JOC The Journal of Organic Chemistry

Article

Tunable Synthesis of 3-Hydroxylisoquinolin-1, 4-dione and Isoquinolin-1-one Enabled by Copper-Catalyzed Radical 6-Endo Aza-Cyclization of 2-Alkynylbenzamide

Renzhi Liu, Meng Li, Wenlin Xie, Hongwei Zhou, Yajing Zhang, and Guanyinsheng Qiu

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b01643 • Publication Date (Web): 22 Aug 2019

Just Accepted

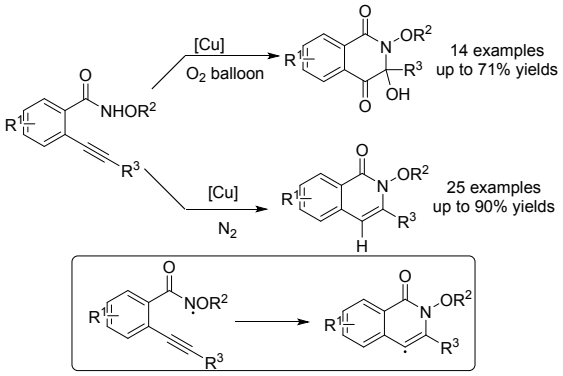
is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Tunable Synthesis of 3-Hydroxylisoquinolin-1, 4-dione and Isoquinolin-1-one Enabled by Copper-Catalyzed Radical 6-*Endo* *Aza*-Cyclization of 2-Alkynylbenzamide

Renzhi Liu,[†] Meng Li,[‡] Wenlin Xie,[†*] Hongwei Zhou,[‡*] Yajing Zhang,[‡] and Guanyinsheng Qiu[†, ‡, *]

[†] School of Chemistry and Chemical Engineering, Hunan University of Science and Technology, Xiangtan 411201, China. Email: xwl2000zsu@163.com (X. W.)

[‡] College of Biological, Chemical Sciences and Engineering, Jiaxing University, Jiaxing 314001, Zhejiang, China. Email: qiuguanyinsheng@mail.zjxu.edu.cn (G. Q.); zhouhw@zju.edu.cn (H. Z.)



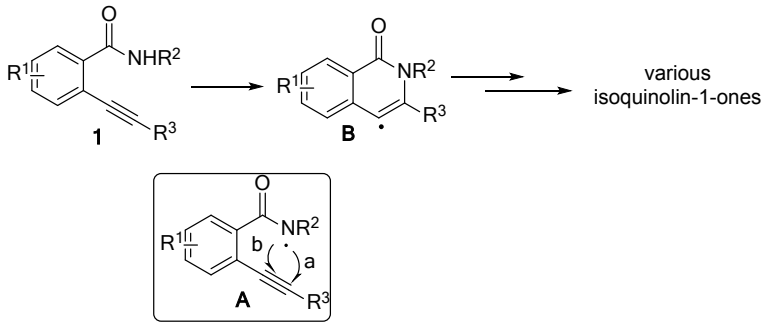
ABSTRACT: In this work, switchable synthesis of isoquinolin-1-one and 3-hydroxylisoquinolin-1,4-dione from 2-alkynylbenzamide is reported. The transformation works well with good yields and a broad reaction scope. The synthetic switch for providing isoquinolin-1-one and 3-hydroxylisoquinolin-1,4-dione is enabled by the use of N_2 or O_2 atmosphere. Mechanism studies show that the reaction proceeds in a regioselective manner via a *N*-center radical 6-*endo-dig aza*-cyclization pathway.

Introduction

Considering its ubiquity of *N*-containing compounds, various *N*-containing synthons were developed for accordingly.[1] Among them, *N*-center radical species was a history-long yet many-issues-unsettled topic in the field of organic chemistry.[2] As such, tremendous efforts were made in past decades, thus enabling significant progress of amidyl-nitrogen radical and imine-nitrogen radical chemistry.[3] To the best of our knowledge, amidyl nitrogen-radical could be achieved through a metal-free process, metal catalysis and photocatalysis *etc*.

On the other hand, 2-alkynylbenzamide was a versatile dual-functional synthon towards many privileged skeletons, such as isoquinolin-1-ones,[4] isoindolin-1-ones,[5] isocoumarin-1-imines[6] and isobenzofuran-1-imines.[7] For 2-alkynylbenzamide-based chemistry, regiochemistry in *N/O* nucleophilicity and *5-exo* cyclization/*6-endo* cyclization was still challenging. Generally, base-promoted cyclization of 2-alkynylbenzamide preferred to undergoing *N*- nucleophilicity 5-*exo-dig* cyclization, whereas, *O*-nucleophilic 6-*endo-dig* cyclization could be realized under Lewis acid catalysis. According to our recent findings, the metal-free radical annulation of 2-alkynylbenzamide dominated in an *O*-nucleophilic cyclization manner, which served as an important supplement of electrophilic cyclization.[8] Given high importance of isoquinolin-1-one structural core,[9] many research groups devoted themself to its synthetic methodology development.[4,12] As we know, a few elegant cases starting from 2-alkynylbenzamide indicated that using indium salt[4a,4b] and platinum salt[4c] as Lewis acid catalysts could convert 2-alkynylbenzamide into isoquinolin-1-one through *N*- nucleophilicity 6-*endo* cyclization. With catalytic $Cu(OAc)_2$ and stoichiometric inorganic base, a two-step procedure from 2-iodobenzamide and terminal alkyne also provided isoquinolin-1-one core.[4d] Inspired by what mentioned above together with our continuous interest in radical chemistry,[10] we would like to disclose a radical process for *N*-center radical-attacked 6-*endo-dig* cyclization of 2-alkynylbenzamide **1**. Copper salt, recognized as cost-low metal salt, was always used in radical transformations.[11] Therefore, in this paper copper salt was employed as catalyst to trigger this projected transformation (Scheme 1).

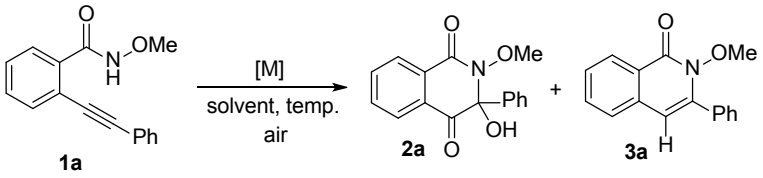
Scheme 1. Radical *6-endo-dig aza*-cyclization of 2-alkynylbenzamide



Theoretically, after being treated with copper salt, the substrate 2-alkynylbenzamide **1** led to a key amidyl *N*-center radical **A** through a SET process. It is hypothesized that the amidyl *N*-center radical **A** occurred to undergo radical 6-*endo-dig aza*-cyclization

to result in the intermediated **B.** It was envisioned that the intermediate **B** could be converted into isoquinolin-1-one derivatives. Very recently, Han and co-workers developed a Cu-catalyzed *N*-center radical-based tandem 5-*exo*-*dig* cyclization of alkyne-tethered *N*-alkoxylamide.[12] This elegant example probably supported the reliability of our above assumption. It is imaginable that this paper herein exploited a distinctive radical model for *N*-attacked *6*-*endo*-*dig* cyclization of 2-alkynylbenzamide. Moreover, this paper also provided an insight into the reactivity of the isoquinolin-1-one radical **B**, a kind of heterocyclic aryl radical. As such, we started to optimize reaction conditions of model reaction.

Table 1. Optimization of the Reaction Conditions[a]



Entry	[M]	Solvent	T (°C)	Yield of **2a** (%)[a,b]	Yield of **3a** (%)[a,b]
1	$Cu(OAc)_2$	DCE	80	19	43
2	CuF_2	DCE	80	21	32
3	$Cu(OTf)_2$	DCE	80	28	41
4	$CuCl_2$	DCE	80	42	37
5	$CuBr_2$	DCE	80	36	49
6	CuCl	DCE	80	29	40
7	CuI	DCE	80	21	38
8	Cu_2O	DCE	80	24	61
9	$CuCl_2$	THF	80	40	36
10	$CuCl_2$	MeCN	80	39	53
11	$CuCl_2$	Toluene	80	17	48
12	$CuCl_2$	1,4-dixane	80	-	57
13	$CuCl_2$	DMF	80	-	49
14	$CuCl_2$	$CHCl_3$	80	41	32
15	$CuCl_2$	DCM	80	32	29
16	$CuCl_2$	DCE	100	41	50
17[c]	$CuCl_2$	DCE	80	47	35

18 [cd]	**$CuCl_2$**	**DCE**	**80**	**51**	**30**
19 [cd]	$CuCl_2$	DCE (4 mL)	80	51	25
20[cd]	$CuCl_2$	DCE (1 mL)	80	45	32
21[de]	$CuCl_2$	DCE	80	50	23
22[cd]	-	DCE	80	-	-
23[f]	$CuCl_2$	DCE	80	-	75
24[fg]	**$CuCl_2$**	**DCE**	**80**	**-**	**82**

[a]Isolated yield based on 2-alkynylbenzamide **1a**. [b]Standard conditions: 2-alknylbenzamide **1a** (0.2 mmol), copper salt (10 mol%), solvent (2 mL), air overnight. [c]O_2 atmoshpere instead of air was conducted. [d]2 mol% $CuCl_2$ was added. [e]bubbling O_2 into the reaction. [f]the reaction was conducted under N_2 atmosphere. [g]20 mol% $CuCl_2$ was added.

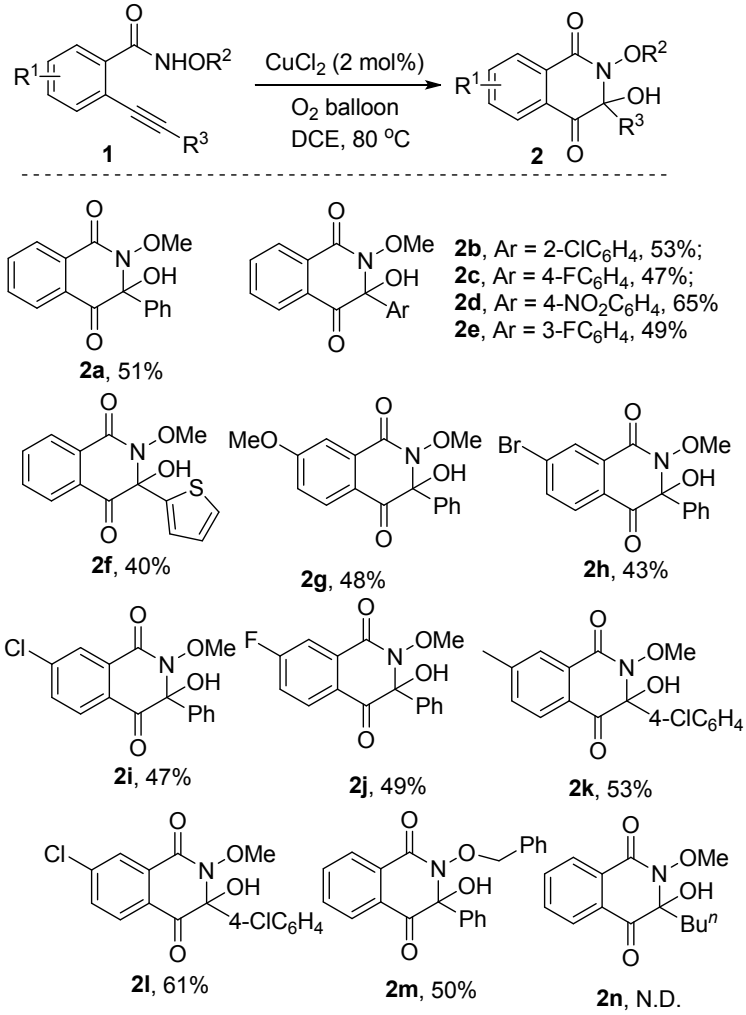
Result and Discussion

Initially, various copper sources were explored. Interestingly, the reactions under air provided two products. Identified with NMR, HRMS, IR, and X-Ray diffraction, the two products were defined as 3-hydroxylisoquinolin-1,4-dione **2a**, which probably resulted from the reaction of the intermediate **B** with O_2, and isoquinolin-1-dione **3a**, which was ascribed to H-abstraction of the intermediate **B**, respectively. Considering high importance of 3-hydroxylisoquinolin-1,4-dione,[9,13] its synthetic methodology development thus attracted our attention. From the screening results, it seemed that copper chloride ($CuCl_2$) was the best choice (entry 4, Table 1), leading to the product 3-hydroxylisoquinolin-1,4-dione **2a** in a 42% yield. Other copper salts did not provide better outcomes (entries 1-8, Table 1). No better yields were produced when various solvents and reaction temperatures were used (entries 9-16, Table 1). It was noteworthy that protonated product isoquinolin-1-one **3a** was not excluded in the process. Interestingly, we observed the reaction efficiency was improved when the reaction was conducted under O_2 atmosphere, and the desired product **2a** and the by-product **3a** were detected in 47% and 35% yields, respectively (entry 17, Table 1). To further supress H-abstraction, we attempted to reduce the loading of copper catalyst. Pleasingly, further decrease of copper loading to 2 mol% improved the reaction efficiency, leading to the 3-hydroxylisoquinolin-1,4-dione **2a** in a 51% yield and isoquinolin-1-one **3a** in 30% yield as well (entry 18, Table 1). Additionally, changing concentration of 1a in DCE did not improve the reaction efficiency

(entries 19-20, Table 1). Bubbling O_2 into the reaction also did not increase the yield of **2a** (entry 21, Table 1). Moreover, we also optimized the reaction conditions for the synthesis of isoquinolin-1-one **3a**. To our delight, the increase of the loading of $CuCl_2$ to 0.2 equiv under N_2 atmosphere improved the reaction efficiency, providing isoquinolin-1-one **3a** in an 82% yield, and 3-hydroxylisoquinolin-1,4-dione **2a** was not observed (entry 24, Table 1).

After optimizing the conditions, we then explored the reaction generality. The results are illustrated in Table 2. A series of 3-hydroxylisoquinolin-1,4-diones **2** was achieved in moderate to good yields. However, the substituent R^3 was solely equal to aryl and heteroaryl groups. The reaction of n-butyl-connected substrate did not provide the final 3-hydroxylisoquinolin-1,4-dione **2n**, but gave rise to a protonated isoquinolin-1-one **3t** in 21% yield.

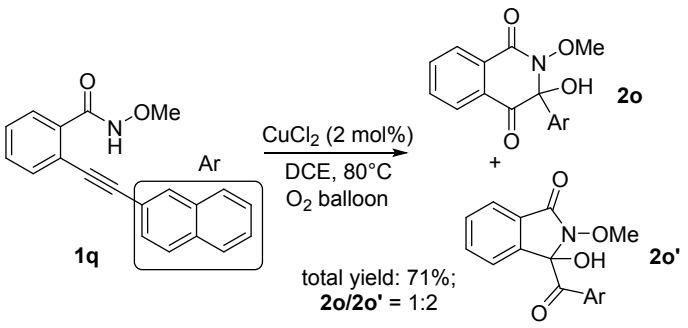
Table 2 Reaction Scope for **2**[a,b]



[a]Reaction conditions: **1** (0.2 mmol), $CuCl_2$ (2 mol%), O_2 balloon in 2 mL of DCE were stirred at 80 °C. [b]Isolated yield based on **1**.

Surprisingly, the reaction of substrate with 4-methoxylaryl **1q** did give rise to an inseperable mixture of 6-*endo-dig aza*-cyclization product **2o** and 5-*exo-dig aza*-cyclization product **2o'**, which was consitent with the hypervalent iodine-mediated results from Zhao and Du.[13] The total yield was 71%, and the ratio of **2o**/**2o'** was 1:2 (Table 3). Other more efficient synthetic methodologies towards 3-hydroxylisoquinolin-1,4-diones **2** are ongoing to be explored in our lab. The results will be reported in due course.

Table 3 Reaction Scope: the Reaction of 4-Methoxylphenylethynylbenzmiade Under O_2 [a]

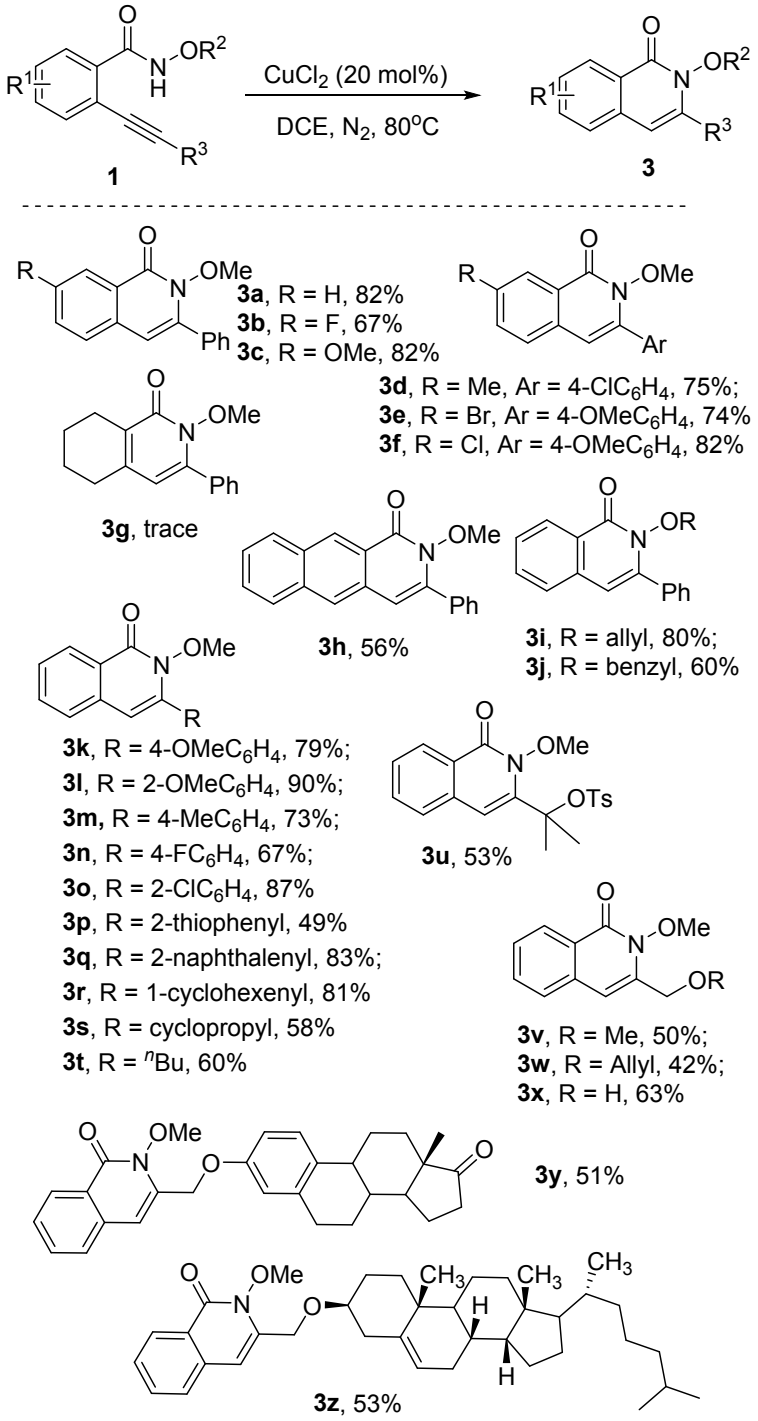


[a)] Isolated yield based on **1q**.

Subsequentially, we also explored the reaction scope for the synthesis of isoquinolin-1-one **3** (Table 4). As expected, a series of substituted isoquinolin-1-one **3** was achieved in moderate to good yields. The substituent effects of R^1 were initially investigated. The results revealed that both electron-donating groups and electron-withdrawing groups were compatible, leading to the desired isoquinolin-1-ones **3a-3f** in 67-82% yields. For example, the reaction with the substrate containing a 5-methoxyl group on R^1 afforded the desired isoquinolin-1-one **3c** in an 82% yield, while the substrate with 5-fluoro substitution provided the corresponding product **3b** in a 67% yield. The reaction of naphthalene-linked substrate **1h** offered the desired isoquinolin-1-one **3h** in a 56% yield. However, cyclohexyl-connected and pyridinyl-connected substrate **1g** was not a good reaction partner.

Various *N*-protecting groups were also examined. Beyond *N*-methoxyl group, *N*-protecting group could be replaced by benzyloxyl and allyloxyl, and the corresponding products **3i** and **3j** were achieved in 80% and 60% yields, respectively. To our surprise, under standard conditions *N*-H, *N*-aryl and *N*-alkyl-linked substrates did not offer the desired isoquinolin-1-ones, but provided *O*-nucleophilic *6-endo-dig* cyclization products isocoumarin-1-imines (data not shown in Table 4).

Table 4 Reaction Scope for **3**[a,b]



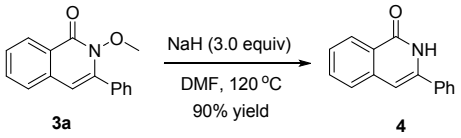
[a]Reaction conditions: **1** (0.2 mmol), $CuCl_2$ (20 mol%), N_2 in 2 mL of DCE were stirred at 80 °C. [b]Isolated yield based on **1**.

Finally, the substituent effect of R^3 in starting materials was also explored accordingly. Based on the established results, it seemed that R^3 could be equal to aryl, heteroaryl and alkyl. The corresponding isoquinolin-1-ones **3k-3x** were obtained in moderate to good yields. For instance, thiopheneethynyl-connected substrate was an effective reaction partner, yielding

the desired isoquinolin-1-one **3p** in moderate yield. Other sensitive functional groups such as cyclohexenyl (entry **3r**, Table 4), cyclopropyl (entry **3s**, Table 4), sulfonate (entry **3u**, Table 4), allyl (entry **3w**, Table 4), and free hydroxyl (entry **3x**, Table 4) were compatible for the reactions.

Interestingly, the reactions of estratrienone-linked 2-alkynylbenzamide **1y** worked well under standard conditions, providing the desired isoquinolin-1-one **3y** in 51% yield (Table 4). With a similar outcome, the isoquinolin-1-one **3z** was also afforded when Cholesterol-connected substrate **1z** was used. Compared to the simple substrates, the reactions with complex substrates were less efficient as we detected several unknown products. The structure identification of these unknown products is ongoing in our lab.

Table 5 Synthetic Elaboration of Isoquinolin-1-one [a]

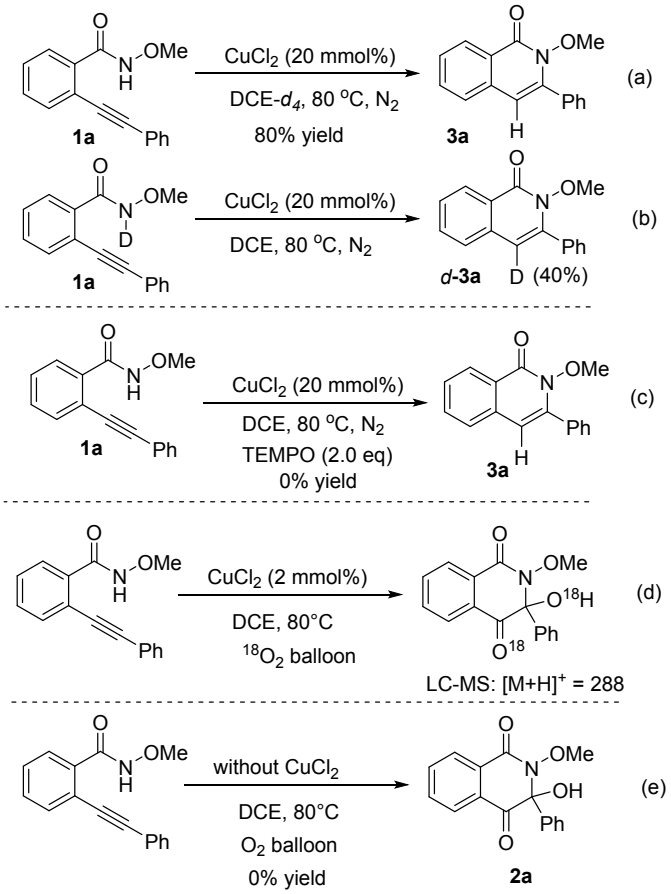


3a **4**

[a)] Isolated yield based on **3a**.

The structural elaboration of isoquinolin-1-one **3** was also tested. As presented in Table 5, 3.0 equiv of NaH enabled removal of methoxyl group in isoquinolin-1-one **3a**, providing isoquinoline **4** in 90% yield (Table 5).

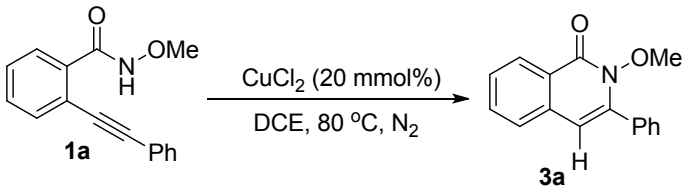
Scheme 2. Mechanistic Studies



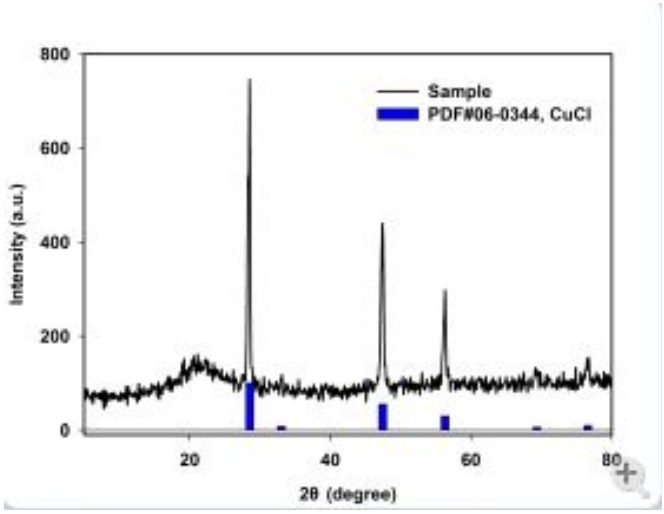
To gain insights into mechanism, several control experiments were carried out. As illustrated in Scheme 2, the deuterium-labled experiments indicated that hydrogen atom in C4-H of isoquinolin-1-one **3a** was not derived from solvent, but probably came from amide N-H of substrate. Secondly, the reaction was totally retarded when 2.0 equiv of TEMPO was added as a radical scavenger, probably suggesting the reaction undergoing a radical pathway. Thirdly, the control reaction under $^{18}O_2$ atmosphere was also conduct, which showed one equivalent of O_2 was installed into the final 3-hydroxylisoquinolin-1,4-dione **2a**. Moreover, the blank reaction without $CuCl_2$ did not give the desired product **2a**. This result implied that the use of copper salt was highly important for this oxidative radical *6-endo-dig aza*-cyclization of 2-alkynylbenzamide.

To identify the valent state of copper salt in the reaction, XRD test on copper species after reaction ran accordingly (Scheme 3). From the result, XRD spectrum of the sample was extremely overlapped with that of CuCl, whose standard XRD spectrum was numbered as PDF#06-0344. This result indicated that in the process $CuCl_2$ was reduced into CuCl, probably providing a solid evidence for the projected radical annulation.

Scheme 3. Mechanistic Studies



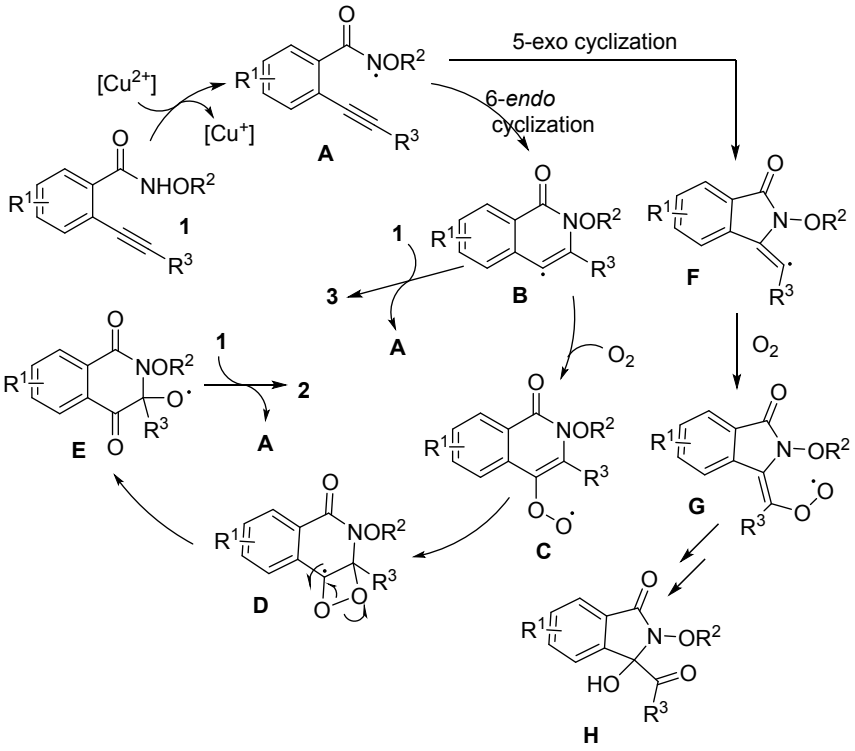
XRD of copper species after reaction:



In light of aforementioned results, a plausible mechanism was proposed in Scheme 4. It is believed that 2-alkynylbenzamide-containing *N*-center radical **A**, generated from treatment of 2-alkynylbenzamide **1** with $CuCl_2$, was a key intermediate.[14] The resulting intermediate **A** occurred to go through *6-endo-dig* aza-cyclization to deliver isoquinolin-1-one radical species **B**. Under N_2 atmosphere, hydrogen abstraction of the intermediate **B** from the starting material **1** afforded the targeted products **3**. Otherwise, under O_2 atmosphere the intermediate **B** was trapped by O_2, leading to the intermediate **C**.[11h] A sequential intramolecular radical cyclization of the intermediate **C** affordeed an intermediate **D**.[15] It was noteworthy that the cyclization from the intermediate **C** to intermediate **D** seemed disfavored. However, Han and co-workers found that anti-Baldwin's rule cyclization was reliable when peroxy radical was involved.[15c] Electron rearrangement of the intermediate **D** together with H-abstraction gave rise to the final products **2**. In some cases, the intermediate **A** occurred to undergo 5-*exo-trig aza*-cyclization to form another radical species **F**, which was trapped by molecular O_2 to provide peroxyl radical species **G**. Followed anti-Baldwin's rule 4-endo cyclization and ring opening, a *5-exo* cyclization oxygenated product **H** was formed. In the process, we reasoned that selectivity of forming intermediate

B and intermediate **F** was subjected to stability of their radical intermediates **B** and **F**. Electronic effect of the R^3 group made significant impact on the stability of the intermediates.

Scheme 4. Proposed Mechanism



In conclusion

We have developed a copper-catalyzed radical cyclization of 2-alkynylbenzamide for the synthesis of isoquinolin-1-one under N_2 atmosphere. Interestingly, the above strategy could be used to the formation of 3-hydroxylisoquinolin-1,4-diones as well when the reaction was conducted in the presence of O_2 balloon. Mechanism studies showed that the reaction proceeds in a regioselective manner via an *N*-center radical-based *6-endo-dig aza*-cyclization pathway.

Experimental Section

General procedure for the synthesis of compound 1a:

To a solution of 2-iodobenzoyl chloride (4 g, 15.0 mmol) in AcOEt/H_2O (v/v = 2:1, 180 mL) were added potassium carbonate (4.14 g, 30 mmol) and methoxyamine hydrochloride (1.5 g, 18.0 mmol). The mixture was stirred at room temperature overnight, and then extracted with AcOEt (3 × 40 mL), washed with water (50 mL) and brine (50 mL) and dried over $MgSO_4$. Evaporation gave a crude solid that was recrystallized from AcOEt and collected by filtration. Then 2-iodo-*N*-methoxybenzamide was provided (white solid, 4.46 g, 84% yield).

Sodium hydride (640 mg, 16 mmol) added into a solution of 2-iodo-*N*-methoxybenzamide (4.05 g, 14.6 mmol) in dry THF (100 mL) at 0°C. After that, Boc_2O (3.83 g, 17.5 mmol) was then added slowly at 0°C. The mixture was stirred at room temperature overnight and then quenched with saturated aqueous NH_4Cl solution (30 mL). The mixture was extracted with AcOEt (3 × 30 mL), washed with saturated aqueous bicarbonate solution (30 mL), brine (30 mL), and dried over $MgSO_4$. Using flash column chromatography, a white solid *tert*-butyl methoxy(2-(phenylethynyl)benzoyl)carbamate was provided (4.80 g, 87% yield).

To a solution of the above solid *tert*-butyl methoxy(2-(phenylethynyl)benzoyl)carbamate (1.56 g, 4.4 mmol) in toluene (20 mL) were successively added $PdCl_2(PPh_3)_2$ (308.8 mg, 0.44 mmol), CuI (41.9 mg, 0.22 mmol), phenylacetylene (1.4 mL, 13.2 mmol) and *tert*-butylamine (0.93 mL , 8.8mmol). The mixture was stirred at 50 °C in oil bath for 3h. After completion of the reaction, the crude was flitrated by chromatography on silica gel (Pentane/Et_2O 9:1 to 8:2) to afford the crude product. Then, the solvent was removed, and trifluoroacetic acid (3 mL) in CH_2Cl_2 (5 mL) was added at 0°C The crude mixture was purified by flash chromatography on silica gel to afford the pure product **1a** in (0.905g, 82%) as a white solid. Other substrates **1** were prepared according to the above procedure.

General procedure for the synthesis of compound 2: *N*-methoxy-2-(phenylethynyl)benzamide **1** (0.2 mmol), $CuCl_2$ (0.02 equiv) were added to a test tube. Under an oxygen atmosphere the solvent DCE (2.0 mL) was added. The mixture was stirred at 80 °C in heating mantle overnight. After the disappearance of substrate as indicated by TLC, the mixture was filtrated. Evaporation of the solvent and purification by flash column chromatograph provided the desired products **2.**

General procedure for the synthesis of compound 3: *N*-methoxy-2-(phenylethynyl)benzamide **1** (0.2 mmol), $CuCl_2$ (0.2 equiv) were added to a test tube. Under a nitrogen atmosphere the solvent DCE (2.0 mL) was added. The mixture was stirred at 80

°C in heating mantle overnight. After the disappearance of substrate as indicated by TLC, the mixture was filtrated. Evaporation of the solvent and purification by flash column chromatograph provided the desired products **3**.

General procedure for the synthesis of compound 4: NaH (3 equiv) was added into a stirred solution of 2-methoxy-3-phenylisoquinolin-1(2H)-one **2a** (0.2 mmol) in DMF (1mL), and the resulting mixture was heated at 120 °C in heating mantle for 1 h. After the reaction was completed, the reaction mixture was allowed to cool to room temperature, and H_2O (8 mL) was added, followed by extraction with DCM (4 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography to give the products **4** as a white solid.

N-methoxy-2-(phenylethynyl)benzamide (**1a**)[4c] Following the general procedure, **1a** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 82%, 906 mg, white solid, mp 107-109 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.88 (s, 1H), 7.83 (d, J = 5.8 Hz, 1H), 7.56 – 7.47 (m, 3H), 7.42 – 7.29 (m, 5H), 3.86 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 165.1, 133.6, 133.0, 131.5, 130.8, 129.5, 129.1, 128.8, 128.5, 122.0, 119.9, 95.1, 87.1, 64.6

2-((2-chlorophenyl)ethynyl)-*N*-methoxybenzamide (**1b**)[13] Following the general procedure, **1b** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 76%, 953 mg, white solid, mp 107-109 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.19 (s, 1H), 8.11 – 8.05 (m, 1H), 7.61 (m, 2H), 7.50 – 7.42 (m, 3H), 7.35 – 7.27 (m, 2H), 3.90 (s, 3H).

2-((4-fluorophenyl)ethynyl)-*N*-methoxybenzamide (**1c**)[13] Following the general procedure, **1c** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 75%, 888 mg, white solid, mp 148-150 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.62 (s, 1H), 7.89 (d, J = 6.3 Hz, 1H), 7.57 – 7.49 (m, 3H), 7.48 – 7.40 (m, 2H), 7.07 (t, J = 8.5 Hz, 2H), 3.89 (s, 3H).

N-methoxy-2-((4-nitrophenyl)ethynyl)benzamide (**1d**) [13] Following the general procedure, **1d** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 69%, 899 mg, white solid, mp 144-146 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.34 (s, 1H), 8.22 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 6.4 Hz, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 7.1 Hz, 1H), 7.52 – 7.42 (m, 2H), 3.90 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 147.4, 133.3, 132.3 (3C), 131.0, 129.7, 129.2, 129.0, 123.7 (3C), 119.4, 92.6, 91.6, 64.7.

2-((3-fluorophenyl)ethynyl)-*N*-methoxybenzamide (**1e**) [13] Following the general procedure, **1e** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 73%, 864 mg, white solid, mp 120-122 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.65 (s, 1H), 7.82 (d, J = 6.7 Hz, 1H), 7.55 (d, J = 7.1 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.35 – 7.29 (m, 2H), 7.20 (d, J = 9.5 Hz, 1H), 7.09 – 7.05 (m, 1H), 3.88 (s, 3H).

N,5-dimethoxy-2-(phenylethynyl)benzamide (**1g**)[13] Following the general procedure, **1g** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 80%, 990 mg, white solid, mp 155-158 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.98 (s, 1H), 7.52 – 7.45 (m, 4H), 7.40 – 7.33 (m, 3H), 6.99 – 6.96 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 164.7, 159.9, 134.9, 134.6, 131.3, 128.9, 128.6, 122.2, 118.1, 114.0, 111.7, 94.0, 87.3, 64.6, 55.6.

5-bromo-*N*-methoxy-2-(phenylethynyl)benzamide (**1h**)[4c] Following the general procedure, **1h** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 80%, 1158 mg, white solid, mp 112-114 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.87 (s, 1H), 8.05 (s, 1H), 7.58 – 7.49 (m, 3H), 7.42 – 7.37 (m, 4H), 3.88 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 163.6, 134.9, 134.3, 134.0, 132.7, 131.5, 129.4, 128.6, 123.2, 121.6, 118.7, 96.4, 86.3, 64.7.

5-chloro-*N*-methoxy-2-(phenylethynyl)benzamide (**1i**)[13] Following the general procedure, **1i** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 78%, 978 mg, white solid, mp 110-112 °C;

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.89 (s, 1H), 7.90 (s, 1H), 7.54 – 7.47 (m, 3H), 7.43 – 7.35 (m, 4H), 3.89 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 163.7, 135.1, 134.8, 134.2, 131.5, 131.1, 129.9, 129.4, 128.6, 121.5, 118.3, 96.3, 86.2, 64.7.

5-fluoro-*N*-methoxy-2-(phenylethynyl)benzamide (**1j**)[13] Following the general procedure, **1j** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 81%, 923 mg, white solid, mp 133-135 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.57 – 7.50 (m, 3H), 7.37 –7.34(m, 3H), 7.17 – 7.11 (m, 1H), 3.88 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 162.3 (d, *J* = 252.2 Hz), 135.7, 135.2 (d, *J* = 8.0 Hz), 131.4, 129.3, 128.6, 121.7, 118.5 (d, *J* = 22.3 Hz), 117.0 (d, *J* = 24.4 Hz), 116.0, 113.5, 95.1, 86.2, 64.6.

2-((4-chlorophenyl)ethynyl)-*N*-methoxy-5-methylbenzamide (**1k**)[13] Following the general procedure, **1k** was purified by silica gel chromatography (EA/PE = 1/5). Yield:74 %, 974 mg, white solid, mp 105-108 °C;

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.67 (s, 1H), 7.68 (s, 1H), 7.43 (d, *J* = 8.1 Hz, 3H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 1H), 3.87 (s, 3H), 2.37 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 165.3, 139.6, 135.0, 133.4, 132.9, 132.6, 131.8, 130.2, 128.9, 120.6, 116.6, 93.3, 88.2, 64.6, 21.3.

5-chloro-2-((4-chlorophenyl)ethynyl)-*N*-methoxybenzamide (**1l**)[13] Following the general procedure, **1l** was purified by silica gel chromatography (EA/PE = 1/5). Yield:70 %, 983 mg, white solid, mp 162-164 °C;

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.68 (s, 1H), 7.85 (s, 1H), 7.49 – 7.40 (m, 4H), 7.34 (d, *J* = 8.1 Hz, 2H), 3.88 (s, 3H).

N-(benzyloxy)-2-(phenylethynyl)benzamide (**1m**)[5d] Following the general procedure, **1m** was purified by silica gel chromatography (EA/PE = 1/5). Yield:80 %, 1151 mg, white solid, mp 129-131 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.86 (s, 1H), 7.97 (s, 1H), 7.58 – 7.52 (m, 1H), 7.46 – 7.32 (m, 9H), 7.28 – 7.25 (m, 3H), 5.06 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 164.9, 135.3, 133.2, 131.6, 131.0, 129.8, 129.1, 128.8, 128.6, 128.5, 128.5, 121.7, 119.9, 95.5, 87.2, 78.4.

2-(hex-1-yn-1-yl)-*N*-methoxybenzamide (**1n**)[4c] Following the general procedure, **1n** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 65%, 661 mg, white solid, mp 79-81 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.08 (s, 1H), 7.94 (d, J = 6.3 Hz, 1H), 7.44 – 7.34 (m, 3H), 3.87 (s, 3H), 2.47 (t, J = 7.1 Hz, 2H), 1.65 – 1.57 (m, 2H), 1.47 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 165.0, 133.3, 132.9, 130.9, 129.8, 128.2, 120.3, 97.4, 79.3, 64.5, 30.4, 22.0, 19.2, 13.5.

N-methoxy-2-(naphthalen-2-ylethynyl)benzamide (**1o**)[13] Following the general procedure, **1o** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 60%, 795 mg, white solid, mp 156-158 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.88 (s, 1H), 8.39 (d, J = 8.3 Hz, 1H), 7.95 – 7.84 (m, 3H), 7.76 (d, J = 7.1 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.4 Hz, 1H), 7.50 – 7.39 (m, 3H), 3.86 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 165.2, 133.5, 133.2, 133.1, 133.0, 131.0, 130.8, 129.7, 129.6, 128.9, 128.4, 127.2, 126.7, 125.9, 125.2, 120.2, 119.6, 93.5, 91.8, 64.6.

N-methoxy-3-(phenylethynyl)-2-naphthamide (**1p**)[4c] Following the general procedure, **1p** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 62%, 821 mg, white solid, mp 130-132 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.84 (s, 1H), 8.46 (d, J = 8.1 Hz, 1H), 7.89 – 7.83 (m, 3H), 7.66 – 7.57 (m, 4H), 7.47 – 7.39 (m, 3H), 3.94 (s, 3H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 165.9, 134.0, 132.7, 132.3, 131.6, 129.4, 129.2, 128.7, 128.3, 127.9, 127.7, 127.0, 125.3, 122.0, 118.1, 100.9, 85.1, 64.7.

N-(allyloxy)-2-(phenylethynyl)benzamide (**1q**) Following the general procedure, **1q** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 40%, 487 mg, white solid, mp 94-96 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.82 (s, 1H), 7.94 (d, J = 7.0 Hz, 1H), 7.60 – 7.51 (m, 3H), 7.48 – 7.33 (m, 5H), 6.05 – 5.95 (m, 1H), 5.33 (d, J = 17.2 Hz, 1H), 5.25 – 5.22 (m, 1H), 4.52 (d, J = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 164.9, 133.4, 133.1, 132.0, 131.6, 130.9, 129.8, 129.2, 128.8, 128.5, 121.9, 120.8, 119.8, 95.4, 87.2, 77.4; HRMS (ESI-TOF) calcd for $C_{18}H_{16}NO_2$+: 278.1176 ($M+H^+$), found: 278.1176

N-methoxy-2-((2-methoxyphenyl)ethynyl)benzamide (**1r**)[4c] Following the general procedure, **1r** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 81%, 1001 mg, white solid, mp 95-97 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.23 (s, 1H), 8.26 – 8.24 (m, 1H), 7.60 – 7.54 (m, 1H), 7.50 – 7.41 (m, 3H), 7.38 – 7.34 (m, 1H), 6.99 – 6.93 (m, 2H), 3.98 (s, 3H), 3.90 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 163.8, 160.2, 133.0, 132.7, 132.0, 131.1, 130.8, 130.7, 128.7, 120.8, 119.5, 111.0, 110.4, 92.7, 92.4, 64.1, 55.8.

N-methoxy-2-(p-tolylethynyl)benzamide (**1s**)[13] Following the general procedure, **1s** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 72%, 840 mg, white solid, mp 109-112 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.87 (s, 1H), 7.92 (d, J = 6.2 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.45 – 7.38 (m, 4H), 7.17 (d, J = 7.9 Hz, 2H), 3.88 (s, 3H), 2.37 (s, 3H).

2-(cyclohex-1-en-1-ylethynyl)-*N*-methoxybenzamide (**1t**) Following the general procedure, **1t** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 62%, 696 mg, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.00 (s, 1H), 7.97 – 7.90 (m, 1H), 7.48 – 7.30 (m, 3H), 6.31 – 6.19 (m, 1H), 3.87 (s, 3H), 2.23 – 2.11 (m, 4H), 1.69 – 1.56 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 164.9, 137.2, 132.9, 132.8, 130.9, 129.8, 128.3, 120.2, 119.9, 97.5, 84.9, 64.6, 28.7, 25.8, 22.1, 21.2; HRMS (ESI-TOF) calcd for $C_{16}H_{18}NO_2$+: 256.1332 ($M+H^+$), found: 256.1332

2-(cyclopropylethynyl)-*N*-methoxybenzamide (**1u**)[4c] Following the general procedure, **1u** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 67%, 634 mg, white solid, mp 80-82 °C ;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.94 (s, 1H), 7.91 (d, J = 6.1 Hz, 1H), 7.43 – 7.31 (m, 3H), 3.89 (s, 3H), 1.53 – 1.46 (m, 1H), 0.97 – 0.91 (m, 2H), 0.88 – 0.82 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 165.1, 133.2, 133.1, 130.9, 129.7, 128.1, 120.2, 100.4, 74.1, 64.5, 8.8, 0.2.

4-(2-(methoxycarbamoyl)phenyl)-2-methylbut-3-yn-2-yl 4-methylbenzenesulfonate (**1v**) Following the general procedure, **1v** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 45%, 766 mg, white solid, mp 118-120 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ:9.92 (s, 1H), 7.88 (d, J = 6.1 Hz, 1H), 7.80 (d, J = 8.2 Hz, 2H), 7.43 – 7.37 (m, 2H), 7.37 – 7,33 (m, 1H), 7.30 (d, J = 8.1 Hz, 2H), 3.83 (s, 3H), 2.41 (s, 3H), 1.64 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 164.3, 145.5, 134.1, 133.2, 131.4, 130.8, 130.6, 130.0, 129.5 (2C), 118.3, 93.0, 84.5, 64.3, 59.7, 23.2, 21.7; HRMS (ESI-TOF) calcd for $C_{20}H_{22}NO_5S$+: 388.1213 ($M+H^+$), found: 388.1215

2-(3-(allyloxy)prop-1-yn-1-yl)-*N*-methoxybenzamide (**1w**) Following the general procedure, **1w** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 54%, 582 mg, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.97 (s, 1H), 7.59 (d, *J* = 6.9 Hz, 1H), 7.37 (d, *J* = 7.2 Hz, 1H), 7.32 – 7.24 (m, 2H), 5.86 – 5.76 (m, 1H), 5.24 (d, *J* = 17.2 Hz, 1H), 5.19 – 5.06 (m, 1H), 4.29 (s, 2H), 4.02 (d, *J* = 5.7 Hz, 2H), 3.74 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 164.9, 134.1, 133.6, 133.1, 130.6, 128.9, 128.7, 119.6, 118.1, 90.8, 84.0, 70.8, 64.2, 57.7; HRMS (ESI-TOF) calcd for $C_{14}H_{16}NO_3$+: 246.1125 ($M+H^+$), found: 246.1125

2-(3-hydroxyprop-1-yn-1-yl)-*N*-methoxybenzamide (**1x**) Following the general procedure, **1x** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 44%, 397 mg, white solid, mp 110-112 °C;

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 10.13 (s, 1H), 7.68 (d, *J* = 6.0 Hz, 1H), 7.42 – 7.29 (m, 3H), 4.47 (s, 2H), 3.95 (s, 1H), 3.81 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 165.3, 133.7, 133.0, 130.8, 129.1, 128.7, 119.8, 93.7, 82.9, 64.4, 51.1; HRMS (ESI-TOF) calcd for $C_{11}H_{12}NO_3$+: 206.0812 ($M+H^+$), found: 206.0818

N-methoxy-2-(3-(((13S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-3-yl)oxy)prop-1-yn-1-yl)benzamide (**1y**) Following the general procedure, **1y** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 38%, 765 mg, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.59 (s, 1H), 7.84 (s, 1H), 7.48 – 7.46 (m, 1H), 7.41 – 7.39 (m, 2H), 7.22 (d, *J* = 8.6 Hz, 1H), 6.81 – 6.79 (m, 1H), 6.73 (s, 1H), 4.91 (s, 2H), 3.77 (s, 3H), 2.92 – 2.87 (m, 2H), 2.51 – 2.44 (m, 1H), 2.38 – 2.36 (m, 1H), 2.26 – 2.19 (m, 1H), 2.14 – 2.07 (m, 1H), 1.95 – 1.90 (m, 1H), 1.63 – 1.49 (m, 4H), 1.48 – 1.39 (m, 4H), 0.88 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 220.9, 155.4, 138.1, 133.3, 133.1, 130.8, 129.6, 129.2, 126.5, 118.9, 114.8, 112.2, 104.9, 90.3, 84.9, 64.4, 60.3, 56.3, 50.3, 47.9, 43.9, 38.2, 35.8, 31.5, 29.6, 26.4, 25.8, 21.5, 13.8; HRMS (ESI-TOF) calcd for $C_{29}H_{32}NO_4$+: 458.2326 ($M+H^+$), found: 458.2316

2-(3-(((3S,8S,10R,13R,14S)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl)oxy)prop-1-yn-1-yl)-*N*-methoxybenzamide (**1z**) Following the general procedure, **1z** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 39%, 984 mg, white solid, mp 126-128 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.77 (s, 1H), 7.91 (s, 1H), 7.50 – 7.38 (m, 3H), 5.38 – 5.32 (m, 1H), 4.45 (d, J = 1.7 Hz, 2H), 3.89 (s, 3H), 3.45 – 3.36 (m, 1H), 2.44 – 2.37 (m, 1H), 2.29 – 2.20 (m, 1H), 2.03 – 1.75 (m, 6H), 1.60 – 1.41 (m, 7H), 1.40 – 1.21 (m, 5H), 1.21 – 1.01 (m, 8H), 0.99 (s, 3H), 0.90 (d, J = 6.3 Hz, 3H), 0.84 (d, J = 6.6 Hz, 6H), 0.66 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 164.7, 140.2, 133.5, 133.3, 130.9, 129.7, 129.0, 122.1, 119.2, 92.4, 83.7, 78.7, 64.5, 56.7, 56.0, 55.8, 50.0, 42.2, 39.7, 39.4, 38.7, 37.0, 36.8, 36.1, 35.7, 31.9, 31.8, 28.2, 28.1, 28.0, 24.2, 23.8, 22.8, 22.5, 21.0, 19.3, 18.7, 11.8; HRMS (ESI-TOF) calcd for $C_{38}H_{56}NO_3$+: 574.4255 ($M+H^+$), found: 574.4255

3-hydroxy-2-methoxy-3-phenyl-2,3-dihydroisoquinoline-1,4-dione (**2a**)[13] Following the general procedure, **2a** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 51%, 29 mg, white solid, mp 138-140 °C;

1H NMR (400 MHz,CDCl3) δ: 8.35 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.82 – 7.78 (m, 1H), 7.67 – 7.63 (m, 1H), 7.41 – 7.39 (m, 2H), 7.31 – 7.27 (m, 3H), 4.93 (s, 1H), 4.04 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, CDCl3) δ: 190.7, 161.5, 136.5, 135.7, 133.4, 130.7, 129.4, 129.1, 128.9, 128.7, 127.5, 126.4, 93.9, 65.3. IR(neat) 3264, 3059, 2937, 1702, 1644, 1579, 1385, 1283, 1132, 993, 869, 757; HRMS (ESI-TOF) calcd for $C_{16}H_{14}NO_4$+: 284.0917 ($M+H^+$), found: 284.0910

3-(2-chlorophenyl)-3-hydroxy-2-methoxy-2,3-dihydroisoquinoline-1,4-dione (**2b**) Following the general procedure, **2b** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 53%, 36 mg, white solid, mp 153-155 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 – 8.09 (m, 3H), 7.78 – 7.70 (m, 2H), 7.47 – 7.43 (m, 1H), 7.40 – 7.32 (m, 2H), 5.60 (s, 1H), 3.41 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 188.5, 161.3, 135.1, 135.0, 133.3, 131.7, 130.6, 130.1, 130.0, 129.8, 128.6, 127.2, 127.0, 90.3, 63.6. IR(neat) 3348, 3227, 2943, 1700, 1655, 1598, 1367, 1284, 1133, 993, 858, 763, 715; HRMS (ESI-TOF) calcd for $C_{16}H_{13}ClNO_4$+: 318.0528 ($M+H^+$), found: 318.0516

3-(4-fluorophenyl)-3-hydroxy-2-methoxy-2,3-dihydroisoquinoline-1,4-dione (**2c**)[13] Following the general procedure, **2c** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 47%, 36 mg, white solid, mp 160-162 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.37 (d, J = 7.7 Hz, 1H), 7.95 (d, J = 7.7 Hz, 1H), 7.84 (t, J = 7.6 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.00 – 6.96 (m, 2H), 4.78 (s, 1H), 4.05 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 190.6, 163.2 (d, J = 249.4 Hz), 161.4, 135.9, 133.5, 132.3 (d, J = 2.9 Hz), 130.6, 128.9, 128.8, 128.5 (d, J = 8.7 Hz), 127.5, 116.0 (d, J = 22.0 Hz), 93.3, 65.4. IR(neat) 3271, 2934, 1701, 1648, 1508, 1284, 1230, 1135, 995, 873, 842, 694; HRMS (ESI-TOF) calcd for $C_{16}H_{13}FNO_4$+: 302.0823 (M+H$^+$), found: 302.0829

3-hydroxy-2-methoxy-3-(4-nitrophenyl)-2,3-dihydroisoquinoline-1,4-dione (**2d**) Following the general procedure, **2d** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 65%, 43mg, white solid, mp 136-138 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, J = 7.7 Hz, 1H), 8.16 – 8.14 (m, 2H), 7.96 (d, J = 7.7 Hz, 1H), 7.90 – 7.86 (m, 1H), 7.74 – 7.70 (m, 1H), 7.61 – 7.59 (m, 2H), 5.00 (s, 1H), 4.04 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 190.1, 161.3, 148.4, 143.5, 136.4, 133.8, 130.6, 129.0, 128.7, 127.8, 127.7, 124.0, 93.1, 65.5. IR(neat) 3276, 3077, 2920, 1706, 1665, 1523, 1347, 996, 837, 712; HRMS (ESI-TOF) calcd for $C_{16}H_{13}N_2O_6$+: 329.0768 (M+H$^+$), found: 329.0792

3-(3-fluorophenyl)-3-hydroxy-2-methoxy-2,3-dihydroisoquinoline-1,4-dione (**2e**) Following the general procedure, **2e** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 49%, 30 mg, white solid, mp 128-130 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.34 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 7.7 Hz, 1H), 7.84 – 7.80 (m, 1H), 7.70 – 7.66 (m, 1H), 7.26 – 7.10 (m, 3H), 6.99 – 6.99 (m, 1H), 5.14 (s, 1H), 4.02 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 190.4, 162.9 (d, J = 247.9 Hz), 161.2, 139.2 (d, J = 6.8 Hz), 135.9, 133.5, 130.6, 130.4 (d, J = 8.1 Hz), 129.0, 128.8, 127.5, 121.9 (d, J = 3.1 Hz), 116.5 (d, J = 21.2 Hz), 114.0 (d, J = 23.5 Hz), 93.2, 65.4. IR(neat) 3259, 2940, 1701, 1647, 1442, 1383, 1271, 1133, 1003, 827, 803, 717; HRMS (ESI-TOF) calcd for $C_{16}H_{13}FNO_4$+: 302.0823 (M+H$^+$), found: 302.0812

3-hydroxy-2-methoxy-3-(thiophen-2-yl)-2,3-dihydroisoquinoline-1,4-dione (**2f**) Following the general procedure, **2f** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 40%, 35 mg, white solid, mp 145-147 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.93 – 7,91 (m, 1H), 7.61 – 7.57 (m, 3H), 7.35 –7.32(m, 2H), 6.95 (t, J = 4.4 Hz, 1H), 5.96 (s, 1H), 4.01 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 186.5, 164.1, 141.2, 136.5, 135.8, 135.6, 133.7, 131.0, 129.6, 128.7, 124.2, 122.9, 89.8, 66.2. IR(neat) 3214, 2925, 1702, 1654, 1411, 1352, 1126, 1065, 1000, 821, 724; HRMS (ESI-TOF) calcd for $C_{14}H_{12}NO_4S$+: 290.0482 ($M+H^+$), found: 290.0480

3-hydroxy-2,7-dimethoxy-3-phenyl-2,3-dihydroisoquinoline-1,4-dione (**2g**)[13] Following the general procedure, **2g** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 48%, 30 mg, white solid, mp 148-151 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, J = 8.6 Hz, 1H), 7.82 (s, 1H), 7.40 – 7.39 (m, 2H), 7.28 (s, 3H), 7.13 (d, 1H), 4.81 (s, 1H), 4.04 (s, 3H), 3.96 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 189.5, 165.8, 161.1, 137.0, 133.5, 129.9, 129.2, 128.8, 126.2, 122.0, 120.6, 111.8, 93.5, 65.2, 56.1. IR(neat) 3261, 3053, 2943, 1686, 1639, 1594, 1448, 1282, 1132, 999, 874, 758; HRMS (ESI-TOF) calcd for $C_{17}H_{16}NO_5$+: 314.1023 ($M+H^+$), found: 314.1027

7-bromo-3-hydroxy-2-methoxy-3-phenyl-2,3-dihydroisoquinoline-1,4-dione (**2h**) Following the general procedure, **2h** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 43%, 31 mg, white solid, mp 175-177 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (s, 1H), 7.79 (s, 2H), 7.39 – 7.37 (m, 2H), 7.33 – 7.29 (m, 3H), 4.75 (s, 1H), 4.04 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 189.8, 160.2, 136.7, 136.2, 132.0, 131.8, 131.6, 129.6, 129.1, 128.9, 127.7, 126.3, 93.9, 65.4. IR(neat) 3277, 2955, 2924, 2854, 1700, 1641, 1581, 1351, 1020, 997, 875, 716; HRMS (ESI-TOF) calcd for $C_{16}H_{13}BrNO_4$+: 362.0022 ($M+H^+$), found: 362.0022

7-chloro-3-hydroxy-2-methoxy-3-phenyl-2,3-dihydroisoquinoline-1,4-dione (**2i**) Following the general procedure, **2i** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 47%, 30 mg, white solid, mp 163-165 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.30 (s, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.62 – 7.59 (m, 1H), 7.41 – 7.36 (m, 2H), 7.31 – 7.30 (m, 3H), 4.98 (s, 1H), 4.03 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 189.6, 160.3, 142.8, 136.2, 133.6, 132.2, 129.6, 129.0, 128.9, 128.8, 127.4, 126.3, 93.9, 65.4. IR(neat) 3287, 2943, 1701, 1646, 1586, 1354, 1136, 977, 875, 747, 718, 690; HRMS (ESI-TOF) calcd for $C_{16}H_{13}ClNO_4$+: 318.0528 ($M+H^+$), found: 318.0533

7-fluoro-3-hydroxy-2-methoxy-3-phenyl-2,3-dihydroisoquinoline-1,4-dione (**2j**)[13] Following the general procedure, **2j** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 49%, 24 mg, white solid, mp 133-135 °C;

^{1}H NMR (400 MHz,$CDCl_3$) *δ*: 8.00 – 7.95 (m, 2H), 7.39 – 7.38 (m, 2H), 7.35 – 7.28 (m, 4H), 4.94 (s, 1H), 4.04 – 4.01 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 189.2, 167.2 (d, *J* = 260.4 Hz), 160.2, 136.3, 134.0 (d, *J* = 9.6 Hz), 130.8 (d, *J* = 9.5 Hz), 129.6, 129.0, 126.3, 125.6, 121.0 (d, *J* = 22.7 Hz), 115.7 (d, *J* = 24.5 Hz), 93.9, 65.3. IR(neat) 3296, 3083, 2946, 1699, 1647, 1602, 1441, 1277, 1156, 1008, 763, 730; HRMS (ESI-TOF) calcd for $C_{16}H_{13}FNO_4$+: 302.0823 (M+H$^+$), found: 302.0822

3-(4-chlorophenyl)-3-hydroxy-2-methoxy-7-methyl-2,3-dihydroisoquinoline-1,4-dione (**2k**)[13] Following the general procedure,**2k** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 53%, 35 mg, white solid, mp 158-160 °C;

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.12 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.48 – 7.43 (m, 1H), 7.34 – 7.32 (m, 2H), 7.25 – 7.23 (m, 2H), 5.05 (s, 1H), 4.02 (s, 3H), 2.49 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 190.2, 161.5, 147.7, 135.5, 135.3, 134.3, 130.5, 129.1, 129.0, 127.9, 127.7, 126.5, 93.3, 65.3, 22.1. IR(neat) 3260, 2940, 1701, 1644, 1599, 1350, 1288, 1160, 1006, 877,826, 742; HRMS (ESI-TOF) calcd for $C_{17}H_{15}ClNO_4$+: 332.0684 (M+H$^+$), found: 332.0648

7-chloro-3-(4-chlorophenyl)-3-hydroxy-2-methoxy-2,3-dihydroisoquinoline-1,4-dione (**2l**) Following the general procedure, **2l** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 61%, 43 mg, white solid, mp 147-149 °C;

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.33 – 8.24 (m, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.66 – 7.61 (m, 1H), 7.34 – 7.26 (m, 4H), 4.92 (s, 1H), 4.02 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 189.4, 160.2, 143.1, 135.9, 134.8, 133.8, 132.0, 129.2, 129.1, 128.9, 127.8, 127.2, 93.4, 65.4. IR(neat) 3314, 2940, 1706, 1644, 1587, 1347, 1139, 1000, 877, 824, 742; HRMS (ESI-TOF) calcd for $C_{16}H_{12}Cl_2NO_4$+: 352.0138 (M+H$^+$), found: 352.0118

2-(benzyloxy)-3-hydroxy-3-phenyl-2,3-dihydroisoquinoline-1,4-dione (**2m**) Following the general procedure, **2m** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 50%, 36 mg, white solid, mp 115-117 °C;

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.39 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 7.7 Hz, 1H), 7.83 (t, *J* = 7.6 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.48 – 7.41 (m, 4H), 7.33 – 7.27 (m, 6H), 5.22 (s, 2H), 4.63 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 190.8, 161.7,

136.7, 135.7, 134.9, 133.4, 130.8, 129.6, 129.3, 129.2, 128.9, 128.7 (2C), 128.3, 127.5, 126.4, 93.8, 79.6. IR(neat) 3309, 3053, 2955, 2925, 1698, 1646, 1447, 1362, 1284, 976, 757, 693; HRMS (ESI-TOF) calcd for $C_{22}H_{18}NO_4$+: 360.1230 ($M+H^+$), found: 360.1246

3-hydroxy-2-methoxy-3-(naphthalen-1-yl)-2,3-dihydroisoquinoline-1,4-dione (**2o**) and 3-(1-naphthoyl)-3-hydroxy-2-methoxyisoindolin-1-one (**2o'**) Following the general procedure, **2o** and **2o'** was purified by silica gel chromatography (EA/PE = 1/5). Total yield 71% (**2o:2o**' = 1:2), 47 mg, white solid.[13]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 7.7 Hz, 0.7H), 8.00 (d, *J* = 7.8 Hz, 1.2H), 7.89 – 7.78 (m, 5.2 H), 7.75 – 7.64 (m, 3 H), 7.57 – 7.34 (m, 8.2 H), 7.25 – 7.16 (m, 2H), 6.04 (s, 1.2H), 4.86 (s, 0.6H), 4.12 (s, 3H), 3.53 (s, 1.6H). ^{13}C{^{1}H} NMR (100 MHz, CDCl3) δ: 199.1, 189.0, 164.4, 162.6, 139.6, 135.4, 134.2, 133.6, 133.5, 133.3, 132.5, 131.6, 130.8, 130.7, 130.1, 129.9, 129.8, 129.1, 128.7, 128.4, 127.6, 127.6, 126.6, 126.4, 126.3, 125.7, 125.1, 125.0, 124.8, 124.4, 124.1, 123.9, 122.4, 91.8, 66.5, 64.5. IR(neat) 3304, 2940, 1705, 1652, 1593, 1358, 1283, 1081, 1008, 870, 796, 723; HRMS (ESI-TOF) calcd for $C_{20}H_{16}NO_4^+$: 334.1074 ($M+H^+$), found: 334.1076

2-methoxy-3-phenylisoquinolin-1(2*H*)-one (**3a**)[4] Following the general procedure, **3a** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 82%, 41 mg, white solid, mp 108-110 °C;

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.44 (d, *J* = 8.0 Hz, 1H), 7.65 – 7.59 (m, 3H), 7.53 – 7.42 (m, 5H), 6.45 (s, 1H), 3.67 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 158.6, 142.0, 135.7, 132.5, 132.4, 129.2 (2C), 128.2, 127.7, 126.6, 126.2, 126.2, 106.7, 63.4. IR(neat) 3056, 2985, 2937, 1656, 1624, 1603, 1480, 1173, 985, 835, 782, 710, 686

7-fluoro-2-methoxy-3-phenylisoquinolin-1(2*H*)-one (**3b**) Following the general procedure, **3b** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 67%, 36 mg, white solid, mp 128-130 °C;

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.11 – 8.05 (m, 1H), 7.61 – 7.58 (m, 2H), 7.54 – 7.50 (m, 1H), 7.46 – 7.44 (m, 3H), 7.39 – 7.34 (m, 1.3 Hz, 1H), 6.45 (s, 1H), 3.67 (d, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 161.2 (d, *J* = 248.3 Hz), 157.8 (d, *J* = 3.5 Hz), 141.3

(d, J = 2.9 Hz), 132.2, 129.3, 129.2, 128.6 (d, J = 8.0 Hz), 128.2, 127.8 (d, J = 8.2 Hz), 125.9, 121.4 (d, J = 23.8 Hz), 112.8 (d, J = 23.1 Hz), 106.1, 63.4. IR(neat) 3065, 2982, 2931, 1655, 1626, 1596, 1492, 1245, 884, 790, 693; HRMS (ESI-TOF) calcd for $C_{16}H_{13}FNO_2^+$: 270.0925 ($M+H^+$), found: 270.0929

2,7-dimethoxy-3-phenylisoquinolin-1(2*H*)-one (**3c**) Following the general procedure, **3c** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 82%, 46 mg, white solid, mp 146-148 °C;

^1H NMR (400 MHz, $CDCl_3$) δ: 7.83 (d, J = 2.1 Hz, 1H), 7.62 – 7.57 (m, 2H), 7.45 – 7.43 (m, 4H), 7.26 – 7.23 (m, 1H), 6.43 (s, 1H), 3.92 (s, 3H), 3.67 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 158.6, 158.3, 139.6, 132.6, 129.8, 129.3, 128.9, 128.1, 127.9, 127.5, 123.3, 107.3, 106.6, 63.3, 55.7. IR(neat) 2391, 2845, 1650, 1633, 1573, 1495, 1363, 1256, 1008, 852,788; HRMS (ESI-TOF) calcd for $C_{17}H_{16}NO_3$+: 282.1125 ($M+H^+$), found: 282.1117

3-(4-chlorophenyl)-2-methoxy-7-methylisoquinolin-1(2*H*)-one (**3d**) Following the general procedure, **3d** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 75%, 45 mg, white solid, mp 137-139 °C;

^1H NMR (400 MHz, $CDCl_3$) δ: 8.22 (s, 1H), 7.53 (d, J = 7.8 Hz, 2H), 7.46 – 7.38 (m, 4H), 6.40 (s, 1H), 3.65 (s, 3H), 2.46 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 158.5, 139.8, 137.1, 135.2, 134.1, 133.2, 131.0, 130.5, 128.4, 127.3, 126.2, 126.2, 106.8, 63.3, 21.4. IR(neat) 3086, 2982, 2931, 1651, 1608, 1496, 1340, 1090, 989, 861, 834, 691; HRMS (ESI-TOF) calcd for $C_{17}H_{15}ClNO_2^+$: 300.0786 ($M+H^+$), found: 300.0740

7-bromo-2-methoxy-3-(4-methoxyphenyl)isoquinolin-1(2*H*)-one (**3e**) Following the general procedure, **3e** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 74%, 53 mg, white solid, mp 148-150 °C;

^1H NMR (400 MHz, $CDCl_3$) δ: 8.55 (s, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.5 Hz, 1H), 6.96 (d, J = 8.5 Hz, 2H), 6.38 (s, 1H), 3.85 (s, 3H), 3.66 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 160.4, 157.6, 142.4, 135.5, 134.5, 130.6, 130.2, 127.7, 127.3, 124.4, 120.1, 113.7, 105.5, 63.3, 55.3. IR(neat) 2968, 2923, 1666, 1617, 1606, 1505, 1238, 1177, 1026, 859, 847; HRMS (ESI-TOF) calcd for $C_{17}H_{15}BrNO_3^+$: 360.0230 ($M+H^+$), found: 360.0252

7-chloro-2-methoxy-3-(4-methoxyphenyl)isoquinolin-1(2*H*)-one (**3f**) Following the general procedure, **3f** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 82%, 52 mg, white solid, mp 133-135 °C;

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.37 (d, *J* = 2.0 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 3H), 7.42 (d, *J* = 8.5 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.38 (s, 1H), 3.85 (s, 3H), 3.65 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 160.4, 157.7, 142.2, 134.2, 132.8, 132.3, 130.6, 127.7, 127.1, 127.0, 124.4, 113.6, 105.5, 63.3, 55.3. IR(neat) 2970,2925, 1667, 1616, 1606, 1505, 1476, 1238, 1177, 1026, 848; HRMS (ESI-TOF) calcd for $C_{17}H_{15}ClNO_3$+: 316.0735 ($M+H^+$), found: 316.0739

2-methoxy-3-phenylbenzo[g]isoquinolin-1(2*H*)-one (**3h**) Following the general procedure, **3h** was purified by silica gel chromatography (EA/PE = 1/15). Yield: 56%, 34 mg, white solid, mp 155-157 °C;

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.38 (t, *J* = 8.7 Hz, 2H), 7.89 (d, *J* = 7.7 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.69 – 7.57 (m, 4H), 7.49 – 7.48 (m, 3H), 7.21 (s, 1H), 3.73 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 158.5, 142.8, 134.8, 134.2, 132.6, 129.3 (2C), 128.8, 128.4, 128.3, 128.2, 127.2, 126.8, 123.9, 123.7, 123.5, 102.4, 63.5. IR(neat) 3059, 2988, 2940, 1650, 1619, 1607, 1435, 1366, 1072, 989, 819, 765, 710; HRMS (ESI-TOF) calcd for $C_{20}H_{16}NO_2$+: 302.1176 ($M+H^+$), found: 302.1170

2-(allyloxy)-3-phenylisoquinolin-1(2*H*)-one (**3i**) Following the general procedure, **3i** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 80%, 44 mg, white solid, mp 100-102 °C;

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.45 (d, *J* = 8.0 Hz, 1H), 7.66 – 7.58 (m, 3H), 7.53 – 7.43 (m, 5H), 6.46 (s, 1H), 5.66 – 5.54 (m, 1H), 5.07 (t, *J* = 13.7 Hz, 2H), 4.39 (d, *J* = 6.4 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.9, 142.6, 135.7, 132.8, 132.4, 130.6, 129.5, 129.1, 128.1, 127.7, 126.6, 126.2, 121.6, 106.4, 76.8. IR(neat) 3062, 2920, 2863, 1652, 1618, 1482, 1176, 980, 910, 756, 699, 687; HRMS (ESI-TOF) calcd for $C_{18}H_{16}NO_2$+: 278.1176 ($M+H^+$), found: 278.1178

2-(benzyloxy)-3-phenylisoquinolin-1(2*H*)-one (**3j**) Following the general procedure, **3j** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 60%, 39 mg, white solid, mp 114-116 °C;

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.51 (d, *J* = 8.0 Hz, 1H), 7.68 – 7.64 (m, 1H), 7.55 – 7.40 (m, 7H), 7.28 – 7.24 (m, 1H), 7.21 – 7.17 (m, 2H), 6.97 – 6.95 (m, 2H), 6.46 (s, 1H), 4.88 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 158.8, 142.7, 135.8, 133.3,

132.8, 132.4, 130.0, 129.6, 129.1, 128.8, 128.3, 128.0, 127.7, 126.6, 126.3, 126.2, 106.4, 77.6. IR(neat) 3059, 3024, 2922, 1650, 1625, 1480, 1173, 966, 769, 751, 718, 688; HRMS (ESI-TOF) calcd for $C_{22}H_{18}NO_2$+: 328.1332 ($M+H^+$), found: 328.1330

2-methoxy-3-(4-methoxyphenyl)isoquinolin-1(2*H*)-one (**3k**)[1] Following the general procedure, **3k** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 79%, 44 mg, white solid, mp 130-132 °C;

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.43 (d, *J* = 7.4 Hz, 1H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.43 (t, *J* = 6.8 Hz, 1H), 6.95 (d, *J* = 7.9 Hz, 2H), 6.40 (s, 1H), 3.85 (s, 3H), 3.67 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 160.3, 141.8, 135.9, 132.4, 130.6, 127.7, 126.4, 126.1, 124.8, 113.6, 106.3, 63.2, 55.3. IR(neat) 3068, 2976, 1655, 1620, 1512, 1292, 1258, 1176, 990, 829, 753; HRMS (ESI-TOF) calcd for $C_{17}H_{16}NO_3$+: 282.1125 ($M+H^+$), found: 282.1123

2-methoxy-3-(2-methoxyphenyl)isoquinolin-1(2*H*)-one (**3l**) Following the general procedure, **3l** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 90%, 51 mg, white solid, mp 150-152 °C;

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.45 (d, *J* = 7.9 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.50 – 7.41 (m, 3H), 7.33 (d, *J* = 7.1 Hz, 1H), 7.04 – 6.95 (m, 2H), 6.39 (s, 1H), 3.78 (s, 3H), 3.72 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 158.6, 157.6, 139.9, 135.9, 132.2, 130.9, 130.7, 127.6, 126.5, 126.4, 126.1, 122.1, 120.2, 110.8, 106.7, 63.6, 55.6. IR(neat) 3059, 2925, 1647, 1621, 1593, 1494, 1255, 1018, 993, 765, 752; HRMS (ESI-TOF) calcd for $C_{17}H_{16}NO_3$+: 282.1125 ($M+H^+$), found: 282.1113

2-methoxy-3-(p-tolyl)isoquinolin-1(2*H*)-one (**3m**) Following the general procedure, **3m** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 73%, 39 mg, white solid, mp 132-134 °C;

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.44 (d, *J* = 8.1 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.51 (d, *J* = 8.0 Hz, 3H), 7.48 – 7.44 (m, 1H), 7.28 – 7.23 (m, 2H), 6.44 (s, 1H), 3.68 (s, 3H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 158.7, 142.1, 139.3, 135.8,132.4, 129.6, 129.1, 128.9, 127.7, 126.4, 126.1, 125.7, 106.5, 63.3, 21.3. IR(neat) 3053, 3027, 2934, 1657, 1619, 1510, 1435, 1172, 986, 828, 810, 689; HRMS (ESI-TOF) calcd for $C_{17}H_{16}NO_2$+: 266.1176 ($M+H^+$), found: 266.1178

3-(4-fluorophenyl)-2-methoxyisoquinolin-1(2*H*)-one (**3n**) Following the general procedure, **3n** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 67%, 36 mg, white solid, mp 131-133 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (d, J = 8.1 Hz, 1H), 7.67 – 7.59 (m, 3H), 7.53 – 7.46 (m, 2H), 7.17 – 7.12 (m, 2H), 6.44 (s, 1H), 3.68 (d, J = 1.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 163.2 (d, J = 249.7 Hz), 158.6, 141.0, 135.6, 132.5, 131.2 (d, J = 8.4 Hz), 128.5 (d, J = 3.5 Hz), 127.8, 126.7, 126.3, 126.2, 115.3 (d, J = 21.8 Hz), 106.7, 63.4. IR(neat) 3053, 2997, 2934, 1656, 1504, 1337, 1218, 1165, 757, 687, 614; HRMS (ESI-TOF) calcd for $C_{16}H_{13}FNO_2$+: 270.0925 (M+H$^+$), found: 270.0921

3-(2-chlorophenyl)-2-methoxyisoquinolin-1(2*H*)-one (**3o**) Following the general procedure, **3o** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 87%, 50 mg, white solid, mp 153-155 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.48 (d, J = 8.0 Hz, 1H), 7.67 – 7.64 (m, 1H), 7.55 – 7.48 (m, 3H), 7.47 – 7.39 (m, 2H), 7.37 – 7.33 (m, 1H), 6.41 (s, 1H), 3.75 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 158.4, 139.4, 135.4, 134.3, 132.5, 131.9, 131.3, 130.6, 129.6, 127.7, 126.9, 126.8, 126.4, 126.3, 107.1, 63.7. IR(neat) 3062, 2985, 2937, 1657, 1626, 1430, 1381, 1251, 1175, 990, 826, 769; HRMS (ESI-TOF) calcd for $C_{16}H_{13}ClNO_2$+: 286.0629 (M+H$^+$), found: 286.0625

2-methoxy-3-(thiophen-2-yl)isoquinolin-1(2*H*)-one (**3p**) Following the general procedure, **3p** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 49%, 25 mg, yellow solid, mp 100-102 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.42 (d, J = 8.0 Hz, 1H), 7.65 – 7.62 (m, 1H), 7.57 (d, J = 3.3 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.48 – 7.45 (m, 2H), 7.14 – 7.10 (m, 1H), 6.74 (s, 1H), 3.90 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 158.7, 135.6, 135.5, 132.7, 132.5, 128.9, 128.5, 127.7, 127.2, 126.7, 126.2, 125.8, 105.5, 63.6. IR(neat) 3071, 2931, 1664, 1611, 1554, 1334, 1265, 1170, 985, 706, 685; HRMS (ESI) calcd for $C_{14}H_{12}NO_2S$+: 258.0583 (M+H$^+$), found: 258.0587

2-methoxy-3-(naphthalen-2-yl)isoquinolin-1(2*H*)-one (**3q**) Following the general procedure, **3q** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 83%, 50 mg, white solid, mp 150-152 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.70 –7.66 (m, 1H), 7.61 – 7.59 (m, 1H), 7.57 – 7.52 (m, 4H), 7.50 – 7.44 (m, 1H), 6.52 (s, 1H), 3.64 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 158.6, 141.0, 135.8, 133.1, 132.5, 132.1, 130.5, 129.9, 128.2, 127.8, 127.7, 126.8, 126.8, 126.7,

126.3, 126.2, 125.7, 124.8, 107.6, 64.1. IR(neat) 3000, 2934, 1657, 1619, 1595, 1437, 1375, 1170, 981, 831, 804, 772; HRMS (ESI-TOF) calcd for $C_{20}H_{16}NO_2$+: 302.1176 ($M+H^+$), found: 302.1186

3-(cyclohex-1-en-1-yl)-2-methoxyisoquinolin-1(2*H*)-one (**3r**) Following the general procedure, **3r** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 81%, 41 mg, white solid, mp 110-112 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (d, J = 8.1 Hz, 1H), 7.61 – 7.56 (m, 1H), 7.46 – 7.38 (m, 2H), 6.28 (s, 1H), 6.05 – 6.01 (m, 1H), 3.94 (s, 3H), 2.35 (s, 2H), 2.22 – 2.17 (m, 2H), 1.76 – 1.65 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 158.7, 145.1, 136.2, 133.1, 132.2, 130.0, 127.6, 126.0 (2C), 125.9, 104.3, 64.0, 28.6, 25.4, 22.5, 21.8. IR(neat) 2994, 2934, 2920, 1661, 1619, 1598, 1429, 1170, 995, 810, 758, 688; HRMS (ESI-TOF) calcd for $C_{16}H_{18}NO_2$+: 256.1332 ($M+H^+$), found: 256.1324

3-cyclopropyl-2-methoxyisoquinolin-1(2*H*)-one (**3s**) Following the general procedure, **3s** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 58%, 29 mg, white solid, mp 100-102 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.37 – 8.35 (m, 1H), 7.58 –7.54 (m, 1H), 7.40 – 7.36 (m, 2H), 6.05 (s, 1H), 4.13 (d, J = 1.3 Hz, 3H), 2.22 – 2.15 (m, 1H), 1.07 – 1.01 (m, 2H), 0.82 – 0.78 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 158.9, 144.6, 135.9, 132.1, 127.5, 125.8, 125.6, 125.5, 100.5, 63.7, 10.5, 7.0. IR(neat) 3074, 2937, 1651, 1621, 1482, 1387, 1253, 1033, 975, 845, 756; HRMS (ESI-TOF) calcd for $C_{13}H_{14}NO_2$+: 216.1019 ($M+H^+$), found: 216.1012

3-butyl-2-methoxyisoquinolin-1(2*H*)-one (**3t**) Following the general procedure, **3t** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 60%, 28 mg, white solid, mp 92-94 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ:8.35 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 7.4 Hz, 1H), 7.42 – 7.35 (m, 2H), 6.23 (s, 1H), 4.05 (s, 3H), 2.68 (t, J = 7.6 Hz, 2H), 1.70 – 1.63 (m, 2H), 1.46 – 1.36 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 158.9, 143.1, 135.9, 132.2, 127.4, 125.7, 125.6, 125.4, 103.4, 63.7, 30.2 (2C), 22.3, 13.8. IR(neat) 2958, 2931, 2872, 2857, 1660, 1625, 1601, 1485, 1170, 754, 682; HRMS (ESI-TOF) calcd for $C_{14}H_{18}NO_2$+: 232.1332 ($M+H^+$), found: 232.1340

2-(1-(2-methoxy-1-oxo-1,2-dihydroisoquinolin-3-yl)propan-2-yl)-4-methylbenzenesulfonic acid (**3u**) Following the general procedure, **3u** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 53%, 41 mg, white solid, mp 110-112 °C;

^{1}H NMR (400 MHz, CDCl3) δ: 7.79 (d, J = 7.9 Hz, 1H), 7.63 – 7.61 (m, 2H), 7.40 – 7.36 (m, 1H), 7.29 – 7.23 (m, 3H), 7.14 (d, J = 7.7 Hz, 1H), 6.25 (s, 1H), 3.65 (d, J = 1.3 Hz, 3H), 2.42 (s, 3H), 1.71 (d, J = 1.0 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 150.2, 147.2, 144.5, 132.7, 131.0, 130.3, 130.1, 129.3, 128.7, 125.9, 123.7, 121.0, 106.2, 66.6, 62.2, 21.6, 20.0. IR(neat) 2982, 2937, 2809, 1624, 1454, 1287, 1151, 1120, 1058, 818, 773, 662, 600, 536; HRMS (ESI) calcd for $C_{20}H_{22}NO_5S$+: 388.1213 ($M+H^+$), found: 388.1213

2-methoxy-3-(methoxymethyl)isoquinolin-1(2*H*)-one (**3v**) Following the general procedure, **3v** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 50%, 22 mg, yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.39 (d, *J* = 8.1 Hz, 1H), 7.63 – 7.60 (m, 1H), 7.50 – 7.43 (m, 2H), 6.49 (s, 1H), 4.50 (s, 2H), 4.11 (s, 3H), 3.49 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 158.8, 138.4, 135.4, 132.3, 127.5, 126.6, 126.5, 126.1, 104.8, 69.0, 64.2, 58.6. IR(neat) 3065, 2940, 2818, 1666, 1630, 1599, 1167, 1102, 980, 819, 751, 682; HRMS (ESI) calcd for $C_{12}H_{14}NO_3$+: 220.0968 ($M+H^+$), found: 220.0962

3-((allyloxy)methyl)-2-methoxyisoquinolin-1(2*H*)-one (**3w**) Following the general procedure, **3w** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 42%, 21 mg, yellow oil;

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.40 (d, *J* = 8.0 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.52 – 7.43 (m, 2H), 6.51 (s, 1H), 6.00 – 5.91 (m, 1H), 5.35 (d, *J* = 17.2 Hz, 1H), 5.25 (d, *J* = 10.4 Hz, 1H), 4.56 (s, 2H), 4.14 (d, *J* = 5.1 Hz, 2H), 4.12 (s, 3H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) *δ*: 158.8, 138.6, 135.4, 133.8, 132.3, 127.5, 126.6, 126.5, 126.1, 117.9, 104.9, 71.7, 66.5, 64.3. IR(neat) 3065, 2934, 2863, 1668, 1631, 1601, 1408, 1170, 1084, 977, 828, 754, 688; HRMS (ESI-TOF) calcd for $C_{14}H_{16}NO_3$+: 246.1125 ($M+H^+$), found: 246.1120

3-(hydroxymethyl)-2-methoxyisoquinolin-1(2*H*)-one (**3x**) Following the general procedure, **3x** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 63%, 23 mg, white solid, mp 99-101 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, J = 7.5 Hz, 1H), 7.38 – 7.34 (m, 1H), 7.29 – 7.22 (m, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.09 (s, 1H), 4.36 (s, 2H), 3.94 (s, 3H), 3.05 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 152.9, 148.6, 131.1, 130.5, 128.1, 125.3, 124.0, 121.0, 102.1, 62.7, 61.4. IR(neat) 3387,3030, 2955, 2928, 1670, 1624, 1595, 1458, 1326, 1158, 1057, 1006, 977, 907, 649; HRMS (ESI-TOF) calcd for $C_{11}H_{12}NO_3$+: 206.0812 ($M+H^+$), found: 206.0818

2-methoxy-3-((((13S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-3-yl)oxy)methyl)isoquinolin-1(2*H*)-one (**3y**) Following the general procedure, **3y** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 51%, 47 mg, white solid, mp 160-162 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.42 (d, J = 8.0 Hz, 1H), 7.66 – 7.62 (m, 1H), 7.52 – 7.47 (m, 2H), 7.24 (d, J = 8.5 Hz, 1H), 6.83 – 6.81 (m, 1H), 6.75 (s, 1H), 6.61 (s, 1H), 5.07 (s, 2H), 4.17 (s, 3H), 2.94 – 2.88 (m, 2H), 2.53 – 2.46 (m, 1H), 2.42 – 2.38 (m, 1H), 2.28 – 2.23 (m, 1H), 2.14 – 1.95 (m, 4H), 1.62 – 1.43 (m, 6H), 0.90 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 220.9, 158.8, 155.9, 138.1, 137.6, 135.3, 133.1, 132.4, 127.6, 126.9, 126.7, 126.6, 126.3, 114.7, 112.2, 105.4, 64.7, 64.5, 50.3, 47.9, 43.9, 38.2, 35.8, 31.5, 29.6, 26.4, 25.8, 21.5, 13.8. IR(neat) 3015, 2929, 2851, 1735, 1659, 1626, 1498, 1354, 1260, 1075, 977, 823, 760, 689; HRMS (ESI-TOF) calcd for $C_{29}H_{32}NO_4$+: 458.2326 ($M+H^+$), found: 458.2322

3-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl)oxy)methyl)-2-methoxyisoquinolin-1(2*H*)-one (**3z**) Following the general procedure, **3z** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 53%, 61 mg, white solid, mp 146-148 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, J = 8.0 Hz, 1H), 7.62 – 7.61 (m, 1H), 7.51 – 7.42 (m, 2H), 6.52 (s, 1H), 5.37 – 5.36 (m, 1H), 4.59 (s, 2H), 4.14 (s, 3H), 3.42 – 3.34 (m, 1H), 2.47 – 2.41 (m, 1H), 2.35 – 2.27 (m, 1H), 2.02 – 1.94 (m, 3H), 1.91 – 1.76 (m, 3H), 1.61 – 1.41 (m, 8H), 1.36 – 1.29 (m, 3H), 1.26 – 1.20 (m, 2H), 1.14 – 1.05 (m, 6H), 1.01 (s, 3H), 0.98 – 0.96 (m, 1H), 0.89 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 1.5 Hz, 3H), 0.83 (d, J = 1.5 Hz, 3H), 0.66 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 158.8, 140.3, 139.4, 135.5, 132.3, 127.5, 126.5, 126.5, 126.1 122.1, 104.6, 79.5, 64.5, 64.3, 56.7, 56.1, 50.1, 42.2, 39.7, 39.5,

39.0, 37.1, 36.8, 36.1, 35.7, 31.9, 31.8, 28.3, 28.2, 28.0, 24.2, 23.8, 22.8, 22.5, 21.0, 19.3, 18.7, 11.8. IR(neat) 3065, 2935, 2858, 1656, 1632, 1097, 757, 685; HRMS (ESI-TOF) calcd for $C_{38}H_{56}NO_3$+: 574.4255 ($M+H^+$), found: 574.4229

3-phenylisoquinolin-1(2*H*)-one (**4**)[4c] Following the general procedure, **4** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 90%, 40 mg, white solid, mp 175-177 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.06 (s, 1H), 8.41 (d, J = 7.9 Hz, 1H), 7.83 – 7.81 (m, 2H), 7.67 (t, J = 7.4 Hz, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.56 – 7.45 (m, 4H), 6.81 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 164.2, 139.7, 138.3, 134.2, 132.8, 129.4, 129.1, 127.4, 126.5 (2C), 126.3, 124.9, 104.4. IR(neat) 3169, 3053, 2994, 1666, 1352, 1149, 867, 762, 690;

ASSOCIATED CONTENT

Supporting Information

Copies of NMR Spectra for compounds **1**, **2**, **3**, and **4** are available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* E-mail: qiuguanyinsheng@mail.zjxu.edu.cn (G. Qiu);

xwl2000zsu@163.com (X.W);

zhouhw@zju.edu.cn (H. Zhou)

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This work was supported by the Natural Science Foundation of China (Nos: 21571058, 21502069 and 21772067), the Natural Science Foundation of Zhejiang (LY19B020004).

REFERENCES

1. For selected reviews, see: (a) Qiu, G.; Wu, J. Generation of *N*-Heterocycles via Tandem Reactions of *N'*-(2-Alkynylbenzylidene)hydrazides. *Chem. Record*. **2016**, *16*, 19-34; (b) Qiu, G.; Kuang, Y.; Wu, J. *N*-Imide Ylide-Based Reactions: C-H Functionalization, Nucleophilic Addition and Cycloaddition. *Adv. Synth. Catal.* **2014**, *356*, 3483-3504; (c) Wu, X.-F. Non-Redox-Metal-Catalyzed Redox Reactions: Zinc Catalysts. *Chem. Asian J.* **2012**, *7*, 2502-2509.

2. For a review, see: (a) Mackiewicz, P.; Furstoss, R. Radicaux amidyl: structure et reactivite. *Tetrahedron* **1978**, 34, 3241-3260; for selected examples, see: (b) Yu, Y.-Y.; Fu, Y.; Xie, M.; Liu, L.; Guo, Q.-F. Controlling Regioselectivity in Cyclization of Unsaturated Amidyl Radicals: 5-*Exo* Versus 6-*Endo*. *J. Org. Chem.* **2007**, *72*, 8025-8032; (c) Yuan, X.; Liu, K.; Li, C. Development of Highly Regioselective Amidyl Radical Cyclization Based on Lone Pair−Lone Pair Repulsion. *J. Org. Chem.* **2008**, *73*, 6166-6171; (d) Chen, Q.; Shen, M.; Tang, Y.; Li, C. Cyclization or Hydrogen Migration: Theoretical Study and Experimental Evidence on the Reactivities of Unsaturated Amidyl Radicals. *Org. Lett.* **2005**, *7*, 1625-1627; (e) Gagosz, F.; Moutrille, C.; Zard, S. A New Tin-Free Source of Amidyl Radicals. *Org. Lett.* **2002**, *4*, 2707-2709.

3. For selected reviews, see: (a) Chen, J.-R.; Hu, X.-Q.; Lu, L-Q.; Xiao, W.-J. Visible light photoredox-controlled reactions of *N*-radicals and radical ions. *Chem. Soc. Rev.* **2016**, *45*, 2044-2056; (b) Minozzi, M.; Nanni, D.; Spagnolo, P. From Azides to Nitrogen-Centered Radicals: Applications of Azide Radical Chemistry to Organic Synthesis. *Chem. Eur. J.* **2009**, *15*, 7830-7840; (c) Zhao, Y.; Xia, W. Recent advances in radical-based C–*N* bond formation viaphoto-/electrochemistry. *Chem. Soc. Rev.* **2018**, *47*, 2591-2608; (d) Jiang, H.; Studer, A. Iminyl-Radicals by Oxidation of α-Imino-oxy Acids: Photoredox-Neutral Alkene Carboimination for the Synthesis of Pyrrolines. *Angew. Chem. Int. Ed.* **2017**, *56*, 12273-12276; (e) Hioe, J.; Sakic, D.; Vrcek, V. The stability of nitrogen-centered radicals. *Org. Biomol. Chem*. **2015**, *13*, 157-169; for examples, see: (f) Han, B.; Yang, X.; Fang, R.; Yu, W.; Wang, C.; Duan, X.; Liu, S. Oxime radical promoted dioxygenation, oxyamination, and diamination of alkenes: synthesis of isoxazolines and cyclic nitrones. *Angew. Chem. Int. Ed.* **2012**, *51*, 8816-8820; (g) Duan, X.; Yang, X.;

Fang, R.; Peng, X.; Yu, W.; Han, B. Hydrazone Radical Promoted Vicinal Difunctionalization of Alkenes and Trifunctionalization of Allyls: Synthesis of Pyrazolines and Tetrahydropyridazines. *J. Org. Chem*. **2013**, *78*, 10692−10704; (h) Duan, X.; Zhou, N.; Fang, R.; Yang, X.; Yu, W.; Han, B. Transition from π Radicals to σ Radicals: Substituent-Tuned Cyclization of Hydrazonyl Radicals. *Angew. Chem. Int. Ed*. **2014**, *53*, 3158 –3162; (i) Liu, R.; Wei, D.; Han, B.; Yu, W. Copper-Catalyzed Oxidative Oxyamination/Diamination of Internal Alkenes of Unsaturated Oximes with Simple Amines. *ACS Catal*. **2016**, *6*, 6525−6530

4. (a) Bianchi, G.; Chiarini, M.; Marinelli, F.; Rossi, L.; Arcadi, A. Product Selectivity Control in the Heteroannulation of o-(1-Alkynyl)benzamides. *Adv. Synth. Catal.* **2010**, *352*, 136-142; (b) Sakai, N.; Annaka, K.; Fujita, A.; Sato, A.; Konakahara, T. $InBr_3$-Promoted Divergent Approach to Polysubstituted Indoles and Quinolines from 2-Ethynylanilines: Switch from an Intramolecular Cyclization to an Intermolecular Dimerization by a Type of Terminal Substituent Group. *J. Org. Chem.* **2008**, *73*, 4160-4165; (c) Ding, D.; Mou, T.; Xue, J.; Jiang, X. Access to divergent benzo-heterocycles via a catalyst-dependent strategy in the controllable cyclization of o-alkynyl-*N*-methoxyl-benzamides. *Chem. Commun.* **2017**, *53*, 5279-5282; (d) Chary, R. G.; Dhananjaya, G.; Prasad, K. V.; Vaishaly, S.; Ganesh, Y. S. S.; Dulla, B.; Kumar, K. S.; M. Pal. A simple access to *N*-(un)substituted isoquinolin-1(2*H*)-ones: unusual formation of regioisomeric isoquinolin-1(4*H*)-ones. *Chem. Commun.* **2014**, *50*, 6797-6800; (e) Yang, Y.; Liu, Y.; Zhu, R.; Liu, C.; Zhang, D. Theoretical Insight into the Mechanism and Origin of Divergent Reactivity in Synthesis of Benzo-Heterocycles from *o*-Alkynylbenzamides Catalyzed by Gold and Platinum Complexes. *J. Org. Chem.* **2019**, *84*, 9705-9713; (f) Sakthivel, K.; Srinivasan, K. Synthesis of 3,3-disubstituted-2,3-dihydroazanaphthoquinones simultaneous alkyne oxidation and nitrile hydration of 2-alkynylarenenitriles. *Org. Biomol. Chem*. **2015**, *46*, 6440-6446.

5. For selected examples, see: (a) Li, D. Y.; Shi, K. J.; Mao, X. F.; Zhao, Z. L.; Wu, X. Y.; Liu, P. N. Selective cyclization of alkynols and alkynylamines catalyzed by potassium tert-butoxide. *Tetrahedron*, **2014**, *70*, 7022-7031; (b) Kanazawa, C.; Terada, M. Dichotomous Control of E/Z-Geometry in Intramolecular Cyclization of o-Alkynylbenzamide Derivatives Catalyzed by Organic Superbase P4-tBu in the Presence/Absence of Water. *Asian. J. Chem*., **2009**, *4*, 1668-1672; (c) Brahmchari, D.; Akhilesh, A. K.; Mehta, S. Regio- and Stereoselective Synthesis of Isoindolin-1-ones through BuLi-Mediated Iodoaminocyclization of 2-(1-Alkynyl)benzamides. *J. Org.*

Chem. **2018**, *83*, 3339-3347; (d) Bantreil, X.; Bourderioux, A.; Mateo, P.; Hagerman, C. E.; Selkti, M.; Brachet, E.; Belmont, P. Phosphine-Triggered Selectivity Switch in Silver-Catalyzed *o*-Alkynylbenzohydroxamic Acid Cycloisomerizations.*Org. Lett*. **2016**, *18*, 4814-4817; (e) Jitunsa, M.; Ueda, M.; Miyata, O. Copper(II)Chloride-Mediated Cyclization Reaction of *N*-Alkoxy-*ortho*-alkynylbenzamides. *Org. Lett*. **2011**, *13*, 518-521.

6. Selected examples, see: (a) Madich, Y.; Alvarez, R.; Aurrecoechea, J. M. Palladium-Catalyzed 6-endo-Selective Oxycyclization–Alkene Addition Cascades of ortho-Alkynylarylcarboxamides and α,β-Unsaturated Carbonyl Compounds. *Eur. J. Org. Chem.*, **2015**, 6298-6305; (b) Bian, M.; Yao, W.; Ding, H.; Ma, C. Highly Efficient Access to Iminoisocoumarins and α-Iminopyrones via AgOTf-Catalyzed Intramolecular Enyne−Amide Cyclization. *J. Org. Chem.*, **2010**, *75*, 269-272; (c) Alvarez, R.; Martinez, C.; Madich, Y.; Denis, J. G.; Aurrecoechea, J. M.; de Lera, A. R. A General Synthesis of Alkenyl-Substituted Benzofurans, Indoles, and Isoquinolones by Cascade Palladium-Catalyzed Heterocyclization/Oxidative Heck Coupling. *Eur. J. Org. Chem.* **2010**, *16*, 12746-12753; (d) Liu, G.; Ye, D.; Zhang, D.; Ding, X.; Jiang, H.; Liu, H. Silver-Catalyzed Intramolecular Cyclization of o-(1-Alkynyl)benzamides: Efficient Synthesis of (1*H*)-Isochromen-1-imines. *Adv. Synth. Catal.*, **2009**, *351*, 2605-2610.

7. Electrophilic cyclization of *o*-alkynylbenzamide: (a) Neto, J. S. S.; Back, D. F.; Zeni, G.. Nucleophilic Cyclization of o-Alkynylbenzamides Promoted by Iron(III) Chloride and Diorganyl Dichalcogenides: Synthesis of 4-Organochalcogenyl-1*H*-isochromen-1-imines. *Eur. J. Org. Chem*., **2015**, 1583-1590; (b) Mehta, S.; Yao, T.; Larock, R. C. Regio- and Stereoselective Synthesis of Cyclic Imidates via Electrophilic Cyclization of 2-(1-Alkynyl)benzamides. A Correction. *J. Org. Chem.*, **2012**, *77*, 10938-10944; (c) Schlemmer, C.; Andernach, L.; Schollmeyer, D.; Straub, B. F.; Opatz, T. Iodocyclization of *o*-Alkynylbenzamides Revisited: Formation of Isobenzofuran-1(3*H)*-imines and 1*H*-Isochromen-1-imines Instead of Lactams. *J. Org. Chem*., **2012**, *77*, 10118-10124; (d) Mehta, S.; Waldo, J. P.; Larock, R. C. Competition Studies in Competition Studies in Alkyne Electrophilic Cyclization Reactions. *J. Org. Chem.*, **2009**, *74*, 1141-1147.

8. (a) Wang, R.-X.; Yuan, S.-T.; Liu, J.-B.; Wu, J.; Qiu, G. Regioselective 5-exo-dig oxy-cyclization of 2-alkynylbenzamide for the synthesis of isobenzofuran-1-imines and isobenzofuran. *Org. Biomol. Chem.* **2018**, *16*, 4501-4508; (b) Wang, Y.-H.; Ouyang, B.; Qiu,

G.; Zhou, H.; J.-B. Liu. Oxidative oxy-cyclization of 2-alkynylbenzamide enabled by TBAB/Oxone: switchable synthesis of isocoumarin-1-imines and isobenzofuran-1-imine. *Org. Biomol. Chem.* **2019**, *17*, 4335-4341.

9. (a) Anikina, L. V.; Vikharev, Y. B.; Gorbunov, A. A.; Shklyaev, Y. V. Synthesis and Analgesic Activity of 3,3-Dialkylsubstituted 3,4-Dihydroisocarbostyryls. *Pharm. Chem. J.* **2013**, *47*, 419-421; (b) Woon, E. C. Y.; Sunderland, P. T.; Paine, H. A.; Lloyd, M. D.; Thompson, A. S.; Threadgill, M. D. One-pot tandem Hurtley–retro-Claisen–cyclisation reactions in the synthesis of 3-substituted analogues of 5-aminoisoquinolin-1-one (5-AIQ), a water-soluble inhibitor of PARPs. *Bioorg. Med. Chem.* **2013**, *21*, 5218-5227.

10. (a) Sheng, Y.; Qiu, G.; Wu, J. Inorganic sulfites as the sulfur dioxide surrogates in sulfonylation reactions. *Chem. Commun.* **2019**, *55*, 1013-1019; (b) Zhou, K.; Zhang, J.; Qiu, G.; Wu, J. Copper(II)-Catalyzed Reaction of 2,3-Allenoic Acids, Sulfur Dioxide, and Aryldiazonium Tetrafluoroborates: Route to 4-Sulfonylated Furan-2(5*H*)-ones. *Org. Lett.* **2019**, *21*, 275-278; (c) Sheng, J.; Li, Y.; Qiu, G. Reductive insertion of sulfur dioxide for the synthesis of trifluoromethyl thiolsulphonates through a one-pot reaction of aniline and trifluoromethanesulfanylamide. *Org. Chem. Front.* **2017**, *4*, 95-100; (d) Liu, T.; Ding, Q.; Zong, Q.; Qiu, G. Radical 5-exo cyclization of alkynoates with 2-oxoacetic acids for synthesis of 3-acylcoumarins. *Org. Chem. Front*. **2015**, *2*, 670-673; (e) Liu, G.; Liu, H.; Qiu, G.; Wu, J. An unexpected silver triflate-catalyzed tandem reaction of *N*′-(2-alkynylbenzylidene)hydrazide with ketene. *Chem. Commun*. **2012**, *48*, 7049-7051.

11. selected copper catalyse radical process, see: (a) Ye, L.; Gu, Q.-S.; Tian, Y.; Meng, X.; Chen, G.-C.; Liu, X.-Y. Structural absorption by barbule microstructures of super black bird of paradise feathers. *Nature. Commun*. **2018**, *9*, 1-8; (b) Zhang, B.; Liang, H.-W.; Yang, J.; Yang, Z.; Wei, Y. Copper-Catalyzed Intermolecular Cyclization between Oximes and Alkenes: A Facile Access to Spiropyrrolines. *ACS Catal.* **2017**, *7*, 5612-5617; (c) Wang, F.; Wang, D.; Wan, X.; Wu, L.; Chen, P.; Liu, G. Enantioselective Copper-Catalyzed Intermolecular Cyanotrifluoromethylation of Alkenes via Radical Process. *J. Am. Chem. Soc.* **2016**, *138*, 15547-15550; (d) Xue, W.; Qu, Z.-W.; Grimme, S.; Oestreich, M. Copper-Catalyzed Cross-Coupling of Silicon Pronucleophiles with Unactivated Alkyl Electrophiles Coupled with Radical Cyclization. *J. Am. Chem. Soc.* **2016**, *138*, 14222-14225; (e) Gao, Y.; Gao, Y.; Tang, X.; Peng, J.; Hu, M.; Wu, W.; Jiang, H. Copper-Catalyzed Oxysulfenylation of Enolates with Sodium Sulfinates: A Strategy To Construct Sulfenylated Cyclic Ethers. *Org. Lett.* **2016**, *18*,

1158-1161; (f) Min, M.-Y.; Song, R.-J.; Ouyang, X.-H.; Li, J.-H. Copper-catalyzed intermolecular oxidative trifluoromethyl-arylation of styrenes with $NaSO_2CF_3$ and indoles involving C–*H* functionalization. *Chem. Commun.* **2019**, *55*, 3646-3649; (g) Pan, J.; Li, X. Y.; Qiu, X.; Luo, X.; Jiao, N. Copper-Catalyzed Oxygenation Approach to Oxazoles from Amines, Alkynes, and Molecular Oxygen. *Org. Lett.* **2018**, *20*, 2762-2765;

12. Chen, F.; Lai, S.-Q.; Zhu, F.-F.; Meng, Q.; Jiang, Y.; Yu, W.; Han, B. Cu-Catalyzed Radical Cascade Annulations of Alkyne-Tethered *N*-Alkoxyamides with Air: Facile Access to Isoxazolidine/1,2-Oxazinane-Fused Isoquinolin-1(2*H*)- ones . *ACS. Catal*. **2018**, *8*, 8925-8931.

13. Yang, C.; Zhang, X.; Zhang-Negrerie, D.; Du, Y.; Zhao, K..PhI$(OCOCF_3)_2$-Mediated Cyclization of *o*-(1-Alkynyl)benzamides: Metal-Free Synthesis of 3-Hydroxy-2,3-dihydroisoquinoline-1,4-dione. *J. Org. Chem.* **2015**, *80*, 5320-5328.

14. (a) De Almeida, M. V.; Barton, D. H. R.; Bytheway, I.; Ferreira, J. A.; Hall, M. B.; Liu, W.; Taylor, D. K.; Thomson, L. Preparation and Thermal Decomposition of *N*,*N*'-Diacyl-*N*,*N*'-Dialkoxyhydrazines: Synthetic Applications and Mechanistic Insights. *J. Am. Chem. Soc*. **1995**, *117*, 4870-4874; (b) Zhou, L.; Yi, H.; Zhu, L.; Qi, X.; Jiang, H.; Liu, C.; Feng, Y.; Lan, Y.; Lei, A. Tuning the Reactivity of Radical through a Triplet Diradical Cu(II) Intermediate in Radical Oxidative Cross-Coupling. *Sci. Rep*. **2015**, *5*, 15934-15946; (c) Shen, K.; Wang, Q. Copper-catalyzed diamination of unactivated alkenes with hydroxylamines. *Chem. Sci.* **2015**, *6*, 4279-4283.

15. (a) Campbell, A. N.; Stahl, S. S. Overcoming the "Oxidant Problem": Strategies to Use O_2 as the Oxidant in Organometallic C–*H* Oxidation Reactions Catalyzed by Pd (and Cu). *Acc. Chem. Res*. **2012**, *45*, 851-863; (b) Das, D. K.; Pampana, V. K. K.; Hwang, K. C. Copper catalyzed photoredox synthesis of α-keto esters, quinoxaline, and naphthoquinone: controlled oxidation of terminal alkynes to glyoxals. *Chem. Sci.* **2018**, *9*, 7318-7326; (c) Peng, X.; Wei, D.; Han, W.; Chen, F.; Yu, W.; Han, B. Dioxygen Activation via Cu-Catalyzed Cascade Radical Reaction: An Approach to Isoxazoline/Cyclic Nitrone-Featured alpha-Ketols. *ACS Catal.* **2017**, *7*, 7830-7834