JOC The Journal of Organic Chemistry

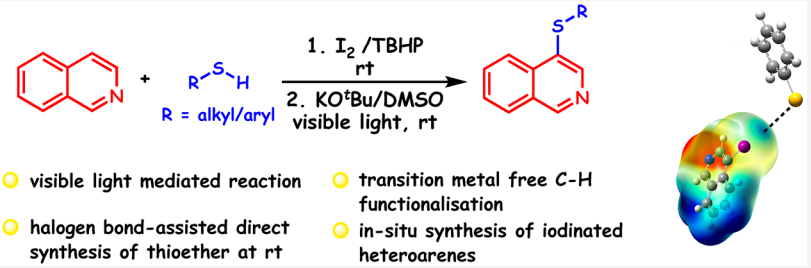
pubs.acs.org/joc Article

Visible-Light-Driven Halogen-Bond-Assisted Direct Synthesis of Heteroaryl Thioethers Using Transition-Metal-Free One-Pot C−I Bond Formation/C−S Cross-Coupling Reaction

Anuradha Nandy, Imran Kazi, Somraj Guha, and Govindasamy Sekar*

Cite This: J. Org. Chem. 2021, 86, 2570−2581 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: An efficient protocol for the synthesis of thioether directly from heteroarenes has been developed in the presence of visible light in a one-pot manner at room temperature. This method involves two sequential reactions in a single pot where the formation of the iodinated heteroarene is followed by a transition-metal-free C−S coupling reaction. A wide range of heteroarene and thiol partners (including aliphatic thiols) have been used for the synthesis of thioethers. NMR studies and DFT calculations revealed the presence of a halogen bond between the thiolate anion (halogen bond acceptor) and iodoheteroarene (halogen bond donor). This halogen bonded complex on photoexcitation facilitates the electron transfer from the thiolate anion to the iodoheteroarene at room temperature.

INTRODUCTION

Organosulfur compounds are immensely important due to their omnipresence. They are widely available in our bodies and the natural environment.[1] Heteroaryl thioethers, a class of organosulfur compounds, are of great significance owing to their role in pharmaceutical, medicinal, and biological compounds. Quinoline-based thioethers are known to show CB2 agonist activity and have a therapeutic effect in osteoporosis, inflammation, pain relief, and cancer treatment (Figure 1A).[2] Also, certain *N*-alkylated 3-phenyl thioquinolinium salts show enhanced activity against fungal pathogens that are associated with AIDS.[3] Moreover, thioether moieties also act as important structural scaffolds for the synthesis of higher-oxidation-state derivatives such as sulfones and sulfoxides.[4]

Considering various utilities of these thioethers, umpteen efforts have been made to synthesize these moieties.[5] Conventional methods of synthesis employ precious transition metal catalysts for the cross-coupling reactions of aryl halides with thiols.[6] On top of that, these methods require specific costly ligands, high temperature, and high catalyst loading to overcome the deactivation of catalyst due to strong coordination of the thiolates to transition metal catalysts (Figure 1B).[6,7] Thus, there arises a need to develop alternative approaches for the C−S bond formation.

Of late, photoredox catalysis is being used as a powerful tool to develop a wide variety of reactions under mild conditions. The application of visible light as a renewable source of energy has garnered much interest from organic chemists in the past decade for the formation of the C−S bond. A one-pot Stadler−Ziegler process for C−S bond formation was developed by Noel and co-workers using $[Ru(bpy)_3Cl_2]\cdot 6H_2O$ as the photocatalyst in 2013.[8] In 2016, Molander and co-workers carried out the thioetherification of aryl bromides using photoredox/Ni-dual catalysis.[9] Fu et al. have developed a general and efficient visible-light photoredox cross-coupling of aryl halides with arenethiols at room temperature using $[fac\text{-}Ir(ppy)_3]$ as the photocatalyst.[10] More recently, a visible-light photoredox catalysis for the synthesis of 2-substituted benzothiazoles was reported by Natarajan et al. using Eosin Y as a photocatalyst.[11]

However, a visible-light-mediated reaction does not necessarily need a photocatalyst. The ground-state association

Received: November 9, 2020
Published: January 25, 2021

https://dx.doi.org/10.1021/acs.joc.0c02672
J. Org. Chem. 2021, 86, 2570−2581

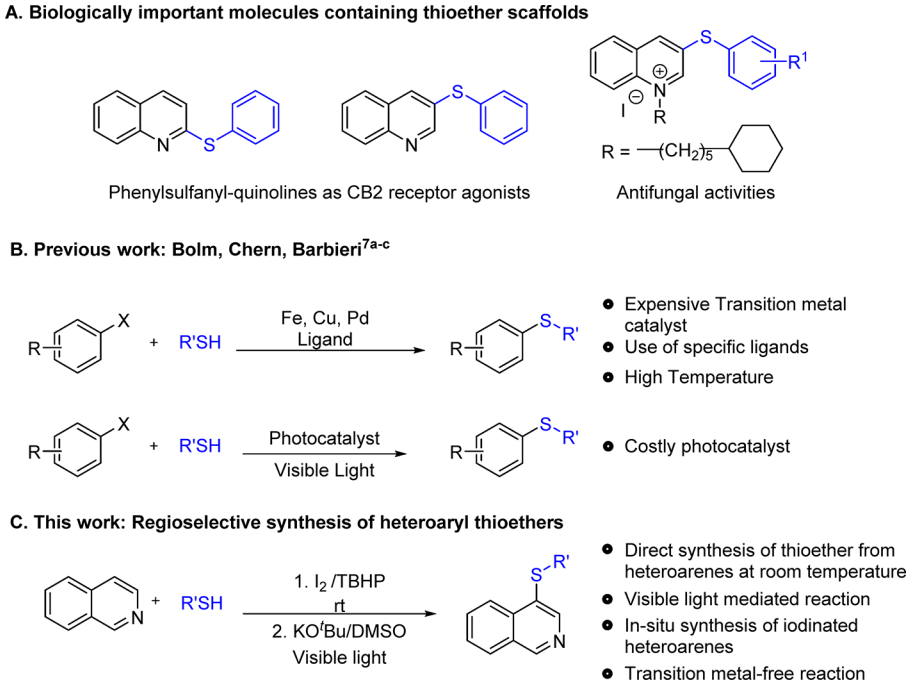


Figure 1. Visible-light-mediated one-pot thioether formation.

between the electron-rich donor (a nucleophile or reducing agent) and an electron-poor acceptor (an electrophile or oxidizing agent) can generate an electron donor−acceptor (EDA) or charge-transfer (CT) complex which can absorb the visible light and undergo photoexcitation to transfer an electron.[12] The ground-state association of the donor and acceptor to form the EDA or CT complex can be aided by several noncovalent interactions and one of these is halogen bond.[13] A halogen-bonded EDA complex can thus facilitate the electron-transfer in its excited state in the presence of visible light.[14] The halogen bond (XB) is an attractive noncovalent interaction between an electrophilic region of a halogen atom and nucleophilic region of a molecule. It has found its utilization in fields such as medicinal chemistry,[15] supramolecular chemistry,[16] and crystal engineering[17] and most importantly in organic synthesis as organocatalysts.[18] In the past demidecade, our research group has delved in probing the application of XB in organic synthesis and in transition-metal-free organocatalysis.[19] Recently, an atom economic XB-assisted electron-catalyzed iodination of heteroarene has also been developed by our group.[18e] Taking this a step further, we wanted to attempt a visible-light-driven halogen-bond-assisted one-pot synthesis of thioether from heteroarenes at room temperature wherein it was presumed that the thiolate anion might act as the electron donor (XB acceptor) and the heteroaryl iodide as the electron acceptor (XB donor). Hence, an intermolecular charge transfer within the thiolate anion−heteroaryl iodide might permit the reaction to take place even in the absence of a photocatalyst.

Thus, an effort was undertaken to synthesize heteroaryl thioethers in a one-pot manner where, first, the iodination step takes place,[19e] and the second C−S bond formation takes place between the thiolate anion and the heteroaryl iodide. The advantage of the current protocol is as enlisted: (1) The use of transition metal catalyst has been eluded which is often expensive and necessitates complete removal from products particularly in the production of synthetic drugs.[20] (2) The reaction takes place in a one-pot fashion avoiding lengthy separation processes associated with the intermediate isolation, thus, saving time and resources.[21] Hence, this new protocol provides a mild and step economic synthesis of heteroaryl thioethers.

RESULTS AND DISCUSSION

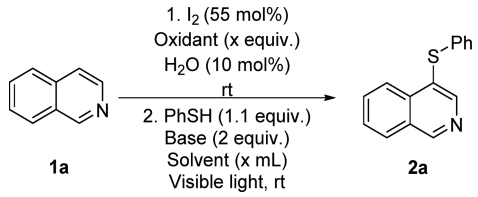
Initially, a trial reaction was kept with 1 equiv of isoquinoline **1a**, 55 mol % of iodine, 50 mol % of TBHP in decane, and 10 mol % water at room temperature. After 18 h, on formation of the iodinated product, 2 equiv of potassium *tert*-butoxide as the base and 1.1 equiv of thiophenol were added to the reaction mixture in 1 mL of DMSO.

Gratifyingly, the C−S cross-coupled product **2a** was obtained in 24 h with high yields (75%) on irradiating the reaction mixture with visible light at room temperature (Table 1, entry 1).

Thus, further optimization was carried out. Increasing the amount of TBHP showed a drastic decline in the yield of **2a** (entry 2). Other oxidizing agents like aqueous TBHP and hydrogen peroxide were unable to give better results (entries 3 and 4). Eventually, it was observed that iodine (55 mol %), TBHP in decane (50 mol %) as the oxidant, and H_2O (10 mol %) was the best suited condition for the iodination step. Focus was thus shifted to the second step of this transformation. Other bases were found to be inferior in comparison to potassium *tert*-butoxide for carrying out the C−S bond formation (entries 5−9). Later, different solvents were evaluated; however, solvents other than DMSO could not provide better results (entries 10−12). Further, on increasing the amount of solvent to 2 mL, an appreciable hike in the yield to 90% was observed (entry 13). However, the yield remained constant on further increasing the quantity of solvent (entry 14). Also, varying the amount of base did not improve the yield of the reaction (entries 15 and 16). Without base, the product **2a** was not obtained, and only the iodinated product was isolated (entry 17). Importantly, the reaction also failed in

https://dx.doi.org/10.1021/acs.joc.0c02672
J. Org. Chem. 2021, 86, 2570−2581

Table 1. Optimization for Thioether Formation[a]



entry	oxidant (equiv)	base (equiv)	solvent (mL)	yield[b] (%)
1	TBHP (0.5)	KO^{t}Bu (2)	DMSO (1)	75
2	TBHP (0.75)	KO^{t}Bu (2)	DMSO (1)	47
3	TBHP$_{aq}$ (0.5)	KO^{t}Bu (2)	DMSO (1)	40[c]
4	H_2O_2 (0.5)	KO^{t}Bu (2)	DMSO (1)	35
5	TBHP (0.5)	LiO^{t}Bu (2)	DMSO (1)	63
6	TBHP (0.5)	NaO^{t}Bu (2)	DMSO (1)	70
7	TBHP (0.5)	NaOEt (2)	DMSO (1)	51
8	TBHP (0.5)	Cs_2CO_3 (2)	DMSO (1)	64
9	TBHP (0.5)	KOH (2)	DMSO (1)	55
10	TBHP (0.5)	KO^{t}Bu (2)	DMF (1)	45
11	TBHP (0.5)	KO^{t}Bu (2)	MeCN (1)	50
12	TBHP (0.5)	KO^{t}Bu (2)	^{t}BuOH (1)	23
13	*TBHP (0.5)*	*KO^{t}Bu (2)*	*DMSO (2)*	*90 (89)*[d]
14	TBHP (0.5)	KO^{t}Bu (2)	DMSO (3)	89
15	TBHP (0.5)	KO^{t}Bu (1)	DMSO (2)	55
16	TBHP (0.5)	KO^{t}Bu (3)	DMSO (2)	84
17	TBHP (0.5)		DMSO (2)	trace
18	TBHP (0.5)	KO^{t}Bu (2)	DMSO (2)	0[e]

[a]Reaction conducted in 1 mmol scale at room temperature under the irradiation of 450 W visible light. [b]Yield calculated by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. [c]70% aqueous TBHP was used. [d]Isolated yield (yield in parentheses). [e]Reaction kept in the dark.

dark conditions (entry 18). Thus, light is indispensable for the C−S cross-coupling reaction. Also, an on−off experiment was conducted to validate the significance of light (Figure 2).

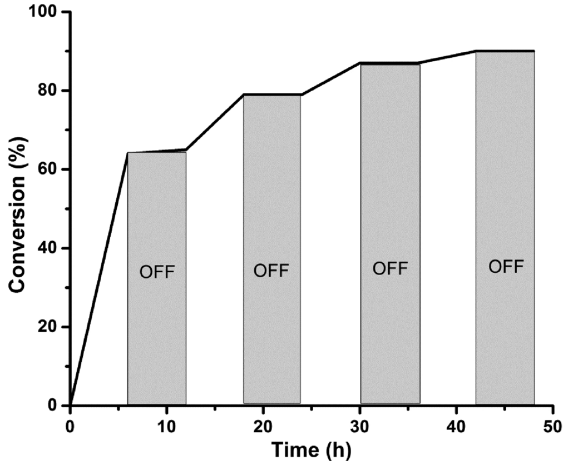
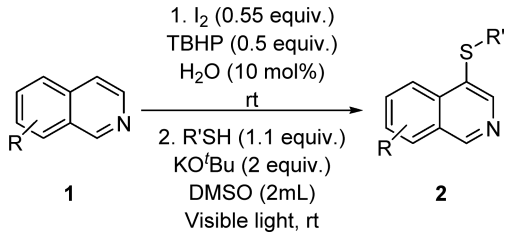


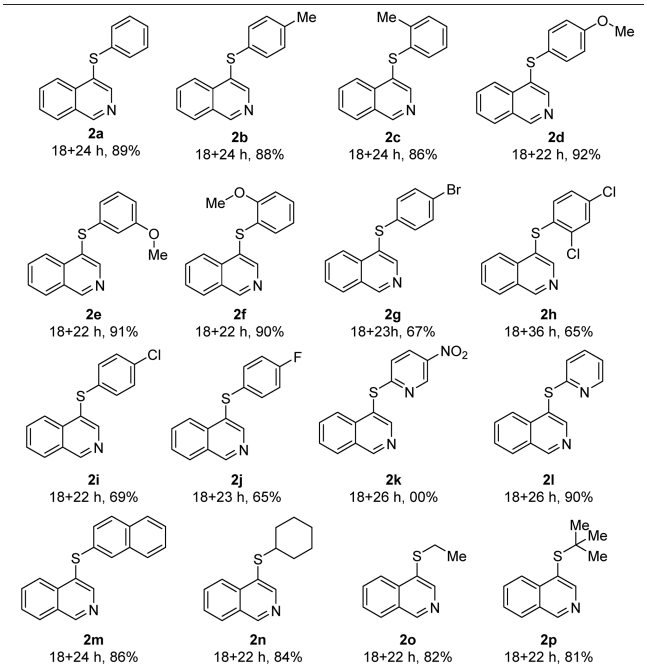
Figure 2. Light on−off experiment.

Finally, the optimized reaction condition was obtained with 1.1 equiv of thiophenol, 2 equiv of potassium *tert*-butoxide as the base, and 2 mL of DMSO as the solvent under the irradiation of visible light to yield 90% of the desired product **2a**.

To probe the scope of the reaction, the methodology was examined with isoquinoline **1a** and several types of thiols, and the results are summarized in Table 2. Substrates with the

Table 2. Scope for Thioether Formation of Isoquinoline[a]





[a]Reaction conducted in 1 mmol scale at room temperature under the irradiation of 450 W visible light. [b]Isolated yield.

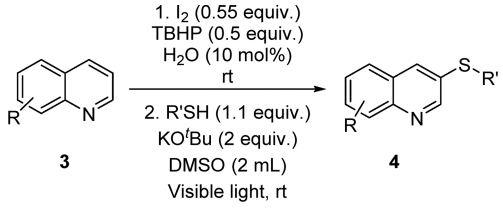
electron-donating methyl and methoxy group underwent the reaction smoothly and provided the corresponding thioether in excellent yields (Table 2, **2b**−**2f**). The structure of the product was established by single-crystal XRD analysis of **2d** (CCDC 1914361).[22] In contrast, moderate to good yields were observed with the thiophenol moiety containing a weak electron-withdrawing group (**2g**−**2j**). In the presence of a strong electron-withdrawing nitro group, even a trace amount of product formation was not observed (**2k**).

The reaction worked well with heterocyclic thiophenol giving 90% yield of the desired product (**2l**). Thiol having a bulky group like naphthalene also provided an excellent yield of product (**2m**). Importantly, aliphatic thiols like cyclohexanethiol, ethanethiol, and *tert*-butylthiol also worked well indicating that $\pi-\pi$ interaction is not responsible for the charge transfer (**2n**−**2p**).

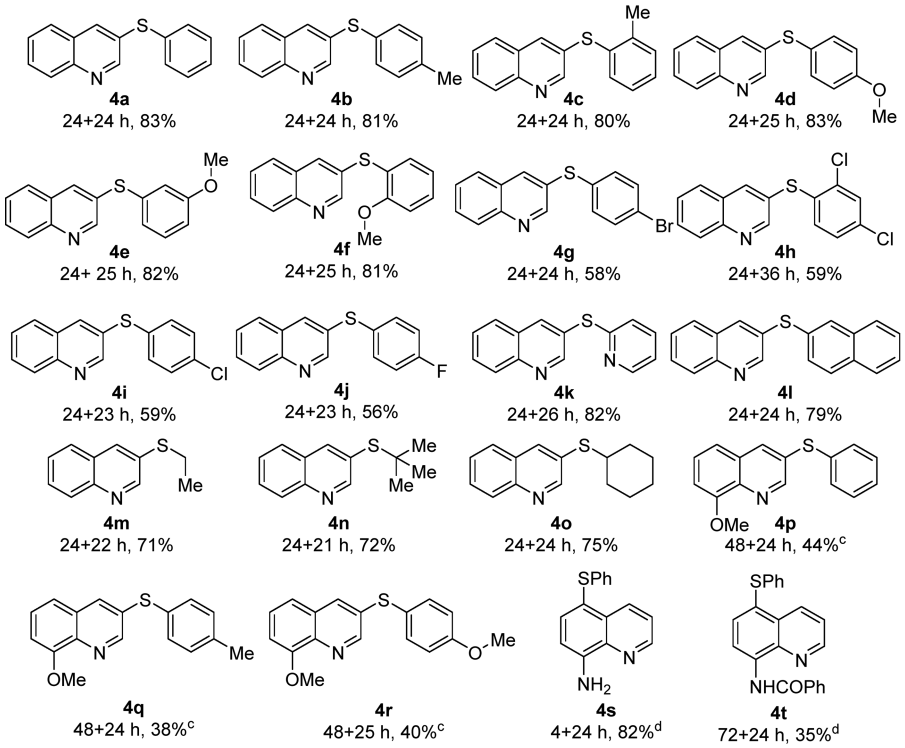
Also, several quinolines were subjected to a C−S bond forming reaction with thiols. Quinoline with thiophenol as its coupling partner gave 83% yield of the thioether in 48 h (Table 3, **4a**). Methyl- and methoxy-group-containing thiophenol worked well under the optimized reaction condition (**4b**−**4f**). A slight decrement in yield was observed in the case of thiol containing a weak electron-withdrawing group like bromo, chloro, and fluoro (**4g**−**4j**). Notably, the reaction gave excellent yields of the corresponding thioether with 2-mercaptopyridine (**4k**) and 2-naphthalene thiol (**4l**) as the coupling partner. Aliphatic thiols also worked well to provide

https://dx.doi.org/10.1021/acs.joc.0c02672
J. Org. Chem. 2021, 86, 2570−2581

Table 3. Scope for Thioether Formation of Quinoline[a]

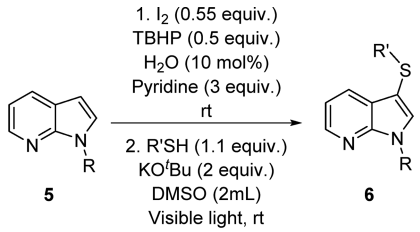


3 4

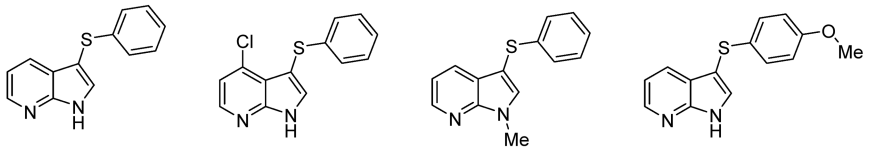


[a]Reaction conducted in 1 mmol scale at room temperature under the irradiation of 450 W visible light. [b]Isolated yield. [c]2 equiv of pyridine used for iodination. [d]3 equiv of pyridine used for iodination.

Table 4. Scope for Thioether Formation of Azaindole[a]



5 6



[a]Reaction conducted in 1 mmol scale at room temperature under the irradiation of 450 W visible light. [b]Isolated yield.

the corresponding heteroaryl thioethers (**4m**−**4o**). However, the 8-substituted quinoline molecule gave low conversion to the iodinated product, thus resulting in low thioether formation (**4p**−**4r**). In 8-aminoquinoline (**4s**), the benzene ring substituted with amine is more electron-rich in comparison to the pyridine ring, and hence, the substitution takes place at the para position of the amino-substituted ring. Thus, the C-5 position of 8-aminoquinoline is more activated for functionalization.[23] Therefore, when the quinoline moiety bearing an amino functional group was subjected to the optimized reaction condition, 5-(phenylthio)quinolin-8-amine was obtained in 82% yield (**4s**). Further, the weakly electron-

https://dx.doi.org/10.1021/acs.joc.0c02672
J. Org. Chem. 2021, 86, 2570−2581

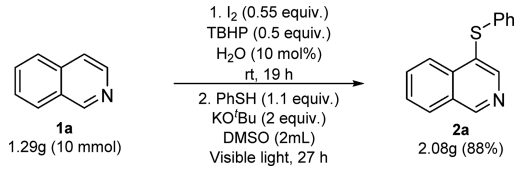
withdrawing 8-benzamide-substituted quinoline molecule was subjected to thioether formation. The corresponding *N*-(5-(phenylthio)quinolin-8-yl)benzamide (**4t**) was attained in 35% yield since the conversion to the iodinated product itself was observed to be less.

Various substituted 7-azaindoles were also examined to undergo the C−S cross-coupling reactions under the optimized conditions (Table 4). 7-Azaindole with thiophenol as its coupling partner gave 90% yield of the thioether in 30 h (Table 4, **6a**). The electron-withdrawing-group-containing 7-azaindoles, 4-chloro-7-azaindole, underwent the optimized reaction conditions smoothly and provided the C−S cross-coupled product in good yields (**6b**).

A slight decrement in the yield was observed for *N*-methyl 7-azaindole in comparison to 7-azaindole (**6c**). The reaction also worked well for 7-azaindole with 4-mercaptoanisole as its coupling partner which gave 88% yield of the thioether in 28 h (**6d**).

To exhibit the practical utility of light-mediated thioether synthesis, a scaled-up reaction (10 mmol, 1.29 g) was performed under the standard conditions. To our delight, this transformation gave 88% isolated yield of the thioether **2a** in 46 h (Scheme 1).

Scheme 1. Gram Scale Reaction



To probe into the reaction mechanism, a series of control experiments were conducted. The reaction was carried out using other halogen bond acceptors. The reaction failed to give the coupled product **2aa** using aniline and **2ab** using phenol as the coupling partner (Figure 3A). With thiophenol as the coupling partner, the reaction gave 90% yield of **2a**, and with benzeneselenol, the reaction gave **2ac** in 89% yield. This is in accordance to the fact that thiol and benzeneselenol are better XB acceptors in comparison to aniline and phenol.[24]

Further, to verify the presence of radical intermediates in the reaction mixture, radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to the reaction mixture under optimized conditions, and a drastic decline in the yield of the product was observed (Figure 3B). Also, the presence of the TEMPO adduct with the thiophenol radical was confirmed with HRMS.[22] Additionally, the EPR experiment gave a radical signal with *g* value 1.9974 which falls in the range for organic radicals (Figure 3C).[25] Thus, EPR studies also corroborate a radical process.

NMR studies were performed to substantiate the presence of XB interaction between 4-iodoisoquinoline and the thiolate anion (Figure 4). ^{13}C NMR for iodoisoquinoline was recorded

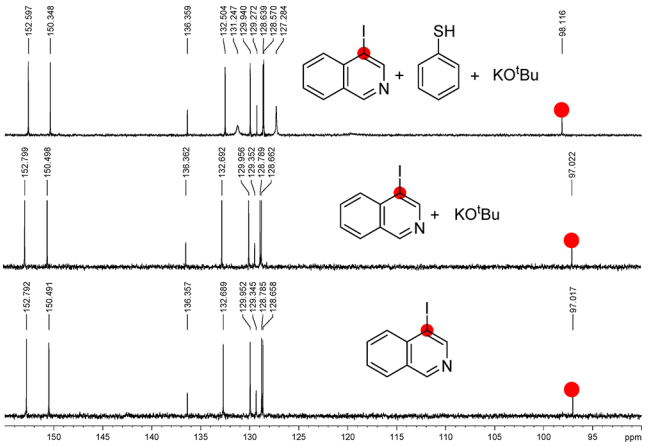
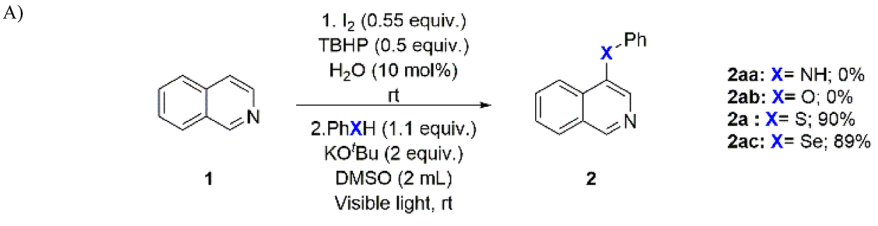
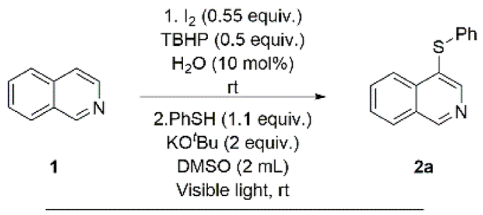


Figure 4. Cutouts of ^{13}C NMR spectra of (a) iodoisoquinoline, (b) iodoisoquinoline and KO^{t}Bu, and (c) iodoisoquinoline, KO^{t}Bu, and thiophenol (1:1:1 ratio) in DMSO-d_6.



B)



Entry	Equiv. used	TEMPO yield (%)	BHT yield (%)
1	1	63	55
2	5	24	29
3	10	9	12

C)

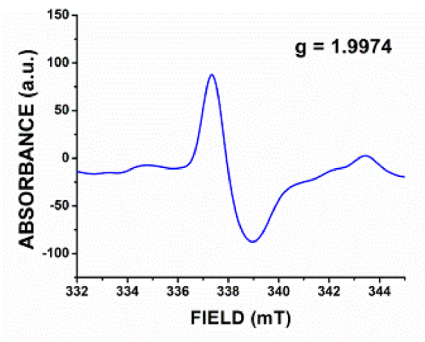


Figure 3. (A) Controlled experiments with different coupling partners. (B) Radical scavenger experiment. (C) Electron paramagnetic resonance (EPR) spectra (X band, room temperature).

https://dx.doi.org/10.1021/acs.joc.0c02672
J. Org. Chem. 2021, 86, 2570−2581

in DMSO-d_6, and peak for the carbon atom adjacent to the iodine was observed at 97.02 ppm. On addition of potassium *tert*-butoxide, a significant shift in the peak was not observed. However, on further adding thiophenol, the peak shifted downfield (ca. 1 ppm). This increase in chemical shift indicates a presence of halogen-bonding between iodoisoquinoline and the thiolate anion due to the lengthening of the C−I bond upon donation of the halogen bond acceptor electrons into orbitals of iodine.[26]

The density functional theory (DFT) calculations also verified the presence of the halogen bond. The distance between the iodine atom of 4-iodoisoquinoline and the sulfur atom of the benzenethiolate anion in the XB complex was found to be 3.38 Å which is less than the sum of van der Waals radii of S and I (3.78 Å) (Figure 5A). The C−I−S bond angle

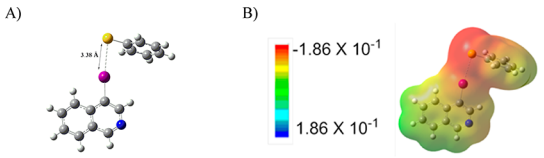


Figure 5. (A) XB complex between 4-iodoisoquinoline and the benzenethiolate anion optimized with DFT using the ωB97X-D functional and 6-311G(d,p) for C, H; 6-311+G(d,p) for N, S; and Def2TZV for I in a vacuum. (B) Calculated electrostatic potential (blue = positive electrostatic potential) on the 0.0004 au isodensity surface (ωB97X-D/Def2TZV).

of the XB complex is 174° which is in accordance with the approximate linearity that is generally observed in XB complexes. Figure 5B displays the mapped electrostatic potential of the XB complex.

A plausible reaction mechanism for the thioether formation from isoquinoline **1a** is delineated in Scheme 2. The iodinated heteroarene **A** forms on reaction of **1a** with iodine and TBHP (in decane).[19e] This is followed by the generation of the thiolate anion in the presence of potassium *tert*-butoxide (KO^tBu) as the base. The thiolate anion and **A** form a halogen-bonded complex **B** which on photoexcitation facilitates an electron transfer.[14a]

The thiolate anion transfers an electron to carry out the formation of intermediate **C**.[27] Elimination of the iodide ion leads to the generation of isoquinoline radical **D**, followed by the formation of radical anion intermediate **E** on coupling with the thiolate anion. Consequent oxidation of the intermediate **E** by another molecule of 4-iodoisoquinoline **A** gives the C−S cross-coupled product **2a**. Alternatively, the thiyl radical thus generated (after electron transfer from the thiolate anion to 4-iodoisoquinoline **A** in the XB complex **B**) can couple with isoquinoline radical **D** to give **2a**.

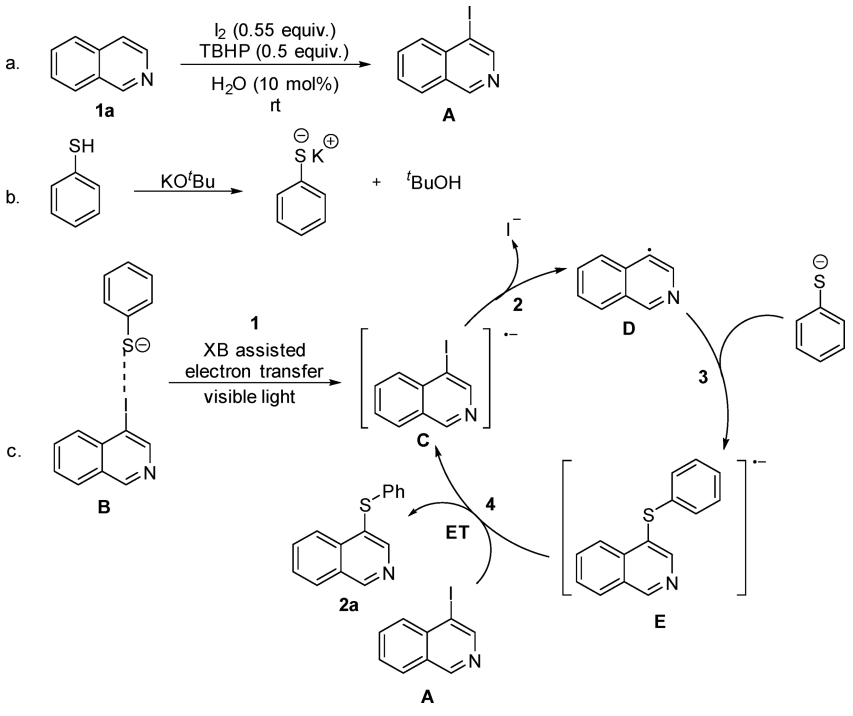
CONCLUSION

In conclusion, we have developed an efficacious methodology for thioether formation directly from heteroarenes at room temperature under visible-light-mediated conditions in a one-pot manner. The protocol involves the *in situ* formation of iodinated heteroarenes followed by a C−S coupling reaction with thiophenol under transition-metal-free conditions. The reaction worked well for a wide array of thiol coupling partners including aliphatic and heteroaromatic thiols to give heteroaryl thioethers in good to excellent yields. NMR spectroscopic analysis and DFT studies support the formation of a halogen-bonded complex between the iodinated heteroarene and the thiolate anion for facilitating the electron transfer.

EXPERIMENTAL SECTION

All reactions were carried out in oven-dried reaction tubes. TBHP in decane, di-*tert*-butyl peroxide, hydrogen peroxide, *tert*-butyl peroxy benzoate, and aqueous TBHP were purchased from Sigma-Aldrich and Fisher Scientific. Iodine was purchased from Avra Synthesis Pvt., Ltd. Various isoquinolines, quinolines, and azaindoles were purchased

Scheme 2. Plausible Reaction Mechanism



https://dx.doi.org/10.1021/acs.joc.0c02672
J. Org. Chem. 2021, 86, 2570−2581

from Alfa Aesar, Sigma-Aldrich, TCI, Avra Synthesis, and Spectrochem Pvt., Ltd., and used directly as received. Various thiols were purchased from Alfa Aesar, Sigma-Aldrich, TCI, Avra Synthesis, and Spectrochem Pvt., Ltd., and used directly. Iodomethane was purchased from Avra Synthesis Pvt., Ltd. DMSO was purchased from Qualigens. Potassium *tert*-butoxide, lithium *tert*-butoxide, sodium *tert*-butoxide, cesium carbonate, potassium carbonate, sodium carbonate, sodium hydroxide, and potassium hydroxide were purchased from Avra Synthesis and Fisher Scientific. All the starting materials were synthesized according to the reported procedures. Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F_{254} precoated plates (0.25 mm) and visualized by UV fluorescence quenching using an 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 the eluent. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using a water bath. A multitube photoreactor was purchased from Lelesil Innovative Systems which was equipped with a 450 W light, a 250 W light, and a 15 W light. The 450 W light has been used as a visible light source emitting in the region 420−700 nm.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 or 500 MHz instrument. ^{1}H NMR is reported relative to residual $CDCl_3$ (δ 7.26 ppm) or DMSO-d_6 (δ 2.50 ppm). ^{13}C NMR is reported relative to residual $CDCl_3$ (δ 77.16 ppm) or DMSO-d_6 (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), and td (triplet of doublet). The coupling constant, J, is reported in Hertz. Melting points were recorded on a Guna capillary melting point apparatus and are corrected with benzoic acid as the reference. FTIR spectra were recorded on a JASCO spectrometer and are reported in frequency of absorption (cm^{-1}) using a dry KBr pellet. The UV−vis spectra were recorded with a JASCO V-650 UV−vis spectrophotometer. High-resolution mass spectra (HRMS) were recorded on a Q-Tof Micro mass spectrometer.

Experimental Procedure for the Synthesis of 4-(Phenylthio)isoquinoline (2a) from Isoquinoline (1a). In an oven-dried reaction tube, isoquinoline **1a** (129 mg, 1 mmol), molecular iodine (140 mg, 0.55 mmol), 0.5 mmol of TBHP (6 M in decane), and H_2O (2 μL, 0.1 mmol) were taken. The reaction mixture was stirred at room temperature until the disappearance of starting material on the TLC plate, followed by the addition of potassium *tert*-butoxide (224 mg, 2 mmol) and thiophenol (112 μL, 1.1 mmol) in DMSO (2 mL) as the solvent. The reaction was kept for continuous stirring under the irradiation of 450 W visible light. After the 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× 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-(phenylthio)isoquinoline **2a** (211 mg, 89% yield).

Experimental Procedure for the Synthesis of 8-Methoxy-3-(phenylthio)quinoline (4m) from 8-Methoxyquinoline (3b). 8-Methoxyquinoline **3b** (159 mg, 1 mmol), molecular iodine (140 mg, 0.55 mmol), and 0.5 mmol of TBHP (6 M in decane) were taken in an oven-dried reaction tube. Pyridine (161 μL, 2 mmol) and H_2O (2 μL, 0.1 mmol) were added into the reaction tube. The reaction mixture was stirred at room temperature (rt) until the disappearance of starting material on the TLC plate, followed by the addition of potassium *tert*-butoxide (224 mg, 2 mmol) and thiophenol (112 μL, 1.1 mmol) in DMSO (2 mL) as the solvent. The reaction was kept for continuous stirring under the irradiation of 450 W visible light. 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× 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 8-methoxy-3-(phenylthio)quinoline **4m** (118 mg, 44% yield).

Experimental Procedure for Synthesis of 5-(Phenylthio)-quinolin-8-amine (4p) from 8-Aminoquinoline (3c). 8-Aminoquinoline **3c** (244 mg, 1 mmol), molecular iodine (140 mg, 0.55 mmol), and 0.5 mmol of TBHP (6 M in decane) were taken in an oven-dried reaction tube. Pyridine (242 μL, 3 mmol) and H_2O (2 μL, 0.1 mmol) were added into the reaction tube. The reaction mixture was stirred at rt until the disappearance of starting material on the TLC plate, followed by the addition of potassium *tert*-butoxide (224 mg, 2 mmol) and thiophenol (112 μL, 1.1 mmol) in DMSO (2 mL) as the solvent. The reaction was kept for continuous stirring under the irradiation of 450 W visible light. 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× 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-(phenylthio)quinolin-8-amine **4p** (206 mg, 82% yield).

Experimental Procedure for Synthesis of 3-(Phenylthio)-7-azaindole (6a) from 7-Azaindole (5a). 7-Azaindole **5a** (118 mg, 1 mmol), molecular iodine (140 mg, 0.55 mmol), and 0.5 mmol of TBHP (6 M in decane) were taken in an oven-dried reaction tube. Pyridine (242 μL, 3 mmol) and H_2O (2 μL, 0.1 mmol) were added into the reaction tube, and the reaction was stirred at room temperature until the disappearance of starting material on the TLC plate, followed by the addition of potassium *tert*-butoxide (224 mg, 2 mmol) and thiophenol (112 μL, 1.1 mmol) in DMSO (2 mL) as the solvent. The reaction was kept for continuous stirring under the irradiation of 450 W visible light. 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× 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 3-(phenylthio)-7-azaindole **6a** (203 mg, 90% yield).

*4-(Phenylthio)isoquinoline (**2a**).* 211 mg, 89% yield; cream colored solid. mp 59−60 °C [57−58 °C, lit.].[28] R_f = 0.30 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3054, 1570, 1481, 1378, 1228, 981, 743. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.23 (s, 1H), 8.65 (s, 1H), 8.26 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.76−7.67 (m, 1H), 7.67−7.58 (m, 1H), 7.26−7.13 (m, 5H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.4, 148.1, 136.4, 135.8, 131.4, 129.3, 129.2, 129.1, 128.3, 127.9, 126.7, 126.4, 124.8. HRMS (TOF MS ES +) m/z: $[M + H]^+$ calcd for $C_{15}H_{12}NS$, 238.0690; found, 238.0702.

*4-(p-Tolylthio)isoquinoline (**2b**).* 222 mg, 88% yield; yellow liquid. R_f = 0.30 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3029, 1564, 1491, 1378, 980, 750. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (s, 1H), 8.56 (s, 1H), 8.27 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.76−7.69 (m, 1H), 7.67−7.60 (m, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 2.30 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 152.8, 147.0, 137.2, 136.1, 131.5, 131.3, 130.3, 130.2, 128.9, 128.3, 127.9, 127.6, 124.7, 21.2. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{16}H_{14}NS$, 252.0847; found, 252.0836.

*4-(o-Tolylthio)isoquinoline (**2c**).* 216 mg, 86% yield; orange liquid. R_f = 0.29 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3060, 1564, 1468, 1378, 982, 748. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (s, 1H), 8.42 (s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.76−7.69 (m, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 7.2 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 2.48 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 152.6, 146.4, 138.2, 135.9, 133.9, 131.3, 130.7, 130.6, 128.9, 128.3, 127.9, 127.3, 127.0, 126.9, 124.5, 20.5. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{16}H_{14}NS$, 252.0847; found, 252.0852.

https://dx.doi.org/10.1021/acs.joc.0c02672
J. Org. Chem. 2021, 86, 2570−2581

*4-((4-Methoxyphenyl)thio)isoquinoline (**2d**).* 246 mg, 92% yield; yellow solid. mp 79−80 °C. R_f = 0.17 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3054, 1593, 1494, 1257, 1030, 736. ^1H NMR (400 MHz, $CDCl_3$): δ 9.13 (s, 1H), 8.39 (s, 1H), 8.28 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.77−7.71 (m, 1H), 7.67−7.59 (m, 2H), 7.38−7.31 (m, 2H), 6.89−6.82 (m, 2H), 3.78 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.7, 151.9, 145.2, 135.3, 133.7, 131.1, 129.4, 128.8, 128.2, 127.8, 124.3, 115.2. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{16}H_{14}NOS$, 268.0796; found, 268.0794.

*4-((3-Methoxyphenyl)thio)isoquinoline (**2e**).* 244 mg, 91% yield; orange liquid. R_f = 0.20 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3059, 1582, 1477, 1239, 1040, 773. ^1H NMR (400 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.68 (s, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H), 7.69−7.61 (m, 1H), 7.14 (t, J = 8.0 Hz, 1H), 6.79−6.67 (m, 3H), 3.70 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.2, 153.6, 148.4, 137.2, 136.6, 131.6, 130.1, 129.1, 128.3, 128.0, 126.0, 124.9, 121.3, 114.5, 112.2, 53.4. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{16}H_{14}NOS$, 268.0796; found, 268.0791.

*4-((2-Methoxyphenyl)thio)isoquinoline (**2f**).* 240 mg, 90% yield; yellow liquid. R_f = 0.33 (20% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3057, 1573, 1471, 1245, 749. ^1H NMR (400 MHz, $CDCl_3$): δ 9.22 (s, 1H), 8.60 (s, 1H), 8.26 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.75−7.67 (m, 1H), 7.66−7.58 (m, 1H), 7.20−7.14 (m, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.77−6.69 (m, 2H), 3.90 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.8, 153.0, 147.7, 136.6, 131.3, 129.9, 128.9 (2C), 128.2, 127.9, 125.7, 124.8, 123.8, 121.4, 110.9, 55.9. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{16}H_{14}NOS$, 268.0796; found, 268.0808.

*4-((4-Bromophenyl)thio)isoquinoline (**2g**).* 212 mg, 67% yield; orange solid. mp 63−64 °C. R_f = 0.27 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3051, 1564, 1474, 1379, 1081, 751. ^1H NMR (400 MHz, $CDCl_3$): δ 9.26 (s, 1H), 8.69 (s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.77−7.70 (m, 1H), 7.69−7.62 (m, 1H), 7.37−7.29 (m, 2H), 7.03 (d, J = 8.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.9, 148.7, 136.5, 135.4, 132.4, 131.7, 130.3, 129.2, 128.5, 128.1, 125.5, 124.7, 120.4. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{15}H_{11}BrNS$, 317.9796; found, 317.9783.

*4-((2,4-Dichlorophenyl)thio)isoquinoline (**2h**).* 200 mg, 65% yield; yellow solid. mp 74−75 °C. R_f = 0.37 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3065, 1564, 1444, 1373, 1094, 807, 752. ^1H NMR (400 MHz, $CDCl_3$): δ 9.35 (s, 1H), 8.78 (s, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.45 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.1, 150.2, 138.3, 136.9, 133.3, 132.2, 130.7, 130.0, 129.3, 128.6, 128.5, 127.5, 126.9, 124.6, 123.0. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{15}H_{10}NSCl_2$, 305.9911; found, 305.9906.

*4-((4-Chlorophenyl)thio)isoquinoline (**2i**).* 188 mg, 69% yield; orange solid. mp 54−55 °C. R_f = 0.27 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3051, 1567, 1480, 1382, 1094, 741. ^1H NMR (400 MHz, $CDCl_3$): δ 9.25 (s, 1H), 8.68 (s, 1H), 8.22 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.9, 148.5, 136.4, 134.6, 132.6, 131.7, 130.2, 129.5, 129.2, 128.4, 128.1, 125.8, 124.7. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{15}H_{11}ClNS$, 272.0301; found, 272.0308.

*4-((4-Fluorophenyl)thio)isoquinoline (**2j**).* 166 mg, 65% yield; yellowish orange liquid. R_f = 0.23 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3053, 1490, 1379, 1226, 1090, 744. ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1H), 8.74 (s, 1H), 8.41 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.91 (t, J = 7.2 Hz, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.45−7.40 (m, 2H), 7.16−7.09 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.1 (C−F, 1JC−F = 245.8 Hz), 153.2, 147.2, 136.0, 132.1 (C−F, 3JC−F = 8.0 Hz), 131.5, 130.3 (C−F, 4JC−F = 3.7 Hz), 129.0, 128.4, 128.0, 127.3, 124.5, 116.6 (C−F, 2JC−F = 22.0 Hz). HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for Molecular formula: C15H11FNS, 256.0596; found, 256.0589.

*4-(Pyridin-2-ylthio)isoquinoline (**2l**).* 214 mg, 90% yield; orange liquid. R_f = 0.20 (20% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3048, 1568, 1450, 1122, 762. ^1H NMR (400 MHz, $CDCl_3$): δ 9.34 (s, 1H), 8.87 (s, 1H), 8.39 (dt, J_1 = 0.8 Hz, J_2 = 4.8 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.78−7.71 (m, 1H), 7.70−7.64 (m, 1H), 7.36 (td, J_1 = 1.6 Hz, J_2 = 7.6 Hz, 1H), 7.02−6.95 (m, 1H), 6.68 (d, J = 8.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.3, 154.8, 150.4, 149.8, 137.4, 136.9, 131.9, 129.3, 128.4, 128.2, 125.2, 123.3, 121.1, 120.2. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}N_2S$, 239.0642; found, 239.0640.

*4-(Naphthalen-2-ylthio)isoquinoline (**2m**).* 248 mg, 86% yield; orange liquid. R_f = 0.38 (15% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3053, 1620, 1564, 1378, 746. ^1H NMR (400 MHz, $CDCl_3$): δ 9.27 (s, 1H), 8.76−8.70 (m, 1H), 8.30 (d, J = 8.8 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.78−7.73 (m, 1H), 7.72−7.66 (m, 3H), 7.65−7.59 (m, 2H), 7.46−7.39 (m, 2H), 7.31 (d, J = 8.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.5, 148.1, 136.4, 133.8, 133.2, 132.1, 131.5, 129.1, 129.0, 128.3, 128.0, 127.8, 127.7, 127.3, 126.9, 126.8, 126.4, 126.1, 124.8. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{19}H_{14}NS$, 288.0847; found, 288.0878.

*4-(Cyclohexylthio)isoquinoline (**2n**).* 204 mg, 84% yield; orange solid. mp 58−60 °C. R_f = 0.33 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3058, 2929, 1620, 1564, 1446, 1258, 989, 753. ^1H NMR (400 MHz, $CDCl_3$): δ 9.17 (s, 1H), 8.67 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.82−7.75 (m, 1H), 7.64 (t, J = 7.6 Hz, 1H), 2.01−1.90 (m, 2H), 1.81−1.70 (m, 2H), 1.63−1.54 (m, 1H), 1.49−1.36 (m, 2H), 1.31−1.22 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.4, 147.9, 137.5, 131.0, 128.9, 128.2, 127.7, 127.1, 125.1, 47.6, 33.7, 26.1, 25.8. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{15}H_{18}NS$, 244.1160; found, 244.1142.

*4-(Ethylthio)isoquinoline (**2o**).* 156 mg, 82% yield; orange liquid. R_f = 0.23 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3049, 1619, 1564, 1378, 1264, 985, 741. ^1H NMR (400 MHz, $CDCl_3$): δ 9.11 (s, 1H), 8.56 (s, 1H), 8.31 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 3.00 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 151.5, 144.5, 136.0, 130.8, 128.6, 128.5, 128.2, 127.7, 124.3, 28.5, 14.6. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{11}H_{12}NS$, 190.0676; found, 190.0690.

*4-(tert-Butylthio)isoquinoline (**2p**).* 176 mg, 81% yield; yellow solid. mp 58−60 °C. R_f = 0.20 (5% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 2959, 1563, 1459, 1159, 754. ^1H NMR (400 MHz, $CDCl_3$): δ 9.21 (s, 1H), 8.72 (s, 1H), 8.58 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.59 (t, J = 7.2 Hz, 1H), 1.28 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.6, 151.9, 139.5, 130.9, 128.9, 127.9, 31.3, 47.9, 125.6, 127.5, 126.2, 125.6, 47.9, 31.3. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{13}H_{16}NS$, 218.1003; found, 218.1023.

*4-(Phenylselanyl)isoquinoline (**2ac**).* 252 mg, 89% yield; yellow liquid. R_f = 0.33 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3055, 1574, 1478, 1265, 897, 743. ^1H NMR (400 MHz, $CDCl_3$): δ 9.22 (s, 1H), 8.77 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 7.2 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.40−7.32 (m, 2H), 7.22−7.14 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.5, 149.2, 137.0, 131.7, 131.4, 130.7, 129.5, 129.2, 128.3, 127.9, 127.2, 126.8, 124.4. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{15}H_{12}NSe$, 286.0135; found, 286.0135.

*3-(Phenylthio)quinoline (**4a**).* 196 mg, 83% yield; yellow liquid. R_f = 0.40 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3056, 1578, 1484, 1265, 741. ^1H NMR (400 MHz, $CDCl_3$): δ 8.82 (s, 1H), 8.13−8.02 (m, 2H), 7.74−7.65 (m, 2H), 7.53 (t, J = 7.2 Hz, 1H), 7.43−7.37 (m, 2H), 7.37−7.27 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.3, 146.7, 137.2, 134.4, 131.5, 130.1, 129.7, 129.6, 129.4, 128.3, 127.9, 127.4, 127.3. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{15}H_{12}NS$, 238.0690; found, 238.0686.

*3-(p-Tolylthio)quinoline (**4b**).* 204 mg, 81% yield; yellow liquid. R_f = 0.40 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3052, 1579, 1491, 1263, 957, 746. ^1H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.96 (s, 1H), 7.71−7.61 (m, 2H), 7.52 (t, J = 7.2 Hz, 1H), 7.35 (d, J = 7.6 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 2.36 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 151.6, 146.5, 138.5, 135.8, 132.5 (2C), 131.4, 130.5, 130.0, 129.4, 128.4, 127.3,

https://dx.doi.org/10.1021/acs.joc.0c02672
J. Org. Chem. 2021, 86, 2570−2581

127.2, 21.3. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{16}H_{14}NS$, 252.0847; found, 252.0844.

*3-(o-Tolylthio)quinoline (**4c**).* 202 mg, 80% yield; yellow liquid. R_f = 0.33 (5% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3060, 1582, 1490, 1355, 956, 751. ^1H NMR (400 MHz, $CDCl_3$): δ 8.77−8.69 (m, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.84 (s, 1H), 7.69−7.61 (m, 2H), 7.54−7.47 (m, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.31−7.23 (m, 2H), 7.20−7.14 (m, 1H), 2.41 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 151.3, 146.5, 140.3, 135.3, 133.5, 132.3, 131.1, 130.6, 129.4, 129.3, 128.7, 128.4, 127.3, 127.2 (2C), 20.7. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{16}H_{14}NS$, 252.0847; found, 252.0859.

*3-((4-Methoxyphenyl)thio)quinoline (**4d**).* 222 mg, 83% yield; pale yellow liquid. R_f = 0.28 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3061, 1588, 1492, 1253, 803. ^1H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.82 (s, 1H), 7.68−7.62 (m, 2H), 7.51 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 8.8 Hz, 2H), 6.97−6.90 (m, 2H), 3.84 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.4, 150.7, 146.3, 135.6, 134.0, 132.9, 129.4, 129.1, 128.4, 127.3, 127.1, 123.1, 115.5, 55.6. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{16}H_{14}NOS$, 268.0796; found, 268.0797.

*3-((3-Methoxyphenyl)thio)quinoline (**4e**).* 220 mg, 82% yield; yellow liquid. R_f = 0.30 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3061, 1584, 1476, 1241, 1040, 759. ^1H NMR (400 MHz, $CDCl_3$): δ 8.88−8.77 (m, 1H), 8.13−8.04 (m, 2H), 7.76−7.65 (m, 2H), 7.54 (t, J = 7.2 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 6.98−6.90 (m, 2H), 6.86−6.79 (m, 1H), 3.76 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.3, 152.4, 146.8, 137.5, 135.7, 130.4, 129.8, 129.7, 129.4, 128.3 (2C), 127.4, 123.4, 116.5, 113.6, 55.4. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{16}H_{14}NOS$, 268.0796; found, 268.0801.

*3-((2-Methoxyphenyl)thio)quinoline (**4f**).* 216 mg, 81% yield; yellow liquid. R_f = 0.20 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3061, 1578, 1472, 1251, 1022, 750. ^1H NMR (400 MHz, $CDCl_3$): δ 8.80 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.04 (s, 1H), 7.72−7.64 (m, 2H), 7.52 (t, J = 7.6 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 6.96−6.88 (m, 2H), 3.84 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.1, 152.1, 146.5, 137.1, 132.9, 129.7 (2C), 129.5, 129.2, 128.4 (2C), 127.3, 122.0, 121.6, 111.4, 56.0. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{16}H_{14}NOS$, 268.0796; found, 268.0801.

*3-((4-Bromophenyl)thio)quinoline (**4g**).* 184 mg, 58% yield; light yellow solid. mp 58−60 °C. R_f = 0.42 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3052, 1572, 1473, 1324, 1078, 814, 752. ^1H NMR (400 MHz, $CDCl_3$): δ 8.85−8.76 (m, 1H), 8.17−8.01 (m, 2H), 7.75−7.67 (m, 2H), 7.58−7.51 (m, 1H), 7.47−7.39 (m, 2H), 7.24−7.19 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.4, 146.9, 137.9, 134.0, 132.7, 132.5, 130.0, 129.4, 129.1, 128.2, 127.5, 127.4, 121.8. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{15}H_{11}NSBr$, 317.9796; found, 317.9777.

*3-((2,4-Dichlorophenyl)thio)quinoline (**4h**).* 180 mg, 59% yield; pale yellow liquid. R_f = 0.37 (5% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3061, 1568, 1446, 1364, 1093, 808, 752. ^1H NMR (400 MHz, $CDCl_3$): δ 8.86 (d, J = 2.4 Hz, 1H), 8.26 (d, J = 2.0 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.81−7.73 (m, 2H), 7.59 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 8.8 Hz, 1H), 7.10 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz 1H), 6.90 (d, J = 2.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.6, 147.5, 141.0, 137.5, 133.5, 131.5, 130.9, 130.7, 129.6, 129.3, 128.3, 127.9, 127.7, 127.6, 125.6. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{15}H_{10}NSCl_2$, 305.9911; found, 305.9900.

*3-((4-Chlorophenyl)thio)quinoline (**4i**).* 160 mg, 59% yield; light yellow solid. mp 52−54 °C. R_f = 0.42 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3060, 1573, 1480, 1358, 1089, 752. ^1H NMR (400 MHz, $CDCl_3$): δ 8.83−8.78 (m, 1H), 8.11−8.05 (m, 2H), 7.74−7.68 (m, 2H), 7.55 (t, J = 7.6 Hz, 1H), 7.32−7.27 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.3, 146.9, 137.7, 133.9, 133.2, 132.5, 129.9, 129.8, 129.5, 129.4, 128.3, 127.5, 127.4. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{15}H_{11}NSCl$, 272.0301; found, 272.0300.

*3-((4-Fluorophenyl)thio)quinoline (**4j**).* 142 mg, 56% yield; brown liquid. R_f = 0.33 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3055, 1586, 1488, 1266, 1229, 746. ^1H NMR (400 MHz, $CDCl_3$): δ 8.77 (s, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.96 (s, 1H), 7.71−7.62 (m, 2H), 7.51 (t, J = 7.6 Hz, 1H), 7.46−7.38 (m, 2H), 7.10−7.00 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.8 (C−F, 1JC−F = 247.5 Hz), 151.5, 146.6, 136.1, 134.4 (C−F, 3JC−F = 8.3 Hz), 130.8, 129.6, 129.3, 128.9 (C−F, 4JC−F = 3.4 Hz), 128.2, 127.4, 127.2, 116.9 (C−F, 2JC−F = 21.9 Hz). HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{15}H_{11}NSF$, 256.0596; found, 256.0599.

*3-(Pyridin-2-ylthio)quinoline (**4k**).* 196 mg, 82% yield; yellow liquid. R_f = 0.33 (20% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3052, 1570, 1415, 1122, 757. ^1H NMR (400 MHz, $CDCl_3$): δ 9.01−8.91 (m, 1H), 8.44−8.37 (m, 2H), 8.13 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.79−7.72 (m, 1H), 7.63−7.54 (m, 1H), 7.53−7.45 (m, 1H), 7.07−7.00 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.4, 154.8, 150.0, 147.5, 141.9, 137.0, 130.5, 129.5, 128.4, 127.8, 127.4, 125.2, 122.0, 120.7. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}N_2S$, 239.0643; found, 239.0639.

*3-(Naphthalen-2-ylthio)quinoline (**4l**).* 228 mg, 79% yield; white solid. mp 70−72 °C. R_f = 0.27 (5% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3054, 1583, 1493, 1358, 956, 744. ^1H NMR (400 MHz, $CDCl_3$): δ 8.90 (s, 1H), 8.12 (d, J = 8.8 Hz, 1H), 8.08 (s, 1H), 7.91 (s, 1H), 7.84−7.76 (m, 2H), 7.75−7.63 (m, 3H), 7.55−7.41 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.1, 146.7, 137.0, 133.8, 132.5, 131.5, 130.5, 130.1, 129.6, 129.4, 128.6, 128.3, 127.8, 127.5, 127.4, 127.3, 126.9, 126.6. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{19}H_{14}NS$, 288.0847; found, 288.0850.

*3-(Ethylthio)quinoline (**4m**).* 134 mg, 71% yield; brown liquid. R_f = 0.33 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3054, 2974, 1578, 1491, 1264, 958, 748. ^1H NMR (400 MHz, $CDCl_3$): δ 8.81 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.98 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.65−7.58 (m, 1H), 7.53−7.46 (m, 1H), 3.00 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 151.6, 146.3, 134.8, 130.7, 129.3, 129.0, 128.2, 127.2, 126.9, 28.0, 14.3. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{11}H_{12}NS$, 190.0690; found, 190.0694.

*3-(tert-Butylthio)quinoline (**4n**).* 156 mg, 72% yield; yellow liquid. R_f = 0.37 (5% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3060, 2965, 1564, 1487, 1364, 1166, 959, 912, 751. ^1H NMR (400 MHz, $CDCl_3$): δ 8.94 (d, J = 2.0 Hz, 1H), 8.32 (d, J = 1.2 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.74−7.68 (m, 1H), 7.53 (t, J = 8.0 Hz, 1H), 1.30 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 156.9, 147.5, 144.5, 130.3, 129.3, 128.0, 127.8, 127.1, 126.8, 46.9, 31.0. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{13}H_{16}NS$, 218.1003; found, 218.1013.

*3-(Cyclohexylthio)quinoline (**4o**).* 182 mg, 75% yield; pale yellow liquid. R_f = 0.42 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3057, 2928, 1489, 1448, 1259, 1078, 958, 900, 750. ^1H NMR (400 MHz, $CDCl_3$): δ 8.95−8.85 (m, 1H), 8.19−8.11 (m, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H), 3.24−3.13 (s, 1H), 2.05−1.93 (m, 2H), 1.83−1.72 (m, 2H), 1.65−1.56 (m, 1H), 1.49−1.21 (m, 5H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.8, 146.8, 138.7, 129.5, 129.4, 129.1, 128.2, 127.3, 127.2, 47.3, 33.5, 26.1, 25.7. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{15}H_{18}NS$, 244.1160; found, 244.1153

*8-Methoxy-3-(phenylthio)quinoline (**4p**).* 118 mg, 44% yield; pale yellow solid. mp 94−96 °C. R_f = 0.15 (20% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3060, 2936, 1570, 1479, 1370, 1260, 1124, 911, 753. ^1H NMR (400 MHz, $CDCl_3$): δ 8.81 (d, J = 2.0 Hz, 1H), 7.99 (d, J = 2.0 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.38 (d, J = 6.8 Hz, 2H), 7.34−7.27 (m, 3H), 7.24 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 4.06 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.5, 150.8, 138.4, 136.7, 134.2, 131.4, 130.9, 129.5, 129.4, 127.8, 127.7, 119.0, 107.8, 56.0. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{16}H_{14}NOS$, 268.0796; found, 268.0800.

*8-Methoxy-3-(p-tolylthio)quinoline (**4q**).* 106 mg, 38% yield; pale yellow liquid. R_f = 0.27 (20% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3050, 2929, 1565, 1485, 1373, 1318, 1124, 756. ^1H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, J = 1.6 Hz, 1H), 7.90 (d, J = 1.6 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.4

https://dx.doi.org/10.1021/acs.joc.0c02672
J. Org. Chem. 2021, 86, 2570−2581

Hz, 1H), 7.16 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 8.0 Hz, 1H), 4.07 (s, 3H), 2.35 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 155.6, 150.2, 138.4, 138.3, 135.5, 132.5, 132.3, 130.5, 129.9, 129.5, 127.6, 119.0, 107.7, 56.1, 21.3. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}NOS$, 282.0952; found, 282.0960.

*8-Methoxy-3-((4-methoxyphenyl)thio)quinoline (**4r**).* 118 mg, 40% yield; pale yellow liquid. R_f = 0.15 (20% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3058, 2940, 1579, 1492, 1374, 1250, 1174, 757. ^1H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J = 2.0 Hz, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.40 (t, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 4.06 (s, 3H), 3.82 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.4, 155.6, 149.2, 138.1, 135.5, 133.7, 133.6, 129.6, 127.6, 122.9, 118.9, 115.4, 107.4, 56.1, 55.6. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}NO_2S$, 298.0901; found, 298.0895.

*5-(Phenylthio)quinolin-8-amine (**4s**).* 206 mg, 82% yield; dark brown solid. mp 74−76 °C. R_f = 0.29 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3477, 3369, 3053, 1601, 1499, 1199, 949, 739. ^1H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, J = 4.0 Hz, 1H), 8.59 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.39 (dd, J_1= 4.0 Hz, J_2= 8.8 Hz, 1H), 7.14 (t, J = 7.2 Hz, 2H), 7.04 (t, J = 7.6 Hz, 1H), 6.99 (d, J = 7.6 Hz, 2H), 6.92 (d, J = 8.0 Hz, 1H), 5.28 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 147.7, 146.3, 139.7, 139.1, 137.8, 134.8, 130.8, 128.9, 126.1, 125.0, 122.6, 114.2, 109.5. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{15}H_{13}N_2S$, 253.0799; found, 253.0801.

*N-(5-(Phenylthio)quinolin-8-yl)benzamide (**4t**).* 125 mg, 35% yield; yellow solid. mp 132−134 °C. R_f = 0.54 (10% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3427, 3355, 3058, 1675, 1522, 1476, 1183, 943, 740. ^1H NMR (400 MHz, $CDCl_3$): δ 10.86 (s, 1H), 8.95 (d, J = 8.0 Hz, 1H), 8.89−8.83 (m, 1H), 8.70 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 7.2 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.64−7.53 (m, 3H), 7.52−7.46 (m, 1H), 7.24−7.16 (m, 2H), 7.15−1.06 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.7, 148.6, 139.6, 137.8, 136.2, 136.1, 135.1, 135.0, 132.2, 129.5, 129.2, 129.0, 127.7, 127.5, 125.9, 123.3, 122.6, 116.5. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{22}H_{17}N_2OS$, 357.1062; found, 357.1066.

*3-(Phenylthio)-7-azaindole (**6a**).* 203 mg, 90% yield; cream solid. mp 176−178 °C. R_f = 0.62 (50% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3011, 2991, 1580, 1473, 1413, 1283, 740, 736. ^1H NMR (400 MHz, $CDCl_3$): δ 11.03 (s, 1H), 8.40 (d, J = 4.8 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.68 (s, 1H), 7.21−7.13 (m, 3H), 7.12−7.05 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.4, 143.4, 138.9, 132.1, 128.9, 128.6, 126.1, 125.2, 122.3, 116.9, 101.5. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{13}H_{11}N_2S$, 227.0643; found, 227.0642.

*4-Chloro-3-(phenylthio)-7-azaindole (**6b**).* 219 mg, 84% yield; white solid. mp 208−210 °C. R_f = 0.65 (50% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3031, 2948, 1585, 1477, 1437, 1269, 793, 738. ^1H NMR (400 MHz, $CDCl_3$): δ 11.02 (s, 1H), 8.30−8.20 (m, 1H), 7.67 (s, 1H), 7.24−7.17 (m, 2H), 7.16−7.06 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 150.1, 144.0, 140.0, 137.9, 133.3, 128.9, 126.3, 125.3, 119.1, 118.5, 102.2. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{13}H_{10}ClN_2S$, 261.0253, found 261.0248.

*1-Methyl-3-(phenylthio)-7-azaindole (**6c**).* 206 mg, 86% yield; brown solid. mp 88−90 °C. R_f = 0.38 (15% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3046, 2945, 1568, 1405, 1300, 772, 743. ^1H NMR (400 MHz, $CDCl_3$): δ 8.43−8.36 (m, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.48 (s, 1H), 7.21−7.14 (m, 2H), 7.13−7.02 (m, 4H), 3.95 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 148.5, 143.9, 139.1, 135.3, 128.9, 128.1, 126.1, 125.1, 122.3, 116.7, 99.8, 31.6. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}N_2S$, 241.0799; found, 241.0796.

*3-((4-Methoxyphenyl)thio)-7-azaindole (**6d**).* 226 mg, 88% yield; cream solid. mp 146−148 °C. R_f = 0.55 (50% ethyl acetate in hexane). FTIR (neat) ν (cm^{-1}): 3061, 2919, 1588, 1445, 1410, 1283, 806, 763. ^1H NMR (400 MHz, $CDCl_3$): δ 11.47 (s, 1H), 8.38 (d, J = 4.4 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.66 (s, 1H), 7.20−7.10 (m, 3H), 6.80−6.70 (m, 2H), 3.74 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.2, 149.3, 143.5, 131.1, 129.1 (2C), 128.5, 122.1, 116.8, 114.7, 103.5, 55.5. HRMS (TOF MS ES+) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}N_2OS$, 257.0749; found, 257.0744.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02672.

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

Accession Codes

CCDC 1914361 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Govindasamy Sekar − *Department of Chemistry, Indian Institute of Technology Madras, Chennai 600 036, Tamil Nadu, India*; orcid.org/0000-0003-2294-0485; Email: gsekar@iitm.ac.in

Authors

Anuradha Nandy − *Department of Chemistry, Indian Institute of Technology Madras, Chennai 600 036, Tamil Nadu, India*

Imran Kazi − *Department of Chemistry, Indian Institute of Technology Madras, Chennai 600 036, Tamil Nadu, India*

Somraj Guha − *Department of Chemistry, Indian Institute of Technology Madras, Chennai 600 036, Tamil Nadu, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02672

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank DST-SERB, New Delhi (EMR/2017/00/001700) for financial support. A.N., I.K., and S.G. thank IIT Madras for the fellowship. High-performance computing centre at IIT Madras is gratefully acknowledged for providing the computing facility.

■ DEDICATION

Dedicated to Prof. Sundarababu Baskaran on the occasion of his 60th birthday

■ REFERENCES

(1) Goncharov, N.; Orekhov, A. N.; Voitenko, N.; Ukolov, A.; Jenkins, R.; Avdonin, P. *Nutraceuticals: Efficacy, Safety and Toxicity*; Gupta, R. C., Ed.; Academic Press, 2016; Chapter 41, pp 555−568.

(2) Saari, R.; Törmä, J.-C.; Nevalainen, T. Microwave-assisted synthesis of quinoline, isoquinoline, quinoxaline and quinazoline derivatives as CB2 receptor agonists. *Bioorg. Med. Chem.* **2011**, *19*, 939−950.

(3) Boateng, C. A.; Zhu, X. Y.; Jacob, M. R.; Khan, S. I.; Walker, L. A.; Ablordeppey, S. Y. Optimization of 3-(phenylthio)quinolinium compounds against opportunistic fungal pathogens. *Eur. J. Med. Chem.* **2011**, *46*, 1789−1797.

(4) Hopkins, A. L.; Ren, J.; Milton, J.; Hazen, R. J.; Chan, J. H.; Stuart, D. I.; Stammers, D. K. Design of Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase with Improved Drug Resistance Properties. 1. *J. Med. Chem.* **2004**, *47*, 5912−5922.
(5) (a) Ji, X.-M.; Zhou, S.-J.; Chen, F.; Zhang, X.-G.; Tang, R.-Y. Direct Sulfenylation of Imidazoheterocycles with Disulfides in an Iodine−Hydrogen Peroxide System. *Synthesis* **2015**, *47*, 659−671. (b) Ge, W.; Wei, Y. Iodine-catalyzed oxidative system for 3-sulfenylation of indoles with disulfides using DMSO as oxidant under ambient conditions in dimethyl carbonate. *Green Chem.* **2012**, *14*, 2066−2070.
(6) (a) Uyeda, C.; Tan, Y.; Fu, G. C.; Peters, J. C. A New Family of Nucleophiles for Photoinduced, Copper-Catalyzed Cross-Couplings via Single-Electron Transfer: Reactions of Thiols with Aryl Halides Under Mild Conditions (0 °C). *J. Am. Chem. Soc.* **2013**, *135*, 9548−9552. (b) Hartwig, J. F. Evolution of a Fourth Generation Catalyst for the Amination and Thioetherification of Aryl Halides. *Acc. Chem. Res.* **2008**, *41*, 1534−1544. (c) Gogoi, P.; Hazarika, S.; Sarma, K.; Sarma, M. J.; Barman, P. Nickel−Schiff base complex catalyzed C−S cross-coupling of thiols with organic chlorides. *Tetrahedron* **2014**, *70*, 7484−7489. (d) Kwong, F. Y.; Buchwald, S. L. A General, Efficient, and Inexpensive Catalyst System for the Coupling of Aryl Iodides and Thiols. *Org. Lett.* **2002**, *4*, 3517−3520. (e) Fernandez-Rodriguez, M. A.; Shen, Q.; Hartwig, J. F. A General and Long-Lived Catalyst for the Palladium-Catalyzed Coupling of Aryl Halides with Thiols. *J. Am. Chem. Soc.* **2006**, *128*, 2180−2181. (f) Alvaro, E.; Hartwig, J. F. Resting State and Elementary Steps of the Coupling of Aryl Halides with Thiols Catalyzed by Alkylbisphosphine Complexes of Palladium. *J. Am. Chem. Soc.* **2009**, *131*, 7858−7868. (g) Beletskaya, I. P.; Ananikov, V. P. Transition-Metal-Catalyzed C−S, C−Se, and C−Te Bond Formation via Cross-Coupling and Atom-Economic Addition Reactions. *Chem. Rev.* **2011**, *111*, 1596−1636. (h) Sayah, M.; Organ, M. G. Carbon−Sulfur Bond Formation of Challenging Substrates at Low Temperature by Using Pd-PEPPSI-IPent. *Chem. - Eur. J.* **2011**, *17*, 11719−11722. (i) Murata, M.; Buchwald, S. L. A general and efficient method for the palladium-catalyzed cross-coupling of thiols and secondary phosphines. *Tetrahedron* **2004**, *60*, 7397−7403.
(7) (a) Correa, A.; Carril, M.; Bolm, C. Iron-Catalyzed S-Arylation of Thiols with Aryl Iodides. *Angew. Chem., Int. Ed.* **2008**, *47*, 2880−2883. (b) Tan, C.-M.; Chen, G. S.; Chen, C.-S.; Chern, J.-W. Microwave-Assisted Cross-Coupling for the Construction of Diaryl Sulfides. *J. Chin. Chem. Soc.* **2011**, *58*, 94−100. (c) Barbiéri, R. S.; Bellato, C. R.; Dias, A. K. C.; Massabni, A. C. Effect of Substitution of $[Pd(PPh_3)_4]$ by Related Compounds as Catalysts in Reactions of Organic Syntheses. *Catal. Lett.* **2006**, *109*, 171−174.
(8) Wang, X.; Cuny, G. D.; Noël, T. A mild, one-pot Stadler-Ziegler synthesis of arylsulfides facilitated by photoredox catalysis in batch and continuous-flow. *Angew. Chem., Int. Ed.* **2013**, *52*, 7860−7864.
(9) Jouffroy, M.; Kelly, C. B.; Molander, G. A. Thioetherification via Photoredox/Nickel Dual Catalysis. *Org. Lett.* **2016**, *18*, 876−879.
(10) Jiang, M.; Li, H.; Yang, H.; Fu, H. Room-Temperature Arylation of Thiols: Breakthrough with Aryl Chlorides. *Angew. Chem., Int. Ed.* **2017**, *56*, 874−879.
(11) Natarajan, P.; Manjeet; Muskan; Brar, N. K.; Kaur, J. J. Visible light photoredox catalysis: conversion of a mixture of thiophenols and nitriles into 2-substituted benzothiazoles via consecutive C−S and C−N bond formation reactions. *Org. Chem. Front.* **2018**, *5*, 1527−1531.
(12) (a) Lima, C. G. S.; Lima, T. de M.; Duarte, M.; Jurberg, I. D.; Paixão, M. W. Organic Synthesis Enabled by Light-Irradiation of EDA Complexes: Theoretical Background and Synthetic Applications. *ACS Catal.* **2016**, *6*, 1389−1407. (b) Foster, R. Electron donor-acceptor complexes. *J. Phys. Chem.* **1980**, *84*, 2135−2141. (c) Kochi, J. K. Charge-transfer excitation of molecular complexes in organic and organometallic chemistry. *Pure Appl. Chem.* **1991**, *63*, 255−264.
(13) (a) Cavallo, G.; Metrangolo, P.; Milani, R.; Pilati, T.; Priimagi, A.; Resnati, G.; Terraneo, G. The Halogen Bond. *Chem. Rev.* **2016**, *116*, 2478−2601. (b) Beale, T. M.; Chudzinski, M. G.; Sarwar, M. G.; Taylor, M. S. Halogen bonding in solution: thermodynamics and applications. *Chem. Soc. Rev.* **2013**, *42*, 1667−1680. (c) Politzer, P.; Murray, J. S.; Clark, T. Halogen bonding: an electrostatically-driven highly directional noncovalent interaction. *Phys. Chem. Chem. Phys.* **2010**, *12*, 7748−7757.
(14) (a) Postigo, A. Electron Donor-Acceptor Complexes in Perfluoroalkylation Reactions. *Eur. J. Org. Chem.* **2018**, *2018*, 6391−6404. (b) Miao, R.; Wang, D.; Xiao, J.; Ma, J.; Xue, D.; Liu, F.; Fang, Y. Halogen bonding matters: visible light-induced photoredox catalyst-free aryl radical formation and its applications. *Phys. Chem. Chem. Phys.* **2020**, *22*, 10212−10218.
(15) (a) Voth, A. R.; Ho, P. S. The role of halogen bonding in inhibitor recognition and binding by protein kinases. *Curr. Top. Med. Chem.* **2007**, *7*, 1336−1348. (b) Battistutta, R.; De Moliner, E.; Sarno, S.; Zanotti, G.; Pinna, L. A. Structural features underlying selective inhibition of protein kinase CK2 by ATP site-directed tetrabromo-2-benzotriazole. *Protein Sci.* **2001**, *10*, 2200−2206. (c) Dobeš, P.; Řezáč, J.; Fanfrlík, J.; Otyepka, M.; Hobza, P. Semiempirical Quantum Mechanical Method PM6-DH2X Describes the Geometry and Energetics of CK2-Inhibitor Complexes Involving Halogen Bonds Well, While the Empirical Potential Fails. *J. Phys. Chem. B* **2011**, *115*, 8581−8589. (d) Wąsik, R.; Łebska, M.; Felczak, K.; Poznański, J.; Shugar, D. Relative Role of Halogen Bonds and Hydrophobic Interactions in Inhibition of Human Protein Kinase CK2α by Tetrabromobenzotriazole and Some C(5)-Substituted Analogues. *J. Phys. Chem. B* **2010**, *114*, 10601−10611. (e) Mondal, S.; Raja, K.; Schweizer, U.; Mugesh, G. Chemistry and Biology in the Biosynthesis and Action of Thyroid Hormones. *Angew. Chem., Int. Ed.* **2016**, *55*, 7606−7630.
(16) (a) Metrangolo, P.; Pilati, T.; Terraneo, G.; Biella, S.; Resnati, G. Anion coordination and anion-templated assembly under halogen bonding control. *CrystEngComm* **2009**, *11*, 1187−1196. (b) Corradi, E.; Meille, S. V.; Messina, M. T.; Metrangolo, P.; Resnati, G. Halogen Bonding versus Hydrogen Bonding in Driving Self-Assembly Processes. *Angew. Chem., Int. Ed.* **2000**, *39*, 1782−1786. (c) Aakeröy, C. B.; Chopade, P. D.; Desper, J. Avoiding "Synthon Crossover" in Crystal Engineering with Halogen Bonds and Hydrogen Bonds. Cryst. *Cryst. Growth Des.* **2011**, *11*, 5333−5336. (d) Aakeröy, C. B.; Fasulo, M.; Schultheiss, N.; Desper, J.; Moore, C. Structural Competition between Hydrogen Bonds and Halogen Bonds. *J. Am. Chem. Soc.* **2007**, *129*, 13772−13773. (e) Aakeröy, C. B.; Baldrighi, M.; Desper, J.; Metrangolo, P.; Resnati, G. Supramolecular Hierarchy among Halogen-Bond Donors. *Chem. - Eur. J.* **2013**, *19*, 16240−16247.
(17) (a) Metrangolo, P.; Resnati, G.; Pilati, T.; Liantonio, R.; Meyer, F. Engineering functional materials by halogen bonding. *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 1−15. (b) Metrangolo, P.; Meyer, F.; Resnati, G.; Ursini, M. Haloperfluorocarbons: Versatile Tectons in Halogen Bonding Based Crystal Engineering. *ACS Symp. Ser.* **2005**, *911*, 514−542. (c) Bertani, R.; Sgarbossa, P.; Venzo, A.; Lelj, F.; Amati, M.; Resnati, G.; Pilati, T.; Metrangolo, P.; Terraneo, G. Halogen bonding in metal−organic−supramolecular networks. *Coord. Chem. Rev.* **2010**, *254*, 677−695. (d) Dey, A.; Metrangolo, P.; Pilati, T.; Resnati, G.; Terraneo, G.; Wlassics, I. The disorder of perfluoroalkyl chains in crystals: Two case histories of interpretation and refinement. *J. Fluorine Chem.* **2009**, *130*, 816−823.
(18) (a) He, W.; Ge, Y.-C.; Tan, C.-H. Halogen-Bonding-Induced Hydrogen Transfer to C = N Bond with Hantzsch Ester. *Org. Lett.* **2014**, *16*, 3244−3247. (b) Saito, M.; Tsuji, N.; Kobayashi, Y.; Takemoto, Y. Direct Dehydroxylative Coupling Reaction of Alcohols with Organosilanes through Si−X Bond Activation by Halogen Bonding. *Org. Lett.* **2015**, *17*, 3000−3003. (c) Takeda, Y.; Hisakuni, D.; Lin, C.-H.; Minakata, S. 2-Halogenoimidazolium Salt Catalyzed Aza-Diels−Alder Reaction through Halogen-Bond Formation. *Org. Lett.* **2015**, *17*, 318−321. (d) Sun, X.; Wang, W.; Li, Y.; Ma, J.; Yu, S. Halogen-Bond-Promoted Double Radical Isocyanide Insertion under Visible-Light Irradiation: Synthesis of 2-Fluoroalkylated Quinoxalines. *Org. Lett.* **2016**, *18*, 4638−4641. (e) Combe, S. H.; Hosseini, A.; Song, L.; Hausmann, H.; Schreiner, P. R. Catalytic Halogen Bond Activation in the Benzylic C−H Bond Iodination with Iodohydantoins. *Org. Lett.* **2017**, *19*, 6156−6159. (f) Wang, Y.; Wang, J.; Li, G.-X.; He, G.; Chen, G. Halogen-Bond-Promoted Photoactivation of

https://dx.doi.org/10.1021/acs.joc.0c02672
J. Org. Chem. 2021, 86, 2570−2581

Perfluoroalkyl Iodides: A Photochemical Protocol for Perfluoroalkylation Reactions. *Org. Lett.* **2017**, *19*, 1442−1445. (g) Jungbauer, S. H.; Walter, S. M.; Schindler, S.; Rout, L.; Kniep, F.; Huber, S. M. Activation of a carbonyl compound by halogen bonding. *Chem. Commun.* **2014**, *50*, 6281−6284. (h) Gliese, J.-P.; Jungbauer, S. H.; Huber, S. M. A halogen-bonding-catalyzed Michael addition reaction. *Chem. Commun.* **2017**, *53*, 12052−12055. (i) Kuwano, S.; Suzuki, T.; Hosaka, Y.; Arai, T. A chiral organic base catalyst with halogen-bonding-donor functionality: asymmetric Mannich reactions of malononitrile with N-Boc aldimines and ketimines. *Chem. Commun.* **2018**, *54*, 3847−3850. (j) Breugst, M.; von der Heiden, D. Mechanisms in Iodine Catalysis. *Chem. - Eur. J.* **2018**, *24*, 9187−9199. (k) Bruckmann, A.; Pena, M. A.; Bolm, C. Organocatalysis through Halogen-Bond Activation. *Synlett* **2008**, *2008* (6), 900−902.

(19) (a) Kazi, I.; Guha, S.; Sekar, G. CBr_4 as a Halogen Bond Donor Catalyst for the Selective Activation of Benzaldehydes to Synthesize α,β-Unsaturated Ketones. *Org. Lett.* **2017**, *19*, 1244−1247. (b) Guha, S.; Kazi, I.; Mukherjee, P.; Sekar, G. Halogen-bonded iodonium ion catalysis: a route to α-hydroxy ketones via domino oxidations of secondary alcohols and aliphatic C−H bonds with high selectivity and control. *Chem. Commun.* **2017**, *53*, 10942−10945. (c) Guha, S.; Kazi, I.; Nandy, A.; Sekar, G. Role of Lewis-Base-Coordinated Halogen(I) Intermediates in Organic Synthesis: The Journey from Unstable Intermediates to Versatile Reagents. *Eur. J. Org. Chem.* **2017**, *2017*, 5497−5518. (d) Guha, S.; Sekar, G. Metal-Free Halogen(I) Catalysts for the Oxidation of Aryl(heteroaryl)methanes to Ketones or Esters: Selectivity Control by Halogen Bonding. *Chem. - Eur. J.* **2018**, *24*, 14171−14182. (e) Kazi, I.; Guha, S.; Sekar, G. Halogen Bond-Assisted Electron-Catalyzed Atom Economic Iodination of Heteroarenes at Room Temperature. *J. Org. Chem.* **2019**, *84*, 6642−6654.

(20) (a) Garrett, C. E.; Prasad, K. The Art of Meeting Palladium Specifications in Active Pharmaceutical Ingredients Produced by Pd-Catalyzed Reactions. *Adv. Synth. Catal.* **2004**, *346*, 889−900. (b) Welch, C. J.; Albaneze-Walker, J.; Leonard, W. R.; Biba, M.; DaSilva, J.; Henderson, D.; Laing, B.; Mathre, D. J.; Spencer, S.; Bu, X.; Wang, T. Adsorbent Screening for Metal Impurity Removal in Pharmaceutical Process Research. *Org. Process Res. Dev.* **2005**, *9*, 198−205.

(21) Hayashi, Y. Pot economy and one-pot synthesis. *Chem. Sci.* **2016**, *7*, 866−880.

(22) See the Supporting Information for details.

(23) (a) Chen, J.; Wang, T.; Wang, T.; Lin, A.; Yao, H.; Xu, J. Copper-catalyzed C5-selective thio/selenocyanation of 8-aminoquinolines. *Org. Chem. Front.* **2017**, *4*, 130−134. (b) Kuninobu, Y.; Nishi, M.; Kanai, M. 5-Position-selective C−H trifluoromethylation of 8-aminoquinoline derivatives. *Org. Biomol. Chem.* **2016**, *14*, 8092−8100.

(24) Beale, T. M.; Chudzinski, M. G.; Sarwar, M. G.; Taylor, M. S. Halogen bonding in solution: thermodynamics and applications. *Chem. Soc. Rev.* **2013**, *42*, 1667−1680.

(25) Borrowman, C. K.; Zhou, S.; Burrow, T. E.; Abbatt, J. P. D. Formation of environmentally persistent free radicals from the heterogeneous reaction of ozone and polycyclic aromatic compounds. *Phys. Chem. Chem. Phys.* **2016**, *18*, 205−212.

(26) Widner, D. L.; Robinson, E. R.; Perez, A. B.; Vang, H. G.; Thorson, R. A.; Driscoll, Z. L.; Giebel, S. M.; Berndt, C. W.; Bosch, E.; Speetzen, E. D.; Bowling, N. P. Comparing Strong and Weak Halogen Bonding in Solution: ^{13}C NMR, UV/Vis, Crystallographic, and Computational Studies of an Intramolecular Model. *Eur. J. Org. Chem.* **2017**, *2017*, 5739−5749.

(27) Studer, A.; Curran, D. The electron is a catalyst. *Nat. Chem.* **2014**, *6*, 765−773.

(28) Cherng, Y.-J. Efficient nucleophilic substitution reactions of quinolyl and isoquinolyl halides with nucleophiles under focused microwave irradiation. *Tetrahedron* **2002**, *58*, 1125−1129.

https://dx.doi.org/10.1021/acs.joc.0c02672
J. Org. Chem. 2021, 86, 2570−2581