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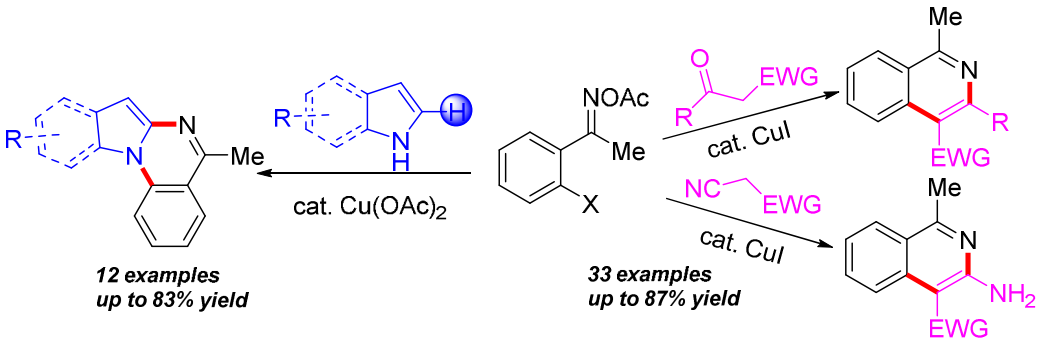


Abstract: A convenient and reliable method for the direct construction of isoquinolines is described. A series of isoquinoline derivatives were synthesized, with high chemo- and regioselectivities, via the copper-catalyzed cascade reaction of 2-haloaryloxime acetates with *β*-diketones, *β*-keto esters and *β*-keto nitriles. This tandem annulation process features inexpensive catalysts, no need of additional ligands, and excellent functional group tolerance, which make it have potential synthetic applications. Furthermore, this strategy could also be used to entry to functionalized indolo[1,2-*a*]quinazolines by using indoles as the counterpart of the 2-haloaryloxime acetates.

INTRODUCTION

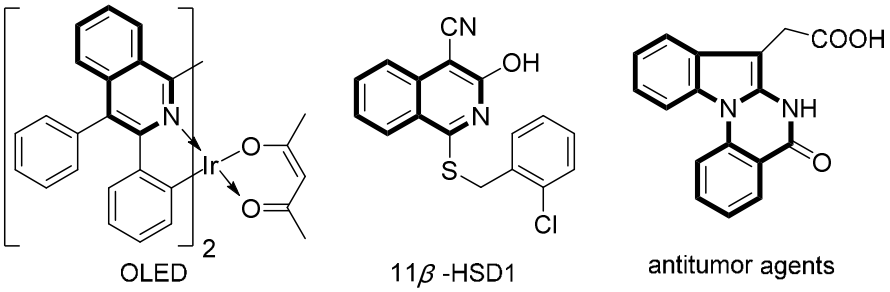
Nitrogen-containing heterocycles are an important subunit of alkaloidal compounds, which widely occur in natural products and pharmaceutical compounds.[1] In fact, isoquinoline and its derivatives have recently been reported to be attractive azaheterocyclic skeletons, with the synthetic use for inhibitors of 11β-HSD1,[2] anti-HIV,[3] the precursor of dopamine agonist and antagonist,[4] ion-channel blocker,[5] chiral ligands,[6] and phosphorescent emitters of OLEDs (Scheme 1).[7] The classic Bischler-Napieralski, Pomeranz-Fritsch, and Pictet-Spengler reactions opened the way to the preparation of isoquinolines.[8] Similarly, indolo[1,2-*a*]quinazoline derivatives represent an important nitrogen-containing tetracyclic motif in a variety of bioactive compounds,[9] such as antitumor agents and Protein Kinase CK2 Inhibitor (Scheme 1).[9a,9b] To the best of our knowledge, the synthesis of functionalized indolo[1,2-*a*]quinazolines is rarely reported.[9,10] Vidal described pioneering work on the synthesis of indolo[1,2-*a*]quinazolines via intramolecular [3+2] cycloadditions of azido-ketenimines.[10c] Recently, Liu and Perumal developed a Cu catalytic system for the synthesis of indolo[1,2-*a*]quinazolines.[10d, 10e] However, the preparation of some practical and sensitive isoquinolines such as 4-cyanoisoquinoline and 3-aminoisoquinoline derivatives is one continuing challenge among general preparative methods and the example of direct functionalization of indoles for the synthesis of indolo[1,2-*a*]quinazoline derivatives have not been described. Thus, the development of efficient procedures for acquisition of isoquinolines and

indolo[1,2-*a*]quinazolines from easily available starting materials remains highly desirable.

Ketoximes and their derivatives are versatile building blocks in organic synthesis, which provide convenient method to a broad range of functionalized *N*-containing heteropolycycles. Generally, two intramolecular cyclization strategies are typically employed: (i) S_N2-type substitution,[11] (ii) iminyl radical reaction.[12] In recent years, great developments in the field of transition-metal (ruthenium,[13] rhodium,[14] and palladium,[15]) catalyzed N–O bond oxidative cleavage of oxime derivatives provided new promising approaches to assemble *N*-containing heterocycles. Practically, a number of elegant studies in copper-catalyzed cyclization of oxime esters to prepare various nitrogen-containing motifs have been reported.[16] For example, Yoshikai described a modular synthesis of pyridine through synergistic copper/iminium catalysis from oximes and enals.[16c] Guan developed efficient synthetic protocols for symmetrical *N*-heterocycle compounds by copper-catalyzed cyclization of oxime esters.[16b, 16d] As our continuing interest in the search for *N*-heterocycle synthesis through copper-catalyzed coupling of ketoxime esters,[17] herein, we present a concise copper-catalyzed Ullmann-type reaction and intramolecular condensation process to construct functionalized isoquinolines and indolo[1,2-*a*]quinazolines under mild reaction conditions from 2-haloaryloxime acetates with active methylene compounds and indoles.

Scheme 1. Representative Examples of Bioactive Tetracyclic Compounds Containing

the Isoquinoline and Indole Motif

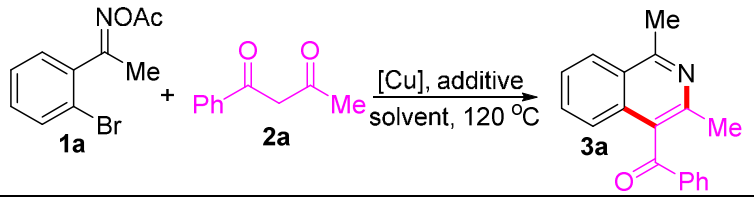


OLED 11β -HSD1 antitumor agents

RESULTS AND DISCUSSION

The investigation was initiated by choosing the reaction of 2-bromoketoxime acetate (**1a**) with 1-phenylbutane-1,3-dione (**2a**) as a model system (Table 1). To our delight, the desired product **3a** was obtained in 83% yield with good regioselectivity in the presence of CuBr and K_2CO_3 (entry 1). A broad range of copper salts were screened, including CuI, CuCl, $Cu(OTf)_2$, and $Cu(OAc)_2$, and CuI was found to be the most effective catalyst for the transformation (entries 2-5). Undoubtedly, no desired product could be obtained in the absence of copper catalysts (entry 6). When we subjected oxime acetate to diketone using Cs_2CO_3 or *t*-BuOK as the additives, 60% and 16% of **3a** was afforded, respectively (entries 7 and 8). The organic base also decreased the yield of **3a** (entries 9 and 10). As predicted, there was no reaction occurred without base (entry 11). This investigation indicated that the base was crucial to the interaction between copper salts and oxime esters. In the presence of CuI and K_2CO_3, only trace amount of the desired product was observed when using toluene, DCE, or CH_3CN as solvent (entries 12-14). Remarkably, the addition of 2 equiv DMF in this reaction system gave a significant improvement (entries 15-17). Therefore, DMF was necessary media for this Cu(I)-catalyzed cascade reaction.

Table 1. Optimization of the reaction conditions[a]



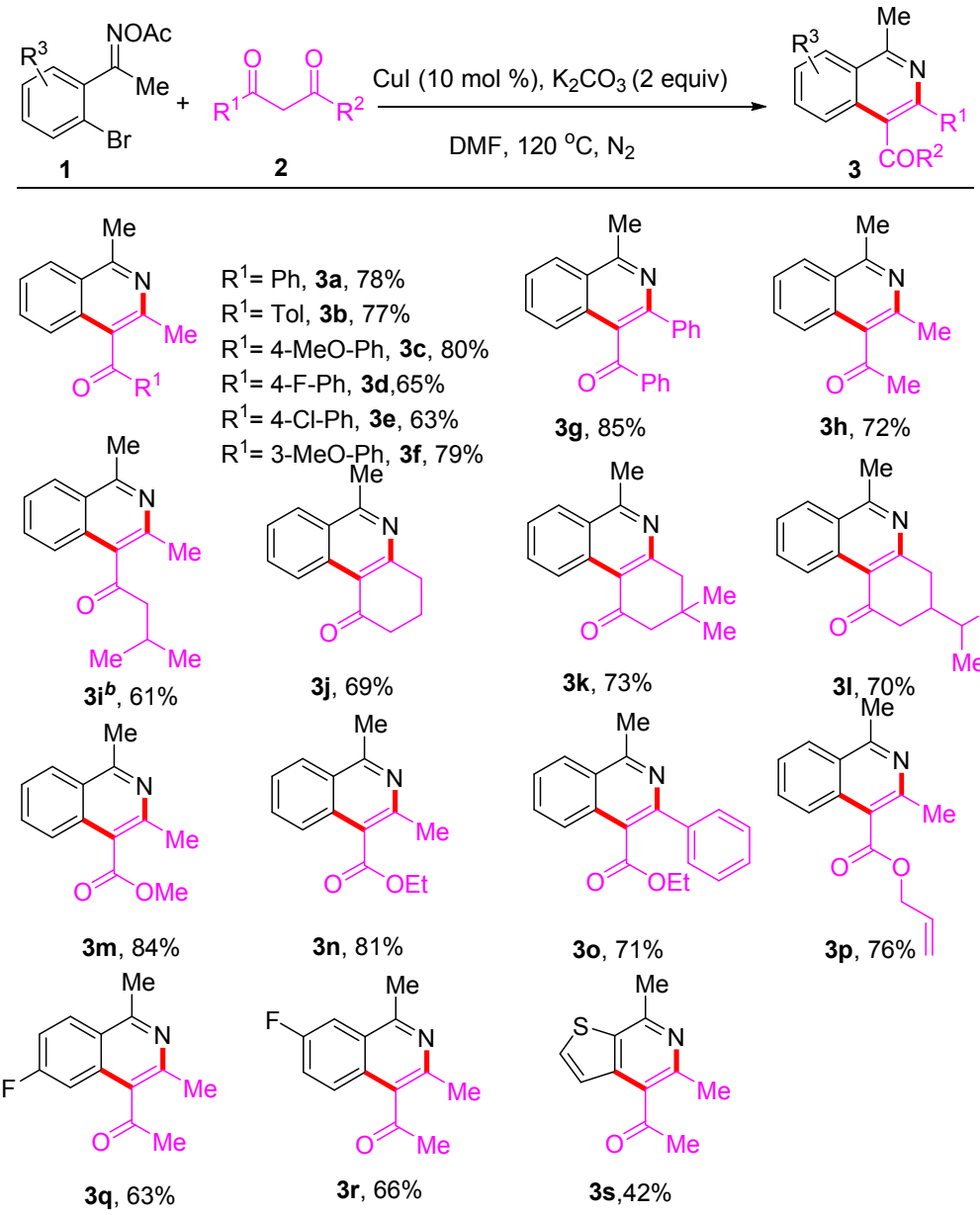
Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	CuBr	K_2CO_3	DMF	83
2	**CuI**	**K_2CO_3**	**DMF**	**86 (78)**
3	CuCl	K_2CO_3	DMF	77
4	$Cu(OTf)_2$	K_2CO_3	DMF	34
5	$Cu(OAc)_2$	K_2CO_3	DMF	73
6	none	K_2CO_3	DMF	0
7	CuI	Cs_2CO_3	DMF	60
8	CuI	*t*-BuOK	DMF	16
9	CuI	DBU	DMF	65
10	CuI	NEt_3	DMF	trace
11	CuI	none	DMF	0
12	CuI	K_2CO_3	toluene	trace
13	CuI	K_2CO_3	DCE	10
14	CuI	K_2CO_3	CH_3CN	trace
15[c]	CuI	K_2CO_3	toluene	62
16[c]	CuI	K_2CO_3	DCE	19
17[c]	CuI	K_2CO_3	CH_3CN	73

[a] Unless otherwise noted, all reactions were performed with **1a** (0.5 mmol), **2a** (0.6 mmol), [Cu] (10 mol %), base (1.0 mmol) and solvent (2 mL) at 120 °C under N_2 atmosphere for 6 h. [b] Determined by GC using dodecane as an internal standard. [c] 2 equiv. DMF of was added.

With the optimized reaction conditions in hand, we investigated the scope of the Cu(I)-catalyzed cyclization reaction. Representative results were summarized in Table 2. A series of benzoylacetones successfully participated in this transformation, affording the isoquinolines **3a-3f** in moderate to excellent yields with high regioselectivity. A single crystal of product **3f** was obtained and its structure was confirmed by single-crystal X-ray analysis.[18] Symmetrical 1,3-diketones also could be

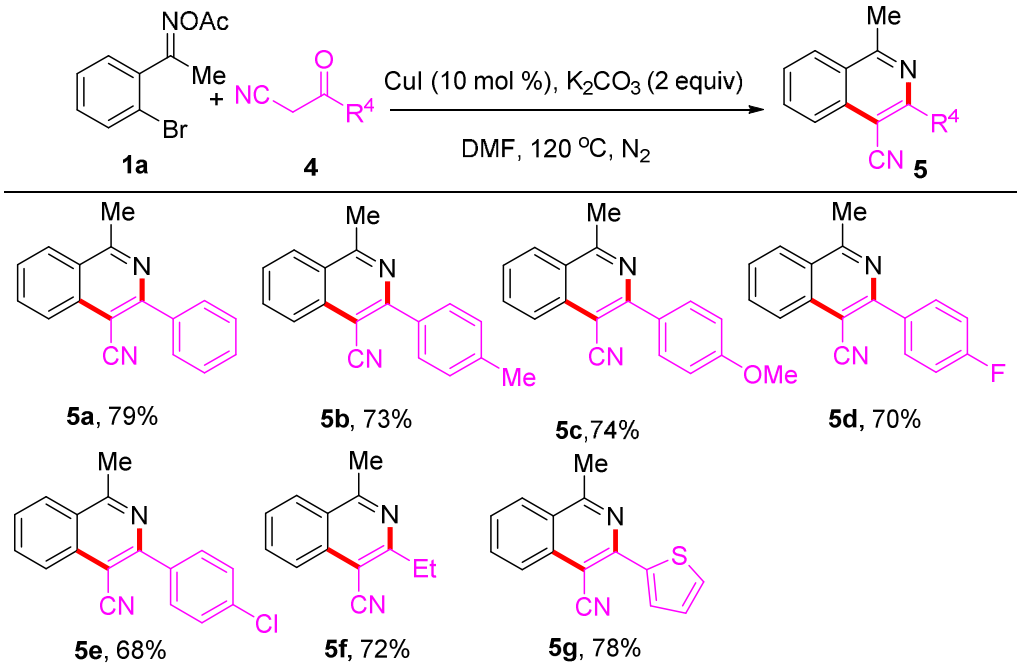
converted to the corresponding products in good yields (**3g** and **3h**). When 6-methylheptane-2,4-dione (**2i**) was employed, this transformation gave a 5.5:1 ratio of regioisomeric cycloadducts **3i** and **3i'** determined by GC-MS, and the former could be separated in 61% yield. Besides, the cyclohexane-1,3-dione could efficiently transfer to the desired tricyclic compound **3j**. Reasonable yields were also obtained with substituted cyclic 1,3-diketones (**3k** and **3l**). Furthermore, different single-ester dicarbonyl compounds could be converted into the desired products in moderate to high yields (**3m-3p**). And under this optimized conditions, when the oximes derived from 1-(2-bromo-4-fluorophenyl)ethan-1-one or 1-(2-bromo-5-fluorophenyl)ethan-1-one participated in this reaction, the corresponding tetraisoquinolines were afforded in reasonable yields (**3q** and **3r**). Notably, the introduction of thiophene heterocycle into this system made this process more useful (**3s**). Moreover, replacing 2-bromoketoxime acetate with 2-iodoketoxime acetate, this transformation also performed successfully and gave the corresponding isoquinolines in excellent yields.

Table 2. Substrate Scope of *β*-Diketones and *β*-Keto Esters for the Synthesis of 1,3,4-Trisubstituted Isoquinolines[a]



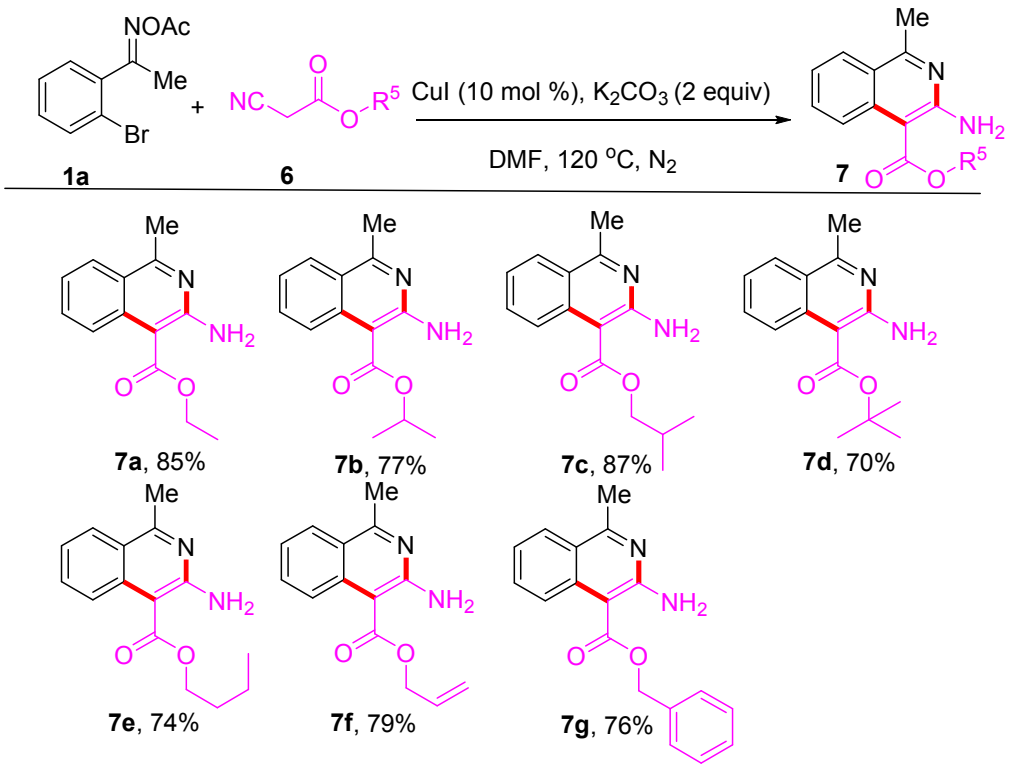
[a] All reactions were performed with **1** (0.5 mmol), **2** (0.6 mmol), K_2CO_3 (1.0 mmol), CuI (10 mol %) in DMF (2 mL) at 120 °C under N_2 atmosphere for 6 h. [b] Regioisomeric cycloadduct **3i'** was also formed in 12% GC yield.

Table 3. Substrate Scope of *β*-Keto Nitriles for the Synthesis of 4-Cyanoisoquinoline Derivatives[a]



[a] Reaction conditions: all reactions were performed with **1a** (0.5 mmol), **4** (0.6 mmol), K_2CO_3 (1.0 mmol), CuI (10 mol %) in DMF (2 mL) at 120 °C under N_2 atmosphere for 6 h.

Table 4. Substrate Scope of 2-Cyanoacetates for the Synthesis of 3-Aminoisoquinoline Derivatives [a]

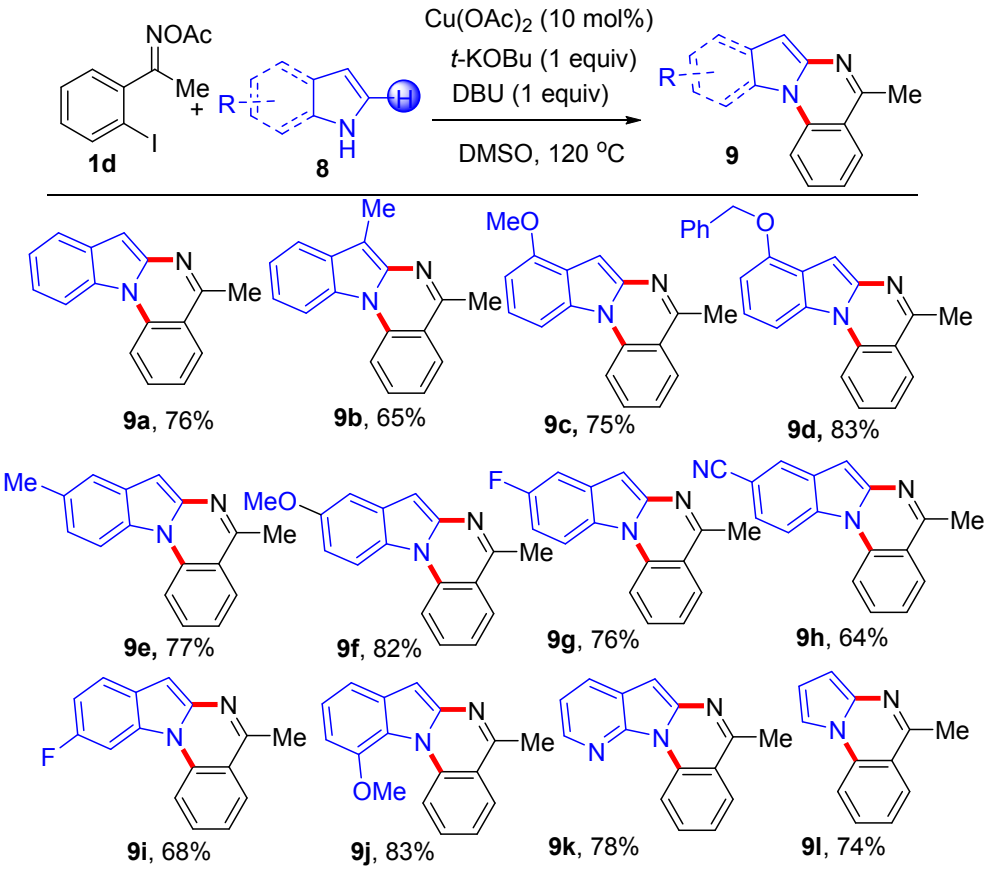


[a] All reactions were performed with **1a** (0.5 mmol), **6** (0.6 mmol), K_2CO_3 (1.0 mmol), CuI (10 mol %) in DMF (2 mL) at 120 °C under N_2 atmosphere for 6 h.

Under the optimal reaction conditions, it is delightful that the coupling reactions of 2-bromoacetophenone oxime acetate (**1a**) and β-keto nitriles **4** were found to be favored to afford 4-cyanoisoquinolines in good yields with high chemoselectivity. The results were tabulated in Table 3. Benzoylacetonitriles with a series of functional groups, such as methyl, methoxy and halogen, could be converted to the desired products in satisfactory yields (**5a-5e**). Additionally, the reaction of 3-oxopentanenitrile (**4f**) and 3-oxo-3-(thiophen-2-yl)propanenitrile (**4g**) also proceeded smoothly under the optimized conditions, affording the corresponding products in 72% and 78% yields, respectively (**5f** and **5g**).

The scope of copper-catalyzed coupling reaction was further expanded to a variety of 2-cyanoacetates (Table 4). Gratifyingly, 3-aminoisoquinoline derivatives could be formed in good yields with complete chemoselectivity when a series of alkyl 2-cyanoacetates were used. (**7a-7e**). We were pleased to find that alkenyl and benzyl 2-cyanoacetate were soomthly converted into the corresponding products in 79% and 76% yields, respectively (**7f** and **7g**).

Table 5. Substrate Scope of Indoles for the Synthesis of Indolo[1,2-*a*]quinazoline Derivatives[a]



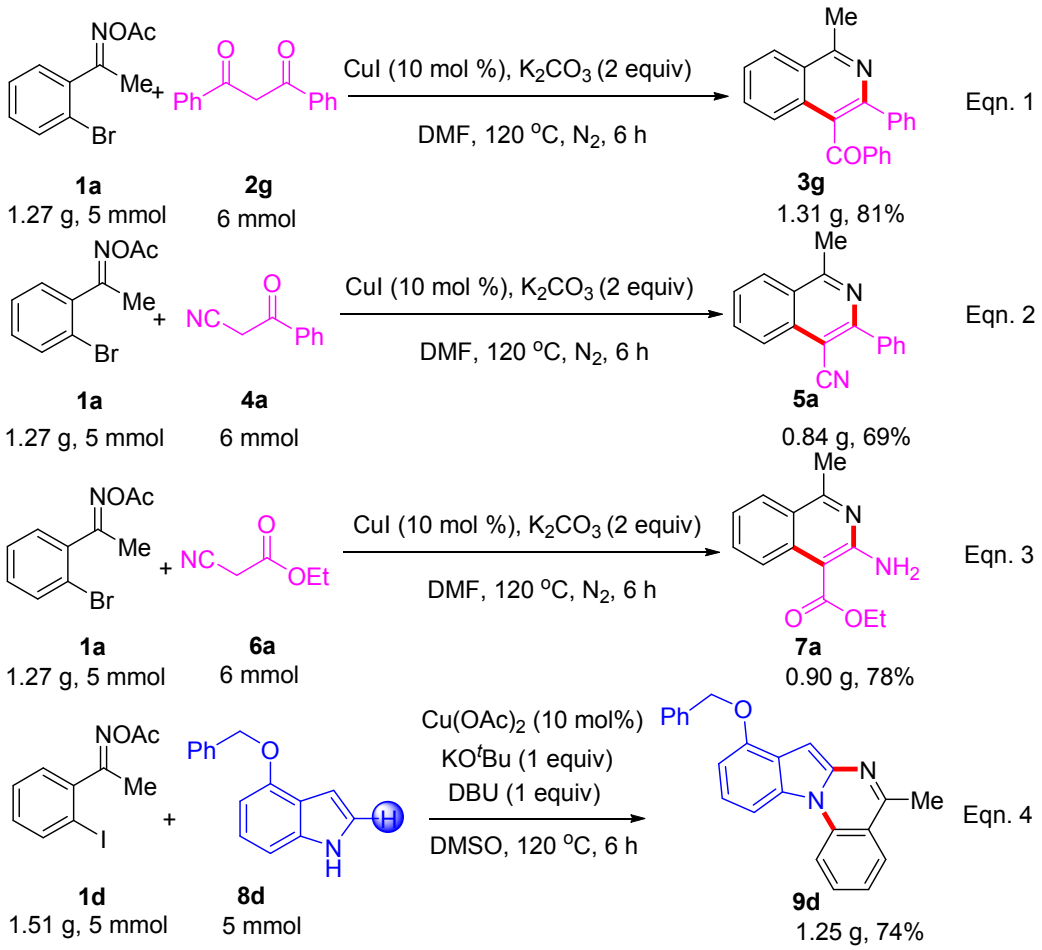
[a] All reactions were performed with **1d** (0.5 mmol), **8** (0.5 mmol), *t*-KOBu (1.0 equiv), DBU (1.0 equiv), $Cu(OAc)_2$ (10 mol %) in DMSO (2 mL) at 120 °C under N_2 atmosphere for 6 h.

Encouraging by the above results, we next investigated the Cu-catalyzed cascade reaction of indole **8a** with easily accessible 2-iodoketoxime acetate **1d**. When this reaction was carried out in DMSO at 120°C, using 10 mol % $Cu(OAc)_2$ as the catalyst, in the presence of 1.0 equiv of KO*t*-Bu and DBU, under N_2 atmosphere for 6 h, the indolo[1,2-*a*]quinazoline product **9a** was successfully observed (for detailed screening of reaction conditions, see the Supporting Information). As exhibited in Table 5, the coupling of 2-iodoketoxime ester with slight steric hindered 3-methylindole gave the desired product **9b** in reasonable yield. For 4-methoxy-1*H*-indole (**8c**) and 4-(benzyloxy)-1*H*-indole (**8d**), the corresponding products **9c** and **9d** were obtained in 75% and 83% yields, respectively. Both electron-donating and electron-withdrawing 5-substituted indoles could also preform smoothly, affording the indolo[1,2-*a*]quinazoline derivatives in moderate to good yields (**9e-9h**). In addition, when 6-fluoro-1*H*-indole and 7-methoxy-1*H*-indole were employed, the transformations gave **9i** and **9j** in 68% and 83% yields, respectively. Notably, pyrrolo[2,3-*b*]pyridine (**8k**) and pyrrole (**8l**) were effective substrates for this cascade annulation to afford the good yields of **9k** and **9l**.

To investigate the practicality of these processes in the synthesis of isoquinoline and indolo[1,2-*a*]quinazoline derivatives, we carried out the reactions in a gram-scale (Scheme 2). When 1.27 g of **1a** was employed, methylene compounds **2g**, **4a**, and **6a** were tolerated under the optimized reaction conditions and gave the corresponding products in 81, 69, and 78% yields, respectively (Scheme 2, Eqn. 1-3). To our delight,

when running the reaction with 1.51 g of **1d**, 1.25 g of product **9d** was obtained in 74% yield (Scheme 2, Eqn. 4).

Scheme 2. Gram-scale Synthesis of Functionalized Isoquinolines (**3g**, **5a**, and **7a**) and Indolo[1,2-*a*]quinazoline **9d**

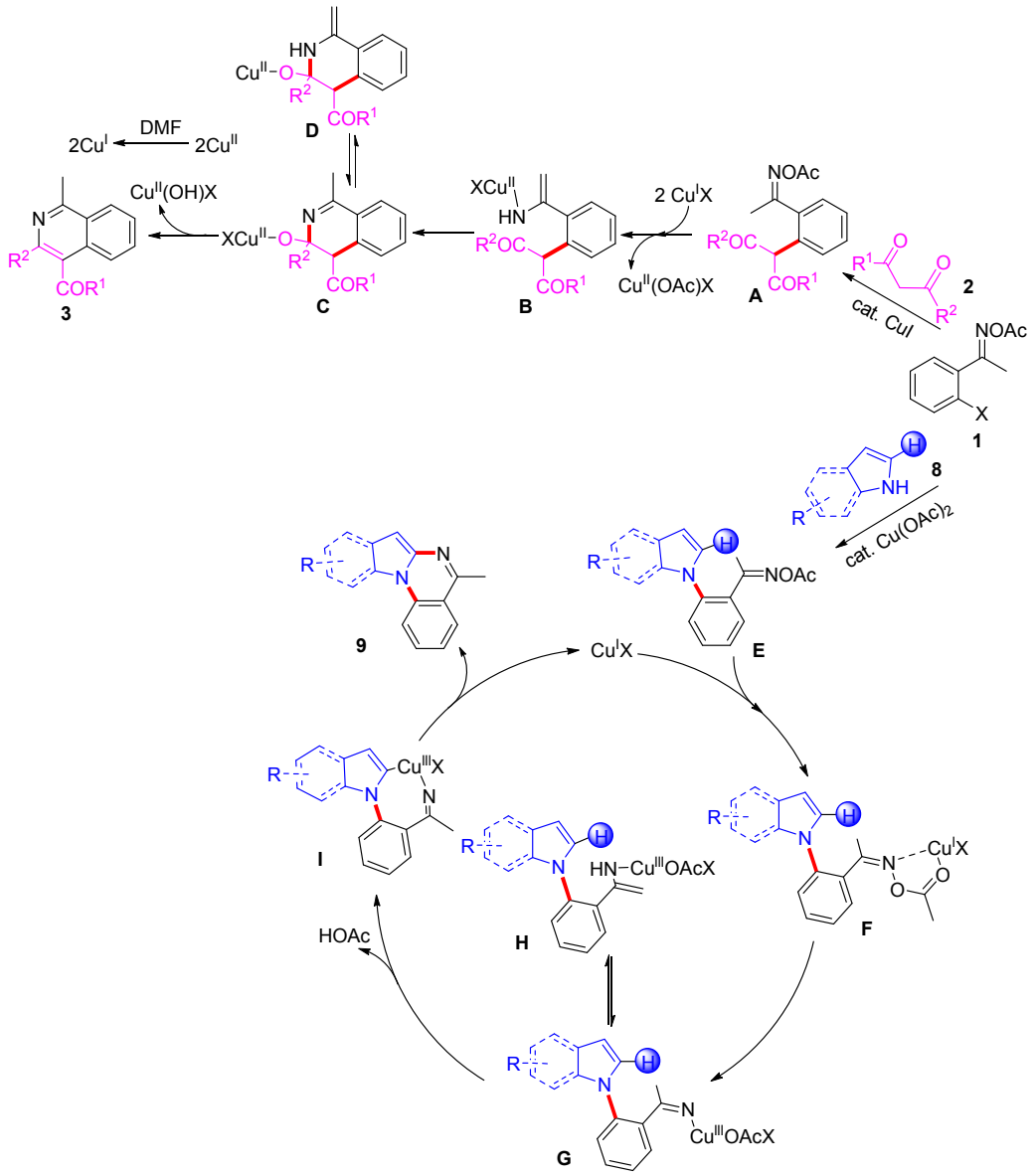


According to the experimental results and literature precedents on oxime derivatives,[16, 17, 19] we proposed a plausible mechanism for this cross-coupling reaction (Scheme 3). In the presence of copper salt, the complex **A** was first obtained through the reaction between *ortho*-haloaryloxime ester **1** with methylene compound

2, namely the Hurtley reaction.[20a, 20c, 20d] Cleavage of the N–O bond of the complex **A** was initiated by CuI, generating copper enamide intermediate **B** and producing Cu^{II} species.[16, 17a, 17d] Subsequently, the copper(II) enamide served as an intramolecular nucleophile towards the carboxide,[20c] affording the corresponding intermediate **C** or **D**. Finally, the 1,3,4-polysubstituted isoquinoline **3** was generated from elimination of intermediate **C** or **D**. The Cu(I) species might be generated *in situ* via the reduction of Cu^{II} by DMF,[21] and then entered into the next catalytic cycle. Additionally, the reactions of *β*-keto nitriles **4** or alkyl 2-cyanoacetates **6** with *ortho*-haloketoximes esters **1** were also proposed through the similar pathway.

With respect to indolo[1,2-*a*]quinazolines synthesis, firstly, copper-catalyzed Ullmann condensation occured between the active *ortho*-iodoketoximes ester and indoles **8** to form **E**.[20b, 20d] Oxidative addition of Cu(I) to **E** afforded the Cu(III)-imino species **G**,[17b, 17c, 19]. Then a copper ring intermediate **I** was generated from *ortho*-C–H activation of intermediate **G** and subsequent reductive elimination would provide the desired product **9**.

Scheme 3. Proposed Mechanism



CONCLUSION

In conclusion, we have developed a copper-catalyzed cascade condensation for divergent syntheses of functionalized isoquinolines and indolo[1,2-*a*]quinazolines from 2-haloketoxime acetates. This protocol provides a powerful method for the construction of a series of nitrogen-containing heterocycles with high chemo- and regioselectivity. Moreover, the success of gram-scale synthesis of functionalized isoquinolines and indolo[1,2-*a*]quinazolines made this process more useful in

synthetic and pharmaceutical chemistry.

EXPERIMENTAL SECTION

General Methods. Melting points were measured by a melting point instrument and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded by using a 400 MHz NMR spectrometer. ^{1}H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm) and $CHCl_3$ (77.0 ppm), respectively. IR spectra were obtained either as potassium bromide pellets or as liquid films between two potassium bromide pellets with an infrared spectrometer. GC-MS was obtained using electron ionization. The data of HRMS were carried out on a high-resolution mass spectrometer (LCMS-IT-TOF). Unless otherwise noted, all purchased chemicals were used without further purification. The ketoxime acetates were prepared according to the literatures.[19a, 22]

General Procedure for the Synthesis of Isoquinolines 3, 5, and 7. The 2-haloketoxime acetates **1** (0.5 mmol), methylene compounds **2**, **4**, or **6** (0.6 mmol), CuI (10 mol %), and K_2CO_3 (2 equiv, 1.0 mmol, 138 mg) were stirred in DMF (2.0 mL) at 120 °C, in a 20 mL tube under N_2 for 6 h. When the reaction was completed (detected by TLC), the mixture was cooled to room temperature. The reaction was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and then evaporated in vacuum. The residue was purified by column chromatography on silica gel to afford the corresponding isoquinolines with petroleum ether /ethyl acetate as the eluent.

General Procedure for the Synthesis of Indolo[1,2-*a*]quinazolines 9. The 2-iodoketoxime acetates **1d** (0.5 mmol), indoles **8** (0.5 mmol), $Cu(OAc)_2$ (10 mol %, 0.05 mmol, 9.08 mg), KO*t*-Bu (1.0 equiv, 0.5 mmol, 56.1 mg), and DBU (1.0 equiv, 0.5 mmol, 76.1 mg) were stirred in DMSO (2.0 mL) at 120 °C, in a 20 mL tube under N_2 for 6 h. When the reaction was completed, the mixture was cooled to room temperature. The reaction was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and then evaporated in vacuum. The residue was purified by column chromatography on silica gel to afford the corresponding indolo[1,2-*a*]quinazolines with petroleum ether /ethyl acetate as the eluent.

4-Benzoyl-1,3-dimethylisoquinolin (3a): Red oil (101 mg, 78 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16-8.14 (m, 1H), 7.83 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.55-7.53 (m, 2H), 7.50-7.46 (m, 1H), 7.45-7.41 (m, 2H), 3.01 (s, 3H), 2.48 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 198.6, 159.4, 146.5, 137.4, 134.1, 133.9, 130.7, 129.8, 129.0, 127.5, 126.6, 125.9, 125.2, 124.5, 22.7, 22.6; HRMS-ESI (m/z): calcd for $C_{18}H_{16}NO$, $[M+H]^+$: 262.1226; found, 262.1228; IR (KBr): 2922, 1666, 1617, 1502, 1393, 1241, 758, 712 cm^{-1}.

1,3-Dimethyl-4-(4-methylbenzoyl)isoquinolin (3b): Yellow needles (104 mg, 77 %), m.p. = 86.5–87.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 7.6 Hz, 2H), 7.56-7.52 (m, 2H), 7.49 (d, J = 8.8 Hz, 1H), 7.27-7.23 (m, 2H), 3.02 (s, 3H), 2.48 (s, 3H), 2.41 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 198.2, 159.2, 146.3, 145.2, 135.1, 134.0, 130.7, 129.9, 129.7, 127.7, 126.6, 125.8, 125.3, 124.6,

22.6, 22.5, 21.8; HRMS-ESI (m/z): calcd for $C_{19}H_{18}NO$, $[M+H]^+$: 276.1383; found, 276.1388; IR (KBr): 2921, 1663, 1605, 1502, 1395, 1246, 759 cm^{-1}.

1,3-Dimethyl-4-(4-methoxybenzoyl)isoquinolin (3c): Red oil (116 mg, 80 %); ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 6.8 Hz,, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.58-7.49 (m, 3H), 6.90 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 3.01 (s, 3H), 2.49 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 197.0, 164.4, 159.1, 146.2, 134.0, 132.2, 130.7, 127.8, 126.5, 125.8, 125.3, 124.7, 114.2, 55.6, 22.6, 22.5; HRMS-ESI (m/z): calcd for $C_{19}H_{18}NO_2$, $[M+H]^+$: 292.1332; found, 292.1336; IR (KBr): 2926, 1657, 1597, 1504, 1393, 1251, 758 cm^{-1}.

4-(4-Fluorobenzoyl)-1,3-dimethylisoquinolin (3d): Yellow needles (91 mg, 65 %), m.p. = 114.3 – 115.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.4 Hz, 1H), 7.88-7.85 (m, 2H), 7.60-7.54 (m, 2H), 7.46 (d, J = 8.0 Hz, 1H), 7.11 (t, J = 8.4 Hz, 2H), 3.02 (s, 3H), 2.48 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 196.9, 166.4 (J = 255.4 Hz), 159.5, 146.4, 134.0 (J = 2.7 Hz), 133.8, 132.5 (J = 9.5 Hz), 130.9, 127.2, 126.7, 125.9, 125.3, 124.4, 116.2 (J = 21.9 Hz), 22.6, 22.5; HRMS-ESI (m/z): calcd for $C_{18}H_{15}FNO$, $[M+H]^+$: 280.1132; found, 280.1138; IR (KBr): 2923, 1667, 1595, 1500, 1391, 1239, 761 cm^{-1}.

4-(4-Chlorobenzoyl)-1,3-dimethylisoquinolin (3e): Yellow needles (93 mg, 63 %), m.p. = 108.9 – 110.2 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19-8.16 (m, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.58-7.54 (m, 2H), 7.46-7.41 (m, 3H), 3.01 (s, 3H), 2.47 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 197.4, 159.7, 146.5, 140.7, 135.8, 133.8, 131.1, 130.9, 129.4, 127.0, 126.7, 125.9, 125.3, 124.4, 22.7, 22.6; HRMS-ESI (m/z): calcd

for $C_{18}H_{15}ClNO$, $[M+H]^+$: 296.0837; found, 296.0843; IR (KBr): 2994, 1667, 1618, 1501, 1397, 756 cm^{-1}.

1,3-Dimethyl-4-(3-methoxybenzoyl)isoquinolin (3f): Red oil (114 mg, 79 %); ^1H NMR (400 MHz, $CDCl_3$) δ 8.17-8.15 (m, 1H), 7.58-7.48 (m, 4H), 7.33-7.26 (m, 2H), 7.15 (d, J = 7.6 Hz, 1H), 3.84 (s, 3H), 3.02 (s, 3H), 2.49 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 198.5, 160.1, 159.4, 146.4, 138.8, 134.0, 130.8, 130.0, 127.6, 126.6, 125.8, 125.2, 124.5, 123.1, 120.7, 113.1, 55.5, 22.7, 22.5; HRMS-ESI (m/z): calcd for $C_{19}H_{18}NO_2$, $[M+H]^+$: 292.1332; found, 292.1336; IR (KBr): 2925, 1666, 1573, 1393, 1262, 810, 763 cm^{-1}.

4-Benzoyl-1-methyl-3-phenylisoquinolin (3g): Yellow needles (137 mg, 85 %), m.p. = 126.4 – 127.7 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26-8.23 (m, 1H), 7.77-7.43 (m, 1H), 7.66-7.63 (m, 4H), 7.60 (d, J = 7.2 Hz, 2H), 7.40 (t, J = 7.2 Hz, 1H), 7.26-7.20 (m, 5H), 3.12 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 198.3, 159.9, 148.7, 139.7,137.8, 134.3, 133.4, 131.0, 129.6, 129.6, 128.4, 128.3, 128.2, 127.5, 127.4, 125.9, 125.8, 125.2, 22.8; HRMS-ESI (m/z): calcd for $C_{23}H_{18}NO$, $[M+H]^+$: 324.1383; found, 324.1387; IR (KBr): 2924, 1663, 1235, 758. cm^{-1}.

4-Acetyl-1,3-dimethylisoquinolin (3h): Red oil (72 mg, 72 %); ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.4 Hz, 1H), 7.70-7.65 (m, 1H), 7.61-7.52 (m, 2H), 2.95 (s, 3H), 2.64 (s, 3H), 2.60 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 206.1, 159.2, 144.5, 132.2, 130.9, 130.1, 126.6, 126.0, 125.2, 123.6, 32.9, 22.5, 22.3; HRMS-ESI (m/z): calcd for $C_{13}H_{14}NO$, $[M+H]^+$: 200.1070; found, 200.1073; IR (KBr): 2923, 1697, 1567, 1204, 761 cm^{-1}.

1,3-Dimethyl-4-(3-methylbutanoyl)isoquinolin (3i): Red oil (73 mg, 61 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 6.8 Hz, 1H), 7.58 (d, J = 7.6 Hz, 2H), 2.95 (s, 3H), 2.78 (d, J = 6.5 Hz, 2H), 2.59 (s, 3H), 2.43-2.36 (m, 1H), 1.06 (d, J = 6.8 Hz, 6H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 208.1, 161.4, 147.6, 133.0, 130.9 130.3, 126.6, 126.0, 125.5, 123.6, 54.5, 29.7, 24.0, 22.7, 22.4, 22.3; HRMS-ESI (m/z): calcd for $C_{16}H_{20}NO$, $[M+H]^+$: 242.1539; found, 242.1543; IR (KBr): 2958, 2927, 1697, 1569, 1394, 1365, 760 cm^{-1}.

6-Methyl-3,4-dihydrophenanthridin-1(2*H*)-one (3j): Yellow needles (73 mg, 69 %), m.p. = 74.5 – 75.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (d, J = 8.8 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.81-7.66 (m, 1H), 7.60-7.56 (m, 1H), 3.27 (t, J = 6.0 Hz, 2H), 2.98 (s, 3H), 2.80-2.76 (m, 2H), 2.25-2.18 (m, 2H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 200.7, 164.0, 160.2, 133.8, 132.5, 126.8, 126.6, 126.4, 125.8, 119.7, 40.6, 33.9, 23.3, 21.9; HRMS-ESI (m/z): calcd for $C_{14}H_{14}NO$, $[M+H]^+$: 212.1070; found, 212.1072; IR (KBr): 2945, 1670, 1562, 1498, 758 cm^{-1}.

3,3,6-Trimethyl-3,4-dihydrophenanthridin-1(2*H*)-one (3k): Red oil (87 mg, 73 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (d, J = 8.8 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.80-7.56 (m, 1H), 7.59-7.55 (m, 1H), 3.16 (s, 2H), 2.97 (s, 3H), 2.62 (s, 2H), 1.15 (s, 6H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 200.9, 164.3, 158.6, 133.5, 132.5, 126.8, 126.5, 126.3, 125.8, 118.7, 54.2, 47.8, 32.8, 28.2, 23.3; HRMS-ESI (m/z): calcd for $C_{16}H_{18}NO$, $[M+H]^+$: 240.1383; found, 240.1387; IR (KBr): 2956, 1671, 1564, 761 cm^{-1}.

3-Isopropyl-6-methyl-3,4-dihydrophenanthridin-1(2*H*)-one (3l): Red oil (86 mg,

70 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (d, J = 8.8 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.80-7.76 (m, 1H), 7.59 - 7.55 (m, 1H), 3.35-3.30 (m, 1H), 3.05-3.01 (m, 1H), 2.97 (s, 3H), 2.86-3.81 (m, 1H), 2.53-2.46 (m, 1H), 2.12-2.06 (m, 1H), 1.74-1.67 (m, 1H), 1.03 (d, J = 6.8, 3H), 1.02 (d, J = 6.8, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 201.2, 164.0, 159.9, 133.7, 132.5, 126.8, 126.5, 126.3, 125.8, 119.3, 44.7, 40.4, 37.8, 32.1, 23.3, 19.7, 19.5; HRMS-ESI (m/z): calcd for $C_{17}H_{20}NO$, $[M+H]^+$: 254.1539; found, 254.1544; IR (KBr): 2960, 1670, 1564, 1499, 1390, 1360, 761 cm^{-1}.

Methyl 1,3-Dimethylisoquinoline-4-carboxylate (3m): Red oil (90 mg, 84 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.70-7.66 (m, 1H), 7.57-7.53 (m, 1H), 4.04 (s, 3H), 2.95 (s, 3H), 2.68 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 169.4, 160.0, 148.4, 133.3, 130.9, 126.6, 125.8, 125.2, 124.3, 121.7, 52.4, 23.0, 22.6; HRMS-ESI (m/z): calcd for $C_{13}H_{14}NO_2$, $[M+H]^+$: 216.1019; found, 216.1023; IR (KBr): 2951, 1725, 1235, 758 cm^{-1}.

Ethyl 1,3-Dimethylisoquinoline-4-carboxylate (3n): Red oil (93 mg, 81 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.71-7.67 (m, 1H), 7.58-7.54 (m, 1H), 4.53 (q, J = 6.8 Hz, 2H), 2.96 (s, 3H), 2.70 (s, 3H), 1.46 (t, J = 7.2 Hz, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 168.9, 159.8, 148.0, 133.3, 131.0, 126.6, 125.8, 125.2, 124.3, 122.1, 61.6, 22.8, 22.5, 14.3; HRMS-ESI (m/z): calcd for $C_{14}H_{16}NO_2$, $[M+H]^+$: 230.1176; found, 230.1177; IR (KBr): 2982, 2928, 1723, 1234, 757 cm^{-1}.

Ethyl 1-Methyl-3-phenylisoquinoline-4-carboxylate (3o): Yellow needles (103 mg, 71 %), m.p. = 87.1 – 88.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.4 Hz, 1H),

8.05 (d, J = 8.4 Hz, 1H), 7.76 (t, J = 8.0 Hz, 1H), 7.70 (d, J = 7.6 Hz, 2H), 7.64 (t, J = 7.6 Hz, 1H), 7.47-7.39 (m, 3H), 4.21 (q, J = 7.2 Hz, 2H), 3.05 (s, 3H), 1.03 (t, J = 7.2 Hz, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 168.9, 160.1, 149.8, 140.4, 133.5, 131.2, 128.9, 128.4, 128.3, 127.3, 125.9, 125.7, 124.8, 122.2, 61.6, 22.8, 13.7; HRMS-ESI (m/z): calcd for $C_{19}H_{18}NO_2$, $[M+H]^+$: 292.1332; found, 292.1331; IR (KBr): 2983, 2926, 1719, 1227, 763, 701 cm^{-1}.

Allyl 1,3-Dimethylisoquinolin-4-carboxylate (3p): Red oil (91 mg, 76 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 6.14-6.04 (m, 1H), 5.46 (d, J = 16.8 Hz, 1H), 5.34 (d, J = 10.6 Hz, 1H), 4.95 (d, J = 6.0 Hz, 2H), 2.96 (s, 3H), 2.70 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 168.6, 160.0, 148.3, 133.3, 131.7, 130.9, 126.6, 125.8, 125.2, 124.3, 121.6, 119.5, 77.3, 66.2, 23.0, 22.6; HRMS-ESI (m/z): calcd for $C_{15}H_{16}NO_2$, $[M+H]^+$: 242.1176; found, 242.1178; IR (KBr): 3075, 2927, 1724, 1227, 760 cm^{-1}.

4-Acetyl-6-fluoro-1,3-dimethylisoquinolin (3q): Red oil (68 mg, 63 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, J = 9.2, 5.6 Hz, 1H), 7.33-7.28 (m, 1H), 7.22 (d, J = 7.6 Hz, 1H), 2.92 (s, 3H), 2.62 (s, 3H), 2.59 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 205.62, 163.6 (d, J = 251.5 Hz), 159.0, 146.1, 133.9, 129.9, 129.1 (d, J = 9.7 Hz), 122.6, 116.8 (d, J = 24.9 Hz), 107.6 (d, J = 22.0 Hz), 32.5, 22.6, 22.5; HRMS-ESI (m/z): calcd for $C_{13}H_{13}FNO$, $[M+H]^+$: 218.0976; found, 218.0982; IR (KBr): 2925, 1698, 1623, 1574, 1414, 1209 cm^{-1}.

4-Acetyl-7-fluoro-1,3-dimethylisoquinolin (3r): Red oil (71 mg, 66 %); ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.73 (d, J = 9.6 Hz, 1H), 7.67-7.63 (m, 1H), 7.49-7.45 (m, 1H), 2.93 (s, 3H), 2.65 (s, 3H), 2.62 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 205.7, 160.4 (d, J = 248 Hz), 158.5 (d, J = 5 Hz), 144.0, 130.1, 129.3, 126.3 (d, J = 9 Hz), 126.2 (d, J = 8 Hz), 121.4 (d, J = 25 Hz), 109.7 (d, J = 21 Hz), 101.4, 32.87, 22.35, 22.06; HRMS-ESI (m/z): calcd for $C_{13}H_{13}FNO$, $[M+H]^+$: 218.0976; found, 218.0980; IR (KBr): 2925, 1698, 1570, 1508, 1394, 1205 cm^{-1}.

4-Acetyl-5,7-dimethylthieno[2,3-*c*]pyridine (3s): Red oil (43 mg, 42 %); ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 5.4 Hz, 1H), 7.37 (d, J = 5.4 Hz, 1H), 2.81 (s, 3H), 2.70 (s, 3H), 2.67 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 204.0, 153.4, 147.8, 142.3, 133.6, 132.5, 128.7, 122.4, 32.1, 23.6, 22.8; HRMS-ESI (m/z): calcd for $C_{11}H_{12}NOS$, $[M+H]^+$: 206.0634; found, 206.0633; IR (KBr): 3054, 2986, 1692, 1265, 743 cm^{-1}.

1-Methyl-3-phenylisoquinoline-4-carbonitrile (5a): Red oil (96 mg, 79 %); ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8.4 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 7.2 Hz, 2H), 7.89 (t, J = 7.6 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H), 7.58-7.51 (m, 3H), 3.09 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 163.1, 156.4, 137.9, 135.9, 132.5, 129.9, 129.5, 128.7, 128.4, 126.3, 125.3, 117.2, 100.9, 23.2; HRMS-ESI (m/z): calcd for $C_{17}H_{13}N_2$, $[M+H]^+$: 245.1073; found, 245.1072; IR (KBr): 2922, 2218, 1551, 1388, 1267, 758, 697 cm^{-1}.

1-Methyl-3-(*p*-tolyl)isoquinoline-4-carbonitrile (5b): Yellow needles (94 mg, 73 %), m.p. = 152.9 – 154.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.0 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 7.6 Hz, 2H), 7.87 (t, J = 7.6 Hz, 1H), 7.70 (t, J = 7.6

Hz, 1H), 7.36 (d, J = 7.2 Hz, 2H), 3.07 (s, 3H), 2.45 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 163.0, 156.5, 140.1, 136.0, 135.2, 132.4, 129.4, 129.4, 128.2, 126.3, 125.2, 125.1, 117.5, 100.4, 23.3, 21.5; HRMS-ESI (m/z): calcd for $C_{18}H_{15}N_2$, $[M+H]^+$: 259.1230; found, 259.1224; IR (KBr): 2923, 2219, 1612, 1552, 1390, 827, 761 cm^{-1}.

3-(4-Methoxyphenyl)-1-methylisoquinoline-4-carbonitrile (5c): Yellow needles (101 mg, 74 %), m.p. = 122.9 – 124.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 8.8 Hz, 2H), 7.87 (t, J = 7.6 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 3.89 (s, 3H), 3.07 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 162.8, 161.1, 156.0, 136.1, 132.4, 131.0, 130.4, 128.1, 126.3, 125.1, 125.0, 117.6, 114.1, 99.7, 55.4, 23.2; HRMS-ESI (m/z): calcd for $C_{18}H_{15}N_2O$, $[M+H]^+$: 275.1179; found, 275.1173; IR (KBr): 2928, 2218, 1606, 1513, 1254, 1178, 838, 760 cm^{-1}.

3-(4-Fluorophenyl)-1-methylisoquinoline-4-carbonitrile (5d): Yellow needles (92 mg, 70 %), m.p. = 85.2 – 87.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, J = 19.6, 7.2 Hz, 2H), 8.08-8.05 (m, 2H), 7.90 (t, J = 7.6 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H), 7.26-7.22 (m, 2H), 3.08 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 163.9, 163.1, (d, J = 249 Hz), 155.25, 135.86, 134.3 (d, J = 3 Hz), 132.65, 131.5 (d, J = 9 Hz), 128.55, 126.33, 125.24, 115.7 (d, J = 22 Hz), 100.7, 23.2; HRMS-ESI (m/z): calcd for $C_{17}H_{12}FN_2$, $[M+H]^+$: 263.0979; found, 263.0974; IR (KBr): 2924, 2219, 1602, 1519, 1385, 1221, 1158, 837, 757 cm^{-1}.

3-(4-Chlorophenyl)-1-methylisoquinoline-4-carbonitrile (5e): Yellow needles (95

mg, 68 %), m.p. = 144.5 – 146.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.4 Hz, 1H), 8.23 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 2H), 7.90 (t, J = 7.6 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.52 (d, J = 7.6 Hz, 2H), 3.07 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 163.2, 155.0, 136.3, 136.2, 135.8, 132.7, 130.8, 128.9, 128.7, 126.3, 125.4, 125.3, 117.2, 100.9, 23.2; HRMS-ESI (m/z): calcd for $C_{17}H_{12}ClN_2$, $[M+H]^+$: 279.0684; found, 279.0684; IR (KBr): 2920, 2220, 1649, 1499, 829, 756 cm^{-1}.

3-Ethyl-1-methylisoquinoline-4-carbonitrile (5f): Yellow needles (70 mg, 72 %), m.p. = 106.2 – 108.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H),7.83 (t, J = 7.6 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 3.18 (q, J = 7.6 Hz, 2H), 3.01 (s, 3H), 1.42 (t, J = 7.6 Hz, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 163.0, 162.1, 135.3, 132.3, 127.8, 126.3, 125.0, 124.6, 116.5, 101.5, 30.8, 23.0, 14.1; HRMS-ESI (m/z): calcd for $C_{13}H_{13}N_2$, $[M+H]^+$: 197.1073; found, 197.1072; IR (KBr): 2922, 2216, 1562, 1502, 764 cm^{-1}.

1-Methyl-3-(thiophen-2-yl)isoquinoline-4-carbonitrile (5g): Yellow needles (97 mg, 78 %), m.p. = 169.0 – 170.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 2.8 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 4.8 Hz, 1H), 7.20 (t, J = 4.4 Hz, 1H), 2.99 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 163.0, 148.9, 142.7, 135.9, 132.6, 130.4, 128.6, 128.6, 128.0, 126.3, 125.1, 125.0, 117.4, 96.2, 22.9; HRMS-ESI (m/z): calcd for $C_{15}H_{11}N_2S$, $[M+H]^+$: 251.0637; found, 251.0641; IR (KBr): 2921, 2212, 1610, 1497, 728 cm^{-1}.

Ethyl 3-Amino-1-methylisoquinoline-4-carboxylate (7a): Yellow needles (98 mg,

85 %), m.p. = 120.3 – 122.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 8.8 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 6.51 (s, 2H), 4.40 (q, J = 7.2 Hz, 2H), 2.74 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 169.1, 164.4, 157.2, 136.9, 131.6, 126.4, 124.8, 122.5, 122.5, 94.5, 60.7, 22.9, 14.5; HRMS-ESI (m/z): calcd for $C_{13}H_{15}N_2O_2$, $[M+H]^+$: 231.1128; found, 231.1127; IR (KBr): 3377, 3240 1663, 1607, 1309, 1224, 743 cm^{-1}.

Isopropyl 3-Amino-1-methylisoquinoline-4-carboxylate (7b): Yellow needles (94 mg, 77 %), m.p. = 99.4 – 101.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.27-7.23 (m, 1H), 6.56 (s, 2H), 5.42-5.36 (m, 1H), 2.82 (s, 3H), 1.46 (d, J = 6.0 Hz, 6H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 168.6, 164.1, 157.0, 136.9, 131.5, 126.3, 124.7, 122.5, 97.8, 68.5, 22.9, 22.2; HRMS-ESI (m/z): calcd for $C_{14}H_{17}N_2O_2$, $[M+H]^+$: 245.1285; found, 245.1283; IR (KBr): 3495, 3283, 1656, 1613, 1221, 748 cm^{-1}.

Isobutyl 3-Amino-1-methylisoquinoline-4-carboxylate (7c): Yellow needles (112 mg, 87 %), m.p. = 92.5 – 94.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.27-7.23 (m, 1H), 6.67 (s, 2H), 4.22 (d, J = 6.8 Hz, 2H), 2.82 (s, 3H), 2.20-2.13 (m, 1H), 1.07 (d, J = 6.8 Hz, 6H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 169.2, 164.4, 157.3, 136.9, 131.6, 126.4, 124.9, 122.5, 122.5, 94.6, 71.2, 27.9, 22.8, 19.5; HRMS-ESI (m/z): calcd for $C_{15}H_{19}N_2O_2$, $[M+H]^+$: 259.1441; found, 259.1440; IR (KBr): 3402, 3285, 2958, 1666, 1611, 1219, 744 cm^{-1}.

***tert*-Butyl 3-Amino-1-methylisoquinoline-4-carboxylate (7d):** Yellow needles (90

mg, 70 %), m.p. = 125.7 – 127.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 8.8 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.57-7.54 (m, 1H), 7.25-7.21 (m, 1H), 6.47 (s, 2H), 2.81 (s, 3H), 1.68 (s, 9H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 168.3, 163.6, 156.7, 136.9, 131.3, 126.3, 124.7, 122.5, 122.4, 96.2, 81.8, 28.7, 22.8; HRMS-ESI (m/z): calcd for $C_{15}H_{19}N_2O_2$, $[M+H]^+$: 259.1441; found, 259.1444; IR (KBr): 3410, 3282, 1658, 1316, 1273, 1149 cm^{-1}.

Butyl 3-Amino-1-methylisoquinoline-4-carboxylate (7e): Yellow needles (95 mg, 74 %), m.p. = 77.3 – 78.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 8.8 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.27-7.24 (m, 1H), 6.63 (s, 2H), 4.43 (t, J = 6.8 Hz, 2H), 2.83 (s, 3H), 1.87-1.80 (m, 2H), 1.57-1.47 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 169.1, 164.2, 157.1, 137.0, 131.7, 126.4, 124.8, 122.6, 122.4, 94.7, 64.8, 30.9, 22.8, 19.5, 13.8; HRMS-ESI (m/z): calcd for $C_{15}H_{19}N_2O_2$, $[M+H]^+$: 259.1441; found, 259.1448; IR (KBr): 3488, 3279, 1663, 1612 1234, 758 cm^{-1}.

Allyl 3-Amino-1-methylisoquinoline-4-carboxylate (7f): Yellow needles (96 mg, 79 %), m.p. = 99.2 – 101.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 8.8 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.25-7.21 (m, 1H), 6.59 (s, 2H), 6.15-6.05 (m, 1H), 5.43 (d, J = 17.2 Hz, 1H), 5.30 (d, J = 10.8 Hz, 1H), 4.90 (d, J = 5.6 Hz, 2H), 2.79 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 168.7, 164.7, 157.4, 136.8, 132.4, 131.7, 126.4, 124.9, 122.6, 122.5, 118.6, 94.1, 65.4, 22.9; HRMS-ESI (m/z): calcd for $C_{14}H_{15}N_2O_2$, $[M+H]^+$: 243.1128; found, 243.1132; IR (KBr): 3354, 3248, 1667, 1615, 1220, 743 cm^{-1}.

Benzyl 3-Amino-1-methylisoquinoline-4-carboxylate (7g): Yellow needles (111 mg, 76 %), m.p. = 115.9 – 117.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.49 (d, J = 7.2 Hz, 2H), 7.42-7.33 (m, 3H), 7.27-7.23 (m, 2H), 5.47 (s, 2H), 2.83 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 168.6, 164.4, 156.9, 137.1, 136.0, 132.1, 128.7, 128.3, 128.3, 126.5, 124.9, 122.8, 122.36, 94.4, 66.6, 22.6; HRMS-ESI (m/z): calcd for $C_{18}H_{17}N_2O_2$, $[M+H]^+$: 293.1285; found, 293.1288; IR (KBr): 3488, 3290, 1665, 1610, 1218, 740 cm^{-1}.

5-Methylindolo[1,2-*a*]quinazoline (9a) : Brown needles (88 mg, 76 %), m.p. = 164.1 – 165.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 8.4 Hz, 1H), 8.28 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 6.8 Hz, 1H), 7.90-7.87 (m, 1H), 7.79-7.45 (m, 1H), 7.46-7.34 (m, 3H), 6.89 (s, 1H), 2.80 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 157.1, 141.8, 138.1, 133.1, 130.2, 129.7, 127.4, 122.8, 122.2, 121.5, 118.4, 114.8, 114.0, 95.6, 22.7; HRMS-ESI (m/z): calcd for $C_{16}H_{13}N_2$, $[M+H]^+$: 233.1073; found, 233.1078; IR (KBr): 3052, 2920, 1597, 1553, 1453, 745 cm^{-1}.

5,7-Dimethylindolo[1,2-*a*]quinazoline (9b): Yellow needles (80 mg, 65 %), m.p. = 157.4 – 158.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.4 Hz, 1H), 8.19-8.17 (m, 1H), 7.82-7.79 (m, 2H), 7.66-7.62 (m, 1H), 7.41-7.36 (m, 2H), 7.26-7.21 (m, 1H), 2.73 (s, 3H), 2.60 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 155.3, 138.4, 138.3, 132.7, 130.2, 129.3, 127.2, 122.3, 122.2, 121.5, 119.5, 118.5, 114.4, 113.7, 102.9, 22.8, 7.8; HRMS-ESI (m/z): calcd for $C_{17}H_{15}N_2$, $[M+H]^+$: 247.1230; found, 247.1231; IR (KBr): 3101, 1565, 1268, 754 cm^{-1}.

8-Methoxy-5-methylindolo[1,2-*a*]quinazoline (9c): Brown needles (98 mg, 75 %), m.p. = 178.3 – 180.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.73 (t, J = 8.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 2H), 7.00 (s, 1H), 6.79 (d, J = 7.6 Hz, 1H), 4.03 (s, 3H), 2.78 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 156.3, 153.7, 140.7, 137.9, 132.8, 131.1, 127.1, 123.0, 122.9, 120.9, 118.6, 114.9, 107.1, 101.7, 92.9, 55.5, 22.7; HRMS-ESI (m/z): calcd for $C_{17}H_{15}N_2O$, $[M+H]^+$: 263.1179; found, 263.1182; IR (KBr): 2926, 1553, 1447, 1243, 752 cm^{-1}.

8-(Benzyloxy)-5-methylindolo[1,2-*a*]quinazoline (9d): Yellow needles (140 mg, 83 %), m.p. = 164.8 – 166.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 8.4 Hz, 1H), 7.86-7.81 (m, 2H), 7.70-7.66 (m, 1H), 7.53 (d, J = 7.6 Hz, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.35-7.24 (m, 3H), 7.06 (s, 1H), 6.81 (d, J = 7.6 Hz, 1H), 5.29 (s, 2H), 2.75 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 156.4, 152.7, 140.8, 137.9, 137.5, 132.8, 131.2, 128.6, 127.8, 127.1, 127.1, 122.9, 122.9, 121.3, 118.6, 114.8, 107.4, 103.5, 93.1, 70.1, 22.7; HRMS-ESI (m/z): calcd for $C_{23}H_{19}N_2O$, $[M+H]^+$: 339.1492; found, 339.1501; IR (KBr): 3034, 2923, 1551, 1446, 749 cm^{-1}.

5,9-Dimethylindolo[1,2-*a*]quinazoline (9e): Brown needles (95 mg, 77 %), m.p. = 164.2 – 166.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.73 (t, J = 8.0 Hz, 1H), 7.64 (s, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 6.79 (s, 1H), 2.78 (s, 3H), 2.54 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 156.8, 142.0, 138.0, 133.0, 131.6, 130.0, 128.5, 127.2, 123.8, 122.6, 121.1, 118.3, 114.7, 113.6, 95.1, 22.7, 21.5; HRMS-ESI (m/z):

calcd for $C_{17}H_{15}N_2$, $[M+H]^+$: 247.1230; found, 247.1234; IR (KBr): 3026, 2917, 1597, 1553, 1455, 746 cm^{-1}.

9-Methoxy-5-methylindolo[1,2-*a*]quinazoline (9f): Brown needles (107 mg, 82 %), m.p. = 168.1 – 169.4 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (t, J = 8.8 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 8.0z, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 7.2 Hz, 1H), 7.04 (d, J = 9.2 Hz, 1H), 6.81 (s, 1H), 3.92 (s, 3H), 2.80 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 156.8, 155.4, 142.4, 137.8, 133.1, 130.8, 127.3, 125.2, 122.6, 118.2, 114.9, 114.4, 112.4, 102.2, 95.3, 55.6, 22.7; HRMS-ESI (m/z): calcd for $C_{17}H_{15}N_2O$, $[M+H]^+$: 263.1179; found, 263.1181; IR (KBr): 3072, 2936, 1594, 1454, 1218, 750 cm^{-1}.

9-Fluoro-5-methylindolo[1,2-*a*]quinazoline (9g): Brown needles (95 mg, 76 %), m.p. = 162.7 – 163.9 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.4 Hz, 1H), 7.99 (dd, J = 9.2, 4.0 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.34-7.31 (m, 1H), 7.23-7.19 (m, 1H), 7.01-7.96 (m, 1H), 6.67 (s, 1H), 2.65 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 158.5 (J = 237.7 Hz), 157.6, 142.9, 137.4, 133.1, 130.5 (J = 10.4 Hz), 127.3, 126.6, 122.9, 118.1, 114.8 (J = 9.7 Hz), 114.23, 110.2 (J = 25.8 Hz), 105.9 (J = 23.2 Hz), 95.4 (J = 4.5 Hz), 22.6; HRMS-ESI (m/z): calcd for $C_{16}H_{12}FN_2$, $[M+H]^+$: 251.0979; found, 251.1012; IR (KBr): 3067, 2924, 1595, 1554, 1452, 751 cm^{-1}.

5-Methylindolo[1,2-*a*]quinazoline-9-carbonitrile (9h): Yellow needles (82 mg, 64 %), m.p. = 233.8 – 234.4 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 8.8 Hz, 1H), 8.12 (s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.83-7.79 (m,

1H), 7.58-7.55 (m, 1H), 7.45 (t, J = 8.0 Hz, 1H), 6.87 (s, 1H), 2.82 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 159.0, 143.2, 137.2, 133.6, 131.2, 129.2, 127.8, 126.4, 124.3, 124.1, 120.0, 118.7, 115.0, 114.6, 105.3, 95.9, 22.9; HRMS-ESI (m/z): calcd for $C_{17}H_{12}N_3$, $[M+H]^+$: 258.1026; found, 258.1025; IR (KBr): 3349, 2920, 2219, 1606, 1455, 746 cm^{-1}.

10-Fluoro-5-methylindolo[1,2-*a*]quinazoline (9i): Yellow needles (85 mg, 68 %), m.p. = 124.5 – 126.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.4 Hz, 1H), 7.94-7.89 (m, 2H), 7.79-7.73 (m, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.18-7.13 (m, 1H), 6.82 (s, 1H), 2.77 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 159.3 (J = 237.1 Hz), 156.7, 142.1, 137.5, 133.0, 129.3 (J = 11.6 Hz), 127.3, 126.0, 123.1, 122.1 (J = 9.7 Hz), 118.4, 114.4, 110.9 (J = 24.1 Hz), 100.8 (J = 28.1 Hz), 95.4 (J = 1.0 Hz), 22.7; HRMS-ESI (m/z): calcd for $C_{16}H_{12}FN_2$, $[M+H]^+$: 251.0979; found, 251.1008; IR (KBr): 3068, 2923, 1607, 1478, 1147, 810, 745 cm^{-1}.

11-Methoxy-5-methylindolo[1,2-*a*]quinazoline (9j): Brown needles (109 mg, 83 %), m.p. = 105.0 – 106.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H), 6.90 (d, J = 7.6 Hz, 1H), 6.85 (s, 1H), 4.03 (s, 3H), 2.81 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 157.6, 147.9, 142.9, 138.1, 132.7, 131.9, 126.1, 123.4, 122.7, 120.6, 118.8, 114.1, 104.4, 96.5, 56.0, 22.5; HRMS-ESI (m/z): calcd for $C_{17}H_{15}N_2O$, $[M+H]^+$: 263.1179; found, 263.1182; IR (KBr): 3060, 1611, 1244, 1176, 746 cm^{-1}.

5-Methylpyrido[3',2':4,5]pyrrolo[1,2-*a*]quinazoline (9k): Yellow needles (91 mg,

78 %), m.p. = 176.6 – 177.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (d, J = 8.4 Hz, 1H), 8.52 (d, J = 3.6 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.78 (t, J = 8.0 Hz, 1H), 7.36-7.29 (m, 2H), 6.74 (s, 1H), 2.80 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 159.1, 143.5, 142.1, 141.1, 137.0, 133.6, 128.6, 126.5, 123.5, 122.0, 118.1, 117.9, 117.7, 92.3, 22.9; HRMS-ESI (m/z): calcd for $C_{15}H_{12}N_3$, $[M+H]^+$: 234.1026; found, 234.1034; IR (KBr): 3045, 2922, 1600, 1544, 758 cm^{-1}.

5-Methylpyrrolo[1,2-*a*]quinazoline (9l): Brown needles (67 mg, 74 %), m.p. = 108.2 – 109.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.71-7.67 (m, 1H), 7.60 (s, 1H), 7.38 (t, J = 7.6 Hz, 1H), 6.82 (t, J = 3.2 Hz, 1H), 6.61 (d, J = 3.6 Hz, 1H), 2.78 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 150.5, 136.6, 133.9, 131.2, 126.1, 122.7, 117.0, 112.9, 112.4, 107.5, 100.1, 21.1; HRMS-ESI (m/z): calcd for $C_{12}H_{11}N_2$, $[M+H]^+$: 183.0917; found, 183.0923; IR (KBr): 3128, 2921, 1600, 1544, 754 cm^{-1}.

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Supporting Information

Spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Crystallographic data for **3f** (CIF)

REFERENCES

(1) For representative references, see: (a) Bentley, K. W. *Nat. Prod. Rep.* **2006**, *23*, 444-463. (b) Zhou, J.; Campbell-Conroy, E. L.; Silina, A.; Uy, J.; Pierre, F.; Hurley, D. J.; Hilgraf, N.; Frieman, B. A.; DeNinno, M. P. *J. Org. Chem*. **2015**, *80*, 70-79.

(2) Wu, S. C.; Yoon, D.; Chin, J.; Kirk, K.; Seethala, R.; Golla, R.; He, B.; Harrity, T.; Kunselman, L. K.; Morgan, N. N.; Ponticiello, R. P.; Taylor, J. R.; Zebo, R.; Harper, T. W.; Li, W.; Wang, M.; Zhang, L.; Sleczka, B. G.; Nayeem, A.; Sheriff, S.; Camac, D. M.; Morin, P. E.; Everlof, J. G.; Li, Y.-X.; Ferraro, C. A.; Kieltyka, K.; Shou, V.; Vathc, M. B.; Zvyaga, T. A.; Gordon, D. A.; Robl, J. A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6693-6698.

(3) (a) Timári, G.; Soós, T.; Hajós, G.; Messmer, A.; Nacsa, J.; Molnár, J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2831-3836. (b) Kashiwada, Y.; Aoshima, A.; Ikeshiro, Y.; Chen, Y. P.; Furukawa, H.; Itoigawa, M.; Fujioka, T.; Mihashi, K.; Cosentino, L. M.; Morris-Natschke, S. L.; Lee, K.-H. *Bioorg. Med. Chem.* **2005**, *13*, 443-448.

(4) Gao, Y. G.; Zong, R.; Campbell, A.; Kula, N. S.; Baldessarini, R. J.; Neumeyer, J. L. *J. Med. Chem.* **1988**, *31*, 1392-1396.

(5) Graulich, A.; Dilly, S.; Farce, A.; Scuve-Moreau, J.; Waroux, O.; Lamy, C.; Chavatte, P.; Seutin, V.; Ligeois, J. F.; *J. Med. Chem.* **2007**, *50*, 5070-5075.

(6) (a) Lim, C. W.; Tissot, O.; Mattison, A.; Hooper, M. W.; Brown, J. M.; Cowley, A. R.; Hulmes, D. I.; Blacker, A. J. *Org. Process Res. Dev.* **2003**, *7*, 379-384. (b) Sweetman, B. A.; Muller-Bunz, H.; Guiry, P. J. *Tetrahedron Lett.* **2005**, *46*, 4643-4646.

(7) (a) Tsuboyama, A.; Iwawaki, H.; Furugori, M.; Mukaide, T.; Kamatani, J.;

Igawa, S.; Moriyama, T.; Miura, S.; Takiguchi, T.; Okada, S.; Hoshino, M.; Ueno, K. *J. Am. Chem. Soc.* **2003**, *125*, 12971-12979. (b) Liu, S.-J.; Zhao, Q.; Chen, R.-F.; Deng, Y.; Fan, Q.-L.; Li, F.-Y.; Wang, L.-H.; Huang, C.-H.; Huang, W. *Chem. Eur. J.* **2006**, *12*, 4351-4361.

(8) For Bischler-Napieralski examples, see: (a) Ishikawa, T.; Shimooka, K.; Narioka, T.; Noguchi, S.; Saito, T.; Ishikawa, A.; Yamazaki, E.; Harayama, T.; Seki, H.; Yamaguchi, K. *J. Org. Chem.* **2000**, *65*, 9143-9151. (b) Xu, X.; Guo, S.; Dang, Q.; Chen, J.; Bai, X. *J. Comb. Chem.* **2007**, *9*, 773-782. For Pomeranz-Fritsch examples, see: (c) Herz, W.; Tocker, S. *J. Am. Chem. Soc.* **1955**, *77*, 6355-6357. For Pictet-Spengler examples, see: (d) Youn, S. W. *J. Org. Chem.* **2006**, *71*, 2521-2523.

(9) (a) Vangrevelinghe, E.; Zimmermann, K.; Schoepfer, J.; Portmann, R.; Fabbro, D.; Furet, P. *J. Med. Chem.* **2003**, *46*, 2656-2662. (b) Ferraris, D. V. *J. Med. Chem.* **2010**, *53*, 4561-4584.

(10) (a) Moore, J. A.; Sutherland, G. J.; Sowerby, R.; Kelly, E. G.; Palermo, S.; Webster, W. *J. Org. Chem.* **1969**, *34*, 887-892. (b) Zabrodnyaya, V. G.; Portnov, Yu. N.; Kost, A. N.; Voronin, V. G. *Khimiya Geterotsiklicheskikh Soedinenii.* **1981**, *6*, 884-2447. (c) Alajarin, M.; Bonillo, B.; Ortin, M.-M.; Orenes, R.-A.; Vidal, A. *Org. Biomol. Chem.* **2011**, *9*, 6741-6749. (d) Kiruthika, S. E.; Perumal, P. T. *Org. Lett.* **2014**, *16*, 484-487. (e) Li, C.; Zhang, L.; Shu, S.; Liu, H. *Beilstein J. Org. Chem.* **2014**, *10*, 2441-2447. (f) Jiang, M.; Xiang, H.; Zhu, F.; Xu, X.; Deng, L.; Yang, C. *Org. Biomol. Chem.* **2015**, *13*, 10122-10126.

(11) For representative references, see: (a) Kusama, H.; Yamashita, Y.; Narasaka, K.

Chem. Lett. **1995**, 5-6. (b) Mori, S.; Uchiyama, K.; Hayashi, Y.; Narasaka, K.; Nakamura, E. *Chem. Lett.* **1998**, 111-112. (c) Yoshida, M.; Kitamura, M.; Narasaka, K. *Chem. Lett.* **2002**, 144-145. (d) Narasaka, K. *Pure Appl. Chem.* **2002**, *74*, 143-149. (e) Yoshida, M.; Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2003-2008. (f) Tanaka, K.; Mori, Y.; Narasaka, K. *Chem. Lett.* **2004**, *33*, 26-27. (g) Counceller, C. M.; Eichman, C. C.; Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2008**, *10*, 1021-1023. (h) Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2010**, *12*, 4576-4579.

(12) For representative references, see: (a) Uchiyama, K.; Ono, A.; Hayashi, Y.; Narasaka, K. *Synlett* **1997**, 445-446. (b) Uchiyama, K.; Ono, A.; Hayashi, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2945-2955. (c) Boivin, J.; Schiano, A.-M.; Zard, S. Z.; Zhang, H. *Tetrahedron Lett.* **1999**, *40*, 4531-4534. (d) Gagosz, F.; Zard, S. Z. *Synlett* **1999**, *12*, 1978-1980. (e) Mikami, T.; Narasaka, K. *Chem. Lett.* **2000**, 338-339. (f) Alonso, R.; Campos, P. J.; García, B.; Rodríguez, M. A. *Org. Lett.* **2006**, *8*, 3521-3523.

(13) For representative ruthenium-catalyzed examples, see: (a) Chinnagolla, R. K.; Pimparkar, S.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 3032-3035. (b) Chinnagolla, R. K.; Pimparkar, S.; Jeganmohan, M. *Chem. Commun.* **2013**, *49*, 3703-3705. (c) Kornhaaß, C.; Kuper, C.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1619-1624.

(14) For representative rhodium-catalyzed examples, see: (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315-1345. (b) Too, P. C.; Chua, S. H.; Wong, S. H.; Chiba, S. *J. Org. Chem.* **2011**, *76*, 6159-6168. (c) Martin, R. M.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2012**, *77*, 2501-2507. (d) Xu, F.; Wang, C.; Wang, D.; Li, X.; Wan, B. *Chem.*

Eur. J. **2013**, *19*, 2252-2255. (e) Shi, Z.; Koester, D.; Boultadakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204-12207. (f) Sun, P.; Wu, Y.; Yang, T.; Wu, X..; Xu, J.; Lin, A.; Yao, H. *Adv. Synth. Catal.* **2015**, *357*, 2469-2473.

(15) For representative palladium-catalyzed examples, see: (a) Gerfaud, T.; Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 572-577. (b) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676-3677. (c) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885-1898. (d) Hong, W. P.; Iosub, A. V.; S. Stahl, S. *J. Am. Chem. Soc.* **2013**, *135*, 13664-13667 (e) Xu, Y.; Hu, W.; Tang, X.; Zhao, J.; Wu, W.; Jiang, H. *Chem. Commun.* **2015**, *51*, 6843-6846.

(16) (a) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918-6919. (b) Ren, Z.-H.; Zhang, Z.-Y.; Yang, B.-Q.; Wang, Y.-Y. Guan, Z.-H. *Org. Lett.* **2011**, *13*, 5394-5397. (c) Wei, Y.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 3756-3759. (d) Ran, L.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Green Chem.* **2014**, *16*, 112-115. (e) Wu, Q.; Zhang, Y.; Cui. S. *Org. Lett.* **2014**, *16*, 1350-1353.

(17) (a) Tang, X.; Huang, L.; Qi, C.; Wu, W.; Jiang, H. *Chem. Commun.* **2013**, *49*, 9597-9599. (b) Huang, H.; Ji, X.; Tang, X.; Zhang, M.; Li, X.; Jiang, H. *Org. Lett.* **2013**, *15*, 6254-6257. (c) Tang, X.; Gao, H.; Yang, J.; Wu, W.; Jiang, H. *Org. Chem. Front.* **2014**, *1*, 1295-1298. (d) Tang, X.; Huang, L.; Yang, J.; Xu, Y.; Wu, W.; Jiang, H. *Chem. Commun.* **2014**, *50*, 14793-14796. (e) Jiang, H.; Yang, J.; Tang, X.; Li, J.; Wu, W. *J. Org. Chem.* **2015**, *80*, 8763−8771.

(18) CCDC 1031548 (**3f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge

Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. A single crystal of product **3f** is in the Supporting Information.

(19) (a) Tang, X.; Huang, L.; Xu, Y.; Yang, J.; Wu, W.; Jiang, H. *Angew. Chem. Int. Ed.* **2014**, *53*, 4205-4208. (b) Huang, H.; Ji, X.; Wu, W.; Jiang, H. *Chem. Soc. Rev.* **2015**, *44*, 1155-1171.

(20) (a) Bryson, T. A.; Stewart, J. J.; Gibson, J. M.; Thomas, P. S.; Berch, J. K.; *Green Chem.* **2003**, *5*, 174-176.(b) Zou,B.; Yuan,Q.; Ma, D. *Org. Lett.* **2007**, *9*, 4291-4294. (c) Wang, B.; Lu, B.; Jiang, Y.; Zhang, Y.; Ma, D. *Org. Lett.* **2008**, *10*, 2761-2763. (d) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6954-6971.

(21) (a) Too, P. C.; Chua, S. H.; Wong, S. H.; Chiba, S. *J. Org. Chem.* **2011**, *76*, 6159-6168. (b) Kim, J.; Chang, S. *J. Am. Chem. Soc.* **2010**, *132*, 10272-10274.

(22) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett*. **2010**, *12*, 5688-5691.