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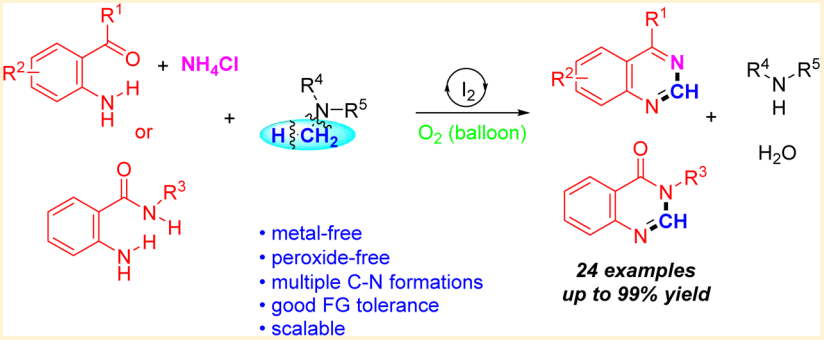
I_2-Catalyzed Aerobic Oxidative C(sp^3)–H Amination/C–N Cleavage of Tertiary Amine: Synthesis of Quinazolines and Quinazolinones

Yizhe Yan,*[,†,‡] Ying Xu,[†] Bin Niu,[†] Huifang Xie,[†] and Yanqi Liu*[,†]

[†]School of Food and Biological Engineering, Zhengzhou University of Light Industry, Zhengzhou 450000, P. R. China

[‡]Henan Collaborative Innovation Center for Food Production and Safety, Zhengzhou 450000, P. R. China

Supporting Information



ABSTRACT: An iodine-catalyzed oxidative C(sp^3)–H amination/C–N cleavage of tertiary amines couducted under an oxygen atmosphere has been developed and affords a route to quinazolines and quinazolinones in good to excellent yields via a domino ring annulation. The method is metal-free, peroxide-free, and operationally simple to implement with a wide scope of substrates and represents a new avenue for multiple C–N bond formations.

INTRODUCTION

Recently, transition metal-free intermolecular or intramolecular oxidative C(sp^3)–H aminations have emerged as important strategies for direct C–N bond formation because of inexpensive, low-toxicity, and atom and step economical advantages.[1] In 2011, hypervalent iodine(III)-mediated intermolecular oxidative C(sp^3)–H aminations were initially developed by Chang and Muniz.[2] Although the reactions avoided the use of metals, stoichiometric iodobenzene was generated as a waste product and the substrates employed remained limited to imides. More recently, we[3] and others[4] have developed iodine or iodide-mediated intramolecular and intermolecular oxidative amination of activated C(sp^3)–H bonds. However, excessive quantities of dangerous peroxide reagents were usually used as oxidants, which limited their broad applications in organic synthesis. Thus, the development of environmentally friendly catalytic systems for oxidative C(sp^3)–H amination remains challenging.

In contrast, tertiary amines serving as a carbon source via C–N bond cleavage have emerged as a useful strategy for C–C bond formation. For example, in 2009, Li reported an interesting iron-catalyzed synthesis of methylene-bridged bis-1,3-dicarbonyl derivatives from 1,3-dicarbonyl compounds using *N*,*N*-dimethylaniline as a methylene donor.[5a] Subsequently, Perumal reported a palladium-catalyzed alkylation of indole via aliphatic C–H bond activation of tertiary amines followed by C–N bond cleavage (Scheme 1a).[5b] Meanwhile, Li also reported a palladium-catalyzed oxidative coupling of trialkylamines with aryl iodides providing alkyl aryl ketones, wherein the ketone carbonyl of the ketones was derived from the carbon atom of trialkylamines.[5c] Recently, Li[5d] and Cheng[5e] also described a new route for C3-formylation of indole via copper-catalyzed C–N bond cleavage using *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as a carbonyl source. Very recently, metal-free C3-formylation of indoles has been reported by Wang[6a] and Li[6b] using *N*,*N*-dimethylaniline or TMEDA as a carbonyl source (Scheme 1b). To the best of our knowledge, tertiary amines as a carbon source for C–N bond formation have rarely been reported.

Quinazolines[7] and quinazolinones[8] are important structural units found in many natural products and pharmaceuticals. Although several good results were achieved,[3b,c,9] the development of more environmentally friendly methods remains highly desirable. As a continuation of our ongoing study of the metal-free synthesis of heterocycles,[3] herein we report a novel and efficient synthesis of quinazolines and quinazolinones via an iodine-catalyzed tandem C(sp^3)–H amination, C–N cleavage, and oxidative cyclization process (Scheme 1c). The additional carbon atom of the heterocyclic ring originates from the *N*-methyl group of tertiary amine. Two C–N bonds were formed in a one-pot reaction under metal-free conditions. Notably, molecular oxygen was used as a green and safe oxidant,

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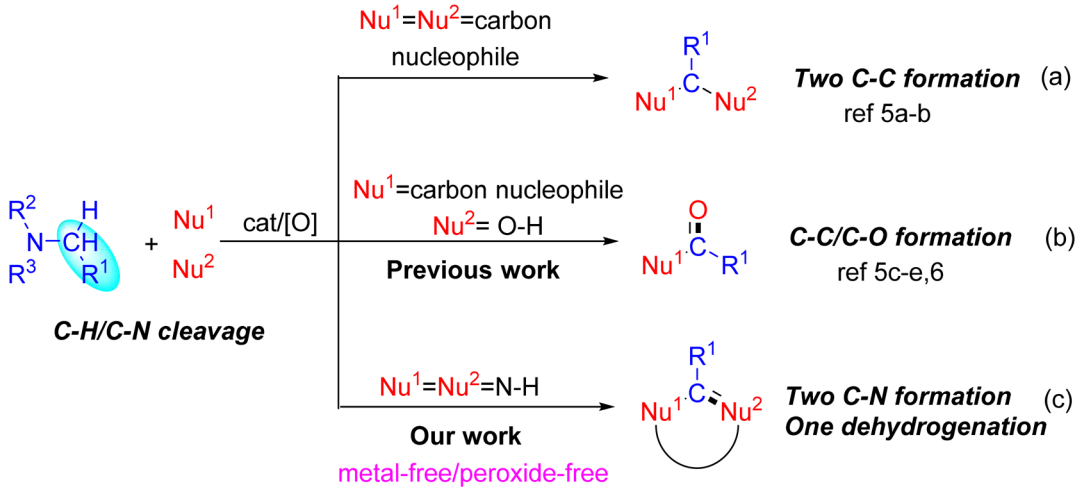
Scheme 1. New Strategies Using Tertiary Amines as a Carbon Source

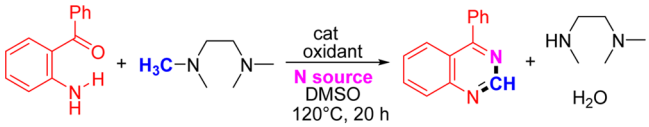


avoiding the use of peroxides, which could lead to explosion at a high temperature.

RESULTS AND DISCUSSION

Initially, we began our study with the reaction of 2-aminobenzophenone (**1a**, 0.2 mmol), TMEDA (**2a**, 2.0 equiv), ammonia (2.0 equiv), *tert*-butyl hydroperoxide (TBHP, 70% in water, 4.0 equiv) as the oxidant, and NIS (20 mol %) as the catalyst. When the reaction mixture was heated in 1 mL of DMSO at 120 °C for 20 h, 4-phenylquinazoline (**3a**) was obtained in 68% isolated yield by flash column chromatography (Table 1, entry 1). Expectedly, in the absence of ammonia or TMEDA, no desired product **3a** was detected, which indicated that ammonia may be the nitrogen source of the product and TMEDA may be the carbon source of the product (Table 1, entries 2 and 3). Then when various iodine reagents were used as the catalyst, molecular iodine gave the best result with a yield of 91% (Table 1, entries 4 and 5). Subsequently, when various nitrogen sources such as NH_4HCO_3, NH_4OAc, and NH_4Cl were examined, NH_4Cl gave the highest yield (97%) of all (Table 1, entries 6−8). Examination of various peroxides, such as di-*tert*-butylperoxide (DTBP), H_2O_2 (30% in water), and $K_2S_2O_8$, did not produce better results (Table 1, entries 9−11). Notably, **3a** was also obtained in 80% yield under air without additional oxidants (Table 1, entry 12). When oxygen (1 atm) was employed as the oxidant, the reaction would efficiently give **3a** in 97% yield (Table 1, entry 13). However, only 25% of **3a** was obtained under a nitrogen atmosphere, which indicated that molecular oxygen is essential for this reaction (Table 1, entry 14). When the reaction was conducted under solvent-free conditions with 10 equiv of TMEDA being used, **3a** was isolated in only 36% yield (Table 1, entry 15), and reducing the load of iodine to 10% decreased the yield of **3a** to 86% (Table 1, entry 16). Thus, an optimal set of conditions was determined as described in entry 13.

Table 1. Optimization of Reaction Conditions[a]



1a **2a** **3a**

entry	catalyst	oxidant	N source	yield (%)[b]
1	NIS	TBHP	NH_3(aq)	68
2	NIS	TBHP	none	not detected
3[c]	NIS	TBHP	NH_3(aq)	not detected
4	I_2	TBHP	NH_3(aq)	91
5	nBu_4NI	TBHP	NH_3(aq)	45
6	I_2	TBHP	NH_4HCO_3	74
7	I_2	TBHP	NH_4OAc	91
8	I_2	TBHP	NH_4Cl	97
9	I_2	DTBP	NH_4Cl	65
10	I_2	H_2O_2	NH_4Cl	96
11	I_2	$K_2S_2O_8$	NH_4Cl	trace
12	I_2	air	NH_4Cl	80
13	I_2	O_2 (1 atm)	NH_4Cl	97
14	I_2	N_2	NH_4Cl	25
15[d]	I_2	O_2	NH_4Cl	36
16[e]	I_2	O_2	NH_4Cl	86

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (TMEDA, 0.4 mmol), N source (0.4 mmol), catalyst (0.04 mmol), oxidant (0.8 mmol), DMSO (1 mL), 120 °C, 20 h. [b]Isolated yield. [c]No TMEDA. [d]Solvent-free, and 10 equiv of TMEDA was used. [e]In 10 mol % iodine.

Under the optimal reaction conditions, various *N*-methylamines **2b**−**2g** were employed as the carbon source for the synthesis of quinazolines (Table 2). First, when various tertiary amines such as 1-methylpiperidine (**2b**), 4-methylmorpholine (**2c**), and *N*,*N*-dimethylaniline (**2d**) were used instead of TMEDA, all the reactions gave the desired product **3a**, and **2d** gave a yield higher than those of **2b** and **2c**. In addition, using secondary amines such as *N*-methylaniline (**2e**), *N*-methylbenzylamine (**2f**), and *N*,*N*′-dimethylethylenediamine (**2g**) as carbon sources, the reaction also would generate **3a** in moderate yield, with **2e** affording a yield higher than those of **2f** and **2g**. These results clearly show that the reactivity of aromatic amines was greater than that of aliphatic amines, and the reactivity of tertiary amines was also greater than that of secondary amines. That was probably associated with the difference in the stability of the iminium iodide intermediate in the reaction pathway.

Subsequently, we investigated the substrate scope of *o*-carbonyl-substituted anilines under the optimized reaction conditions (Table 3). First, when R^1 was an aromatic substituent, substrates **1a**−**1h** could give products **3a**−**3h**, respectively, in excellent yields regardless of the electron-

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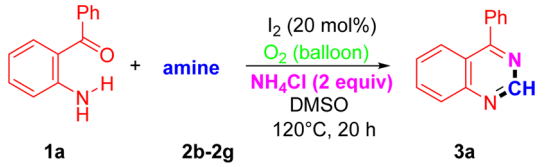
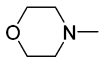
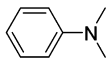
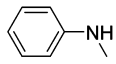
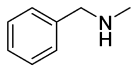
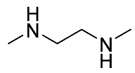
Table 2. Substrate Scope of Various Amines[a]



1a 2b-2g 3a

entry	amine		yield(%)[b]
1		**2b**	30%
2		**2c**	28%
3		**2d**	80%
4		**2e**	58%
5		**2f**	29%
6		**2g**	20%

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), NH_4Cl (0.4 mmol), I_2 (0.04 mmol), DMSO (1 mL), O_2 (1 atm), 120 °C, 20 h. [b]Isolated yield.

withdrawing (F, Cl, or Br) or electron-donating (Me) group(s) on the phenyl ring.

However, none of the desired product **3i** was obtained with **1i** bearing 2,4,6-trimethyl substituents on the phenyl ring as a substrate because of the steric effect. When R^1 was a 2-naphthyl substituent, product **3j** was obtained in a 99% isolated yield. In contrast, when R^1 was an aliphatic substituent, substrates **1k**–**1q** could give products **3k**–**3q**, respectively, in lower yields except of **1n**. Obviously, the reactivity of tertiary alkyl substituents was greater than that of the secondary and primary alkyl substituent. Finally, when Cl, Br, and NO_2 groups were introduced into position 5 of 2-aminobenzophenone, the desired products **3r**–**3t** were obtained in excellent yields. Notably, carbon–halogen bonds of the substrates remained intact during all the reactions, providing an additional handle for further derivatization. To investigate the practicability of this method, a synthesis of **3a** could be scalable from 0.2 to 10 mmol with a 90% yield, which indicated that this method could be widely applied during organic synthesis.

We next expected to utilize this novel approach for the synthesis of quinazolinones (Table 4). To our delight, the reaction of 2-amino-*N*-phenylbenzamide (**4a**) with TMEDA under standard conditions gave the desired 3-phenylquinazolin-4(3*H*)-one (**5a**) in 78% isolated yield. Similarly, 2-amino-*N*-alkylbenzamide **4b**–**4e** also afforded products **5b**–**5e**, respectively, in moderate yield (48–62%). Unfortunately, none of the desired product **5f** was formed when 2-aminobenzamide (**4f**) was used as a substrate.

To gain insight into the mechanistic aspects of the reaction, several control experiments were conducted (Scheme 2). First, radical trapping experiments were conducted, and we observed that the reaction was not inhibited at all in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as a radical scavenger (Scheme 2a). This observation implied that the reaction might not proceed via a radical pathway, which is in contrast to our previous work.[3a−c] According to Li's report,[5a] HCHO was possibly generated as an intermediate. However, when the reaction was completed, the mixture still exhibited a brown color because of the presence of iodine. The presence of HCHO could not be detected by the Nash test on the basis of a color change.

A similar reaction was performed by replacing **1a** with **6** under standard conditions (Scheme 2b). Neither Nash product **7a** nor its oxidation product, **7b**, was detected, indicating an absence of intermediate HCHO. Moreover, a ^{15}N labeling experiment was also conducted, affording [^{15}N]**3a** in 99% yield, which unambiguously established that the nitrogen atom of quinazolines was derived from NH_4Cl, rather than TMEDA (Scheme 2c).

On the basis of results described above and previous reports,[3,5,6,10]a plausible mechanism is proposed for the formation of the quinazolines (Scheme 3). Initially, the reaction of TMEDA with iodine gives an aminium iodide **A** and then generates an iminium iodide **B** by removing one molecular HI.[11] Subsequently, nucleophilic addition of **1a** to **B** provides an intermediate **C** by removal of another molecular HI. Intermediate **D** could be formed via an elimination of **C**. Then through nucleophilic addition of ammonia, **D** is transformed into addition intermediate **E**. Finally, **3a** is obtained via a tandem condensation–oxidation process of **E**. Notably, two molecular HI generated in situ are oxidized by oxygen to regenerate iodine to complete the I_2/I^- catalytic cycle.

■ CONCLUSIONS

We have developed an iodine-catalyzed aerobic domino reaction for the synthesis of quinazolines and quinazolinones. Two C–N bonds are formed in a one-pot process via C–H/C–N cleavage. The additional carbon atom of heterocycles originates from the *N*-methyl moiety of TMEDA. This novel approach is (1) metal-free, (2) peroxide-free, (3) and operationally simple and (4) has a broad substrate scope that distinguishes it from other known quinazoline and quinazolinone syntheses. Ongoing studies are being conducted to expand the synthetic utility of this versatile catalytic system.

■ EXPERIMENTAL SECTION

Unless otherwise indicated, all commercial reagents and solvents were used without additional purification. Chemical shifts (in parts per million) of ^1H NMR spectra were referenced to tetramethylsilane (δ 0) in $CDCl_3$ as an internal standard. ^{13}C NMR spectra were calibrated with $CDCl_3$ (δ 77.00). HRMS (EI) was conducted on a TOF mass analyzer.

Preparation of Substrates. Substrates **1a**, **1r**, **1t**, **2**, and **4f** are commercially available. Other substrates **1** and **4** were prepared using previously reported literature procedures.[4g,12]

Synthesis of ***4a****.*[12] Isatoic anhydride (815 mg, 5 mmol) was dissolved in EtOH (10 mL) with aniline (916 μL, 5 mmol) and I_2 (127 mg, 0.5 mmol). The mixture was stirred under reflux overnight. After cooling, the reaction mixture was concentrated in vacuo, diluted with EtOAc, washed with saturated aq $Na_2S_2O_3$, washed with brine, and dried over anhydrous Na_2SO_4. The organic phase was concentrated in

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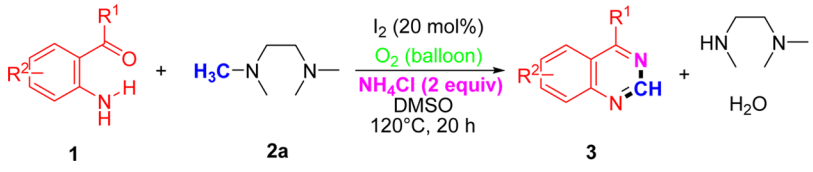
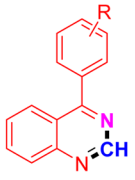
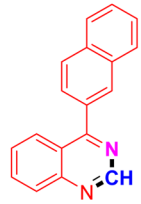
Table 3. Substrate Scope of *o*-Carbonyl Anilines[a]



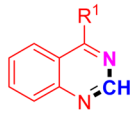
1 2a 3



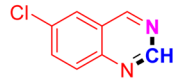
3a, R = H, 97%
3b, R = 4-F, 98%
3c, R = 4-Cl, 96%
3d, R = 4-Br, 95%
3e, R = 3,5-di-F,97%
3f, R = 3-Cl, 96%
3g, R = 4-Me, 98%
3h, R = 3-Me, 96%
3i, R = 2,4,6-tri-Me, n.d.[b]



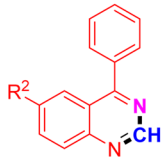
3j, 99%



3k, R^1 = *t*Bu, 85%
3l, R^1 = *i*Pr,82%
3m, R^1 = cyclopentyl, 71%
3n, R^1 = cyclopropyl, n.d.[c]
3o, R^1= *n*Bu, 35%
3p, R^1 = hexadecyl, 25%



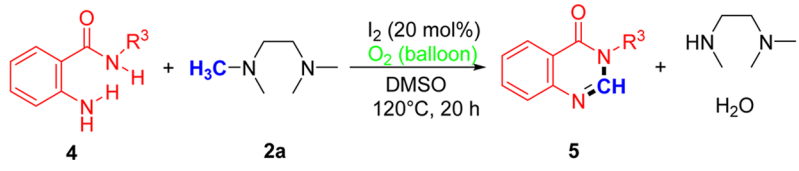
3q, 32%



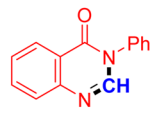
3r, R^2 = Cl,98%
3s, R^2 = Br, 96%
3t, R^2 = NO_2, 82%

[a]Reaction conditions: **1** (0.2 mmol), **2a** (TMEDA, 0.4 mmol), NH_4Cl (0.4 mmol), I_2 (0.04 mmol), DMSO (1 mL), O_2 (1 atm), 120 °C, 20 h. [b]**1i** was recovered. [c]Unknown complex mixture.

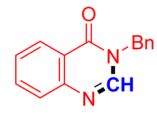
Table 4. Substrate Scope of 2-Aminobenzamides[a]



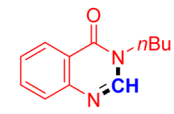
4 2a 5



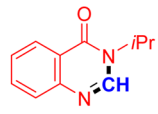
5a, 78%



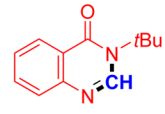
5b, 62%



5c, 55%



5d, 56%



5e, 48%

5f, n.d.

[a]Reaction conditions: **4** (0.2 mmol), **2a** (TMEDA, 0.4 mmol), I_2 (0.04 mmol), DMSO (1 mL), O_2 (1 atm), 120 °C, 20 h.

vacuum and purified with a chromatographic column on silica gel, giving 2-amino-*N*-phenylbenzamide (**4a**) as a light yellow solid (742 mg, 70% yield).

Synthesis of ***4b–4e.***[12] Isatoic anhydride (815 mg, 5 mmol) in DMF was treated with benzylamine (547 μL, 5 mmol) at 50–60 °C for 1 h. After the reaction had reached completion, the mixture was washed with H_2O and extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuum under reduced pressure, and purified with a chromatographic column on silica gel, giving 2-amino-*N*-(phenylmethyl)-benzamide (**4b**) as a white solid (1.1 g, 98% yield).

4c–4e were synthesized according to the procedure for **4b**.

General Procedure for the Synthesis of Quinazolines and Quinazolinones. Substrate **1** (0.2 mmol), I_2 (11.6 mg, 20 mol %), NH_4Cl (21.4 mg, 0.4 mmol), *N*-methylamines **2** (0.4 mmol), and DMSO (1.0 mL) were successively added to a 10 mL thick wall pressure reaction tube with a three-way valve. After oxygen displacement, the mixture was stirred using an oxygen balloon at 120 °C as monitored by TLC. The solution was then cooled to rt, diluted with EtOAc (5 mL), and washed with brine. The aqueous layers was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated under

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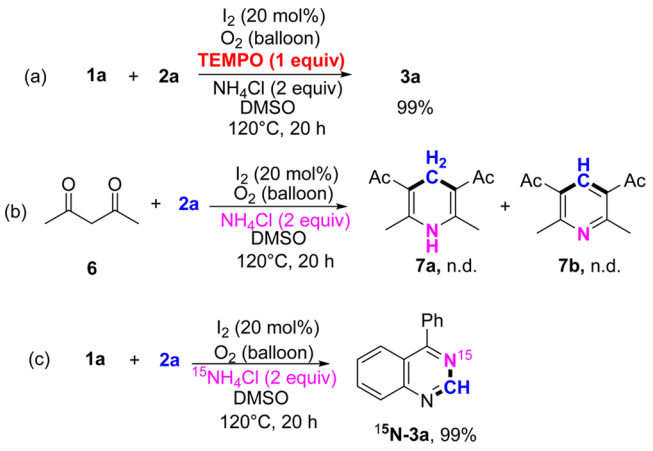
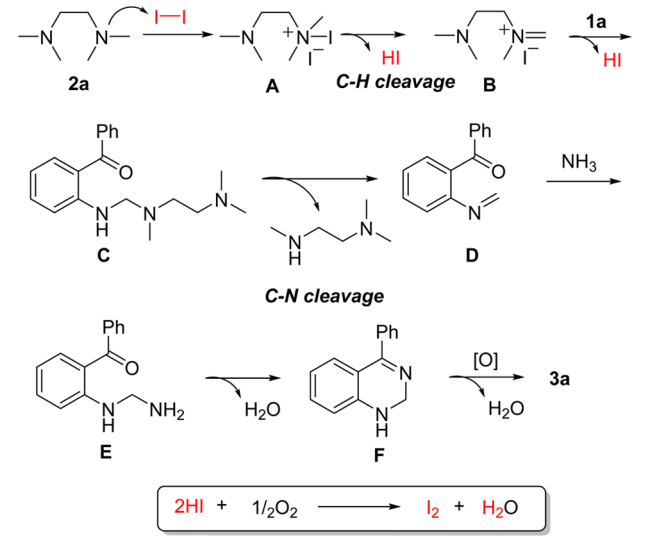
Scheme 2. Control Experiments and a ^{15}N Labeling Experiment



Scheme 3. A Proposed Mechanism



vacuum. The residue was purified by column chromatography on silica gel (3:1 petroleum ether/ethyl acetate) to afford the desired quinazolines **3**.

The experimental procedure for quinazolinones **5** was similar to the procedure for **3** without the addition of NH_4Cl.

Characterization Data for the Products. *4-Phenylquinazoline (**3a**).*[3b] Yield: 97% (40 mg). Light yellow solid. Mp: 95−97 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.39 (s, 1 H, N=CH-N or 2−Ar-H), 8.13 (d, J = 8.8 Hz, 2 H, 5,8-Ar-H), 7.95−7.90 (m, 1 H, 7-Ar-H), 7.82−7.76 (m, 2 H, 2′,6′-Ph-H), 7.64−7.56 (m, 4 H, 6-Ar-H and 3′,4′,5′-Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5 (C=N), 154.5 (N=CH-N), 150.9 (C), 137.0 (C), 133.7 (CH), 130.1 (CH), 129.9 (CH), 128.8 (CH), 128.6 (CH), 127.7 (CH), 127.1 (CH), 123.1 (C).

*4-(4-Fluorophenyl)quinazoline (**3b**).*[3b] Yield: 98% (43.9 mg). Light yellow solid. Mp: 91−93 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.37 (s, 1 H, N=CH-N), 8.13 (dd, J_1 = 13.2 Hz, J_2 = 8.4 Hz, 2 H, 5,8-Ar-H), 7.96−7.91 (m, 1 H, 7-Ar-H), 7.83−7.79 (m, 2 H, 2′,6′-Ph-H), 7.67−7.62 (m, 1 H, 6-Ar-H), 7.31−7.26 (m, 2 H, 3′,5′-Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3 (C=N), 164.0 (d, J_{C-F} = 249.3 Hz, C-F), 154.5 (N=CH-N), 151.0 (C), 133.8 (CH), 133.2 (d, J_{C-F} = 3.1 Hz, C), 132.0 (d, J_{C-F} = 8.6 Hz, CH), 128.9 (CH), 127.9 (CH), 126.7 (CH), 123.0 (C), 115.8 (d, J_{C-F} = 21.7 Hz, CH).

*4-(4-Chlorophenyl)quinazoline (**3c**).*[3b] Yield: 96% (46.1 mg). Light yellow solid. Mp: 116−118 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1 H, N=CH-N), 8.14−8.07 (m, 2 H, 5,8-Ar-H), 7.96−7.91 (m, 1 H, 7-Ar-H), 7.79−7.71 (m, 2 H, 2′,6′-Ph-H), 7.66−7.62 (m, 1 H, 6-Ar-H), 7.58−7.55 (m, 2 H, 3′,5′-Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1 (C=N), 154.6 (N=CH-N), 151.1 (C), 136.4 (C-Cl), 135.5 (C), 133.8 (CH), 131.3 (CH), 129.0 (CH), 128.9 (CH), 127.9 (CH), 126.6 (CH), 122.9 (C).

*4-(4-Bromophenyl)quinazoline (**3d**).*[3b] Yield: 95% (54 mg). Light yellow solid. Mp: 152−154 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1 H, N=CH-N), 8.16−8.07 (m, 2 H, 5,8-Ar-H), 7.96−7.91 (m, 1 H, 7-Ar-H), 7.75−7.61 (m, 5 H, 6-Ar-H and Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2 (C=N), 154.5 (N=CH-N), 151.1 (C), 135.9 (C), 133.9 (CH), 131.9 (CH), 131.5 (CH), 129.0 (CH), 128.0 (CH), 126.6 (CH), 124.8 (C-Br), 122.9 (C).

*4-(3,5-Difluorophenyl)quinazoline (**3e**).*[3b] Yield: 97% (47 mg). Light yellow solid. Mp: 100−102 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.39 (s, 1 H, N=CH-N), 8.15 (d, J = 8.4 Hz, 1 H, 8-Ar-H), 8.11−8.07 (m, 1 H, 5-Ar-H), 7.98−7.93 (m, 1 H, 7-Ar-H), 7.69−7.64 (m, 1 H, 6-Ar-H), 7.36−7.30 (m, 2 H, 2′,6′-Ph-H), 7.07−7.00 (m, 1 H, 4′-Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7 (t, J_{C-F} = 2.6 Hz, C=N), 164.2 (dd, J_{C-F1} = 249.1 Hz, J_{C-F2} = 12.4 Hz, C-F_1 and C-F_2), 154.5 (N=CH-N), 151.2 (C), 140.1 (t, J_{C-F} = 9.2 Hz, C), 134.1 (CH), 129.2 (CH), 128.3 (CH), 126.1 (CH), 122.6 (C), 113.1 (dd, J_{C-F1} = 18.9 Hz, J_{C-F2} = 7.5 Hz, CH-CF_1 and CH-CF_2), 105.4 (t, J_{C-F} = 25.0 Hz, CF_1-CH-CF_2).

*4-(3-Chlorophenyl)quinazoline (**3f**).*[3b] Yield: 96% (46.1 mg). Light yellow solid. Mp: 81−83 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1 H, N=CH-N), 8.14 (d, J = 8.4 Hz, 1 H, 8-Ar-H), 8.10−8.07 (m, 1 H, 5-Ar-H), 7.97−7.91 (m, 1 H, 7-Ar-H), 7.79 (t, J = 1.6 Hz, 1 H, 6-Ar-H), 7.68−7.62 (m, 2 H, 2′,6′-Ph-H), 7.58−7.49 (m, 2 H, 4′,5′-Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8 (C=N), 154.5 (N=CH-N), 151.1 (C), 138.8 (C-Cl), 134.7 (C), 133.9 (CH), 130.1 (CH), 129.88 (CH), 129.86 (CH), 129.0 (CH), 128.1 (CH), 128.0 (CH), 126.5 (CH), 122.9 (C).

*4-(p-Tolyl)quinazoline (**3g**).*[3b] Yield: 98% (43.1 mg). Light yellow solid. Mp: 32−34 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.37 (s, 1 H, N=CH-N), 8.18−8.09 (m, 2 H, 5,8-Ar-H), 7.93−7.88 (m, 1 H, 7-Ar-H), 7.70 (dd, J_1 = 6.4 Hz, J_2 = 1.6 Hz, 2 H, 2′,6′-Ph-H), 7.63−7.58 (m, 1 H, 6-Ar-H), 7.39 (d, J = 8.0 Hz, 2 H, 3′,5′-Ph-H), 2.48 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4 (C=N), 154.7 (N=CH-N), 151.1 (C), 140.3 (C), 134.3 (C), 133.6 (CH), 130.0 (CH), 129.3 (CH), 128.9 (CH), 127.6 (CH), 127.2 (CH), 123.2 (C), 21.4 (CH_3).

*4-(m-Tolyl)quinazoline (**3h**).*[3b] Yield: 96% (42.3 mg). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1 H, N=CH-N), 8.15−8.09 (m, 2 H, 5,8-Ar-H), 7.93−7.88 (m, 1 H, 7-Ar-H), 7.62−7.54 (m, 3 H, 6-Ar-H and 2′,6′-Ph-H), 7.45 (t, J = 7.6 Hz, 1 H, 5′-Ph-H), 7.39 (d, J = 7.6 Hz, 1 H, 4′-Ph-H), 2.48 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5 (C=N), 154.6 (N=CH-N), 151.0 (C), 138.5 (C), 137.0 (C), 133.6 (CH), 130.7 (CH), 130.4 (CH), 128.8 (CH), 128.3 (CH), 127.6 (CH), 127.14 (CH), 127.08 (CH), 123.2 (C), 21.4 (CH_3).

*4-(Naphthalen-2-yl)quinazoline (**3j**).*[3b] Yield: 99% (50.7 mg). Yellow solid. Mp: 133−135 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.43 (s, 1 H, N=CH-N), 8.26 (d, J = 1.6 Hz, 1 H, 1′-Nap-H), 8.21−8.13 (m, 2 H, 5,8-Ar-H), 8.03 (d, J = 8.8 Hz, 1 H, 7-Ar-H), 7.96−7.87 (m, 4 H, 3′4′,5′,8′-Nap-H), 7.62−7.54 (m, 3 H, 6-Ar-H and 6′,7′-Nap-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3 (C=N), 154.6 (N=CH-N), 151.1 (C), 134.4 (C), 133.9 (C), 133.7, 132.8 (C), 130.2 (CH), 128.9 (CH), 128.6 (CH), 128.4 (CH), 127.8 (CH), 127.3 (CH), 127.1 (CH), 126.8 (CH), 126.7 (CH), 123.3 (C).

*4-(tert-Butyl)quinazoline (**3k**).*[3b] Yield: 85% (31.6 mg). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 9.23 (s, 1 H, N=CH-N), 8.47 (dd, J_1 = 8.8 Hz, J_2 = 0.8 Hz, 1 H, 8-Ar-H), 8.07 (dd, J_1 = 8.8 Hz, J_2 = 0.8 Hz, 1 H, 5-Ar-H), 7.85−7.80 (m, 1 H, 7-Ar-H), 7.61−7.56 (m, 1 H, 6-Ar-H), 1.66 (s, 9 H, $3CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8 (C=N), 153.7 (N=CH-N), 151.0 (C), 132.4 (CH), 130.1 (CH), 126.5 (CH), 126.2 (CH), 123.1 (C), 40.0 (C), 30.7 (CH_3).

*4-Isopropylquinazoline (**3l**).*[3b] Yield: 82% (28.2 mg). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 9.23 (s, 1 H, N=CH-N), 8.18 (d, J = 8.4 Hz, 1 H, 8-Ar-H), 8.05 (d, J = 8.4 Hz, 1 H, 5-Ar-H), 7.90−7.85 (m, 1 H, 7-Ar-H), 7.66−7.61 (m, 1 H, 6-Ar-H), 3.94 (h, J = 6.8 Hz, 1 H,

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CH), 1.45 (d, J = 6.8 Hz, 6 H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8 (C═N), 154.7 (N═CH-N), 150.0 (C), 133.2 (CH), 129.3 (CH), 127.3 (CH), 124.1 (CH), 123.1 (C), 30.9 (CH), 21.7 (CH_3).

*4-Cyclopentylquinazoline (**3m**).*[3b] Yield: 71% (27.7 mg). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 9.23 (s, 1 H, N═CH-N), 8.21 (d, J = 8.4 Hz, 1 H, 8-Ar-H), 8.04 (d, J = 8.4 Hz, 1 H, 5-Ar-H), 7.90−7.65 (m, 2 H, 6,7-Ar-H), 4.05−4.00 (m, 1 H, CH), 2.22−2.10 (m, 4 H, $2CH_2$), 1.94−1.91 (m, 2 H, CH_2), 1.80−1.78 (m, 2 H, $2CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7 (C═N), 154.7 (N═CH-N), 149.8 (C), 133.3 (CH), 129.1 (CH), 128.3 (CH), 127.3 (CH), 124.6 (C), 42.4 (CH), 32.7 (CH_2), 26.2 (CH_2).

*4-Butylquinazoline (**3o**).* Yield: 35% (13 mg). Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 9.22 (s, 1 H, N═CH-N), 8.15 (d, J = 8.4 Hz, 1 H, 8-Ar-H), 8.04 (d, J = 8.4 Hz, 1 H, 5-Ar-H), 7.91−7.86 (m, 1 H, 7-Ar-H), 7.67−7.64 (m, 1 H, 6-Ar-H), 3.29 (t, J = 8.0 Hz, 2 H, CH_2), 1.91−1.85 (m, 2 H, CH_2), 1.54−1.48 (m, 2 H, CH_2), 1.00 (t, J = 7.6 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8 (C═N), 154.6 (N═CH-N), 149.9 (C), 133.5 (CH), 129.2 (CH), 127.5 (CH), 124.7 (CH), 124.0 (C), 34.4 (CH_2), 31.1 (CH_2), 22.9 (CH_2), 13.9 (CH_3). HRMS (EI) calcd for $C_{12}H_{14}N_2$ m/z 186.1157, found m/z 186.1145.

*4-Hexadecylquinazoline (**3p**).* Yield: 25% (17.7 mg). Yellow solid. Mp: 48−50 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.22 (s, 1 H, N═CH-N), 8.14 (dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz, 1 H, 8-Ar-H), 8.04 (d, J = 8.8 Hz, 1 H, 5-Ar-H), 7.91−7.86 (m, 1 H, 7-Ar-H), 7.66−7.62 (m, 1 H, 6-Ar-H), 3.27 (t, J = 8.0 Hz, 2 H, CH_2), 1.91−1.86 (m, 2 H, CH_2), 1.50−1.45 (m, 2 H, CH_2), 1.41−1.35 (m, 2 H, CH_2), 1.35−1.24 [m, 22 H, -$(CH_2)_{11}$-], 0.88 (t, J = 6.8 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8 (C═N), 154.6 (N═CH-N), 149.9 (C), 133.5 (CH), 129.2 (CH), 127.4 (CH), 124.7 (CH), 124.0 (CH), 34.7 (CH_2), 31.9 (CH_2), 29.74 (CH_2), 29.67 (CH_2), 29.63 (CH_2), 29.60 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3). HRMS (EI) calcd for $C_{24}H_{38}N_2$ m/z 354.3035, found m/z 354.3027.

*6-Chloroquinazoline (**3q**).*[3b] Yield: 32% (10.5 mg). Light yellow solid. Mp: 140−142 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.37 (s, 1 H, 4-Ar-H), 9.35 (s, 1 H, 2-Ar-H), 8.02 (d, J = 8.8 Hz, 1 H, 8-Ar-H), 7.94 (d, J = 2.0 Hz, 1 H, 5-Ar-H), 7.87 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1 H, 7-Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3 (CH═N), 155.5 (N═CH-N), 148.5 (C), 135.2 (CH), 133.7 (C-Cl), 130.3 (CH), 125.8 (CH), 125.6 (C).

*6-Chloro-4-phenylquinazoline (**3r**).*[3b] Yield: 98% (47 mg). Light yellow solid. Mp: 134−136 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1 H, N═CH-N), 8.11 (d, J = 2.0 Hz, 1 H, 5-Ar-H), 8.08 (d, J = 9.2 Hz, 1 H, 8-Ar-H), 7.85 (dd, J_1 = 9.2 Hz, J_2 = 2.4 Hz, 1 H, 7-Ar-H), 7.79−7.74 (m, 2 H, 2′,6′-Ph-H), 7.63−7.58 (m, 3 H, 3′,4′,5′-Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7 (C═N), 154.8 (N═CH-N), 149.5 (C), 136.5 (C), 134.7 (CH), 133.5 (C-Cl), 130.6 (CH), 130.4 (CH) 129.8 (CH), 128.8 (CH), 125.8 (CH), 123.7 (C).

*6-Bromo-4-phenylquinazoline (**3s**).*[3b] Yield: 96% (54.5 mg). Light yellow solid. Mp: 144−146 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.39 (s, 1 H, N═CH-N), 8.28 (d, J = 1.2 Hz, 1 H, 5-Ar-H), 8.00−7.96 (m, 2 H, 7,8-Ar-H), 7.79−7.74 (m, 2 H, 2′,6′-Ph-H), 7.63−7.58 (m, 3 H, 3′,4′,5′-Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6 (C═N), 154.8 (N═CH-N), 149.7 (C), 137.3 (CH), 136.5 (C), 130.7 (CH), 130.4 (CH), 129.9 (CH), 129.2 (CH), 128.9 (CH), 124.2 (C), 121.6 (C-Br).

*6-Nitro-4-phenylquinazoline (**3t**).*[3b] Yield: 82% (41.2 mg). Light yellow solid. Mp: 130−132 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.52 (s, 1 H, N═CH-N), 9.08 (d, J = 2.4 Hz, 1 H, 5-Ar-H), 8.67 (dd, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1 H, 7-Ar-H), 8.27 (d, J = 9.2 Hz, 1 H, 8-Ar-H), 7.84−7.81 (m, 2 H, 2′,6′-Ph-H), 7.68−7.62 (m, 3 H, 3′,4′,5′-Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5 (C═N), 157.2 (N═CH-N), 153.4 (C), 146.0 (C-NO_2), 135.8 (C), 131.07 (CH), 131.05 (CH), 130.1 (CH), 129.1 (CH), 127.0 (CH), 124.1 (CH), 122.0 (C).

*3-Phenylquinazolin-4(3H)-one (**5a**).*[13] Yield: 78% (34.6 mg). Yellow solid. Mp: 138−140 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.38−8.35 (m, 1H, 5-Ar-H), 8.15 (s, 1H, N═CH-N), 7.83−7.76 (m, 2H, 7,8-Ar-H), 7.58−7.42 (m, 6H, 6-Ar-H and Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7 (C═O), 147.8 (C), 146.0 (N═CH-N), 137.4 (C), 134.6 (CH), 129.6 (CH), 129.1 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 127.0 (CH), 122.4 (C).

*3-Benzylquinazolin-4(3H)-one (**5b**).*[13] Yield: 62% (29.3 mg). Light yellow solid. Mp: 120−121 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H, 5-Ar-H), 8.18 (s, 1H, N═CH-N), 7.79−7.71 (m, 2H, 7,8-Ar-H), 7.54−7.49 (m, 1H, 6-Ar-H), 7.38−7.26 (m, 5H, Ph-H), 5.21 (s, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9 (C═O), 147.6 (C), 146.4 (N═CH-N), 135.6 (C), 134.3 (CH), 129.0 (CH), 128.3 (CH), 128.0 (CH), 127.4 (CH), 127.2 (CH), 126.9 (CH), 122.0 (C), 49.6 (CH_2).

*3-Butylquinazolin-4(3H)-one (**5c**).*[14] Yield: 55% (22.2 mg). Light yellow solid. Mp: 71−73 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H, 5-Ar-H), 8.09 (s, 1H, N═CH-N), 7.79−7.71 (m, 2H, 7,8-Ar-H), 7.54−7.28 (m, 1H, 6-Ar-H), 4.02 (t, J = 7.4 Hz, 2H, CH_2), 1.83−1.75 (m, 2H, CH_2), 1.46−1.39 (m, 2H, CH_2), 0.98 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9 (C═O), 147.6 (C), 146.7 (N═CH-N), 134.2 (CH), 127.3 (CH), 127.1 (CH), 126.7 (CH), 122.0 (C), 46.9 (CH_2), 31.4 (CH_2), 19.8 (CH_2), 13.6 (CH_3).

*3-Isopropylquinazolin-4(3H)-one (**5d**).*[13] Yield: 56% (21 mg). Yellow solid. Mp: 91−93 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H, 5-Ar-H), 8.13 (s, 1H, N═CH-N), 7.78−7.69 (m, 2H, 7,8-Ar-H), 7.53−7.48 (m, 1H, 6-Ar-H), 5.20 (h, J = 6.8 Hz, 1H, CH), 1.50 (d, J = 6.8 Hz, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6 (C═O), 147.5 (C), 143.5 (N═CH-N), 134.1 (CH), 127.2 (CH), 127.1 (CH), 126.8 (CH), 121.9 (C), 46.0 (CH), 22.0 (CH_3).

*3-(tert-Butyl)quinazolin-4(3H)-one (**5e**).*[13] Yield: 48% (19.4 mg). Light yellow solid. Mp: 66−68 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.43 (s, 1H, N═CH-N), 8.30 (d, J = 8.0 Hz, 1H, 5-Ar-H), 7.76−7.74 (m, 2H, 7,8-Ar-H), 7.53−7.49 (m, 1H, 6-Ar-H), 1.78 (s, 9H, $3CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9 (C═O), 147.1 (C), 144.0 (N═CH-N), 133.9 (CH), 126.9 (CH), 126.64 (CH), 126.62 (CH), 123.0 (C), 60.8 (C), 28.6 (CH_3).

^{15}N Labeling Experiment. [^{15}N]Ammonium chloride (^{15}N, 99%, catalog no. NLM-467-1) was purchased from Cambridge Isotope Laboratories, Inc., without further purification.

Substrate **1** (0.2 mmol), I_2 (11.6 mg, 20 mol %), $^{15}NH_4Cl$ (21.8 mg, 0.4 mmol), TMEDA (60 μL, 0.4 mmol), and DMSO (1.0 mL) were successively added to a 10 mL reaction tube with a three-way valve. After oxygen displacement, the mixture was stirred using an oxygen balloon at 120 °C as monitored by TLC. The solution was then cooled to rt, diluted with EtOAc (5 mL), and washed with brine. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by column chromatography on silica gel (3:1 petroleum ether/ethyl acetate) to afford the desired product [^{15}N]**3a** (41 mg, 99% yield).

*[3-^{15}N]-4-Phenylquinazoline ([^{15}N]**3a**).* Light yellow solid. Mp: 85−87 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.39 (d, J = 14.8 Hz, 1H, N═CH−^{15}N), 8.16−8.12 (m, 2 H, 5,8-Ar-H), 7.95−7.90 (m, 1 H, 7-Ar-H), 7.82−7.76 (m, 2 H, 2′,6′-Ph-H), 7.64−7.57 (m, 4 H, 6-Ar-H and 3′,4′,5′-Ph-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4 (C═N), 154.4 (d, J = 4.3 Hz, N═CH−^{15}N), 150.9 (d, J = 3.1 Hz, C), 136.9 (d, J = 7.1 Hz, C), 133.7 (CH), 130.1 (CH), 129.9 (d, J = 1.7 Hz, CH), 128.7 (CH), 128.6 (CH), 127.7 (CH), 127.1 (CH), 123.1 (d, J = 1.4 Hz, C). HRMS (EI) calcd for $C_{14}H_{10}N^{15}N$ m/z 207.0814, found m/z 207.0804.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR and HRMS spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00474.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yanyizhe@mail.ustc.edu.cn.
*E-mail: liuyanqi@zzuli.edu.cn.

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Notes

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■ REFERENCES

(1) For recent reviews on C−H amination, see: (a) Armstrong, A.; Collins, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2282. (b) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874. (c) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, *45*, 5061. (d) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (e) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (f) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518. (g) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (h) Collet, F.; Lescot, C.; Dauban, P. *Chem. Soc. Rev.* **2011**, *40*, 1926. (i) Zalatan, D. N.; Du Bois, J. *Top. Curr. Chem.* **2010**, *292*, 347. (j) Yuan, J. W.; Liu, C.; Lei, A. W. *Chem. Commun.* **2015**, *51*, 1394.

(2) (a) Kim, H. J.; Kim, J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 16382. (b) Souto, J. A.; Zian, D.; Muniz, K. *J. Am. Chem. Soc.* **2012**, *134*, 7242.

(3) (a) Yan, Y. Z.; Zhang, Y. H.; Zha, Z. G.; Wang, Z. Y. *Org. Lett.* **2013**, *15*, 2274. (b) Yan, Y. Z.; Zhang, Y. H.; Feng, C. T.; Zha, Z. G.; Wang, Z. Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 8077. (c) Yan, Y. Z.; Wang, Z. Y. *Chem. Commun.* **2011**, *47*, 9513.

(4) For oxidative amination of C(sp^3)−H bonds attached to an electron-withdrawing group, see: (a) Ma, L. J.; Wang, X. P.; Yu, W.; Han, B. *Chem. Commun.* **2011**, *47*, 11333. (b) Lamani, M.; Prabhu, K. R. *Chem.—Eur. J.* **2012**, *18*, 14638. (c) Xie, J.; Jiang, H. L.; Cheng, Y. X.; Zhu, C. J. *Chem. Commun.* **2012**, *48*, 979. (d) Tian, J. S.; Ng, K. W. J.; Wong, J. R.; Loh, T. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9105. (e) Lao, Z. Q.; Zhong, W. H.; Lou, Q. H.; Li, Z. J.; Meng, X. B. *Org. Biomol. Chem.* **2012**, *10*, 7869. (f) Lv, Y. H.; Li, Y.; Xiong, T.; Lu, Y.; Liu, Q.; Zhang, Q. *Chem. Commun.* **2014**, *50*, 2367. For benzylic C−H bond amination, see: (g) Zhang, J. T.; Zhu, D. P.; Yu, C. M.; Wan, C. F.; Wang, Z. Y. *Org. Lett.* **2010**, *12*, 2841. (h) Xue, Q. C.; Xie, J.; Li, H. M.; Cheng, Y. X.; Zhu, C. J. *Chem. Commun.* **2013**, *49*, 3700. (i) Zhao, D.; Wang, T.; Shen, Q.; Li, J. X. *Chem. Commun.* **2014**, *50*, 4302.

(5) (a) Li, H. J.; He, Z. H.; Guo, X. W.; Li, W. J.; Zhao, X. H.; Li, Z. P. *Org. Lett.* **2009**, *11*, 4176. (b) Ramachandiran, K.; Muralidharan, D.; Perumal, P. T. *Tetrahedron Lett.* **2011**, *52*, 3579. (c) Liu, Y.; Yao, B.; Deng, C. L.; Tang, R. Y.; Zhang, X. G.; Li, J. H. *Org. Lett.* **2011**, *13*, 2184. (d) Zhang, L.; Peng, C.; Zhao, D.; Wang, Y.; Fu, H. J.; Shen, Q.; Li, J. X. *Chem. Commun.* **2012**, *48*, 5928. (e) Chen, J.; Liu, B.; Liu, D.; Liu, S.; Cheng, J. *Adv. Synth. Catal.* **2012**, *354*, 2438.

(6) (a) Li, L. T.; Li, H. Y.; Xing, L. J.; Wen, L. J.; Wang, P.; Wang, B. *Org. Biomol. Chem.* **2012**, *10*, 9519. (b) Li, X.; Gu, X. Y.; Li, Y. J.; Li, P. X. *ACS Catal.* **2014**, *4*, 1897.

(7) (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166. (b) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223. (c) Foster, B. A.; Coffrey, H. A.; Morin, M. J.; Rastinejad, F. *Science* **1999**, *286*, 2507. (d) Gundla, R.; Kazemi, R.; Sanam, R.; Muttineni, R.; Dayam, J. A. R. P. R.; Neamati, N. *J. Med. Chem.* **2008**, *51*, 3367. (e) Doyle, L. A.; Ross, D. D. *Oncogene* **2003**, *2*, 7340. (f) Fry, D. W.; Kraker, A. J.; McMichael, A.; Ambroso, L. A.; Nelson, J. M.; Leopold, W. R.; Connors, R. W.; Bridges, A. J. *Science* **1994**, *265*, 1093. (g) Luth, A.; Lowe, W. *Eur. J. Med. Chem.* **2008**, *43*, 1478. (h) Mendes da Silva, J. F.; Walters, M.; AlDamluji, S.; Ganellin, C. R. *Bioorg. Med. Chem.* **2008**, *16*, 7254. (i) Burris, H. A., III. *Oncologist* **2004**, *9*, 10.

(8) (a) Cohen, E.; Klarberg, B.; Vaughan, J. R., Jr. *J. Am. Chem. Soc.* **1959**, *81*, 5508. (b) Chen, K.; Al Aowad, A. F.; Adelstein, S. J.; Kassis, A. I. *J. Med. Chem.* **2007**, *50*, 663. (c) Parmar, S. S.; Kumar, R. *J. Med. Chem.* **1968**, *11*, 635. (d) Ma, J.; Li, P.; Li, X.; Shi, Q.; Wan, Z.; Hu, D.; Jin, L.; Song, B. *J. Agric. Food Chem.* **2014**, *62*, 8928. (e) Rörsch, F.; Buscato, E.; Deckmann, K.; Schneider, G.; Schubert-Zsilavecz, M.; Geisslinger, G.; Proschak, E.; Grösch, S. *J. Med. Chem.* **2012**, *55*, 3792.

(9) (a) Witt, A.; Bergman, J. *Curr. Org. Chem.* **2003**, *7*, 659. (b) Uff, B. C.; Joshi, B. L. *J. Chem. Soc., Perkin Trans. 1* **1986**, *12*, 2295.

(10) For reviews on oxidative functionalization of tertiary amine, see: (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (d) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (e) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464. (f) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2013**, *52*, 2.

(11) For the iminium iodide intermediate, see: (a) Leonard, N. J.; Leubner, G. H. *J. Am. Chem. Soc.* **1949**, *71*, 3408. (b) Dhineshkumar, J.; Lamani, M.; Alagiri, K.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 1092.

(12) Zhao, D.; Wang, T.; Li, J.-X. *Chem. Commun.* **2014**, *50*, 6471.

(13) Xiao, Z. L.; Yang, M. G.; Li, P.; Carter, P. H. *Org. Lett.* **2009**, *11*, 1421.

(14) Punthasee, P.; Vanitcha, A.; Wacharasindhu, S. *Tetrahedron Lett.* **2010**, *51*, 1713.

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