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Metal-free late-stage C(sp^2)–H functionalization of *N*-aryl amines with various sodium salts†

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Metal-free consecutive C(sp^2)–X (X = Cl, Br, S, N) bond formations of *N*-aryl amines (cyclic, fused, carbamate, and aminium radicals) were achieved under mild conditions using [bis(trifluoroacetoxy)iodo] benzene (PIFA) and simple nonharmful sodium salts. This direct and selective C(sp^2)–H functionalization showed excellent functional group compatibility, cost effectiveness, and late-stage applicability for the synthesis of biologically active natural products. Two mechanisms were proposed to explain the *ortho*- or *para*-preference, as well as the accelerating effect of CH_3NO_2.

Introduction

N-Aryl cyclic amines are impressive ring frameworks that have vast synthetic utility and are found in numerous natural products and biologically active molecules (Fig. 1).[1–4] For example, brucine, an indole-based alkaloid, has several pharmacological properties, such as antitumor, antiapoptotic, analgesic, and anti-inflammatory properties.[2] Brucine has also been used in traditional Chinese medicine for its therapeutic effects against arthritic and traumatic pain.[3] Furthermore, synthetic derivatives of brucine are better allosteric modulators of M_1 muscarinic receptors compared to brucine.[4] Therefore, the development of novel synthetic methods for the late-stage functionalization of *N*-aryl cyclic amines, such as brucine, can provide powerful tools for efficient structure–activity relationship (SAR) studies in medicinal chemistry and process chemistry.[4,5]

Metal-free C(sp^2)–H functionalization is an atom economical strategy that is important for environmental sustainability.[6] In particular, direct C–C and C–heteroatom bond formations on bioactive ring frameworks, such as *N*-aryl cyclic amines, can lead to significant advances in the pharmaceutical industry and drug discovery. To our knowledge, selectivity is a major issue in C(sp^2)–X functionalization. Recently, the selective functionalization of aminoaryl compounds was reported under both metal catalysis and metal-free conditions.[7] However, we believe that such functionalization requires improvements in three areas: (i) substituent diversity, resulting from the scope of reactions/substrates/reagents; (ii) cost-effectiveness, including environmental cost; and (iii) eligibility for late-stage functionalization.

Hypervalent iodine reagents are widely used as cost-effective metal-free oxidants in C–C and C–heteroatom bond formation reactions.[8] Among iodoarene(III) derivatives, PIFA has emerged as a powerful oxidant for C(sp^2)–H functionalization.[9] Before or during our study, direct functionalization has been reported, including *o*-chlorination,[9a] thiocyanation,[9b] sulfenylation,[9b] *o*-azidation,[9c] *p*-bromination,[9d] *p*-iodination,[9d] *p*-alkoxylation,[9e] *p*-acetoxylation,[9e] and nitration,[9f] using PIFA and two types of substrates, namely, phenolic derivatives and *N*-acyl aniline derivatives (Scheme 1). Despite their efficiency, these methodologies have limitations regarding late-stage synthesis. The use of $AlCl_3$ leads to safety issues, such as risk of handling, while TMSNCS and $TMSN_3$ are highly volatile liquids that are incompatible with moisture and can cause explosions when used in large-scale. These disadvantages have significantly restricted their industrial use in the pharmaceutical sector. The current best conditions for a less toxic and benign reaction are PIFA-mediated *p*-bromination and *p*-iodination using excess NaBr/NaI in ethanol as reported by Li and

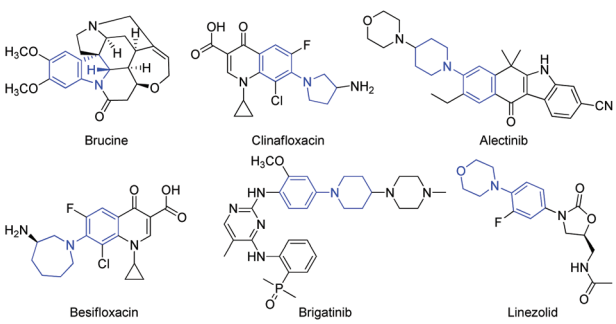

Fig. 1 Representative bioactive *N*-aryl cyclic amines.

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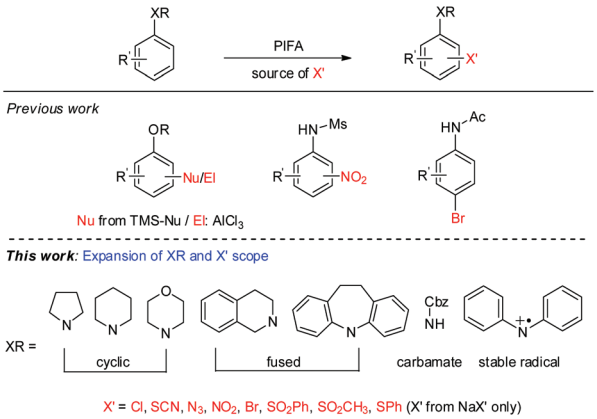


Scheme 1 PIFA-mediated C(sp^2)–H functionalizations.

An.[9d] During or after our study, NaX/PIFA conditions were also applied to activated imidazopyridine[9g] or imidazole/indole.[9h] However, current NaX methods provide limited reactivity with a more activated position (indole, imidazole) or the *p*-position of anilide.[9d,g,h]

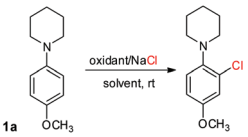
Results and discussion

Optimization of C(sp^2)–X functionalization using CH_3NO_2

Recently, we reported a novel *o*-nitration *via* C(sp^3)–N bond cleavage/C(sp^2)–N bond formation using PIFA/NaCN/CH_3NO_2.[9i] In the spite of clarified mechanism, C(sp^2)–H functionalization in this method was limited to *o*-nitration. However, we strongly expected that this mechanism could be applied to diverse functionalizations. Therefore, how to achieve the following three advances under facile conditions was considered: (i) broad scope of reactions/substrates/reagents; (ii) cost effectiveness; and (iii) eligibility for late-stage functionalization. Herein, we report a metal-free (and Lewis-acid-free) PIFA + NaX method for cost-effective and diverse direct C(sp^2)–X (Cl, Br, SCN, NO_2, N_3, SO_2R, SR) functionalizations applicable to late-stage substitution. This research was initiated using 1-(4-methoxyphenyl)piperidine (**1a**) as a model substrate with two possible reactive sites (C(sp^2)–H or C(sp^3)–H activation) to investigate chlorination conditions, as described in Table 1.

Initially, the chlorination of **1a** (1.0 equiv.) was performed using NaCl (2.0 equiv.) in the presence of PIFA (2.0 equiv.) in DCM at rt, which gave the desired product **2a** in 23% yield (Table 1, entry 1). However, at the end of the reaction, insoluble solid NaCl was observed in the reaction mixture. Similarly, various solvents were tested in sequence (entries 2–9). No reaction was observed in CH_3CN and THF (entries 3 and 4), while **2a** was isolated in 38%–55% yields when the reaction was performed in MeOH, EtOH, and DMF (entries 5–7). Unsurprisingly, CH_3NO_2 did not increase the yield of the desired product (entry 8). However, screening of various polar and nonpolar solvents indicated that the poor NaCl solubility resulted in poor-to-moderate yields of the desired product. Therefore, we reasoned that the reaction conditions employed were not favorable for the formation of **2a**.

Table 1 Optimization of chlorination conditions[a]



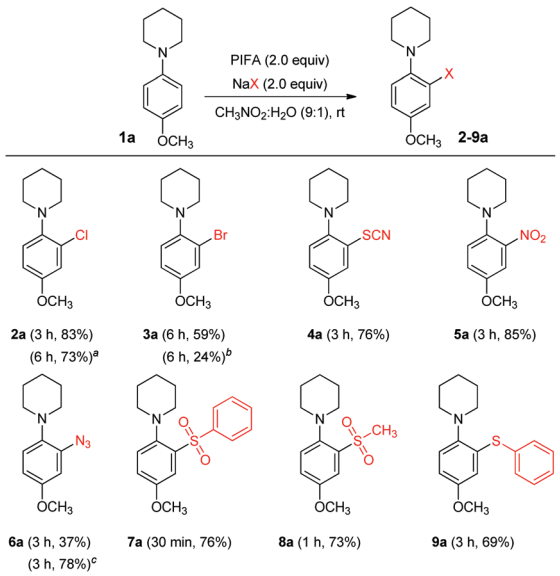
Entry	Oxidant	Solvent	Time (h)	Yield[b] (%)
1	PIFA	DCM	6	23
2	PIFA	$CHCl_3$	10	<10
3	PIFA	CH_3CN	10	n.d.
4	PIFA	THF	10	n.d.
5	PIFA	MeOH	6	47
6	PIFA	EtOH	6	38
7	PIFA	DMF	6	55
8	PIFA	CH_3NO_2	6	13
9	PIFA	DMSO	10	Trace
10	PIFA	$CH_3NO_2/H_2O(9:1)$	3	83
11	PIFA	$THF/H_2O(9:1)$	3	53
12	PIFA	$CH_3CN/H_2O(9:1)$	3	41
13	PIFA	$C_2H_5NO_2/H_2O(9:1)$	3	79
14	PIFA	$PhNO_2/H_2O(9:1)$	10	n.d.
15	PIDA	$CH_3NO_2/H_2O(9:1)$	10	33
16	IBX	$CH_3NO_2/H_2O(9:1)$	10	17
17	DMP	$CH_3NO_2/H_2O(9:1)$	10	Trace

[a] Reaction conditions: **1a** (1.0 equiv.), oxidant (2.0 equiv.), NaCl (2.0 equiv.) at room temperature (rt). [b] Isolated yield. n.d. = not detected.

Accordingly, the conditions were modified to study the reaction using various organic solvents in combination with water as a cosolvent. To our delight, the mixed aqueous–organic solvents produced higher yields (entries 10–13). Among these solvents, CH_3NO_2/H_2O (9 : 1, v/v) exhibited the highest efficiency and provided the desired product **2a** in 83% yield (entry 10). Furthermore, various other nitro solvents were subjected to the above reaction conditions. Replacing CH_3NO_2 with $C_2H_5NO_2$ also afforded **2a** in a slightly lower yield (entry 13), while $PhNO_2$ failed to provide any products (entry 14). Further screening of the reaction conditions with other hypervalent iodine compounds, such as (diacetoxyiodo)benzene (PIDA), 2-iodoxybenzoic acid (IBX), and Dess–Martin periodinane (DMP), also afforded **2a**, but in low yields, even after a reaction time of 10 h (entries 15–17).

Scope of the introduced functionality (X)

The optimal chlorination conditions used for **1a** were then used to investigate other sodium salts (Scheme 2). The PIFA + NaX in CH_3NO_2 were also successfully applied using NaBr and the corresponding product **3a** was obtained in 59% yield. Unfortunately, this process was not compatible with NaI and NaF. However, this method was not limited to halogenation; gratifyingly, various inorganic functionalizations using NaSCN, $NaNO_2$, and NaN_3 were applicable under identical conditions, resulting in excellent isolated yields (**4a–6a**). Notably, oxidative azidation of **1a** under the optimal conditions resulted in a complex mixture (**6a** obtained in 37% yield). Fortunately, using CH_3NO_2 without water afforded **6a** as the sole product in 78%



Scheme 2 Scope of various functionalization reactions. Reaction conditions: **1a** (1.0 equiv.), PIFA (2.0 equiv.), NaX (2.0 equiv.) in CH_3NO_2/H_2O (9 : 1, v/v) at rt. [a] NaX is TMSCl. [b] NaX is NBS. [c] **1a** (1.0 equiv.), PIFA (2.0 equiv.), NaN_3 (2.0 equiv.) in CH_3NO_2 at rt.

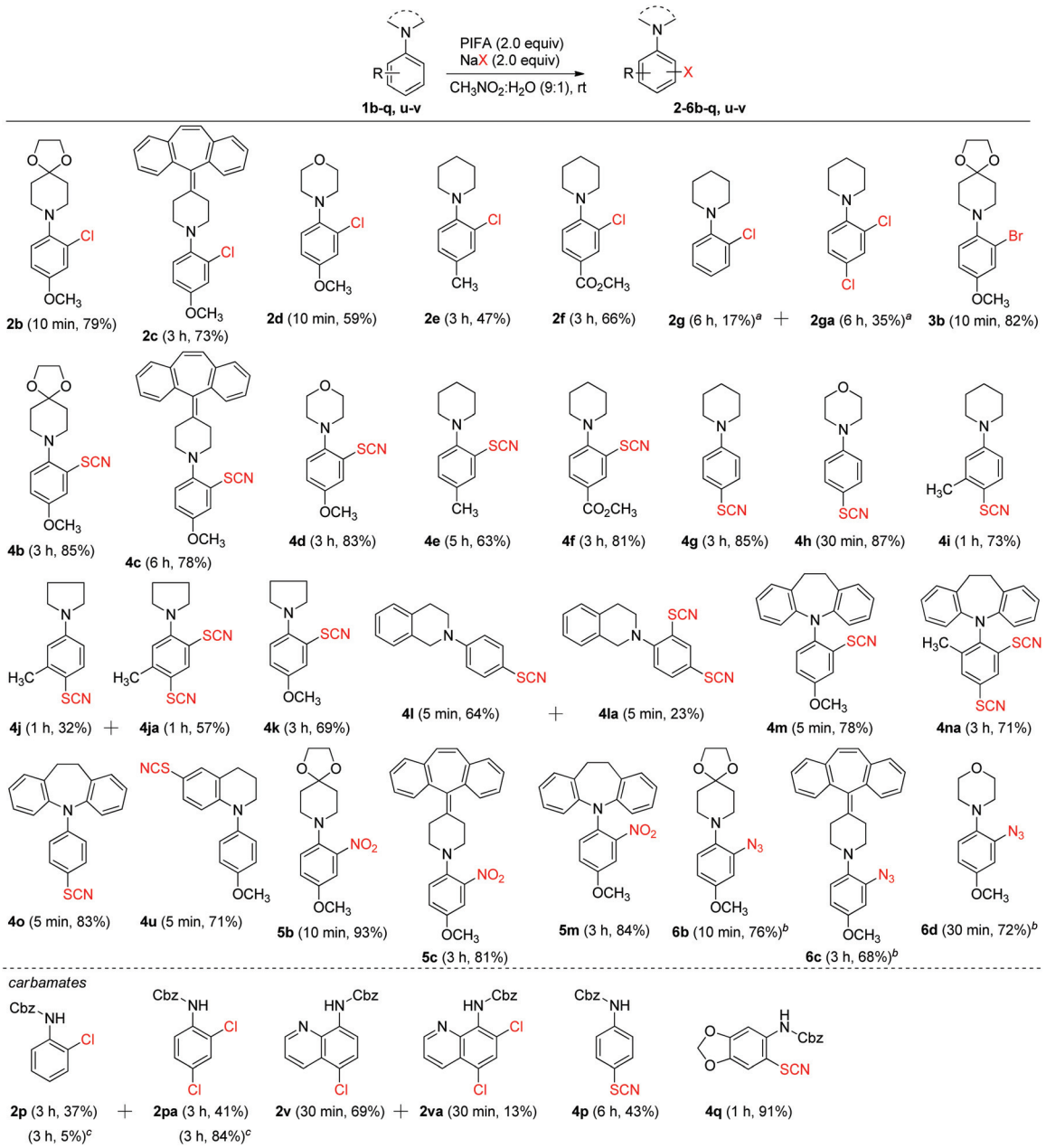
isolated yield. Interestingly, although NaN_3 has been used as an additive for iodine(III) reactions in the literature,[10a,b] azidation product **6a** was obtained instead of cross-coupling with CH_3NO_2.[11] We suspected that our method could contribute to the above conversion. In fact, nitromethane, a polar solvent, has previously been used for PIFA-promoted reactions.[12] However, during our studies on PIFA-mediated reactions, CH_3NO_2 played a new role as a nitrating agent.[9i] These conditions were also suitable for C(sp^2)–X functionalization. To further explore the reaction scope, TMSCl and NBS (reported activators of PIFA oxidative reactions)[10c,d] were subjected to the above optimized reaction conditions. Substrate **1a** was successfully converted into expected C–X products **2a** and **3a** with the recovered **1a**. TMSCl (–Cl) or NBS (–Br) resulted in lower product yields compared with NaCl or NaBr. Furthermore, we investigated innovative organo-C(sp^2)–H functionalization using readily available organosulfur sodium salts, such as sodium benzenesulfinate ($NaSO_2Ph$), sodium methanesulfinate ($NaSO_2CH_3$), and sodium benzenethiolate (NaSPh) using a similar reaction pathway, which afforded the desired organosulfur products **7a**, **8a**, and **9a** in 69%–76% yields.[9d,e,13]

Substrate scope of *p*-substitution and *o*,*p*-disubstitution

The substrate scope for C(sp^2)–H functionalization was examined under the optimal conditions as shown in Scheme 2, with the results summarized in Scheme 3. First, diverse electron-rich cyclic amines were tested with sodium salts (NaX). These substrates were successfully converted into the expected C(sp^2)-functionalized products **2b–2e**, **3b**, **4b–4e**, **4k**, **4m**, **5b–5c**, **5m** and **6b–6d** with excellent yields, while *p*-Me groups gave slightly decreased yields (Scheme 3, **2e** and **4e**). Interestingly, 1,2,3,4-tetrahydroquinoline substrate **1u** underwent 6-thiocyanation (sole product **4u** in 71% yield) instead of 2-thiocyanation, making us speculate on the *para*-preference of the thiocyanation. Next, replacing *p*-OCH_3 (electron-donating) with *p*-CO_2CH_3 (electron-withdrawing) gave the desired products in up to 81% yields (**2f** and **4f**). Furthermore, *p*-unsubstituted substrates were examined (**1g–1j**, **1l**, **1n**, and **1o**). Surprisingly, thiocyanation showed regioselectivity between the *ortho*- and *para*-positions, producing predominantly *p*-substituted product **4g** under the optimal conditions. Morpholine and dibenzoazepine (tricyclic) showed similar regioselectivity and efficient yields (**4h**, **4i**, and **4o** as sole isolable products). More reactive five-membered ring and tetrahydroisoquinoline substrates showed less discrimination, producing *o*,*p*-di-SCN-substituted products **4ja** and **4la** along with **4j** and **4l**. In the case of substrate **1n**, the Me-substituent on the arene ring accelerated thiocyanation to afford di-SCN along with mono-SCN before the complete disappearance of substrate **1n**. At the end of the reaction the di-SCN product **4na** could be obtained with a trace amount of the mono-SCN product. In short, reactivity of thiocyanation and reaction rate critically depend on the substrate structure: (1) cyclic amine group (*e.g.* 5 ring >6 ring) and (2) a substituent of the aryl group. While *H*4-isoquinoline **1l** was reactive enough to produce the mono- (**4l**) and di-thiocyanation product (**4la**), pyrrolidine (5-ring) and benzoazepine (7-fused ring) could produce di-thiocyanation products (**4ja** and **4na**) under the assistance of electron-donating substituents. Notably, formation of products **4na** and **4o** can prove that the methyl group was critical for mono-/di-competition. In contrast to thiocyanation, the chlorination of compound **1g** was unsuccessful under the optimized conditions shown in Table 1, leading to substrate decomposition. Notably, a decreased PIFA loading (from 2.0 equiv. to 1.0 equiv.) with an excess solvent ratio of CH_3NO_2/H_2O (2 mL) afforded *o*-chlorinated product **2g** along with *o*,*p*-dichloro product **2ga** in low yields. The solvent quantity was also found to have a major impact on chlorination. Furthermore, the reaction with other sodium salts resulted in the detection of either decomposition or oxidative biaryl coupling products.[14] *ortho*-Preference of the chlorination with poor conversion made us suggest different mechanisms between thiocyanation and halogenation. Notably, the difference in the reaction rate between **4b** and **2b** (or **3b**) could be another evidence of this suggestion. Finally, we extended the scope of C(sp^2)-functionalization from cyclic amines to amides (carbamates). When substrates **1p** and **1q** were subjected to the thiocyanation reaction, *p*-selective thiocyanation product **4p** and *o*-thiocyanation product **4q** were obtained in 43% and 91% yields. However, the chlorination of **1p** and **1v** (derivative of 8-aminoquinoline)[15] gave similar results to that of **2g**, producing **2p** and **2v** along with **2pa** and **2va**. Notably, chlorination was accelerated by the addition of CH_3COONa (1.0 equiv.), giving an increased yield of the *o*,*p*-di-Cl product **2pa** (84%).

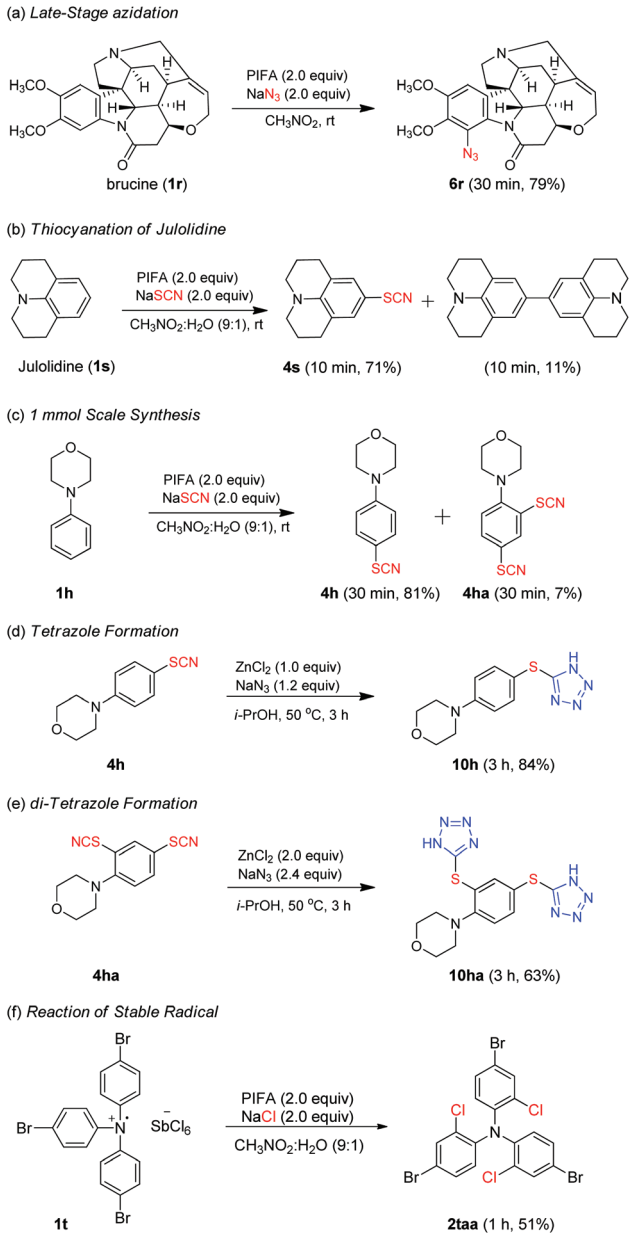
Late-stage C(sp^2)–X functionalization with NaX

We next turned our attention to late-stage functionalization. Therefore, commercially available brucine (**1r**) was used for



Scheme 3 Substrate scope of various functionalizations. Reaction conditions: **1b–q**, **1u–v** (1.0 equiv.) in CH_3NO_2/H_2O (1 mL; 9 : 1, v/v). [a] **1g** (1.0 equiv.), PIFA (1.0 equiv.), and NaCl (1.2 equiv.) in CH_3NO_2 : H_2O (2 mL; 9 : 1, v/v). [b] **1a–1d** (1.0 equiv.) in CH_3NO_2 (1 mL). [c] Addition of CH_3COONa (1.0 equiv.).

selective C(sp^2)–H azidation with PIFA (2.0 equiv.) and NaN_3 (2.0 equiv.) in nitromethane at rt. Gratifyingly, without the interference of other functional groups of brucine (3° amines, alkenes, homoallylic ethers, and amides),[16] C(sp^2)–H functionalization afforded **6r** (79% yield) as shown in Scheme 4(a). After success with brucine, the reactivity of julolidine was investigated. As julolidine derivatives are mainly useful for preparing dyes (or probes) and photoconductive materials, and due to their pharmacological activities, such as anti-hepatitis B activity,[17] our *p*-SCN functionalization would be valuable for extending the julolidine scaffold. The SCN^- ion underwent smooth coupling with julolidine **1s** to form product **4s** in 71% yield, as shown in Scheme 4(b). **6r** and **4s** are novel examples that highlight the scope of this method. In addition, the efficiency of thiocyanation was maintained on an increased scale, giving 81% yield, as shown in Scheme 4(c). Notably, a trace amount of di-SCN product **4ha** (7% yield) was observed along with **4h**. Finally, we obtained an example application of thiocyanation products **4h** and **4ha** through the modification into mono- and di-tetrazoles **10h** and **10ha**, as shown in Scheme 4(d) and (e).[18] As tetrazoles are biologically privileged motifs,[19] they can be highly useful in applications. In detail,



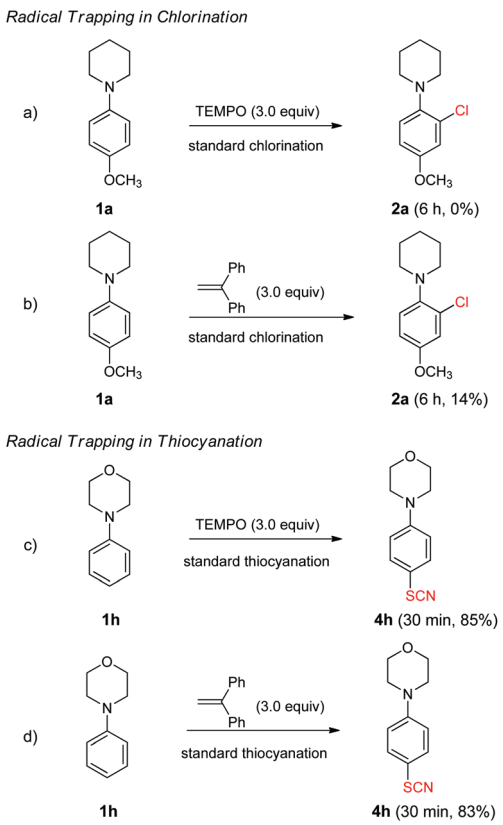
Scheme 4 Synthetic applications.

because tetrazole is a well-known bioisostere of $-CO_2H$, drug candidates having terazole are present in COX2 inhibitors such as celecoxib analogues or antiulcer agents. In particular, *S*-tetrazole is observed in antibiotics,[19] protease inhibitors,[20] or activators of autophagic flux and phospholipase D.[21] To further illustrate the efficiency of these methods, the chlorination of stable radical **1t**, which shares the substructure of our substrates, was conducted. Interestingly, this reaction gave the optimal outcome, with trichlorinated product **2taa** obtained from NaCl and $SbCl_6^-$, as shown in Scheme 4(f). Triarylamine of **2taa** is commonly used to synthesize conductive polymers and high-spin polyradicals exhibiting ferromagnetic coupling, representing another useful application.[22]

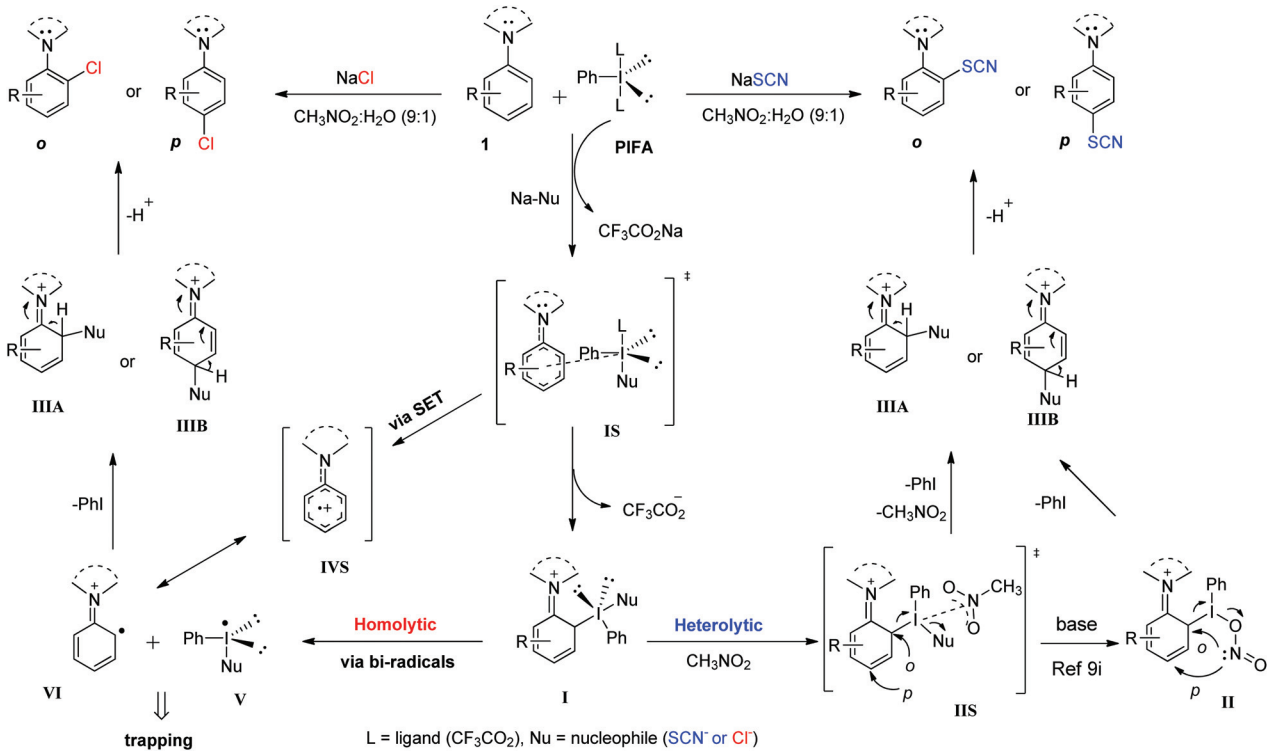
Reaction mechanism based on radical trapping

To gain an understanding of the C(sp^2)–H functionalization mechanism, we conducted chlorination and thiocyanation in the presence of 2,2,6,6-tetramethylpiperidin-1-yl-oxidanyl (TEMPO) and 1,1-diphenylethylene as radical scavengers under the optimal conditions (Scheme 5). The chlorination reaction with excess TEMPO (3.0 equiv.) did not give product **2a** at all indicating a homolytic mechanism. 1,1-Diphenylethylene (3.0 equiv.), another radical scavenger, dramatically decreased the isolation yield of product **2a** from 83% to 14%. In contrast, neither TEMPO nor 1,1-diphenylethylene affected the isolation yield of thiocyanation and its reaction time. The identical results using the radical scavengers supported that C(sp^2)-thiocyanation did not follow a single electron transfer (SET) mechanism. Considering that the reaction with TMSNCS was reported to follow a SET mechanism,[9b] the ionic mechanism of NaSCN is surprising. Based on the experimental results and previous literature,[23] mechanistic models were proposed for oxidative C(sp^2)–H functionalization, as shown in Scheme 6.

First, PIFA coordinates with the *N*-aryl cyclic amine *via* halogen–π interactions between the benzene ring and iodine to give intermediate **I**. CF_3CO_2Na elimination can be attributed to ligand exchange with SCN^- or Cl^-. CH_3NO_2 seems to act as an additive[9i,23e,f] affording the complex through coordination with intermediate **I**. Nucleophilic attack on the *o*- or *p*-position *via* transition state **IIS** then generates intermediate **IIIA** or **IIIB**



Scheme 5 Control experiment.



Scheme 6 Plausible mechanistic pathway for C(sp^2)–H functionalization.

with the loss of PhI and CH_3NO_2. While coordination between intermediate **I** and CH_3NO_2 can be replicated using other solvents, CH_3NO_2 can give additional intermediate **II** *via* C(sp^3)–N cleavage[9i] to accelerate the reaction. Finally, the aromaticity can be recovered by the loss of a proton from **IIIA** or **IIIB**, which gives the final products. When integrating the mechanism with the experimental results (Scheme 3), we propose that the electron density of the aromatic group in substrates (**4j** and **4k**, **4na** and **4o**, and **4p** and **4q**) affects the initiation of thiocyanation to give intermediate **I**, while the steric environment near the *o*-iodo complex provides *p*-regioselectivity. After *p*-substitution, *p*-substituted **4k**, **4o**, and **4p** were not sufficiently reactive for the next substitution. When comparing nitration[9i] and thiocyanation using our method (NaCN *vs.* NaSCN), despite the similar nucleophilicity of the anions, CN^- was consumed as a base and SCN^- could attack iminium intermediate **II** due to its basicity (pK_a of conjugated acids in water: HCH_2NO_2 (10) > *HCN (9.4)* ≫ HN_3 (4.72) > HSCN (4.0) > HNO_2 (3.29) ≫ HCl). However, halogenation or azidation, following a homolytic mechanism, can be explained by the generation of iodanyl radical **V**. As reported previously,[23] initial homolytic cleavage of the I–X bond can produce iodanyl radical **V** and iminium radical **VI**. When TEMPO trapping was conducted, chlorination was stopped, with no consumption of substrate **1a** observed, but no trapped products from substrate derivatives, including radical **VI**, were isolated. Therefore, we predict that the formation of intermediate **IIIA** or **IIIB** is very fast and the capture of radical **V** stops the reaction.

Furthermore, although a SET mechanism needs to be considered based on Kita's charge-transfer (CT) complex of electron-rich arenes,[23c] our method does not use either a fluoroalcohol solvent or a Lewis acid. Therefore, a CT-complex *via* SET and biradicals *via* radical cleavage need to be considered together for the homolytic mechanism. When integrating the mechanism with experimental results (Scheme 3), radical **VI** seems to prefer *o*-substitution over *p*-substitution based on products **2g** and **2p**, owing to the different steric environment at the *o*-position. The ratio of *o*-chlorinated product **2p** to *o*,*p*-dichlorinated product **2pa** could be adjusted by altering the acidity of the reaction mixture.

Conclusions

The metal-free and readily available $ArI(O_2CF_3)_2$ and NaX method has been used to achieve C(sp^2)–X bond formations (halogenation, azidation, nitration, thiocyanation, and sulfonylation). This straightforward C–H functionalization was functional-group-compatible, cost-effective, and applicable to the late-stage synthesis of pharmacological molecules, such as brucine and julolidine. In particular, the method required neither metal catalysts nor strong acids, proving to be environmentally friendly and cost effective at room temperature. The mechanism of *ortho*- or *para*-preference could be achieved with the coordination of nitromethane. Consecutive C–X formation, *via* *p*- and *o*-functionalization, encouraged us to design a

regiospecific reaction according to the reactivity of nucleophiles and substrates. Notably, the known additives acted as reactants in our method to indicate the future direction of study. Furthermore, the nonionic mechanism presents the possibility for *o*-selective functionalization in the near future. We believe that this method will be highly attractive for the functionalization of natural products.

Experimental

General procedure for the synthesis of compounds 1a–1o and 1u

The following reaction procedure is a slightly modified reported procedure.[24] A mixture of $Pd_2(dba)_3$ (0.137 g, 0.15 mmol, 3 mol%), ligand (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl) (0.164 g, 0.40 mmol, 8 mol%) and 5.0 mL of dry toluene was added into an oven dried seal tube. The resulting solution was degassed with N_2 for 1 hour. Then, bromoarene (5.0 mmol, 1.0 equiv.), cyclic amine (6.0 mmol, 1.2 equiv.), and ^{t}BuONa (0.672 g, 7.0 mmol, 1.4 equiv.) were sequentially added with a syringe to the reaction mixture. Then the reaction mixture was heated to 100 °C for 20 h. After completion of the reaction, the resulting reaction mixture was slowly brought to rt, and then quenched by adding water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/EtOAc (20 : 1) as the eluent to afford the desired products.

1-(4-Methoxyphenyl)piperidine (1a). Light yellow oil, 94% yield (0.90 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.93–6.88 (m, 2H), 6.84–6.80 (m, 2H), 3.75 (s, 3H), 3.05–2.98 (m, 4H), 1.71 (dt, J = 11.4, 5.7 Hz, 4H), 1.57–1.50 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.51, 146.91, 118.71, 114.27, 55.51, 52.27, 26.13, 24.18 ppm. The analytical data are consistent with the literature.[25a]

8-(4-Methoxyphenyl)-1,4-dioxa-8-azaspiro[4.5]decane (1b). Light yellow solid, mp 63–65 °C, 87% yield (1.08 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.96–6.87 (m, 2H), 6.85–6.78 (m, 2H), 3.97 (s, 4H), 3.75 (s, 3H), 3.26–3.10 (m, 4H), 1.91–1.76 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.69, 145.61, 118.91, 114.32, 107.03, 64.27, 55.50, 49.34, 34.83 ppm; the analytical data are consistent with the literature.[25b]

4-(5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)-1-(4-methoxyphenyl) piperidine (1c). White solid, mp 117–119 °C, 78% yield (1.48 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (dd, J = 11.4, 4.3 Hz, 4H), 7.27–7.20 (m, 4H), 6.92 (s, 2H), 6.88–6.84 (m, 2H), 6.83–6.78 (m, 2H), 3.75 (s, 3H), 3.25–3.17 (m, 2H), 2.84–2.77 (m, 2H), 2.47 (ddd, J = 13.3, 9.0, 4.1 Hz, 2H), 2.28 (ddd, J = 13.7, 5.8, 3.6 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.59, 145.80, 139.06, 135.32, 134.81, 133.67, 131.01, 128.47, 128.23, 127.79, 126.30, 118.67, 114.35, 55.55, 52.90, 30.12 ppm; LRMS (ESI, m/z): 380 ($[M + H]^+$).

4-(4-Methoxyphenyl)morpholine (1d). Yellow solid, mp 70–71 °C, 85% yield (0.82 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.93–6.80 (m, 4H), 3.89–3.80 (m, 4H), 3.75 (s, 3H), 3.09–2.99 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.92, 145.60, 117.76, 114.46, 67.00, 55.51, 50.77 ppm; the analytical data are consistent with the literature.[25c]

1-(*p*-Tolyl)piperidine (1e). Light yellow oil, 88% yield (0.77 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.09–6.98 (m, 2H), 6.89–6.78 (m, 2H), 3.13–2.98 (m, 4H), 2.24 (s, 3H), 1.68 (dt, J = 11.4, 5.7 Hz, 4H), 1.61–1.45 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.26, 129.48, 128.64, 116.93, 51.29, 25.95, 24.29, 20.40 ppm; the analytical data are consistent with the literature.[25a]

Methyl 4-(piperidin-1-yl)benzoate (1f). Light yellow solid, mp 89–91 °C, 71% yield (0.78 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (d, J = 9.1 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H), 3.35–3.30 (m, 4H), 1.74–1.60 (m, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.25, 154.50, 131.22, 118.65, 113.56, 51.57, 48.79, 25.40, 24.36 ppm; the analytical data are consistent with the literature.[25d]

1-Phenylpiperidine (1g). Light yellow oil, 93% yield (0.75 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 (dddd, J = 9.0, 7.2, 3.5, 1.5 Hz, 2H), 6.96–6.90 (m, 2H), 6.84–6.78 (m, 1H), 3.18–3.09 (m, 4H), 1.74–1.66 (m, 4H), 1.56 (ddd, J = 6.3, 5.7, 1.8 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.24, 128.96, 119.13, 116.49, 50.65, 25.86, 24.31 ppm; the analytical data are consistent with the literature.[25c]

4-Phenylmorpholine (1h). Light yellow solid, mp 54–56 °C, 89% yield (0.73 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2H), 6.92 (d, J = 7.9 Hz, 2H), 6.88 (t, J = 7.3 Hz, 1H), 3.90–3.82 (m, 4H), 3.21–3.12 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.27, 129.18, 120.04, 115.70, 66.94, 49.36 ppm; the analytical data are consistent with the literature.[25c]

1-(*m*-Tolyl)piperidine (1i). Light yellow oil, 76% yield (0.67 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 (t, J = 7.8 Hz, 1H), 6.79–6.68 (m, 2H), 6.63 (d, J = 7.4 Hz, 1H), 3.19–3.04 (m, 4H), 2.29 (s, 3H), 1.68 (dt, J = 14.9, 5.7 Hz, 4H), 1.60–1.48 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.33, 138.52, 128.80, 120.11, 117.41, 113.67, 50.78, 25.91, 24.35, 21.77 ppm; the analytical data are consistent with the literature.[25e]

1-(*m*-Tolyl)pyrrolidine (1j). Light yellow oil, 73% yield (0.59 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14–7.07 (m, 1H), 6.48 (d, J = 7.5 Hz, 1H), 6.37 (d, J = 6.1 Hz, 2H), 3.32–3.17 (m, 4H), 2.30 (s, 3H), 2.01–1.89 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.04, 138.72, 128.96, 116.33, 112.34, 108.88, 47.56, 25.43, 21.84 ppm; the analytical data are consistent with the literature.[25f]

1-(4-Methoxyphenyl)pyrrolidine (1k). Light orange solid, mp 43–45 °C, 77% yield (0.68 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.92–6.78 (m, 2H), 6.56 (d, J = 8.4 Hz, 2H), 3.75 (s, 3H), 3.23 (d, J = 5.7 Hz, 4H), 2.03–1.95 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 130.87, 127.65, 115.00, 55.99, 48.47, 25.35 ppm; the analytical data are consistent with the literature.[25f]

2-Phenyl-1,2,3,4-tetrahydroisoquinoline (1l). Orange solid, mp 45–47 °C, 79% yield (0.83 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (dd, J = 8.4, 7.4 Hz, 2H), 7.22–7.11 (m, 4H), 6.98 (d, J = 8.2 Hz, 2H), 6.82 (t, J = 7.2 Hz, 1H), 4.40 (s, 2H), 3.56 (t, J = 5.9 Hz, 2H), 2.98 (t, J = 5.8 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.54, 134.86, 134.45, 129.19, 128.51, 126.53, 126.31,

126.01, 118.64, 115.12, 50.71, 46.50, 29.11 ppm; the analytical data are consistent with the literature.[25g]

5-(4-Methoxyphenyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine (1m). High viscous brown oil; 67% yield (1.0 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45–7.41 (m, 2H), 7.29–7.25 (m, 4H), 7.22 (td, J = 7.4, 1.4 Hz, 2H), 6.73 (d, J = 9.1 Hz, 2H), 6.59 (d, J = 9.1 Hz, 2H), 3.76 (s, 3H), 3.02 (s, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.95, 143.96, 143.65, 138.42, 130.83, 130.66, 130.20, 128.63, 126.96, 126.80, 126.71, 119.43, 117.90, 114.33, 114.02, 55.73, 31.03 ppm; the analytical data are consistent with the literature.[25h]

5-(*o*-Tolyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine (1n). White solid, mp 107–109 °C, 81% yield (1.16 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (ddt, J = 12.9, 7.2, 6.6 Hz, 4H), 7.07 (dd, J = 7.4, 1.6 Hz, 2H), 6.95–6.84 (m, 2H), 6.76 (td, J = 7.3, 0.9 Hz, 2H), 6.48 (dd, J = 8.5, 0.8 Hz, 2H), 3.20 (s, 4H), 2.06 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.31, 144.92, 137.51, 132.30, 132.22, 131.67, 130.31, 127.66, 127.25, 126.25, 121.04, 119.84, 37.16, 18.00 ppm; the analytical data are consistent with the literature.[25h]

5-Phenyl-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine (1o). White solid, mp 99–101 °C, 87% yield (1.18 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, J = 7.7 Hz, 2H), 7.29–7.17 (m, 6H), 7.09 (t, J = 8.0 Hz, 2H), 6.70 (t, J = 7.2 Hz, 1H), 6.58 (d, J = 8.1 Hz, 2H), 2.98 (s, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.06, 143.43, 138.34, 130.91, 130.14, 128.82, 127.06, 127.04, 117.44, 112.54, 77.22, 77.00, 76.79, 30.84 ppm; the analytical data are consistent with the literature.[25h]

1-(4-Methoxyphenyl)-1,2,3,4-tetrahydroquinoline (1u). White solid, mp 69–71 °C, 81% yield (0.97 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18–7.13 (m, 2H), 7.03–6.98 (m, 1H), 6.94–6.85 (m, 3H), 6.62 (td, J = 7.3, 1.0 Hz, 1H), 6.47 (dd, J = 8.2, 0.6 Hz, 1H), 3.81 (s, 3H), 3.57–3.50 (m, 2H), 2.86 (t, J = 6.4 Hz, 2H), 2.08–1.99 (m, 2H)pp; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.76, 145.53, 141.35, 129.29, 127.66, 126.46, 122.93, 117.16, 114.82, 114.29, 55.46, 51.64, 27.86, 22.50 ppm; the analytical data are consistent with the literature.[25i]

Synthetic procedure of compounds 1p–1q and 1v

To a mixture of aniline (3.25 mmol, 1.0 equiv.) and Na_2CO_3 (6.5 mmol, 2.0 equiv.) 3.0 mL THF/H_2O (v/v = 1 : 1) was added, and then the reaction mixture was cooled to 0 °C. A solution of benzyl chloroformate (CbzCl) (3.38 mmol, 1.04 equiv.) in THF was slowly added dropwise to the reaction mixture. After the addition, the reaction mixture was continuously stirred for 3 h at rt. After completion of the reaction, checked by TLC, the organic solvent was removed under reduced pressure and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was concentrated *in vacuo* and the crude product was purified by column chromatography over silica gel (gradient elution of EtOAc/hexane 1 : 15).

Benzyl phenylcarbamate (1p)

White solid, mp 71–73 °C, 91% yield (0.67 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42–7.35 (m, 6H), 7.35–7.31 (m, 1H), 7.30 (t, J = 8.0 Hz, 2H), 7.06 (t, J = 7.4 Hz, 1H), 6.70 (s, 1H), 5.19 (s, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.29, 137.73, 136.02, 129.35, 129.06, 128.91, 128.82, 128.73, 128.61, 128.56, 128.36, 128.31, 126.98, 123.51, 118.64, 67.01 ppm; the analytical data are consistent with the literature.[25j]

Benzyl benzo[*d*][1,3]dioxol-5-ylcarbamate (1q). White solid, mp 95–97 °C, 83% yield (0.73 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45–7.29 (m, 5H), 7.09 (s, 1H), 6.69 (dd, J = 30.0, 8.0 Hz, 2H), 6.55 (s, 1H), 5.93 (d, J = 2.3 Hz, 2H), 5.18 (s, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.96, 136.05, 128.61, 128.35, 128.32, 108.10, 101.24, 67.02 ppm; the analytical data are consistent with the literature.[25k]

Benzyl quinolin-8-ylcarbamate (1v). White solid, mp 75–77 °C, 87% yield (0.79 g); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.77 (dd, J = 4.2, 1.7 Hz, 1H), 8.45 (d, J = 6.2 Hz, 1H), 8.14 (dd, J = 8.2, 1.6 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.50–7.37 (m, 6H), 7.35 (ddd, J = 7.3, 3.8, 1.2 Hz, 1H), 5.29 (s, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.41, 148.12, 138.22, 136.23, 134.67, 128.61, 128.31, 128.29, 128.02, 127.31, 121.63, 120.66, 114.64, 66.96 ppm; the analytical data are consistent with the literature.[25l]

General procedure for C(sp^2)–H functionalization

Cyclic amine (0.15 mmol, 1.0 equiv.) and NaX (0.3 mmol, 2.0 equiv.) (NaX = NaCl or NaBr or NaSCN or $NaNO_2$ or $NaSO_2Ph$ or $NaSO_2CH_3$ or NaSPh) were dissolved in a 1 mL mixture of nitromethane and water (9 : 1) and PIFA (0.3 mmol, 2.0 equiv.) was cautiously added portionwise to the reaction mixture, and then the solution was stirred at room temperature for 5 min to 8 h, monitored by TLC. Then, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with a saturated solution of $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc) to afford the corresponding products.

1-(2-Chloro-4-methoxyphenyl)piperidine (2a). White solid, mp 44–46 °C, 83% yield (28.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.98 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 2.9 Hz, 1H), 6.76 (dd, J = 8.8, 2.9 Hz, 1H), 3.76 (s, 3H), 2.88 (s, 4H), 1.73 (dt, J = 11.1, 5.6 Hz, 4H), 1.59–1.52 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.34, 144.19, 129.79, 120.98, 115.96, 112.85, 55.64, 53.40, 26.37, 24.24 ppm; FT-IR ν 2936, 1496, 1209, 1044, 872, 862 cm^{-1}; HRMS (EI, m/z): M^+ calculated for $C_{12}H_{16}ClNO$ 225.0920, found 225.0924.

8-(2-Chloro-4-methoxyphenyl)-1,4-dioxa-8-azaspiro[4.5]decane (2b). Light yellow solid, mp 56–58 °C, 79% yield (34.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.01 (d, J = 8.8 Hz, 1H), 6.95 (d, J = 2.9 Hz, 1H), 6.76 (dd, J = 8.8, 2.9 Hz, 1H), 4.00 (s, 4H), 3.76 (s, 3H), 3.12–2.94 (m, 4H), 1.97–1.82 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.63, 143.06, 129.81, 121.22, 115.96, 112.87, 107.06, 64.29, 55.64, 50.17, 35.41 ppm; FT-IR ν 2957, 1496, 1208, 1107, 1039, 903, 863 cm^{-1}; HRMS (EI, m/z): M^+ calculated for $C_{14}H_{18}ClNO_3$ 283.0975, found 283.0977.

1-(2-Chloro-4-methoxyphenyl)-4-(5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)piperidine (2c). Yellow solid, mp 146–148 °C, 73% yield (45.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37–7.30 (m,

4H), 7.24 (d, J = 7.5 Hz, 4H), 6.97–6.92 (m, 3H), 6.90 (d, J = 8.9 Hz, 1H), 6.72 (dd, J = 8.8, 2.9 Hz, 1H), 3.74 (s, 3H), 3.07–3.01 (m, 2H), 2.61 (dd, J = 14.1, 5.8 Hz, 2H), 2.52 (ddd, J = 13.4, 9.3, 4.0 Hz, 2H), 2.34–2.28 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.50, 143.16, 139.14, 134.80, 131.00, 128.55, 128.19, 127.77, 126.26, 121.10, 115.98, 112.82, 95.67, 55.63, 53.73, 30.62 ppm; FT-IR ν 2923, 1496, 1212, 1044, 801, 742 cm^{-1}; HRMS (EI, m/z): M^+ calculated for $C_{27}H_{24}ClNO$ 413.1546, found 413.1546.

4-(2-Chloro-4-methoxyphenyl)morpholine (2d). Brown liquid, 59% yield (20.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.98 (dd, J = 19.1, 5.9 Hz, 2H), 6.79 (dd, J = 8.8, 2.9 Hz, 1H), 3.94–3.84 (m, 4H), 3.78 (s, 3H), 3.05–2.93 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.92, 142.52, 129.79, 120.96, 116.19, 113.05, 67.28, 55.68, 52.16 ppm; FT-IR ν 2922, 1490, 1218, 1117, 1046, 939, 874 cm^{-1}; HRMS (EI, m/z): M^+ calculated for $C_{11}H_{14}ClNO_2$ 227.0713, found 227.0712.

1-(2-Chloro-4-methylphenyl)piperidine (2e). Light yellow liquid, 47% yield (15.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 (d, J = 1.8 Hz, 1H), 7.00 (ddd, J = 8.1, 1.4, 0.6 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 2.93 (s, 4H), 2.26 (s, 3H), 1.73 (dt, J = 11.1, 5.6 Hz, 4H), 1.60–1.54 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.13, 133.01, 130.94, 128.65, 127.99, 120.18, 53.08, 26.30, 24.27, 20.38 ppm; FT-IR ν 2927, 1497, 1235, 1068, 870, 813 cm^{-1}; HRMS (EI, m/z): M^+ calculated for $C_{12}H_{16}ClN$ 209.0971, found 209.0974.

Methyl 3-chloro-4-(piperidin-1-yl)benzoate (2f). Brown liquid, 66% yield (25.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (d, J = 2.0 Hz, 1H), 7.86 (dd, J = 8.4, 2.0 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 3.88 (s, 3H), 3.09–3.02 (m, 4H), 1.79–1.72 (m, 4H), 1.61 (dt, J = 11.8, 6.0 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.13, 154.47, 132.06, 129.10, 127.81, 124.14, 119.54, 52.33, 52.05, 26.02, 24.16 ppm; FT-IR ν 2934, 1721, 1597, 1435, 1244, 1120, 768 cm^{-1}; HRMS (EI, m/z): M^+ calculated for $C_{13}H_{16}ClNO_2$ 253.0870, found 253.0869.

1-(2-Chlorophenyl)piperidine (2g). Yellow liquid, 17% yield (addition of 1.0 equiv. PIFA) (5.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38–7.32 (m, 1H), 7.23–7.14 (m, 1H), 7.03 (dd, J = 8.0, 1.4 Hz, 1H), 6.93 (ddd, J = 9.1, 5.7, 1.9 Hz, 1H), 3.03–2.88 (m, 4H), 1.79–1.70 (m, 4H), 1.58 (t, J = 7.3 Hz, 2H) pp; ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.38, 130.49, 127.40, 123.11, 121.17, 120.44, 52.89, 26.26, 24.27 ppm; FT-IR ν 2933, 2851, 1442, 1238, 1042, 746 cm^{-1}; HRMS (EI, m/z): M^+ calculated for $C_{11}H_{14}ClN$ 195.0815, found 195.0817.

1-(2,4-Dichlorophenyl)piperidine (2ga). Yellow liquid, 35% yield (addition of 1.0 equiv. PIFA) (12.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, J = 2.5 Hz, 1H), 7.16 (dd, J = 8.6, 2.5 Hz, 1H), 6.94 (d, J = 8.6 Hz, 1H), 3.03–2.84 (m, 4H), 1.73 (dt, J = 11.2, 5.6 Hz, 4H), 1.58 (d, J = 11.4 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.40, 130.16, 129.58, 127.55, 127.44, 121.19, 52.87, 26.16, 24.15 ppm; FT-IR ν 2921, 2851, 1532, 1478, 1233, 751, 690 cm^{-1}; HRMS (EI, m/z): M^+ calculated for $C_{11}H_{13}Cl_2N$ 229.0425, found 229.0426.

Benzyl(2-chlorophenyl)carbamate (2p). White solid, mp 44–46 °C, 37% yield (15.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, J = 7.6 Hz, 1H), 7.59–7.31 (m, 6H), 7.32–7.11 (m, 2H), 6.99 (td, J = 7.7, 1.4 Hz, 1H), 5.22 (s, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.99, 135.77, 134.64, 133.46, 129.06, 128.74, 128.70, 128.67, 128.59, 128.49, 128.44, 127.92, 127.76, 123.78, 122.06, 119.89, 67.33 ppm; FT-IR ν 1695, 1528, 1441, 1235, 1034, 740 cm^{-1}; HRMS (EI, m/z): M^+ calculated for $C_{14}H_{12}ClNO_2$ 261.0557, found 261.0554.

Benzyl(2,4-dichlorophenyl)carbamate (2pa). White solid, mp 75–77 °C, 84% yield (addition of 1.0 equiv. CH_3COONa) (37.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, J = 8.4 Hz, 1H), 7.55–7.32 (m, 6H), 7.26–7.21 (m, 1H), 7.15 (s, 1H), 5.22 (s, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.84, 135.56, 133.46, 129.06, 128.74, 128.70, 128.66, 128.59, 128.49, 128.44, 128.23, 127.91, 127.76, 123.77, 122.51, 120.61, 67.53 ppm; FT-IR ν 2919, 2850, 1687, 1522, 1474, 1238, 745, 694 cm^{-1}; HRMS (EI, m/z): M^+ calculated for $C_{14}H_{11}Cl_2NO_2$ 295.0167, found 295.0167.

Benzyl(5-chloroquinolin-8-yl)carbamate (2v). White solid, mp 99–101 °C, 69% yield (32.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.81 (dd, J = 4.2, 1.5 Hz, 1H), 8.54 (dd, J = 8.5, 1.6 Hz, 1H), 8.39 (d, J = 7.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.55 (dd, J = 8.5, 4.2 Hz, 1H), 7.47 (d, J = 7.3 Hz, 2H), 7.43–7.38 (m, 2H), 7.35 (dd, J = 8.4, 6.2 Hz, 1H), 5.28 (s, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.27, 148.59, 138.71, 136.05, 133.98, 133.29, 128.64, 128.38, 128.36, 127.15, 125.97, 123.47, 122.37, 114.57, 67.13 ppm; HRMS (ESI, m/z): $[M + H]^+$ calculated for $C_{17}H_{14}ClN_2O_2$ 313.0738, found 313.0768.

Benzyl(5,7-dichloroquinolin-8-yl)carbamate (2va). Yellow solid, mp 141–143 °C, 13% yield (7.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.91 (dd, J = 4.2, 1.6 Hz, 1H), 8.51 (dd, J = 8.5, 1.6 Hz, 1H), 7.76 (s, 1H), 7.70 (s, 1H), 7.54 (dd, J = 8.5, 4.2 Hz, 1H), 7.46–7.40 (m, 2H), 7.42–7.30 (m, 3H), 5.26 (s, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.59, 150.86, 143.64, 135.96, 133.29, 131.19, 129.76, 128.67, 128.54, 128.36, 128.26, 125.22, 122.33, 67.73 ppm; HRMS (ESI, m/z): $[M + H]^+$ calculated for $C_{17}H_{13}Cl_2N_2O_2$ 347.0349, found 347.0364.

1-(2-Bromo-4-methoxyphenyl)piperidine (3a). Red viscous liquid, 59% yield (24.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14 (d, J = 2.9 Hz, 1H), 6.98 (d, J = 8.8 Hz, 1H), 6.81 (dd, J = 8.8, 2.9 Hz, 1H), 3.76 (s, 3H), 2.87 (s, 4H), 1.73 (dt, J = 11.0, 5.6 Hz, 4H), 1.55 (d, J = 4.9 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.61, 145.50, 121.31, 120.91, 118.89, 113.61, 55.68, 53.81, 26.36, 24.21 ppm; FT-IR ν 2937, 1492, 1208, 1103, 1036, 737 cm^{-1}; HRMS (EI, m/z): M^+ calculated for $C_{12}H_{16}BrNO$ 269.0415, found 269.0420.

8-(2-Bromo-4-methoxyphenyl)-1,4-dioxa-8-azaspiro[4.5]decane (3b). White solid, mp 89–91 °C, 82% yield (40.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14 (d, J = 2.9 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 6.81 (dd, J = 8.8, 2.9 Hz, 1H), 4.00 (s, 4H), 3.76 (s, 3H), 3.10–2.94 (m, 4H), 1.96–1.83 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.89, 144.36, 121.52, 120.88, 118.88, 113.60, 107.08, 64.28, 55.67, 50.55, 35.42 ppm; FT-IR ν 2957, 1491, 1208, 1106, 1038, 736 cm^{-1}; HRMS (EI, m/z): M^+ calculated for $C_{14}H_{18}BrNO_3$ 327.0470, found 327.0473.

1-(4-Methoxy-2-thiocyanatophenyl)piperidine (4a). Brown liquid, 76% yield (28.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 (d, J = 2.7 Hz, 1H), 7.11 (d, J = 8.7 Hz, 1H), 6.81 (dd, J = 8.7, 2.7

Hz, 1H), 3.83 (s, 3H), 2.80–2.71 (m, 4H), 1.71–1.65 (m, 4H), 1.57–1.53 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.02, 143.29, 127.38, 122.84, 114.49, 112.51, 110.64, 55.74, 54.21, 26.37, 23.82 ppm; FT-IR ν 2936, 2155, 1493, 1221, 1044, 859 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{13}H_{16}N_2OS$ 248.0983, found 248.0983.

8-(4-Methoxy-2-thiocyanatophenyl)-1,4-dioxa-8-azaspiro[4.5] decane (4b). White solid, mp 86–87 °C, 85% yield (39.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 (t, J = 5.4 Hz, 2H), 6.81 (dd, J = 8.7, 2.8 Hz, 1H), 4.00 (s, 4H), 3.83 (s, 3H), 3.00–2.84 (m, 4H), 1.93–1.77 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.25, 142.22, 127.09, 123.01, 114.54, 112.15, 110.84, 106.51, 64.36, 55.75, 51.24, 35.45 ppm; FT-IR ν 2926, 2156, 1492, 1294, 1109, 1038, 735 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{15}H_{18}N_2O_3S$ 306.1038, found 306.1041.

4-(5*H*-Dibenzo[*a*,*d*][7]annulen-5-ylidene)-1-(4-methoxy-2-thiocyanatophenyl)piperidine (4c). Light yellow solid, mp 153–154 °C, 78% yield (51.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (ddd, J = 6.6, 3.7, 1.7 Hz, 4H), 7.26–7.20 (m, 4H), 7.13 (d, J = 2.7 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 6.94 (s, 2H), 6.77 (dd, J = 8.7, 2.7 Hz, 1H), 3.81 (s, 3H), 2.86–2.79 (m, 2H), 2.60 (dd, J = 19.9, 13.9 Hz, 2H), 2.45 (ddd, J = 13.3, 9.2, 4.0 Hz, 2H), 2.32–2.25 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.15, 142.28, 138.89, 134.73, 134.49, 134.16, 130.99, 128.38, 128.24, 127.84, 127.10, 126.39, 122.92, 114.51, 112.22, 110.82, 55.74, 54.65, 30.60 ppm; FT-IR ν 2924, 2155, 1493, 1215, 1042, 756, 741 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{28}H_{24}N_2OS$ 436.1609, found 436.1610.

4-(4-Methoxy-2-thiocyanatophenyl)morpholine (4d). Light yellow solid, mp 92–94 °C, 83% yield (31.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 (dd, J = 5.7, 4.5 Hz, 2H), 6.85 (dd, J = 8.7, 2.8 Hz, 1H), 3.84 (s, 3H), 3.83–3.78 (m, 4H), 2.88–2.81 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.49, 141.58, 127.10, 123.17, 114.78, 111.81, 111.09, 67.23, 55.78, 52.89 ppm; FT-IR ν 2960, 2156, 1493, 1217, 1114, 933, 735 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{12}H_{14}N_2O_2S$ 250.0776, found 250.0780.

1-(4-Methyl-2-thiocyanatophenyl)piperidine (4e). Light yellow liquid, 63% yield (22.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.11–7.01 (m, 2H), 2.83–2.73 (m, 4H), 2.36 (s, 3H), 1.72–1.66 (m, 4H), 1.53–1.53 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.95, 136.65, 129.33, 126.41, 125.49, 121.73, 112.55, 54.02, 26.32, 23.87, 21.09 ppm; FT-IR ν 2935, 2155, 1491, 1233, 1108, 925, 818 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{13}H_{16}N_2S$ 232.1034, found 232.1035.

Methyl 4-(piperidin-1-yl)-3-thiocyanatobenzoate (4f). Light yellow liquid, 81% yield (34.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 (d, J = 1.8 Hz, 1H), 7.99 (dd, J = 8.3, 1.8 Hz, 1H), 7.19 (d, J = 8.3 Hz, 1H), 3.92 (s, 3H), 2.96–2.84 (m, 4H), 1.78–1.69 (m, 4H), 1.60 (dt, J = 11.3, 5.8 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.70, 154.75, 130.72, 128.48, 127.60, 124.98, 121.24, 111.12, 53.60, 52.38, 26.04, 23.79 ppm; FT-IR ν 2935, 2154, 1724, 1493, 1245, 858 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{14}H_{16}N_2O_2S$ 276.0932, found 276.0931.

1-(4-Thiocyanatophenyl)piperidine (4g). Light yellow solid, mp 44–46 °C, 85% yield (28.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47–7.35 (m, 2H), 6.88 (d, J = 9.0 Hz, 2H), 3.29–3.20 (m, 4H), 1.71–1.65 (m, 4H), 1.64–1.59 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.00, 134.01, 116.43, 112.27, 109.03, 49.20, 25.34, 24.20 ppm; FT-IR ν 2931, 2153, 1590, 1500, 1240, 1129, 815 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{12}H_{14}N_2S$ 218.0878, found 218.0877.

1-(3-Methyl-4-thiocyanatophenyl)piperidine (4i). Brown liquid, 73% yield (25.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, J = 8.7 Hz, 1H), 6.79 (d, J = 2.7 Hz, 1H), 6.72 (dd, J = 8.7, 2.8 Hz, 1H), 3.31–3.18 (m, 4H), 2.48 (s, 3H), 1.75–1.64 (m, 4H), 1.63–1.57 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.52, 142.32, 135.72, 117.57, 114.10, 111.90, 108.67, 49.16, 25.38, 24.24, 21.36 ppm; FT-IR ν 2935, 2152, 1590, 1490, 1243, 1129, 736 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{13}H_{16}N_2S$ 232.1034, found 232.1031.

1-(3-Methyl-4-thiocyanatophenyl)pyrrolidine (4j). White solid, mp 109–111 °C, 32% yield (10.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, J = 8.6 Hz, 1H), 6.45 (d, J = 2.6 Hz, 1H), 6.38 (dd, J = 8.6, 2.8 Hz, 1H), 3.29 (ddd, J = 6.6, 4.3, 2.6 Hz, 4H), 2.51 (s, 3H), 2.09–1.96 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.78, 142.87, 136.43, 114.04, 112.46, 110.68, 105.11, 47.51, 25.47, 21.40 ppm; FT-IR ν 2923, 2146, 1592, 1497, 1386, 1114, 831 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{12}H_{14}N_2S$ 218.0878, found 218.0875.

1-(5-Methyl-2,4-dithiocyanatophenyl)pyrrolidine (4ja). White solid, mp 67–69 °C, 57% yield (24.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (s, 1H), 6.75 (s, 1H), 3.54 (t, J = 6.6 Hz, 4H), 2.52 (s, 3H), 2.07–1.98 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.04, 145.25, 143.81, 118.84, 111.63, 110.91, 110.29, 105.65, 51.61, 25.78, 21.23 ppm; FT-IR ν 2919, 2154, 1581, 1478, 1134, 735, 703 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{13}H_{13}N_3S_2$ 275.0551, found 275.0547.

1-(4-Methoxy-2-thiocyanatophenyl)pyrrolidine (4k). Light yellow liquid, 69% yield (24.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14 (d, J = 2.8 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H), 6.83 (dd, J = 8.7, 2.8 Hz, 1H), 3.82 (s, 3H), 3.08–2.96 (m, 4H), 1.99–1.90 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.47, 140.94, 125.71, 122.48, 115.25, 112.36, 111.71, 55.79, 53.32, 24.65 ppm; FT-IR ν 2923, 2155, 1492, 1284, 1228, 1044 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{12}H_{14}N_2OS$ 234.0827, found 234.0826.

2-(4-Thiocyanatophenyl)-1,2,3,4-tetrahydroisoquinoline (4l). Orange solid, mp 114–116 °C, 64% yield (26.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53–7.40 (m, 2H), 7.24–7.10 (m, 4H), 6.94–6.85 (m, 2H), 4.45 (s, 2H), 3.59 (t, J = 5.9 Hz, 2H), 2.98 (t, J = 5.9 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.38, 134.80, 134.29, 133.61, 128.28, 126.75, 126.47, 126.37, 114.76, 112.33, 108.38, 49.29, 45.13, 28.91 ppm; FT-IR ν 2927, 2154, 1592, 1500, 1265, 734 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{16}H_{14}N_2S$ 266.0878, found 266.0880.

2-(2,4-Dithiocyanatophenyl)-1,2,3,4-tetrahydroisoquinoline (4la). Orange solid, mp 61–63 °C, 23% yield (11.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, J = 2.1 Hz, 1H), 7.58 (dd, J = 8.3, 2.1 Hz, 1H), 7.31 (d, J = 8.3 Hz, 1H), 7.21 (ddd, J = 17.0, 11.5, 6.9 Hz, 3H), 7.07 (d, J = 7.0 Hz, 1H), 4.15 (s, 2H), 3.26 (t, J = 5.8 Hz, 2H), 3.03 (t, J = 5.7 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.82, 133.44, 133.33, 131.67, 129.06, 128.77, 128.17, 126.89, 126.31, 126.21, 123.85, 122.20, 110.72, 110.40, 109.89,

54.22, 50.65, 28.97 ppm; FT-IR ν 2925, 2155, 1582, 1483, 1135, 737 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{17}H_{13}N_3S_2$ 323.0551, found 323.0550.

5-(4-Methoxy-2-thiocyanatophenyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine (4m). White solid, mp 153–155 °C, 78% yield (42.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.7 Hz, 1H), 7.35–7.21 (m, 3H), 7.17–7.04 (m, 3H), 7.03–6.86 (m, 2H), 6.62 (dd, *J* = 8.3, 0.8 Hz, 1H), 6.55 (d, *J* = 8.9 Hz, 1H), 3.93 (s, 3H), 3.32–3.15 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.99, 146.13, 143.39, 134.84, 134.47, 134.37, 134.29, 133.28, 130.21, 129.85, 128.43, 126.78, 122.99, 122.08, 121.35, 116.12, 113.66, 111.31, 109.65, 55.95, 36.87, 35.12 ppm; FT-IR ν 2923, 2154, 1497, 1234, 1047, 755, 731 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{22}H_{18}N_2OS$ 358.1140, found 358.1139.

5-(2-Methyl-4,6-dithiocyanatophenyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine (4na). White solid, mp 141–143 °C, 71% yield (43.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54–7.33 (m, 3H), 7.29 (s, 2H), 7.21 (d, *J* = 6.5 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.44 (d, *J* = 8.8 Hz, 2H), 3.20 (s, 4H), 2.01 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.93, 144.15, 137.04, 133.71, 133.58, 132.84, 130.93, 130.05, 128.66, 128.54, 122.60, 113.07, 111.38, 37.11, 17.52 ppm; FT-IR ν 2923, 2856, 2152, 2104, 1578, 1474, 1297, 812 cm^{-1}; HRMS (ESI, *m*/*z*): $[M + Na]^+$ calculated for $C_{23}H_{17}N_3NaS_2$ 422.0762, found 422.0776.

5-(4-Thiocyanatophenyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine (4o). White solid, mp 175–176 °C, 83% yield (41.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 7.3, 1.4 Hz, 2H), 7.31–7.19 (m, 8H), 6.65–6.52 (m, 2H), 2.98 (s, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.83, 142.45, 137.89, 134.15, 131.18, 129.36, 127.75, 127.38, 113.97, 112.34, 108.55, 30.60 ppm; FT-IR ν 2927, 2155, 1592, 1501, 1247, 803 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{21}H_{16}N_2S$ 328.1034, found 328.1038.

1-(4-Methoxyphenyl)-6-thiocyanato-1,2,3,4-tetrahydroquinoline (4u). White solid, mp 89–91 °C, 71% yield (32.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (d, *J* = 1.3 Hz, 1H), 7.16–7.10 (m, 2H), 7.04 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.97–6.91 (m, 2H), 6.36 (d, *J* = 8.7 Hz, 1H), 3.83 (s, 3H), 3.65–3.53 (m, 2H), 2.85 (t, *J* = 6.3 Hz, 2H), 2.06 (dt, *J* = 12.5, 6.2 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.68, 147.71, 139.57, 134.05, 131.86, 128.15, 124.09, 115.20, 114.79, 112.67, 106.85, 55.48, 51.68, 27.75, 21.84 ppm; HRMS (ESI, *m*/*z*): $[M + Na]^+$ calculated for $C_{17}H_{16}N_2NaOS$ 319.0876, found 319.0863.

Benzyl(4-thiocyanatophenyl)carbamate (4p). White solid, mp 83–85 °C, 43% yield (18.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53–7.46 (m, 4H), 7.43–7.34 (m, 5H), 6.81 (s, 1H), 5.22 (s, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.88, 139.77, 135.58, 132.46, 128.72, 128.61, 128.44, 119.82, 117.19, 111.05, 67.48 ppm; FT-IR ν 2920, 2851, 2152, 1713, 1590, 1220, 1043, 811, 689 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{15}H_{12}N_2O_2S$ 284.0619, found 284.0616.

Benzyl(6-thiocyanatobenzo[*d*][1,3]dioxol-5-yl)carbamate (4q). White solid, mp above 250 °C, 91% yield (45.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.52–7.32 (m, 5H), 7.15 (s, 1H), 7.06 (s, 1H), 6.03 (s, 2H), 5.23 (s, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.23, 151.50, 135.48, 128.71, 128.61, 128.50, 113.50, 109.92, 102.49, 77.25, 77.04, 76.83, 67.74 ppm; FT-IR ν 2919, 2851, 2157, 1697, 1529, 1233, 1066, 877 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{16}H_{12}N_2O_4S$ 328.0518, found 328.0518.

1-(4-Methoxy-2-nitrophenyl)piperidine (5a). Red liquid, 85% yield (30.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J* = 1.1 Hz, 1H), 7.13 (d, *J* = 9.0 Hz, 1H), 7.04 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.81 (s, 3H), 2.94–2.89 (m, 4H), 1.73–1.65 (m, 4H), 1.57–1.53 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.38, 144.60, 141.18, 123.09, 120.09, 109.36, 55.87, 54.02, 26.22, 24.05 ppm; FT-IR ν 2936, 1529, 1301, 1225, 1043, 802 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{12}H_{16}N_2O_3$ 236.1161, found 236.1163.

8-(4-Methoxy-2-nitrophenyl)-1,4-dioxa-8-azaspiro[4.5]decane (5b). Yellow solid, mp 107–109 °C, 93% yield (41.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29–7.26 (m, 1H), 7.19 (d, *J* = 9.0 Hz, 1H), 7.05 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.99 (s, 4H), 3.81 (s, 3H), 3.12–2.98 (m, 4H), 1.92–1.79 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.99, 145.17, 140.17, 123.50, 119.97, 109.40, 106.79, 64.31, 55.88, 51.18, 35.35 ppm; FT-IR ν 2962, 1528, 1266, 1107, 1040, 734, 703 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{14}H_{18}N_2O_5$ 294.1216, found 294.1219.

4-(5*H*-Dibenzo[*a*,*d*][7]annulen-5-ylidene)-1-(4-methoxy-2-nitrophenyl)piperidine (5c). Orange solid, mp 167–168 °C, 81% yield (52.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37–7.30 (m, 4H), 7.26–7.24 (m, 3H), 7.24–7.20 (m, 2H), 7.06 (d, *J* = 9.0 Hz, 1H), 7.01 (dd, *J* = 9.0, 2.9 Hz, 1H), 6.93 (s, 2H), 3.79 (s, 3H), 3.05–2.99 (m, 2H), 2.71–2.64 (m, 2H), 2.49 (ddd, *J* = 13.6, 9.5, 4.1 Hz, 2H), 2.32–2.26 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.98, 134.75, 130.99, 128.49, 128.21, 127.82, 126.33, 123.29, 120.02, 109.40, 55.87, 54.46, 30.51 ppm; FT-IR ν 2926, 1528, 1362, 1221, 1092, 802 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{27}H_{24}N_2O_3$ 424.1787, found 424.1786.

5-(4-Methoxy-2-nitrophenyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine (5m). Brown solid, mp 136–137 °C, 84% yield (44.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, *J* = 9.2 Hz, 1H), 7.18 (dd, *J* = 8.5, 2.5 Hz, 3H), 7.12–6.99 (m, 7H), 3.82 (s, 3H), 3.19 (s, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.61, 144.28, 141.57, 136.56, 133.94, 130.69, 126.58, 125.34, 124.85, 124.75, 120.23, 109.79, 55.99, 32.47 ppm; FT-IR ν 2924, 1527, 1487, 1264, 1037, 758 cm^{-1}; HRMS (EI, *m*/*z*): M^+ Calcd for $C_{21}H_{18}N_2O_3$ 346.1317, found 346.1317.

1-(4-Methoxy-2-(phenylsulfonyl)phenyl)piperidine(7a). White solid; mp 111–112 °C; 76% yield (38.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.7 Hz, 2H), 7.81 (d, *J* = 3.0 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 1H), 7.11 (dd, *J* = 8.7, 3.0 Hz, 1H), 3.88 (s, 3H), 2.69–2.43 (m, 4H), 1.55–1.33 (m, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.57, 146.90, 142.71, 137.73, 132.27, 128.21, 127.43, 125.63, 121.31, 113.81, 55.90, 54.84, 25.60, 23.87 ppm; FT-IR ν 2928, 2145, 1515, 1311, 1114, 876 cm^{-1}; HRMS (ESI, *m*/*z*): $[M + H]^+$ calculated for $C_{18}H_{22}NO_3S$ 332.1320, found 332.1316.

1-(4-Methoxy-2-(methylsulfonyl)phenyl)piperidine (8a). Light orange solid, mp 99–101 °C, 73% yield (29.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (d, *J* = 3.0 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.11 (dd, *J* = 8.7, 3.0 Hz, 1H), 3.83 (s, 3H), 3.37 (s, 3H), 3.24–2.89 (bs, 2H), 2.88–2.47 (bs, 2H), 1.96–1.52 (m, 6H)

ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.64, 146.46, 137.76, 125.24, 121.02, 112.99, 55.85, 55.29, 42.73, 26.44, 23.99 ppm; FT-IR ν 2936, 2800, 1492, 1294, 1137, 1018, 758 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{13}H_{19}NO_3S$ 269.1086, found 269.1090.

1-(4-Methoxy-2-(phenylthio)phenyl)piperidine (9a). Brown viscous liquid, 69% yield (31.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55–7.46 (m, 2H), 7.40–7.31 (m, 3H), 7.00 (d, J = 8.6 Hz, 1H), 6.63 (dd, J = 8.6, 2.9 Hz, 1H), 6.31 (d, J = 2.9 Hz, 1H), 3.60 (s, 3H), 2.96–2.81 (bs, 4H), 1.71 (dt, J = 11.1, 5.6 Hz, 4H), 1.54 (d, J = 5.1 Hz, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.18, 144.51, 136.70, 134.53, 133.28, 129.37, 128.21, 120.72, 113.30, 110.50, 55.29, 53.90, 26.52, 24.28 ppm; FT-IR ν 2930, 2851, 1611, 1482, 1209, 1044, 749 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{18}H_{21}NOS$ 299.1344, found 299.1344.

General procedure for azidation

Cyclic amine (0.15 mmol, 1.0 equiv.) and NaN_3 (0.3 mmol, 2.0 equiv.) were dissolved in 1 mL of nitromethane and PIFA (0.3 mmol, 2.0 equiv.) was cautiously added portionwise to the reaction mixture, and then the solution was stirred at room temperature for 30 min to 8 h, monitored by TLC. Then, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with 10 mL saturated solution of $NaHCO_3$ and 5 mL brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc, 20 : 1) to afford the corresponding products.

1-(2-Azido-4-methoxyphenyl)piperidine (6a). Brown liquid, 78% yield (27.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.98 (d, J = 8.8 Hz, 1H), 6.63 (dd, J = 8.8, 2.8 Hz, 1H), 6.59 (d, J = 2.8 Hz, 1H), 3.77 (s, 3H), 2.89–2.83 (m, 4H), 1.74 (dt, J = 11.2, 5.7 Hz, 4H), 1.57–1.51 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.03, 139.79, 134.47, 121.17, 110.31, 106.15, 55.55, 53.76, 25.93, 24.17 ppm; FT-IR ν 2936, 2109, 1503, 1442, 1225, 1045 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{12}H_{16}N_4O$ 232.1324, found 232.1328.

8-(2-Azido-4-methoxyphenyl)-1,4-dioxa-8-azaspiro[4.5]decane (6b). Brown liquid, 76% yield (33.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.02 (d, J = 8.7 Hz, 1H), 6.63 (dd, J = 8.7, 2.8 Hz, 1H), 6.60 (d, J = 2.8 Hz, 1H), 4.00 (s, 4H), 3.77 (s, 3H), 3.09–2.94 (m, 4H), 1.97–1.82 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.30, 138.51, 134.45, 121.43, 110.31, 106.89, 106.16, 64.30, 55.55, 50.60, 34.96 ppm; FT-IR ν 2957, 2109, 1504, 1214, 1109, 1041, 735 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{14}H_{18}N_4O_3$ 290.1379, found 290.1384.

1-(2-Azido-4-methoxyphenyl)-4-(5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)piperidine (6c). Brown viscous liquid, 68% yield (43.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40–7.33 (m, 4H), 7.28–7.23 (m, 4H), 6.96 (s, 2H), 6.92 (d, J = 8.7 Hz, 1H), 6.65–6.57 (m, 2H), 3.78 (s, 3H), 3.07–3.00 (m, 2H), 2.68–2.60 (m, 2H), 2.55 (ddd, J = 13.4, 9.4, 4.0 Hz, 2H), 2.37–2.31 (m, 2H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.20, 139.08, 134.80, 131.00, 128.53, 128.20, 127.78, 126.29, 121.35, 110.30, 106.20, 55.54, 54.21, 30.16 ppm; FT-IR ν 2937, 2108, 1504, 1221, 1044, 737 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{27}H_{24}N_4O$ 420.1950, found 420.1953.

4-(2-Azido-4-methoxyphenyl)morpholine (6d). Brown liquid, 72% yield (25.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.97 (d, J = 8.7 Hz, 1H), 6.66 (dd, J = 8.7, 2.8 Hz, 1H), 6.62 (d, J = 2.8 Hz, 1H), 3.89–3.84 (m, 4H), 3.78 (s, 3H), 2.95 (dd, J = 5.4, 3.8 Hz, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.45, 137.94, 134.37, 120.91, 110.41, 106.30, 66.90, 55.57, 52.43 ppm; FT-IR ν 2959, 2110, 1504, 1219, 1115, 1035, 735 cm^{-1}; HRMS (EI, *m*/*z*): M^+ calculated for $C_{11}H_{14}N_4O_2$ 234.1117, found 234.1120.

Late-stage azidation of brucine

Brucine **1r** (0.1 g, 0.254 mmol) and NaN_3 (0.033 g, 0.508 mmol) were dissolved in 3 mL of nitromethane and PIFA (0.218 g, 0.508 mmol) was cautiously added portionwise to the reaction mixture, and then the solution was stirred at rt for 10 to 30 min, monitored by TLC. Then, the reaction mixture was diluted with water (3 mL) and extracted with chloroform (3 × 15 mL). The organic layer was washed with 10 mL saturated solution of $NaHCO_3$ and 5 mL brine solution, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography ($MeOH/CH_2Cl_2$, 1 : 20) to afford the desired product **6r** as a light brown solid; mp above 250 °C; 79% yield (87.4 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (s, 1H), 5.91 (s, 1H), 4.76 (s, 1H), 4.28 (d, J = 8.4 Hz, 1H), 4.14 (dd, J = 13.8, 7.0 Hz, 1H), 4.06 (dd, J = 13.7, 6.0 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.73 (dd, J = 23.7, 12.6 Hz, 2H), 3.20 (dd, J = 9.4, 8.1 Hz, 1H), 3.16–3.06 (m, 2H), 2.88–2.70 (m, 2H), 2.62 (dd, J = 17.4, 3.3 Hz, 1H), 2.43–2.26 (m, 2H), 1.66 (dd, J = 12.5, 5.9 Hz, 1H), 1.48 (d, J = 14.5 Hz, 1H), 1.31–1.28 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.14, 153.33, 139.90, 138.90, 129.42, 127.86, 114.00, 97.76, 77.55, 64.61, 61.77, 60.48, 56.34, 56.18, 52.67, 52.32, 49.24, 48.41, 42.40, 38.58, 31.21, 26.86 ppm; FT-IR ν 2907, 2104, 1660, 1397, 1045, 837 cm^{-1}; HRMS (ESI, *m*/*z*): $[M + H]^+$ calculated for $C_{23}H_{26}N_5O_4$ 436.1985, found 436.1978.

Thiocyanation of julolidine

Julolidine **1s** (20.8 mg, 0.12 mmol) and NaSCN (19.4 mg, 0.24 mmol) were dissolved in a 1.0 mL mixture of nitromethane and water (9 : 1) and PIFA (103.2 mg, 0.24 mmol) was cautiously added portionwise to the reaction mixture, and then the solution was stirred at rt for 10 to 30 min, monitored by TLC. Then, the reaction mixture was diluted with water (3 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with 10 mL saturated solution of $NaHCO_3$ and 5 mL brine solution, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc, 20 : 1) to afford the desired product **4s** as a white solid; mp 99–100 °C; 71% yield (20.0 mg); ^{1}H NMR (600 MHz, acetone-d_6) δ 6.99 (s, 2H), 3.28–3.18 (m, 4H), 2.71 (t, J = 6.4 Hz, 4H), 1.96–1.86 (m, 4H) ppm; ^{13}C NMR (150 MHz, acetone) δ 145.55, 132.65, 123.76, 113.02, 104.87, 50.23, 28.17, 22.00 ppm; FT-IR ν 2849, 2145, 1516, 1313, 1202, 875 cm^{-1}; HRMS (ESI, *m*/*z*): $[M + H]^+$ calculated for $C_{13}H_{15}N_2S$ 231.0956, found 231.0950.

1 mmol scale synthesis of 4h. To a dried round-bottom flask were added 4-phenylmorpholine **1h** (163.2 mg, 1.0 mmol) and NaSCN (162.1 mg, 2.0 mmol) and they were dissolved in a 6.0 mL mixture of nitromethane and water (9 : 1). [Bis(trifluoroacetoxy)iodo]benzene (PIFA) (860.0 mg, 2.0 mmol) was cautiously added portionwise to the reaction mixture at 0 °C and then the solution was stirred at rt for 10 to 30 min, monitored by TLC. Then, the reaction mixture was diluted with water (3 mL) and extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with 10 mL saturated solution of $NaHCO_3$ and 5 mL brine solution, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/EtOAc, 20 : 1) to afford the desired product 4-(4-thiocyanatophenyl)morpholine **4h** as a white solid, mp 90–92 °C, 81% yield (178.4 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50–7.40 (m, 2H), 6.89 (dd, J = 9.6, 2.5 Hz, 2H), 3.93–3.79 (m, 4H), 3.24–3.15 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.51, 133.72, 116.15, 111.90, 111.15, 66.54, 48.04 ppm; FT-IR ν 2960, 2155, 1494, 1204, 1115, 737 cm^{-1}; HRMS (EI, m/z): M^+ calculated for $C_{11}H_{12}N_2OS$ 220.0670, found 220.0674, and di-SCN product 4-(2,4-dithiocyanatophenyl)morpholine **4ha** as a light yellow solid; mp 82–83 °C; 7% yield (19.4 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, J = 2.1 Hz, 1H), 7.58 (dd, J = 8.3, 2.1 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 3.94–3.75 (m, 4H), 3.01–2.87 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.38, 131.68, 128.71, 127.94, 123.69, 122.67, 110.10, 109.76, 66.88, 52.33 ppm; FT-IR ν 2851, 2163, 2145, 1586, 1314, 1113, 876 cm^{-1}; HRMS (ESI, m/z): $[M + H]^+$ calculated for $C_{12}H_{12}N_3OS_2$ 278.0422, found 278.0418.

Tetrazole formation[18]

A dried round-bottom flask was charged with a solution of **4h** (1.0 equiv.) in isopropyl alcohol (3 mL). Then, NaN_3 (1.2 equiv.) and $ZnCl_2$ (1.0 equiv.) were added to the reaction mixture.

Di-tetrazole formation

A dried round-bottom flask was charged with a solution of **4ha** (1.0 equiv.) in isopropyl alcohol (3 mL). Then, NaN_3 (2.4 equiv.) and $ZnCl_2$ (2.0 equiv.) were added to the reaction mixture.

The reaction mixture was then continuously stirred at 50 °C for 1.5 to 3 h until **4h** or **4ha** was completely consumed (TLC). After completion of the reaction, the solvent was evaporated from the reaction mixture under reduced pressure. Afterward, a solution of 5% NaOH (10 mL) was added to the mixture and it was stirred for 20 min at rt. The suspension of $Zn(OH)_2$ was filtered and washed with 5% NaOH (10 ml). Next, the pH of the combined filtrate was adjusted to 1.0 with con. HCl, but precipitation did not occur. Afterward, the filtrate was extracted with ethyl acetate (3 × 15 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography ($MeOH/CH_2Cl_2$, 1 : 4) to afford the desired products.

4-(4-((1*H*-Tetrazol-5-yl)thio)phenyl)morpholine (10h). White solid, mp above 250 °C, 84% yield (22.0 mg); ^{1}H NMR (600 MHz, CD_3OD) δ 7.42–7.31 (m, 2H), 6.92 (d, J = 8.8 Hz, 2H), 3.85–3.74 (m, 4H), 3.19–3.09 (m, 4H) ppm; ^{13}C NMR (150 MHz, CD_3OD) δ 157.80, 153.18, 135.08, 120.68, 117.29, 67.82, 49.84 ppm; FT-IR ν 2838, 1500, 1235, 1116, 923, 817 cm^{-1} HRMS (ESI, m/z): $[M + H]^+$ calculated for $C_{11}H_{14}N_5OS$ 264.0919, found 264.0913.

4-(2,4-Bis((1*H*-tetrazol-5-yl)thio)phenyl)morpholine (10ha). White solid, mp above 250 °C, 63% yield (23.0 mg); ^{1}H NMR (600 MHz, CD_3OD) δ 7.13–7.02 (m, 2H), 6.70 (s, 1H), 3.86–3.72 (m, 4H), 3.04–2.92 (m, 4H) ppm; ^{13}C NMR (150 MHz, CD_3OD) δ 156.68, 154.99, 150.09, 134.86, 131.09, 130.52, 130.21, 122.35, 68.27, 53.20 ppm; FT-IR ν 2971, 1501, 1236, 1112, 930, 818 cm^{-1}; HRMS (ESI, m/z): $[M + H]^+$ calculated for $C_{12}H_{14}N_9OS_2$ 364.0763, found 364.0760.

Tris(4-bromo-2-chlorophenyl)amine (2taa). 1t (0.03 mmol, 1.0 equiv.) and NaCl (0.06 mmol, 2.0 equiv.) were dissolved in a 1 mL mixture of nitromethane and water (9 : 1) and PIFA (0.06 mmol, 2.0 equiv.) was cautiously added portionwise to the reaction mixture, and then the solution was stirred at rt for 1 h, monitored by TLC. Then, the reaction mixture was diluted with chloroform, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography with hexane only to afford the corresponding product **2taa** as a white solid; mp 56–58 °C; 51% yield (9.0 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, J = 2.2 Hz, 3H), 7.31–7.28 (m, 3H), 6.74 (d, J = 8.6 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.55, 133.94, 131.40, 130.74, 127.51, 118.18 ppm; FT-IR ν 2919, 2850, 1469, 1299, 1084, 813, 705 cm^{-1}; HRMS (ESI, m/z): $[M + H]^+$ calculated for $C_{18}H_{10}Br_3Cl_3N$ 583.7403, found 583.7405.

Conflicts of interest

There are no conflicts to declare.

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