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Article

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Copper-mediated Oxidative Functionalization of C(sp^3)-H Bonds with Isoquinolines: Two-step Synthesis of 5-Oxaprotoberberinones

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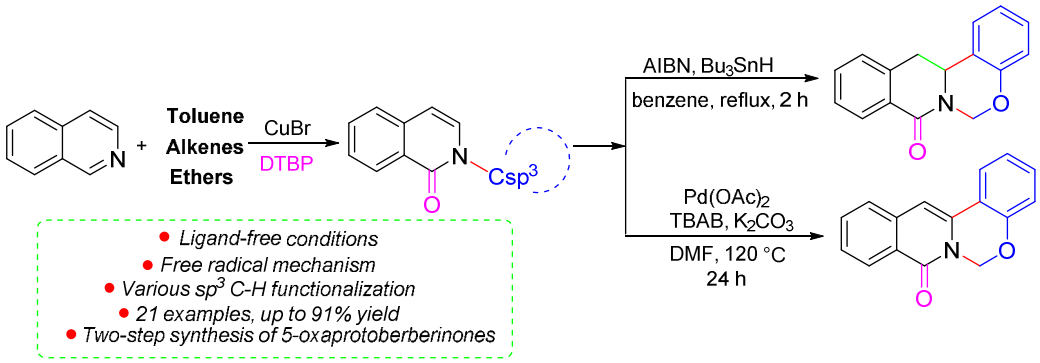


Abstract:

A copper-mediated oxidative functionalization of C(sp^3)-H bonds with isoquinolines via a radical process without ligands was achieved. The present system exhibits a novel pathway for the preparation of *N*-alkyl (benzyl) isoquinolin-1(2*H*)-ones in moderate to high yields. In addition, this procedure provides a simple method to afford 5-oxaprotoberberinones and their derivatives by two steps.

Introduction

Isoquinolin-1(2*H*)-ones are important structural motifs found in natural products.[1] Therefore, isoquinolin-1(2*H*)-ones have been employed in the synthesis of pharmaceutical compounds, such as dehydrogusanlung D, 6*H*,8*H*-isoquino[2,3-*c*][1,3]benzoxazin-8-one (**1ab**), and isoindolo [2,1-*b*]isoquinolin-5(7*H*)-one (Figure 1).[2] From the foregoing, the studying on the synthetic method of isoquinolin-1(2*H*)-ones becomes significant. However, after a brief survey of the

literature, we have found a lack of general methods for the preparation of these kinds of compounds. Meanwhile, most of the synthesis of these compounds involved various expensive metals as catalysts[3].

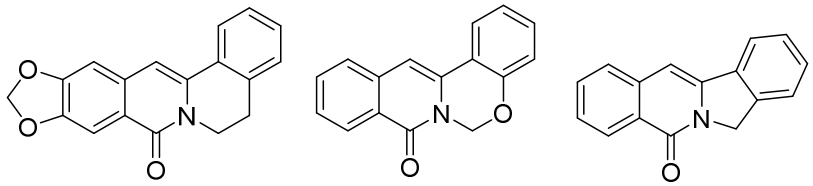
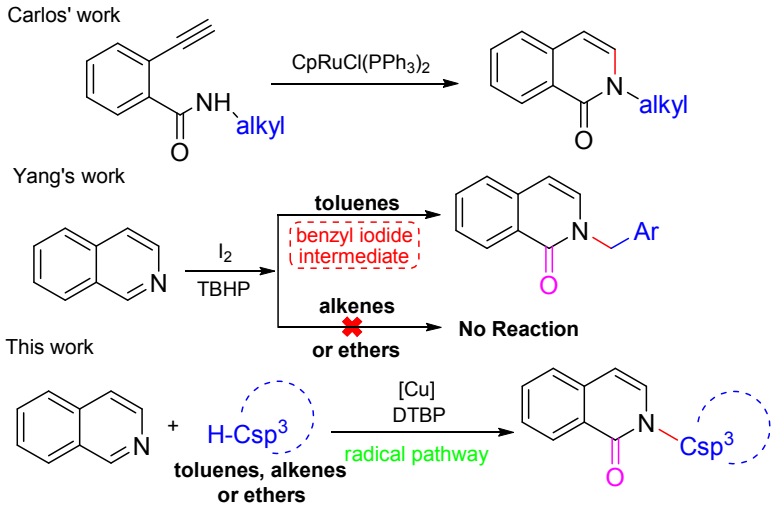


Figure 1. Examples of isoquinolin-1(2*H*)-one-fused natural products and pharmaceutics.

Over the past few decades, there were some ways to synthesize *N*-alkylisoquinolin-1(2*H*)-ones.[4] For example, Carlos[4a] disclosed that $CpRuCl(PPh_3)_2$ could catalyze cycloisomerizations of aromatic homo- and bis-homopropargy licamines/amides to afford several nitrogen heterocyclic rings in high yields. Anderson[4f] disclosed that the conversion of *O*-alkylated 2-hydroxy pyridines, quinolines, and pyrimidines promoted by LiI gave the corresponding *N*-alkylated heterocycles via *O*- to *N*-alkyl migration. However, these methods are often limited for involving expensive noble metal catalysts, complicated ligands and infrequent substrates. For the preparation of *N*-benzylisoquinolin-1(2*H*)-ones, only a few methods were reported using isoquinolines as a substrate. Examples include work by Arakawa[5] and co-workers who reported that *N*-benzylisoquinolin-1(2*H*)-ones were generated in low yields by treating isoquinolines with benzyl bromides in the presence of a large amount of $K_3Fe(CN)_6$ and KOH. Recently, Yang[6] disclosed a novel method to produce *N*-benzylisoquinolin-1(2*H*)-ones in moderate to high yields utilizing isoquinolines and toluene (**2a**) as reactants in the presence of catalytic amount of iodine as the initiator. This method is simple and highly effective. However a limitation of this procedure is that only toluenes and their derivatives acted as the effective substrates because the reaction

occurred in the presence of benzyl iodides intermediate. C–N bond formation via C(sp^3)−H activation of alkyl/benzyl has gained much interest in recent years[7]. Wide variety of Cu salts has been employed in these reactions.[8] Therefore, we tried to find reaction system which has the wider scope of substrates to achieve the construction of *N*-alkyl(benzyl)isoquinolin-1(2*H*)-ones via C(sp^3)−H activation. Herein, we would like to report an effective method of oxidative functionalization of various C (sp^3)-H bonds with isoquinolines via a radical process (Scheme 1).



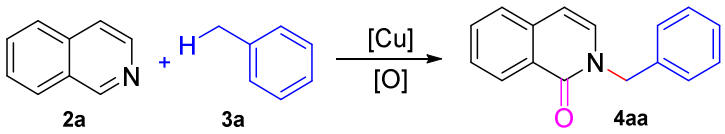
Scheme 1. Various pathways for the construction of *N*-substituted isoquinolin-1(2*H*)-ones.

Results and Discussion

The initial explorations were completed by using isoquinoline **(2a)** and toluene **(3a)** as substrates under different reaction conditions, including optimization of catalysts, oxidants and temperature to yield desired *N*-benzylisoquinolinone **4aa**. The results are summarized in Table 1. The reaction was initially carried out by using CuOAc and di-*tert*-butyl peroxide (DTBP) as a catalyst and an oxidant, respectively (Table 1, entry 1). A small amount of the corresponding product **4aa** was obtained after heating at 120 °C for 8 h under nitrogen atmosphere in the sealed tube. Inspired by this discovery, different kinds of Cu catalysts such as CuCl, CuSCN, Cu_2O, CuBr,

CuOAc and Cu powder were employed in the reaction (Table 1, entries 1-8). We found that CuBr showed the best results for this reaction. Meanwhile, several oxidants [such as *tert*-butyl hydroperoxide (TBHP), *tert*-butyl perbenzoate (TBPB), $K_2S_2O_8$, etc.] were tested for this transformation. It turned out that only DTBP exhibited reaction activity for the transformation, but TBHP, TBPB, $K_2S_2O_8$ and dicumyl peroxide (DCP) did not induce the reaction (Table 1, entries 9-12). Then, the reaction was carried out by using different amounts of CuBr and DTBP. We found that the best result was obtained with 1.0 equiv of CuBr and 4.0 equiv of DTBP (Table 1, entries 13-17). When the reaction was completed at 100℃, the yields of the target product **4aa** were

Table 1 Optimization of reaction conditions[a]



2a **3a** **4aa**

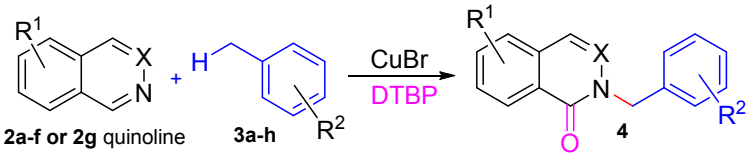
Entry	[Cu] (equiv)	Oxidant (equiv)	Temp (℃)	Yield[b] (%)
1	CuOAc (0.2)	DTBP (2.0)	120	12
2	CuSCN (0.2)	DTBP (2.0)	120	trace
3	CuI (0.2)	DTBP (2.0)	120	trace
4	Cu_2O (0.2)	DTBP (2.0)	120	trace
5	CuCl (0.2)	DTBP (2.0)	120	trace
6	CuBr (0.2)	DTBP (2.0)	120	27
7	$CuBr_2$ (0.2)	DTBP (2.0)	120	trace
8	Cu (0.2)	DTBP (2.0)	120	17
9	CuBr (0.2)	TBHP (2.0)	120	trace
10	CuBr (0.2)	TBPB (2.0)	120	trace
11	CuBr (0.2)	$K_2S_2O_8$ (2.0)	120	trace
12	CuBr (0.2)	DCP (2.0)	120	trace
13	CuBr (0.5)	DTBP (2.0)	120	42
14	CuBr (1.0)	DTBP (2.0)	120	57
15	CuBr (1.0)	DTBP (3.0)	120	67
16	CuBr (1.0)	DTBP (4.0)	120	77
17	CuBr (1.0)	DTBP (5.0)	120	75
18	**CuBr (1.0)**	**DTBP (4.0)**	**100**	**78**

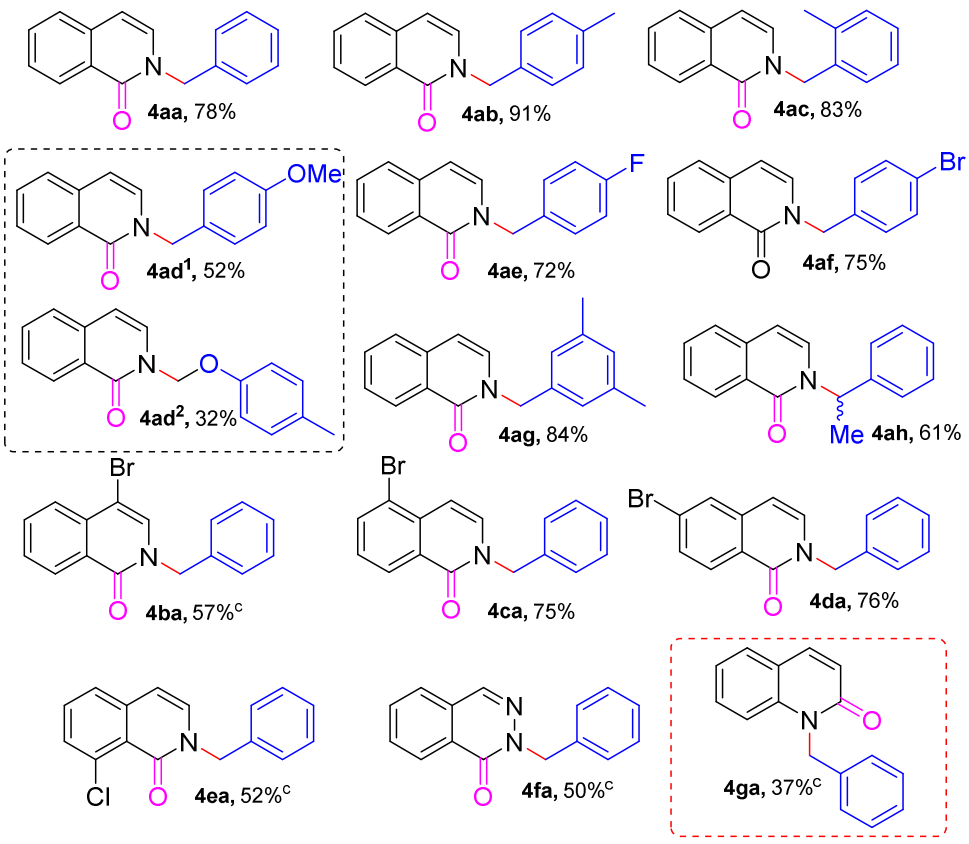
[a]Reaction conditions: **2a** (0.30 mmol), **3a** (1.5 mL), 8 h, under N_2 atmosphere. [b] Yield of isolated product.

slightly raised (Table 1, entry 18). On the basis of the results shown in Table 1, the reaction was carried out with 0.3 mmol of isoquinoline (**2a**), 1.5 mL of toluene substrates, 0.3 mmol of CuBr and 1.2 mmol of DTBP at 100 °C for 8 h.

With optimized conditions in hand, we further carried out the reaction by using various isoquinolines and methylbenzene derivatives to investigate the scope and generality of this protocol (Table 2). A range of methylbenzene derivatives bearing electron-donating and electron-withdrawing groups reacted with isoquinoline **(2a)** to give the target *N*-benzylisoquinolinones **4**. The reaction occurred in high yields by using methylbenzene derivatives bearing electron-donating substituents as substrates, such as *p*-dimethylbenzene (**3b**), *o*-dimethylbenzene (**3c**) and 1,3,5-trimethylbenzene (**3g**). It is worth noting that we obtained two different products **4ad**[1] and **4ad**[2] when 4-methylanisole (**3d**) was used as a substrate. Meanwhile, different substituted isoquinolines were examined under the standard reaction conditions. The lower yields of the corresponding products **4ba** and **4ea** were observed in the presence of substituents at the 4 or 8 position of isoquinolines. To our delight, apart from isoquinolines, phthalazine **(2f)** and quinoline **(2g)** could also be used as substrates with methylbenzene **(3a)** to afford the desired compounds **4fa** and **4ga** respectively in moderate yields under the reaction conditions.

Table 2 Scope of the reaction [a,b] affording products **4**.



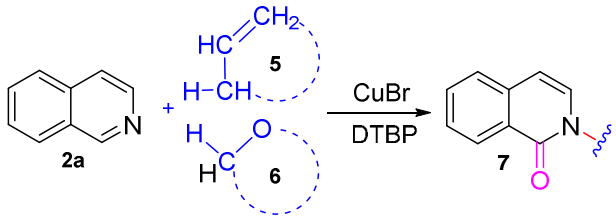


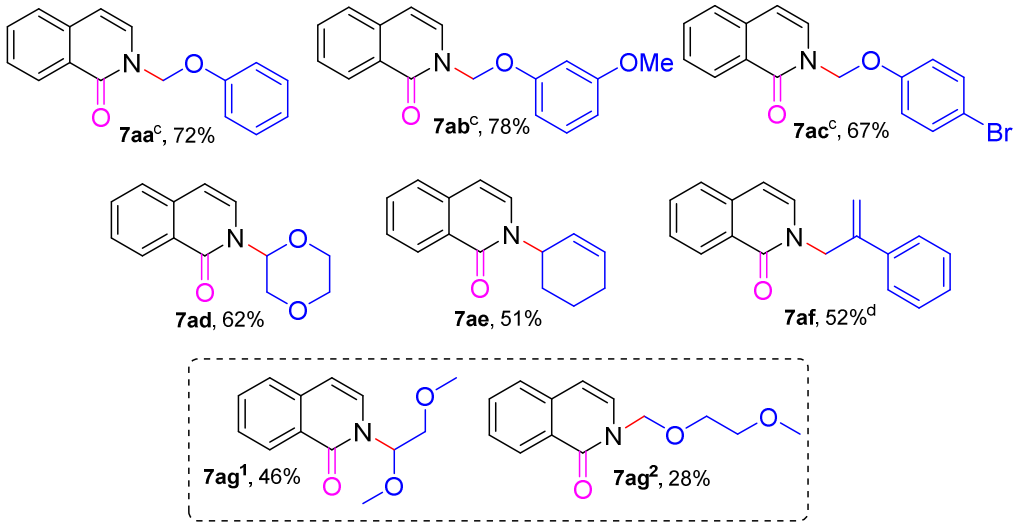
[a]Reaction conditions: **2** (0.30 mmol), **3** (1.5 mL), CuBr (1.0 equiv) and DTBP (4.0 equiv), 4-10 h, under N_2 atmosphere. [b] Yield of isolated product. [c]120°C for 12 h.

Encouraged by the exciting results, we tried to apply a few other types of compounds containing C(sp^3)-H bonds such as 1,4-dioxane (**6d**), cyclohexene (**5e**), 1,2-dimethoxyethane (**6g**), methoxybenzene (**6a**) and their derivatives into this transformation under the typical reaction conditions. It is nice to see that these compounds could act as the effective substrates in the coupling reactions with isoquinoline (**2a)** in moderate yields and the results were summarized in Table 3. The ratio of the regioisomeric products **7ag**[1] and **7ag**[2] in reaction of isoquinoline (**2a**) with 1,2-dimethoxyethane (**6g**) is 46% : 28%. Meanwhile, we could not found the target compounds when isoquinoline (**2a**) reacts with ethers or alkenes by using Yang's method[6] (Scheme 1). Besides, we found an interesting phenomenon in the course of the experiments. A mixture of two products (**7ac** and **8aa** or **7ah** and **8aa**) in varying proportions were observed when

the reaction was completed at 120 °C by using 2-bromoanisole or 4-bromoanisole (**6c** or **6h**) as a substrate (Scheme 2). The result showed that this competing exchange reaction existed at higher temperatures utilizing anisoles with bromine group as a substrate.

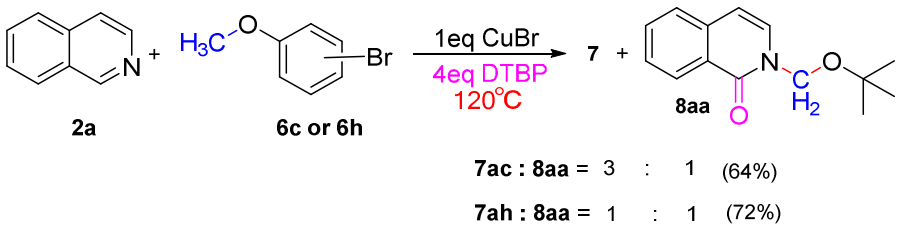
Table 3 Scope of the reaction [a,b] affording products **7**.





[a]Reaction conditions: **2a** (0.30 mmol), **5** or **6** (1.5 mL), CuBr (1.0 equiv) and DTBP (4.0 equiv), 100 °C, 6-10 h, under N_2 atmosphere. [b] Yield of isolated product. [c]6.0 equiv of DTBP.

[d]2-Phenylpropene as a substrate.



Scheme 2. Intermolecular exchange reaction.

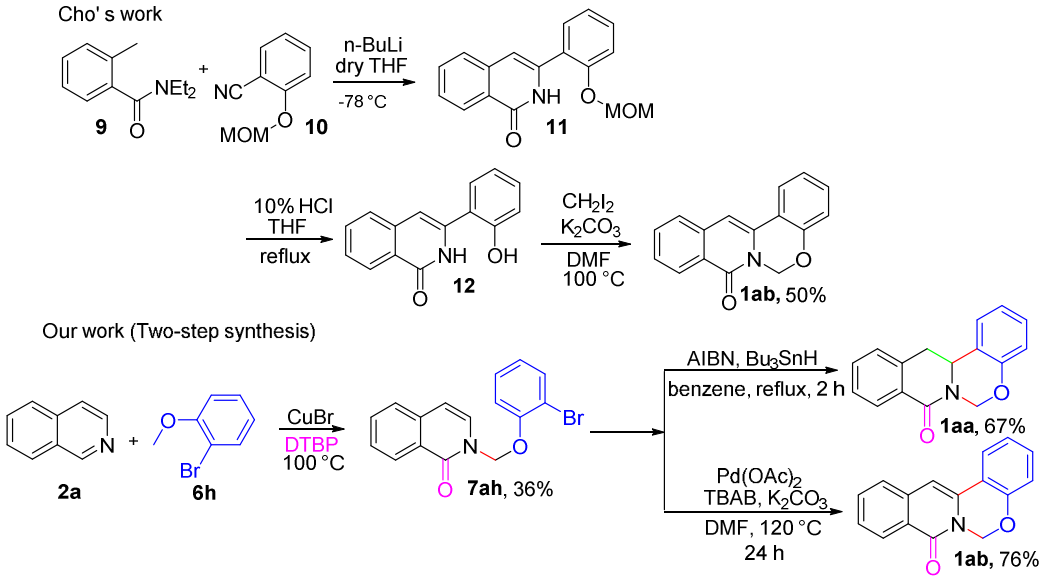
Furthermore, the versatile synthetic utilization of *N*-benzylisoquinolinones **4** was studied, and

the results are summarized in Scheme 3. For the synthesis of 5-oxaprotoberberinones, as far as we know, only one method has been reported. Protoberberines are important natural isoquinoline alkaloids. In 2014, Cho[9] first employed *o*-toluamide **9** and MOM (methoxymethyl) protected *o*-cyanophenol **10** as substrates to yield the target cross-coupling product **1ab**. The reaction was carried out in dry tetrahydrofuran (THF) utilizing n-butyllithium as an additive at -78℃. Then, MOM group was removed to afford phenol **12** in the presence of 10% HCl or trifluoroacetic acid. Finally, unsubstituted 5-oxaprotoberberinone **1ab** was obtained in moderate yield by S_N2 reaction, in which compound **12** reacts with diiodomethane by using K_2CO_3 as base. Cho's method has some drawbacks, such as intricate pre-process, harsh conditions and long steps. Therefore, a more convenient method for the generation of this class of compounds is still required. Herein we present a new way for the preparation of 5-oxaprotoberberinones by two steps using the method reported above in this article. The corresponding compound **1ab** was provided in 76% yield utilizing readily available starting materials. Besides, its derivative **1aa** could also be easily assembled in moderate yield by this novel two-step procedure based on Argade's method[10]. Furthermore, isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one (topoisomerase I inhibitor) could also be produced by using the above reported method and Daich' s method[11] in combination (Figure 1).

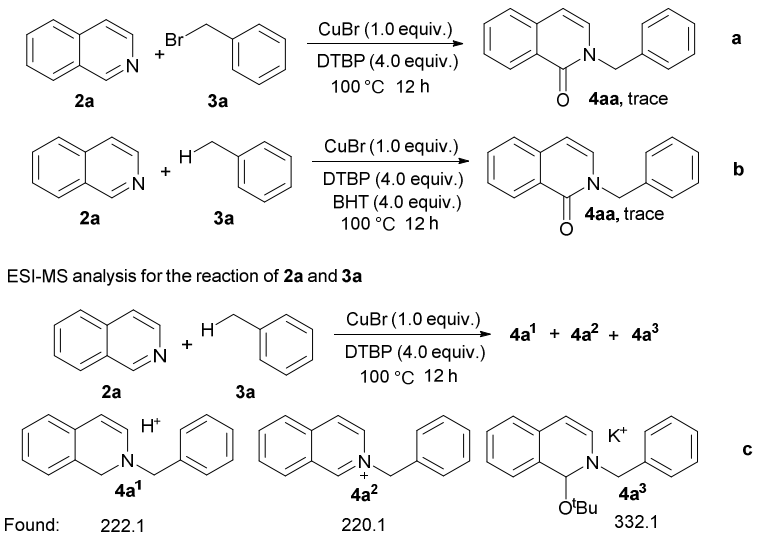
To investigate the mechanism, several control experiments were completed (Scheme 4). Firstly, when the reaction was carried out under the standard condition by using benzyl bromide intead of toluene, we could not find the target compound **4a** (Scheme 4a). This shows that the corresponding product could not be obtained by benzyl bromide intermediate. When 4 equiv of 2,6-di-*tert*-butyl-4 -methylphenol (BHT) was introduced to this transformation under the optimized conditions, no desired product was detected (Scheme 4b). It turned out that the free

radical inhibitor completely suppressed the reaction. Finally, we tried to take advantage of ESI-MS analysis on the model reaction of **2a** and **3a** to further probe the reaction pathway. When the reaction was completed under the standard condition, we took a few samples from the reaction mixture and directly analyzed by ESI-MS in positive ion mode. Several peaks with m/z signals characterized for cationic intermediates were trapped. On the analysis of the present m/z signals, structures of the cationic intermediates were proposed, the results were summarized in Scheme 4c. The results indicated that benzylic radical firstly attack the nitrogen of C=N in the pathway to get the carbon radical intermediate.

On the basis of these preliminary results above, together with previous studies[7,8], we proposed a plausible mechanism in Scheme 5. Initially, the reaction between $[Cu]^{I}$ and DTBP would give copper(II) alkoxide **A** and *tert*-butoxy radical **B**. Meanwhile, homolysis of other DTBP gives **B** under heating, Benzyl radical **C** would be generated by abstracting hydrogen from toluene by **B**. Subsequently, isoquinoline **2a** reacts with **A** to afford

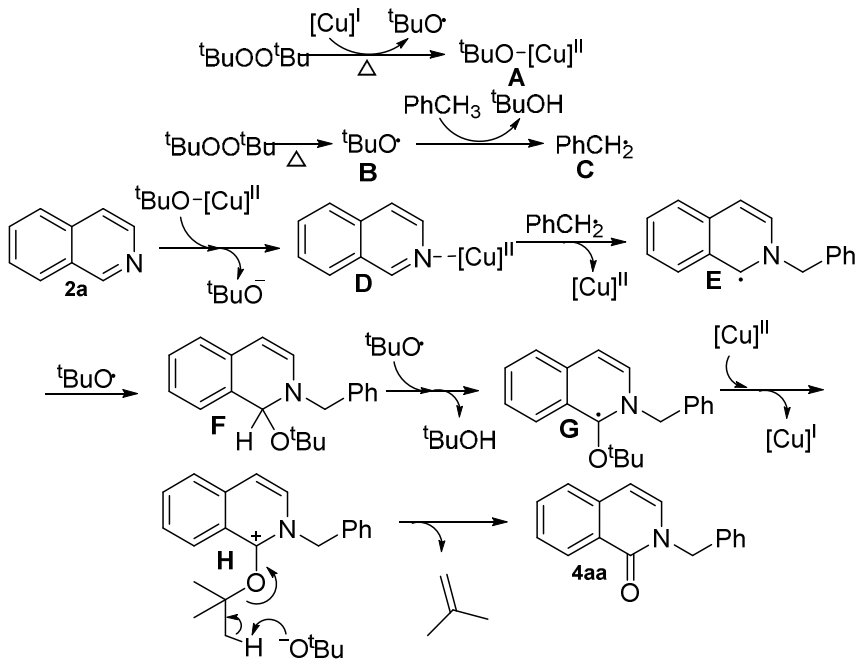


Scheme 3. Transformations of 2-[(2-bromophenoxy)methyl]isoquinolin-1(2*H*)-one (**6ah**).



Scheme 4. Control experiment.

intermediate **D,** which combined with the benzyl radical **C** to produce the intermediate **E**. Then **E** works with **B** to afford the corresponding compound **F**. The reaction of compound **F** with *tert*-butoxy radical **B** would generate free radical intermediate **G** which would reduce the $[Cu]^{II}$ to $[Cu]^{I}$ and simultaneously generate carbonium ion intermediate **H**. Finally, the desired product **4aa** was formed with the release of tertiary butyl cation which would generate isobutene involving *tert*-butoxy ion. Our hypothesis accounts for 1.0 equiv of CuBr employed in this transformation. Quantitative intermediate **D** was yielded to afford compound **F.** Uncoordinated isoquinolines would lose their stability to result in side reaction in the presence of DTBP when the amount of Cu salts was reduced.



Scheme 5. Plausible mechanism for the synthesis of **4aa**.

Conclusion

In conclusion, we have developed an efficient and practical copper-mediated oxidative functionalization of azaarenes with various C(sp^3)−H bonds via a radical process in moderate to high yields without any ligands. This novel transformation provided a useful strategy for the synthesis of *N*-benzyl/alkyl isoquinolinone utilizing readily available starting substrates. Importantly, 5-oxaprotoberberinones and their derivatives could be concisely prepared by using this method. Further investigation of this procedure to focus on the detailed reaction mechanism and synthetic applications is underway in our laboratory.

Experimental Section

General Procedure for the Synthesis of the Target Compounds 4

DTBP (1.2 mmol) was added to a solution of **2** (0.3 mmol), **3** (1.5 mL) and CuBr (0.3 mmol), and the reaction mixture was stirred under nitrogen atmosphere at 100℃ for 4-10 h. Afterwards

the resulting mixture was cooled to room temperature, transferred to silica gel column directly and purified by column chromatography with petroleum ether/ethyl acetate (20:1) as eluent to give **4**.

General Procedure for the Synthesis of the Target Compounds 7

DTBP (1.2 mmol) was added to a solution of **2a** (0.3 mmol), **5** or **6** (1.5 mL) and CuBr (0.3 mmol), and the reaction mixture was stirred under nitrogen atmosphere at 100℃ for 4-10 h. Afterwards the resulting mixture was cooled to room temperature, transferred to silica gel column directly and purified by column chromatography with petroleum ether/ethyl acetate (20:1) as eluent to give **7**.

2-Benzylisoquinolin-1(2*H*)-one (4aa),[6] yellow solid. Yield: 54.9 mg (78%); mp 65−66 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.33-7.28 (m ,5H), 7.08 (d, J = 8.0 Hz, 1H), 6.48 (d, J = 8.0 Hz, 1H), 5.22 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 137.0, 136.9, 132.2, 131.2, 128.8, 128.1, 127.9, 127.8, 126.8, 126.4, 125.9, 106.3, 51.7.

2-(4-methylbenzyl)isoquinolin-1(2*H*)-one (4ab),[6] yellow solid. Yield: 67.9 mg (91%); mp 103−105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 4.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.08-7.06 (m ,3H), 7.47 (d, J = 8.0 Hz, 1H), 5.18 (s, 2H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 137.5, 137.0, 133.9, 132.1, 131.2, 129.4, 128.0, 128.0, 126.8, 126.4, 125.8, 106.2, 51.4, 21.0.

2-(2-methylbenzyl)isoquinolin-1(2*H*)-one (4ac),[6] Yellow solid. Yield: 62.0 mg (83%); mp 109−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 4.0 Hz, 2H), 7.21-7.15 (m ,3H), 7.05 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.46 (d, J = 8.0 Hz, 1H), 5.22 (s, 2H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 136.9, 136.5,

134.4, 132.2, 130.8, 130.7, 128.4, 128.1, 128.0, 126.8, 126.3, 126.2, 125.9, 106.3, 49.3, 19.1.

2-(4-methoxybenzyl)isoquinolin-1(2*H*)-one (4ad[1]),[6] Yellow solid. Yield: 41.3 mg (52%); mp 107−108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 8.0 Hz, 1H), 7.62(d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 2H), 6.46 (d, J = 8.0 Hz, 1H), 5.15 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 159.3, 137.0, 132.1, 131.1, 129.5, 129.1, 128.0, 126.8, 126.4, 125.8, 114.2, 106.2, 55.2, 51.2.

2-(4-methoxybenzyl)isoquinolin-1(2*H*)-one (4ad[2]), white soild. Yield: 25.4 mg (32%); mp 117−118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 8.0 Hz, 2H), 6.49 (d, J = 8.0 Hz, 1H), 5.94 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 154.1, 137.0, 132.6, 131.8, 130.1, 129.4, 128.2, 127.0, 126.1, 126.0, 115.9, 106.8, 74.2, 20.4. HRMS (ESI) m/z: calcd for $C_{17}H_{19}N_2O_2$: 283.1441 $[M+NH_4]^+$; found: 283.1426.

2-(4-fluorobenzyl)isoquinolin-1(2*H*)-one (4ae),[6] white solid. Yield: 54.6 mg (72%); mp 107−108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 7.08-6.98 (m ,3H), 6.49 (d, J = 8.0 Hz, 1H), 5.17 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (d, $^{1}J_{C\text{-}F}$ = 250.0 Hz), 162.2, 137.0, 132.7, 132.7, 132.3, 131.1, 129.8, 129.7, 128.0, 127.0, 126.3, 125.9, 115.8, 115.6, 106.6, , 51.2.

2-(4-bromobenzyl)isoquinolin-1(2*H*)-one (4af),[6] yellow solid. Yield: 70.4 mg (75%); mp 157−158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.52-7.44 (m ,4H), 7.21 (d, J = 4.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 5.16 (s ,2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 136.9, 135.9, 132.3, 131.9, 131.0, 129.6, 128.0, 127.0, 126.3, 125.9, 121.8, 106.6, 51.2.

2-(3,5-dimethylbenzyl)isoquinolin-1(2*H*)-one (4ag),[6] white solid. Yield: 66.3 mg (84%); mp 100−103 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 8.0 Hz, 1H), 7.62 (m ,1H), 7.49(d, J = 8.0 Hz, 2H), 7.07 (d, J = 4.0 Hz, 1H), 6.92-6.90 (m ,3H), 6.46 (d, J = 8.0 Hz, 1H), 5.14 (s, 2H), 2.27 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 138.4, 137.0, 136.8, 132.1, 131.3, 129.5, 128.1, 126.8, 125.8, 125.8, 125.7, 106.2, 51.5, 21.2.

2-(1-phenylethyl)isoquinolin-1(2*H*)-one (4ah),[6] yellow oil. Yield: 45.6 mg (61%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 8.0 Hz, 1H), 7.64-7.60 (m ,1H), 7.51-7.46 (m ,2H), 7.35-7.26 (m ,5H), 6.91 (d, J = 8.0 Hz, 1H), 6.59-6.54 (m ,1H), 6.44 (d, J = 8.0 Hz, 1H), 1.76 (d, J = 4.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 140.6, 136.6, 132.1, 128.7, 128.2, 127.9, 127.7, 127.3, 126.7, 126.1, 125.7, 106.4, 52.1, 18.7.

2-benzyl-4-bromoisoquinolin-1(2*H*)-one (4ba),[6] yellow solid. Yield: 53.5 mg (57%); mp 112−113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 8.0 Hz, 1H), 7.82-7.73 (m ,2H), 7.58-7.55 (m ,1H), 7.35-7.26 (m, 6H), 5.20 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 136.2, 135.5, 133.0, 132.9, 131.7, 131.6, 128.9, 128.5, 128.1, 128.0, 127.9, 125.8, 51.7.

2-benzyl-5-bromoisoquinolin-1(2*H*)-one (4ca),[6] yellow solid. Yield: 70.4 mg (75%); mp 110−113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 8.0 Hz, 1H), 7.87-7.85 (m ,1H), 7.32-7.16 (m ,7H), 6.82 (d, J = 8.0 Hz, 1H), 5.21 (s ,2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 136.5, 136.3, 136.0, 132. 5, 128.9, 128.0, 127.9, 127.8, 127.7, 127.4, 120.6, 105.0, 51.9.

2-benzyl-6-bromoisoquinolin-1(2*H*)-one (4da),[6] Yellow solid. Yield: 71.6 mg (76%); mp 112−113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.0 Hz, 1H), 7.66-7.56 (m ,2H), 7.32-7.26 (m ,5H), 7.10 (d, J = 8.0 Hz, 1H), 6.38 (d, J = 8.0 Hz, 1H), 5.19 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 138.4, 136.5, 132.6, 130.1, 129.9, 128.9, 128.3, 128.0, 127.9, 127.4, 125.0, 105.2,

51.8.

2-benzyl-8-chloroisoquinolin-1(2*H*)-one (4ea), yellow oil. Yield: 41.9 mg (52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.0 Hz, 2H), 7.36-7.25 (m, 6H), 7.09 (d, J = 8.0 Hz, 1H), 6.39 (d, J = 8.0 Hz, 1H), 5.17 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 140.1, 136.7, 135.7, 132.1, 131.9, 130.1, 128.9, 128.8, 128.1, 127.8, 125.1, 105.8, 51.8. HRMS (ESI) m/z: calcd for $C_{17}H_{13}ClNO_3$: 314.0589 $[M+COOH]^-$; found: 314.0586.

2-benzylphthalazin-1(2*H*)-one (4fa),[6] white solid. Yield: 35.4 mg (50%); mp 84−87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 8.0 Hz, 1H), 8.13 (s, 1H), 7.70-7.24 (m ,8H), 5.40 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 138.0, 137.0, 133.1, 131.6, 130.0, 129.7, 128.6, 128.5, 127.7, 126.8, 126.0, 54.6.

1-benzylquinolin-2(1*H*)-one (4ga),[6] brown solid. Yield: 26.1 mg (37%); mp 64−67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.44-7.40 (m ,1H), 7.31-7.16 (m, 7H), 6.82 (d, J = 8.0 Hz, 1H), 5.56 (s, 2H).

2-(phenoxymethyl)isoquinolin-1(2*H*)-one (7aa), White solid. Yield: 54.2 mg (72%); mp 99−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 8.0 Hz, 1H), 7.66-7.63 (m ,1H), 7.51-7.48 (m, 2H), 7.28-7.24 (m ,3H), 7.08 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.0 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 5.99 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 156.2, 137.0, 132.7, 129.7, 129.3, 128.2, 127.1, 126.10, 126.0, 122.4, 115.9, 106.9, 73.9. HRMS (ESI) m/z: calcd for $C_{16}H_{13}NO_2Na$: 274.0838 $[M+Na]^+$; found: 274.0844.

2-((3-methoxyphenoxy)methyl)isoquinolin-1(2*H*)-one (7ab), yellow oil. Yield: 65.8 mg (78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.25-7.14 (m, 2H), 6.67 (s, 2H), 6.56-6.50 (m, 2H), 5.96 (s, 2H), 3.75 (s, 3H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ 162.0, 160.9, 157.3, 137.0, 132.7, 130.1, 129.4, 128.2, 127.1, 126.1, 126.0, 108.4, 107.8, 106.9, 102.0, 73.8, 55.3. HRMS (ESI) m/z: calcd for $C_{18}H_{16}NO_5$: 326.1034 $[M+COOH]^-$; found: 326.1043.

2-((4-bromophenoxy)methyl)isoquinolin-1(2*H*)-one (7ac), white solid. Yield: 66.1 mg (67%); mp 151−152 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 8.0 Hz, 1H), 7.67-7.63 (m ,1H), 7.51-7.47 (m, 2H), 7.37-7.35 (m ,2H), 7.21 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 8.0 Hz, 2H), 6.52 (d, J = 8.0 Hz, 1H), 5.95 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 155.1, 137.0, 132.9, 132.6, 129.2, 128.2, 127.3, 126.7, 126.1, 117.7, 114.9, 107.3, 73.8. HRMS (ESI) m/z: calcd for $C_{16}H_{12}BrNO_2Na$: 351.9944 $[M+Na]^+$; found: 351.9926.

2-(1,4-dioxan-2-yl)isoquinolin-1(2*H*)-one (7ad), White solid. Yield: 43.0 mg (62%); mp 118−120 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 8.0 Hz, 1H), 7.67-7.63 (m, 1H), 7.51-7.40 (m, 2H), 7.39 (d, J = 8.0 Hz, 1H), 6.54 (d, J = 8.0 Hz, 1H), 6.27-6.24 (m, 1H), 4.05-4.03 (m, 3H), 3.83 (d, J = 12.0 Hz, 1H), 3.74-3.70 (m, 1H), 3.48-3.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 136.6, 132.6, 128.0, 126.9, 126.5, 125.9, 125.7, 106.3, 78.7, 68.8, 67.2, 65.8. HRMS (ESI) m/z: calcd for $C_{13}H_{13}NO_3Na$: 254.0788 $[M+Na]^+$; found: 254.0793.

2-(cyclohex-2-en-1-yl)isoquinolin-1(2*H*)-one (7ae), colorless oil. Yield: 34.4 mg (51%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 8.0 Hz, 1H), 7.62-7.48 (m, 3H), 7.20 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 6.13 (d, J = 8.0 Hz, 1H), 5.71-5.60 (m, 2H), 2.15 (s, 3H), 1.78-1.63 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 136.8, 133.3, 132.0, 128.6, 128.0, 126.9, 126.6, 126.1, 125.7, 105.7, 51.1, 29.6, 24.7, 20.2. HRMS (ESI) m/z: calcd for $C_{15}H_{15}NONa$: 248.1046 $[M+Na]^+$; found: 248.1050.

2-(2-phenylallyl)isoquinolin-1(2*H*)-one (7af), yellow oil. Yield: 40.7 mg (52%); ^1H NMR (400

MHz, $CDCl_3$) δ 8.45 (d, J = 8.0 Hz, 1H), 7.63-7.59 (m, 4H), 7.34-7.25 (m, 3H), 7.07 (d, J = 8.0 Hz, 1H), 6.45 (d, J = 8.0 Hz, 1H), 5.56 (s, 1H), 5.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 143.6, 138.1, 137.0, 132.1, 130.6, 128.5, 128.2, 128.1, 127.9, 126.8, 126.2, 125.8, 115.1, 106.2, 50.8. HRMS (ESI) m/z: calcd for $C_{18}H_{14}NO$: 260.1081 $[M-H]^-$; found: 260.1110.

2-(1,2-dimethoxyethyl)isoquinolin-1(2*H*)-one (7ag[1]), colorless oil. Yield: 32.2 mg (46%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 8.0 Hz, 1H), 7.67-7.63 (m, 1H), 7.53-7.47 (m, 2H), 7.27 (d, J = 8.0 Hz, 1H), 6.57 (d, J = 4.0 Hz, 1H), 6.28-6.25 (m, 1H), 3.65 (d, J = 4.0 Hz, 2H), 3.41 (s, 3H), 3.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 136.8, 132.5, 128.0, 126.8, 126.1, 126.0, 125.9, 106.3, 83.9, 73.2, 59.4, 56.8. HRMS (ESI) m/z: calcd for $C_{13}H_{15}NO_3K$: 272.0684 $[M+K]^+$; found: 272.0654.

2-((2-methoxyethoxy)methyl)isoquinolin-1(2*H*)-one (7ag[2]), colorless oil. Yield: 19.6 mg (32%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 8.0 Hz, 1H), 7.66-7.63 (m, 1H), 7.51-7.47 (m, 2H), 7.21 (d, J = 8.0 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 5.50 (s, 2H), 3.75-3.74 (m, 2H), 3.53-3.52 (m, 2H), 3.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 137.1, 132.6, 130.2, 128.1, 126.9, 126.1, 125.9, 106.5, 76.9, 71.5, 68.5, 58.9. HRMS (ESI) m/z: calcd for $C_{13}H_{15}NO_3K$: 272.0684 $[M+K]^+$; found: 272.0657.

2-((2-bromophenoxy)methyl)isoquinolin-1(2*H*)-one (7ah), White solid. Yield: 35.5 mg (36%); mp 148−149 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 8.0 Hz, 1H), 7.66-7.62 (m, 1H), 7.53-7.47 (m, 3H), 7.30-7.24 (m, 3H), 6.90-6.86 (m, 1H), 6.53 (d, J = 8.0 Hz, 1H), 6.05 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 152.6, 137.0, 133.5, 132.8, 129.4, 128.7, 128.2, 127.1, 126.1, 126.0, 124.0, 116.6, 113.3, 107.1, 74.6. HRMS (ESI) m/z: calcd for $C_{16}H_{13}BrNO_2$: 330.0124 $[M+H]^+$; found: 330.0145.

13,13a-Dihydro-6*H*,8*H*-isoquino[2,3-*c*][1,3]benzoxazin-8-one (1aa),[10] white solid. Yield: 18.2 mg (67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 4.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.41-7.37 (m, 1H), 7.27-7.21 (m, 3H), 7.08-7.00 (m, 2H), 6.47 (d, J = 16.0 Hz, 1H), 5.08-5.03 (m, 1H), 4.60 (d, J = 8.0 Hz, 1H), 3.28-3.24 (m, 1H), 3.04-2.96 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 153.8, 137.0, 132.5, 128.7, 128.4, 128.1, 127.5, 127.2, 126.0, 123.6, 122.3, 118.0, 70.9, 52.9, 37.0. HRMS (ESI) m/z: calcd for $C_{16}H_{14}NO_2$: 252.1019 $[M+H]^+$; found: 252.1017.

6*H*,8*H*-Isoquino[2,3-*c*][1,3]benzoxazin-8-one (1ab),[9] white solid. Yield: 20.4 mg (76%); mp 174−175 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.66-7.63 (m, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.48-7.44 (m, 1H), 7.38-7.34 (m, 1H), 7.18-7.14 (m, 1H), 7.09 (d, J = 8.0 Hz, 1H), 6.89 (s, 1H), 5.91 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 154.1, 136.7, 133.2, 132.7, 131.0, 128.0, 126.7, 126.4, 125.2, 124.1, 123.5, 119.1, 117.7, 100.9, 71.6.

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Associated content

Supporting Information: ^{1}H and ^{13}C NMR spectral data of all compounds found in the SI.

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