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Copper(II) catalyzed heterobenzylic C(sp^3)-H activation: two efficient halogenation methodologies towards heterobenzyl halides

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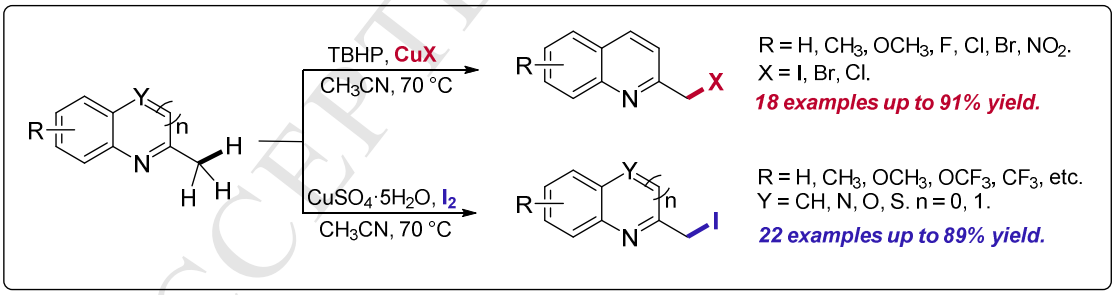
Abstract

Two practical and simple synthetic methodologies towards various heterobenzyl halides were developed. A series of 2-halomethylquinolines were readily prepared by the one-pot reaction of 2-methylquinolines with CuX (X = I, Br, Cl) and TBHP in CH_3CN. A large variety of heterobenzyl iodides, including 2-iodomethylquinolines, 2-iodomethylquinoxalines, 2-iodiomethylbenzooxazole, and 2-iodiomethylbenzothiazole, were efficiently synthesized by one-pot reaction of 2-methylheterocycles with iodine in the presence of $CuSO_4 \cdot 5H_2O$ in CH_3CN.

Keywords: Copper(II) catalyst; 2-halomethylazaarenes; C(sp^3)-H halogenation; one-pot procedure

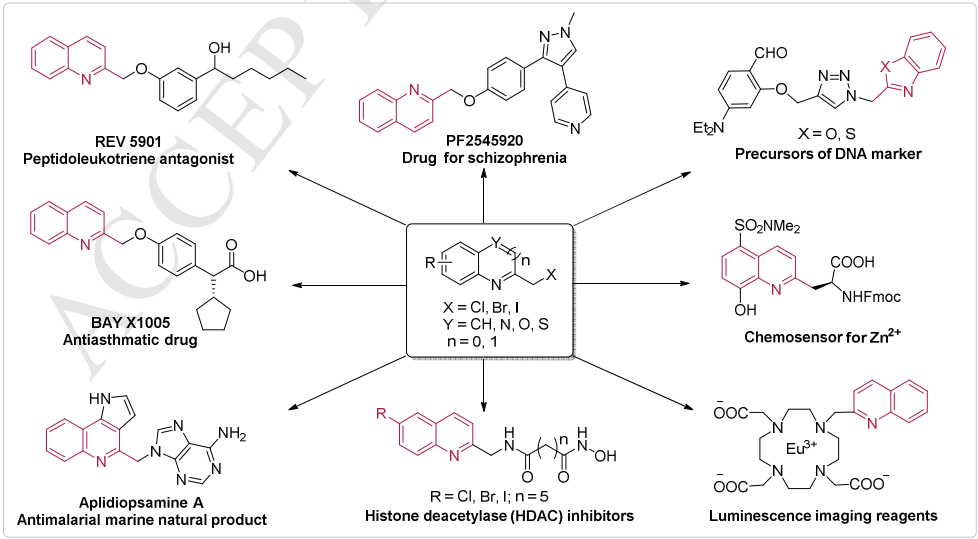


1. Introduction

Organic halides are generally applied as crucial synthetic precursors for organic synthesis. For example, the substitution reactions of organic halides with various nucleophiles (e.g. cyanide, thiocyanate, azide, amine etc.) could afford various organic compounds.[1] Organic halides are also indispensable starting reactants in coupling reactions, such as Stille, Suzuki, Heck, Sonogashira, and Buchwald-Hartwig reactions.[2] Meanwhile, organometallic compounds, such as Grignard reagents, Gilman reagents, are made from organic halides.[3] Generally, chloro- or bromoalkanes can be synthesized by free radical halogenation reaction of alkanes with chlorine or bromine. In contrast, the direct free radical iodination of alkanes by iodine is not feasible experimentally because of its large activation energy of hydrogen atom-abstraction step.[4] The iodination of alkanes is thus especially challenging. As a consequence, in the past few decades, many efforts have been made for the synthesis of organoiodides.

Heterocycles are reported in more than 90% of the new synthetic biologically active compounds.[5] Among them, quinolines, oxazoles, thiazoles and quinoxalines are the most commonly existence skeleton structure in medicinal and agricultural compounds. Considerable efforts have been attributed to their synthesis and functionalization over the past decades.[6] It is especially worth mentioning that heterobenzyl halides are

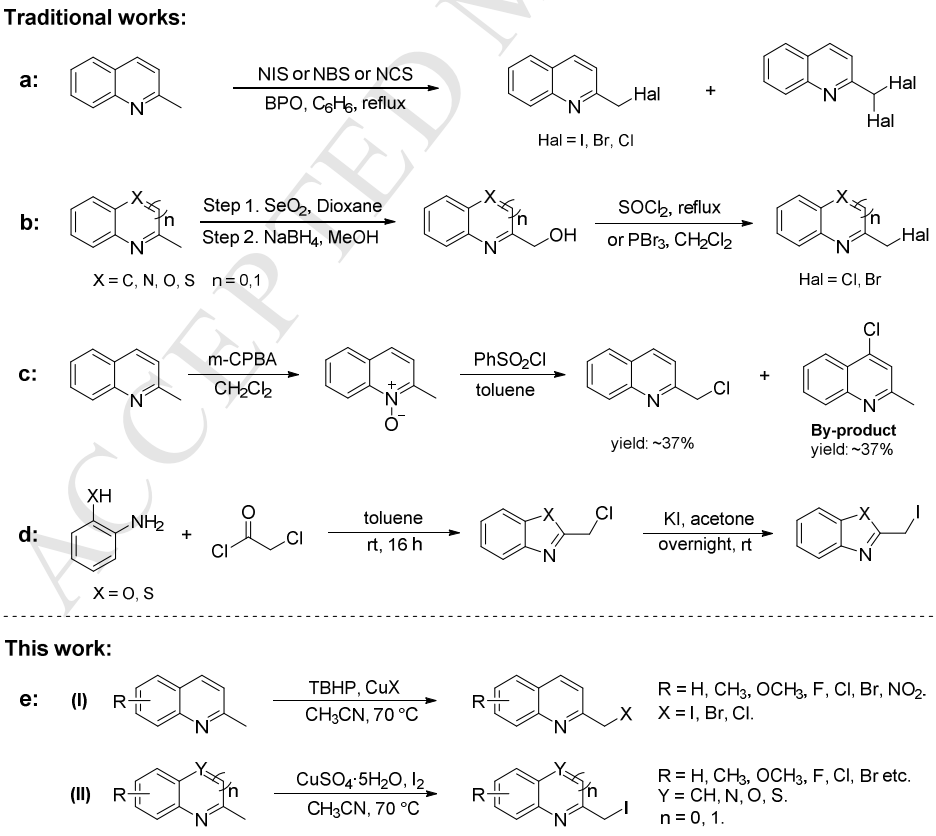
extremely important synthetic precursors for numerous biologically important compounds.[7] For example, as illustrated in Scheme 1, heterobenzyl halides, especially 2-halomethylquinolines, have frequently served as key synthetic building blocks for many clinical drugs,[7a-i] luminescence imagings,[7j] chemosensors,[7k-l] and numerous other biologically active heterocyclic compounds.[7m] Scheme 2 shows four traditional synthetic methods for some important heterobenzyl halides, in particular 2-halomethylquinolines. The most traditional method for 2-halomethylquinolines is free radical halogenation of 2-methylquinolines with NIS, NBS or NCS, respectively (Scheme 2a). However, the main drawback is that multi-halogenation is usually difficult to avoid.[7d,7g,8] Scheme 2b shows a multi-step synthetic approach for some heterobenzyl halides. After oxidation followed by reduction, the



Scheme 1. Various applications of the heterobenzyl halides.

starting 2-methylazaarenes are initially changed to their corresponding benzylic alcohols, which then react with $SOCl_2$ or PBr_3 to produce the target heterobenzyl halides.[7m,7k,9] Scheme 2c shows a two-step method reported previously for synthesizing 2-chloromethylquinoline, however, owing to the formation of equal amount of by-product, the yield is generally low.[7a,10] Scheme 2d shows a widely used cyclization method for the synthesis of 2-chloromethylbenzooxazole or 2-chloromethylbenzothiazol, however, an additional time-consuming synthetic procedure is required if one wants to get 2-iodomethylbenzooxazole or 2-iodomethylbenzothiazol.[11] Recently, microwave-assisted halogenation with 1,2-dicholoethane/1,2-dibromoethane[12a] for some heterobenzyl chlorides/bromides, and PPh_3 induced iodination reaction for 2-iodomethylquinolines[12b] were reported successively, however, some drawbacks such as harsh or inconvenient reaction conditions, as well as relative narrow substituent scopes are still waiting to be overcome. Thus, the development of simple, facile and efficient synthetic methods for various heterobenzyl halides from readily available reagents is highly required. Herein, we disclose two practical and simple synthetic methodologies towards various heterobenzyl halides (Scheme 2e). As shown in Scheme 2e-I, a series of 2-halomethylquinolines were readily prepared by the one-pot reaction of 2-methylquinolines with CuX (X = I,

Br, Cl) and TBHP in CH_3CN. Then we developed the second synthetic methodology as shown in Scheme 2e-II, by which a large variety of heterobenzyl iodides, including 2-iodomethylquinolines, 2-iodomethylquinoxalines, 2-iodiomethylbenzooxazole, and 2-iodiomethylbenzothiazole, were efficiently synthesized by one-pot reaction of 2-methylheterocycles direct with iodine in the presence of $CuSO_4 \cdot 5H_2O$ in CH_3CN. The remarkable merits of the two synthetic methodologies include cheap and easily available reactants, high regioselectivity, a wide scope of products, as well as an efficient one-pot synthetic procedure.



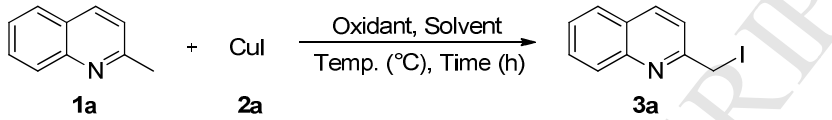
Scheme 2. Comparison of traditional works with this work.

2. Results and discussion

We started with establishing the optimal reaction conditions for the first reaction shown by Scheme **2e-I**. The optimal reaction conditions were screened by using the model reaction of 2-methylquinoline (**1a**) with CuI (**2a**) (Table 1). Initially, the model reaction was carried out in the presence of various oxidants, such as O_2 in air, $K_2S_2O_8$, TBHP, DTBP or H_2O_2. The target compound **3a** was obtained in yields of trace, 32%, 43%, 27% and 13%, respectively (entries 1-5). TBHP gave the highest yield of 2-iodomethylquinoline (**3a**) among all the oxidants tested (entry 3). Then the amount of TBHP was screened (entries 6-9). It can be seen that a satisfied yield (81%, entry 8) was obtained as 8 eq. of TBHP was employed. Following that, a suitable amount of CuI was screened (entries 8, 10-11). The results showed that 1.2 eq. of CuI brought about the best yield (89%). Subsequently, influences of different solvents on the model reaction were investigated (entries 10, 12-17). It can be seen that the reaction did not occur in DMSO and DMF (entries 12-13), however, the reaction occurred in THF (yield: 59%), *p*-dioxane (yield: 67%), CH_2Cl_2 (yield: 57%) and toluene (yield: 17%). Among all the solvents tested, CH_3CN brought the most satisfied yield of **3a** (89%, entry 10). The following investigation on temperature (entries 10, 18-20) and reaction time (entries 10, 21-24) indicated that the initially used temperature (70 °C) and reaction time (8 h), as shown by entry 10, were still the best

choices. Thus, the optimized reaction conditions are: 2-metylquinoline (0.5 mmol), CuI (1.2 eq.) in the presence of TBHP (8 eq.) at 70 °C for 8 h (as indicated by entry 10).

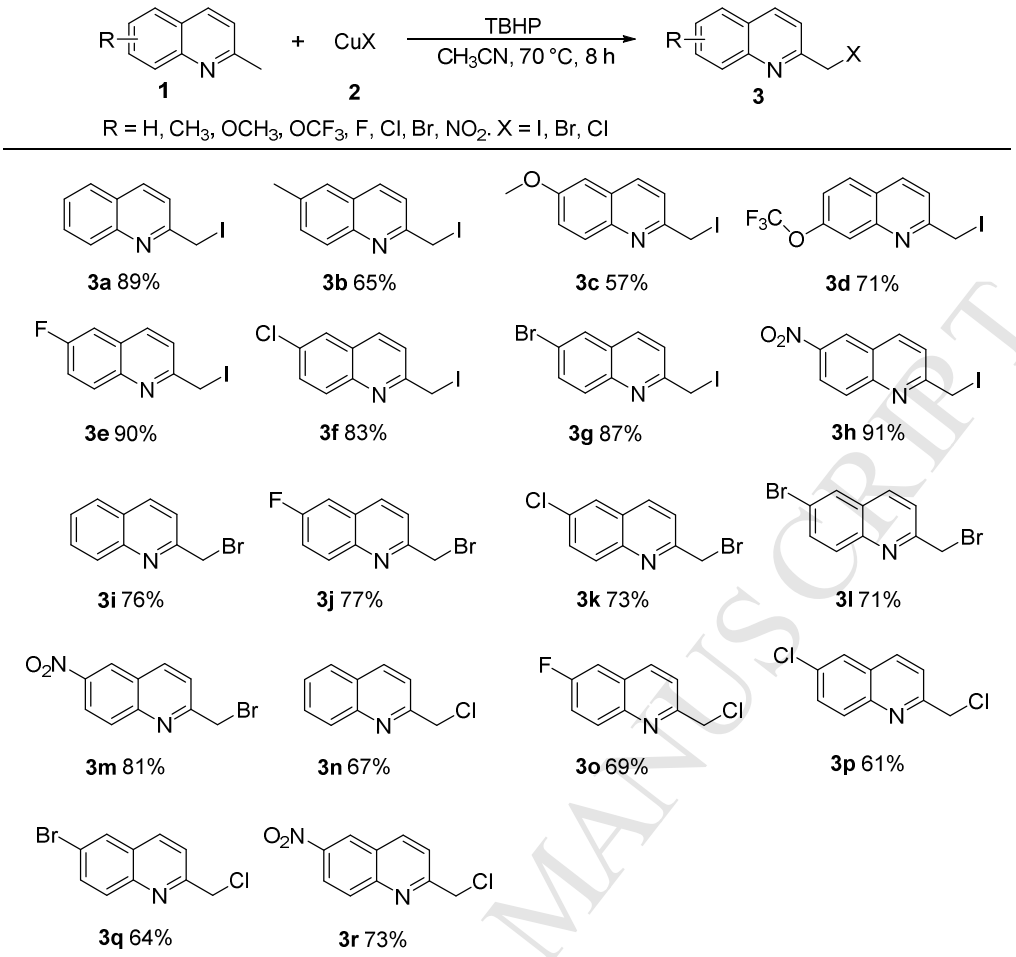
Table 1. Optimization of reaction conditions[a]



Entry	2a (eq.)	Oxidant (eq.)	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	CuI (1.0)	O_2 (air)	CH_3CN	70	8	trace[c]
2	CuI (1.0)	$K_2S_2O_8$ (2)	CH_3CN	70	8	32
3	CuI (1.0)	TBHP (2)	CH_3CN	70	8	43
4	CuI (1.0)	DTBP (2)	CH_3CN	70	8	27
5	CuI (1.0)	H_2O_2 (2)	CH_3CN	70	8	13
6	CuI (1.0)	TBHP (4)	CH_3CN	70	8	55
7	CuI (1.0)	TBHP (6)	CH_3CN	70	8	75
8	CuI (1.0)	TBHP (8)	CH_3CN	70	8	81
9	CuI (1.0)	TBHP (10)	CH_3CN	70	8	76
10	**CuI (1.2)**	**TBHP (8)**	**CH_3CN**	**70**	**8**	**89**
11	CuI (1.4)	TBHP (8)	CH_3CN	70	8	87
12	CuI (1.2)	TBHP (8)	DMSO	70	8	n.r.[c]
13	CuI (1.2)	TBHP (8)	DMF	70	8	n.r.[c]
14	CuI (1.2)	TBHP (8)	THF	70	8	59
15	CuI (1.2)	TBHP (8)	*p*-dioxane	70	8	67
16	CuI (1.2)	TBHP (8)	CH_2Cl_2	70	8	57
17	CuI (1.2)	TBHP (8)	toluene	70	8	17
18	CuI (1.2)	TBHP (8)	CH_3CN	30	8	53
19	CuI (1.2)	TBHP (8)	CH_3CN	50	8	57
20	CuI (1.2)	TBHP (8)	CH_3CN	90	8	87
21	CuI (1.2)	TBHP (8)	CH_3CN	70	4	49
22	CuI (1.2)	TBHP (8)	CH_3CN	70	6	71
23	CuI (1.2)	TBHP (8)	CH_3CN	70	10	85
24	CuI (1.2)	TBHP (8)	CH_3CN	70	12	83

[a]Optimal conditions: **1a** (0.5 mmol), **2a** (1.0-1.4 eq.), oxidant (2-10 eq.), solvent (2 mL) at 30-90 °C for 4-12 h. [b]Isolated yields. [c]Detected by TLC. n.r. = no reaction. 70% aqueous solution of TBHP and 30% aqueous solution of H_2O_2 were used.

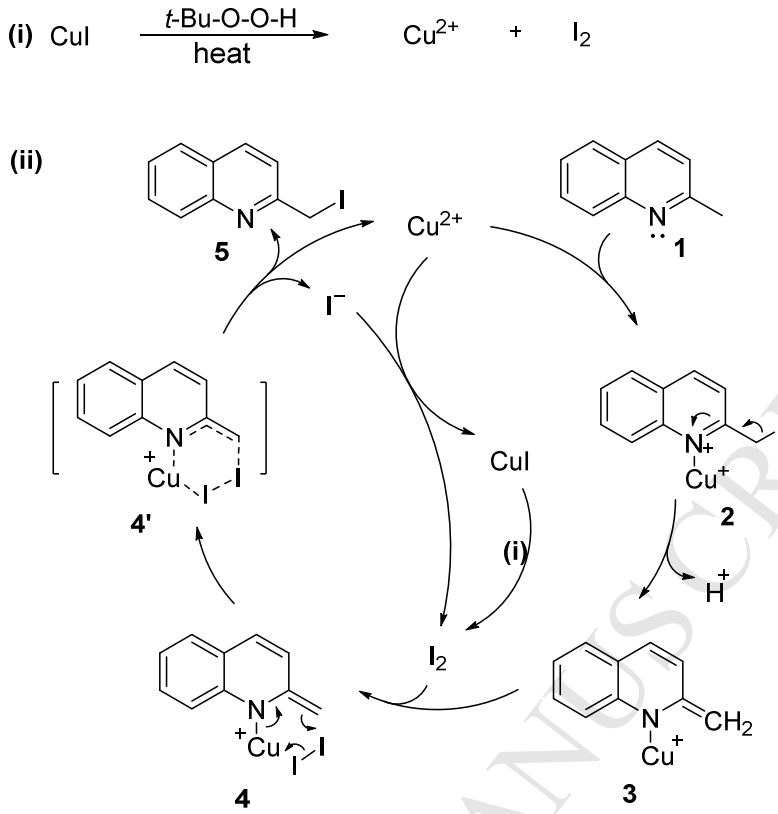
With the optimal reaction conditions in hand, the other 2-methylquinolines and CuX (X = I, Br, Cl), were then employed to examine the scope of the reaction (Scheme 3). It can be seen that, under optimal reaction conditions, various 2-methylquinolines bearing electron donating group (-CH_3, -OCH_3, -OCF_3) or electron withdrawing groups (-F, -Cl, -Br, -NO_2) reacted well with CuI, giving the corresponding 2-iodiomethylquinoline derivatives **3a**-**h** in good to excellent yields. Electronic effects were observed in those cases. It can be seen that 2-methylquinolines bearing electron withdrawing groups tended to give relatively high yields, in which, 2-methylquinoline with the strongest electron withdrawing nitro group gave the highest yield of **3h**. It was pleased that CuBr and CuCl were well capable of reacting with various 2-methylquinolines, affording the corresponding 2-bromomethylquinolines (**3i**-**m**) and 2-cholomethylquinolines (**3n**-**r**) in good to excellent yields.



Scheme 3. Scope of the halogenation reaction of 2-methylquinolines.

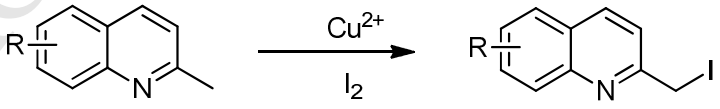
It is especially worth mentioning that after the reaction of 2-methylquinolines and CuI, the organic phase of extraction always presented a purple color, and the water phase presented a blue color. The previously reported works[6c,13] have already proved that TBHP can oxidize Cu(I) into Cu(II), and I^- into I_2. Thus the purple color in organic phase should be caused by the presence of I_2, and the blue color in water phase indicated the presence of Cu^{2+}. The further starch-iodine test of the organic phase also gave a positive result. Base on the observations, a

possible reaction mechanism was thus proposed accordingly as shown in Scheme 4. Initially, CuI was oxidized by *t*-BuOOH to produce Cu^{2+} and I_2 (Scheme 4-i). Then the lone pair of electrons on the nitrogen atom in 2-methylquinoline (**1**) coordinated to Cu^{2+} to give intermediate **2**,[13d] which subsequently was deprotonated to yield complex **3**. Following that, I_2 started to approach complex **3** in the orientation shown by **4**, resulting in an energetically favorable six-membered ring containing transition state (**4'**). After that, a multi-electron rearrangement in the six-membered ring started to occur, leading to the formation of target 2-iodomethylquinoline (**5**), together with Cu^{2+} and I^-. Finally, Cu^{2+} oxidize I^- to form I_2 and CuI ($2Cu^{2+} + 4I^- = 2CuI + I_2$). Meanwhile, THBP oxidize CuI to form Cu^{2+} and I_2. The regenerated Cu^{2+} and I_2 were then reused for another reaction cycle (Scheme 4-ii).



Scheme 4. Proposed reaction mechanism for the halogenation of 2-methylquinolines.

It was realized that Cu^{2+} and I_2 were in fact real reactants for the above-mentioned iodination reaction. Thus, we further developed another methodology towards 2-iodomethylheterocycles using Cu^{2+} as catalyst and I_2 as the halogen source (Scheme 5).



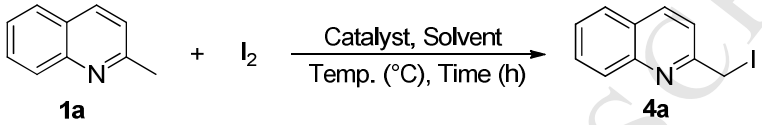
Scheme 5. A new synthetic method to 2-iodiomethylheterocycles.

We initiated the study by establishing the optimal experimental conditions using 2-methylquinoline (**1a**) and I_2 as the starting substrates

as summarized in Table 2. It was pleased to observe that **1a** did react with I_2 in the presence of 0.2 eq. of different copper(II) salts, including $CuCl_2$, $CuBr_2$, $Cu(acac)_2$, $CuSO_4 \cdot 5H_2O$, or $Cu(OAc)_2 \cdot H_2O$, in CH_3CN at 70 °C for 3 h, giving **4a** in different yields (Table 2, entries 1-5). Among those tested copper(II) salts, $CuSO_4 \cdot 5H_2O$ resulted the highest yield of **4a** (35%, entry 4). Following that, the amount of $CuSO_4 \cdot 5H_2O$ was investigated (entries 4 and 6-8). The yield of **4a** increased from 35% to 62% as the amount of $CuSO_4 \cdot 5H_2O$ increased from 0.2 eq. to 0.4 eq. (entries 4 and 6-7), and then began to drop a little bit as the amount reached up to 0.5 eq. (entry 8). The amount of I_2 was also surveyed. The yield of **4a** increased from 62% to 83% with the increase of I_2 from 0.5 eq. to 0.75 eq. (entries 7 and 9), and then decreased a little bit to 81% as the amount of I_2 was continuously raised (entry 10). Investigation on the influence of various solvents was subsequently carried out (entries 9 and 11-18). Among all the solvents tested, including DMF, DMSO, EtOH, *p*-dioxane, toluene, THF, CH_2Cl_2 and DCE, CH_3CN still brought about the highest yield (83%) (entry 9). The influence of temperature on the reaction was further investigated as shown in entries 9, 19-21. The yield of **4a** increased dramatically from 27% to 83% as the temperature was raised from 30 °C to 70 °C, and then decreased to 79% as the temperature was continuously raised to 90 °C (entry 21). Finally, the influence of reaction time on the model reaction was investigated. The yield increased remarkably from 29%

to 83% as the reaction time prolonged from 1 h to 3 h (entries 9, 22-23), and then did not change a lot as the reaction time continuously increased to 4 and 5 h (entries 24 and 25). Thus, the best yield was obtained by employing 0.5 mmol 2-methylquinoline, 0.75 eq. of I_2, 0.4 eq. of $CuSO_4 \cdot 5H_2O$ and 2 mL CH_3CN at 70 °C for 3 h, as indicated by entry 9.

Table 2. Optimization of reaction conditions[a]

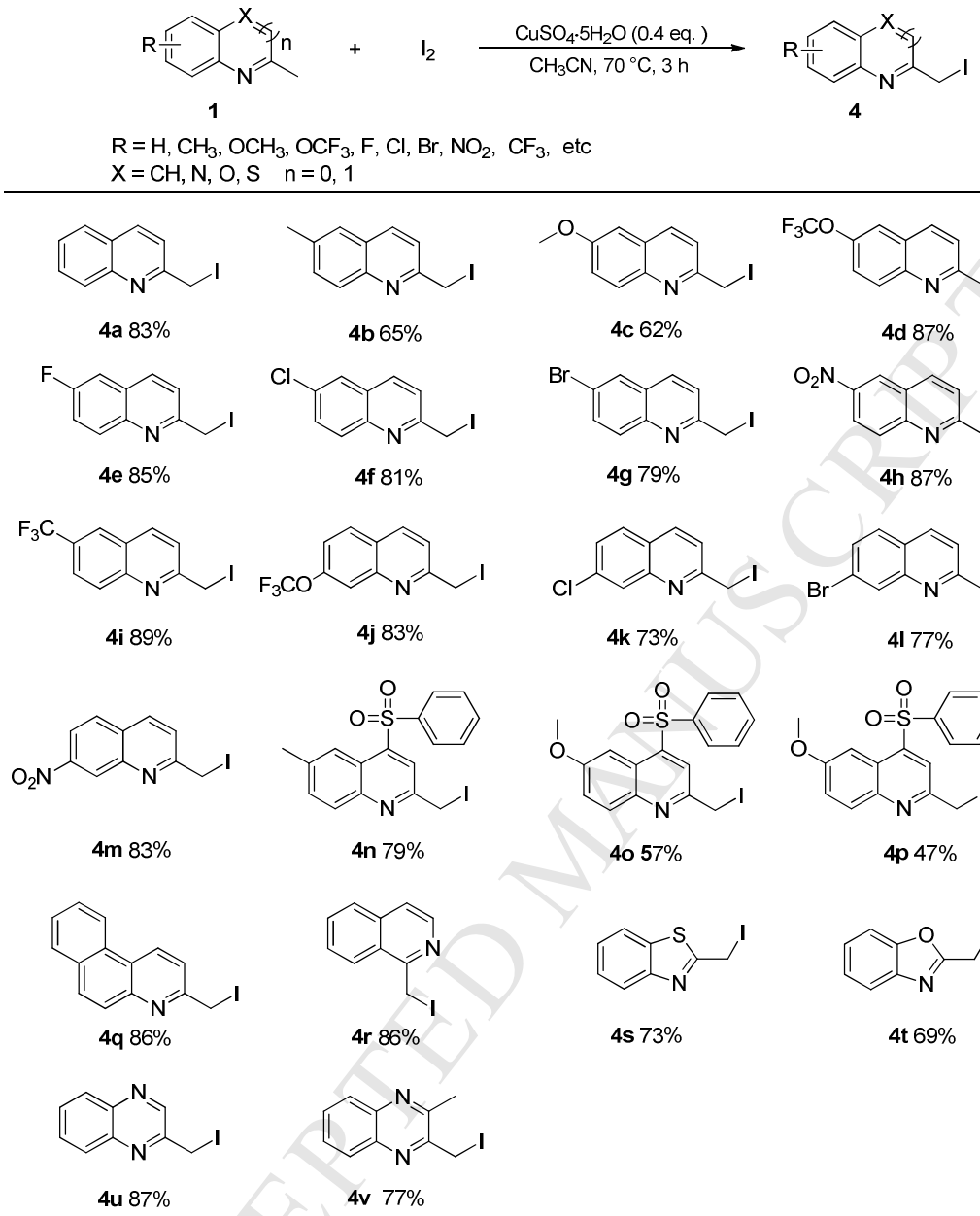


1a **4a**

Entry	I_2 (eq.)	Catalyst (eq.)	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	0.5	$CuCl_2$ (0.2)	CH_3CN	70	3	27
2	0.5	$CuBr_2$ (0.2)	CH_3CN	70	3	29
3	0.5	$Cu(acac)_2$ (0.2)	CH_3CN	70	3	30
4	0.5	$CuSO_4 \cdot 5H_2O$ (0.2)	CH_3CN	70	3	35
5	0.5	$Cu(OAc)_2 \cdot H_2O$ (0.2)	CH_3CN	70	3	33
6	0.5	$CuSO_4 \cdot 5H_2O$ (0.3)	CH_3CN	70	3	53
7	0.5	$CuSO_4 \cdot 5H_2O$ (0.4)	CH_3CN	70	3	62
8	0.5	$CuSO_4 \cdot 5H_2O$ (0.5)	CH_3CN	70	3	61
9	**0.75**	**$CuSO_4 \cdot 5H_2O$ (0.4)**	**CH_3CN**	**70**	**3**	**83**
10	1.0	$CuSO_4 \cdot 5H_2O$ (0.4)	CH_3CN	70	3	81
11	0.75	$CuSO_4 \cdot 5H_2O$ (0.4)	DMF	70	3	23
12	0.75	$CuSO_4 \cdot 5H_2O$ (0.4)	DMSO	70	3	27
13	0.75	$CuSO_4 \cdot 5H_2O$ (0.4)	EtOH	70	3	34
14	0.75	$CuSO_4 \cdot 5H_2O$ (0.4)	*p*-dioxane	70	3	67
15	0.75	$CuSO_4 \cdot 5H_2O$ (0.4)	toluene	70	3	17
16	0.75	$CuSO_4 \cdot 5H_2O$ (0.4)	THF	70	3	59
17	0.75	$CuSO_4 \cdot 5H_2O$ (0.4)	CH_2Cl_2	70	3	57
18	0.75	$CuSO_4 \cdot 5H_2O$ (0.4)	DCE	70	3	79
19	0.75	$CuSO_4 \cdot 5H_2O$ (0.4)	CH_3CN	30	3	27
20	0.75	$CuSO_4 \cdot 5H_2O$ (0.4)	CH_3CN	50	3	57
21	0.75	$CuSO_4 \cdot 5H_2O$ (0.4)	CH_3CN	90	3	79
22	0.75	$CuSO_4 \cdot 5H_2O$ (0.4)	CH_3CN	70	1	29
23	0.75	$CuSO_4 \cdot 5H_2O$ (0.4)	CH_3CN	70	2	47
24	0.75	$CuSO_4 \cdot 5H_2O$ (0.4)	CH_3CN	70	4	81
25	0.75	$CuSO_4 \cdot 5H_2O$ (0.4)	CH_3CN	70	5	80

[a]Optimal conditions: **1a** (0.5 mmol), I_2 (0.5-1.0 eq.), catalyst (0.2-0.5 eq.), solvent (2 mL) at 30-90 °C for 1-5 h. [b]Isolated yields.

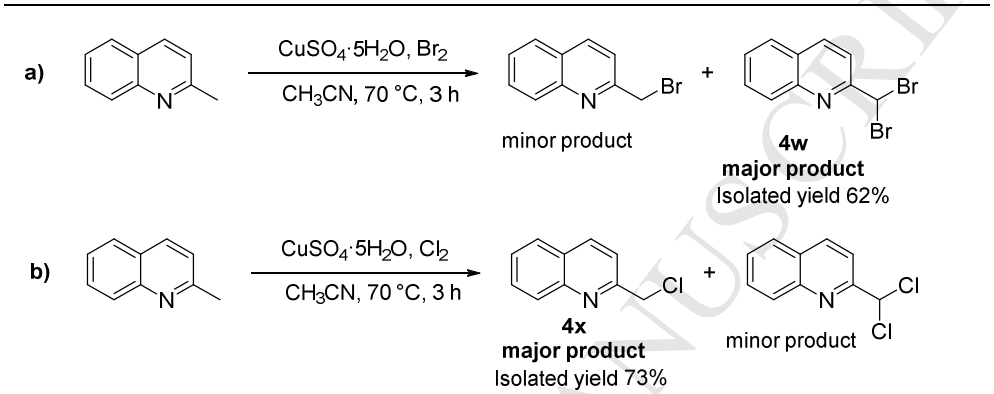
With the optimal reaction conditions in hand, we then examined the substrate scope of the iodination reaction (Scheme 6). As it can be seen, a variety of substituted 2-methylquinoline bearing electron donating groups (-OCH_3, -CH_3, -OCF_3) or electron withdrawing groups (-F, -Cl, -Br, -NO_2, -CF_3) reacted well with iodine, affording the corresponding 2-iodiomethylquinoline **4a-m** in good to excellent yields. Moreover, disubstituted 2-methylquinolines, including 2,6-dimethyl-4-(phenylsulfonyl)quinoline, 6-methoxy-2-methyl-4-(phenylsulfonyl)quinoline, and 6-methoxy-2-methyl-4-tosylquinoline, all worked well with the new synthetic method, affording the corresponding iodination products **4n-p** in moderate to good yields with excellent regioselectivity. To our surprise, our newly developed methodology even progressed well with many other important methylazarenes, including 3-methylbenzoquinoline (**4q**), 1-methylisoquinoline (**4r**), 2-methylbenzothiazole (**4s**), 2-methylbenzooxazole (**4t**), 2-methylquinoxaline (**4u**) as well as 2,3-dimethylquinoxaline (**4v**), leading to the corresponding products (**4q-v**) in moderate to excellent yields.



Scheme 6. Scope of the iodination reaction of 2-methylheterocycles.

When Br_2 was used as reactant in the second method (Scheme 7a), the disubstituted product, 2-(dibromomethyl)-quinoline (**4w**), instead of 2-bromomethylquinoline was finally obtained as the major product. When Cl_2 was used as reactant in the second method (Scheme 7b),

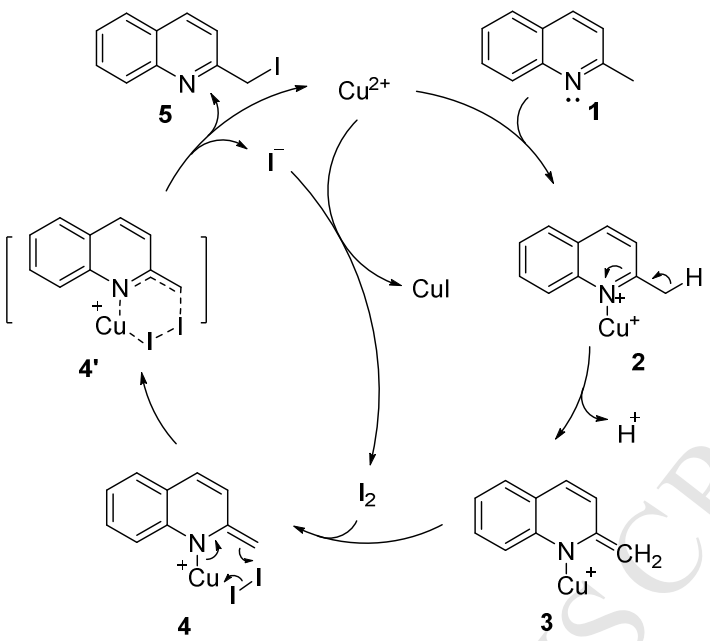
2-cholomethylquinoline (**4x**) was successfully obtained as the major product. However, using toxic Cl_2 gas is dangerous and inconvenient. Thus, the first method is still deserved to be kept for synthesis of 2-bromomethylquinolines and 2-cholomethylquinolines.



Reaction conditions: a) 2-methylquinoline (0.5 mmol), Br_2 (0.375 mmol), $CuSO_4·5H_2O$ (0.2 mmol), CH_3CN (2 mL). b) 2-methylquinoline (0.5 mmol), $CuSO_4·5H_2O$ (0.2 mmol), CH_3CN (2 mL), Cl_2 (slowly bubbled into the mixture). The obtained reaction mixtures were analyzed by GC-MS.

Scheme 7. Bromination and chlorination of 2-methylquinoline using method II.

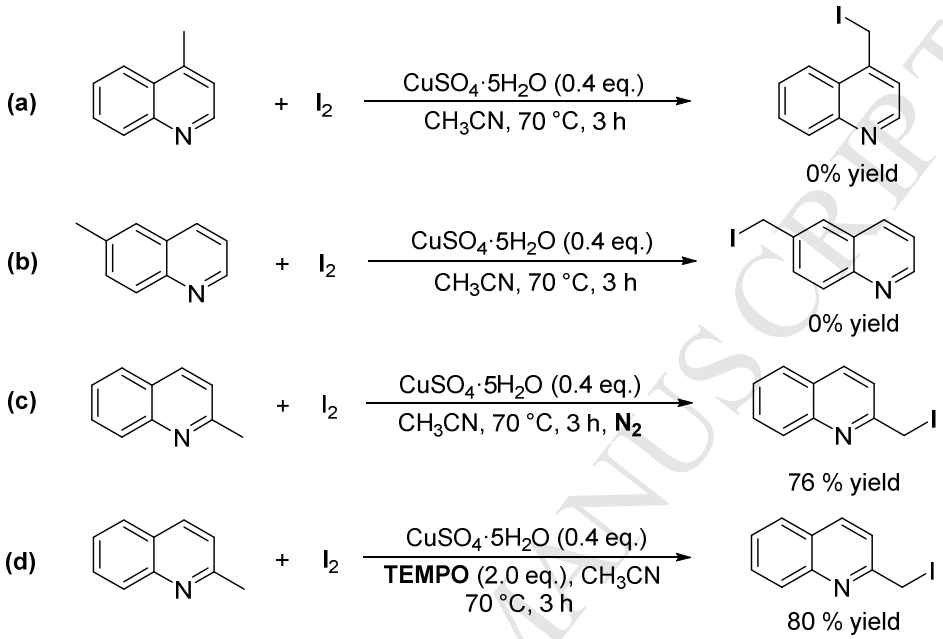
The related reaction mechanism was proposed as shown in Scheme 8. The reaction cycle shown in Scheme 8 is just same as that shown in Scheme 4-ii. The additional information given by Scheme 8 is that I^-, resulted from the reaction, was oxidized by Cu^{2+} to regenerate I_2 as well as CuI. The regenerated I_2 could be used for further reaction cycle and the formation of CuI drove the reaction to completion.



Scheme 8. Proposed reaction mechanism for the iodination of 2-methylheterocycles.

Additionally, several control experiments were carried out to explore the related reaction mechanism as shown in Scheme 9. When 4-methylquinoline or 6-methylquinoline were employed to react with I_2 in the presence of $CuSO_4 \cdot 5H_2O$ in CH_3CN, corresponding iodination compounds were not detected (Scheme 9a-b). These additional control experiments might well serve as the experimental support for the proposed mechanism that indicates the essentiality of coordination of copper(II) to nitrogen.[13d] When the reaction was carried out under N_2 protection (Scheme 9c) or in the presence of the widely used radical scavenger 2,2,6,6-tetra-methyl-l-piperidinyloxy (TEMPO) (Scheme 9d), the both reactions proceeded smoothly, which possibly rule out the

requirement of oxygen and the involvement of radical intermediates. These additional experiments strongly backed up the above proposed mechanism.



Scheme 9. Additional studies for mechanism.

3. Conclusions

In conclusion, we developed two practical and simple synthetic methodologies towards various heterobenzyl halides. A series of 2-halomethylquinolines were readily prepared by the one-pot reaction of 2-methylquinolines with CuX (X = I, Br, Cl) and TBHP in CH_3CN. Based on the success of the first synthetic methodology, we developed the second synthetic methodology, by which a large variety of heterobenzyl iodides, including 2-iodomethylquinolines, 2-iodomethylquinoxaline, 2-iodiomethylbenzooxazole and 2-iodiomethylbenzothiazole, were

efficiently synthesized by one-pot reaction of 2-methylheterocycles direct with iodine in the presence of $CuSO_4 \cdot 5H_2O$ in CH_3CN. The remarkable merits of the synthetic methodologies are cheap and easily available reactants, high regioselectivity, a wide scope of products, as well as an efficient one-pot synthetic procedure. The methodologies will undoubtedly become practical choices for preparation of many kinds of 2-halomethylazaarenes, many of which are indispensable synthetic precursors of numerous biologically targets.

4. Experimental Section

4.1 Materials and method

All reagents were purchased from Sigma-Aldrich, J&KCHEMICA or TCI (Shanghai) and used without further purification. TLC was performed on silica gel plates and preparative chromatograph on columns of silica gel (200-300 mesh). ^{1}H, ^{13}C NMR spectra were recorded with a Bruker Avance 400 MHz spectrometer operating at 400.13, 100.61 MHz, respectively, with ^{13}C NMR spectra being recorded with broad band proton decoupled. All NMR spectra were recorded in $CDCl_3$ at room temperature (20 ± 2 °C). ^{1}H and ^{13}C chemical shifts are quoted in parts per million downfield from TMS. High resolution mass spectra (HR MS) were obtained with a Waters Micromass Q-Tof Micro instrument using the ESI technique.

4.2 General procedure for the synthesis of 2-halomethylquinoline

derivatives (method I).

2-Methylquinoline derivatives (0.5 mmol), cuprous halide (0.75 mmol), TBHP (8.0 eq., 70% aqueous solution) and CH_3CN (2 mL) were stirred at 70 °C for 8 h. Then, the reaction mixture was diluted by water and extracted with CH_2Cl_2 (3 × 15 mL). The X_2 (X =I, Br, Cl) in organic phase was quenched by $Na_2S_2O_3$. The combined organic layers were washed with saturated NH_4Cl aqueous solution and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. The desired product was obtained by silica gel chromatography (petroleum ether/ethyl acetate, v/v = 10/1).

4.3 General procedure for the synthesis of 2-iodiomethylazaarenes (method II).

2-Methylazaarenes (0.5 mmol), iodine (0.375 mmol, 95.3 mg), $CuSO_4 \cdot 5H_2O$ (0.2 mmol, 50 mg) and CH_3CN (2 mL) were stirred at 70 °C for 3 h. Then, the reaction mixture was diluted by water and extracted with CH_2Cl_2 (3 × 15 mL). The residue I_2 in organic phase was quenched by $Na_2S_2O_3$. The combined organic layers were washed with saturated NH_4Cl aqueous solution and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. The desired product was obtained by silica gel chromatography (petroleum ether/ethyl acetate, v/v = 10/1).

2-iodiomethylquinoline (method I: **3a**, method II: **4a**)[12b]. Yellow oil,

method I: **3a** yield: 89%, method II: **4a** yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.67 (s, 2H), 7.50-7.55 (m, 2H), 7.71 (m, 1H), 7.78 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 6.9, 121.1, 126.9, 127.1, 127.5, 129.1, 130.0, 137.2, 147.6, 158.4. HRMS Calcd for $C_{10}H_8IN$ $[M + H]^+$: m/z 269.9774, Found 269.9781.

2-(iodomethyl)-6-methylquinoline (method I: **3b**, method II: **4b**)[12b]. Yellow oil, method I: **3b** yield: 65%, method II: **4b** yield: 65%.^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.52 (s, 3H), 4.67 (s, 2H), 7.48 (d, J = 8.4 Hz, 1H), 7.54 (m, 2H, 5), 7.93 (d, J = 9.2 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 7.0, 21.6, 121.1, 126.4, 127.1, 128.7, 132.3, 136.6, 136.9, 146.1, 157.4. HRMS Calcd for $C_{11}H_{10}IN$ $[M + H]^+$: m/z 283.9931, Found 283.9933.

2-(iodomethyl)-6-methoxyquinoline (method I: **3c**, method II: **4c**)[12b]. Yellow oil, method I: **3c** yield: 57%, method II: **4c** yield: 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.93 (s, 3H), 4.67 (s, 2H), 7.05 (d, J = 2.4 Hz, 1H), 7.37 (dd, J = 2.8 Hz, J = 9.6 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 9.2 Hz, 1H), 8.01 (d, J = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 7.1, 55.6, 105.1, 121.4, 122.6, 128.1, 130.5, 136.0, 143.6, 155.7, 158.1. HRMS Calcd for $C_{11}H_{10}INO$ $[M + H]^+$: m/z 299.9880, Found 299.9883.

2-(iodomethyl)-7-(trifluoromethoxy)quinoline (method I: **3d**, method II: **4j**). Yellow oil, method I: **3d** yield: 71%, method II: **4j** yield: 83%. ^{1}H

NMR (400 MHz, $CDCl_3$) δ: 4.66 (s, 2H), 7.39 (dd, J = 2 Hz, J = 8.8 Hz, 1H), 7.54 (d, J = 8.8 Hz), 7.82 (d, J = 9.2 Hz, 1H), 7.89 (s, 2H), 8.13 (d, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 6.2, 119.0, 119.2, 120.9, 121.6 (J_{C-F} = 34.9 Hz), 125.3, 129.3, 137.0, 148.0, 150.0, 160.0.^{19}F NMR (376 MHz, $CDCl_3$) δ: -58.2. HRMS Calcd for $C_{11}H_7F_3INO$ $[M + H]^+$: m/z 353.9597, Found 353.9596.

6-fluoro-2-(iodomethyl)quinoline (method I: **3e**, method II: **4e**)[12b]. Yellow oil, method I: **3e** yield: 90%, method II: **4e** yield: 85%.^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.66 (s, 2H), 7.42 (m, 1H), 7.49 (m, 1H), 7.54 (d, J = 8.4 Hz, 1H), 8.05 (m, 1H), 8.07 (d, J = 8.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 6.4, 110.7 (J_{C-F} = 21.6 Hz), 120.2 (J_{C-F} = 25.5 Hz), 121.9, 127.7 (J_{C-F} = 10.1 Hz), 131.6 (J_{C-F} = 9.3 Hz), 136.6 (J_{C-F} = 5.2 Hz), 144.6, 157.8, 160.6 (J_{C-F} = 247.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -112.4. HRMS Calcd for $C_{10}H_7FIN$ $[M + H]^+$: m/z 287.9680, Found 287.9681.

6-chloro-2-(iodomethyl)quinoline (method I: **3f**, method II: **4f**). Yellow oil, method I: **3f** yield: 83%, method II: **4f** yield: 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.65 (s, 2H), 7.54 (d, J = 8.4 Hz, 1H), 7.66 (m, 1H), 7.77 (s, 1H), 7.97 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 6.4, 122.0, 126.2, 127.6, 130.7, 130.9, 132.6, 136.3, 146.0, 158.8. HRMS Calcd for $C_{10}H_7ClIN$ $[M + H]^+$: m/z 303.9384, Found 303.9391.

6-bromo-2-(iodomethyl)quinoline (method I: **3g**, method II: **4g**)[12b].

Yellow oil, method I: **3g** yield: 87%, method II: **4g** yield: 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.65 (s, 2H), 7.54 (d, J = 8.4 Hz, 1H), 7.78 (dd, J = 2.4 Hz, J = 9.2 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 6.4, 120.7, 122.0, 128.1, 129.6, 130.8, 133.4, 136.2, 146.2, 158.9. HRMS Calcd for $C_{10}H_7BrIN$ $[M + H]^+$: m/z 347.8879, Found 347.8879.

2-(iodomethyl)-6-nitroquinoline (method I: **3h**, method II: **4h**). Yellow oil, method I: **3h** yield: 91%, method II: **4h** yield: 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.69 (s, 2H), 7.68 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 9.2 Hz, 1H), 8.30 (d, J = 8.8 Hz, 1H), 8.48 (dd, J = 2.4 Hz, J = 9.2 Hz, 1H), 8.76 (d, J = 2.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 5.6, 123.0, 123.4, 124.2, 124.4, 125.8, 130.9, 138.8, 149.7, 162.5. HRMS Calcd for $C_{10}H_7IN_2O_2$ $[M + H]^+$: m/z 314.9625, Found 314.9628.

2-(bromomethyl)quinoline (method I: **3i**)[12a]. Yellow oil, yield: 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.73 (s, 2H), 7.55-7.59 (m, 2H), 7.75 (m, 1H), 7.83 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 34.2, 121.2, 127.1, 127.4, 127.6, 129.1, 130.1, 137.5, 147.3, 156.9. HRMS Calcd for $C_{10}H_8BrN$ $[M + H]^+$: m/z 221.9913, Found 221.9915.

2-(bromomethyl)-6-fluoroquinoline (method I: **3j**)[7m]. Yellow oil, yield: 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.70 (s, 2H), 7.43 (m, 1H), 7.50 (m, 1H), 7.59 (d, J = 8.4 Hz, 1H), 8.07 (m, 1H), 8.13 (d, J = 8.4 Hz, 1H). ^{13}C

NMR (101 MHz, $CDCl_3$) δ: 18.5, 110.7 (J_{C-F} = 22.9 Hz), 120.3 (J_{C-F} = 25.2 Hz), 122.0, 128.0 (J_{C-F} = 11.5 Hz), 131.7 (J_{C-F} = 9.2 Hz), 136.7 (J_{C-F} = 6.9 Hz), 144.5, 156.3, 160.8 (J_{C-F} = 242.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -112.0. HRMS Calcd for $C_{10}H_7BrFN$ $[M + H]^+$: m/z 239.9819, Found 239.9821.

2-(bromomethyl)-6-chloroquinoline (method I: **3k**)[7m]. Yellow oil, yield: 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.70 (s, 2H), 7.60 (d, J = 8.4 Hz, 1H), 7.67 (dd, J = 2.4 Hz, J = 9.2 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 8.01 (d, J = 9.2 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 34.1, 122.1, 126.2, 127.9, 130.89, 130.9, 132.9, 136.4, 145.9, 157.2. HRMS Calcd for $C_{10}H_7BrClN$ $[M + H]^+$: m/z 255.9523, Found 255.9525.

6-bromo-2-(bromomethyl)quinoline (method I: **3l**)[7m]. Yellow oil, yield: 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.69 (s, 2H), 7.59 (d, J = 8.4 Hz, 1H), 7.80 (dd, J = 2.0 Hz, J = 8.8 Hz, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 34.1, 121.0, 122.1, 128.4, 129.6, 131.0, 133.5, 136.3, 146.1, 157.4. HRMS Calcd for $C_{10}H_7Br_2N$ $[M + H]^+$: m/z 299.9018, Found 299.9016.

2-(bromomethyl)-6-nitroquinoline (method I: **3m**)[12a]. Yellow oil, yield: 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.73 (s, 2H), 7.74 (d, J = 8.8 Hz, 1H), 8.20 (d, J = 9.2 Hz, 1H), 8.37 (d, J = 8.8 Hz, 1H), 8.50 (dd, J = 2.0 Hz, J = 9.2 Hz, 1H), 8.79 (d, J = 2.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 33.5, 122.3, 123.1, 123.4, 124.2, 124.3, 126.1, 131.2, 139.0,

160.8. HRMS Calcd for $C_{10}H_7BrN_2O_2$ $[M + H]^+$: m/z 266.9764, Found 266.9768.

2-(chloromethyl)quinoline (method I: **3n**, method II: **4x**)[12a]. Yellow oil, method I: **3n** yield: 67%, method II: **4x** yield: 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.68 (s, 2H), 7.51-7.60 (m, 2H), 7.72 (m, 1H), 7.79 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 6.9, 121.1, 126.9, 127.1, 127.5, 129.1, 130.0, 137.2, 147.6, 158.4. HRMS Calcd for $C_{10}H_8ClN$ $[M + H]^+$: m/z 178.0418, Found 178.0424.

2-(chloromethyl)-6-fluoroquinoline (method I: **3o**)[12a]. Yellow oil, yield: 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.83 (s, 2H), 7.45 (m, 1H), 7.51 (m, 1H), 7.63 (d, J = 8.8 Hz, 1H), 8.08 (m, 1H), 8.16 (d, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 47.2, 110.7 ($J_{C\text{-}F}$ = 21.7 Hz), 120.3 ($J_{C\text{-}F}$ = 25.6 Hz), 121.3, 128.1 ($J_{C\text{-}F}$ = 10.0 Hz), 131.7 ($J_{C\text{-}F}$ = 8.2 Hz), 136.7 ($J_{C\text{-}F}$ = 4.5 Hz), 144.5, 156.1 ($J_{C\text{-}F}$ = 3.0 Hz), 160.7 ($J_{C\text{-}F}$ = 247.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -112.0. HRMS Calcd for $C_{10}H_7ClFN$ $[M + H]^+$: m/z 196.0324, Found 196.0327.

6-chloro-2-(chloromethyl)quinoline (method I: **3p**)[12a]. Yellow oil, yield: 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.82 (s, 2H), 7.63 (d, J = 8.8 Hz, 1H), 7.67 (dd, J = 2.0 Hz, J = 9.2 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 8.01 (d, J = 8.8 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 47.1, 121.4, 126.3, 128.0, 130.86, 130.9, 132.8, 136.4, 145.8, 157.1.

HRMS Calcd for $C_{10}H_7Cl_2N$ $[M + H]^+$: m/z 212.0028, Found 212.0030.

6-bromo-2-(chloromethyl)quinoline (method I: **3q**)[8b]. Yellow oil, yield: 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.82 (s, 2H), 7.64 (d, J = 8.4 Hz, 1H), 7.80 (dd, J = 2.0 Hz, J = 8.8 Hz, 1H), 7.94 (d, J = 9.2 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 58.5, 120.9, 121.4, 128.5, 129.6, 130.9, 133.5, 136.3, 146.0, 157.2. HRMS Calcd for $C_{10}H_7BrClN$ $[M + H]^+$: m/z 255.9523, Found 255.9525.

2-(chloromethyl)-6-nitroquinoline (method I: **3r**)[12a]. Yellow oil, yield: 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.87 (s, 2H), 7.80 (d, J = 8.4 Hz, 1H), 8.21 (d, J = 9.2 Hz, 1H), 8.41 (d, J = 8.4 Hz, 1H), 8.51 (dd, J = 2.4 Hz, J = 9.2 Hz, 1H), 8.81 (d, J = 2.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 58.5, 122.3, 123.1, 123.4, 124.3, 126.2, 131.1, 139.0, 149.4, 160.6. HRMS Calcd for $C_{10}H_7ClN_2O_2$ $[M + H]^+$: m/z 223.0269, Found 223.0271.

2-(iodomethyl)-6-(trifluoromethoxy)quinoline (method II: **4d**). Yellow oil, yield: 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.67 (s, 2H), 7.59 (m, 3H), 8.10 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 6.3, 117.6, 120.5 ($J_{C\text{-}F}$ = 260.1 Hz), 122.1, 124.0, 127.2, 131.4, 137.0, 145.8, 147.2, 159.1. ^{19}F NMR (376 MHz, $CDCl_3$)δ: -58.3. HRMS Calcd for $C_{11}H_7F_3INO$ $[M + H]^+$: m/z 353.9597, Found 353.9597.

2-(iodomethyl)-6-(trifluoromethyl)quinoline (method II: **4i**). Yellow oil, yield: 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.68 (s, 2H), 7.61 (d, J = 8.8

Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 8.09 (s, 1H), 8.13-8.20 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 6.1, 122.3, 123.9 (J_{C-F} = 270.6 Hz), 125.4 (J_{C-F} = 4.4 Hz), 125.6 (J_{C-F} = 2.9 Hz), 128.6 (J_{C-F} = 32.7 Hz), 130.3, 137.9, 148.5, 160.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.4. HRMS Calcd for $C_{11}H_7F_3IN$ $[M + H]^+$: m/z 337.9648, Found 337.9646.

7-chloro-2-(iodomethyl)quinoline (method II: **4k**)[12b]. Yellow oil, yield: 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.64 (s, 2H), 7.46-7.51 (m, 2H, 3, 6-H), 7.70 (d, J = 8.4 Hz, 1H), 8.03 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 6.4, 121.3, 125.4, 127.9, 128.2, 128.7, 135.8, 137.0, 147.9, 159.6. HRMS Calcd for $C_{10}H_7ClIN$ $[M + H]^+$: m/z 303.9384, Found 303.9388.

7-bromo-2-(iodomethyl)quinoline (method II: **4l**). Yellow oil, yield: 77%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.65 (s, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.61-7.67 (m, 2H), 8.09 (d, J = 8.4 Hz, 1H), 8.23 (d, J = 0.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 6.3, 121.4, 124.1, 125.6, 128.7, 130.4, 131.5, 132.7, 137.1, 159.6. HRMS Calcd for $C_{10}H_7BrIN$ $[M + H]^+$: m/z 347.8879, Found 347.8879.

2-(iodomethyl)-7-nitroquinoline (method II: **4m**). Yellow oil, yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.70 (s, 2H), 7.69 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 8.22 (d, J = 8.8 Hz, 1H), 8.32 (dd, J = 9.2 Hz, J = 2.4 Hz, 1H), 8.95 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 5.5, 120.3, 124.1, 125.4, 129.1, 130.1, 133.2, 137.0, 146.6, 161.2. HRMS Calcd for

$C_{10}H_7INO_2$ $[M + H]^+$: m/z 314.9625, Found 314.9623.

2-(iodomethyl)-6-methyl-4-(phenylsulfonyl)quinoline (method II: **4n**). Yellow oil, yield: 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.52 (s, 3H), 4.72 (s, 2H), 7.53-7.64 (m, 4H), 7.98-8.01 (m, 3H), 8.23 (0s, 1H), 8.31 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 5.66, 22.3, 121.2, 121.6, 122.9, 127.9, 129.5, 129.9, 133.1, 134.0, 139.5, 140.1, 144.9, 147.6, 157.2. HRMS Calcd for $C_{17}H_{14}INO_2S$ $[M + H]^+$: m/z 423.9863, Found 423.9869.

2-(iodomethyl)-6-methoxy-4-(phenylsulfonyl)quinoline (method II: **4o**). Yellow oil, yield: 57%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.90 (s, 3H), 4.73 (s, 2H), 7.37 (m, 1H), 7.52-7.56 (m, 2H), 7.62 (m, 1H), 7.97-7.99 (m, 3H), 7.78 (d, J = 2.8 Hz, 1H), 8.32 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 5.8, 55.7, 102.1, 121.8, 122.6, 123.7, 127.8, 129.5, 131.6, 140.0, 140.1, 143.7, 145.2, 155.3, 159.4. HRMS Calcd for $C_{17}H_{14}INO_3S$ $[M + H]^+$: m/z 439.9817, Found 439.9814.

2-(iodomethyl)-6-methoxy-4-tosylquinoline (method II: **4p**). Yellow oil, yield: 47%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.40 (s, 3H), 3.91 (s, 3H), 4.72 (s, 2H), 7.32-7.36 (m, 2H), 7.38 (d, J = 2.8 Hz, 1H), 7.80 (s, 1H), 7.87 (d, 2H), 7.98 (d, 1H), 8.30 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 5.8, 25.8, 55.7, 102.2, 121.6, 122.5, 123.6, 127.9, 130.1, 131.6, 137.1, 144.1, 145.18, 145.23, 155.3, 159.4. HRMS Calcd for $C_{18}H_{16}INO_3S$ $[M + H]^+$: m/z 453.9974, Found 453.9972.

3-(iodomethyl)benzo[f]quinoline (method II: **4q**)[12b]. Yellow oil, yield:

86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.71 (s, 2H), 7.61-7.68 (m, 3H), 7.88-7.97 (m, 3H), 7.65 (m, 1H), 8.53 (d, J = 8.0 Hz, 1H), 8.83 (d, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 6.6, 121.1, 122.6, 124.2, 127.2, 127.4, 127.8, 128.7, 129.4, 131.3, 131.76, 131.85, 147.7, 157.9. HRMS Calcd for $C_{14}H_{10}IN$ $[M + H]^+$: m/z 319.9931, Found 319.9929.

1-(iodomethyl)isoquinoline (method II: **4r**). Yellow oil, yield: 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.01 (s, 2H), 7.62 (d, J = 6.0 Hz, 1H), 7.70-7.72 (m, 2H), 7.88 (m, 1H), 8.20 (m, 1H), 8.44 (d, J = 6.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 3.3, 121.0, 125.3, 125.9, 127.4, 127.6, 130.6, 136.8, 142.1, 157.3. HRMS Calcd for $C_{10}H_8IN$ $[M + H]^+$: m/z 269.9774, Found 269.9779.

2-(iodomethyl)benzo[d]thiazole (method II: **4s**)[11b]. Yellow oil, yield: 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.80 (s, 2H), 7.42 (m, 1H), 7.42 (m, 1H), 7.48 (m, 1H), 7.84 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: -3.1, 121.8, 123.3, 125.8, 126.6, 136.2, 152.9, 167.4. HRMS Calcd for C_8H_6INS $[M + H]^+$: m/z 275.9338, Found 275.9226.

2-(iodomethyl)benzo[d]oxazole (method II: **4t**)[11b]. Yellow oil, yield: 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.52 (s, 2H), 7.33-7.40 (m, 2H), 7.52 (m, 1H), 7.70 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: -10.9, 110.8, 120.3, 124.8, 125.8, 141.4, 151.0, 162.5. HRMS Calcd for C_8H_6INO $[M + H]^+$: m/z 259.9567, Found 259.9567.

2-(iodomethyl)quinoxaline (method II: **4u**). Yellow oil, yield: 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.69 (s, 2H), 7.74-7.80 (m, 2H), 8.02-8.11 (m, 2H), 8.96 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 2.47, 129.1, 129.2, 130.2, 130.6, 141.4, 141.6, 145.3, 153.6. HRMS Calcd for $C_9H_7IN_2$ [M + H]$^+$: m/z 270.9727, Found 270.9730.

2-(iodomethyl)-3-methylquinoxaline (method II: **4v**). Yellow oil, yield: 67%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.82 (s, 3H), 4.69 (s, 2H), 7.69-7.74 (m, 2H), 7.99-8.01 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 4.1, 22.8, 128.4, 128.8, 129.4, 130.1, 140.9, 141.7, 152.3, 152.5. HRMS Calcd for $C_{10}H_9IN_2$ [M + H]$^+$: m/z 284.9883, Found 284.9885.

2-(dibromomethyl)quinoline (method II: **4w**). Yellow oil, yield: 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.74 (s, 1H), 4.69 (s, 2H), 7.50 (t, 1H), 7.67 (t, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 42.4, 119.5, 127.5, 127.8, 127.9, 129.5, 130.4, 138.2, 145.7, 158.4. HRMS Calcd for $C_{10}H_7Br_2N$ [M + H]$^+$: m/z 299.9018, Found 299.9023.

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