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Facile Synthesis of 3-Substituted Isoquinolines Derivatives via Microwave-assisted Tandem Three-component Coupling Cyclization

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A novel three-component reaction of *o*-bromobenzaldehyde, terminal alkynes and *tert*-butyl amine has been established, which proceeded smoothly to give 3-substituted isoquinolines in good yields in the presence of palladium/copper catalysts under microwave irradiation.

Keywords palladium/copper-catalyst, microwave, isoquinolines, tandem reaction, coupling cyclization

Introduction

Isoquinoline is an important heterocyclic skeleton that serves as key structural units in a broad range of natural products as well as building block in important pharmaceuticals.[1] Isoquinoline species are also utilized as chiral ligands for transition metal catalysts,[2] and their iridium complexes are used in organic light-emitting diodes.[3] In recent years, 3-substituted isoquinoline derivatives are becoming inspiring owing to their prominent biological activities. Decumbenine B (Figure 1, structure **A**), a 3-arylisoquinoline alkaloid isolated from plant tubers of *Coridalis decumbens*, has been recognized as a promising inhibitor for controlling spontaneous contraction of the intestine.[4] Another kind of 3-arylisoquinoline derivatives with structure type **B** has been concluded to be useful for regulating the expression of apolipoprotein A-I (ApoA-I), and thus useful for treatment and prevention of cardiovascular diseases and related disease states.[5] Similarly, structur type C has been reported with potential for treatment of inflammation.[6] In addition, a number of synthetic 3-substituted isoquinolines with potent antitumor cytotoxicities and topoisomerase I inhibitory activities have also been reported.[7]

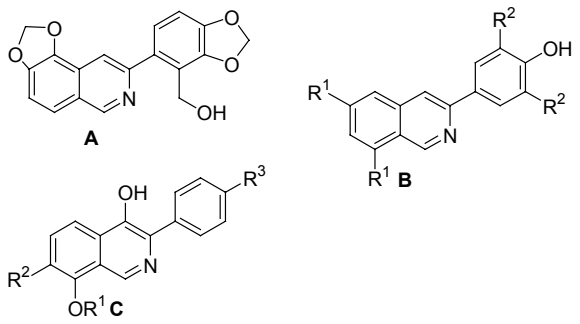

Figure 1 Selected biologically active 3-substituted isoquinoline derivatives.

Because of their biological and/or physical properties, the efficient synthesis of the isoquinoline ring system has received considerable attention of synthetic chemists. Although many methods for the synthesis of this important ring system are known, the traditional methods such as the Bischler-Napieralski reaction,[8] the Pomeranz-Fritsch reaction,[9] and the Pictet-Spengler reaction[10] suffered from some drawbacks such as the harsh reaction conditions, tedious reaction procedures, low yield, which hampered their general utilization, especially for those with more substituents in 3-aryl group. In recent years, some mild and efficient synthesis of isoquinoline has been developed. For instance, Pfeffer[11] and Heck[12] have reported a methodology to synthesize substituted isoquinoline utilizing stoichiometric amount of palladium salts. Moreover, Larock and co-workers have developed an extremely efficient metal-mediated method using 2-iodobenzaldimine and substituted terminal acetylenes as starting materials in the syntheis of a wide variety of 3,4-disubstituted isoquinolines.[13]

Tandem reactions and multicomponent reactions[14] in which several bond-forming steps take place in one pot are powerful tools for the construction of some biologically interesting molecules from readily accessible components. Recently, considerable efforts have been

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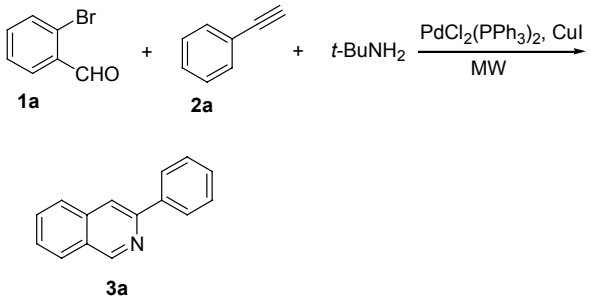
made to develop efficient methods for the synthesis of isoquinoline analogues using multicomponent reaction manner.[15] However, to the best of our knowledge, the multicomponent synthetic approach to isoquinoline using the *o*-bromobenzaldehyde as starting material involving a Sonogashira coupling reaction as a key step is scarce. Although, the example reported by Abbiati starting from *o*-bromobenzaldehyde, terminal alkynes and aqueous ammonia *via* the Sonogashira coupling and/or imination-cyclization tandem procedure achieved the isoquinolines successfully.[16] this three-component method needed a comparable high reaction temperature and a long time microwave irradiation to achieve a low or moderate product yield, moreover, the scope of the substrate was confined to the aromatic alkynes, not suitable for the aliphatic linear alkynes. We were intrigued to further simplify and optimize the approach using an economic multicomponent manner. Herein, we wish to report a palladium/copper co-catalyzed tandem three-component coupling-cyclization reaction for the synthesis of 3-substituted isoquinolines with the readily available materials of *o*-bromobenzaldehyde, a terminal alkyne, and a primary amine under microwave irradiation conditions. Our multicomponent strategy provided a highly efficient approach to the preparation of isoquinoline derivatives with reduced reaction times and improved yields. Furthermore, the tandem reaction sequence was evidenced by NMR spectrum. Notably, the substrate scope is quite broad, which makes this method an inspiring approach to the isoquinolines library with structural diversity.

Results and Discussion

We initially examined the possibility of achieving a three-component tandem reaction using a model reaction that included 1.0 equiv. 2-bromobenzaldehyde, 1.2 equiv. phenylacetylene, 3 equiv. *tert*-butyl amine with 5% $PdCl_2(PPh_3)_2$ and 10% CuI as the catalyst in 2 mL DMF (Table 1). We isolated the desired 3-substituted isoquinoline product in quite low yield when we mixed the three components in one pot at elevated temperature with a long reaction time under conventional heating (Table 1, Entry 1). Microwave-assisted organic synthesis (MAOS) has gained acceptance as a valuable tool for accelerating organic reaction rates and highly improving yields.[17] One of the most extensively studied reaction types in MAOS are transition-metal catalyzed reactions. Carbon-carbon and carbon-heteroatom bond-forming reactions, which typically require hours or days to reach completion, can be significantly accelerated by employing microwave heating in a sealed vial.[18] We thus examined the effect of microwave irradiation on our three-component reaction by using a single-mode *smithsynthesizer*™ microwave system with optic fiber for detecting their temperature (Table 1, Entries 2—9). We noticed that when the reaction temperature was improved from 100 to 140 ℃ the yield increased from

Table 1 Optimization of temperature and MW power[a]



Entry	Temp./℃	Power/W	Yield[c]/%
1[b]	130	—	19
2	100	—	20
3	120	—	32
4	140	—	41
5	160	—	18
6	—	100	40
7	—	120	49
8	—	140	65
9		160	59

[a] All reactions were run by employing 1.0 equiv. **1a**, 1.2 equiv. **2a**, 3 equiv. *t*-butyl amine, 3 equiv. Et_3N in 2 mL DMF with 5% $PdCl_2(PPh_3)_2$ and 10% CuI catalyst under microwave irradiation for 15 min. [b] Conventional heating for 24 h. [c] Isolated yield.

20% to 41% under microwave irradiation for 15 min (Table 1, Entries 2 and 4). However, the product yield decreased dramatically when the reaction temperature was further increased to 160 ℃ (Table 1, Entry 5). It is interesting that microwave power is more efficacious for increasing product yield than the temperature adjustment. When the reactant was irradiated at 100 W, a comparable yield was observed as the irradiation temperature fixed at 140 ℃ (Table 1, Entry 6), whereas the maximum reaction temperature only reached to 100 ℃ during the microwave irradiation. By increasing the microwave power to 140 W the desired product was obtained in a satisfying 65% yield in 15 min. Correspondingly, the maximum temperature of the reaction system was about 135 ℃ at the fixed microwave power 140 W. A further increase of microwave power gave a worse result (Table 1, Entry 9). From these results, it was clearly indicated that microwave irradiation at 140 W was more suitable for our further reaction optimization.

The effect of various palladium catalysts on the reaction was then investigated in the presence of 10 mol% of CuI co-catalyst with Et_3N as base under microwave irradiation. The catalyst $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ afford comparable desired product under this reaction conditions (Table 2, compare Entry 2 with Entry 4). Considering the easy handle of $PdCl_2(PPh_3)_2$, we select catalyst $PdCl_2(PPh_3)_2$ for further reaction optimization. In an effort to reduce the amount of the palladium cata-

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lyst, one reaction was run in which the amount of $PdCl_2(PPh_3)_2$ was reduced from 5 to 2.5 mol%. However, a significant decrease in the product yield was observed (Table 2, Entry 5). CuI is a very important co-catalyst in the Sonogashira coupling reaction and it also plays a key role in the cyclizaiton step for the formation of isoquinoline. We noticed that the yield of **3a** was improved by increasing the amount of CuI. For example, when CuI was increased from the catalytic amount (10 mol%) to a substoichiometric amount (40 mol%), the yield of product **3a** was dramatically improved from 65% to 82%. However, further improve the amount of CuI to 60 mol%, a much lower yield was obtained, beside a mixture of unidentified products. For comparison purpose, a reaction without the palladium catalyst was carried out in the presence of 40 mol% CuI, a scarce result was observed (Table 2, Entry 16).

Table 2 Optimization of the reaction conditions[a]

Entry	Catalyst (5 mol%)	CuI/mol%	Base	Time/min	Yield[b]/%
1	$Pd(OAc)_2$	10	Et_3N	15	34
2	$Pd(PPh_3)_4$	10	Et_3N	15	67
3	$PdCl_2(PhCN)_2$	10	Et_3N	15	trace
4	$PdCl_2(PPh_3)_2$	10	Et_3N	15	65
5[c]	$PdCl_2(PPh_3)_2$	10	Et_3N	15	52
6	$PdCl_2(PPh_3)_2$	20	Et_3N	15	72
7	$PdCl_2(PPh_3)_2$	40	Et_3N	15	82
8	$PdCl_2(PPh_3)_2$	60	Et_3N	15	51
9	$PdCl_2(PPh_3)_2$	40	K_3PO_4	15	30
10	$PdCl_2(PPh_3)_2$	40	K_2CO_3	15	51
11	$PdCl_2(PPh_3)_2$	40	Na_2CO_3	15	63
12[d]	$PdCl_2(PPh_3)_2$	40	*t*-$BuNH_2$	15	32
13	$PdCl_2(PPh_3)_2$	40	Et_3N	30	61
14	$PdCl_2(PPh_3)_2$	40	Et_3N	10	81
15	$PdCl_2(PPh_3)_2$	40	Et_3N	5	79
16	—	40	Et_3N	15	44

[a] All reactions were run by employing 1.0 equiv. **1a**, 1.2 equiv. **2a**, 3 equiv. *t*-butyl amine and 3 equiv. base in 2 mL DMF under microwave irradiation. [b] Isolated yield. [c] 2.5 mol% $PdCl_2(PPh_3)_2$. [d] The reaction was run in 2 mL *t*-$BuNH_2$.

The base effect on the reaction was also evaluated. Of all the bases we examined, triethyl amine was superior. The reaction could proceed in the presence of all kinds of bases including K_3PO_4, K_2CO_3, Na_2CO_3 and *t*-$BuNH_2$, although a lower yield was observed (Table 1, compare Entry 7 with 9—12).

Finally, we optimized the microwave irradiation time. When the irradiation time was prolonged from 15 to 30 min, the isolated product yield decreased from 82% to 61% due to the product decomposition. However, there is no significant change in the yield when the irradiation time was reduced from 15 to 5 min. Thus, we chose the following reaction conditions as optimum for all subsequent three-component reaction: 5 mol% $PdCl_2(PPh_3)_2$, 40 mol% CuI, 3 equiv. Et_3N under microwave irradiation at 140 W for 5 min.

With the optimized conditions in hand, the scope of the three-component tandem coupling-cyclization reaction was then investigated, and the results are summarized in Table 3. The scope of this reaction is quite general. A variety of functionalized terminal acetylenes have been employed in this palladium/copper-catalyzed process. For instance, the aryl-, alkenyl- and alkyl-substituted acetylenes all tolerated the reaction conditions and afforded the desired isoquinolines in good yields. The phenylacetylenes bearing electron-withdrawing fluorine substituent on both *ortho* and *para* position afforded the corresponding isoquinolines in moderate yield under the standard reaction condition (Table 3, Entry 2). Interestingly, the less steric hindered *p*-fluoro substituted phenylacetylene required a twofold reaction time to give a slightly higher yield (Table 3, Entry 3). In comparison, when an electron-donating methyl group was introduced on the phenylacetylene, despite a longer reaction time required for the sterically crowded *o*-methyl phenylacetylene substrate, the reaction yields are higher (Table 3, Entries 5 and 6). However, when a methoxyl group appeared on the *meta*-position of phenylacetylene, only a 58% isolated yield was obtained. Moreover, an alkyne bearing a bulky substituent such as a naphthalene group can also participate in this reaction and afforded the isoquinoline in moderate yield (Table 3, Entry 7). The reactions proceed smoothly when the terminus of the carbon-carbon triple bond is substituted by an alkyl group. The aliphatic linear alkyne, which failed to participate in the three component synthesis of isoquinolines elsewhere,[16] was successfully converted to the corresponding isoquinoline (Table 3, Entry 9). In addition, when cyclic aliphatic alkyne such as ethynylcyclohexane was employed as the substrate, the 3-position cyclohexyl substituted isoquinoline **3j** was prepared in good yield in a prolonged irradiation time. Furthermore, 1-ethynylcyclohex-1-ene can also take part in this three-component coupling cyclization to give the alkenyl substituted product **3k** in good yield.

The scope of the tandem three-component synthesis approach to the 3-substituted isoquinoline by changing the substituted pattern on the 2-bromobenzaldehyde framework was next investigated. The highly substituted benzaldehyde (**1b**) substrate provided the desired isoquinoline derivative **3l** in moderate yield. While in the presence of an electron-withdrawing fluorine substituent (**1c**) the best results were obtained in a threefold irradiation time. In addition, the benzodioxole can be converted to the desired isoquinoline **3n** in a slightly lower yield under our standard experimental conditions. Interestingly, bicyclic heteropyridine derivative **3o**, which might show interesting biological properties, was constructed successfully in good yield.

Theoretically speaking, there are two possible routes to the final desired product isoquinoline because the

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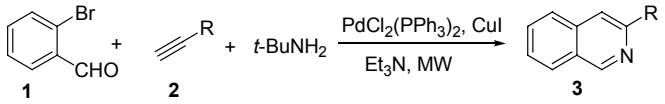
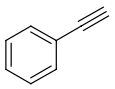
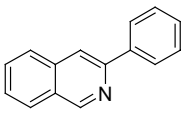
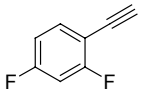
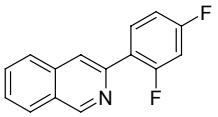
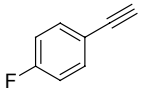
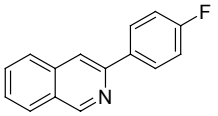
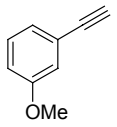
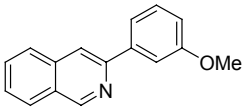
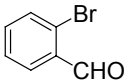
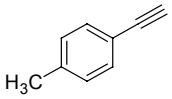
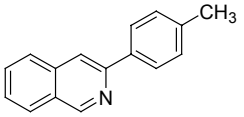
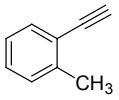
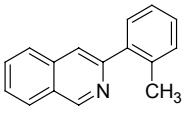
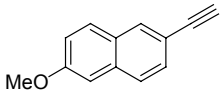
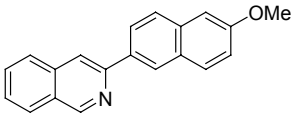
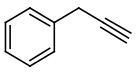
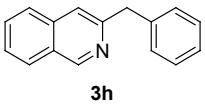
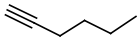
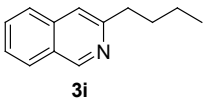
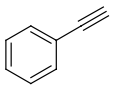
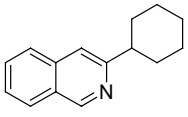
Table 3 Synthesis of 3-substituted isoquinoline derivatives **3a**[a]



Entry	Aldehyde **1**	Alkyne **2**	t^b/min	Product **3**	Yield[c]/%
1			5	 **3a**	79
2			5	 **3b**	61
3			10	 **3c**	67
4			10	 **3d**	58
5	 **1a**		5	 **3e**	76
6			10	 **3f**	73
7			15	 **3g**	56
8			10	 **3h**	75
9			5	 **3i**	57
10			30	 **3j**	62

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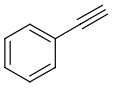
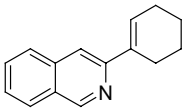
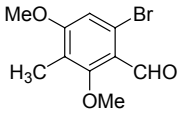
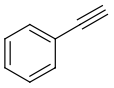
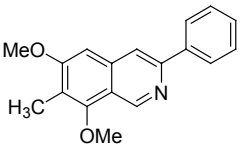
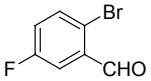
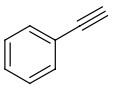
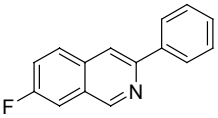
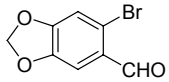
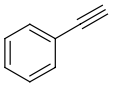
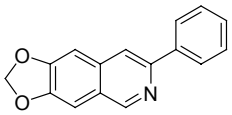
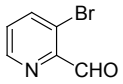
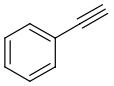
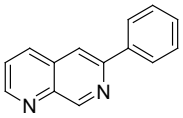
Continued

Entry	Aldehyde **1**	Alkyne **2**	t^b/min	Product **3**	Yield^c/%
11			15	 **3k**	74
12	 **1b**		5	 **3l**	58
13	 **1c**		15	 **3m**	61
14	 **1d**		5	 **3n**	46
15	 **1d**		5	 **3o**	56

[a] All reactions were conducted using 1.0 equiv. aldehyde **1**, 1.2 equiv. alkyne **2**, 5 mol% $PdCl_2(PPh_3)_2$, 40 mol% CuI, 3 equiv. *t*-butyl amine and 3 equiv. Base in 2 mL DMF under microwave irradiation. [b] All reactions were monitored by TLC until the disappearance of the starting aldehyde. [c] Isolated yield.

starting material 2-bromobenzaldehyde **1a** bears two different functional groups (Scheme 1). In route A, the formyl group is converted to the *tert*-butylimine **1aa** firstly, which is subsequently subjected to a Sonogashira reaction to furnish the iminoalkyne **1ac**. Finally, **1ac** was converted to isoquinoline. In an alternative route B, Sonogashira coupling product **1ab** was formed in advance of butylimine **1aa** in the reaction system. To demonstrate the reaction sequence of this tandem three-component synthesis of isoquinoline, we have monitored the reaction process by ^{1}H NMR (Figure 2). Samples from the reaction medium were removed at intervals and immediately analyzed by ^{1}H NMR spectroscopy. ^{1}H NMR analysis showed that *tert*-butylimine **1aa** formed very quickly. Starting material **1a** coverted to **1aa** after microwave irradiation for 0.5 min and a small amount iminoalkyne **1ac** also appeared at the same time. After microwave irradiation for 1 min, the iminoalkyne **1ac** became apparent. The desired product isoquinoline **3a** appeared after microwave irradiation for 2 min. The rate of the transformation from the intermediate **1ac** to **3a** was faster than that of intermediate **1aa** to **1ac**. All the characteristic peaks assigned to the intermediates **1aa** and **1ac** disappeared by comparison with the authentic sample after microwave irradiation for 5 min, which indicated the desired transformation occurred in this tandem three-component reaction system.

In conclusion, we have developed a rapid and efficient tandem three-component reaction for the synthesis of 3-substituted isoquinolines, which formed one carbon-carbon and two carbon-nitrogen bonds in one pot. The reaction scope is quite broad and acceptable and good yields were achieved by employing the readily available 2-bromobenzaldehyde and various terminal alkynes as starting materials. This methodology could be applied to the construction of a highly potent isoquinoline library to provide structural diversity and biological activity.

Experimental

General

Unless otherwise noted, all materials were commercially available and were used directly without further purification. All solvents were redistilled before use. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 600 spectrometer and resonances (δ) are given relative to tetramethylsilane. ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 600 (150

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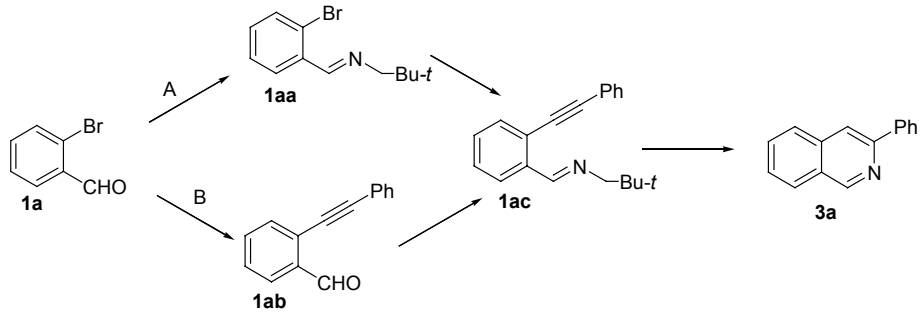
Scheme 1 Two possible pathways to target **3a**



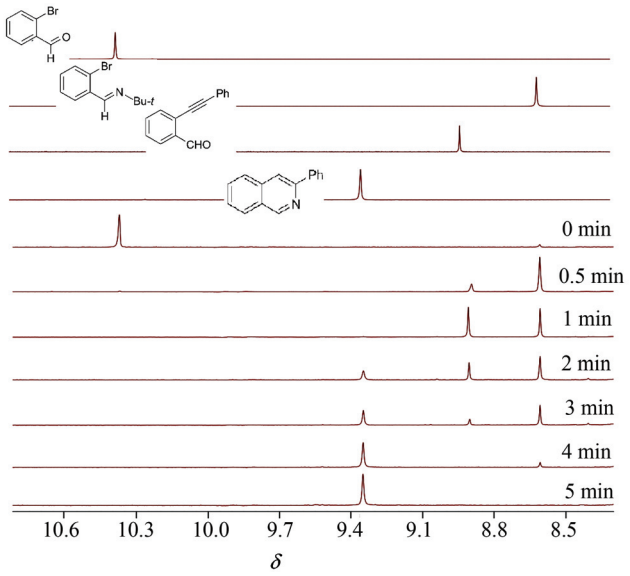


Figure 2 ^{1}H NMR monitor the reaction process of the three-component reaction system under MW.

MHz) spectrometer and resonances (δ) are given relative to the center line of a triplet at δ 77.0 of chloroform-*d*. The following abbreviations were used to designate chemical shift mutiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. HRMS were obtained on a WATERS MALDI SYNAPT G2 HDMS equipped with an electrospray source (MA, USA).

General procedure for the microwave assisted synthesis of 3-substituted isoquinoline 3

2-Bromobenzaldehyde **1** (0.50 mmol), a terminal alkyne **2** (0.60 mmol), $PdCl_2(PPh_3)_2$ (0.025 mmol), CuI (0.20 mmol), *t*-$BuNH_2$ (1.5 mmol) and Et_3N (1.5 mmol) in DMF (2 mL) were mixed in a sealed 10 mL microwave vial. The reaction mixture was irradiated in a *Smithsynthesizer*^{TM} microwave system at 140 W for 5 min or until disappearance of the starting aldehyde as monitored by thin layer chromatography. The reaction mixture was poured into water and neutralized with 1 mol/L HCl. The aqueous phase was extracted with diethyl ether (10 mL×3). The organic layers were combined and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel eluting with ethyl acetate and petroleum ether.

3-Phenylisoquinoline[3a,16] (3a) Yield 79%, yellow solid, m.p. 99—101 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.34 (s, 1H), 8.14 (d, J=7.8 Hz, 2H), 8.06 (s, 1H), 7.97 (d, J=8.4 Hz, 1H), 7.85 (d, J=8.4 Hz, 1H), 7.68 (t, J=7.2 Hz, 1H), 7.57 (t, J=7.2 Hz, 1H), 7.54—7.43 (m, 2H), 7.42 (t, J=9.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 152.3, 151.2, 139.5, 136.5, 130.4, 128.7, 128.4, 127.7, 127.5, 127.0, 126.9, 126.8, 116.4; HRMS (ESI) calcd for $C_{15}H_{12}N$ $[M+H]^+$ 206.0970, found 206.0979.

3-(2,4-Difluorophenyl)isoquinoline (3b) Yield 61%, yellow solid, m.p. 87—89 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.32 (s, 1H), 8.17—8.15 (m, 1H), 8.13 (s, 1H), 7.99 (d, J=8.4 Hz, 1H), 7.86 (d, J=7.8 Hz, 1H), 7.70 (t, J=7.5 Hz, 1H), 7.61 (t, J=7.5 Hz, 1H), 7.03 (t, J=7.8 Hz, 1H), 6.97—6.94 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 163.6 (d, $J_{C\text{-}^{19}F}$=12.3 Hz), 161.9 (d, $J_{C\text{-}^{19}F}$=12.0 Hz), 161.3 (d, $J_{C\text{-}^{19}F}$=11.7 Hz), 159.7 (d, $J_{C\text{-}^{19}F}$=12.0 Hz), 152.3, 145.6, 136.2, 132.2 (d, $J_{C\text{-}^{19}F}$=9.3 Hz), 130.6, 127.5 (d, $J_{C\text{-}^{19}F}$=10.8 Hz), 127.0, 123.9 (d, J=11.4 Hz), 120.6 (d, $J_{C\text{-}^{19}F}$=10.2 Hz), 111.8 (d, $J_{C\text{-}^{19}F}$=21.9 Hz), 104.4 (t, $J_{C\text{-}^{19}F}$=26.1 Hz); IR (KBr) v: 1618, 1599, 1579, 1505, 1443, 1262, 1136, 1106, 964, 845, 827, 760 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{10}F_2N$ $[M+H]^+$ 242.0781, found 242.0814.

3-(4-Fluorophenyl)isoquinoline (3c) Yield 67%, yellow solid, m.p. 125—127 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.32 (s, 1H), 8.12—8.10 (m, 2H), 8.02 (s, 1H), 7.99 (d, J=8.4 Hz, 1H), 7.87 (d, J=8.4 Hz, 1H), 7.71 (t, J=7.5 Hz, 1H), 7.59 (t, J=7.5 Hz, 1H), 7.19 (t, J=8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 164.0, 162.3, 152.3, 150.1, 136.5, 135.6, 130.5, 128.6 (d, $J_{C\text{-}^{19}F}$=9.2 Hz), 127.5 (d, $J_{C\text{-}^{19}F}$=9.2 Hz), 127.0, 126.7, 116.1, 115.6 (d, $J_{C\text{-}^{19}F}$=21.3 Hz); IR (KBr) v: 1622, 1600, 1579, 1508, 1448, 1226, 1156, 1128, 836 cm^{-1}. HRMS (ESI) calcd for $C_{15}H_{11}FN$ $[M+H]^+$ 224.0876, found 224.0899.

3-(3-Methoxyphenyl)isoquinoline[19] (3d) Yield 58%, yellow solid, m.p. 80—82 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.31 (s, 1H), 8.03 (s, 1H), 7.95 (d, J=7.8 Hz, 1H), 7.83 (d, J=7.8 Hz, 1H), 7.72 (s, 1H), 7.69—7.65 (m, 2H), 7.55 (t, J=7.5 Hz, 1H), 7.41 (t,

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J=7.8 Hz, 1H), 6.97—6.96 (m, 1H), 3.91 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 160.0, 152.2, 150.9, 141.0, 136.5, 130.4, 129.7, 127.7, 127.4, 127.0, 126.8, 119.3, 116.6, 114.5, 112.0, 55.3; HRMS (ESI) calcd for $C_{16}H_{14}NO$ $[M+H]^+$ 236.1075, found 236.1093.

3-*p*-Tolylisoquinoline[16,20] (3e) Yield 76%, yellow solid, m.p. 69—71 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.33 (s, 1H), 8.04—8.02 (m, 3H), 7.98 (d, J=7.8 Hz, 1H), 7.86 (d, J=8.4 Hz, 1H), 7.69 (t, J=7.2 Hz, 1H), 7.57 (t, J=7.2 Hz, 1H), 7.32 (d, J=7.8 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 152.3, 151.2, 138.4, 136.7, 136.6, 130.4, 129.5, 129.4, 127.5, 127.4, 126.8, 126.7, 115.9, 21.2; HRMS (ESI) calcd for $C_{16}H_{14}N$ $[M+H]^+$ 220.1126, found 220.1126.

3-*o*-Tolylisoquinoline[20] (3f) Yield 73%, yellow solid, m.p. 73—75 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.34 (s, 1H), 8.02 (d, J=7.8 Hz, 1H), 7.86 (d, J=7.8 Hz, 1H), 7.75 (s, 1H), 7.72 (t, J=7.8 Hz, 1H), 7.62 (t, J=7.5 Hz, 1H), 7.50 (d, J=6.6 Hz,1H), 7.32—7.30 (m, 3H), 2.42 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 153.6, 151.7, 140.4, 136.1, 136.0, 130.6, 130.3, 130.0, 128.0, 127.4, 127.1, 127.0, 126.6, 125.8, 120.0, 20.4; HRMS (ESI) calcd for $C_{16}H_{14}N$ $[M+H]^+$ 220.1126, found 220.1137.

3-(6-Methoxynaphthalen-2-yl)isoquinoline (3g) Yield 56%, yellow solid, m.p. 161—163 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.38 (s, 1H), 8.59 (s, 1H), 8.22 (d, J=7.8 Hz, 1H), 8.18 (s, 1H), 8.01 (d, J=7.8 Hz, 1H), 7.91—7.87 (m, 3H), 7.71 (t, J=7.5 Hz, 1H), 7.59 (t, J=7.2 Hz, 1H), 7.20—7.19 (m, 2H), 3.96 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 158.0, 152.4, 151.2, 136.7, 134.6, 130.5, 130.2, 129.1, 127.6, 127.5, 127.2, 126.9, 126.8, 126.1, 125.1, 119.1, 116.2, 105.6, 95.3, 55.3; IR (KBr) v: 1621, 1570, 1483, 1461, 1386, 1261, 1227, 1185, 1160, 1119, 855 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{16}NO$ $[M+H]^+$ 286.1232, found 286.1218.

3-Benzylisoquinoline[21] (3h) Yield 75%, yellow solid, m.p. 57—59 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.22 (s, 1H), 7.93 (d, J=8.4 Hz, 1H), 7.72 (d, J=8.4 Hz, 1H), 7.64 (t, J=7.5 Hz, 1H), 7.54 (t, J=7.2 Hz, 1H), 7.43(s, 1H), 7.33—7.32 (m, 4H), 7.25—7.23 (m, 1H), 4.32 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 154.3, 152.2, 139.7, 136.3, 130.2, 129.1, 128.4, 127.3, 127.0, 126.5, 126.2, 126.1, 118.6, 44.2; HRMS (ESI) calcd for $C_{16}H_{14}N$ $[M+H]^+$ 220.1126, found 220.1144.

3-Butylisoquinoline[22] (3i) Yield 57%, yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.20 (s, 1H), 7.93 (d, J=8.4 Hz, 1H), 7.75 (d, J=8.4 Hz, 1H), 7.65 (t, J=7.5 Hz, 1H), 7.53 (t, J=7.8 Hz, 1H), 7.47 (s, 1H), 2.94 (t, J=7.8 Hz, 2H), 1.83—1.78 (m, 2H), 1.45—1.41 (m, 2H), 0.97 (t, J=7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 155.7, 152.0, 136.4, 130.1, 127.3, 126.9, 126.1, 125.9, 117.8, 37.7, 32.1, 22.4, 13.9. HRMS (ESI) calcd for $C_{13}H_{16}N$ $[M+H]^+$ 186.1283, found 186.1270.

3-Cyclohexylisoquinoline[13e,13f] (3j) Yield 62%, Yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.21 (s, 1H), 7.91 (d, J=8.4 Hz, 1H), 7.74 (d, J=8.4 Hz, 1H), 7.62 (t, J=7.2 Hz, 1H), 7.50 (t, J=7.5 Hz, 1H), 7.453 (s, 1H), 2.88—2.83 (m, 1H), 2.08—2.06 (m, 2H), 1.91—1.88 (m, 2H), 1.79—1.77 (m, 1H), 1.64—1.57 (m, 2H), 1.50—1.44 (m, 2H), 1.36—1.29 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 159.9, 151.7, 136.6, 130.1, 127.4, 127.1, 126.2, 116.1, 116.0, 45.9, 33.1, 26.6, 26.1; HRMS (ESI) calcd for $C_{15}H_{18}N$ $[M+H]^+$ 212.1439, found 212.1449.

3-Cyclohexenylisoquinoline[13a,13e,13f] (3k) Yield 74%, yellow solid, m.p. 107—109 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.20 (s, 1H), 7.93 (d, J=8.4 Hz, 1H), 7.78 (d, J=8.4 Hz, 1H), 7.64 (t, J=7.5 Hz, 1H), 7.60 (s, 1H), 7.52 (t, J=7.5 Hz, 1H), 7.01 (br, 1H), 2.59 (br, 2H), 2.33—2.32 (m, 2H), 1.87—1.85 (m, 2H), 1.74—1.71 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 152.3, 151.5, 136.5, 135.5, 130.2, 128.3, 127.4, 127.3, 126.6, 126.3, 114.1, 26.1, 25.9, 22.9, 22.1; HRMS (ESI) calcd for $C_{15}H_{16}N$ $[M+H]^+$ 210.1283, found 210.1288.

6,8-Dimethoxy-7-methyl-3-phenylisoquinoline (3l) Yield 58%, yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.43 (s, 1H), 8.11 (d, J=7.2 Hz, 2H), 7.96 (s, 1H), 7.50 (t, J=7.5 Hz, 2H), 7.42—7.41 (m, 1H), 6.92 (s, 1H), 3.99—3.98 (m, 6H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 160.9, 155.2, 151.2, 146.7, 139.7, 137.3, 128.6, 128.3, 126.8, 121.1, 118.1, 115.6, 99.8, 62.2, 55.7, 9.3; IR (KBr) v: 1623, 1572, 1484, 1485, 1400, 1248, 1227, 1192, 1149, 1119, 1022, 959, 880, 765,694 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{18}NO_2$ $[M+H]^+$ 280.1338, found 280.1326.

7-Fluoro-3-phenylisoquinoline[13a] (3m) Yield 61%, yellow solid, m.p. 124—126 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.30 (s, 1H), 8.11 (d, J=7.2 Hz, 2H), 8.07 (s, 1H), 7.90—7.88 (m, 1H), 7.62—7.60 (m, 1H), 7.53—7.47 (m, 3H), 7.43 (t, J=7.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 161.5, 159.9, 151.5 (d, $J_{C\text{-}^{19}F}$=6.9 Hz), 150.9, 139.2, 133.6, 129.5 (d, $J_{C\text{-}^{19}F}$=6.9 Hz), 128.7 (d, $J_{C\text{-}^{19}F}$=34.5 Hz), 128.1, 126.8, 121.1 (d, $J_{C\text{-}^{19}F}$=25.4 Hz), 116.2, 110.5 (d, $J_{C\text{-}^{19}F}$=20.7 Hz). HRMS (ESI) calcd for $C_{15}H_{11}FN$ $[M+H]^+$ 224.0876, found 224.0885.

7-Phenyl-[1,3]dioxolo[4,5-*g*]isoquinoline[13a] (3n) Yield 46%, yellow solid, m.p. 119—121 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.07 (s, 1H), 8.07 (d, J=7.8 Hz, 2H), 7.91 (s, 1H), 7.50—7.48 (m, 2H), 7.41—7.39 (m, 1H), 7.22 (s, 1H), 7.13 (s, 1H), 6.11 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 150.9, 150.3, 150.0, 148.2, 139.5, 134.9, 128.6, 128.2, 126.6, 124.8, 116.2, 102.9, 102.6, 101.5; HRMS (ESI) calcd for $C_{16}H_{12}NO_2$ $[M+H]^+$ 250.0868, found 250.0891.

6-Phenyl-1,7-naphthyridine[23] (3o) Yield 56%, yellow solid, m.p. 132—134 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.37 (s, 1H), 9.11—9.10 (m, 1H), 8.36 (s, 1H), 8.32 (d, J=8.4 Hz, 1H), 8.18 (d, J=7.8 Hz, 2H), 7.56—7.51 (m, 3H), 7.48—7.47 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 155.0, 154.9, 152.6, 151.2, 138.7, 135.5, 129.1, 128.8, 127.1, 122.5, 122.1, 117.7; HRMS (ESI) calcd for $C_{14}H_{11}N_2$ $[M+H]^+$ 207.0922, found 207.0930.

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