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Synthesis of Quinazolines from *N,N′*-Disubstituted Amidines via I_2/KI-Mediated Oxidative C−C Bond Formation

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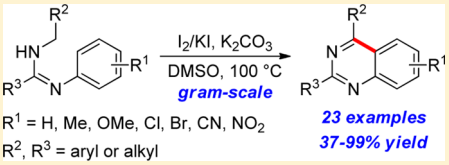
Supporting Information

ABSTRACT: An I_2/KI-promoted oxidative C−C bond formation reaction from C(sp^3)−H and C(sp^2)−H bonds has been used to construct quinazoline skeletons from *N,N′*-disubstituted amidines. The required substrates are readily prepared from the corresponding acyl chlorides, anilines, and alkyl/benzylamines by sequential amidation, chlorination, and amination reactions. Under the optimal oxidative cyclization conditions, all these amidines were conveniently transformed into the expected products in moderate to good yields. This practical and environmentally benign approach works well with crude amidine intermediates and can also be carried out on a gram scale.



INTRODUCTION

Quinazoline is an important structural motif occurring frequently in natural products[1] and synthetic molecules with diverse pharmacological properties,[2] including anticonvulsant,[3] anti-inflammatory,[4] anticancer,[5] and antimicrobial activities.[6] Vasicine, a natural quinazoline alkaloid isolated from *Adhatoda vasica*, displays bronchodilatory activity both *in vitro* and *in vivo*.[7] Prazosin is an orally available sympatholytic drug for the treatment of hypertension, anxiety, and post-traumatic stress disorder. Vandetanib is the first drug approved by FDA to treat late-stage medullary thyroid cancer, and recently, 2-arylquinazolines were identified as novel inhibitors of HIV-1 capsid assembly[8] (Figure 1).

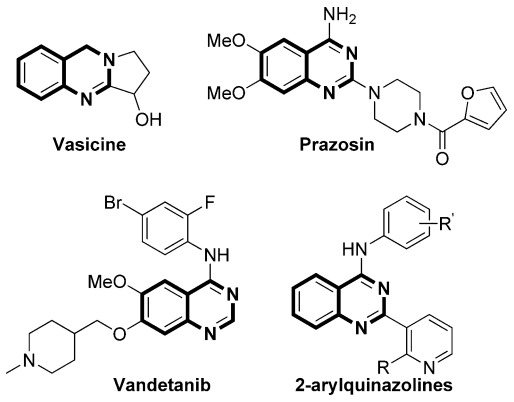
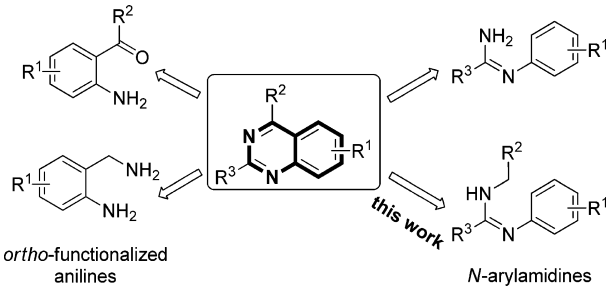


Figure 1. Representative bioactive quinazoline derivatives.

There are two general strategies for construction of the quinazoline skeleton (Scheme 1). For example, substituted quinazolines can be prepared from easily available *ortho*-functionalized anilines, such as 2-aminobenzylamines[9] and 2-aminobenzoketones.[10] Alternatively, reactions to access quinazoline derivatives have been developed using *N*-arylamidines as substrates, in which preactivation at the *ortho*-position of the *N*-aryl ring is unnecessary. In 2005, Mahajan[11] reported a microwave-promoted synthesis of quinazolines from *N*-arylamidines and aldehydes. Several transition metal-catalyzed reactions[12] have been established to produce quinazolines. In 2014, Long[13] described a PhI(OAc)$_2$-mediated synthesis of multisubstituted quinazolines from arylamidines; later, Tang[14] achieved such an oxidative cyclization reaction using visible light.

Scheme 1. Construction of Quinazoline Skeletons from *ortho*-Functionalized Anilines and *N*-Arylamidines



Molecular iodine, an inexpensive and low-toxic oxidant, enables various oxidative C−X (X = C, N, O, or S) bond construction reactions from C−H bonds enabling synthesis of heterocyclic compounds.[15] In particular, I_2-mediated oxidative C−C bond formation is a valuable tool for the synthesis of complex structures in an atom- and step-economic fashion. For example, Ma et al.[15e] have developed a series of iodine-mediated intramolecular dearomative oxidative coupling (IDOC) reactions of indoles for the total synthesis of indoline alkaloids, and Wu and co-workers[16] exploited oxidative cross-coupling reactions of aryl methyl ketones with different aromatic rings utilizing molecular iodine. In 2010, Li[17] reported an I_2-promoted 3*H*-indole synthesis from *N*-aryl enamines. In

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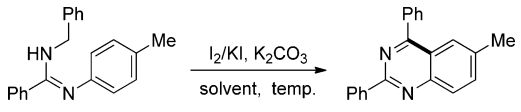
this paper, we report an I_2/KI-mediated oxidative C−C bond formation reaction to produce quinazolines from *N*,*N*′-disubstituted amidines.

RESULTS AND DISCUSSION

Amidine substrates (**1**) can be readily prepared from the corresponding acyl chlorides, anilines, and alkyl/benzylamines by sequential amidation, chlorination, and amination reactions.[13,18] Initially, amidine **1b** was chosen as the model substrate for the optimization of the reaction conditions (Table 1). Screening of commonly used solvents (entries 1−4)

Table 1. Reaction Conditions Optimization for the Synthesis of Quinazoline 2b[a]



1b **2b**

entry	I_2/equiv	additive	solvent	temp	time/h	yield[b]
1	2.4	–	CH_2Cl_2	reflux	6	trace
2	2.4	–	1,4-dioxane	reflux	5	28%
3	2.4	–	MeCN	reflux	2	32%
4	2.4	–	DMSO	100 °C	2	93%
5	2.0	–	DMSO	100 °C	5	79%
6	2.4	–	DMSO	80 °C	3	72%
7	2.4	–	DMSO	120 °C	1.5	78%
8	**2.4**	**KI**	**DMSO**	**100 °C**	**4**	**97%**

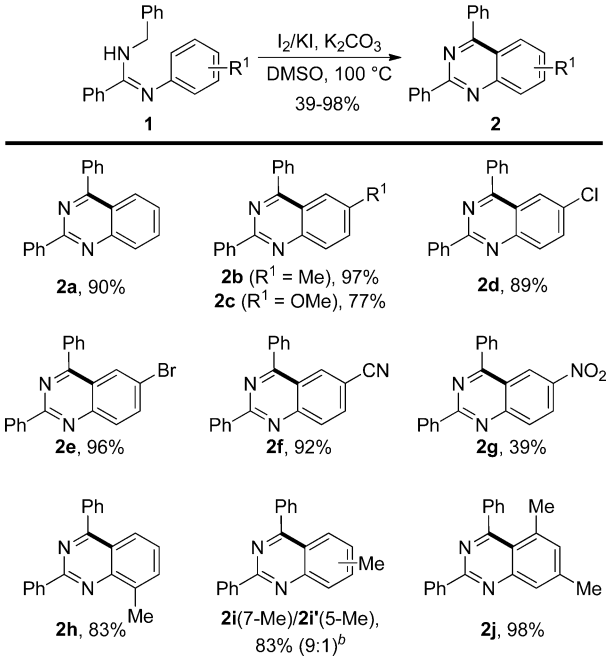
[a]Optimal reaction conditions (entry 8): To a well-stirred mixture of I_2 (0.96 mmol) and KI (0.96 mmol) in DMSO (2.5 mL) were added substrate **1b** (0.4 mmol), K_2CO_3 (1 mmol), and another 2.5 mL of DMSO in sequence, and then the mixture was heated to 100 °C for 4 h. [b]Isolated yields are given.

suggested that DMSO is the most effective medium for this I_2-mediated oxidative cyclization of **1b** to the quinazoline **2b** in the presence of potassium carbonate (K_2CO_3). Total consumption of the substrate requires at least 2.4 equiv of iodine, and the optimal reaction temperature is 100 °C (entry 4). Addition of potassium iodide (KI)[19] to the reaction system further improves the yield of the desired product (**2b**) (entry 8).

With the optimized conditions (Table 1, entry 8) in hand, we investigated the substrate scope of *N*′-aryl substituted amidines to determine the scope and generality of this method (Scheme 2). All the substrates tested were smoothly converted to the corresponding quinazolines (**2a**−**j**) in moderate to excellent yield. This methodology is compatible with both electron-donating groups (EDG) and electron-withdrawing groups (EWG) on the *N*′-phenyl ring. The substrate containing a nitro group (**1g**), the strongest EWG, was also successfully cyclized to the expected quinazoline product (**2g**), although in somewhat lower yield. Regioselective formation of quinazoline **2i** rather than **2i**′ was observed during the cyclization of *meta*-methyl substrate (**1i**), and this could be due to steric hindrance during the formation of the 5-methyl product (**2i**′).

In light of these encouraging results, we further examined the substituent effect of the R^2 and R^3 moieties on this I_2/KI-mediated oxidative C−C bond formation reaction (Scheme 3). When R^2 is an aromatic ring, it can tolerate both EDGs (**2k**−**l**) and EWGs (**2m**−**n**). 4-(4-Pyridyl)quinazoline (**2o**) is also obtained in acceptable yield from the corresponding substrate.

Scheme 2. Substrate Scope of R^1 Group on the *N*′-Phenyl Ring[a]



[a]Optimal reaction conditions: To a well-stirred mixture of I_2 (0.96 mmol) and KI (0.96 mmol) in DMSO (2.5 mL) were added substrate **1** (0.4 mmol), K_2CO_3 (1 mmol), and another 2.5 mL of DMSO in sequence, and then it was heated to 100 °C (isolated yields are given). [b]The ratio was determined by ^{1}H NMR.

Replacement of the aryl groups at the R^2 position with aliphatic groups led to 4-alkyl quinazolines (**2p**−**q**) in somewhat lower yields. Substrates bearing substituted phenyl (**1r**−**t**), α-naphthyl (**1u**), and 2-furyl groups (**1v**) at the R^3 position are all cyclized into the expected products (**2r**−**v**) in good yields. In addition, the 2-*tert*-butyl substituted quinazoline (**2w**) was also successfully prepared from the corresponding amidine.

To assess the practicality of the present methodology, we performed the quinazoline synthesis directly from simple amines and acyl chlorides, omitting purification of the amidine intermediate. The reaction of 4-methylaniline and benzoyl chloride at the 6 mmol scale afforded the desired product (**2b**) in gram scale via sequential amidation, chlorination, and amination, followed by I_2/KI-mediated oxidative cyclization (Scheme 4). The overall yield of this sequential synthetic process is comparable to that of the reactions via a purified amidine (**1b**).

A tentative reaction mechanism for the oxidative cyclization of the amidine (**1**) to quinazoline (**2**) is proposed in Scheme 5. First, oxidation of substrate **1** by molecular iodine under basic conditions gives an imine intermediate **B**. Then, iodine-mediated iodocyclization of this imine (**B**) generates a plausible *N*-iodo species **C**, containing a new C−C bond. Finally, base-promoted deprotonation followed by elimination of one molecule of hydrogen iodide (HI) produces the quinazoline framework (**2**).

CONCLUSIONS

In summary, we have developed an I_2/KI-mediated oxidative C−C bond formation reaction from C(sp^3)−H and C(sp^2)−H bonds. This practical and transition-metal-free approach provides facile access to a variety of multisubstituted quinazo-

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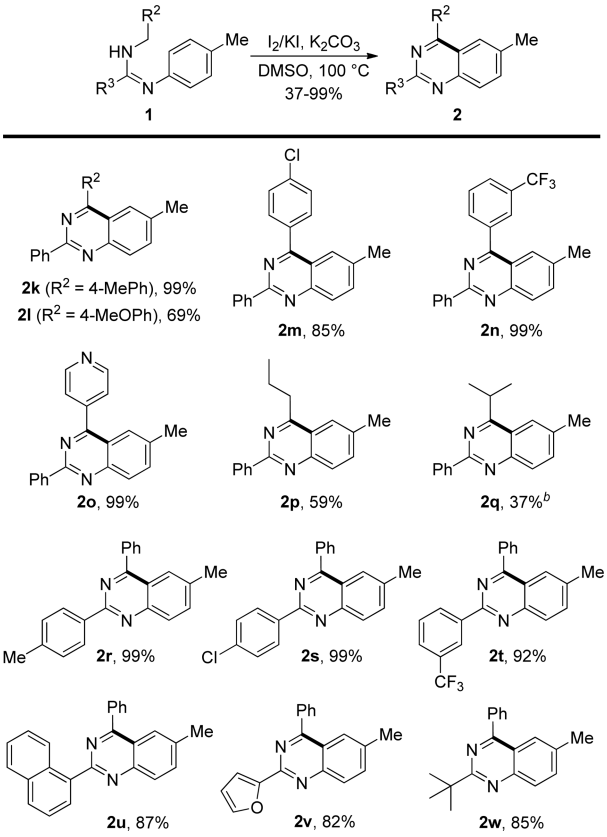
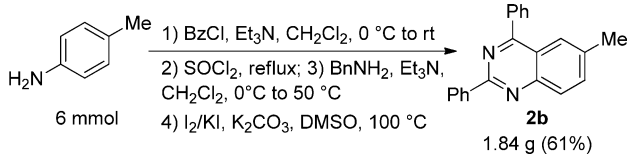
Scheme 3. Substrate Scope of R^2 and R^3 Groups[a]

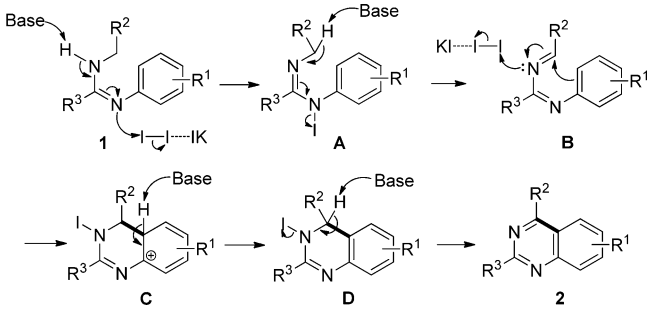


[a]Optimal reaction conditions: To a well-stirred mixture of I_2 (0.96 mmol) and KI (0.96 mmol) in DMSO (2.5 mL) were added substrate **1** (0.4 mmol), K_2CO_3 (1 mmol), and another 2.5 mL of DMSO in sequence, and then it was heated to 100 °C (isolated yields are given). [b]The reaction was performed at 110 °C.

Scheme 4. Gram-Scale Synthesis of Quinazoline 2b Omitting the Isolation of Amidine Intermediate



Scheme 5. Proposed Mechanism for the Formation of Quinazoline 2



line derivatives from readily accessible *N,N′*-disubstituted amidines. Sequential synthesis of the products from simple amines and acyl chlorides without isolation of the amidine intermediates can be conveniently conducted on a gram scale.

EXPERIMENTAL SECTION

General Information. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz (100 MHz for ^{13}C NMR) spectrometer. Chemical shift values are given in parts per million (ppm) relative to the internal standard, tetramethylsilane (TMS). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; hept, heptet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets. The coupling constants (J) are reported in hertz (Hz). Melting points were determined on a micromelting point apparatus and are uncorrected. High-resolution mass spectra (HRMS-ESI) were obtained on a TOF-Q mass spectrometer. Flash column chromatography was performed over silica gel 200−300 mesh, and the solvents were distilled prior to use. CH_2Cl_2, used in the preparation of substrates (**1**), was dried over calcium hydride (CaH_2) and distilled prior to use; DMSO, used in the synthesis of quinazolines (**2**), was analytical reagent grade and used without any pretreatment. All the chemicals (AR grade) were purchased from commercial sources and used without further purification.

*General Procedure A for the Preparation of Substrates **1a−j**.* At 0 °C, a mixture of amine **4** (3.0 mmol) and Et_3N (0.5 mL, 3.6 mmol) in anhydrous CH_2Cl_2 (10 mL) was treated slowly with acyl chloride **3** (3.3 mmol) and stirred at 0 °C for 10 min, and then at room temperature for another 20 min. The reaction was quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated to afford the amide (**5**) as a white solid. This crude amide was stirred in thionyl chloride (5 mL) at reflux for 6 h and then concentrated. The resulting residue was redissolved in toluene (5 mL × 2) and evaporated again to provide the imidoyl chloride (**6**) as a yellow oil/solid. A mixture of an aniline (**7**, 3.3 mmol) and Et_3N (0.84 mL, 6 mmol) in anhydrous CH_2Cl_2 (10 mL) was stirred at 0 °C for 10 min and then treated with a solution of the above imidoyl chloride (**6**) in anhydrous CH_2Cl_2 (5 mL). The reaction was stirred at 0 °C for 10 min and then heated at reflux for another 2 h. After cooling to room temperature, it was quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated, and purified through silica gel column chromatography to afford substrates **1a−j** (see Scheme S1 in Supporting Information).

*General Procedure B for the Preparation of Substrates **1k−w**.* At 0 °C, a mixture of aniline **7** (3.0 mmol) and Et_3N (0.5 mL, 3.6 mmol) in anhydrous CH_2Cl_2 (10 mL) was treated slowly with acyl chloride **3** (3.3 mmol) and stirred at 0 °C for 10 min, and then at room temperature for another 20 min. The reaction was quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated to afford the amide (**8**) as a white solid. The crude amide (**8**) was stirred in thionyl chloride (5 mL) at reflux for 6 h and then concentrated. The resulting residue was redissolved in toluene (5 mL × 2) and evaporated again to provide the imidoyl chloride (**9**) as a yellow oil/solid. A mixture of an amine (**4**, 3.3 mmol) and Et_3N (0.84 mL, 6 mmol) in anhydrous CH_2Cl_2 (10 mL) was stirred at 0 °C for 10 min and then treated with a solution of the above imidoyl chloride (**9**) in anhydrous CH_2Cl_2 (5 mL). The reaction was stirred at 0 °C for 10 min and then heated to reflux for another 2 h. After cooling to room temperature, it was quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified through silica gel column chromatography to afford substrates **1k−w** (see Scheme S2 in Supporting Information).

*N-Benzyl-N′-phenylbenzimidamide (**1a**).* Eluent: EtOAc/petroleum ether (PE) 15:85; yield: 456 mg, 53%; white solid, mp 98−99 °C (lit[13] 99−100 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.43 (s, 1H), 7.36 (t, J = 6.8 Hz, 2H), 7.31−7.22 (m, 6H, overlapped with the peak of chloroform), 7.06 (t, J = 6.4 Hz, 2H), 6.83−6.80 (m, 1H), 6.68−6.66 (m, 2H), 4.78 (br, s, 1H), 4.69 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 150.8, 139.0, 135.1, 129.2, 128.7, 128.6, 128.4, 128.3, 128.2, 127.5, 123.1, 121.4, 46.2; HRMS (m/z) $[M + H]^+$ calcd for $C_{20}H_{19}N_2$, 287.1543, found 287.1543.

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*N-Benzyl-N′-(p-tolyl)benzimidamide (**1b**).* Eluent: EtOAc/PE 15:85; yield: 496 mg, 55%; white solid, mp 125−126 °C (lit[14] 126−127 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.43 (s, 1H), 7.36 (t, J = 7.2 Hz, 2H), 7.31−7.23 (m, 6H, overlapped with the peak of chloroform), 6.86 (d, J = 7.6 Hz, 2H), 6.56 (d, J = 6.8 Hz, 2H), 4.69 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 148.1, 139.1, 135.3, 130.5, 129.1, 129.0, 128.7, 128.6, 128.3, 128.2, 127.4, 122.9, 46.2, 20.8; HRMS (m/z) [M + H]$^+$ calcd for $C_{21}H_{21}N_2$, 301.1699, found 301.1697.

*N-Benzyl-N′-(4-methoxyphenyl)benzimidamide (**1c**).* Eluent: EtOAc/PE 33:67; yield: 722 mg, 76%; white solid, mp 123−124 °C (lit[14] 115−117 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.42 (s, 1H), 7.36 (t, J = 7.2 Hz, 2H), 7.31−7.22 (m, 6H, overlapped with the peak of chloroform), 6.64−6.57 (m, 4H), 4.68 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 154.5, 144.0, 139.1, 135.3, 129.1, 128.7, 128.6, 128.3, 128.1, 127.4, 123.8, 113.7, 55.4, 46.2; HRMS (m/z) [M + H]$^+$ calcd for $C_{21}H_{21}N_2O$, 317.1648, found 317.1646.

*N-Benzyl-N′-(4-chlorophenyl)benzimidamide (**1d**).* Eluent: EtOAc/PE 10:90; yield: 568 mg, 59%; white solid, mp 104−105 °C (lit[13] 101−102 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 2H), 7.36 (t, J = 7.2 Hz, 2H), 7.32−7.21 (m, 6H, overlapped with the peak of chloroform), 7.00 (d, J = 8.0 Hz, 2H), 6.58 (d, J = 7.6 Hz, 2H), 4.84 (br, s, 1H), 4.67 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 149.5, 138.7, 134.7, 129.4, 128.8, 128.50, 128.47, 128.4, 128.1, 127.5, 126.5, 124.3, 46.2; HRMS (m/z) [M + H]$^+$ calcd for $C_{20}H_{18}ClN_2$, 321.1153, found 321.1156.

*N-Benzyl-N′-(4-bromophenyl)benzimidamide (**1e**).* Eluent: EtOAc/PE 10:90; yield: 669 mg, 61%; gray solid, mp 105−106 °C (lit[14] 105−106 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 2H), 7.37 (t, J = 7.2 Hz, 2H), 7.32−7.22 (m, 6H, overlapped with the peak of chloroform), 7.15 (d, J = 7.6 Hz, 2H), 6.54 (d, J = 6.8 Hz, 2H), 4.83 (br, s, 1H), 4.67 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 150.0, 138.7, 134.6, 131.4, 129.5, 128.8, 128.5, 128.1, 127.6, 124.8, 114.2, 46.2; HRMS (m/z) [M + H]$^+$ calcd for $C_{20}H_{18}BrN_2$, 365.0648, found 365.0650.

*N-Benzyl-N′-(4-cyanophenyl)benzimidamide (**1f**).* Eluent: EtOAc/PE 10:90; yield: 738 mg, 79%; white solid, mp 113−114 °C (lit[14] 117−119 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.20 (m, 12H, overlapped with the peak of chloroform), 6.69 (d, J = 8.4 Hz, 2H), 5.07 (s, 1H), 4.68 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 155.6, 138.3, 134.0, 132.7, 130.0, 128.8, 128.7, 128.4, 128.1, 127.7, 123.6, 120.0, 104.0, 46.3; HRMS (m/z) [M + H]$^+$ calcd for $C_{21}H_{18}N_3$, 312.1495, found 312.1499.

*N-Benzyl-N′-(4-nitrophenyl)benzimidamide (**1g**).*[14] Eluent: EtOAc/PE 10:90; yield: 487 mg, 49%; yellow solid, mp 131−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97−7.93 (m, 2H), 7.43−7.22 (m, 10H, overlapped with the peak of chloroform), 6.69 (d, J = 8.8 Hz, 2H), 5.14 (br, s, 1H), 4.70 (s, 1H), 4.69 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 141.9, 138.2, 133.9, 130.1, 128.9, 128.8, 128.4, 128.1, 127.7, 124.7, 123.0, 46.4; HRMS (m/z) [M + H]$^+$ calcd for $C_{20}H_{18}N_3O_2$, 332.1394, found 332.1405.

*N-Benzyl-N′-(o-tolyl)benzimidamide (**1h**).* Eluent: EtOAc/PE 10:90; yield: 703 mg, 78%; white solid, mp 71−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.18 (m, 10H, overlapped with the peak of chloroform), 7.01 (d, J = 5.2 Hz, 1H), 6.82 (s, 1H), 6.73 (s, 1H), 6.39 (s, 1H), 4.82 (br, s, 1H), 4.70 (s, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 149.5, 139.4, 135.4, 130.1, 129.8, 129.3, 128.7, 128.3, 128.1, 127.3, 125.9, 122.4, 121.6, 46.0, 18.5; HRMS (m/z) [M + H]$^+$ calcd for $C_{21}H_{21}N_2$, 301.1699, found 301.1691.

*N-Benzyl-N′-(m-tolyl)benzimidamide (**1i**).* Eluent: EtOAc/PE 10:90; yield: 757 mg, 84%; white solid, mp 110−111 °C (lit[14] 106−107 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.24 (m, 10H, overlapped with the peak of chloroform), 6.92 (t, J = 7.2 Hz, 1H), 6.63 (d, J = 6.8 Hz, 1H), 6.57 (s, 1H), 6.42 (s, 1H), 4.76 (br, s, 1H), 4.69 (s, 2H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 150.7, 139.1, 138.0, 135.2, 129.2, 128.7, 128.6, 128.3, 128.1, 127.4, 123.9, 122.2, 120.0, 46.2, 21.4; HRMS (m/z) [M + H]$^+$ calcd for $C_{21}H_{21}N_2$, 301.1699, found 301.1696.

*N-Benzyl-N′-(3,5-dimethylphenyl)benzimidamide (**1j**).* Eluent: EtOAc/PE 15:85; yield: 557 mg, 59%; white solid, mp 84−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.23 (m, 9H), 6.46 (s, 2H), 6.31 (s, 2H), 4.67 (s, 3H), 2.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 150.5, 139.2, 137.7, 135.2, 129.1, 128.7, 128.5, 128.3, 128.1, 127.4, 123.1, 120.8, 46.2, 21.3; HRMS (m/z) [M + H]$^+$ calcd for $C_{22}H_{23}N_2$, 315.1856, found 315.1856.

*N-(4-Methylbenzyl)-N′-(p-tolyl)benzimidamide (**1k**).* Eluent: EtOAc/PE 20:80; yield: 585 mg, 62%; white solid, mp 98−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.15 (m, 9H, overlapped with the peak of chloroform), 6.85 (d, J = 7.2 Hz, 2H), 6.56 (d, J = 6.4 Hz, 2H), 4.63 (s, 3H), 2.34 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 148.1, 137.1, 136.0, 135.4, 130.5, 129.4, 129.1, 128.6, 128.3, 128.2, 122.9, 46.1, 21.2, 20.8; HRMS (m/z) [M + H]$^+$ calcd for $C_{22}H_{23}N_2$, 315.1856, found 315.1858.

*N-(4-Methoxybenzyl)-N′-(p-tolyl)benzimidamide (**1l**).* Eluent: EtOAc/PE 30:70; yield: 971 mg, 98%; light yellow solid, mp 117−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.22 (m, 7H, overlapped with the peak of chloroformR), 6.90−6.85 (m, 4H), 6.56 (d, J = 6.4 Hz, 2H), 4.61 (s, 3H), 3.80 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 157.1, 148.1, 135.4, 131.1, 130.5, 129.5, 129.1, 129.0, 128.6, 128.3, 122.9, 114.1, 55.3, 45.7, 20.8; HRMS (m/z) [M + H]$^+$ calcd for $C_{22}H_{23}N_2O$, 331.1805, found 331.1806.

*N-(4-Chlorobenzyl)-N′-(p-tolyl)benzimidamide (**1m**).* Eluent: EtOAc/PE 20:80; yield: 633 mg, 63%; white solid, mp 94−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.32 (m, 9H, overlapped with the peak of chloroform), 6.86 (d, J = 7.6 Hz, 2H), 6.54 (d, J = 5.2 Hz, 2H), 4.65 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 137.7, 135.1, 133.1, 130.7, 129.4, 129.2, 129.0, 128.8, 128.5, 128.3, 122.7, 45.3, 20.8; HRMS (m/z) [M + H]$^+$ calcd for $C_{21}H_{20}ClN_2$, 335.1310, found 335.1318.

*N′-(p-Tolyl)-N-(3-(trifluoromethyl)benzyl)benzimidamide (**1n**).* Eluent: EtOAc/PE 20:80; yield: 685 mg, 62%; white solid, mp 75−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.63 (d, J = 6.4 Hz, 1H), 7.55−7.44 (m, 2H), 7.25 (m, 5H, overlapped with the peak of chloroform), 6.86 (d, J = 6.8 Hz, 2H), 6.55 (s, 2H), 4.74 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 147.7, 140.4, 135.0, 131.4, 131.2 (d, J = 31.7 Hz, partially overlapped with other peaks), 130.8, 130.4, 129.3, 129.1, 128.5, 128.4, 124.7, 124.16 (q, J = 271.1 Hz, partially overlapped with other peaks), 124.10 (q, J = 3.6 Hz), 122.7, 45.4, 20.8; HRMS (m/z) [M + H]$^+$ calcd for $C_{22}H_{20}F_3N_2$, 369.1573, found 369.1571.

*N-(Pyridin-4-ylmethyl)-N′-(p-tolyl)benzimidamide (**1o**).* Eluent: EtOAc/PE 20:80; yield: 488 mg, 54%; white solid, mp 212−213 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.53 (s, 1H), 7.33−7.25 (m, 7H, overlapped with the peak of chloroform), 6.86 (d, J = 4.8 Hz, 2H), 6.52 (s, 2H), 5.02 (br, s, 1H), 4.70 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 149.9, 148.5, 134.8, 130.9, 129.4, 129.1, 128.4, 122.5, 44.6, 20.8; HRMS (m/z) [M + H]$^+$ calcd for $C_{20}H_{20}N_3$, 302.1652, found 302.1650.

*N-Butyl-N′-(p-tolyl)benzimidamide (**1p**).* Eluent: EtOAc/PE 33:67; yield: 607 mg, 76%; white solid, mp 91−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.20 (m, 5H), 6.83 (d, J = 7.6 Hz, 2H), 6.51 (d, J = 7.6 Hz, 2H), 4.44 (br, s, 1H), 3.49 (s, 2H), 2.17 (s, 3H), 1.68−1.60 (m, 2H), 1.51−1.41 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 148.3, 135.7, 130.3, 128.9, 128.6, 128.2, 122.9, 121.7, 41.7, 31.5, 20.8, 20.4, 14.0; HRMS (m/z) [M + H]$^+$ calcd for $C_{18}H_{23}N_2$, 267.1856, found 267.1858.

*N-Isobutyl-N′-(p-tolyl)benzimidamide (**1q**).* Eluent: EtOAc/PE 30:70; yield: 631 mg, 79%; white solid, mp 84−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of tautomers, *peaks of the minor one) δ 7.61* (m, 0.3H), 7.42* (m, 0.5H), 7.24−7.22 (m, 4.3H), 7.15* (m, 0.3H), 6.85* (m, 0.3H), 6.83 (d, J = 7.6 Hz, 1.7H), 6.51 (d, J = 7.2 Hz, 1.7H), 4.68* (br, s, 0.2H), 4.49 (br, s, 0.8H), 3.34 (s, 1.7H), 2.83* (s, 0.3H), 2.33* (s, 0.5H), 2.17 (s, 2.6H), 1.96 (hept, J = 6.4 Hz, 1H), 1.02 (d, J = 6.4 Hz, 5.2H), 0.75* (m, 0.9H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of tautomers, *peaks of the minor one) δ 159.4*, 157.6, 148.4, 146.9*, 136.2*, 135.9, 132.0*, 130.2, 129.5*, 128.9, 128.6, 128.2, 122.9, 121.7, 52.4*, 49.2, 30.0*, 28.3, 20.7, 20.5, 19.8*;

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HRMS (m/z) [M + H]$^+$ calcd for $C_{18}H_{23}N_2$, 267.1856, found 267.1856.

*N-Benzyl-4-methyl-N′-(p-tolyl)benzimidamide (**1r**).* Eluent: EtOAc/PE 20:80; yield: 877 mg, 93%; white solid, mp 76−77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 7.14 (s, 2H), 7.05 (s, 2H), 6.89 (s, 2H), 6.60 (s, 2H), 4.65 (s, 3H), 2.28 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 148.1, 139.0, 132.1, 130.5, 129.1, 128.7, 128.5, 128.0, 127.4, 122.8, 120.4, 46.3, 21.4, 20.8; HRMS (m/z) [M + H]$^+$ calcd for $C_{22}H_{23}N_2$, 315.1856, found 315.1854.

*N-Benzyl-4-chloro-N′-(p-tolyl)benzimidamide (**1s**).* Eluent: EtOAc/PE 10:90; yield: 723 mg, 72%; white solid, mp 92−93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 2H), 7.34 (t, J = 7.2 Hz, 2H), 7.28 (d, J = 6.8 Hz, 1H), 7.15 (m, 4H), 6.86 (d, J = 7.2 Hz, 2H), 6.52 (d, J = 6.8 Hz, 2H), 4.74 (br, s, 1H), 4.63 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 147.8, 139.0, 135.1, 133.6, 130.8, 130.0, 129.2, 128.8, 128.6, 128.2, 127.5, 122.7, 46.2, 20.8; HRMS (m/z) [M + H]$^+$ calcd for $C_{21}H_{20}ClN_2$, 335.1310, found 335.1309.

*N-Benzyl-N′-(p-tolyl)-3-(trifluoromethyl)benzimidamide (**1t**).* Eluent: EtOAc/PE 5:95; yield: 1.006g, 91%; white solid, mp 103−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of tautomers, *peaks of the minor one) δ 7.89−7.67* (m, 0.8H), 7.53−7.23 (m, 8H, overlapped with the peak of chloroform), 7.13−7.12* (m, 0.8H), 6.86 (d, J = 6.8 Hz, 1.6H), 6.82−6.81* (m, 0.2H), 6.52 (d, J = 6.0 Hz, 1.6H), 5.04* (br, s, 0.2H), 4.77 (br, s, 0.8H), 4.67 (s, 1.6H), 4.17−4.16* (m, 0.3H), 2.30* (s, 0.6H), 2.18 (s, 2.4H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of tautomers, *peaks of the minor one) δ 157.6*, 155.5, 147.5, 146.1*, 138.7, 138.6*, 136.6*, 136.0, 132.7*, 132.1, 131.7*, 131.0, 130.7 (q, J = 32.2 Hz), 130.3*, 129.2, 129.0*, 128.8, 128.2, 127.6, 126.9*, 126.5*, 125.8 (d, J = 3.5 Hz), 125.3 (d, J = 3.7 Hz), 123.7 (q, J = 271.0 Hz), 122.7, 121.3*, 48.9*, 46.3, 20.9*, 20.7; HRMS (m/z) [M + H]$^+$ calcd for $C_{22}H_{20}F_3N_2$, 369.1573, found 369.1575.

*N-Benzyl-N′-(p-tolyl)-1-naphthimidamide (**1u**).* Eluent: EtOAc/PE 20:80; yield: 967 mg, 92%; light yellow solid, mp 96−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.74 (t, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 1H), 7.45 (m, 4H), 7.37 (t, J = 7.2 Hz, 2H), 7.30 (d, J = 6.8 Hz, 1H), 7.22−7.17 (m, 1H), 6.82 (d, J = 7.6 Hz, 2H), 6.61 (d, J = 7.2 Hz, 2H), 4.86 (br, s, 1H), 4.73 (s, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 148.0, 139.1, 133.3, 133.0, 132.8, 130.6, 129.1, 128.7, 128.3, 128.2, 128.1, 127.81, 127.77, 127.5, 126.9, 126.5, 126.0, 122.9, 46.4, 20.8; HRMS (m/z) [M + H]$^+$ calcd for $C_{25}H_{23}N_2$, 351.1856, found 351.1855.

*N-Benzyl-N′-(p-tolyl)furan-2-carboximidamide (**1v**).*[20] Eluent: EtOAc/PE 5:95; yield: 610 mg, 70%; white solid, mp 74−75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.43 (s, 1H), 7.37 (t, J = 7.6 Hz, 2H), 7.31−7.24 (m, 2H, overlapped with the peak of chloroform), 7.07 (d, J = 8.4 Hz, 2H), 6.72 (d, J = 8.0 Hz, 2H), 6.21 (s, 1H), 5.67 (s, 1H), 5.55 (br, s, 1H), 4.66 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 145.7, 144.6, 141.6, 139.1, 131.4, 129.7, 128.7, 128.2, 127.4, 121.3, 114.6, 111.6, 45.5, 20.9; HRMS (m/z) [M + H]$^+$ calcd for $C_{19}H_{19}N_2O$, 291.1492, found 291.1493.

*N-Benzyl-N′-(p-tolyl)pivalimidamide (**1w**).* Eluent: EtOAc/PE 30:70; yield: 606 mg, 72%; white solid, mp 41−42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.21 (m, 3H, overlapped with the peak of chloroform), 7.16 (d, J = 6.8 Hz, 2H), 6.96 (d, J = 7.6 Hz, 2H), 6.69 (d, J = 8.4 Hz, 2H), 4.52 (s, 1H), 3.98 (s, 2H), 2.26 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 148.7, 139.4, 129.8, 129.0, 128.6, 127.8, 127.4, 121.0, 48.5, 38.8, 29.3, 20.8; HRMS (m/z) [M + H]$^+$ calcd for $C_{19}H_{25}N_2$, 281.2012, found 281.2014.

*General Procedure for the Synthesis of Products (**2**).* A mixture of iodine (244 mg, 0.96 mmol) and KI (160 mg, 0.96 mmol) in DMSO (2.5 mL) was stirred at room temperature for 10 min and then treated with substrate **1** (0.40 mmol), followed by addition of K_2CO_3 (139 mg, 1 mmol) and a further 2.5 mL of DMSO. The reaction was heated to 100 °C until TLC indicated the conversion was complete. After cooling to room temperature, it was quenched with 5% $Na_2S_2O_3$ (15 mL) and then extracted with EtOAc (15 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and then purified through silica gel column chromatography to afford the desired product **2**.

*2,4-Diphenylquinazoline (**2a**).* 3 h; eluent: EtOAc/PE 1:99; yield: 102 mg, 90%; white solid, mp 109−110 °C (lit[14] 112−113 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71−8.68 (m, 2H), 8.17−8.11 (m, 2H), 7.90−7.85 (m, 3H), 7.61−7.49 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 160.3, 152.0, 138.2, 137.7, 133.6, 130.5, 130.2, 130.0, 129.2, 128.7, 128.6, 127.0, 121.7; HRMS (m/z) [M + H]$^+$ calcd for $C_{20}H_{15}N_2$, 283.1230, found 283.1230.

*6-Methyl-2,4-diphenylquinazoline (**2b**).* The 0.5 mmol scale reaction was carried out using purified substrate **1b**, 4 h; yield: 115 mg, 97%; the 6 mmol scale synthesis was performed using crude substrate **1b** (obtained via General Procedure A), 5 h; overall yield: 1.077 g, 61% (from 4-methylaniline). Eluent: EtOAc/PE 2:98; white solid, mp 174−176 °C (lit[14] 167−170 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 7.2 Hz, 2H), 8.06 (d, J = 8.8 Hz, 1H), 7.87 (m, 3H), 7.72 (d, J = 8.8 Hz, 1H), 7.61−7.59 (m, 3H), 7.54−7.48 (m, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 159.7, 150.7, 138.4, 138.0, 137.3, 135.9, 130.4, 130.3, 129.9, 129.0, 128.67, 128.65, 128.64, 125.7, 121.8, 22.0; HRMS (m/z) [M + H]$^+$ calcd for $C_{21}H_{17}N_2$, 297.1386, found 297.1384.

*6-Methoxy-2,4-diphenylquinazoline (**2c**).* 3.5 h; eluent: EtOAc/PE 3:97; yield: 96 mg, 77%; light yellow solid, mp 141−142 °C (lit[14] 142−144 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66−8.63 (m, 2H), 8.06 (d, J = 9.2 Hz, 1H), 7.91−7.88 (m, 2H), 7.60−7.46 (m, 7H), 7.38 (d, J = 2.8 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 158.7, 158.1, 148.2, 138.4, 138.0, 130.7, 130.1, 129.9, 129.8, 128.6, 128.5, 128.3, 126.2, 122.5, 104.4, 55.7; HRMS (m/z) [M + H]$^+$ calcd for $C_{21}H_{17}N_2O$, 313.1335, found 313.1336.

*6-Chloro-2,4-diphenylquinazoline (**2d**).* 5 h; eluent: EtOAc/PE 1:99; yield: 113 mg, 89%; white solid, mp 195−196 °C (lit[14] 194−195 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68−8.65 (m, 2H), 8.10−8.07 (m, 2H), 7.87−7.84 (m, 2H), 7.79 (dd, J = 9.2, 2.4 Hz, 1H), 7.62−7.59 (m, 3H), 7.54−7.49 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 160.5, 150.5, 137.8, 137.1, 134.5, 132.6, 130.9, 130.8, 130.3, 130.1, 128.8, 128.7, 128.6, 125.8, 122.2; HRMS (m/z) [M + H]$^+$ calcd for $C_{20}H_{14}ClN_2$, 317.0846, found 317.0857.

*6-Bromo-2,4-diphenylquinazoline (**2e**).* 4.5 h; eluent: EtOAc/PE 1:99; yield: 139 mg, 96%; white solid, mp 205−207 °C (lit[14] 203−205 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68−8.65 (m, 2H), 8.25 (d, J = 2.0 Hz, 1H), 8.03−8.00 (m, 1H), 7.95−7.91 (m, 1H), 7.87−7.84 (m, 2H), 7.62−7.60 (m, 3H), 7.54−7.50 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 160.5, 150.7, 137.8, 137.12, 137.06, 131.0, 130.8, 130.3, 130.1, 129.1, 128.8, 128.7, 128.6, 122.7, 120.7; HRMS (m/z) [M + H]$^+$ $C_{20}H_{14}BrN_2$ calcd for, 363.0316, found 363.0305.

*2,4-Diphenylquinazoline-6-carbonitrile (**2f**).* 7 h; eluent: EtOAc/PE 3:97; yield: 113 mg, 92%; white solid, mp 231−233 °C (lit[14] 224−225 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 2H), 8.50 (s, 1H), 8.21 (d, J = 7.6 Hz, 1H), 7.99 (d, J = 7.2 Hz, 1H), 7.86 (s, 2H), 7.66 (s, 3H), 7.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 162.5, 153.3, 137.2, 136.4, 134.1, 133.7, 131.6, 130.83, 130.76, 130.2, 129.1, 129.0, 128.7, 121.2, 118.3, 110.4; HRMS (m/z) [M + H]$^+$ calcd for $C_{21}H_{14}N_3$, 308.1182, found 308.1173.

*6-Nitro-2,4-diphenylquinazoline (**2g**).* 6 h; eluent: EtOAc/PE 3:97; yield: 51 mg, 39%; white solid, mp 246−248 °C (lit[14] 245−257 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, J = 2.4 Hz, 1H), 8.75−8.72 (m, 2H), 8.64 (dd, J = 9.2, 2.4 Hz, 1H), 8.25 (d, J = 9.2 Hz, 1H), 7.93−7.90 (m, 2H), 7.68−7.65 (m, 3H), 7.58−7.54 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 162.9, 154.5, 145.5, 137.1, 136.4, 131.8, 131.04, 130.99, 130.3, 129.2, 129.1, 128.8, 127.0, 124.3, 120.5; HRMS (m/z) [M + H]$^+$ calcd for $C_{20}H_{14}N_3O_2$, 328.1081, found 328.1078.

*8-Methyl-2,4-diphenylquinazoline (**2h**).* 5 h; eluent: EtOAc/PE 1:99; yield: 98 mg, 83%; white solid, mp 115−117 °C (lit[21] 123 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76−8.73 (m, 2H), 7.93 (d, J = 8.4 Hz, 1H), 7.87−7.84 (m, 2H), 7.70 (d, J = 6.8 Hz, 1H), 7.58−7.54 (m, 3H), 7.52−7.48 (m, 3H), 7.40 (t, J = 7.6 Hz, 1H), 2.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 159.0, 151.0, 138.6, 138.1, 137.5, 133.3, 130.4, 130.3, 129.7, 128.7, 128.49, 128.46, 126.5, 124.7, 121.6,

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17.6; HRMS (m/z) [M + H]$^+$ calcd for $C_{21}H_{17}N_2$, 297.1386, found 297.1382.

*7-Methyl-2,4-diphenylquinazoline (**2i**) and 5-Methyl-2,4-diphenylquinazoline (**2i′**).*[13] 5 h; eluent: EtOAc/PE 3:97; yield: 83 mg, 70% (**2i**:**2i′** = 9:1 by ^{1}H NMR); white solid, mp 155−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$, *peaks of **2i′**) δ 8.69−8.66 (m, 1.8H), 8.65−8.63* (m, 0.2H), 8.01* (m, 0.1H), 8.00 (d, J = 8.4 Hz, 0.9H), 7.93 (s, 0.9H), 7.89−7.86 (m, 1.8H), 7.76−7.72* (m, 0.2H), 7.60−7.57 (m, 3.1H), 7.54−7.48 (m, 3.1H), 7.36 (dd, J = 8.8, 1.6 Hz, 0.9H), 7.32−7.31* (m, 0.1H), 2.59 (s, 2.7H), 2.08* (s, 0.3H); ^{13}C NMR (100 MHz, $CDCl_3$, *peaks of **2i′**) δ 168.6*,167.8, 160.3, 158.6*, 153.1*, 152.3, 144.5, 142.1*, 138.4, 137.9, 136.2*, 133.2*, 130.4, 130.2, 129.8, 129.3, 129.1*, 129.0*, 128.6, 128.52, 128.51, 128.3*, 128.1, 127.5*, 126.7, 122.1*, 119.9, 23.9*, 22.1; HRMS (m/z) [M + H]$^+$ calcd for $C_{21}H_{17}N_2$, 297.1386, found 297.1381.

*5,7-Dimethyl-2,4-diphenylquinazoline (**2j**).*[22] 3 h; eluent: EtOAc/PE 2:98; yield: 122 mg, 98%; white solid, mp 149−151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64−8.60 (m, 2H), 7.80 (s, 1H), 7.56−7.45 (m, 8H), 7.15 (s, 1H), 2.53 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 158.8, 153.5, 143.9, 142.2, 138.0, 135.7, 132.5, 130.3, 129.02, 128.97, 128.6, 128.5, 128.2, 126.5, 120.3, 23.8, 21.9; HRMS (m/z) [M + H]$^+$ calcd for $C_{22}H_{19}N_2$, 311.1543, found 311.1543.

*6-Methyl-2-phenyl-4-(p-tolyl)quinazoline (**2k**).*[23] 5 h; eluent: EtOAc/PE 2:98; yield: 123 mg, 99%; white solid, mp 179−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68−8.65 (m, 2H), 8.05 (d, J = 8.8 Hz, 1H), 7.90 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.73−7.69 (m, 1H), 7.54−7.48 (m, 3H), 7.41 (d, J = 8.0 Hz, 2H), 2.51 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 159.6, 150.5, 140.0, 138.4, 137.0, 135.7, 135.1, 130.3, 130.1, 129.3, 128.8, 128.6, 128.5, 125.7, 121.7, 21.9, 21.5; HRMS (m/z) [M + H]$^+$ calcd for $C_{22}H_{19}N_2$, 311.1543, found 311.1527.

*4-(4-Methoxyphenyl)-6-methyl-2-phenylquinazoline (**2l**).* 2.5 h; eluent: EtOAc/PE 3:97; yield: 90 mg, 69%; white solid, mp 167−168 °C (lit[24] 160−165 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 6.8 Hz, 2H), 8.04 (d, J = 8.8 Hz, 1H), 7.92 (s, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 1H),7.54−7.48 (m, 3H), 7.12 (d, J = 8.4 Hz, 2H), 3.94 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 161.2, 159.5, 150.5, 138.4, 137.0, 135.7, 131.8, 130.4, 130.3, 128.8, 128.54, 128.50, 125.7, 121.6, 114.0, 55.5, 21.9; HRMS (m/z) [M + H]$^+$ calcd for $C_{22}H_{19}N_2O$, 327.1492, found 327.1499.

*4-(4-Chlorophenyl)-6-methyl-2-phenylquinazoline (**2m**).* 5 h; eluent: EtOAc/PE 2:98; yield: 112 mg, 85%; white solid, mp 189−191 °C (lit[24] 181−183 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 6.8 Hz, 2H), 8.04 (d, J = 8.4 Hz, 1H), 7.83−7.80 (m, 3H), 7.71 (d, J = 8.8 Hz, 1H), 7.58−7.48 (m, 5H), 2.51 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 159.6, 150.7, 138.2, 137.4, 136.3, 136.1, 136.0, 131.5, 130.4, 129.0, 128.9, 128.6, 128.5, 125.2, 121.5, 21.9. HRMS (m/z) [M + H]$^+$ calcd for $C_{21}H_{16}ClN_2$, 331.0997, found 331.0992.

*6-Methyl-2-phenyl-4-(3-(trifluoromethyl)phenyl)quinazoline (**2n**).* 5 h; eluent: EtOAc/PE 2:98; yield: 144 mg, 99%; white solid, mp 203−204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 6.4 Hz, 2H), 8.15 (s, 1H), 8.05 (t, J = 8.8 Hz, 2H), 7.84 (d, J = 6.8 Hz, 1H), 7.74−7.51 (m, 6H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 159.6, 150.7, 138.7, 138.0, 137.7, 136.1, 133.4, 131.2 (q, J_{C-F} = 32.2 Hz), 130.5, 129.1, 129.0, 128.6, 128.5, 126.9 (q, J_{C-F} = 3.6 Hz), 126.4 (q, J_{C-F} = 3.6 Hz), 124.9, 124.0 (q, J_{C-F} = 270.8 Hz), 121.4, 22.0; HRMS (m/z) [M + H]$^+$ calcd for $C_{22}H_{16}F_3N_2$, 365.1260, found 365.1250.

*6-Methyl-2-phenyl-4-(pyridin-4-yl)quinazoline (**2o**).* 3.5 h; eluent: EtOAc/PE 80:20; yield: 117 mg, 99%; brown solid, mp 134−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 5.6 Hz, 2H), 8.66−8.63 (m, 2H), 8.09 (d, J = 9.2 Hz, 1H), 7.78−7.57 (m, 4H), 7.55−7.50 (m, 3H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 159.7, 150.7, 150.0, 145.5, 138.0, 137.9, 136.4, 130.6, 129.2, 128.6, 128.5, 124.6, 124.4, 121.2, 22.0; HRMS (m/z) [M + H]$^+$ calcd for $C_{20}H_{16}N_3$, 298.1339, found 298.1337.

*6-Methyl-2-phenyl-4-propylquinazoline (**2p**).* 1.5 h; eluent: EtOAc/PE 1:99; yield: 62 mg, 59%; brown solid, mp 100−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63−8.60 (m, 2H), 7.96 (d, J = 8.4 Hz, 1H), 7.85 (s, 1H), 7.67 (dd, J = 8.8, 1.6 Hz, 1H), 7.54−7.47 (m, 3H), 3.28 (t, J = 7.6 Hz, 2H), 2.57 (s, 3H), 2.05−2.00 (sext, J = 7.6 Hz, 2H), 1.12 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 159.4, 149.2, 138.6, 136.8, 135.5, 130.1, 129.1, 128.5, 128.4, 123.5, 122.5, 36.5, 22.0, 21.8, 14.3; HRMS (m/z) [M + H]$^+$ calcd for $C_{18}H_{19}N_2$, 263.1543, found 263.1549.

*4-Isopropyl-6-methyl-2-phenylquinazoline (**2q**).* 5.5 h; eluent: EtOAc/PE 1:99; yield: 39 mg, 37%; white solid, mp 102−103 °C (lit[25] 120 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67−8.65 (m, 2H), 7.98 (d, J = 8.4 Hz, 1H), 7.90 (s, 1H), 7.67 (dd, J = 8.4, 1.6 Hz, 1H), 7.54−7.45 (m, 3H), 3.93 (hept, J = 6.8 Hz, 1H), 2.57 (s, 3H), 1.50 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 159.4, 149.5, 138.8, 136.6, 135.3, 130.1, 129.3, 128.5, 123.0, 121.6, 31.1, 29.7, 22.0, 21.8; HRMS (m/z) [M + H]$^+$ calcd for $C_{18}H_{19}N_2$, 263.1543, found 263.1543.

*6-Methyl-4-phenyl-2-(p-tolyl)quinazoline (**2r**).*[26] 5 h; eluent: EtOAc/PE 1:99; yield: 123 mg, 99%; white solid, mp 174−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 8.0 Hz, 2H), 8.01 (d, J = 8.4 Hz, 1H), 7.87−7.84 (m, 3H), 7.67 (dd, J = 8.8, 2.0 Hz, 1H), 7.60−7.56 (m, 3H), 7.31 (d, J = 8.0 Hz, 2H), 2.48 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 159.7, 150.6, 140.5, 138.0, 136.9, 135.7, 135.6, 130.2, 129.7, 129.3, 128.8, 128.5, 125.6, 121.6, 21.9, 21.6; HRMS (m/z) [M + H]$^+$ calcd for $C_{22}H_{19}N_2$, 311.1543, found 311.1556.

*2-(4-Chlorophenyl)-6-methyl-4-phenylquinazoline (**2s**).*[12e] 5 h; eluent: EtOAc/PE 1:99; yield: 131 mg, 99%; white solid, mp 182−183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64−8.60 (m, 2H), 8.04 (d, J = 8.8 Hz, 1H), 7.87−7.85 (m, 3H), 7.73 (dd, J = 8.8, 2.0 Hz, 1H), 7.62−7.59 (m, 3H), 7.50−7.47 (m, 2H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 158.6, 150.5, 137.8, 137.4, 136.9, 136.5, 135.9, 130.1, 129.9, 128.8, 128.7, 128.6, 125.7, 121.7, 21.9; HRMS (m/z) [M + H]$^+$ calcd for $C_{21}H_{16}ClN_2$, 331.0997, found 331.1008.

*6-Methyl-4-phenyl-2-(3-(trifluoromethyl)phenyl)quinazoline (**2t**).* 5 h; eluent: EtOAc/PE 1:99; yield: 134 mg, 92%; white solid, mp 175−176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.87 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.88−7.85 (m, 3H), 7.75−7.72 (m, 2H), 7.64−7.60 (m, 4H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 158.1, 150.5, 139.2, 137.8, 137.6, 136.1, 131.7, 131.1 (q, J = 32.1 Hz), 130.1, 129.96, 128.9, 128.6, 126.7 (q, J = 3.7 Hz), 125.7, 125.4 (q, J = 3.9 Hz), 123.0 (q, J = 270.6 Hz, partially overlapped with other peaks), 121.9, 21.9; HRMS (m/z) [M + H]$^+$ calcd for $C_{22}H_{16}F_3N_2$, 365.1260, found 365.1260.

*6-Methyl-2-(naphthalen-1-yl)-4-phenylquinazoline (**2u**).* 7.5 h; eluent: EtOAc/PE 3:97; yield: 121 mg, 87%; white solid, mp 164−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.79 (dd, J = 8.8, 1.2 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 8.04−8.02 (m, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.93−7.88 (m, 4H), 7.73 (dd, J = 8.4, 1.2 Hz, 1H), 7.66−7.61 (m, 3H), 7.54−7.49 (m, 2H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 159.6, 150.6, 137.9, 137.2, 135.9, 135.7, 134.6, 133.5, 130.2, 129.8, 129.3, 128.9, 128.8, 128.6, 128.1, 127.7, 126.9, 126.1, 125.7, 125.6, 121.7, 21.9; HRMS (m/z) [M + H]$^+$ calcd for $C_{25}H_{19}N_2$, 347.1543, found 347.1552.

*2-(Furan-2-yl)-6-methyl-4-phenylquinazoline (**2v**).* 5 h; eluent: EtOAc/PE 10:90; yield: 94 mg, 82%; white solid, mp 191−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.8 Hz, 1H), 7.83−7.79 (m, 3H), 7.71−7.68 (m, 2H), 7.60−7.57 (m, 3H), 7.47−7.45 (m, 1H), 6.58 (q, J = 1.6 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 153.0, 152.9, 150.1, 145.0, 137.4, 137.2, 136.1, 130.0, 129.9, 128.64, 128.56, 125.8, 121.6, 113.7, 112.1, 21.9; HRMS (m/z) [M + H]$^+$ calcd for $C_{19}H_{15}N_2O$, 287.1179, found 287.1179.

*2-(tert-Butyl)-6-methyl-4-phenylquinazoline (**2w**).* 5 h; eluent: EtOAc/PE 1:99; yield: 94 mg, 85%; white solid, mp 60−61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.4 Hz, 1H), 7.82−7.79 (m, 3H), 7.64 (dd, J = 8.4, 1.6 Hz, 1H), 7.58−7.52 (m, 3H), 2.47 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 166.7, 150.0, 138.2, 136.4, 135.1, 130.2, 129.5, 128.7, 128.4, 125.3, 120.9, 39.6, 29.8, 21.8; HRMS (m/z) [M + H]$^+$ calcd for $C_{19}H_{21}N_2$, 277.1699, found 277.1714.

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■ ASSOCIATED CONTENT

Supporting Information

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Schemes for the preparation of substrates **1**, and copies of ^{1}H and ^{13}C NMR spectra of compounds **1** and **2** (PDF)

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Notes

The authors declare no competing financial interest.

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