV-Vis spectra for titration of 1 equivalent I_2 with isoquinoline (0 equivalent to 26 equivalents) in hexane and of 1 equivalent I_2 + 1 equivalent TBHP with isoquinoline (0 equivalent to 26 equivalents in hexane.

recorded in hexane, the band near 522 nm completely disappeared and two new bands emerged with the maxima at 420 nm (blue-shifted band, BS) and at 325 nm (charge–transfer band, CT) (Figure 2A). In figure 2B, CT band merged with the broad absorption band of isoquinoline **1a** at 325 nm. To solve this problem, UV-Vis spectrum of the mixture of 40 equivalents **1a** and 1 equivalent iodine was recorded in hexane with 40 equivalents solution of **1a** in hexane as blank. Due to this, the absorption band of **1a** was completely cancelled out and the new CT band clearly emerged with maxima at 325 nm. This experimental result supported the formation of XB interaction between **1a** and iodine and is corroborated with the literature reports (Figure 2B).[19]

The Density Functional Theory calculations gave evidence of the formation of halogen bond between isoquinoline and iodine. The distance between the nitrogen atom and the iodine atom of XB complex **1a** and I_2 is 2.62 Å which is lesser than the sum of Van der Waals radii of N and I (3.53 Å) and higher than the sum of covalent radii of N and I (2.10 Å) (Figure 2C).[17a] The TD–DFT calculation was also performed to realize the nature of CT transition which is an important component of halogen bond.[17a,22f] The calculation predicted the presence of two absorption maxima at λ=417 nm with low oscillator strength ($f = 0.022$) and at λ=312 nm with high oscillator strength ($f = 0.061$). These two values corroborated with the experimentally observed BS band at λ=420 nm with low absorbance and CT band at λ=325 nm with high absorbance.[17a]

Further insight into the CT transition was obtained by visualizing the difference between the total electron density of the excited state (corresponding to λ=312 nm) and total electron density of the ground state.[17a,20] The blue region indicates a positive difference in electron density (i.e. the electron density in excited state is higher than the electron density in ground state). The red region indicates a negative difference in electron density (i.e. the electron density in excited state is lower than the electron density in ground state). It is clear from figure 2D that electron moves from **1a** (electron-donor) to iodine (electron-acceptor) in excited state correspond to CT transition.

Next, we tried to find how the oxidizing agent affects the XB interaction between **1a** and iodine. For this purpose, we compared the binding constant for the XB interaction between **1a** and iodine in the presence and absence of TBHP. The binding constants were calculated using UV-Vis titration of iodine with increasing concentration of **1a** in the presence and absence of TBHP. The data was fitted (1:1 model) using Bindfit.[17a,21]

The binding constant for the XB interaction between the iodine and **1a** was found to be K_1= 160.90 M^{-1} in presence of TBHP and K_2= 149.49 M^{-1} in absence of TBHP (Figure 2E). This experiment clearly showed that the oxidizing agent does not significantly affect the halogen–bonding interaction between iodine and **1a**. Thus we anticipated that, in our system, TBHP could not oxidize iodine to the more electrophilic hypoiodite (iodine(I)) or iodate (iodine(V)) which are capable of forming stronger XB bonds.[22] In fact, the oxidation of iodine in the presence of peroxides is associated with the undesired Bray–Liebhafsky oscillatory reaction which is responsible for the excess consumption of peroxides.[22b,23] We assume that the formation of a stable halogen–bonded complex between **1a** and iodine under solvent–free condition prevents the background Bray–Liebhafsky reaction and thus helps to reduce the amount of terminal oxidant required for the reaction.

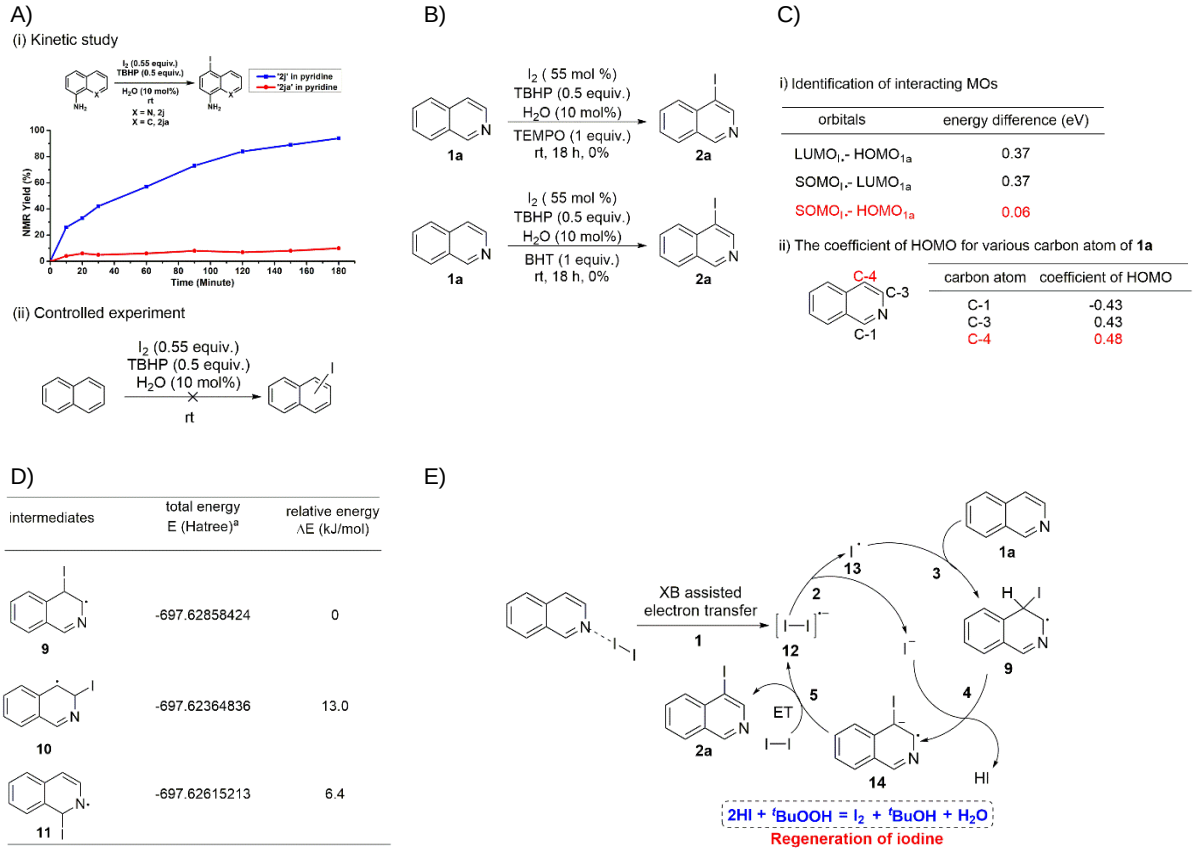


Figure 3. A) (i) Yield versus time profile of heteroarenes iodination reaction; y-axis: yield of **2j** and **2ja** in %, x-axis: time in min. yields were determined by ^{1}H NMR spectroscopy. (ii) The role of halogen bond in electron transfer for isoquinoline system. B) Mechanistic probe by controlled experiments. C). Identifying the regioselectivity with molecular orbital analysis with DFT using ωB97X-D functional and 6-311G(d,p) for C,H; 6-311+G(d,p) for N; aug-cc-pVTZ-PP for I in Vacuum. D). Thermodynamic stability of various radical intermediates with DFT using ωB97X-D functional and 6-311G(d,p) for C,H; 6-311+G(d,p) for N; aug-cc-pVTZ-PP for I in Vacuum.[17b] [a]Energy of both the isomers (R and S) were calculated.[17a] The most stable isomers were taken to obtain the energy differences. E) A plausible mechanistic pathway for iodination of isoquinoline.

To investigate the role of XB in the iodination process, a kinetic study of the reaction was performed (Figure 3A (i)). The rate of the iodination of 8-aminoquinoline **1j** was significantly faster than the rate of the iodination of 1-naphthylamine **1ja**. A significant difference in the rate of the reaction was observed when 8-aminoquinoline (blue line) and 1-naphthylamine (red line) were treated under optimized conditions (0.55 equiv. of iodine, 0.5 equiv. of TBHP, 10 mol% of H_2O and 5 equiv. pyridine). This kinetic study strongly indicated that the formation of halogen bond between **1a** and iodine is responsible for the success of this iodination process. Later, we compare the reactivity of naphthalene and isoquinoline under optimized conditions. In case of naphthalene, even trace amount of iodinated compound was not observed (Figure 3A (ii)). This result also indicated that the XB interaction between the substrate and iodine is crucial for the success of the reaction.

Finally, the presence of radical intermediates was checked for the reaction mixture. The radical trapping experiment was carried out with radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-Di-tert-butyl-4-methylphenol (BHT) and no product formation was observed (Figure 3B). This indicates that the reaction proceeds via radical pathway. The reason behind the regio–selectivity of this iodination process was rationalized by several quantum chemical calculations performed with DFT following reported literature.[20]

Firstly, we examined the energies of the frontier orbitals of **1a** and iodine radical (I•) in order to identify the interacting orbitals of **1a** and I• during the reaction. It was observed that the SOMO of I• interacts with the HOMO of **1a** as they are closer in energy than the other combinations (Figure 3C(i)). The Natural Population Analysis (NPA) of **1a** with DFT showed that the C–4 position has the largest contribution to HOMO (coefficient=0.48) among the three carbons in heterocyclic ring of **1a**.[17a] Thus, kinetically, the addition of I• to **1a** is favorable at C–4 position (Figure 3C(ii)). Next, the thermodynamic stability of three possible radical intermediates which can be formed by the addition of I• to **1a** was examined. It was observed that the total energy of the intermediate **10** and **11** is higher than the total energy of intermediate **9** (Figure 3D). Therefore, the formation of the intermediate **9** (corresponding to C–4 iodination product) is thermodynamically more stable than the formation of other two intermediates **10** and **11** (corresponding to C–3 and C–1 iodination products respectively). Hence, both the kinetically–controlled and thermodynamically–controlled pathways lead to the formation of intermediate **9** which further transformed to the product **2a**.

A plausible reaction pathway for the regioselective iodination of isoquinoline is depicted in Figure 3E. The reaction pathway is initiated by an XB assisted ET to iodine from isoquinoline (step 1). In step 2, **12** dissociates into anion I^- and iodine radical (I•). In step 3, addition of iodine radical to isoquinoline takes place to generate the 4-iodo-3,4-dihydroisoquinoline radical **9**. In step 4, **9** is deprotonated by I^- to provide the radical anion intermediate **14**. Finally, in step 5, the electron transfer from radical anion species **14** to iodine occurs to generate the intermediate **12** along with 4-iodoisoquinoline. The TBHP oxidizes HI and regenerates molecular iodine.[24]

CONCLUSION

In conclusion, for the first time, the halogen–bond has been employed as an efficient tool to enable an electron–catalyzed regioselective iodination of hetero aryls under mild reaction conditions. The halogen bond between hetero–aryl substrates (electron–donor) and iodine (electron–acceptor) lowers the activation energy of the electron–transfer (ET) from the former to the latter. The mechanistic experiments and the quantum chemical calculations demonstrate the formation of halogen bond and the presence of radical intermediates in reaction mixture. The formation of halogen bond is not only helping in a ET under mild condition, it also stops the unwanted Bray–Liebhafsky reaction and thus helps to reduce the amount of terminal oxidant required for the reaction. The quantum chemical study shows that both the kinetically-controlled and thermodynamically–controlled pathways lead to a single regioisomer. This work shows that halogen–bond assisted electron–transfer can be an efficient tool to generate the reactive radical intermediates under mild reaction conditions. This result encourages the new possibilities of exploiting the halogen bond–assisted ET in designing a wide variety of new electron–catalyzed radical–molecule reactions under transition metal–free conditions.

The advantages of the XB–assisted electron–catalyzed iodination of quinolines and other heteroarenes can be summarized as follows: (1) The method is highly atom economic and green. Only 0.55 equiv. of iodine and 0.50 equiv. TBHP is sufficient to drive the reaction to completion. (2) It precludes the use of transition metal catalysts which are expensive, toxic and have a strict limit of level in pharmaceutical products.[25] (3) The reaction proceeds smoothly at room temperature under solvent free condition. The solvent free reactions reduce the amount of waste generated from reactions and were designated as one of the top priority in green chemistry research areas by ACS Green Chemistry Pharmaceutical Roundtable.[26]

EXPERIMENTAL SECTION

All reactions were carried out in oven dried reaction tubes. TBHP in decane, di-tert-butyl peroxide, palladium acetate and DABCO were purchased from Sigma-Aldrich chemical company. Iodomethane, ethylbromide, 1-iodopropane, 1-bromopentane, 1-bromooctane, benzyl bromide and iodobenzene were purchased from Avra Synthesis Pvt. Ltd. Various isoquinolines, quinolines and azaindoles were purchased from Alfa Aesar, Sigma-Aldrich, TCI, Avra synthesis, Spectrochem Pvt. Ltd. and used directly as received. Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching using appropriate mixture of ethyl acetate and hexanes as eluting solvent mixtures. Silica gel for column chromatography (particle size 100-200 mesh) was purchased from Avra Synthesis Pvt. Ltd. and used for column chromatography using hexanes and ethyl acetate mixture as eluent. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a Bruker 400 0r 500 MHz instrument. ^{1}H NMR is reported relative to residual CDCl3 (δ 7.26 ppm) or DMSO-d6 (δ 2.50 ppm). $^{13}C\{^{1}H\}$ NMR is reported relative to residual CDCl3 (δ 77.16 ppm) or DMSO-d6 (δ 39.52 ppm). Chemical shifts were recorded in parts per million (ppm) and multiplicities are as indicated: s (singlet,) d (doublet,) t (triplet,) q (quartet,) quint (quintet), sext (sextet), dd (doublet of doublet,) m (multiplet,) tt (triplet of triplet,) td (triplet of doublet). Coupling constant, J, are reported in Hertz. Melting points were recorded on a Guna capillary melting point apparatus and are corrected with benzoic acid as reference. FTIR spectra were recorded on a JASCO spectrometer and are reported in frequency of absorption (cm-1) using dry KBr pellet. The UV–Vis spectra was recorded in JASCO V-650 UV-VIS Spectrophotometer. High resolution mass spectra (HRMS) were recorded on Q-Tof Micro mass spectrometer.

Experimental procedure for synthesis of 4-iodoisoquinoline (2a) from isoquinoline (1a):

Isoquinoline (129 mg, 1 mmol), molecular iodine (140 mg, 0.55 mmol) and 0.5 mmol TBHP (6M in decane) were taken in an oven dried reaction tube. H_2O (2 μL, 0.1 mmol) was added into the reaction tube and the reaction was stirred at room temperature. After completion of the reaction, it was quenched with aqueous saturated $Na_2S_2O_3$ solution (10 mL). The reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with water (2 X 10 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure to produce crude product which was purified by silica gel column chromatography (hexanes / ethyl acetate) to give 4-iodoisoquinoline **2a** (240 mg, 94% yield).

Experimental procedure for synthesis of 5-iodoquinolin-8-amine (2j) from 8-aminoquinoline (1j):

In an oven-dried reaction tube, 8-aminoquinoline (122 mg, 0.5 mmol), molecular iodine (70 mg, 0.275 mmol) and 0.25 mmol TBHP (6 M in decane) were taken. Pyridine (121 μL, 1.5 mmol.) and H_2O (2 μL, 0.1 mmol) were added into the reaction tube and the reaction was stirred at room temperature. After completion of the reaction, the reaction was quenched with aqueous saturated $Na_2S_2O_3$ solution (10 mL). The reaction mixture was extracted with ethyl acetate (15 mL) and water (2 X 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The reaction mixture was purified by silica gel column chromatography (hexanes/ ethyl acetate) to give 5-iodoquinolin-8-amine **2j** (124 mg, 92% yield).

Experimental procedure for synthesis of 3-iodo-7-azaindole (4) from 7-azaindole (3):

7-Azaindole (59 mg, 0.5 mmol), molecular iodine (70 mg, 0.275 mmol) and 0.25 mmol TBHP (6M in decane) were taken in an oven dried reaction tube. Pyridine (121 μL, 1.5 mmol) and H_2O (2 μL, 0.1 mmol) were added into the reaction tube and the reaction was stirred at room temperature. After completion of the reaction, the reaction mixture was quenched with aqueous saturated $Na_2S_2O_3$ solution (10 mL). The reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with water (2 X 10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to produce crude product which was purified by silica gel column chromatography (hexanes / ethyl acetate) to give 3-iodo-7-azaindole **4a** (111 mg, 91% yield).

4-Iodoisoquinoline (2a): 120 mg, 94% yield; light yellow solid; mp 88–90 °C [93-94 °C, lit];[27] R_f= 0.36 (10% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (t, *J*=8.0 Hz, 1H), 7.75–7.83 (m, 1H), 7.89 (d, *J*=7.6 Hz, 1H), 7.99 (d, *J*=8.4 Hz, 1H), 8.93 (s, 1H), 9.13 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 97.0, 128.3, 128.5, 129.8, 130.8, 132.1, 137.2, 151.1, 152.7; FTIR (KBr): 754, 950, 1373, 2928 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for C_9H_7NI: 255.9623; found: 255.9595.

3-Iodoquinoline (2b): 115 mg, 90% yield; light yellow solid; mp 60–62 °C [60-62 °C, lit];[27] R_f= 0.34 (5% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.59 (m, 1H), 7.68–7.76 (m, 2H), 8.06 (d, *J*=8.4 Hz, 1H), 8.51–8.55 (m, 1H), 9.03 (d, *J*=2.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 89.9, 126.9, 127.5, 129.6, 130.0, 130.2, 143.9, 146.4, 155.7; FTIR

(KBr): 749, 938, 1573, 3056 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for C_9H_7NI: 255.9623; found: 255.9633.

3-Iodo-6-methylquinoline (2c): 100 mg, 74% yield; light yellow solid; mp 106–108 ºC [112-113 ºC, lit];[15a] R_f= 0.18 (5% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 2.53 (s, 3H), 7.44 (s, 1H), 7.55 (dd, J_1=2.0 Hz, J_2=8.8 Hz, 1H), 7.94 (d, J=8.8 Hz, 1H), 8.42 (d, J=1.6 Hz, 1H), 8.94–8.96 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 21.8, 89.9, 125.7, 129.2, 130.1, 132.5, 137.6, 143.2, 145.0, 154.8; FTIR (KBr): 814, 1021, 1570, 2925 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_{10}H_9NI$: 269.9780; found: 269.9775.

3-Iodo-6-methoxyquinoline (2d): 93 mg, 65% yield; light yellow solid; mp 108–110 ºC [116-117 ºC, lit];[15a] R_f= 0.25 (5% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 6.92–6.96 (m, 1H), 7.34–7.40 (m, 1H), 7.97 (d, J=9.2 Hz, 1H), 8.41–8.46 (m, 1H), 8.85–8.90 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 55.7, 90.7, 104.2, 123.0, 131.0, 131.2, 142.5, 142.7, 153.1, 158.4; FTIR (KBr): 822, 1024, 1219, 1489, 2922 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_{10}H_9NOI$: 285.9729; found: 285.9745.

6-Butyl-3-iodoquinoline (2e): 110 mg, 71% yield; pale yellow liquid; R_f= 0.21 (5% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J=7.2 Hz, 3H), 1.32–1.43 (m, 2H), 1.67 (quint, J=7.2 Hz, 2H), 2.78 (t, J=7.6 Hz, 2H), 7.44 (s, 1H), 7.56 (dd, J_1=1.2 Hz, J_2=8.8 Hz, 1H), 7.95 (d, J=8.4 Hz, 1H), 8.42–8.46 (m, 1H), 8.95 (d, J=1.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 14.1, 22.4, 33.4, 35.7, 89.9, 125.1, 129.3, 130.1, 131.8, 142.5, 143.3, 145.2, 154.8; FTIR (KBr): 805, 1067, 1493, 2956 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_{13}H_{15}NI$: 312.0249; found: 312.0231.

6-Chloro-3-iodoquinoline (2f): 87 mg, 60% yield; light yellow solid; mp 120–122 ºC [118-119 ºC, lit];[15a] R_f= 0.24 (2% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62–7.69 (m, 2H), 7.98 (d, J=8.8 Hz, 1H), 8.43 (s, 1H), 8.98–9.02 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 91.2, 125.5, 130.4, 131.1, 131.2, 133.4, 142.8, 144.8, 156.0; FTIR (KBr): 827, 900, 1074, 1570 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for C_9H_6NClI: 289.9234; found: 289.9226.

3-Iodo-8-methoxyquinoline (2g): 77 mg, 54% yield; light yellow solid; mp 110–112 ºC [116-117 ºC, lit][15a]; R_f= 0.18 (15% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 3H), 6.99 (d, J=7.6 Hz, 1H), 7.19 (d, J=8.4 Hz, 1H), 7.40 (t, J=8.0 Hz, 1H), 8.43 (d, J=1.6 Hz, 1H), 8.95 (d, J=2.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 56.2, 91.1, 108.2, 118.6,

128.0, 131.1, 138.4, 143.6, 154.4, 155.7; FTIR (KBr): 758, 1118, 1261, 1559, 2960 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_{10}H_9NOI$: 285.9729; found: 285.9728.

8-Ethoxy-3-iodoquinoline (2h): 69 mg, 46% yield; light yellow solid; mp 120–122 ºC; R_f= 0.33 (15% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 1.58–1.64 (m, 3H), 4.28–4.34 (m, 2H), 7.06 (d, *J*=6.4 Hz, 1H), 7.23–7.28 (m, 1H), 7.43–7.47 (m, 1H), 8.48–8.50 (m, 1H), 9.04–9.06 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 14.8, 64.5, 90.9, 109.2, 118.4, 128.0, 131.3, 138.6, 143.7, 154.5, 155.0; FTIR (KBr): 754, 1115, 1557, 2980 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_{11}H_{11}NOI$: 299.9885; found: 299.9856.

3-Iodo-8-nitroquinoline (2i): 72 mg, 48% yield; light yellow solid; mp 116–118 ºC [121-122 ºC, lit][28]; R_f= 0.34 (15% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (t, *J*=7.6 Hz, 1H), 7.93 (d, *J*=8.0 Hz, 1H), 8.06 (d, *J*=7.2 Hz, 1H), 8.63–8.67 (m, 1H), 9.15–9.20 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 92.2, 124.4, 126.5, 130.5, 131.1, 137.8, 143.9, 158.1; FTIR (KBr): 767, 1086, 1342, 1527, 1628, 3034; HRMS (m/z): $[M+H]^+$ calculated for $C_9H_6N_2O_2I$: 300.9474; found: 300.9478.

5-Iodoquinolin-8-amine (2j): 124 mg, 92% yield; yellow solid; mp 126–128 ºC [123-124 ºC, lit];[29] R_f= 0.36 (5% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 5.08 (s, 2H), 6.72 (d, *J*=8.0 Hz, 1H), 7.42–7.47 (m, 1H), 7.82 (d, *J*=8.0 Hz, 1H), 8.24–8.29 (m, 1H), 8.69–8.73 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 81.1, 111.4, 123.1, 130.2, 138.1, 139.2, 140.2, 145.1, 148.0; FTIR (KBr): 778, 820, 1498, 3313 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_9H_8N_2I$: 270.9732; found: 270.9708.

5-Iodo-N-methylquinolin-8-amine (2k): 111 mg, 78% yield; yellow solid; mp 82–84 ºC; R_f= 0.43 (2% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 3.01 (d, *J*=5.2 Hz, 3H), 6.26 (s, 1H), 6.42 (d, *J*=8.0 Hz, 1H), 7.41–7.46 (m, 1H), 7.88 (d, *J*=8.4 Hz, 1H), 8.26 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H), 8.65 (dd, J_1=1.2 Hz, J_2=4.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 30.0, 78.6, 105.9, 123.0, 129.8, 138.6, 139.1, 140.2, 146.8, 147.3; FTIR (KBr): 778, 1356, 1518, 1573, 2987, 3400 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_{10}H_{10}N_2I$: 284.9888; found: 284.9881.

N-Ethyl-5-iodoquinolin-8-amine (2l): 122 mg, 82% yield; yellow liquid; R_f= 0.41 (2% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, *J*=7.2 Hz, 3H), 3.27–3.37 (m, 2H), 6.18 (s, 1H), 6.43 (d, *J*=8.0 Hz, 1H), 7.40–7.46 (m, 1H), 7.85 (d, *J*=8.0 Hz, 1H), 8.25 (d, *J*=8.4 Hz, 1H), 8.62–8.68 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 14.6, 37.9, 78.4, 106.3, 122.9,

129.9, 138.6, 139.1, 140.2, 145.8, 147.2; FTIR (KBr): 797, 1148, 1377, 1579, 2969, 3315 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_{11}H_{12}N_2I$: 299.0045; found: 299.0023.

5-Iodo-N-propylquinolin-8-amine (2m): 130 mg, 83% yield; yellow liquid; R_f= 0.38 (2% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, *J*=7.2 Hz, 3H), 1.79 (sext, *J*=7.6 Hz, 2H), 3.20–3.29 (m, 2H), 6.28 (s, 1H), 6.43 (d, *J*=8.0 Hz, 1H), 7.39–7.45 (m, 1H), 7.85 (d, *J*=8.4 Hz, 1H), 8.24 (d, *J*=8.4 Hz, 1H), 8.62–8.67 (m, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 11.9, 22.5, 45.2, 78.2, 106.3, 122.9, 129.9, 138.6, 139.1, 140.2, 145.9, 147.2; FTIR (KBr): 736, 1146, 1374, 1577, 2961 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_{12}H_{14}N_2I$: 313.0202; found: 313.0201.

5-Iodoquinolin-6-amine (2n): 115 mg, 83% yield; yellow solid; mp 122–124 °C; R*f*= 0.15 (25% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 4.60 (s, 2H), 7.20 (d, *J*=8.8 Hz, 1H), 7.31–7.37 (m, 1H), 7.86 (d, *J*=8.8 Hz, 1H), 8.20 (d, *J*=8.4 Hz, 1H), 8.58–8.63 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 81.0, 120.2, 122.9, 130.9, 131.4, 137.9, 143.9, 146.1, 147.1; FTIR (KBr): 755, 922, 1550, 3186, 3306 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_9H_8N_2I$: 270.9732; found: 270.9744.

N-Ethyl-5-iodoquinolin-6-amine (2o): 125 mg, 84% yield; yellow solid; mp 102–104 °C; R_f= 0.38 (25% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, *J*=6.8 Hz, 3H), 3.33–3.41 (m, 2H), 4.67 (s, 1H), 7.20 (d, *J*=9.2 Hz, 1H), 7.30–7.35 (m, 1H), 7.95 (d, *J*=8.8 Hz, 1H), 8.17–8.22 (m, 1H), 8.57 (dd, J_1=1.2 Hz, J_2=4.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 15.2, 39.2, 82.1, 116.5, 122.9, 131.1, 131.6, 138.0, 143.5, 146.6, 146.7; FTIR (KBr): 797, 933, 1151, 1608, 2967 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_{11}H_{12}N_2I$: 299.0045; found: 299.0059.

5-Iodo-N-propylquinolin-6-amine (2p): 128 mg, 82% yield; yellow liquid; R_f= 0.09 (5% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, *J*=7.2 Hz, 3H), 1.74 (sext, *J*=7.2 Hz, 2H), 3.25–3.33 (m, 2H), 4.76 (s, 1H), 7.20 (d, *J*=9.2 Hz, 1H), 7.29–7.35 (m, 1H), 7.95 (d, *J*=9.2 Hz, 1H), 8.19 (d, *J*=8.8 Hz, 1H), 8.54–8.60 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 11.7, 22.9, 46.3, 82.1, 116.6, 122.9, 131.0, 131.6, 138.0, 143.5, 146.5, 146.6; FTIR (KBr): 799, 1140, 1346, 1609, 2960 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_{12}H_{14}N_2I$: 313.0201; found: 313.0215.

8-Iodoisoquinolin-5-amine (2q): 125 mg, 84% yield; yellow solid; mp 138–140 °C; R_f= 0.38 (20% ethyl acetate in hexanes); ^1H NMR (400 MHz, DMSO-d6) δ 6.23 (s, 2H), 6.70 (d, *J*=8.4

Hz, 1H), 7.83 (d, *J*=8.0 Hz, 1H), 7.90 (d, *J*=6.0 Hz, 1H), 8.46 (d, *J*=5.6 Hz, 1H), 9.10 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-D6) δ 78.0, 112.5, 115.4, 126.9, 128.2, 139.2, 141.9, 145.4, 155.4; FTIR (KBr): 779, 817, 1460, 1500, 3303 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_9H_8N_2I$: 270.9732; found: 270.9715.

3-Iodo-7-azaindole (4a): 111 mg, 91% yield; light pink solid; mp 194–196 °C [201-204 °C, lit];[30] R_f= 0.09 (5% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, DMSO-d6) δ 7.15 (dd, J_1=4.8 Hz, J_2=8.0 Hz, 1H), 7.65–7.71 (m, 2H), 8.23–8.26 (m, 1H), 12.09 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-D6) δ 54.5, 116.6, 122.1, 128.2, 130.6, 143.9, 148.1; FTIR (KBr): 757, 960, 1406, 1579, 3401 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_7H_6N_2I$: 244.9576; found: 244.9586.

3-Iodo-1-methyl-7-azaindole (4b): 111 mg, 86% yield; white solid; mp 126–128 °C [117-119 °C, lit];[31] R_f= 0.44 (20% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 7.13 (dd, J_1=4.4 Hz, J_2=8.0 Hz, 1H), 7.28 (s, 1H), 7.70 (dd, J_1=1.2 Hz, J_2=8.0 Hz, 1H), 8.32–8.36 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 31.6, 52.9, 116.5, 123.2, 129.3, 133.1, 144.1, 147.6; FTIR (KBr): 754, 929, 1569 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_8H_8N_2I$: 258.9732; found: 258.9726.

3-Iodo-1-ethyl-7-azaindole (4c): 112 mg, 82% yield; light yellow solid; mp 63–65 °C; R_f= 0.29 (5% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (t, *J*=7.2 Hz, 3H), 4.35 (q, *J*=7.2 Hz, 2H), 7.10–7.15 (m, 1H), 7.33 (s, 1H), 7.70 (dd, J_1=1.6 Hz, J_2=8.0 Hz, 1H), 8.33 (dd, J_1=1.6 Hz, J_2=4.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 15.9, 39.8, 53.0, 116.6, 123.3, 129.3, 131.5, 143.9, 144.0, 147.0; FTIR (KBr): 766, 927, 1309, 1564, 2977 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_9H_{10}N_2I$: 272.9889; found: 272.9861.

3-Iodo-1-propyl-7-azaindole (4d): 116 mg, 81% yield; pale yellow liquid; R_f= 0.18 (2% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, *J*=7.2 Hz, 3H), 1.89 (sext, *J*=7.6 Hz, 2H), 4.26 (t, *J*=7.2 Hz, 2H), 7.10–7.14 (m, 1H), 7.32 (s, 1H), 7.70 (dd, J_1=1.6 Hz, J_2=8.0 Hz, 1H), 8.32 (dd, J_1=1.2 Hz, J_2=4.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 11.5, 23.9, 46.7, 52.9, 116.6, 123.2, 129.3, 132.2, 143.9, 147.3; FTIR (KBr): 774, 935, 1348, 1596, 2964 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_{10}H_{12}N_2I$: 287.0045; found: 287.0063.

3-Iodo-1-pentyl-7-azaindole (4e): 127 mg, 81% yield; light pink liquid; R_f= 0.27 (2% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.8 Hz, 3H), 1.27–1.39 (m, 4H), 1.81–1.90 (m, 2H), 4.28 (t, *J*=7.6 Hz, 2H), 7.09–7.14 (m, 1H), 7.31 (s, 1H), 7.70 (dd, J_1=1.6

Hz, J_2=8.0 Hz, 1H), 8.33 (dd, J_1=1.2 Hz, J_2=4.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 14.0, 22.4, 29.1, 30.3, 45.0, 52.9, 116.5, 123.2, 129.2, 132.1, 143.9, 147.3; FTIR (KBr): 766, 936, 1309, 1563, 2957 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_{12}H_{16}N_2I$: 315.0358; found: 315.0341.

3-Iodo-1-octyl-7-azaindole (4f): 143 mg, 80% yield; light pink liquid; R_f= 0.32 (2% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J*=6.8 Hz, 3H), 1.21–1.35 (m, 10H), 1.85 (quint, *J*=7.6 Hz, 2H), 4.28 (t, *J*=7.2 Hz, 2H), 7.09–7.14 (m, 1H), 7.31 (s, 1H), 7.70 (dd, J_1=1.6 Hz, J_2=8.0 Hz, 1H), 8.32 (dd, J_1=1.6 Hz, J_2=4.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 14.2, 22.7, 26.9, 29.2, 29.3, 30.6, 31.9, 45.0, 52.9, 116.5, 123.2, 129.2, 132.1, 143.9, 147.3; FTIR (KBr): 764, 935, 1309, 1598, 2926 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_{15}H_{22}N_2I$: 357.0828; found: 357.0817.

3-Iodo-1-benzyl-7-azaindole (4g): 122 mg, 73% yield; white solid; mp 96–98 ºC; R_f= 0.38 (5% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 5.48 (s, 2H), 7.12–7.18 (m, 1H), 7.20–7.35 (m, 6H), 7.72 (d, *J*=7.6 Hz, 1H), 8.33–8.38 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 48.2, 54.1, 116.9, 123.2, 127.9, 128.0, 129.0, 129.4, 131.9, 137.2, 144.3, 147.5; FTIR (KBr): 762, 931, 1308, 1566, 2926, 3038 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_{14}H_{12}N_2I$: 335.0045; found: 335.0034.

3-Iodo-1-phenyl-7-azaindole (4h): 120 mg, 75% yield; yellow liquid; R_f= 0.18 (2% ethyl acetate in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (dd, J_1=4.5 Hz, J_2=7.5 Hz, 1H), 7.36 (t, *J*=7.5 Hz, 1H), 7.52 (t, *J*=7.5 Hz, 2H), 7.62 (s, 1H), 7.71 (d, *J*=8.0 Hz, 2H), 7.79 (d, *J*=8.0 Hz, 1H), 8.39 (d, *J*=4.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 56.6, 117.7, 120.0, 124.2, 127.0, 129.6, 129.7, 132.0, 137.8, 138.3, 144.9, 147.2; FTIR (KBr): 762, 979, 1315, 1506, 1595, 3047 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_{13}H_{10}N_2I$: 320.9889; found: 320.9892.

4-chloro-3-Iodo-7-azaindole (4i): 120 mg, 86% yield; white solid; mp 195 ºC (decomposed); R_f= 0.33 (20% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J*=5.2 Hz, 1H), 7.80 (s, 1H), 8.18 (d, *J*=4.8 Hz, 1H), 12.40 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 49.7, 116.4, 117.0, 133.1, 134.9, 143.8, 148.5; FTIR (KBr): 824, 1298, 1392, 1498, 1596, 3010 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_7H_5ClN_2I$: 278.9186; found: 278.9193.

5-bromo-3-Iodo-7-azaindole (4j): 131 mg, 81% yield; white solid; mp 210 ºC (decomposed); R_f= 0.38 (20% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.86 (d, *J*=2.0 Hz, 1H), 8.31 (d, *J*=2.0 Hz, 1H), 12.35 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 53.6,

111.6, 123.8, 129.9, 132.5, 143.9, 146.5; FTIR (KBr): 772, 891, 1275, 1394, 1628, 3114, 3478 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_7H_5BrN_2I$: 322.8681; found: 322.8683.

4-Iodonaphthalen-1-amine (2ja): 10% yield after 3 h (yield was determined by ^{1}HNMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard), White solid; R_f= 0.21 (2% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (br s, 2H), 7.05 (d, *J*=8.8 Hz, 1H), 7.43–7.51 (m, 2H), 7.67 (d, *J*=8.8 Hz, 1H), 7.73–7.83 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 79.2, 120.1, 121.3, 123.0, 125.9, 126.5, 128.7, 134.1, 135.5, 142.7; FTIR (KBr): 789, 1398, 1622, 3048, 3318 cm^{-1}. HRMS (m/z): $[M+H]^+$ calculated for $C_{10}H_9NI$: 269.9780; found: 269.9761.

Synthetic transformation of 4-iodoisoquinoline (2a) to 4-styrylisoquinoline (6)[18a]

In an oven dried reaction tube equipped with magnetic pellet, 4-iodoisoquinoline (128 mg, 0.5 mmol), styrene (86 μL, 0.75 mmol), Et_3N (1 mmol) and $Pd(OAc)_2$ (5 mol%) were taken. 2 mL of acetonitrile was added into the reaction tube and the reaction mixture was stirred at 90 °C under closed atmosphere. After complete consumption of the starting material, the reaction was stopped, and cooled to room temperature. Then the reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with water and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure to produce crude product which was purified by silica gel column chromatography (hexanes / ethyl acetate).

(*Z*/*E*)-4-Styrylisoquinoline (6): 85 mg (6.7:1), 73% yield; yellow liquid; R_f= 0.19 (10% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J*=8.2 Hz, 1H), 7.30–7.36 (m, 1H), 7.39–7.45 (m, 2H), 7.59–7.64 (m, 3H), 7.67–7.72 (m, 1H), 7.72–7.78 (m, 1H), 7.99 (d, *J*=8.4 Hz, 1H), 8.14–8.18 (m, 1H), 8.75–8.77 (m, 1H), 9.17 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 120.6, 122.5, 123.0, 126.9, 127.3, 128.2, 128.3, 128.8, 128.9, 130.6, 133.4, 133.9, 137.2, 140.5, 151.9 ("*Z*"-isomer value given); FTIR (KBr): 759, 1390, 1501, 1620, 3029 cm^{-1}; HRMS (m/z): $[M+Na]^+$ calculated for $C_{17}H_{13}NNa$: 254.0945; found: 254.0963.

Synthetic transformation of 4-iodoisoquinoline (2a) to 4-phenylisoquinoline (8)[18b]

4-Iodoisoquinoline (128 mg, 0.5 mmol), phenylboronic acid (85 mg, 0.7 mmol), $Pd(OAc)_2$ (5 mol%), DABCO (6 mol%) and K_2CO_3 (3 equiv.) were taken in an oven dried pressure tube equipped with magnetic pellet. 2 mL of acetone was added into the reaction tube and the reaction mixture was stirred at 110 °C under closed atmosphere. After complete consumption of the starting material, the reaction was stopped, and cooled to room temperature and acetone

was evaporated by rotary evaporator under reduced pressure. Then, water (10 mL) was added into the reaction mixture. The product was extracted into ethyl acetate and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure to produce crude product which was purified by silica gel column chromatography (hexanes/ethyl acetate).

4-Phenylisoquinoline (8): 97 mg, 95% yield; pale yellow liquid; R_f= 0.15 (5% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.54 (m, 5H), 7.59–7.70 (m, 2H), 7.92 (d, *J*=8.0 Hz, 1H), 8.04 (d, *J*=4.0 Hz, 1H), 8.49 (s, 1H), 9.26 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 124.9, 127.3, 128.0, 128.1, 128.6, 128.7, 130.2, 130.7, 133.4, 134.3, 137.1, 142.9, 152.1; FTIR (KBr): 759, 1390, 1501, 1620, 3029 cm^{-1}; HRMS (m/z): $[M+H]^+$ calculated for $C_{15}H_{12}N$: 206.0969; found: 206.0963.

Experimental procedure for synthesis of *N*-methylquinolin-8-amine from 8-aminoquinoline[32]

To a solution of 8-aminoquinoline (1 mmol) in DMF (5 mL) was added 1 mmol of K_2CO_3. After stirring at room temperature for 30 minutes, 1.2 mmol of iodomethane was added drop wise. The resulting mixture was stirred at room temperature for 24 hours. After completion of the reaction, the reaction mixture was quenched with aqueous saturated $Na_2S_2O_3$ and extracted with ethyl acetate (two times). The combined organic layer was washed with water and dried with anhydrous Na_2SO_4. The organic layer was then concentrated under vacuum and purified by silica gel column chromatography (hexanes / ethyl acetate).

***N*-methylquinolin-8-amine (1j):** 98 mg, 62% yield; yellow liquid; R_f= 0.44 (5% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.05 (s, 3H), 6.14 (s, 1H), 6.65 (d, *J*=7.5 Hz, 1H), 7.05 (d, *J*=8.0 Hz, 1H), 7.34–7.38 (m, 1H), 7.41 (t, *J*=8.0 Hz, 1H), 8.06 (dd, J_1=1.5 Hz, J_2=4.0 Hz, 1H), 8.71 (dd, J_1=1.5 Hz, J_2=4.0 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 30.2, 104.3, 113.8, 121.5, 128.0, 128.7, 136.1, 138.4, 146.0, 146.9.

Experimental procedure for synthesis of *N*-ethylquinolin-8-amine from 8-aminoquinoline[33]

To a solution of 8-aminoquinoline (1 mmol) in DMF (5 mL) was added 1 mmol of K_2CO_3. After stirring at room temperature for 30 minutes, 1.5 mmol of ethyl bromide was added drop wise. The resulting mixture was stirred at room temperature for 36 hours. After completion of the reaction, the reaction mixture was quenched with aqueous saturated $Na_2S_2O_3$ and extracted

with ethyl acetate (two times). The combined organic layer was washed with water and dried with anhydrous Na_2SO_4. The organic layer was then concentrated under vacuum and purified by silica gel column chromatography (hexanes / ethyl acetate).

***N*-ethylquinolin-8-amine (1k):** 88 mg, 51% yield; yellow liquid; R_f= 0.31 (1% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, *J*=7.2 Hz, 3H), 3.36 (q, *J*=6.8 Hz, 2H), 6.05 (s, 1H), 6.67 (d, *J*=7.6 Hz, 1H), 7.04 (d, *J*=8.4 Hz, 1H), 7.32–7.43 (m, 2H), 8.02–8.08 (m, 1H), 8.69–8.74 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.8, 38.1, 104.7, 113.7, 121.4, 127.9, 128.8, 136.1, 138.3, 145.1, 146.9.

Experimental procedure for synthesis of *N*-propylquinolin-8-amine from 8-aminoquinoline

To a solution of 8-aminoquinoline (1 mmol) in DMF (5 mL) was added 1 mmol of K_2CO_3. After stirring at room temperature for 30 minutes, 1.2 mmol of 1-iodopropane was added drop wise. The resulting mixture was stirred at room temperature for 36 hours. After completion of the reaction, the reaction mixture was quenched with aqueous saturated $Na_2S_2O_3$ and extracted with ethyl acetate (two times). The combined organic layer was washed with water and dried with anhydrous Na_2SO_4. The organic layer was then concentrated under vacuum and purified by silica gel column chromatography (hexanes / ethyl acetate).

***N*-propylquinolin-8-amine (1l):** 123 mg, 66% yield; yellow liquid; R_f= 0.38 (1% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, *J*=7.2 Hz, 3H), 1.76–1.86 (m, 2H), 3.29 (d, *J*=7.2 Hz, 1H), 6.14 (s, 1H), 6.67 (d, *J*=7.6 Hz, 1H), 7.01–7.05 (m, 1H), 7.34–7.37 (m, 1H), 7.37–7.41 (m, 1H), 8.05 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H), 8.71 (dd, J_1=1.6 Hz, J_2=4.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.9, 22.6, 45.4, 104.6, 113.6, 121.4, 128.0, 128.8, 136.1, 138.3, 145.1, 146.8. HRMS (m/z): $[M+H]^+$ calculated for $C_{12}H_{15}N_2$: 187.1235; found: 187.1245.

Experimental procedure for synthesis of *N*-ethylquinolin-6-amine from 6-aminoquinoline[34]

To a solution of 8-aminoquinoline (1 mmol) in DMF (5 mL) was added 1 mmol of K_2CO_3. After stirring at room temperature for 30 minutes, 1.5 mmol of ethyl bromide was added drop wise. The resulting mixture was stirred at room temperature for 48 hours. After completion of the reaction, the reaction mixture was quenched with aqueous saturated $Na_2S_2O_3$ and extracted

with ethyl acetate (two times). The combined organic layer was washed with water and dried with anhydrous Na_2SO_4. The organic layer was then concentrated under vacuum and purified by silica gel column chromatography (hexanes / ethyl acetate).

***N*-ethylquinolin-6-amine (1n):** 71 mg, 41% yield; brown liquid; R_f= 0.27 (30% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (t, *J*=7.0 Hz, 3H), 3.27 (q, *J*=7.5 Hz, 2H), 6.69 (d, *J*=2.5 Hz, 1H), 7.08 (dd, J_1=3.0 Hz, J_2=9.0 Hz, 1H), 7.24–7.28 (m, 1H), 7.87 (d, *J*=9.0 Hz, 1H), 7.90–7.94 (m, 1H), 8.60 (dd, J_1=1.5 Hz, J_2=4.5 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 14.8, 38.6, 102.9, 121.5, 121.6, 130.2, 130.4, 133.9, 143.2, 146.1, 146.4.

Experimental procedure for synthesis of *N*-propylquinolin-6-amine from 6-aminoquinoline

To a solution of 8-aminoquinoline (1 mmol) in DMF (5 mL) was added 1 mmol of K_2CO_3. After stirring at room temperature for 30 minutes, 1.2 mmol of 1-iodopropane was added drop wise. The resulting mixture was stirred at room temperature for 48 hours. After completion of the reaction, the reaction mixture was quenched with aqueous saturated $Na_2S_2O_3$ and extracted with ethyl acetate (two times). The combined organic layer was washed with water and dried with anhydrous Na_2SO_4. The organic layer was then concentrated under vacuum and purified by silica gel column chromatography (hexanes / ethyl acetate).

***N*-propylquinolin-6-amine (1o):** 106 mg, 57% yield; liquid brown; R_f= 0.21 (30% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, *J*=7.2 Hz, 3H), 1.65–1.76 (m, 2H), 3.17 (t, *J*=7.2 Hz, 2H), 3.50–3.90 (m, 1H), 6.67 (d, *J*=2.4 Hz, 1H), 7.07 (dd, J_1=2.8 Hz, J_2=9.2 Hz, 1H), 7.22–7.27 (m, 1H), 7.86 (d, *J*=9.2 Hz, 1H), 7.91 (d, *J*=8.4 Hz, 1H), 8.57–8.61 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.8, 22.6, 45.8, 102.8, 121.5, 121.6, 130.1, 130.4, 134.0, 143.1, 145.9, 146.5. HRMS (m/z): $[M+H]^+$ calculated for $C_{12}H_{15}N_2$: 187.1235; found: 187.1232.

Experimental procedure for synthesis of *N*-methyl-7-azaindole from 7-azaindole[35]

In a round bottom flask 7-azaindole (1 mmol) and DMF (10 mL) were taken. Then the reaction mixture was cooled down to 0 ^{o}C and 2 mmol of 60% NaH was added and stirred for 1 hour. After 1 hour, 1.2 mmol of iodomethane was added and the reaction was continued for 4 hours. After completion of the reaction, it was quenched with cold water and extracted with ethyl acetate. Then the combined organic layer was dried with anhydrous Na_2SO_4. The organic layer

was then concentrated under vacuum and purified by silica gel column chromatography (hexanes / ethyl acetate).

***N*-methyl-7-azaindole (3b):** 112 mg, 85% yield; pale yellow liquid; R_f= 0.14 (5% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 6.45 (d, *J*=3.2 Hz, 1H), 7.03–7.08 (m, 1H), 7.18 (d, *J*=3.2 Hz, 1H), 7.88–7.93 (m, 1H), 8.32–8.35 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 31.4, 99.4, 115.6, 120.7, 128.9, 129.1, 142.9, 147.9.

Experimental procedure for synthesis of *N*-ethyl-7-azaindole from 7-azaindole[36]

In a round bottom flask 7-azaindole (1 mmol) and DMF (10 mL) were taken. Then the reaction mixture was cooled down to 0 ºC and 2 mmol of 60% NaH was added and stirred for 1 hour. After 1 hour, 1.5 mmol of ethyl bromide was added and the reaction was continued for 8 hours. After completion of the reaction, it was quenched with cold water and extracted with ethyl acetate. Then the combined organic layer was dried with anhydrous Na_2SO_4. The organic layer was then concentrated under vacuum and purified by silica gel column chromatography (hexanes / ethyl acetate).

***N*-ethyl-7-azaindole (3c):** 111 mg, 76% yield; pale yellow liquid; R_f= 0.14 (5% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (t, *J*=6.0 Hz, 3H), 4.35 (q, *J*=5.6 Hz, 2H), 6.45 (d, *J*=2.8 Hz, 1H), 7.02–7.06 (m, 1H), 7.23 (d, *J*=2.4 Hz, 1H), 7.90 (dd, J_1=1.6 Hz, J_2=6.4 Hz, 1H), 8.32 (dd, J_1=1.2 Hz, J_2=3.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 15.8, 39.4, 99.5, 115.6, 120.8, 127.4, 128.8, 142.8, 147.3.

Experimental procedure for synthesis of *N*-propyl-7-azaindole from 7-azaindole[37]

In a round bottom flask 7-azaindole (1 mmol) and DMF (10 mL) were taken. Then the reaction mixture was cooled down to 0 ºC and 2 mmol of 60% NaH was added and stirred for 1 hour. After 1 hour, 1.2 mmol of 1-iodopropane was added and the reaction was continued for 3 hours. After completion of the reaction, it was quenched with cold water and extracted with ethyl acetate. Then the combined organic layer was dried with anhydrous Na_2SO_4. The organic layer was then concentrated under vacuum and purified by silica gel column chromatography (hexanes / ethyl acetate).

***N*-propyl-7-azaindole (3d):** 130 mg, 81% yield; pale yellow liquid R_f= 0.17 (5% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, *J*=7.2 Hz, 3H), 1.84–1.96 (m, 2H), 4.26 (t,

J=7.2 Hz, 2H), 6.44 (d, *J*=3.2 Hz, 1H), 7.01–7.07 (m, 1H), 7.21 (d, *J*=3.2 Hz, 1H), 7.90 (d, *J*=7.6 Hz, 1H), 8.29–8.35 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 11.5, 23.8, 46.4, 99.3, 115.6, 120.7, 128.1, 128.8, 142.8, 147.6.

Experimental procedure for synthesis of *N*-pentyl-7-azaindole from 7-azaindole[37]

In a round bottom flask 7-azaindole (1 mmol) and DMF (10 mL) were taken. Then the reaction mixture was cooled down to 0 ºC and 2 mmol of 60% NaH was added and stirred for 1 hour. After 1 hour, 1.5 mmol of 1-bromopentane was added and the reaction was continued for 4 hours. After completion of the reaction, it was quenched with cold water and extracted with ethyl acetate. Then the combined organic layer was dried with anhydrous Na_2SO_4. The organic layer was then concentrated under vacuum and purified by silica gel column chromatography (hexanes / ethyl acetate).

***N*-pentyl-7-azaindole (3e):** 155 mg, 83% yield; pale yellow liquid; R_f= 0.28 (5% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84–0.91 (m, 3H), 1.28–1.41 (m, 4H), 1.80–1.93 (m, 2H), 4.29 (t, *J*=7.2 Hz, 2H), 6.42–6.46 (m, 1H), 7.00–7.07 (m, 1H), 7.19–7.23 (m, 1H), 7.90 (d, *J*=7.6 Hz, 1H), 8.29–8.35 (s, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 14.1, 22.5, 29.2, 30.3, 44.7, 99.3, 115.6, 120.7, 128.0, 128.8, 142.8, 147.6.

Experimental procedure for synthesis of *N*-octyl-7-azaindole from 7-azaindole

In a round bottom flask 7-azaindole (1 mmol) and DMF (10 mL) were taken. Then the reaction mixture was cooled down to 0 ºC and 2 mmol of 60% NaH was added and stirred for 1 hour. After 1 hour, 1.5 mmol of 1-bromopentane was added and the reaction was continued for 2 hours. After completion of the reaction, it was quenched with cold water and extracted with ethyl acetate. Then the combined organic layer was dried with anhydrous Na_2SO_4. The organic layer was then concentrated under vacuum and purified by silica gel column chromatography (hexanes / ethyl acetate).

***N*-octyl-7-azaindole (3f):** 207 mg, 90% yield; pale yellow liquid; R_f= 0.44 (5% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J*=6.4 Hz, 3H), 1.22–1.33 (m, 10H), 1.83–1.89 (m, 2H), 4.28 (t, *J*=7.6 Hz, 2H), 6.44 (d, *J*=3.2 Hz, 1H), 7.01–7.06 (m, 1H), 7.21 (d, *J*=3.2 Hz, 1H), 7.89 (dd, J_1=1.6 Hz, J_2=8.0 Hz, 1H), 8.32 (dd, J_1=1.2 Hz, J_2=4.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 14.2, 22.7, 27.0, 29.3, 29.4, 30.5, 31.9, 44.7, 99.3, 115.6, 120.7,

128.1, 128.8, 142.7, 142.8, 147.5. HRMS (m/z): $[M+H]^+$ calculated for $C_{15}H_{23}N_2$: 231.1861; found: 231.1863.

Experimental procedure for synthesis of *N*-benzyl-7-azaindole from 7-azaindole[38]

In a round bottom flask 7-azaindole (1 mmol) and DMF (10 mL) were taken. Then the reaction mixture was cooled down to 0 ^oC and 2 mmol of 60% NaH was added and stirred for 1 hour. After 1 hour, 1.5 mmol of 1-benzylbromide was added and the reaction was continued for 2 hours. After completion of the reaction, it was quenched with cold water and extracted with ethyl acetate. Then the combined organic layer was dried with anhydrous Na_2SO_4. The organic layer was then concentrated under vacuum and purified by silica gel column chromatography (hexanes / ethyl acetate).

***N*-benzyl-7-azaindole (3g):** 140 mg, 67% yield; white solid; mp 225–228 ^oC; R_f= 0.32 (5% ethyl acetate in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 5.51 (s, 2H), 6.45–6.50 (m, 1H), 7.04–7.10 (m, 1H), 7.15–7.23 (m, 3H), 7.24–7.33 (m, 3H), 7.92 (d, *J*=8.0 Hz, 1H), 8.32–8.38 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 47.9, 100.2, 116.0, 120.6, 127.6 (2C), 127.7, 128.0, 128.8, 128.9, 137.9, 143.2, 147.9.

Experimental procedure for synthesis of *N*-phenyl-7-azaindole from 7-azaindole[39]

A dried round-bottom flask equipped with a magnetic stirrer bar was charged with CuI (5 mol%) and N-hydroxyphthalimide (10 mol%). To the reaction mixture, sodium methoxide (1.5 equiv.) in DMSO was added. After stirring at room temperature for 30 minutes, a mixture of iodobenzene and 7-azaindole in DMSO was added to the flask and the reaction mixture was stirred at 110 ^oC. After completion of the reaction, it was cooled to room temperature. Then the reaction mixture was extracted with ethyl acetate. The combined organic layer was washed with water and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure to produce crude product which was purified by silica gel column chromatography (hexanes / ethyl acetate).

***N*-phenyl-7-azaindole (3h):** 89 mg, 46% yield; pale yellow solid; R_f= 0.28 (5% ethyl acetate in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 6.63 (d, *J*=3.5 Hz, 1H), 7.12–7.16 (m, 1H), 7.32–7.37 (m, 1H), 7.51–7.56 (m, 3H), 7.75–7.79 (m, 2H), 7.96–8.00 (m, 1H), 8.39 (dd, J_1=1.5 Hz, J_2=4.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 101.7, 116.8, 121.7, 124.1, 126.4, 128.0, 129.2, 129.5, 138.6, 143.7, 147.6.

Experimental procedure for synthesis of Ethyl 1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate from 7-azaindole[40]

In a round bottom flask 7-azaindole (1 mmol) and THF (5 mL) were taken. Then the reaction mixture was cooled down to 0 ^{o}C and 2 mmol of 60% NaH was added and stirred for 1 hour. After 1 hour, 1.5 mmol of Ethyl chloroformate was added and the reaction was continued for 2 hours. After completion of the reaction, it was quenched with cold water and extracted with ethyl acetate. Then the combined organic layer was dried with anhydrous Na_2SO_4. The organic layer was then concentrated under vacuum and purified by silica gel column chromatography (hexanes / ethyl acetate).

Ethyl 1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (3k): 141 mg, 74% yield; colourless liquid; R_f= 0.28 (15% ethyl acetate in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (t, *J*=7.2 Hz, 3H), 4.54 (q, *J*=7.2 Hz, 2H), 6.54 (d, *J*=4.0 Hz, 1H), 7.17–7.22 (m, 1H), 7.72 (d, *J*=4.0 Hz, 1H), 7.88 (dd, J_1=1.2 Hz, J_2=8.0 Hz, 1H), 8.47–8.52 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 14.5, 63.7, 105.3, 118.8, 123.3, 126.6, 129.4, 145.2, 148.1, 149.9.

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Notes

The authors declare no competing financial interest.

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Computational details, ^{1}H and $^{13}C\{^{1}H\}$NMR spectra for all compounds, X-ray structure and brief crystal data of compound **2j**.

X-ray crystallographic file of compound **2j**.

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17. (a) See supporting information for details. (b) Thermodynamic stability of various electrophilic intermediates with DFT using ωB97X-D functional and 6-311G(d,p) for C,H; 6-311+G(d,p) for N; aug-cc-pVTZ-PP for I in Vacuum (more detailed see Figure S5, Supporting information).

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