Silver Triflate Catalyzed Reaction of 2-Alkynylbenzaldoxime with Phenol: A General and Facile Route to 1-Aroxyisoquinolines

Danqing Zheng,[a] Zhiyong Wang,*[b] Jie Wu*[a,c]

[a] Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, P. R. of China
Fax +86(21)65641740; E-mail: jie_wu@fudan.edu.cn

[b] School of Chemistry and Chemical Engineering, Chongqing University, 174 Shazhengjie Road, Chongqing 400044, P. R. of China

[c] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. of China

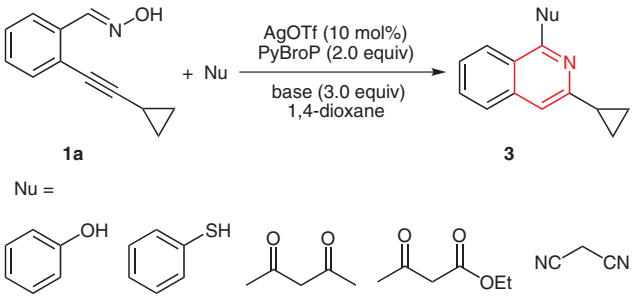
Received 12 May 2011; revised 1 June 2011

Abstract: 2-Alkynylbenzaldoxime reacts with phenol under the catalysis of silver triflate in the presence of bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP) under mild conditions, leading to the formation of 1-aroxyisoquinolines in good to excellent yields.

Key words: cyclizations, isoquinoline, phosphorus ligands, phenol, silver triflate

Recently, our laboratory became interested in the development of methodologies for the generation of nitrogen-containing heterocycles,[1] which continue to receive much interest due to their ubiquity in nature, as well as their extensive presence as part of the skeletal backbone of many therapeutic agents.[2] Of these heterocycles, 1-substituted isoquinoline is a common structural unit in biologically active natural products and small molecule chemotherapeutics.[3] Usually, the displacement of 1-haloisoquinolines with nucleophiles and transition-metal-catalyzed coupling reactions of 1-haloisoquinolines are involved in their preparation.[4] However, in most cases, the use of harsh conditions, high temperature, strong base, or expensive metal catalysts is inevitable. Additionally, phosphorus oxychloride ($POCl_3$), which is a toxic compound, has to be employed for the generation of 1-haloisoquinolines for further elaboration.[5] Therefore, the development of novel and efficient routes for rapid access to 1-substituted isoquinolines under mild conditions is in high demand.

Recently, Londregan and co-workers reported the synthesis of 2-substituted pyridines through the reaction of pyridine-*N*-oxide with nucleophiles, promoted by a phosphonium salt.[6] In the meantime, we and others discovered that, in the presence of a silver catalyst, 2-alkynylbenzaldoxime could be easily converted into isoquinoline-*N*-oxide, which is a useful intermediate for the formation of nitrogen-containing heterocycles.[7,8] Encouraged by the results developed by Londregan,[6] we envisioned that 1-substituted isoquinolines could be produced through the reaction of 2-alkynylbenzaldoxime with nucleophiles in the presence of a silver catalyst and a suitable phosphonium salt. Herein, we wish to disclose our preliminary result on the generation of 1-aroxyisoquinolines via a silver triflate catalyzed reaction of 2-alkynylbenzaldoxime with phenol in the presence of bromo-tris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP) under mild conditions.

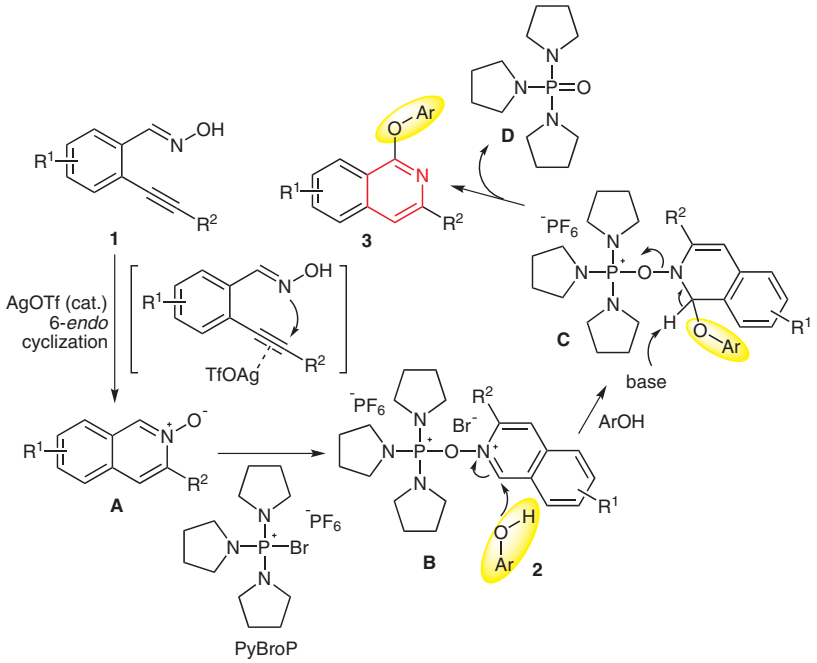


Scheme 1 Initial studies on silver triflate catalyzed reaction of 2-alkynylbenzaldoxime **1a** with various nucleophiles

As mentioned above, we have demonstrated that 2-alkynylbenzaldoxime can readily undergo a directed cyclization to yield isoquinoline-*N*-oxide in the presence of a silver catalyst. Thus, the initial studies were carried out with the silver triflate catalyzed reaction of 2-alkynylbenzaldoxime **1a** with various nucleophiles in the presence of PyBroP and different bases in 1,4-dioxane (Scheme 1). Gratifyingly, the reaction worked well to furnish the desired product **3a** when phenol was employed in the reaction. To our surprise, only a trace amount of product was detected when thiophenol was used as a replacement. The utilization of carbon nucleophiles such as pentane-2,4-dione, ethyl 3-oxobutanoate, and malononitrile in the reaction of 2-alkynylbenzaldoxime **1a** was unsuccessful.

With these results in hand, we further explored the optimized conditions for the reaction of 2-alkynylbenzaldoxime **1a** with phenol. Initially, the reaction was performed in various solvents in the presence of silver triflate (10 mol%), PyBroP (2.0 equiv), and *N*,*N*-diisopropylethylamine (3.0 equiv). 1,4-Dioxane was found to be the best choice, and the expected 3-cyclopropyl-1-phenoxyisoquinoline (**3a**) was afforded in 65% yield. Inferior yields were obtained when the reaction was performed in other solvents (THF, CH_2Cl_2, MeCN, toluene, DCE). No product was generated in a control experiment without the

SYNTHESIS 2011, No. 17, pp 2810–2816
Advanced online publication: 14.07.2011
DOI: 10.1055/s-0030-1260121; Art ID: H49911SS



Scheme 2 A possible mechanism for silver triflate catalyzed reaction of 2-alkynylbenzaldoxime **1** with phenol **2**

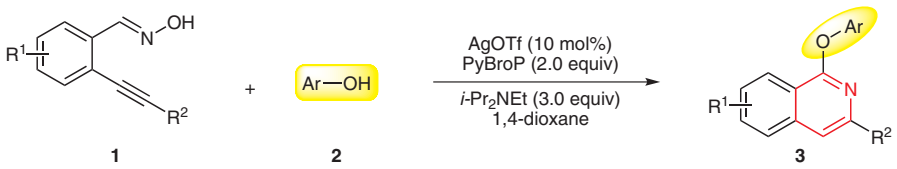
addition of PyBroP. Reducing the amount of PyBroP or silver catalyst diminished the reactivity of this transformation. Additionally, a screening trial for the base revealed that the reaction worked most efficiently in the presence of *N*,*N*-diisopropylethylamine as the base in 1,4-dioxane. No better results were obtained when other bases [Et_3N, DBU, pyridine, NaOAc] were employed in the reaction.

We believe that the reaction proceeds as shown in Scheme 2. The first step involves the formation of isoquinoline-*N*-oxide **A** via a silver triflate catalyzed 6-*endo*-cyclization of 2-alkynylbenzaldoxime **1**. The isoquinoline-*N*-oxide **A** reacts with PyBroP through nucleophilic substitution to generate intermediate **B**. Subsequent intermolecular nucleophilic addition of phenol **2** occurs to afford intermediate **C**, which then undergoes deprotonation to produce the expected 1-aroxyisoquinoline **3** with the release of tris(pyrrolidinophosphine) oxide **D**.

With this promising result in hand, we started to explore the scope of the reaction of 2-alkynylbenzaldoxime **1** with phenol **2** under the preliminary optimized conditions [AgOTf (10 mol%), PyBroP (2.0 equiv), *i*-Pr_2NEt (3.0 equiv), 1,4-dioxane]; the results are illustrated in Table 1. First, reactions of 2-alkynylbenzaldoxime **1a** with various phenols **2** were examined under the standard protocol. The sterically bulky 2,6-dimethylphenol (**2b**) reacted with 2-alkynylbenzaldoxime **1a** leading to formation of the desired 1-aroxyisoquinoline **3b** in 60% yield (Table 1, entry 2). A higher yield (68%) was obtained when 4-methoxyphenol (**2c**) was used as a replacement (Table 1, entry 3). Reaction of 2-alkynylbenzaldoxime **1a** with 4-*tert*-butylphenol (**2d**) worked well to produce the corresponding product **3d** in 76% yield (Table 1, entry 4). Phenols with electron-withdrawing groups attached to the aromatic ring were all good partners in the transformation. For instance, 2-alkynylbenzaldoxime **1a** reacted with 4-chlorophenol (**2e**), affording to the expected product **3e** in 61% yield (Table 1, entry 5). It is noteworthy that the ester group was tolerated under the standard conditions (Table 1, entry 6). 2-Alkynylbenzaldoximes with a range of substituents attached to the triple bond were also tested. For example, 2-alkynylbenzaldoxime **1b** reacted with phenol **2a** or **2d**, giving rise to the corresponding product **3g** or **3h** in 71 and 76% yields, respectively (Table 1, entries 7 and 8). 2-Alkynylbenzaldoxime **1c**, with a *p*-methylphenyl group attached to the triple bond, was also suitable for the reaction with 4-*tert*-butylphenol **2d** (66% yield; Table 1, entry 9). A similar yield was obtained with 2-alkynylbenzaldoxime **1d** when R^2 was *n*-butyl (Table 1, entry 10). Next, we examined the reactions of 2-alkynylbenzaldoximes with various substituents on the aromatic ring. Methyl-, methoxy-, chloro-, and fluoro-substituted 2-alkynylbenzaldoximes showed good reactivity in the reaction with phenols. For instance, almost quantitative yield was isolated when dimethoxy-substituted 2-alkynylbenzaldoxime **1h** reacted with phenol **2a** (98% yield; Table 1, entry 16) under the standard conditions.

In conclusion, we have presented a general and facile route for the synthesis of 1-aroxyisoquinolines via a silver triflate catalyzed reaction of 2-alkynylbenzaldoxime with phenol. The diverse substrate scope, combined with an operationally simple procedure, may make this methodology attractive. The construction of a library of 1-aroxyisoquinolines is ongoing.

Table 1 Synthesis of 1-Aroxyisoquinolines **3** via Silver Triflate Catalyzed Reaction of 2-Alkynylbenzaldoxime with Phenol



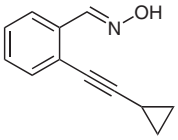
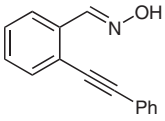
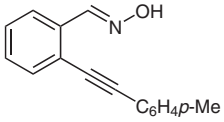
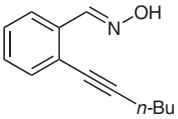
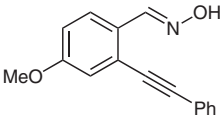
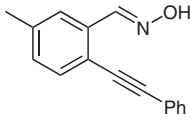
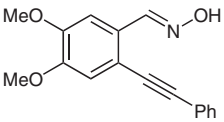
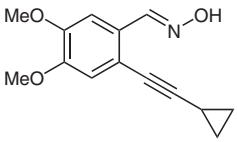
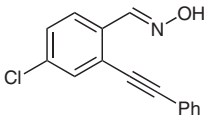
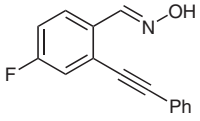
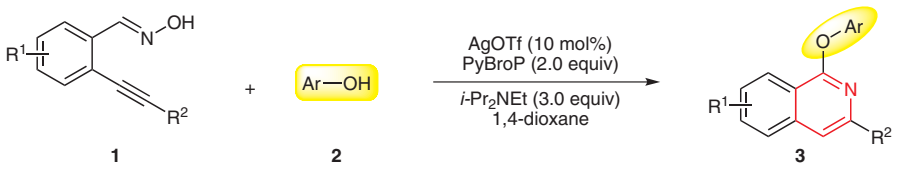
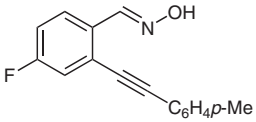
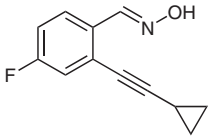
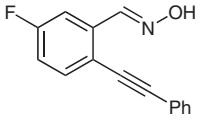
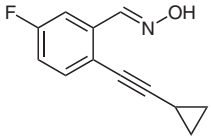
Entry	2-Alkynylbenzaldoxime **1**		Phenol **2**		Product **3**	Yield (%)[a]
1	**1a**		**2a**	PhOH	**3a**	65
2			**2b**	2,6-$Me_2C_6H_3OH$	**3b**	60
3			**2c**	4-$MeOC_6H_4OH$	**3c**	68
4			**2d**	4-*t*-BuC_6H_4OH	**3d**	76
5			**2e**	4-ClC_6H_4OH	**3e**	61
6			**2f**	4-$EtO_2CC_6H_4OH$	**3f**	65
7	**1b**		**2a**	PhOH	**3g**	71
8			**2d**	4-*t*-BuC_6H_4OH	**3h**	76
9	**1c**		**2d**	4-*t*-BuC_6H_4OH	**3i**	66
10	**1d**		**2d**	4-*t*-BuC_6H_4OH	**3j**	66
11	**1e**		**2a**	PhOH	**3k**	58
12			**2d**	4-*t*-BuC_6H_4OH	**3l**	83
13	**1f**		**2d**	4-*t*-BuC_6H_4OH	**3m**	83
14	**1g**		**2a**	PhOH	**3n**	72
15			**2d**	4-*t*-BuC_6H_4OH	**3o**	86
16	**1h**		**2a**	PhOH	**3p**	98
17			**2d**	4-*t*-BuC_6H_4OH	**3q**	98
18	**1i**		**2d**	4-*t*-BuC_6H_4OH	**3r**	75
19	**1j**		**2a**	PhOH	**3s**	70
20			**2d**	4-*t*-BuC_6H_4OH	**3t**	88

Table 1 Synthesis of 1-Aroxyisoquinolines **3** via Silver Triflate Catalyzed Reaction of 2-Alkynylbenzaldoxime with Phenol (continued)



1 2 3

Entry	2-Alkynylbenzaldoxime **1**	Phenol **2**		Product **3**	Yield (%)[a]
21	**1k** 	**2d**	4-*t*-BuC_6H_4OH	**3u**	61
22	**1l** 	**2a**	PhOH	**3v**	65
23		**2d**	4-*t*-BuC_6H_4OH	**3w**	74
24	**1m** 	**2d**	4-*t*-BuC_6H_4OH	**3x**	67
25	**1n** 	**2d**	4-*t*-BuC_6H_4OH	**3y**	82

[a] Isolated yield based on 2-alkynylbenzaldoxime **1**.

Unless otherwise stated, all commercial reagents were used without additional purification. All solvents were dried and distilled according to standard procedures. PyBroP was purchased from Aldrich and used as received. 2-Alkynylbenzaldoximes 1 were synthesized via Sonogashira coupling[9a] and condensation reaction[9b] according to the literature. Flash column chromatography was performed using silica gel (60 Å pore size, 32–63 μm, standard grade). Analytical thin-layer chromatography was performed using glass plates precoated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr (house vacuum) at 25–35 °C. ^{1}H and ^{13}C NMR spectra of samples dissolved in $CDCl_3$ were recorded on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz, respectively, and are reported in ppm from internal tetramethylsilane on the δ scale. High-resolution mass spectral data were recorded on a micrOTOF II mass spectrometer operating in the positive electrospray ionization mode.

1-Aroxyisoquinolines 3; General Procedure

2-Alkynylbenzaldoxime **1** (0.3 mmol) was added to a solution of AgOTf (10 mol%) in 1,4-dioxane (0.8 mL) under N_2. After stirring at 70 °C for 30 min, PyBroP (0.6 mmol), phenol **2** (0.36 mmol) and *i*-Pr_2NEt (0.9 mmol) were added, followed by 1,4-dioxane (0.4 mL). The mixture was stirred at 25 °C until completion of reaction (indicated by TLC, typically overnight). The mixture was purified directly by flash column chromatography (EtOAc–*n*-hexane, 1:50) to give the desired product **3**.

3-Cyclopropyl-1-phenoxyisoquinoline (3a)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 8.4 Hz, 1 H), 7.60–7.67 (m, 2 H), 7.44–7.48 (m, 1 H), 7.39 (t, *J* = 8.4 Hz, 2 H), 7.18–7.23 (m, 4 H), 1.91–1.98 (m, 1 H), 0.77–0.79 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 154.3, 153.5, 139.4, 130.9, 129.2, 125.8, 125.7, 124.5, 124.3, 122.0, 118.2, 112.4, 16.9, 9.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{15}NO$: 262.1232; found: 262.1250.

3-Cyclopropyl-1-(2,6-dimethylphenoxy)isoquinoline (3b)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 8.4 Hz, 1 H), 7.61–7.70 (m, 2 H), 7.49 (t, *J* = 8.0 Hz, 1 H), 7.14 (s, 1 H), 7.07–7.11 (m, 3 H), 2.09 (s, 6 H), 1.85–1.92 (m, 1 H), 0.68–0.71 (m, 2 H), 0.60–0.64 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 153.7, 151.1, 139.4, 131.4, 130.8, 128.3, 125.7, 125.6, 125.0, 124.3, 117.5, 111.7, 16.8, 16.7, 8.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{19}NO$: 290.1545; found: 290.1567.

3-Cyclopropyl-1-(4-methoxyphenoxy)isoquinoline (3c)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.0 Hz, 1 H), 7.58–7.66 (m, 2 H), 7.43–7.47 (m, 1 H), 7.11–7.19 (m, 3 H), 6.89–6.92 (m, 2 H), 3.82 (s, 3 H), 1.90–1.97 (m, 1 H), 0.77–0.78 (d, *J* = 6.4 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4, 156.4, 153.4, 147.6, 139.3, 130.8, 125.7, 125.6, 124.3, 122.9, 114.2, 112.0, 109.2, 55.8, 16.8, 9.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}NO_2$: 292.1338; found: 292.1341.

1-(4-*tert*-Butylphenoxy)-3-cyclopropylisoquinoline (3d)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.4 Hz, 1 H), 7.58–7.66 (m, 2 H), 7.44 (dt, *J* = 1.2, 8.0 Hz, 1 H), 7.39 (d, *J* = 8.8 Hz, 2 H), 7.16 (d, *J* = 8.8 Hz, 3 H), 1.92–1.99 (m, 1 H), 1.36 (s, 9 H), 0.78–0.82 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 153.4, 151.7, 146.9, 139.2, 130.6, 125.8, 125.5, 125.4, 124.2, 120.9, 118.2, 111.9, 34.5, 316, 16.7, 8.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{23}NO$: 318.1858; found: 318.1848.

1-(4-Chlorophenoxy)-3-cyclopropylisoquinoline (3e)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.4 Hz, 1 H), 7.60–7.68 (m, 2 H), 7.46 (dt, *J* = 1.2, 8.0 Hz, 1 H), 7.33–7.38 (m, 2 H), 7.15–7.19 (m, 3 H), 1.92–1.97 (m, 1 H), 0.76–0.82 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 153.4, 152.7, 139.4, 130.9, 129.23, 125.9, 125.7, 124.1, 123.4, 123.1, 118.0, 112.6, 16.8, 9.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}ClNO$: 296.0842; found: 296.0835.

Ethyl 4-(3-Cyclopropylisoquinolin-1-yloxy)benzoate (3f)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.0 Hz, 1 H), 8.08–8.12 (m, 2 H), 7.62–7.71 (m, 2 H), 7.48 (dt, *J* = 1.6, 8.4 Hz, 1 H), 7.26–7.31 (m, 2 H), 7.23 (s, 1 H), 4.37–4.42 (m, 2 H), 1.94–1.99 (m, 1 H), 1.41 (t, *J* = 7.2 Hz, 3 H), 0.77–0.83 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 159.4, 158.2, 153.5, 147.6, 139.5, 131.1, 131.0, 126.0, 125.7, 124.1, 121.5, 118.1, 113.1, 61.2, 16.8, 14.6, 9.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{19}NO_3$: 334.1443; found: 334.1451.

1-Phenoxy-3-phenylisoquinoline (3g)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 8.4 Hz, 1 H), 8.01 (d, *J* = 7.6 Hz, 2 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 7.86 (s, 1 H), 7.76 (t, *J* = 7.6 Hz, 1 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 7.54 (t, *J* = 7.6 Hz, 2 H), 7.42–7.45 (m, 4 H), 7.30–7.40 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 154.3, 147.9, 139.7, 139.0, 131.1, 129.6, 128.9, 128.7, 127.1, 127.0, 126.8, 124.9, 124.5, 122.2, 119.2, 111.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{15}NO$: 298.1232; found: 298.1230.

1-(4-*tert*-Butylphenoxy)-3-phenylisoquinoline (3h)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 8.4 Hz, 1 H), 7.93–7.96 (m, 2 H), 7.82 (d, *J* = 8.4 Hz, 1 H), 7.77 (s, 1 H), 7.66–7.70 (m, 1 H), 7.53–7.58 (m, 1 H), 7.44–7.47 (m, 2 H), 7.37 (t, *J* = 7.6 Hz, 2 H), 7.28–7.32 (m, 3 H), 1.38 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 151.8, 147.9, 147.4, 139.5, 139.0, 131.0, 128.7, 128.6, 127.0, 126.9, 126.7, 126.3, 124.5, 121.3, 119.2, 111.8, 34.7, 31.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{23}NO$: 354.1858; found: 354.1837.

1-(4-*tert*-Butylphenoxy)-3-*p*-tolylisoquinoline (3i)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 8.0 Hz, 1 H), 7.80–7.85 (m, 3 H), 7.74 (s, 1 H), 7.65–7.69 (m, 1 H), 7.54 (t, *J* = 8.0 Hz, 1 H), 7.43–7.47 (m, 2 H), 7.28–7.31 (m, 2 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 2.35 (s, 3 H), 1.38 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 151.9, 148.2, 147.4, 139.7, 138.6, 136.4, 131.1, 129.6, 126.9, 126.8, 126.7, 126.3, 124.5, 121.4, 119.2, 111.3, 31.9, 31.8, 21.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{25}NO$: 368.2014; found: 368.1998.

3-Butyl-1-(4-*tert*-butylphenoxy)isoquinoline (3j)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 8.0 Hz, 1 H), 7.69 (d, *J* = 8.0 Hz, 1 H), 7.62 (t, *J* = 7.2 Hz, 1 H), 7.49 (t, *J* = 7.2 Hz, 1 H), 7.41 (d, *J* = 8.8 Hz, 2 H), 7.21 (t, *J* = 5.6 Hz, 2 H), 7.13 (s, 1 H), 2.71 (t, *J* = 7.6 Hz, 2 H), 1.62–1.70 (m, 2 H), 1.35 (s, 9 H), 1.23–1.31 (m, 2 H), 0.89 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6, 153.5, 152.2, 146.9, 139.5, 130.8, 126.3, 126.2, 126.0, 124.4, 120.7, 118.7, 113.8, 37.4, 34.6, 31.8, 31.6, 22.5, 14.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{27}NO$: 334.2171; found: 334.2157.

6-Methoxy-1-phenoxy-3-phenylisoquinoline (3k)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.8 Hz, 1 H), 7.91–7.93 (m, 2 H), 7.70 (s, 1 H), 7.45 (t, *J* = 8.0 Hz, 2 H), 7.17–7.38 (m, 7 H), 7.11 (d, *J* = 2.4 Hz, 1 H), 3.95 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.7, 159.9, 154.3, 148.7, 141.7, 139.1, 129.5, 128.8, 128.6, 126.7, 126.2, 124.7, 122.1, 119.3, 114.2, 111.5, 105.4, 55.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{17}NO_2$: 328.1338; found: 328.1342.

1-(4-*tert*-Butylphenoxy)-6-methoxy-3-phenylisoquinoline (3l)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 8.8 Hz, 1 H), 7.92 (d, *J* = 7.6 Hz, 2 H), 7.67 (s, 1 H), 7.44 (d, *J* = 8.8 Hz, 2 H), 7.36 (t, *J* = 6.8 Hz, 2 H), 7.29 (t, *J* = 8.0 Hz, 3 H), 7.16 (dd, *J* = 2.4, 8.8 Hz, 1 H), 7.09 (d, *J* = 2.4 Hz, 1 H), 3.92 (s, 3 H), 1.37 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.7, 159.9, 151.9, 148.8, 147.3, 141.7, 139.3, 128.8, 128.6, 126.8, 126.3, 126.2, 121.2, 119.2, 114.3, 111.5, 105.4, 55.7, 34.7, 31.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{25}NO_2$: 384.1964; found: 384.1993.

1-(4-*tert*-Butylphenoxy)-7-methyl-3-phenylisoquinoline (3m)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (s, 1 H), 7.92 (d, *J* = 7.6 Hz, 2 H), 7.69–7.72 (m, 2 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 7.35 (t, *J* = 7.6 Hz, 2 H), 7.29 (d, *J* = 8.4 Hz, 3 H), 2.54 (s, 3 H), 1.38 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5, 151.9, 147.3, 147.1, 139.2, 137.7, 137.0, 133.1, 128.7, 128.3, 126.7, 126.6, 126.2, 123.4, 121.2, 119.3, 111.7, 34.6, 31.7, 22.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{25}NO$: 368.2014; found: 368.2016.

6,7-Dimethoxy-1-phenoxy-3-phenylisoquinoline (3n)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.6 Hz, 2 H), 7.64 (s, 1 H), 7.61 (s, 1 H), 7.42 (t, *J* = 8.0 Hz, 2 H), 7.30–7.33 (m, 4 H), 7.18–7.26 (m, 2 H), 7.07 (s, 1 H), 4.00 (d, *J* = 5.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 154.5, 153.5, 150.2, 146.8, 139.3, 136.2, 129.5, 128.8, 128.3, 126.5, 124.6, 122.1, 114.0, 111.2, 105.7, 102.9, 56.4, 56.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{19}NO_3$: 358.1443; found: 358.1433.

1-(4-*tert*-Butylphenoxy)-6,7-dimethoxy-3-phenylisoquinoline (3o)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 7.2 Hz, 2 H), 7.64 (d, *J* = 6.8 Hz, 2 H), 7.45 (d, *J* = 8.8 Hz, 2 H), 7.35 (t, *J* = 7.6 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 3 H), 7.09 (s, 1 H), 4.01 (d, *J* = 4.8 Hz, 6 H), 1.37 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 153.4, 152.0, 150.1, 147.2, 146.9, 139.4, 136.1, 128.7, 128.2, 126.5, 126.3, 121.2, 114.1, 111.1, 105.6, 102.9, 56.3, 56.2, 34.7, 31.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{27}NO_3$: 414.2069; found: 414.2052.

3-Cyclopropyl-6,7-dimethoxy-1-phenoxyisoquinoline (3p)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (s, 1 H), 7.38 (t, *J* = 8.0 Hz, 2 H), 7.19 (t, *J* = 7.6 Hz, 3 H), 7.06 (s, 1 H), 6.96 (s, 1 H), 3.99 (s, 6 H), 1.87–2.04 (m, 1 H), 0.75–0.77 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 154.6, 153.3, 152.3, 149.2, 136.1, 129.8, 129.2, 124.3, 121.8, 111.6, 104.5, 102.8, 56.3, 56.2, 16.7, 8.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{19}NO_3$: 322.1443; found: 322.1430.

1-(4-*tert*-Butylphenoxy)-3-cyclopropyl-6,7-dimethoxyisoquinoline (3q)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (s, 1 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 7.04 (s, 1 H), 6.95 (s, 1 H), 3.98 (d, *J* = 3.2 Hz, 6 H), 1.91–1.96 (m, 1 H), 1.34 (s, 9 H), 0.77–0.79 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 153.3, 152.5, 149.2, 146.9, 136.1, 126.5, 126.1, 120.8, 115.0, 111.4, 104.5, 102.9, 56.2, 56.1, 34.6, 31.8, 16.8, 8.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{27}NO_3$: 378.2069; found: 378.2077.

1-(4-*tert*-Butylphenoxy)-6-chloro-3-phenylisoquinoline (3r)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 1.6 Hz, 1 H), 7.91 (d, *J* = 7.2 Hz, 2 H), 7.74 (t, *J* = 6.0 Hz, 2 H), 7.61 (dd, *J* = 1.6, 8.8 Hz, 1 H), 7.46 (d, *J* = 8.8 Hz, 2 H), 7.27–7.38 (m, 5 H), 1.38 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 151.5, 148.5, 147.8, 138.7, 137.9, 132.6, 132.0, 128.9, 128.5, 126.8, 126.5, 126.4, 123.8, 121.3, 119.8, 111.3, 34.8, 31.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{22}ClNO$: 388.1468; found: 388.1472.

6-Fluoro-1-phenoxy-3-phenylisoquinoline (3s)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (dd, *J* = 5.6, 9.2 Hz, 1 H), 7.90 (d, *J* = 7.2 Hz, 2 H), 7.71 (s, 1 H), 7.40–7.48 (m, 3 H), 7.22–7.37 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2 (d, $^1J_{C–F}$ = 250.4 Hz), 159.9, 153.9, 149.3, 141.4 (d, $^3J_{C–F}$ = 10.3 Hz), 138.6, 129.6, 128.9, 128.8, 127.6 (d, $^3J_{C–F}$ = 9.7 Hz), 126.8, 125.0, 122.2, 117.0 (d, $^2J_{C–F}$ = 24.9 Hz), 116.1, 111.4 (d, $^4J_{C–F}$ = 4.6 Hz), 110.6 (d, $^2J_{C–F}$ = 21.9 Hz).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{14}FNO$: 316.1138; found: 316.1137.

1-(4-*tert*-Butylphenoxy)-6-fluoro-3-phenylisoquinoline (3t)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (dd, *J* = 5.6, 9.2 Hz, 1 H), 7.60 (d, *J* = 7.2 Hz, 2 H), 7.37 (s, 1 H), 7.14 (d, *J* = 8.8 Hz, 2 H), 6.95–7.10 (m, 7 H), 1.06 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2 (d, $^1J_{C–F}$ = 250.0 Hz), 159.9, 151.6, 149.4, 147.7, 141.3 (d, $^3J_{C–F}$ = 10.4 Hz), 138.8, 128.9 (d, $^3J_{C–F}$ = 10.4 Hz), 127.7, 127.6, 126.9, 126.4, 121.4, 116.9 (d, $^2J_{C–F}$ = 24.9 Hz), 116.2, 111.3 (d, $^4J_{C–F}$ = 4.6 Hz), 110.6 (d, $^2J_{C–F}$ = 21.0 Hz), 34.7, 33.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{22}FNO$: 372.1764; found: 372.1738.

1-(4-*tert*-Butylphenoxy)-6-fluoro-3-*p*-tolylisoquinoline (3u)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (dd, *J* = 5.6, 8.8 Hz, 1 H), 7.82 (d, *J* = 8.0 Hz, 2 H), 7.67 (s, 1 H), 7.46 (d, *J* = 8.4 Hz, 3 H), 7.24–7.35 (m, 4 H), 7.18 (d, *J* = 8.0 Hz, 1 H), 2.35 (s, 3 H), 1.38 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2 (d, $^1J_{C–F}$ = 249.8 Hz), 159.8, 151.6, 149.4, 147.6, 141.4 (d, $^3J_{C–F}$ = 9.5 Hz), 138.9, 135.9, 129.5, 128.9, 127.6 (d, $^3J_{C–F}$ = 9.7 Hz), 126.8, 126.3, 121.3, 116.7 (d, $^2J_{C–F}$ = 24.8 Hz), 110.8 (d, $^4J_{C–F}$ = 4.6 Hz), 110.4 (d, $^2J_{C–F}$ = 21.0 Hz), 34.7, 31.8, 21.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{24}FNO$: 386.1920; found: 386.1930.

3-Cyclopropyl-6-fluoro-1-phenoxyisoquinoline (3v)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (dd, *J* = 5.6, 9.2 Hz, 1 H), 7.39 (t, *J* = 8.0 Hz, 2 H), 7.16–7.27 (m, 5 H), 7.11 (s, 1 H), 1.88–1.95 (m, 1 H), 0.76–0.81 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2 (d, $^1J_{C–F}$ = 249.3 Hz), 160.0, 155.1, 153.9, 141.1 (d, $^3J_{C–F}$ = 10.5 Hz), 129.3 (d, $^4J_{C–F}$ = 4.0 Hz), 127.4 (d, $^3J_{C–F}$ = 9.9 Hz), 124.7, 122.0, 115.7 (d, $^2J_{C–F}$ = 24.9 Hz), 115.1, 112.0 (d, $^4J_{C–F}$ = 4.6 Hz), 109.2 (d, $^2J_{C–F}$ = 21.0 Hz), 16.9, 9.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}FNO$: 280.1138; found: 280.1149.

1-(4-*tert*-Butylphenoxy)-3-cyclopropyl-6-fluoroisoquinoline (3w)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (dd, *J* = 5.6, 8.8 Hz, 1 H), 7.39 (d, *J* = 8.8 Hz, 2 H), 7.25 (dd, *J* = 2.4, 9.6 Hz, 1 H), 7.13–7.20 (m, 3 H), 7.09 (s, 1 H), 1.91–1.94 (m, 1 H), 1.36 (s, 9 H), 0.79–0.83 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1 (d, $^1J_{C–F}$ = 249.3 Hz), 160.0, 155.2, 151.6, 147.4, 141.0 (d, $^3J_{C–F}$ = 10.3 Hz), 127.5 (d, $^3J_{C–F}$ = 9.9 Hz), 126.1, 121.1, 115.6 (d, $^2J_{C–F}$ = 24.9 Hz), 115.3, 111.8 (d, $^4J_{C–F}$ = 4.6 Hz), 109.2 (d, $^2J_{C–F}$ = 20.9 Hz), 34.7, 31.8, 16.9, 9.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}FNO$: 336.1764; found: 336.1751.

1-(4-*tert*-Butylphenoxy)-7-fluoro-3-phenylisoquinoline (3x)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (dd, *J* = 2.4, 9.2 Hz, 1 H), 7.90–7.92 (m, 2 H), 7.79 (dd, *J* = 2.8, 8.8 Hz, 1 H), 7.73 (s, 1 H), 7.44–7.47 (m, 3 H), 7.36 (t, *J* = 7.6 Hz, 2 H), 7.27–7.31 (m, 3 H), 1.37 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1 (d, $^1J_{C–F}$ = 246.7 Hz), 159.6, 151.6, 147.6 (d, $^3J_{C–F}$ = 6.8 Hz), 147.5, 138.9, 136.5, 129.4, 129.3, 128.6 (d, $^3J_{C–F}$ = 14.7 Hz), 126.7, 126.3, 121.4 (d, $^2J_{C–F}$ = 24.9 Hz), 121.3, 119.9, 111.4 (d, $^4J_{C–F}$ = 1.5 Hz), 108.6 (d, $^2J_{C–F}$ = 22.2 Hz), 34.7, 31.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{22}FNO$: 372.1764; found: 372.1748.

1-(4-*tert*-Butylphenoxy)-3-cyclopropyl-7-fluoroisoquinoline (3y)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (dd, *J* = 2.4, 9.6 Hz, 1 H), 7.64 (m, 1 H), 7.39 (d, *J* = 8.8 Hz, 3 H), 7.16 (d, *J* = 8.8 Hz, 3 H), 1.91–1.97 (m, 1 H), 1.36 (s, 9 H), 0.79–0.83 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3 (d, $^1J_{C-F}$ = 244.5 Hz), 159.6 (d, $^4J_{C-F}$ = 5.5 Hz), 153.0 (d, $^4J_{C-F}$ = 2.5 Hz), 151.6, 147.3, 136.3, 128.0 (d, $^3J_{C-F}$ = 8.1 Hz), 126.1, 121.1 (d, $^2J_{C-F}$ = 25.0 Hz), 121.0, 118.8 (d, $^3J_{C-F}$ = 8.6 Hz), 111.8, 108.3 (d, $^2J_{C-F}$ = 21.9 Hz), 34.7, 31.8, 16.8, 9.1.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{22}FNO$: 336.1764; found: 336.1761.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals /toc/synthesis.

Acknowledgment

Financial support from the National Natural Science Foundation of China (No. 20972030) is gratefully acknowledged.

References

(1) For selected recent examples, see: (a) Li, S.; Wu, J. *Org. Lett.* **2011**, *13*, 712. (b) Chen, Z.; Zheng, D.; Wu, J. *Org. Lett.* **2011**, *13*, 848. (c) Luo, Y.; Pan, X.; Wu, J. *Org. Lett.* **2011**, *13*, 1150. (d) Luo, Y.; Hong, L.; Wu, J. *Chem. Commun.* **2011**, *47*, 5298. (e) Chen, Z.; Ye, C.; Gao, L.; Wu, J. *Chem. Commun.* **2011**, *47*, 5623. (f) Chen, Z.; Wu, J. *Org. Lett.* **2010**, *12*, 4856. (g) Chen, Z.; Yu, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 6356. (h) Ye, S.; Yang, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 5238. (i) Ye, S.; Yang, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 2950.

(2) (a) Zheng, G.; Dwoskin, L. P.; Deaciuc, A. G.; Zhu, J.; Jones, M. D.; Crooks, P. A. *Bioorg. Med. Chem.* **2005**, *13*, 3899. (b) Wilson, K. J.; van Niel, M. B.; Cooper, L.; Bloomfield, D.; O'Connor, D.; Fish, L. R.; MacLeod, A. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2643. (c) Campeau, L.-C.; Fagnou, K. *Chem. Soc. Rev.* **2007**, *36*, 1058. (d) Laird, T. *Org. Process Res. Dev.* **2006**, *10*, 851.

(3) For selected examples, see: (a) Bentley, K. W. *The Isoquinoline Alkaloids*, Vol. 1; Harwood Academic: Australia, **1998**. (b) Trotter, B. W.; Nanda, K. K.; Kett, N. R.; Regan, C. P.; Lynch, J. J.; Stump, G. L.; Kiss, L.; Wang, J.; Spencer, R. H.; Kane, S. A.; White, R. B.; Zhang, R.; Anderson, K. D.; Liverton, N. J.; McIntyre, C. J.; Beshore, D. C.; Hartman, G. D.; Dinsmore, C. J. *J. Med. Chem.* **2006**, *49*, 6954. (c) Ramesh, P.; Reddy, N. S.; Venkateswarlu, Y. *J. Nat. Prod.* **1999**, *62*, 780. (d) Kaneda, T.; Takeuchi, Y.; Matsui, H.; Shimizu, K.; Urakawa, N.; Nakajyo, S. *J. Pharmacol. Sci.* **2005**, *98*, 275. (e) Marchand, C.; Antony, S.; Kohn, K. W.; Cushman, M.; Ioanoviciu, A.; Staker, B. L.; Burgin, A. B.; Stewart, L.; Pommier, Y. *Mol. Cancer Ther.* **2006**, *5*, 287. (f) Balasubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*, Vol. 5; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, **1996**, 245–300. (g) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341.

(4) (a) Yang, H. *Tetrahedron Lett.* **2009**, *50*, 3081. (b) Smits, R. A.; Lim, H. D.; Hanzer, A.; Zuiderveld, O. P.; Guaita, E.; Adami, M.; Coruzzi, G.; Leurs, R.; de Esch, I. J. P. *J. Med. Chem.* **2008**, *51*, 2457. (c) Fish, P. V.; Barber, C. G.; Brown, D. G.; Butt, R.; Collis, M. G.; Dickinson, R. P.; Henry, B. T.; Horne, V. A.; Huggins, J. P.; King, E.; O'Gara, M.; McCleverty, D.; McIntosh, F.; Phillips, C.; Webster, R. *J. Med. Chem.* **2007**, *50*, 2341. (d) Doherty, S.; Knight, J. G.; McGrady, J. P.; Ferguson, A. M.; Ward, N. A. B.; Harrington, R. W. *Adv. Synth. Catal.* **2010**, *352*, 201. (e) Lee, B. K.; Biscoe, M. R.; Buchwald, S. L. *Tetrahedron Lett.* **2009**, *50*, 3672. (f) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586. (g) Chen, G.; Lam, W. H.; Fok, W. S.; Lee, H. W.; Kwong, F. Y. *Chem. Asian J.* **2007**, *2*, 306. (h) Xie, X.; Zhang, T. Y.; Zhang, Z. *J. Org. Chem.* **2006**, *71*, 6522. (i) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2005**, *44*, 1371. (j) Kumar, K.; Michalik, D.; Castro, I. G.; Tillack, A.; Zapf, A.; Arlt, M.; Heinrich, T.; Böttcher, H.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 746. (k) Burton, G.; Cao, P.; Li, G.; Rivero, R. *Org. Lett.* **2003**, *5*, 4373.

(5) Gamage, S. A.; Spicer, J. A.; Rewcastle, G. W.; Milton, J.; Sohal, S.; Dangerfield, W.; Mistry, P.; Vicker, N.; Charlton, P. A.; Denny, W. A. *J. Med. Chem.* **2002**, *45*, 740.

(6) (a) Londregan, A. T.; Jennings, S.; Wei, L. *Org. Lett.* **2010**, *12*, 5254. (b) Londregan, A. T.; Jennings, S.; Wei, L. *Org. Lett.* **2011**, *13*, 1840.

(7) (a) Qiu, G.; Ding, Q.; Ren, H.; Peng, Y.; Wu, J. *Org. Lett.* **2010**, *12*, 3975. (b) Ren, H.; Luo, Y.; Ye, S.; Wu, J. *Org. Lett.* **2011**, *13*, 2552. (c) Ye, S.; Wang, H.; Wu, J. *ACS Comb. Sci.* **2011**, *13*, 120. (d) Ye, S.; Gao, K.; Wu, J. *Adv. Synth. Catal.* **2010**, *352*, 1746. (e) Ye, S.; Wang, H.; Wu, J. *Eur. J. Org. Chem.* **2010**, 6436. (f) Chen, Z.; Yu, X.; Su, M.; Yang, X.; Wu, J. *Adv. Synth. Catal.* **2009**, *351*, 2702. (g) Ding, Q.; Wang, Z.; Wu, J. *J. Org. Chem.* **2009**, *74*, 921. (h) Ding, Q.; Wang, Z.; Wu, J. *Tetrahedron Lett.* **2009**, *50*, 198. (i) Ding, Q.; Wu, J. *Adv. Synth. Catal.* **2008**, *350*, 1850. (j) Zheng, D.; Chen, Z.; Liu, J.; Wu, J. *Org. Biomol. Chem.* **2011**, *9*, 4763.

(8) (a) Yeom, H.-S.; Lee, J.-E.; Shin, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 7040. (b) Yeom, H.-S.; Kim, S.; Shin, S. *Synlett* **2008**, 924. (c) Huo, Z.; Tomeba, H.; Yamamoto, Y. *Tetrahedron Lett.* **2008**, *49*, 5531.

(9) (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86. (b) MacNevin, C. J.; Moore, R. L.; Liotta, D. C. *J. Org. Chem.* **2008**, *73*, 1264.