JOC The Journal of Organic Chemistry

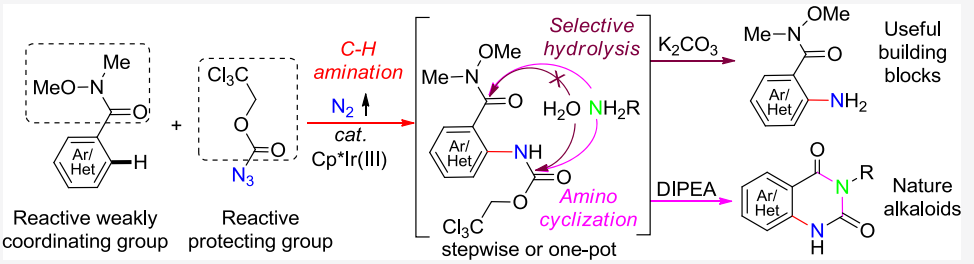
pubs.acs.org/joc Article

Iridium-Catalyzed C−H Amination of Weinreb Amides: A Facile Pathway toward Anilines and Quinazolin-2,4-diones

Xunqing Dong,[⊥] Panpan Ma,[⊥] Tao Zhang, Hitesh B. Jalani, Guigen Li, and Hongjian Lu*

Cite This: https://dx.doi.org/10.1021/acs.joc.0c01789 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: C−H amination of arenes directed by weakly coordinating Weinreb amides has been achieved with an iridium catalyst and 2,2,2-trichloroethoxycarbonyl (Troc) azide as an aminating agent, providing a robust method of producing synthetic useful *ortho*-TrocNH aryl Weinreb amides. Taking advantage of the reactivity of Weinreb amide and Troc groups in the amination products, selective hydrolysis was achieved as an attractive process for the synthesis of *ortho*-NH_2 aryl Weinreb amides, which are the building blocks useful in the synthesis of bioactive compounds, and cascade aminocyclization with primary amines was successful and provided an efficient pathway for the construction of quinazolin-2,4-diones, which are present in various alkaloids and natural products.

INTRODUCTION

Transition-metal-catalyzed C−H amination of arenes has emerged as an important strategy for the installation of the C−N bond in a variety of substrates and has now become a widely accepted method in organic synthesis.[1] This transformation provides atom- and step-economical synthetic routes toward arylamines, which are ubiquitously found in natural products and drug candidates,[2] and also restricts the waste generation associated with the traditional method via a nitration and reduction process. Among the amination reactions, the directing group (DG) assisted C−H amination of arenes via transition-metal catalysis is a popular strategy, wherein the aminating reagents used are limited to amines with protecting groups (PG).[3] When the DG and/or PG are not present in the final amination products, the necessary introduction and removal of the DG and PG is ultimately a kind of burden from the atom- and step-economic point of view. Catalytic C−H functionalization assisted by a transient or removable DG has been achieved for the efficient and streamlined synthesis;[4] however, the use of DG and PG, which are transformable, has not been well developed in catalytic C−H amination.[3]

N-Methoxy-*N*-methyl (Weinreb) amides are reliable and one of the important acyl surrogates frequently found to be used in the total synthesis of natural products.[5] Methods utilizing Weinreb amides for the directed C−H bond functionalization are useful and important.[6] However, there are two major challenges in the C−H amination of Weinreb amides. First, the weak coordinating ability and facile cleavage of the N−O bond in these compounds makes them vulnerable in the activation of strong aryl C−H bonds. Second, the nitrogen atom in amination products has the tendency to coordinate with the metal catalysts, which reduce the activity of catalysts. Only one example has been reported to date incorporating Weinreb amides in metal-catalyzed C−H amination reactions, wherein dioxazolones attached to the electron-withdrawing *m*- or *p*-trifluoromethylphenyl group were used as aminating agents (Figure 1A).[7] Introduction of the strong electron-withdrawing group attached to the nitrogen atom can enhance the reactivity of aminating reagents and reduce the coordination ability of amination products, and eventually this could lead to minimization of side reactions.

Because of the unique advantages of organic azides, they have recently drawn significant attention in catalytic C−H amination reactions.[8] They are simple and easy to prepare,[9] greener in terms of environmental point of view since the reactions involved them don't require an external oxidizing

Received: July 27, 2020
Published: September 24, 2020

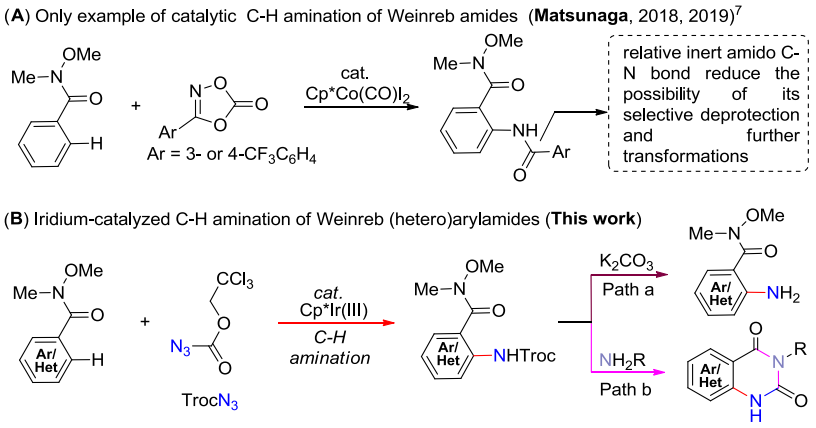


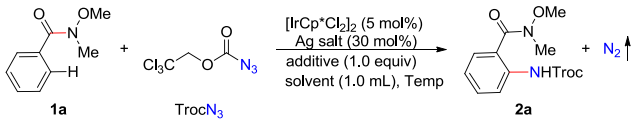
Figure 1. Catalytic C−H amination of aryl Weinreb amides.

agent and N_2 is the only by-product. The ability to use azides in aqueous solution[10] and to be compatible with versatile functional groups[11] broadens the range of substrates that can be tolerated. Different types of organic azides, such as sulfonyl, phosphoryl, carbonyl, alkoxycarbonyl, phenyl, and alkyl azides, have been utilized as efficient aminating reagents.[8] Among these, 2,2,2-trichloroethoxycarbonyl azide ($TrocN_3$) is interesting[12] because the strong electron-withdrawing nature of the Troc group increases the reactivity of $TrocN_3$ and reduces the coordinating ability of the amination products. In addition, the Troc group can be easily transferred, and this provides an opportunity for further chemical transformations of the amination products. Recently, we have used $TrocN_3$ to facilitate strongly coordinating groups such as amide-,[13a] pyridine, and ketoxime[13b]-directed metal-catalytic C−H amination reactions. Continuing our efforts toward the development of mild and efficient catalytic C−H amination using organic azides,[13,14] we report herein our findings on Ir-catalyzed C−H amination of Weinreb amides enabled by $TrocN_3$ (Figure 1B). With the aid of a weakly coordinating Weinreb amide group and the strong electron-withdrawing Troc group, the reactions could work for both phenyl and heteroaryl C−H bonds. Taking advantage of the reactivity of both Weinreb amide and Troc groups in the amination products, the selective hydrolysis produced *ortho*-NH_2 aryl Weinreb amides, which are building blocks useful in synthetic chemistry (Figure 1B, path a),[15] and the cascade amino-cyclization provided this protocol as an efficient strategy for the construction of quinazolin-2,4-diones, a scaffold embedded in a variety of natural quinolones and related alkaloids (Figure 1B, path b).[16]

RESULTS AND DISCUSSION

Inspired by the metal-catalyzed C−H amination developed by Chang et al.,[8] and our previous work using azides as amino sources,[13,14] we examined the reaction of Weinreb amide **1a** with $TrocN_3$ under our previously developed reaction conditions for C−H amination reactions directed by strong coordinating groups (Table 1, entry 1. See details in Table S1 in the Supporting Information (SI)).[13a] The expected product **2a** was obtained in only 12% yield. When CsOAc was replaced with *n*-pentanoic acid, the yield of **2a** was increased to 32% (entry 2). Upon changing the base from NaOAc to KOAc, **2a** was obtained in 88% yield (entries 3 and 4). Various Ag salts (entries 5−8) and additives (entries 9−12) were then screened, and it was found that AgOTf combined with

Table 1. Optimization of Reaction Conditions[a]



entry	Ag salt	additive	solvent	temp (°C)	yield[b]
1	$AgNTf_2$	CsOAc	PhCl	80	12%
2	$AgNTf_2$	$^nC_4H_9CO_2H$	DCE	80	32%
3	$AgNTf_2$	NaOAc	DCE	80	54%
4	$AgNTf_2$	KOAc	DCE	80	63%
5	AgOTf	KOAc	DCE	80	88%
6	$AgSbF_6$	KOAc	DCE	80	62%
7	$AgPF_6$	KOAc	DCE	80	37%
8	Ag salt[c]	KOAc	DCE	80	ND
9	AgOTf	CsOAc	DCE	80	21%
10	AgOTf	NaOAc	DCE	80	25%
11	AgOTf	CF_3CO_2Na	DCE	80	14%
12	AgOTf	$^tBuCO_2Na$	DCE	80	ND
13	AgOTf	KOAc	solvent[d]	80	ND
14	AgOTf	KOAc	DCE	60	60%
15	AgOTf	KOAc	DCE	100	48%
16		KOAc	DCE	80	ND
17	AgOTf		DCE	80	ND
18[e]	AgOTf	KOAc	DCE	80	ND
19	AgOTf	KOAc[f]	DCE	80	46%
20	AgOTf	KOAc[g]	DCE	80	25%

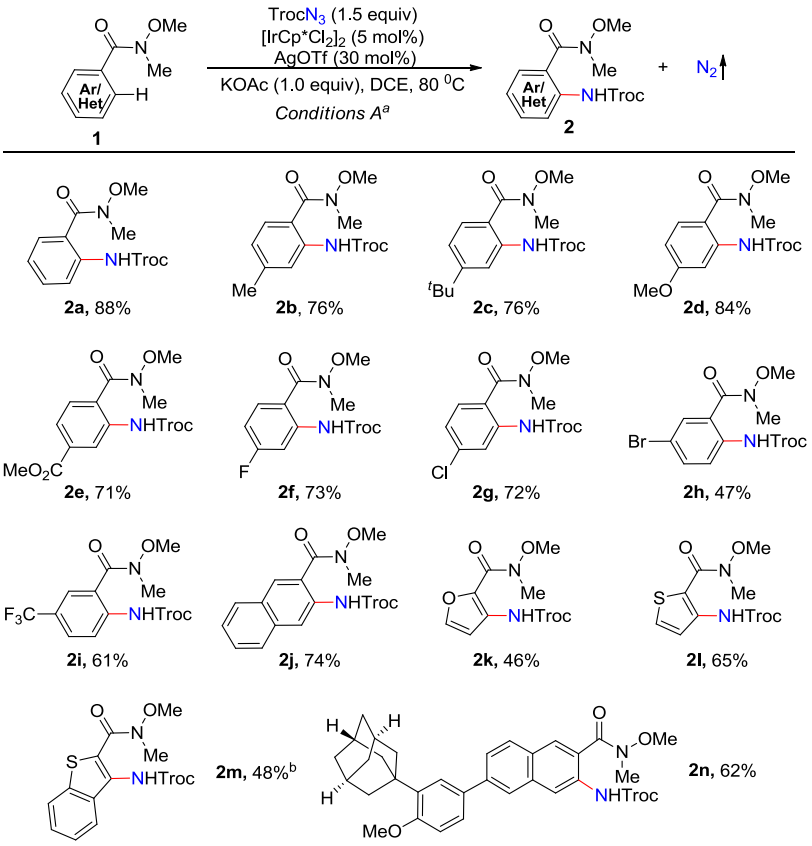
[a]Reaction conditions: **1a** (0.1 mmol), $TrocN_3$ (0.15 mmol), catalyst (5 mol %), Ag salt (30 mol %), additive (1.0 equiv), solvent (1.0 mL), N_2, temp, and 24 h. [b]Crude ^1H NMR yields determined using CH_2Br_2 as an internal standard. [c]Ag_2CO_3, AgOAc, or AgOTs was used. [d]CH_3CN, dimethylformamide (DMF), or tetrahydrofuran (THF) was used. [e]No $[IrCp^*Cl_2]_2$. [f]KOAc (50 mol %). [g]KOAc (20 mol %).

KOAc gave the best yield. The solvents were screened (entry 13), and it was found that 1,2-dichloroethane (DCE) is optimal. Changes in the reaction temperature failed to improve the yield (entries 14 and 15), and no **2a** was formed in the absence of an additive, the silver salt, or the catalyst (entries 16−18). The reaction does not work well with the catalytic amount of KOAc (entries 19−20).

Next, we turned our attention to the exploration of the reaction of Weinreb amides under the optimized conditions (Scheme 1). Electron-donating functional groups, such as methyl, methoxy, and *tert*-butyl, and electron-withdrawing

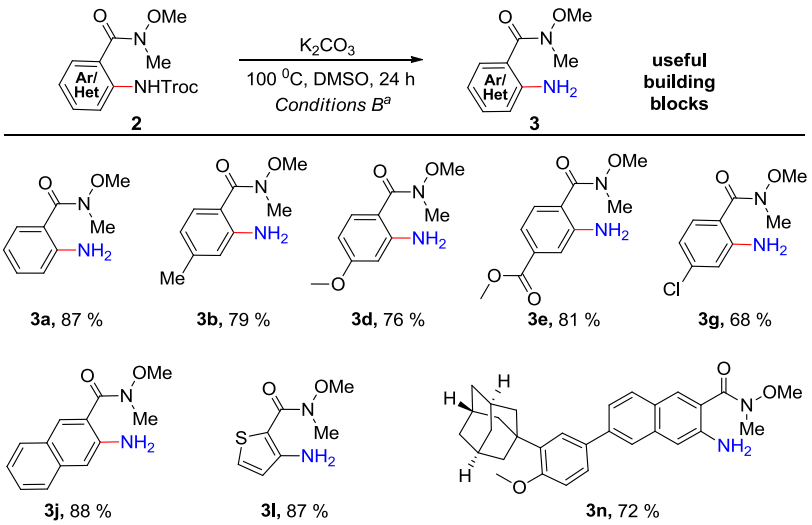
https://dx.doi.org/10.1021/acs.joc.0c01789
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 1. Scope of Weinreb Amides



[a]Conditions A: **1** (0.2 mmol), $TrocN_3$ (0.3 mmol), $[IrCp^*Cl_2]_2$ (5 mol %), AgOTf (30 mol %), KOAc (1.0 equiv), DCE, N_2, 80 °C, 24 h, and isolated yield. [b]95 °C.

Scheme 2. Synthesis of *ortho*-NH_2 Aryl Weinreb Amides via a Selective Deprotection Process

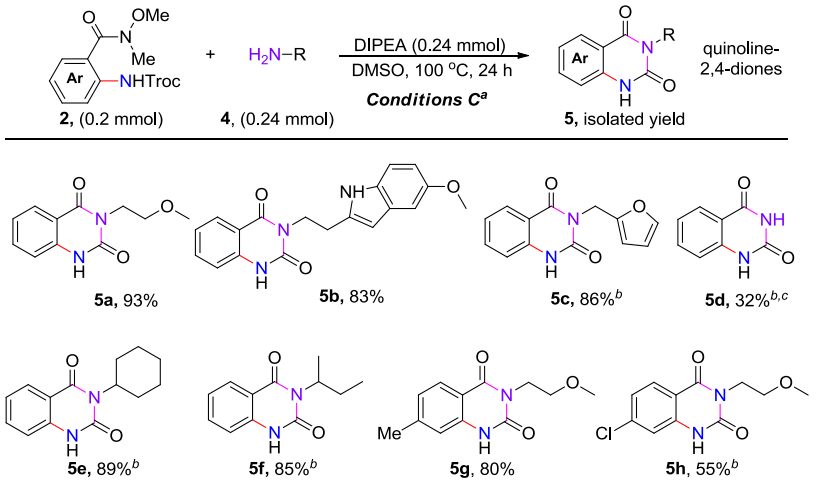


[a]Conditions B: **2** (0.2 mmol), K_2CO_3 (0.8 mmol), DMSO (2 mL), 100 °C, and 24 h.

groups, such as an ester group in the phenyl ring, were found to be compatible with the reaction, providing amination products **2a**–**e** in good yields. Halogenated aryl Weinreb amides were reacted and resulted in amination products **2f**–**h**, which can be useful for further cross-coupling transformations. In the case of the meta-substituted aryl Weinreb amides, the amination occurred preferably at the less hindered position, and the yield of the desired product is moderate (**2h** and **2i**). For the reaction of *ortho*-CF_3, *ortho*-CH_3, or *meta*-OMe phenyl Weinreb amide, no desired C–H amination product was observed. When 2-naphthyl Weinreb amide was used, the reaction proceeded well with high regioselectivity and a single isomer **2j** was formed in 74% yield. Furan or thiophene substrates had been seldom used in the catalytic C–H

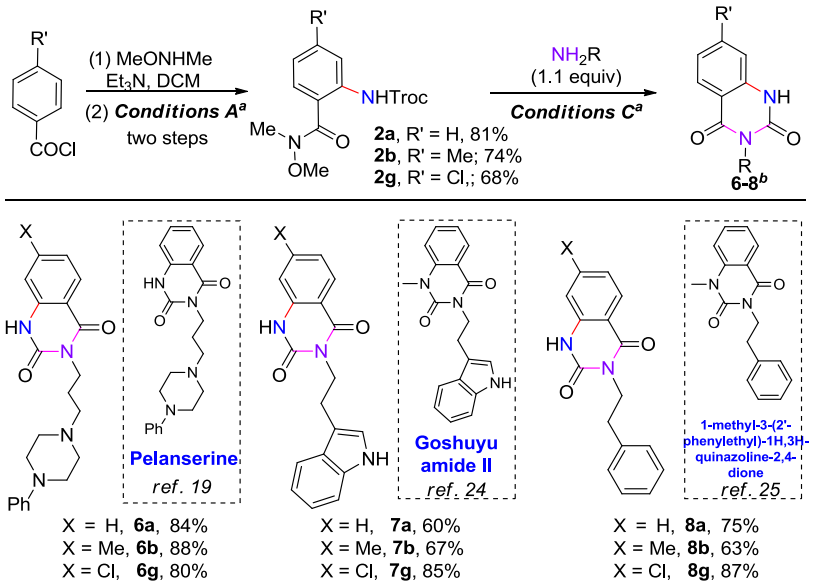
https://dx.doi.org/10.1021/acs.joc.0c01789
J. Org. Chem. XXXX, XXX, XXX–XXX

Scheme 3. Synthesis of Quinolin-2,4-diones via a Cascade Aminocyclization Strategy



[a]Conditions C: **2** (0.2 mmol), RNH_2 **4** (0.24 mmol), DIPEA (0.24 mmol), DMSO (2 mL), 100 °C, 24 h, and isolated yield. [b]Using NaO^{t}Bu (0.8 mmol) instead of DIPEA (0.24 mmol). [c]Using NH_4Cl (0.24 mmol) instead of **4**.

Scheme 4. Synthesis of Natural Alkaloids and Their Derivatives



[a]See the notes in Schemes 1 and 3. [b]Isolated yield based on substrate **2**.

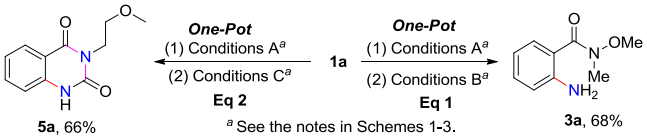
amination reactions.[17] Interestingly, both furan and thiophene were found to be suitable for this reaction and gave the amination products **2k**−**m** in moderate yield. No desired C−H amination product was observed in the reaction of *N*-methoxy-*N*-methylpicolinamide. Finally, the reaction with the topical retinoid adapalene proceeded to provide an aminated derivative **2n** in good yield. Functionalization of such drug derivatives could be useful in scaffold/target repurposing and exploration of further elaboration of clinically approved drugs to fuel drug discovery projects.

The products with Troc and Weinreb amide functional groups may face a site selectivity problem when treated with a nucleophile owing to the different electrophilic properties of these two amide carbonyls. We were interested in the conversion of the amination products to anilines since the expected *ortho*-NH_2 aryl Weinreb amides are very useful intermediates for the synthesis of bioactive compounds.[15] Since aprotic polar solvents are known to enhance the basicity of CO_3^{2-},[18] the Troc group in the amination product was easily removed by K_2CO_3 in dimethyl sulfoxide (DMSO), while the Weinreb amide group remained intact (Scheme 2, see details in Table S2 in the SI). Both electron-rich and electron-deficient anilines **3a**, **3b**, **3d**, **3e**, and **3g** were obtained in high yield. Naphthalene and thiophene derivatives were also found to be suitable, and the corresponding primary arylamine **3j** and heteroarylamine **3l** were achieved in high yields. Since the relatively mild conditions were used, the *o*-amino adapalene derivative **3n** was also isolated in 72% yield. These results show that the carbonyl group present in the Troc group is relatively more electrophilic than the carbonyl group in the Weinreb amide, and this can support future synthetic manipulations.

The reactive Troc and Weinreb amide functionalities in amination products obtained in our protocol could provide an opportunity to facilitate cascade reactions to synthesize complex molecules efficiently. Quinazolin-2,4-diones are

https://dx.doi.org/10.1021/acs.joc.0c01789
J. Org. Chem. XXXX, XXX, XXX−XXX

commonly prepared from 1,2-bifunctional aromatic reagents, such as anthranilic acid or its analogues, and more diversified products are not available through this chemistry.[19] Our strategy to facilitate the cyclization reaction of *ortho*-TrocNH aryl Weinreb amides with primary amines provides an efficient method for the synthesis of quinazolin-2,4-diones (Scheme 3, see details in Table S3). 2-Methoxyethylamine was selected as a nucleophile, which reacted with the *ortho*-TrocNH phenyl Weinreb amide **2a**. After optimization of the reaction conditions, the cascade reaction proceeded under the influence of *N*,*N*-diisopropylethylamine (DIPEA) and provided the desired quinazolin-2,4-dione **5a** in high yield. Diverse amines, including 5-methoxyindole-3-ethylamine, furan-2-methylamine, cyclohexylamine, isobutylamine, and even ammonia, which was in situ generated, have been successfully utilized to obtain the target products **5a**–**f** with moderate to good yields. Substituted aryl Weinreb amides also reacted well to achieve the desired products **5g** and **5h** in good yields.

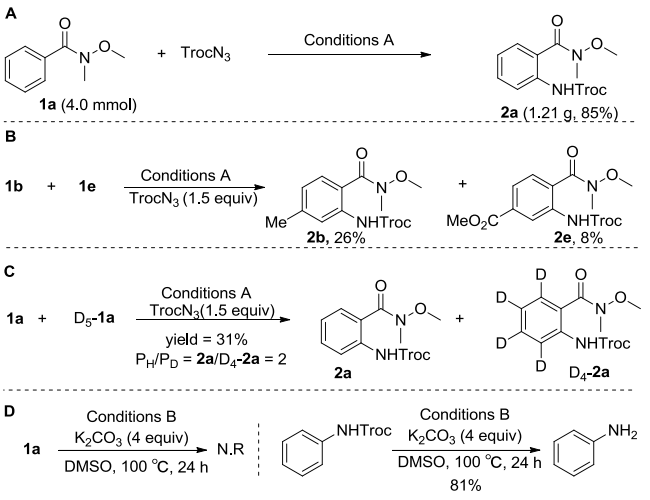


To improve the practicality of this methodology, two-step one-pot reactions have been performed. From readily available **1a**, the *o*-NH_2 phenyl Weinreb amide **3a** (eq 1) or the quinazolin-2,4-dione **5a** (eq 2) could be prepared in good yield without the purification of the intermediate **2a**. The sequences represent two convenient routes for the synthesis of valuable *ortho*-NH_2 (hetero)aryl Weinreb amides and quinazolin-2,4-diones.

Pelanserine, structurally related to the cardiovascular drug ketanserin (3-(2-(4-(4-fluorobenzoyl)piperidin-1-yl)ethyl)-quinazoline-2,4(1*H*,3*H*)-dione), which contains a quinazolin-2,4-dione fragment,[20] is a well known established potent antihypertensive agent.[21] Quinazolin-2,4-dione is also a key fragment in natural alkaloids, such as goshuyuamide II from *Evodia officinalis* and *Evodia rutaecarpa*,[22] wuchuyuamide II from the fruit of Evodia rutaecarpa,[23] and 1-methyl-3-(2′-phenylethyl)-1*H*,3*H*-quinazoline-2,4-dione from the seed husks of *Zanthoxylum arborescens*.[24] As shown in Scheme 4, pelanserine (**6a**) can be prepared in good yield. Derivatives of pelanserine (**6b** and **6g**) could be readily prepared due to the general availability of the substituted aryl carboxylic acids. As a synthetic precursor for both goshuyuamide II and wuchuyuamide II,[25] **7a** and its derivatives **7b** and **7g** were achieved in good yield through the cascade aminocyclization of **2a** with tryptamine. 3-Phenethylquinazoline-2,4(1*H*,3*H*)-dione **8a**, a synthetic precursor of 1-methyl-3-(2′-phenylethyl)-1*H*,3*H*-quinazoline-2,4-dione,[26] and its derivatives **8b** and **8g** were also obtained in good yields.

To evaluate the practical applicability of this protocol, we conducted a gram-scale reaction of **1a** under conditions A and the product **2a** was isolated in 85% yield (Scheme 5A). The intermolecular competitive reaction suggested that Weinreb amide with the electron-donating group (**1b**) is more favorable than that with an electron-withdrawing group (**1e**) (Scheme 5B). Kinetic isotope effects were observed on the basis of an intermolecular competition experiment in one vessel (P_H/P_D = 2) (Scheme 5C). Under conditions B, the Weinreb amide group in **1a** remained intact, while the Troc group in aniline was removed (Scheme 5D).

Scheme 5. Gram-Scale Synthesis and Control Experiments



Based on the related refs 6a, 13a, and 14, we proposed the reaction mechanism in Scheme 6. Compound **1** undergoes a C–H activation/amination sequence to form intermediate **V**. The protonation of **V** by acetic acid forms desired **2** and regenerates catalytic species **I**.

CONCLUSIONS

In summary, we have developed an iridium-catalyzed C(sp^2)–H amination directed by a weakly coordinating Weinreb amide. With 2,2,2-trichloroethoxycarbonyl azide as an aminating agent, both arylamides and heteroarylamides are suitable substrates in this attractive process, which produces synthetically useful *ortho*-TrocNH (hetero)aryl Weinreb amides. Various electron-withdrawing-, electron-donating-, and halogen-substituents on the aromatic ring are compatible in this reaction, which exhibits excellent functional group tolerance. Benefitting from the reactive Weinreb amide and a Troc group assembled in amination products, selective deprotection or cascade aminocyclization was achieved smoothly and hence providing efficient ways to construct *ortho*-NH_2 aryl Weinreb amides and quinazolin-2,4-dione derivatives, which are useful building blocks in organic synthesis. In addition, this method allows the synthesis of some naturally occurring alkaloids and related bioactive compounds. Thus, the Weinreb amide directed C–H amination using the amino sources with reactive protecting groups can help to expand the synthesis of complex molecules.

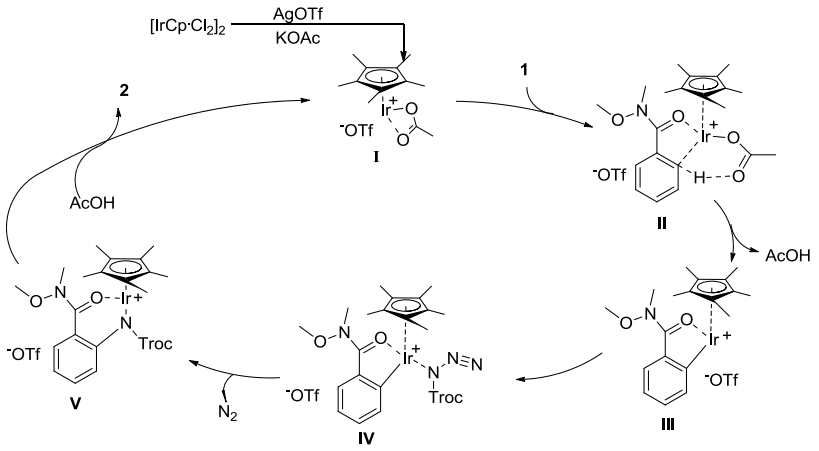
EXPERIMENTAL SECTION

General Information. Unless otherwise mentioned, all commercial reagents and solvents were obtained from commercial suppliers and used without further purification. $IrCl_3 \cdot 3H_2O$ was purchased from Shanxi Kaida Chemical Engineering (China) Co., Ltd. AgOTf and $AgNTf_2$ were purchased from Nanjing Luxury Catalytic Materials Co., Ltd. $[IrCp^*Cl_2]_2$,[11] known benzamides (**1a**, **1c**, **1g**, **1i**, **1j**, **1k**),[27a] **1b**,[27b] (**1d**, **1f**, **1l**),[27c] **1h**,[27d] and azides[13a] were prepared according to the literature procedures.

Thin-layer chromatography (TLC) was performed on precoated silica gel GF254 plates. Visualization of TLC was achieved by the use of UV light (254 nm). Column chromatography was performed on silica gel (300–400 mesh) using a proper eluent. ^1H NMR was recorded on FT AM 400 (400 MHz). Chemical shifts were reported in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane or chloroform-*d* ($CDCl_3$) at 7.26 ppm. The following abbreviations were used to describe peak splitting

https://dx.doi.org/10.1021/acs.joc.0c01789
J. Org. Chem. XXXX, XXX, XXX–XXX

Scheme 6. Proposed Mechanism



patterns: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, td = triplet of doublet, ddd = doublet of doublet of doublet, and m = multiplet. Coupling constants, *J*, were reported in hertz (Hz). The fully decoupled ^{13}C NMR was recorded on FT AM 400 (100 MHz). Chemical shifts were reported in ppm referenced to the center of a triplet at 77.0 ppm of chloroform-*d*. Infrared (IR) spectra were recorded neat in the KBr cell. Frequencies are given in centimeter inverse (cm^{-1}), and only selected absorbance is reported. High-resolution mass spectra (HRMS) were obtained using the UHD Accurate-Mass Q-TOF.

Synthesis of Starting Material 1e. To a solution of *N,O*-dimethylhydroxylamine hydrochloride (582.2 mg, 6.0 mmol) and Et_3N (1.821 g, 18.0 mmol) in CH_2Cl_2 (20 mL) was slowly added benzoyl chloride (990.0 mg, 5.0 mmol) at 0 °C and the reaction mixture was stirred at room temperature (RT) for 5 h. The reaction mixture was quenched with 1 M HCl (30 mL), extracted with CH_2Cl_2 three times, and then dried over Na_2SO_4. The crude product was concentrated under reduced pressure and purified by flash chromatography on a silica gel column with petroleum ether (PE)/ethyl acetate (EA) 1:6 (v/v) to give methyl-4-(methoxy(methyl)-carbamoyl)benzoate (**1e**), TLC R_f = 0.4 (EA/PE = 1:2); white solid; 880.8 mg, yield: 79%; m.p.: 90−91 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 2H), 3.90 (s, 3H), 3.50 (s, 3H), 3.34 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.0, 166.4, 138.3, 131.7, 129.2, 128.1, 61.2, 52.3, 33.4; IR (neat): 3021, 2984, 2952, 2818, 1722, 1658, 1279, 1112, 740, 727 cm^{-1}; HRMS (electrospray ionization (ESI)) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{13}NO_4Na$ 246.0743; found 246.0742.

Synthesis of Starting Materials 1m and 1n. To a 50 mL flask were added acid (5.0 mmol), *N,O*-dimethylhydroxylamine hydrochloride (582.2 mg, 6.0 mmol), DIPEA (1.29 g, 10 mmol), HOBt (810.7 mg, 6.0 mmol), and EDCI (1.150 g, 6.0 mmol), then 20 mL of DMF was added under N_2. The reaction mixture was stirred at room temperature (RT) overnight. Then, the reaction mixture was quenched with H_2O (20 mL), extracted with EA three times, and then dried over Na_2SO_4. The crude product was concentrated under reduced pressure and purified by flash chromatography on a silica gel column with PE/EA to give **1**.

*N-Methoxy-N-methylbenzo[b]thiophene-2-carboxamide (**1m**).* TLC R_f = 0.5 (EA/PE = 1:5); colorless oil; 552.5 mg, yield: 50%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.87 (dd, *J* = 11.6, 7.8 Hz, 2H), 7.45−7.38 (m, 2H), 3.83 (s, 3H), 3.43 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.5, 142.6, 138.1, 133.3, 131.3, 126.5, 125.3, 124.7, 122.3, 61.9, 33.2; IR (neat): 3059, 2969, 2934, 1707, 1631, 1514, 1381, 1273, 763, 749 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{11}NO_2SNa$ 244.0408; found 244.0402. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:15 (v/v).

*6-(3-((3r,5r,7r)-Adamantan-1-yl)-4-methoxyphenyl)-N-methoxy-N-methyl-2-naphthamide (**1n**).* TLC R_f = 0.5 (EA/PE = 1:4); white solid; m.p.: 192−193 °C; 2.23 g, yield: 98%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.00 (s, 1H), 7.92 (dd, *J* = 17.3, 8.6 Hz, 2H), 7.80−7.74 (m, 2H), 7.60 (d, *J* = 2.2 Hz, 1H), 7.54 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 3.59 (s, 3H), 3.43 (s, 3H), 2.23−2.16 (m, 6H), 2.13−2.08 (m, 3H), 1.84−1.76 (m, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.9, 158.8, 140.6, 139.0, 134.7, 132.8, 131.3, 130.9, 129.2, 128.5, 127.7, 126.3, 126.0, 125.7, 125.5, 124.7, 112.1, 61.1, 55.2, 40.6, 37.22, 37.15, 33.9, 29.1; IR (neat): 3308, 2903, 2848, 1747, 1637, 1480, 1261, 1238, 764, 750 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{30}H_{34}NO_3$ 456.2533; found 456.2528. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:12 (v/v).

Experimental Procedure for Product 2. To a Schlenk flask equipped with a stirrer were added benzamide **1** (0.2 mmol), $TrocN_3$ (65.1 mg, 0.3 mmol), $[IrCp^*Cl_2]_2$ (8.0 mg, 0.01 mmol), AgOTf (15.4 mg, 0.06 mmol), KOAc (19.6 mg, 0.2 mmol), and DCE (2 mL) under N_2. The reaction mixture was stirred at 80 °C (heating mantle) for 24 h. The solution was concentrated in vacuo and purified by column chromatography to give **2**.

*2,2,2-Trichloroethyl(2-(methoxy(methyl)carbamoyl)phenyl)-carbamate (**2a**).* TLC R_f = 0.5 (PE/DCM/Et_2O = 10:10:1); yellowish solid; 62.3 mg, yield: 88%; m.p.: 85−86 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.13 (d, *J* = 7.0 Hz, 1H), 7.55 (d, *J* = 7.0 Hz, 1H), 7.48−7.40 (m, 1H), 7.15−7.04 (m, 1H), 4.81 (s, 2H), 3.56 (s, 3H), 3.39 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.6, 151.8, 136.9, 131.7, 128.9, 122.7, 120.8, 95.2, 74.5, 61.5, 34.2; IR (neat): 3319, 2959, 2936, 2820, 1751, 1523, 1209, 1100, 765, 749 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{13}Cl_3N_2O_4Na$ 376.9839; found 376.9833. Purified by chromatography on silica gel, eluting with petroleum ether/DCM/Et_2O 30:10:1 (v/v/v).

*Gram-Scale Synthesis of **2a**.* To a Schlenk flask equipped with a stirrer were added benzamide **1a** (4.0 mmol), $TrocN_3$ (0.66 g, 6.0 mmol), $[IrCp^*Cl_2]_2$ (0.158 g, 2.0 mmol), AgOTf (0.308 g, 1.2 mmol), KOAc (0.392 mg, 4.0 mmol), and DCE (2 mL) under N_2. The reaction mixture was stirred at 80 °C (heating mantle) for 24 h. The solution was concentrated in vacuo and purified by column chromatography to give **2a** (1.21g, 85%).

*2,2,2-Trichloroethyl(2-(methoxy(methyl)carbamoyl)-5-methylphenyl)carbamate (**2b**).* TLC R_f = 0.6 (EA/PE = 1:5); white solid; 55.9 mg, yield: 76%; m.p.: 100−101 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.97 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 7.9 Hz, 1H), 4.80 (s, 2H), 3.55 (s, 3H), 3.36 (s, 3H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.9, 151.8, 142.5, 137.1, 129.0, 123.5, 121.2, 118.6, 95.3, 74.5, 61.4, 34.3, 21.8; IR (neat): 3309, 3243, 2959, 2935, 1751, 1579, 1526, 1221, 1100, 821, 715 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_{15}Cl_3N_2O_4Na$ 390.9995; found 390.9993. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:15 (v/v).

*2,2,2-Trichloroethyl(5-(tert-butyl)-2(methoxy(methyl)-carbamoyl)phenyl)carbamate (**2c**).* TLC R_f = 0.6 (EA/PE = 1:5);

https://dx.doi.org/10.1021/acs.joc.0c01789
J. Org. Chem. XXXX, XXX, XXX−XXX

white solid; 62.3 mg, yield: 76%; m.p.: 128−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.20 (s, 1H), 7.50 (d, J = 8.3 Hz, 1H), 7.10 (dd, J = 8.3, 1.6 Hz, 1H), 4.81 (s, 2H), 3.58 (s, 3H), 3.37 (s, 3H), 1.33 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.8, 155.5, 151.9, 137.0, 128.7, 119.9, 118.0, 95.3, 74.5, 61.4, 35.2, 34.4, 31.1; IR (neat): 3308, 2965, 2903, 2868, 1750, 1575, 1522, 1416, 1204, 1112, 830, 715 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{16}H_{21}Cl_3N_2O_4Na$ 433.0465; found 433.0461. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:15 (v/v).

*2,2,2-Trichloroethyl(5-methoxy-2-(methoxy(methyl)carbamoyl)-phenyl)carbamate (**2d**).* TLC R_f = 0.5 (EA/PE = 1:5); white solid; 64.5 mg, yield: 84%; m.p.: 71−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.84 (s, 1H), 7.58 (d, J = 8.8 Hz, 1H), 6.59 (dd, J = 8.8, 2.5 Hz, 1H), 4.80 (s, 2H), 3.85 (s, 3H), 3.55 (s, 3H), 3.36 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.0, 162.3, 151.7, 139.9, 130.9, 112.5, 108.9, 104.8, 95.2, 74.5, 61.2, 55.4, 34.4; IR (neat): 3296, 3118, 2962, 2936, 1752, 1583, 1525, 1200, 1097, 970, 714 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{13}H_{15}Cl_3N_2O_5Na$ 406.9945; found 406.9943. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:15 (v/v).

*Methyl-4-(methoxy(methyl)carbamoyl)-3-(((2,2,2-trichloroethoxy)carbonyl)amino)benzoate (**2e**).* TLC R_f = 0.5 (PE/DCM/MeOH = 10:10:1); white solid; 58.5 mg, yield: 71%; m.p.: 143−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.76 (s, 1H), 7.77 (d, J = 6.3 Hz, 1H), 7.63 (d, J = 6.3 Hz, 1H), 4.83 (s, 2H), 3.93 (s, 3H), 3.53 (s, 3H), 3.40 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.7, 166.0, 151.8, 136.9, 132.9, 129.0, 123.9, 121.9, 95.1, 74.6, 61.7, 52.5, 33.7; IR (neat): 3317, 3002, 2953, 2851, 1752, 1580, 1526, 1206, 1112, 755 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{14}H_{15}Cl_3N_2O_6Na$ 434.9894; found 434.9889. Purified by chromatography on silica gel, eluting with PE/DCM/MeOH 30:10:1 (v/v/v).

*2,2,2-Trichloroethyl(5-fluoro-2-(methoxy(methyl)carbamoyl)-phenyl)carbamate (**2f**).* TLC R_f = 0.5 (EA/PE = 1:5); brown liquid; 54.3 mg, yield: 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.01 (d, J = 11.0 Hz, 1H), 7.64 (dd, J = 8.7, 6.4 Hz, 1H), 6.77 (td, J = 8.7, 2.5 Hz, 1H), 4.81 (s, 2H), 3.54 (s, 3H), 3.38 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.0, 164.3 (d, $^1J_{C-F}$ = 251 Hz), 151.6, 139.9 (d, $^3J_{C-F}$ = 12 Hz), 131.3 (d, $^3J_{C-F}$ = 10 Hz), 116.4, 109.5 (d, $^2J_{C-F}$ = 22 Hz), 107.7 (d, $^2J_{C-F}$ = 29 Hz), 95.1, 74.6, 61.5, 33.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −105.3; IR (neat): 3304, 3114, 2961, 2937, 1755, 1599, 1526, 1213, 1119, 987, 714 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{12}H_{12}Cl_3FN_2O_4Na$ 394.9745; found 394.9741. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:15 (v/v).

*2,2,2-Trichloroethyl(5-chloro-2-(methoxy(methyl)carbamoyl)-phenyl)carbamate (**2g**).* TLC R_f = 0.5 (EA/PE = 1:5); white solid; 55.9 mg, yield: 72%; m.p.: 67−68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.26 (s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.06 (dd, J = 8.4, 2.0 Hz, 1H), 4.81 (s, 2H), 3.54 (s, 3H), 3.38 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.8, 151.6, 138.6, 137.8, 130.2, 122.7, 120.6, 119.1, 95.1, 74.6, 61.6, 33.8; IR (neat): 3305, 3114, 2957, 2935, 1752, 1578, 1513, 1206, 1106, 821, 714 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{12}H_{12}Cl_4N_2O_4Na$ 410.9449; found 410.9442. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:15 (v/v).

*2,2,2-Trichloroethyl(4-bromo-2-(methoxy(methyl)carbamoyl)-phenyl)carbamate (**2h**).* TLC R_f = 0.5 (EA/PE = 1:5); colorless oil; 40.6 mg, yield: 47%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.06 (d, J = 9.0 Hz, 1H), 7.71 (d, J = 2.4 Hz, 1H), 7.56 (dd, J = 9.0, 2.4 Hz, 1H), 4.81 (s, 2H), 3.57 (s, 3H), 3.40 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.1, 151.7, 136.1, 134.5, 131.6, 122.5, 115.4, 95.1, 74.6, 61.7, 33.8, 27.8; IR (neat): 3310, 2953, 2934, 2849, 1750, 1513, 1257, 1207, 1102, 753 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{12}H_{12}BrCl_3N_2O_4Na$ 454.8944; found 454.8945. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:15 (v/v).

*2,2,2-Trichloroethyl(2-(methoxy(methyl)carbamoyl)-4-(trifluoromethyl)phenyl)carbamate (**2i**).* TLC R_f = 0.5 (EA/PE = 1:5); yellowish solid; 51.5 mg, yield: 61%; m.p.: 125−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.37 (d, J = 8.8 Hz, 1H), 7.90 (s, 1H), 7.72−7.68 (m, 1H), 4.83 (s, 2H), 3.56 (s, 3H), 3.42 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.3, 151.6, 140.4, 128.6 (d, $^3J_{C-F}$ = 4 Hz), 126.5 (d, $^3J_{C-F}$ = 4 Hz), 125.0, 124.5 (d, $^2J_{C-F}$ = 33 Hz), 122.3, 120.5, 95.0, 74.7, 61.7, 33.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.3; IR (neat): 3308, 2996, 2954, 2935, 1753, 1595, 1530, 1329, 1207, 979, 723 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{13}H_{13}Cl_3F_3N_2O_4$ 422.9894; found 422.9897. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:15 (v/v).

*2,2,2-Trichloroethyl(3-(methoxy(methyl)carbamoyl)naphthalen-2-yl)carbamate (**2j**).* TLC R_f = 0.5 (EA/PE = 1:5); yellowish solid; 59.8 mg, yield: 74%; m.p.: 120−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.55 (s, 1H), 8.09 (s, 1H), 7.81 (t, J = 8.9 Hz, 2H), 7.53 (t, J = 7.1 Hz, 1H), 7.44 (t, J = 7.2 Hz, 1H), 4.86 (s, 2H), 3.57 (s, 3H), 3.45 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.5, 152.0, 134.6, 132.9, 129.8, 128.8, 128.3, 127.6, 125.7, 121.8, 118.0, 95.3, 74.6, 61.6, 34.3; IR (neat): 3319, 3056, 2956, 2935, 1749, 1643, 1537, 1210, 1123, 971, 715 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{16}H_{15}Cl_3N_2O_4Na$ 426.9995; found 426.9989. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:15 (v/v).

*2,2,2-Trichloroethyl(2-(methoxy(methyl)carbamoyl)furan-3-yl)-carbamate (**2k**).* TLC R_f = 0.5 (EA/PE = 1:5); white solid; 31.8 mg, yield: 46%; m.p.: 68−69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.39 (d, J = 1.6 Hz, 1H), 7.26 (s, 1H), 4.81 (s, 2H), 3.84 (s, 3H), 3.35 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.1, 151.5, 144.3, 135.8, 129.9, 106.1, 95.0, 74.7, 62.3, 33.7; IR (neat): 3308, 3135, 2958, 2934, 1752, 1619, 1492, 1260, 1204, 779 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{10}H_{12}Cl_3N_2O_5$ 344.9807; found 344.9798. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:15 (v/v).

*2,2,2-Trichloroethyl(2-(methoxy(methyl)carbamoyl)thiophen-3-yl)carbamate (**2l**).* TLC R_f = 0.5 (EA/PE = 1:5); white solid; 47.1 mg, yield: 65%; m.p.: 101−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H), 7.96 (d, J = 5.5 Hz, 1H), 7.49 (d, J = 5.6 Hz, 1H), 4.82 (s, 2H), 3.79 (s, 3H), 3.36 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.9, 151.5, 145.5, 132.1, 120.6, 107.9, 95.2, 74.7, 61.8, 32.7; IR (neat): 3033, 3131, 2936, 2851, 1748, 1565, 1458, 1344, 1209, 721 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{10}H_{12}Cl_3N_2O_4S$ 360.9578; found 360.9570. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:15 (v/v).

*2,2,2-Trichloroethyl(2-(methoxy(methyl)carbamoyl)benzo[b]-thiophen-3-yl)carbamate (**2m**).* TLC R_f = 0.5 (EA/PE = 1:5); white solid; 39.6 mg, yield: 48%; m.p.: 110−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (s, 1H), 8.05 (d, J = 8.1 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 4.87 (s, 2H), 3.81 (s, 3H), 3.40 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.4, 152.4, 139.9, 138.7, 132.2, 127.5, 125.8, 124.2, 122.1, 114.0, 95.3, 74.9, 62.3, 33.0; IR (neat): 3259, 3060, 2950, 2935, 1751, 1572, 1535, 1376, 1210, 1121, 754 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{14}H_{14}Cl_3N_2O_4S$ 410.9735; found 410.9738. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:15 (v/v).

*2,2,2-Trichloroethyl(7-(3-((3r,5r,7r)-adamantan-1-yl)-4-methoxyphenyl)-3-(methoxy(methyl)carbamoyl)naphthalen-2-yl)-carbamate (**2n**).* TLC R_f = 0.5 (Et_2O/DCM/PE = 1:10:10); white solid; 79.8 mg, yield: 62%; m.p.: 205−206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.62 (s, 1H), 8.11 (s, 1H), 7.99 (s, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.60 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 4.88 (s, 2H), 3.90 (s, 3H), 3.60 (s, 3H), 3.47 (s, 3H), 2.18 (s, 6H), 2.11 (s, 3H), 1.81 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.6, 159.0, 152.1, 141.4, 139.1, 133.4, 132.5, 129.7, 128.7, 126.0, 125.7, 125.6, 124.6, 117.9, 112.1, 74.6, 61.6, 55.2, 40.7, 40.7, 37.2, 37.2, 34.4, 29.2, 29.1; IR (neat): 3326, 3005, 2904, 2849, 1746, 1640, 1533, 1261, 763, 750 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{33}H_{35}Cl_3N_2O_5Na$

https://dx.doi.org/10.1021/acs.joc.0c01789
J. Org. Chem. XXXX, XXX, XXX−XXX

667.1504; found 667.1503. Purified by chromatography on silica gel, eluting with Et_2O/DCM/PE 1:10:30 (v/v/v).

Experimental Procedure for Product 3. To a Schlenk flask equipped with a stirrer were added **2** (0.2 mmol), K_2CO_3 (110.6 mg, 0.8 mmol), and DMSO (2 mL). The reaction mixture was stirred at 100 °C (heating mantle) for 24 h. Then, the reaction mixture was quenched with saturated NaCl solution (2 mL), extracted with EA three times, and then dried over Na_2SO_4. The solution was concentrated in vacuo and purified by column chromatography to give **3**.

*2-Amino-N-methoxy-N-methylbenzamide (**3a**).* TLC R_f = 0.5 (EA/PE = 1:1); brown liquid; 31.3 mg, yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 7.7 Hz, 1H), 7.17 (d, J = 7.1 Hz, 1H), 6.69 (t, J = 7.3 Hz, 2H), 4.63 (s, 2H), 3.59 (s, 3H), 3.34 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.04, 146.76, 131.43, 129.21, 117.28, 116.90, 116.69, 61.12, 34.36.; IR (neat): 3461, 3361, 2933, 2858, 1619, 1588, 1492, 1379, 977, 753 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_9H_{13}N_2O_2$ 181.0978; found 181.0972. Purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate 1:3 (v/v).

*One-Pot Experimental Procedure for **3a**.* To a Schlenk flask equipped with a stirrer were added benzamide **1a** (16.5 mg, 0.1 mmol), $TrocN_3$ (32.5 mg, 0.15 mmol), $[IrCp^*Cl_2]_2$ (4.0 mg, 0.005 mmol), AgOTf (7.7 mg, 0.03 mmol), KOAc (9.8 mg, 0.1 mmol), and DCE (1 mL) under N_2. The reaction mixture was stirred at 80 °C (heating mantle) for 24 h. The reaction was cooled to room temperature. Then, the solution was concentrated in vacuo. Then, to the reaction mixture were added K_2CO_3 (55.3 mg, 0.4 mmol) and DMSO (1 mL). The reaction mixture was stirred at 100 °C (heating mantle) for 24 h. Then, the reaction mixture was quenched with saturated NaCl solution (1 mL), extracted with EA three times, and then dried over Na_2SO_4. The solution was concentrated in vacuo and purified by column chromatography to give **3a** (12.2 mg, yield: 68%).

*2-Amino-N-methoxy-N,4-dimethylbenzamide (**3b**).* TLC R_f = 0.5 (EA/PE = 1:1); brown oil; 30.7 mg, yield: 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 7.7 Hz, 1H), 6.61−6.41 (m, 2H), 4.52 (s, 2H), 3.56 (s, 3H), 3.30 (s, 3H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.4, 147.2, 141.9, 129.4, 117.9, 117.1, 114.3, 61.0, 34.5, 21.5; IR (neat): 3705, 2966, 124, 1454, 1345, 1054, 1032, 474 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{10}H_{14}N_2O_2Na$ 217.0947; found 217.0942. Found 426.9989. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:3 (v/v).

*2-Amino-N,4-dimethoxy-N-methylbenzamide (**3d**).* TLC R_f = 0.5 (EA/PE = 1:1); colorless oil; 31.9 mg, yield: 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.7 Hz, 1H), 6.23 (d, J = 8.7 Hz, 1H), 6.17 (s, 1H), 4.90 (s, 2H), 3.77 (s, 3H), 3.58 (s, 3H), 3.32 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.4, 162.4, 149.8, 131.4, 109.3, 103.5, 100.8, 60.9, 55.1, 34.6; IR (neat): 3706, 2972, 1621, 1454, 1054, 1032, 1012 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{10}H_{14}N_2O_3Na$ 233.0896; found 233.0890. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:3 (v/v).

*Methyl 3-Amino-4-(methoxy(methyl)carbamoyl)benzoate (**3e**).* TLC R_f = 0.5 (EA/PE = 1:1); colorless oil; 38.6 mg, yield: 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.35 (m, 2H), 7.33 (d, J = 8.0 Hz, 1H), 4.67 (s, 2H), 3.89 (s, 3H), 3.55 (s, 3H), 3.34 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.1, 166.7, 146.5, 132.5, 129.2, 121.2, 117.7, 117.6, 61.3, 52.2, 33.8; IR (neat): 3705, 2971, 1633, 1453, 1054, 1032, 1013 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{11}H_{14}N_2O_4Na$ 261.0846; found 261.0840. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:3 (v/v).

*2-Amino-4-chloro-N-methoxy-N-methylbenzamide (**3g**).* TLC R_f = 0.5 (EA/PE = 1:1); brown oil; 29.1 mg, yield: 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.3 Hz, 1H), 6.69 (d, J = 2.0 Hz, 1H), 6.64 (dd, J = 8.4, 2.0 Hz, 1H), 4.77 (s, 2H), 3.56 (s, 3H), 3.33 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.2, 148.3, 137.2, 130.7, 116.9, 116.2, 115.1, 61.2, 34.0; IR (neat): 3356, 2931, 1618, 1418, 1380, 1261, 915, 760 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_9H_{11}ClN_2O_2Na$ 237.0401; found 237.0399. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:3 (v/v).

*3-Amino-N-methoxy-N-methyl-2-naphthamide (**3j**).* TLC R_f = 0.5 (EA/PE = 1:1); red solid; 40.5 mg, yield: 88%; m.p.: 73−75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 7.3 Hz, 1H), 7.40 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 7.23 (ddd, J = 8.1, 6.7, 1.2 Hz, 1H), 7.02 (s, 1H), 4.53 (s, 2H), 3.59 (s, 3H), 3.40 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.4, 143.1, 135.5, 129.2, 128.4, 127.6, 126.6, 125.5, 122.9, 121.6, 110.4, 61.3, 34.1; IR (neat): 3566, 2926, 1638, 1507, 1456, 974, 668 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{13}H_{14}N_2O_2Na$ 253.0947; found 253.0941. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:3 (v/v).

*3-Amino-N-methoxy-N-methylthiophene-2-carboxamide (**3l**).* TLC R_f = 0.5 (EA/PE = 1:1); colorless oil; 32.4 mg, yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 3.0 Hz, 1H), 6.53 (d, J = 5.5 Hz, 1H), 5.94 (s, 2H), 3.76 (s, 3H), 3.29 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.7, 155.8, 131.9, 119.4, 99.3, 61.6, 32.8; IR (neat): 3461, 3342, 2931, 1715, 1584, 1456, 967, 766 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_7H_{10}N_2O_2SNa$ 209.0355; found 209.0349. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:3 (v/v).

*6-(3-((3r,5r,7r)-Adamantan-1-yl)-4-methoxyphenyl)-3-amino-N-methoxy-N-methyl-2-naphthamide (**3n**).* TLC R_f = 0.5 (EA/PE = 1:1); red solid; 67.7 mg, yield: 72%; m.p.: 156−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.77−7.70 (m, 2H), 7.56 (d, J = 2.4 Hz, 1H), 7.49 (ddd, J = 8.5, 4.9, 2.1 Hz, 2H), 7.08 (s, 1H), 6.97 (d, J = 8.5 Hz, 1H), 4.62 (s, 2H), 3.89 (s, 3H), 3.61 (s, 3H), 3.42 (s, 3H), 2.18 (m, 6H), 2.10 (m, 3H), 1.80 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.4, 158.7, 143.5, 140.8, 138.8, 135.9, 133.2, 129.1, 128.8, 125.9, 125.6, 125.4, 122.9, 122.7, 121.0, 112.1, 110.5, 61.3, 55.2, 40.7, 37.20, 37.17, 34.2, 29.2; IR (neat): 3647, 3360, 2903, 2848, 1867, 1646, 1417, 1237 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{30}H_{34}N_2O_3Na$ 493.2461; found 493.2459. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:3 (v/v).

Experimental Procedure for Products 5−8. To a Schlenk flask equipped with a stirrer were added **2** (0.2 mmol), DIPEA (31.0 mg, 0.24 mmol), amine (0.24 mmol), and DMSO (2 mL). The reaction mixture was stirred at 100 °C (heating mantle) for 24 h. Then, the reaction mixture was quenched with saturated NaCl solution (2 mL), extracted with EA three times, and then dried over Na_2SO_4. The solution was concentrated in vacuo and purified by column chromatography to give the desired product.

*3-(2-Methoxyethyl)quinazoline-2,4(1H,3H)-dione (**5a**).* TLC R_f = 0.5 (EA/PE = 1:1); white solid; 41.1 mg, yield: 93%; m.p.: 147−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.79 (s, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.61−7.57 (m, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 8.1 Hz, 1H), 4.35 (t, J = 5.8 Hz, 2H), 3.73 (t, J = 5.8 Hz, 2H), 3.38 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.5, 152.4, 138.7, 135.0, 128.3, 123.4, 115.2, 114.5, 69.4, 58.8, 39.9; IR (neat): 3186, 3058, 2926, 2896, 1709, 1656, 1451, 1114, 1012, 757 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{11}H_{12}N_2O_3Na$ 243.0746; found 243.0741. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:3 (v/v).

*One-Pot Experimental Procedure for **5a**.* To a Schlenk flask equipped with a stirrer were added benzamide **1a** (16.5 mg, 0.1 mmol), $TrocN_3$ (32.5 mg, 0.15 mmol), $[IrCp^*Cl_2]_2$ (4.0 mg, 0.005 mmol), AgOTf (7.7 mg, 0.03 mmol), KOAc (9.8 mg, 0.1 mmol), and DCE (1 mL) under N_2. The reaction mixture was stirred at 80 °C (heating mantle) for 24 h. The reaction was cooled to room temperature. Then, the solution was concentrated in vacuo. To the reaction mixture were added DIPEA (15.5 mg, 0.12 mmol), amine **4a** (9.0 mg, 0.12 mmol), and DMSO (1 mL). The reaction mixture was stirred at 100 °C (heating mantle) for 24 h. Then, the reaction mixture was quenched with saturated NaCl solution (1 mL), extracted with EA three times, and then dried over Na_2SO_4. The solution was concentrated in vacuo and purified by column chromatography to give **5a** (14.5 mg, yield: 66%).

https://dx.doi.org/10.1021/acs.joc.0c01789
J. Org. Chem. XXXX, XXX, XXX−XXX

*3-(2-(5-Methoxy-1H-indol-2-yl)ethyl)quinazoline-2,4(1H,3H)-dione (**5b**).* TLC R_f = 0.5 (DCM/MeOH = 50:1); yellowish solid; 55.6 mg, yield: 83%; m.p.: 233−234 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (s, 1H), 10.68 (s, 1H), 7.97 (d, J = 6.0 Hz, 1H), 7.71−7.58 (m, 1H), 7.36−7.08 (m, 5H), 6.72 (d, J = 7.0 Hz, 1H), 4.16 (s, 2H), 3.74 (s, 3H), 2.95 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 162.4, 153.5, 150.6, 139.9, 135.4, 131.9, 128.1, 127.8, 123.9, 122.9, 115.5, 114.3, 112.5, 111.5, 111.3, 100.7, 55.6, 41.1, 24.0; IR (neat): 3400, 2957, 2920, 2851, 1709, 1646, 1454, 1207, 763, 747 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{19}H_{18}N_3O_3$ 336.1349; found 336.1348. Purified by chromatography on silica gel, eluting with DCM/MeOH 150:1 (v/v).

*3-(2-(Furan-2-yl)ethyl)quinazoline-2,4(1H,3H)-dione (**5c**).* TLC R_f = 0.5 (EA/PE = 1:1); white solid; 44.1 mg, yield: 86%; m.p.: 227−228 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.53 (s, 1H), 7.93 (d, J = 6.1 Hz, 1H), 7.72−7.61 (s, 1H), 7.53 (s, 1H), 7.26−7.10 (s, 2H), 6.37 (s, 1H), 6.30 (s, 1H), 5.07 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 162.0, 150.8, 150.2, 142.5, 139.8, 135.7, 127.9, 123.1, 115.7, 114.1, 111.0, 108.4, 37.0; IR (neat): 3355, 2955, 2922, 2852, 1714, 1661, 1455, 1282, 761, 751 cm^{-1}; 3355, 2955, 2922, 2852, 1714, 1661, 1455, 1282, 761, 751 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{14}H_{12}N_2O_3Na$ 279.0746; found 279.0740. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:3 (v/v).

*Quinazoline-2,4(1H,3H)-dione (**5d**).* TLC R_f = 0.5 (EA/PE = 1:1); white solid; 10.3 mg, yield: 32%; m.p.: 183−185 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.31 (s, 1H), 11.16 (s, 1H), 7.92 (d, J = 7.0 Hz, 1H), 7.67 (t, J = 7.7 Hz, 1H), 7.21 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 163.3, 150.8, 141.3, 135.4, 127.4, 122.8, 115.9, 114.8; IR (neat): 3566, 2921, 1697, 1507, 1338, 1297, 1054, 1032, 756 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_8H_6N_2O_2Na$ 185.0321; found 185.0322. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:3 (v/v).

*3-Cyclohexylquinazoline-2,4(1H,3H)-dione (**5e**).* TLC R_f = 0.5 (EA/PE = 1:1); white solid; 43.5 mg, yield: 89%; m.p.: 255−256 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.32 (s, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.22−7.09 (m, 2H), 4.72 (m, 1H), 2.43−2.31 (m, 2H), 1.84−1.74 (m, 2H), 1.61−1.55 (m, 2H), 1.37−1.25 (m, 2H), 1.22−1.00 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 162.7, 150.7, 139.8, 135.7, 127.9, 122.8, 115.2, 114.6, 53.2, 28.8, 26.5, 25.6; IR (neat): 3675, 2988, 2925, 2899, 1712, 1659, 1275, 1260, 1066, 764, 750 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{14}H_{17}N_2O_2$ 245.1291; found 245.1293. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:3 (v/v).

*3-(sec-Butyl)quinazoline-2,4(1H,3H)-dione (**5f**).* TLC R_f = 0.5 (EA/PE = 1:2); white solid; 37.1 mg, yield: 85%; m.p.: 130−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 8.12 (d, J = 7.5 Hz, 1H), 7.64−7.57 (m, 1H), 7.24−7.18 (m, 1H), 7.12 (d, J = 8.1 Hz, 1H), 5.20−5.03 (m, 1H), 2.28−2.16 (m, 1H), 1.96−1.86 (m, 1H), 1.56 (d, J = 6.9 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.0, 152.8, 138.9, 134.8, 128.4, 123.2, 114.9, 114.8, 51.7, 26.3, 17.9, 11.5; IR (neat): 3297, 3068, 2967, 2935, 1713, 1661, 1445, 1287, 757, 693 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{12}H_{15}N_2O_2$ 219.1134; found 219.1128. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:6 (v/v).

*3-(2-Methoxyethyl)-7-methylquinazoline-2,4(1H,3H)-dione (**5g**).* TLC R_f = 0.5 (EA/PE = 1:1); white solid; 37.4 mg, yield: 80%; m.p.: 211−213 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (s, 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 6.89 (s, 1H), 4.34 (t, J = 5.8 Hz, 2H), 3.72 (t, J = 5.8 Hz, 2H), 3.39 (s, 3H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.4, 152.3, 146.4, 138.7, 128.3, 124.8, 115.0, 112.2, 69.4, 58.8, 39.8, 22.0; IR (neat): 3545, 2920, 1867, 1731, 1660, 1488, 1032, 668 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{12}H_{14}N_2O_3Na$ 257.0896; found 257.0894. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:3 (v/v).

*7-Chloro-3-(2-methoxyethyl)quinazoline-2,4(1H,3H)-dione (**5h**).* TLC R_f = 0.5 (EA/PE = 1:1); white solid; 27.9 mg, yield: 55%; m.p.: 218−220 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.25 (d, J = 8.5, 2.1 Hz, 1H), 7.19 (s, 1H), 4.07 (t, J = 6.1 Hz, 2H), 3.52 (t, J = 6.1 Hz, 2H), 3.25 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 161.7, 150.5, 141.0, 139.8, 130.0, 123.2, 115.0, 113.1, 68.8, 58.4.; IR (neat): 3566, 2929, 1790, 1661, 1507, 1108, 772, 471 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{11}H_{11}ClN_2O_3Na$ 277.0350; found 277.0345. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:3 (v/v).

*3-(3-(4-Phenylpiperazin-1-yl)propyl)quinazoline-2,4(1H,3H)-dione (**6a**).* TLC R_f = 0.5 (EA/PE = 5:1); white solid; 61.1 mg, yield: 84%; m.p.: 192−193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.66 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.63−7.53 (m, 1H), 7.27−7.21 (m, 3H), 7.12 (d, J = 8.1 Hz, 1H), 6.89 (d, J = 8.2 Hz, 2H), 6.84 (t, J = 7.3 Hz, 1H), 4.27−4.15 (m, 2H), 3.14 (t, J = 5.0 Hz, 4H), 2.62 (t, J = 5.0 Hz, 4H), 2.56 (t, J = 7.1 Hz, 2H), 1.98 (p, J = 7.0 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.5, 152.3, 151.3, 138.6, 135.0, 129.1, 128.4, 123.4, 119.7, 116.0, 115.0, 114.7, 56.0, 53.1, 49.1, 39.6, 24.9; IR (neat): 3566, 2919, 2320, 1666, 1417, 1230, 925, 757 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{21}H_{25}N_4O_2$ 365.1972; found 365.1970. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 5:3 (v/v).

*7-Methyl-3-(3-(4-phenylpiperazin-1-yl)propyl)quinazoline-2,4-(1H,3H)-dione (**6b**).* TLC R_f = 0.5 (EA/PE = 5:1); white solid; 66.5 mg, yield: 88%; m.p.: 183−185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 7.2 Hz, 2H), 7.03 (d, J = 8.1 Hz, 1H), 6.92−6.80 (m, 4H), 4.19 (t, J = 7.3 Hz, 2H), 3.14 (t, J = 5.0 Hz, 4H), 2.61 (t, J = 5.0 Hz, 4H), 2.56 (t, J = 7.1 Hz, 2H), 2.42 (s, 3H), 1.97 (m, J = 7.1 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.7, 152.0, 151.3, 141.3, 139.3, 129.9, 129.1, 124.1, 119.7, 116.1, 114.8, 113.2, 55.9, 53.1, 49.2, 39.8, 24.8; IR (neat): 3566, 2919, 1790, 1646, 1373, 1231, 759, 484 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{22}H_{27}N_4O_2$ 379.2129; found 379.2128. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 5:3 (v/v).

*7-Chloro-3-(3-(4-phenylpiperazin-1-yl)propyl)quinazoline-2,4-(1H,3H)-dione (**6g**).* TLC R_f = 0.5 (EA/PE = 5:1); white solid; 63.7 mg, yield: 80%; m.p.: 206−208 °C; ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.26−7.18 (m, 3H), 7.10 (d, J = 1.8 Hz, 1H), 6.90 (d, J = 7.7 Hz, 2H), 6.84 (t, J = 7.3 Hz, 1H), 4.23−4.13 (m, 2H), 3.15 (t, J = 5.0 Hz, 4H), 2.62 (t, J = 5.0 Hz, 4H), 2.56 (t, J = 7.1 Hz, 2H), 1.97 (p, J = 7.1 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.7, 152.0, 151.3, 141.3, 139.3, 129.9, 129.1, 124.1, 119.7, 116.1, 114.8, 113.2, 55.9, 53.1, 49.2, 39.8, 24.8; IR (neat): 3566, 2918, 2321, 1730, 1660, 1423, 1245, 756 cm^{-1}; HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{21}H_{24}ClN_4O_2$ 399.1583; found 399.1578. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 5:3 (v/v).

*3-(2-(1H-Indol-3-yl)ethyl)quinazoline-2,4(1H,3H)-dione (**7a**).* TLC R_f = 0.5 (EA/PE = 5:1); white solid; 36.6 mg, yield: 60%; m.p.: 274−276 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (s, 1H), 10.90−10.81 (m, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.75−7.63 (m, 2H), 7.36 (d, J = 8.0 Hz, J = 8.0 Hz, 1H), 7.27−7.18 (m, 3H), 7.09 (t, J = 7.5 Hz, 1H), 7.05−6.97 (t, 1H), 4.23−4.11 (m, 2H), 3.04−2.92 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 162.4, 150.6, 139.9, 136.8, 135.4, 127.9, 127.7, 123.3, 123.0, 121.5, 118.8, 115.6, 114.3, 111.9, 111.5, 41.2, 24.0; IR (neat): 3566, 2918, 2308, 1770, 1688, 1507, 1388, 668 cm^{-1}; HRMS (ESI) m/z: [M + Na]$^+$ calcd for $C_{18}H_{15}N_3O_2Na$ 328.1056; found 328.1050. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 5:3 (v/v).

*3-(2-(1H-Indol-3-yl)ethyl)-7-methylquinazoline-2,4(1H,3H)-dione (**7b**).* TLC R_f = 0.5 (EA/PE = 5:1); white solid; 42.7 mg, yield: 67%; m.p.: 279−280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.42 (s, 1H), 10.86 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.21 (s, 1H), 7.11−6.97 (m, 4H), 4.15 (t, J = 8.2 Hz, 2H), 2.97 (t, J = 8.2 Hz, 2H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 162.3, 150.8, 146.1, 140.0, 136.8, 127.8, 127.7, 124.3, 123.3, 121.5, 118.83, 118.80, 115.3, 112.1, 111.9, 111.5, 41.1,

https://dx.doi.org/10.1021/acs.joc.0c01789
J. Org. Chem. XXXX, XXX, XXX−XXX

24.0, 21.9; IR (neat): 3567, 2920, 2848, 1645, 1054, 1032, 1032, 467 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{17}N_3O_2Na$ 342.1213; found 342.1206. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 5:3 (v/v).

*3-(2-(1H-Indol-3-yl)ethyl)-7-chloroquinazoline-2,4(1H,3H)-dione (**7g**).* TLC R_f = 0.5 (EA/PE = 5:1); white solid; 57.6 mg, yield: 85%; m.p.: 285−287 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1H), 10.85 (s, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.25 (m, 3H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 4.14 (t, *J* = 8.2 Hz, 2H), 2.98 (t, *J* = 8.1 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 161.69, 150.5, 141.0, 139.7, 136.8, 130.0, 127.7, 123.3, 123.2, 121.5, 118.82, 118.76, 114.9, 113.3, 111.9, 111.4, 41.3, 23.9; IR (neat): 3566, 2920, 2847, 1748, 1645, 1455, 1032, 1017 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{14}ClN_3O_2Na$ 362.0667; found 362.0671. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 5:3 (v/v).

*3-Phenethylquinazoline-2,4(1H,3H)-dione (**8a**).* TLC R_f = 0.5 (EA/PE = 5:1); white solid; 39.9 mg, yield: 75%; m.p.: 215−217 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.45 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.66 (s, 1H), 7.34−7.28 (m, 2H), 7.22 (dt, *J* = 16.1, 8.0 Hz, 5H), 4.11 (dd, *J* = 9.3, 6.7 Hz, 2H), 2.88 (dd, *J* = 9.3, 6.7 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 162.3, 150.5, 139.9, 139.1, 135.5, 129.1, 128.9, 127.8, 126.8, 123.0, 115.6, 114.2, 41.7, 33.8; IR (neat): 3566, 2920, 1715, 1649, 1454, 1281, 1032, 760 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{14}N_2O_2Na$ 289.0947; found 289.0942. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 5:3 (v/v).

*7-Methyl-3-phenethylquinazoline-2,4(1H,3H)-dione (**8b**).* TLC R_f = 0.5 (EA/PE = 5:1); white solid; 35.3 mg, yield: 63%; m.p.: 218−219 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.38 (s, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.33−7.27 (m, 2H), 7.25−7.19 (m, 3H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.96 (s, 1H), 4.10 (t, *J* = 4.0 Hz, 2H), 2.87 (m, *J* = 8.0 Hz, 2H), 2.38 (t, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 162.1, 150.6, 146.1, 139.9, 139.1, 129.1, 128.9, 127.8, 126.8, 124.4, 115.3, 112.0, 41.7, 33.8, 21.9; IR (neat): 3566, 2920, 2848, 1714, 1649, 1488, 1281, 1032 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{16}N_2O_2Na$ 303.1104; found 303.1096. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 5:3 (v/v).

*7-Chloro-3-phenethylquinazoline-2,4(1H,3H)-dione (**8g**).* TLC R_f = 0.5 (EA/PE = 5:1); white solid; 52.2 mg, yield: 87%; m.p.: 239−241 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.56 (s, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.33−7.22 (m, 6H), 7.20 (d, *J* = 2.0 Hz, 1H), 4.12−4.05 (t, *J* = 8.0 Hz, 2H), 2.87 (t, *J* = 8.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 161.6, 150.4, 141.0, 139.8, 139.0, 130.0, 129.1, 128.9, 126.8, 123.2, 115.0, 113.2, 41.8, 33.7; IR (neat): 3566, 2919, 2849, 1748, 1646, 1488, 1417, 1034 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{13}ClN_2O_2Na$ 323.0558; found 323.0555. Purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 5:3 (v/v).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01789.

Experimental details and characterization data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Hongjian Lu − *Institute of Chemistry and BioMedical Sciences, Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China;* orcid.org/0000-0001-7132-3905; Email: hongjianlu@nju.edu.cn

Authors

Xunqing Dong − *Institute of Chemistry and BioMedical Sciences, Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China*

Panpan Ma − *Institute of Chemistry and BioMedical Sciences, Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China*

Tao Zhang − *Institute of Chemistry and BioMedical Sciences, Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China*

Hitesh B. Jalani − *Department for Management of Science and Technology Development and Faculty of Applied Sciences, Ton Duc Thang University, Ho Chi Minh City 758307, Vietnam;* orcid.org/0000-0002-2442-9798

Guigen Li − *Institute of Chemistry and BioMedical Sciences, Jiangsu Key Laboratory of Advanced Organic Materials, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China; Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061, United States;* orcid.org/0000-0002-9312-412X

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c01789

Author Contributions

$^{\perp}$X.D. and P.M. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We would like to acknowledge the financial support from the National Natural Science Foundation of China (21871131), the Natural Science Foundation of Jiangsu Province (BK20191244), and the Fundamental Research Funds for the Central Universities (020514380131).

■ REFERENCES

(1) For selected reviews, see: (a) Song, G.-Y.; Wang, F.; Li, X.-W. C−C, C−O and C−N Bond Formation via Rhodium(iii)-Catalyzed Oxidative C−H Activation. *Chem. Soc. Rev.* **2012**, *41*, 3651−3678. (b) Louillat, M. L.; Patureau, F. W. Oxidative C−H Amination Reactions. *Chem. Soc. Rev.* **2014**, *43*, 901−910. (c) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. C−H Nitrogenation and Oxygenation by Ruthenium Catalysis. *Chem. Commun.* **2014**, *50*, 29−39. (d) Jiao, J.; Murakami, K.; Itami, K. Catalytic Methods for Aromatic C−H Amination: An Ideal Strategy for Nitrogen-Based Functional Molecules. *ACS Catal.* **2016**, *6*, 610−633. (e) Hazelard, D.; Nocquet, P. A.; Compain, P. Catalytic C−H Amination at Its Limits: Challenges and Solutions. *Org. Chem. Front.* **2017**, *4*, 2500−2521. (f) Park, Y.; Kim, Y.; Chang, S. Transition Metal-Catalyzed C−H Amination: Scope, Mechanism, and Applications. *Chem. Rev.* **2017**, *117*, 9247−9301. (g) Timsina, Y. N.; Gupton, B. F.; Ellis, K. C. Palladium-Catalyzed C−H Amination of $C(sp^2)$ and $C(sp^3)$−H Bonds: Mechanism and Scope for N-Based Molecule Synthesis. *ACS Catal.* **2018**, *8*, 5732−5776. (h) Singh, R.; Mukherjee, A. Metalloporphyrin Catalyzed C−H Amination. *ACS Catal.* **2019**, *9*, 3604−3617.

(2) (a) Hili, R.; Yudin, A. K. Making Carbon-Nitrogen Bonds in Biological and Chemical Synthesis. *Nat. Chem. Biol.* **2006**, *2*, 284−287. (b) Rappoport, Z., Ed. *The Chemistry of Anilines*; Wiley-VCH: Weinheim, Germany, 2007. (c) Ricci, A. *Amino Group Chemistry:*

From Synthesis to the Life Sciences; Wiley-VCH: Weinheim, Germany, 2008.

(3) For selected reviews: (a) Corbet, M.; Campo, F. D. 8-Aminoquinoline: A Powerful Directing Group in Metal-Catalyzed Direct Functionalization of C−H Bonds. *Angew. Chem., Int. Ed.* **2013**, *52*, 9896−9898. (b) Rouquet, G.; Chatani, N. Catalytic Functionalization of C(sp^2)-H and C(sp^3)-H Bonds by Using Bidentate Directing Groups. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726−11743. (c) Zhang, M.; Zhang, Y.-F.; Jie, X.-M.; Zhao, H.-Q.; Li, G.; Su, W.-P. Recent Advances in Directed C−H Functionalizations Using Monodentate Nitrogen-based Directing Groups. *Org. Chem. Front.* **2014**, *1*, 843−895. (d) Chen, Z.-K.; Wang, B.-J.; Zhang, J.-T.; Yu, W.-L.; Liu, Z.-X.; Zhang, Y.-H. Transition Metal-catalyzed C−H Bond Functionalizations by the Use of Diverse Directing Groups. *Org. Chem. Front.* **2015**, *2*, 1107−1295. (e) Daugulis, O.; Roane, J.; Tran, L. D. Bidentate, Monoanionic Auxiliary-directed Functionalization of Carbon−hydrogen Bonds. *Acc. Chem. Res.* **2015**, *48*, 1053−1064. (f) Huang, Z.-X.; Lim, H. N.; Mo, F.-Y.; Young, M. C.; Dong, G.-B. Transition Metal-catalyzed Ketone-directed or Mediated C−H Functionalization. *Chem. Soc. Rev.* **2015**, *44*, 7764−7786. (g) Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. A simple and Versatile Amide Directing Group for C−H Functionalizations. *Angew. Chem., Int. Ed.* **2016**, *55*, 10578−10599. (h) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; et al. A Comprehensive Overview of Directing Groups Applied in Metal-catalysed C−H Functionalisation Chemistry. *Chem. Soc. Rev.* **2018**, *47*, 6603−6743.

(4) (a) Rousseau, G.; Breit, B. Removable Directing Groups in Organic Synthesis and Catalysis. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450−2494. (b) Zhang, F.-Z.; Spring, D. R. Arene C-H Functionalisation Using a Removable/Modifiable or a Traceless Directing Group Strategy. *Chem. Soc. Rev.* **2014**, *43*, 6906−6919. (c) Yadav, M. R.; Rit, R. K.; Shankar, M.; Sahoo, A. K. Reusable and Removable Directing Groups for C (sp^2)−H Bond Functionalization of Arenes. *Asian J. Org. Chem.* **2015**, *4*, 846−864. (d) Zhang, F.-L.; Hong, K.; Li, T.-J.; Park, H.; Yu, J.-Q. Functionalization of C (sp^3)-H Bonds Using a Transient Directing Group. *Science* **2016**, *351*, 252−256. (e) Gandeepan, P.; Ackermann, L. Transient Directing Groups for Transformative C−H Activation by Synergistic Metal Catalysis. *Chem.* **2018**, *4*, 199−222. (f) Rej, S.; Chatani, N. Rhodium-Catalyzed C(sp^2) − or C(sp^3)−H Bond Functionalization Assisted by Removable Directing Groups. *Angew. Chem., Int. Ed.* **2019**, *58*, 8304−8329.

(5) (a) Mentzel, M.; Hoffmann, H. M. R. *N*-Methoxy-*N*-methylamides (Weinreb Amides) in Modern Organic Synthesis. *J. Prakt. Chem.* **1997**, *339*, 517−524. (b) Singh, J.; Satyamurthi, N.; Aidhen, I. S. The Growing Synthetic Utility of Weinreb's Amide. *J. Prakt. Chem.* **2000**, *342*, 340−347.

(6) (a) Kalepu, J.; Pilarski, L. T. Weinreb Amides as Directing Groups for Transition Metal-Catalyzed C−H Functionalizations. *Molecules* **2019**, *24*, 830−852. For the pioneering work in Weinreb amide directed C−H functionalizations, see: (b) Yang, F.-Z.; Ackermann, L. Ruthenium-Catalyzed C−H Oxygenation on Aryl Weinreb Amides. *Org. Lett.* **2013**, *15*, 718−720.

(7) (a) Kawai, K.; Bunno, Y.; Yoshino, T.; Matsunaga, S. Weinreb Amide Directed Versatile C−H Bond Functionalization under (η5-Pentamethylcyclopentadienyl)cobalt(III) Catalysis. *Chem. − Eur. J.* **2018**, *24*, 10231−10237. (b) Tanimoto, I.; Kawai, K.; Sato, A.; Yoshino, T.; Matsunaga, S. One-Step Synthesis of 4H-3,1-Benzoxazin-4-ones from Weinreb Amides and 1,4,2-Dioxazol-5-ones via Cobalt-Catalyzed C−H Bond Activation. *Heterocycles* **2019**, *99*, 118−125.

(8) (a) Katsuki, T. Azide Compounds: Nitrogen Sources for Atom-efficient and Ecologically Benign Nitrogen-atom-transfer Reactions. *Chem. Lett.* **2005**, *34*, 1304−1309. (b) Cenini, S.; Gallo, E.; Caselli, A.; Ragaini, F.; Fantauzzi, S.; Piangiolino, C. Coordination Chemistry of Organic Azides and Amination Reactions Catalyzed by Transition Metal Complexes. *Coord. Chem. Rev.* **2006**, *250*, 1234−1253. (c) 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. (d) Driver, T. G. Recent Advances in Transition Metal-Catalyzed *N*-Atom Transfer Reactions of Azides. *Org. Biomol. Chem.* **2010**, *8*, 3831−3846. (e) Lu, H.; Zhang, X. P. Catalytic C−H Functionalization by Metalloporphyrins: Recent Developments and Future directions. *Chem. Soc. Rev.* **2011**, *40*, 1899−1909. (f) Uchida, T.; Katsuki, T. Asymmetric Nitrene Transfer Reactions: Sulfimidation, Aziridination and C-H Amination Using Azide Compounds as Nitrene Precursors. *Chem. Rec.* **2014**, *14*, 117−129. (g) Intrieri, D.; Zardi, P.; Caselli, A.; Gallo, E. Organic Azides: "Energetic Reagents" for the Intermolecular Amination of C−H Bonds. *Chem. Commun.* **2014**, *50*, 11440−11453. (h) Shin, K.; Kim, H.; Chang, S. Transition-Metal-Catalyzed C−N Bond Forming Reactions Using Organic Azides as the Nitrogen Source: A Journey for the Mild and Versatile C−H Amination. *Acc. Chem. Res.* **2015**, *48*, 1040−1052. (i) Huang, D.; Yan, G. Recent Advances in Reactions of Azides. *Adv. Synth. Catal.* **2017**, *359*, 1600−1619.

(9) (a) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. Organic Azides: An Exploding Diversity of a Unique Class of Compounds. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188−5240. (b) Meng, G.-Y.; Guo, T.-J.; Ma, T.-C.; Zhang, J.; Shen, Y.-C.; Sharpless, K. B.; Dong, J.-J. Modular Click Chemistry Libraries for Functional Screens Using a Diazotizing Reagent. *Nature* **2019**, *574*, 86−89.

(10) (a) Ali, M. A.; Yao, X.-Y.; Li, G.-G.; Lu, H.-J. Rhodium-Catalyzed Selective Mono- and Diamination of Arenes with Single Directing Site "On Water". *Org. Lett.* **2016**, *18*, 1386−1389. (b) Yang, L. Z.; Zhang, Y. P.; Zou, X. D.; Lu, H.; Li, G. Visible-Light-Promoted Intramolecular C−H Amination in Aqueous Solution: Synthesis of Carbazoles. *Green Chem.* **2018**, *20*, 1362−1366.

(11) Zhang, T.; Hu, X.-J.; Wang, Z.; Yang, T.-T.; Sun, H.; Li, G.-G.; Lu, H.-J. Carboxylate-assisted Iridium-Catalyzed C−H Amination of Arenes with Biologically Relevant Alkyl Azides. *Chem. − Eur. J.* **2016**, *22*, 2920−2924.

(12) Organic azides with low molecular weight tend to be explosive, see (a) Scriven, E. F. V.; Turnbull, K. Azides: Their Preparation and Synthetic Uses. *Chem. Rev.* **1988**, *88*, 297−368. $BocN_3$ has been utilized in C−H amination, see (b) Kim, H.; Park, G.; Park, J.; Chang, S. A Facile Access to Primary Alkylamines and Anilines via Ir(III)-Catalyzed C−H Amidation Using Azidoformates. *ACS Catal.* **2016**, *6*, 5922−5929. $TrocN_3$ has higher molecular weight than $BocN_3$ and might be easier to be handled, and the decomposition temperature of $TrocN_3$ is 157 °C, see (c) Lu, H.-J.; Subbarayan, V.; Tao, J.-R.; Zhang, X. P. Cobalt(II)-Catalyzed Intermolecular Benzylic C−H Amination with 2,2,2-Trichloroethoxycarbonyl Azide ($TrocN_3$). *Organometallics* **2010**, *29*, 389−393.

(13) (a) Zhang, T.; Wang, Z.; Hu, X.; Yu, M.; Deng, T.; Li, G.; Lu, H. Cesium Carboxylate-Promoted Iridium Catalyzed C−H Amidation/Cyclization with 2,2,2−Trichloroethoxycarbonyl Azide. *J. Org. Chem.* **2016**, *81*, 4898−4905. (b) Zhang, T.; Hu, X.-J.; Dong, X.-Q.; Li, G.-G.; Lu, H.-J. Iridium-Catalyzed Unreactive C(sp^3)−H Amination with 2,2,2-Trichloroethoxycarbonyl Azide. *Org. Lett.* **2018**, *20*, 6260−6264.

(14) Selected examples: (a) Lu, H.-J.; Li, C.-Q.; Jiang, H.-L.; Lizardi, C. L.; Zhang, X. P. Chemoselective Amination of Propargylic C(sp^3)−H Bonds by Cobalt(II) − Based Metalloradical Catalysis. *Angew. Chem., Int. Ed.* **2014**, *53*, 7028−7032. (b) Zhang, Y.-P.; Dong, X.-Q.; Wu, Y.-N.; Li, G.-G.; Lu, H.-J. Visible-Light-Induced Intramolecular C(sp^2)−H Amination and Aziridination of Azidoformates via a Triplet Nitrene Pathway. *Org. Lett.* **2018**, *20*, 4838−4842. (c) Zhang, T.; Dong, X.-Q.; Jalani, H. B.; Zou, J.-Q.; Li, G.-G.; Lu, H.-J. Iridium-Catalyzed C−H Amination/Cyclization for Medium to Large N-Heterocycle-Fused Dihydroquinazolinones. *Org. Lett.* **2019**, *21*, 3706−3710.

(15) For selected examples: (a) Goodell, J. R.; Puig-Basagoiti, F.; Forshey, B. M.; Shi, P.; Ferguson, D. M. Identification of Compounds with Anti-West Nile Virus Activity. *J. Med. Chem.* **2006**, *49*, 2127−2137. (b) Carter, M. C.; Alber, D. G.; Robert, C.; Baxter, S. K.; Budworth, J.; ChubbG, A.; Cockerill, G. S.; Dowdell, V. C. L.; Henderson, E. A.; Keegan, S. J.; Kelsey, R. D.; Lockyer, M. J.; Stables, J. N.; Wilson, L. J.; Powell, K. L. 1,4-Benzodiazepines as Inhibitors of

https://dx.doi.org/10.1021/acs.joc.0c01789
J. Org. Chem. XXXX, XXX, XXX−XXX

Respiratory Syncytial Virus. *J. Med. Chem.* **2006**, *49*, 2311−2319. (c) Treweek, J. B.; Sun, C.; Mayorov, A. V.; Qi, L.; Levy, C. L.; Roberts, A. J.; Dickerson, T. J.; Janda, K. D. Prevention of Drug-Induced Memory Impairment by Immunopharmacotherapy. *J. Med. Chem.* **2008**, *51*, 6866−6875. (d) Acker, T. M.; Khatri, A.; Vance, K. M.; Slabber, C.; Bacsa, J.; Snyder, J. P.; Traynelis, S. F.; Liotta, D. C. Structure−Activity Relationships and Pharmacophore Model of a Noncompetitive Pyrazoline Containing Class of GluN2C/GluN2D Selective Antagonists. *J. Med. Chem.* **2013**, *56*, 6434−6456.

(16) (a) Rivero, I. A.; Espinoza, K.; Somanathan, R. Syntheses of Quinazoline-2,4-dione Alkaloids and Analogues from Mexican Zanthoxylum Species. *Molecules* **2004**, *9*, 609−616. (b) Michael, J. P. Quinoline, quinazoline and acridone alkaloids. *Nat. Prod. Rep.* **2007**, *24*, 223−246.

(17) Wippich, J.; Truchan, N.; Bach, T. Rhodium-Catalyzed N-tert-Butoxycarbonyl (Boc) Amination by Directed C-H Bond Activation. *Adv. Synth. Catal.* **2016**, *358*, 2083−2087.

(18) Chakraborti, A. K.; Sharma, L.; Sharma, U. A Mild and Chemoselective Method for Deprotection of Aryl Acetates and Benzoates under Non-Hydrolytic Condition. *Tetrahedron* **2001**, *57*, 9343−9346.

(19) (a) Jiarong, L.; Xian, C.; Daxin, S.; Shuling, M.; Qing, L.; Qi, Z.; Jianhong, T. A New and Facile Synthesis of Quinazoline-2,4(1H,3H)-diones. *Org. Lett.* **2009**, *11*, 1193−1196. (b) Dou, G.-L.; Wang, M.-M.; Shi, D.-Q. One-Pot Synthesis of Quinazolinone Derivatives from Nitro-Compounds with the Aid of Low-Valent Titanium. *J. Comb. Chem.* **2009**, *11*, 151−154. (c) Wu, X.; Yu, Z. Metal and Phosgene-free Synthesis of 1H-quinazoline-2,4-diones by Selenium-catalyzed Carbonylation of *o*-Nitrobenzamides. *Tetrahedron Lett.* **2010**, *51*, 1500−1503.

(20) (a) Leysen, J. E.; Niemegeers, C. E.; Van Nueten, J. M.; Lauduron, P. M. [3H] Ketanserin (R 41 468), a Selective 3H−ligand for Serotonin2 Receptor Binding Sites. Binding properties, Brain Distribution, and Functional Role. *Mol. Pharmacol.* **1982**, *21*, 301−314. (b) Darchen, F.; Scherman, D.; Laduron, P. M.; Henry, J. P. Ketanserin Binds to the Monoamine Transporter of Chromaffin Granules and of Synaptic Vesicles. *Mol. Pharmacol.* **1988**, *33*, 672−677.

(21) Hayao, S.; Havera, H. J.; Strycker, W. G.; Leipzig, T. J.; Kulp, R. A.; Hartzler, H. E. New Sedative and Hypotensive 3-Substituted 2,4(1H,3H)-Quinazolinediones. *J. Med. Chem.* **1965**, *8*, 807−811.

(22) (a) Jin, H.-Z.; Du, J.-L.; Zhang, W.-D.; Chen, H.-S.; Lee, J.-H.; Lee, J.-J. A Novel Alkaloid from the Fruits of Evodia Officinalis. *J. Asian Nat. Prod. Res.* **2007**, *9*, 685−688. (b) Shoji, N.; Umeyama, A.; Iuchi, A.; Saito, N.; Arihara, S.; Nomoto, K.; Ohizumi, Y. Two Novel Alkaloids from *Evodia rutaecarpa*. *J. Nat. Prod.* **1989**, *52*, 1160−1162.

(23) Zuo, G.-Y.; Yang, X.-S.; Hao, X.-J. Two New Indole Alkaloids from *Evodia rutaecarpa*. *Chin. Chem. Lett.* **2000**, *11*, 127−128.

(24) Dreyer, D. L.; Bayer, R. C. Chemotaxonomy of the Rutaceae. Part XIII. Alkaloids of some Mexican Zanthoxylum species. *Phytochemistry* **1980**, *19*, 935−939.

(25) Li, X.; Lee, Y.-R.; Kim, S.-H. Concise Synthesis of Pelanserine, Goshuyuamide II, and Wuchuyuamide II with Quinazolinedione Nuclei. *Bull. Korean Chem. Soc.* **2011**, *32*, 3480−3482.

(26) Rivero, I. A.; Espinoza, K.; Somanathan, R. Syntheses of Quinazoline-2,4-dione Alkaloids and Analogues from Mexican Zanthoxylum Species. *Molecules* **2004**, *9*, 609−616.

(27) (a) Phetcharawetch, J.; Betterley, N. M.; Soorukram, D.; Pohmakotr, M.; Reutrakul, V.; Kuhakarn, C. Synthesis of Difluoromethyl Ketones from Weinreb Amides, and Tandem Addition/Cyclization of o-Alkynylaryl Weinreb Amides. *Eur. J. Org. Chem.* **2017**, *2017*, 6840−6850. (b) Kumar, G. D. K.; Chavarria, G. E.; Charlton-Sevcik, A. K.; Arisp, W. M.; MacDonough, M. T.; Strecker, T. E.; Chen, S. E.; Siim, B. G.; Chaplin, D. J.; Trawick, M. L.; Pinney, K. G. Bioorg. Design, Synthesis, and Biological Evaluation of Potent Thiosemicarbazone Based Cathepsin L Inhibitors. *Med. Chem. Lett.* **2010**, *20*, 1415−1419. (c) Muir, C. W.; Kennedy, A. R.; Redmondb, J. M.; Watson, A. J. B. Synthesis of Functionalised 4H-quinolizin-4-ones via Tandem Horner−Wadsworth−Emmons Olefination/cyclisation. *Org. Biomol. Chem.* **2013**, *11*, 3337−3340. (d) Rudzinski, D. M.; Kellya, C. B.; Leadbeater, N. E. A Weinreb Amide Approach to the Synthesis of Trifluoromethylketones. *Chem. Commun.* **2012**, *48*, 9610−9612.

https://dx.doi.org/10.1021/acs.joc.0c01789
J. Org. Chem. XXXX, XXX, XXX−XXX