JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

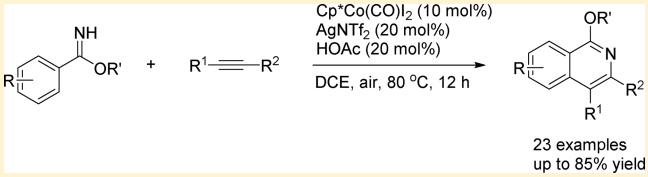
Synthesis of Isoquinolines from Benzimidates and Alkynes via Cobalt(III)-Catalyzed C−H Functionalization/Cyclization

Shasha Gong,[†] Wanlin Xi,[†] Zhenhua Ding,* and Haiying Sun*

Jiangsu Key Laboratory of Drug Design and Optimization, Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, China

Supporting Information

ABSTRACT: C−H alkenylation/annulation of benzimidates with alkynes has been realized by using a Cp*Co(III) catalyst under air. A series of substituted isoquinolines were obtained with moderate to good yields under mild reaction conditions.



Isoquinoline represents a ubiquitous structural motif that occurs in a broad range of biologically active compounds and pharmaceuticals.[1] Consequently, the development of efficient preparative methods for isoquinoline derivatives has attracted considerable attention from synthetic chemists. In the past several decades, transition-metal-catalyzed C−H activation has emerged as a powerful method for the construction of heterocycles.[2] The formation of isoquinoline compounds through direct C−H functionalization has also been developed.[3] Most of these transformations were achieved by expensive second-row transition metals, especially rhodium,[4] ruthenium,[5] and palladium[6] complexes. In this context, the exploitation of naturally abundant first-row transition-metal catalysts has received special attention.[7] Recently, high-valent cobalt complexes have been reported as efficient catalysts for direct C−H functionalization.[8] In particular, the formation of biologically and pharmaceutically active heterocycles through cobalt(III)-catalyzed C−H activation has received considerable attention.[9]

Various N-containing directing groups have been used in Co(III)-catalyzed C−H activation. Aryl imidates as one type of easily achieved compounds have also been investigated in C−H functionalization and exhibited good reactivity.[10] Our interest in cobalt(III)-catalyzed C−H activation and isoquinoline construction motivated us to explore the reaction of ethyl benzimidate **1a** and diphenylacetylene **2a** catalyzed by cobalt(III) catalyst. We began our investigation with an evaluation of a range of cobalt sources, silver(I) salts, additives, solvents, and temperatures (Table 1). The cobalt(III) complex $Cp^*Co(CO)I_2$ (10 mol %) combined with silver(I) salt (10 mol %) and KOAc (20 mol %) in dichloromethane (DCE) promoted the reaction (entries 1−4). The silver(I) salt is essential for this transformation (entry 5), and $AgNTf_2$ gave optimal results (entry 4). The reaction yields decreased to 10% without KOAc (entry 6). Replacement of KOAc with K_2CO_3 led catalytic inhibition, while HOAc showed a slight improvement of the reaction and afforded the product in 81% yield (entry 8). When the reaction temperature was lowered to 50 °C and room temperature, the product was obtained in 44% and 25% yields, respectively. The other solvents did not improve the reaction yields. As for the other cobalt sources, $CoBr_2$ and $Co(OAc)_2$ were entirely ineffective under the reaction conditions.

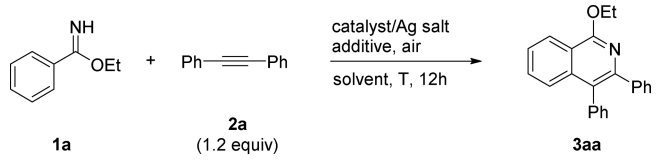
With the optimized reaction conditions in hand, we next examined the substrate scope of substituted benzimidates **1** (Scheme 1). Benzimidates bearing halogen substituents including fluoro and chloro could be tolerated under the present conditions, and the corresponding products were obtained in 78% (**3ba**) and 65% (**3ca**), respectively. Both electron-withdrawing and electron-donating substituents such as nitro (**3da**), acetyl (**3ea**), methoxy (**3fa**), and methyl groups (**3ga**) were tolerated well in this reaction. A 4-phenyl-substituted benzimidate also underwent the reaction with good reactivity (**3ha**). The reaction also proceeded when indole-4-carbimidate was used as substrate and afforded a fused indole ring in 50% yield (**3ia**). The terephthalimidate also participated the reaction and gave a fluorescent compound with moderate yields (**3ja**). It was found that the reaction of other alkyl benzimidates even with some steric hindrance were also viable under the present reaction conditions and afforded the products in good yields (**3ka**, **3la**, **3ma**). The substrate 4-hydroxybutyl benzimidate underwent the reaction and gave the product in moderate yield with the hydroxyl group untouched (**3na**).

We then investigated the scope of alkynes **2** (Scheme 2). Symmetrical aliphatic alkyne 4-octyene participated smoothly in the reaction and afforded the annulation product **3ab** in 65% yield. The reaction of benzimidate with unsymmetrical aliphatic alkyne **2c** provided the products **3dc** and **3dc′** in 44% yields in a 1:1 ratio. 1-Phenyl-1-propyne underwent the reaction, and the products **3dd** and **3dd′** were obtained in 60% yields without regioselectivity. The structure of **3dd′** was determined by the NOE spectrum. Diarylalkyne also gave the desired products in moderate to good yields. Methoxy, fluoro, and chloro

Received: May 2, 2017
Published: June 30, 2017

DOI: 10.1021/acs.joc.7b01052
J. Org. Chem. 2017, 82, 7643−7647

Table 1. Optimize Reaction Conditions[a]

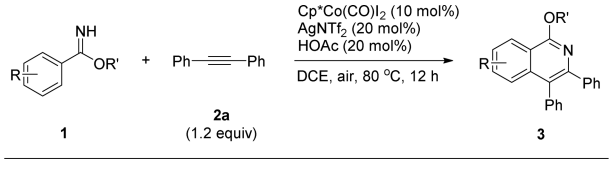


1a 2a (1.2 equiv) 3aa

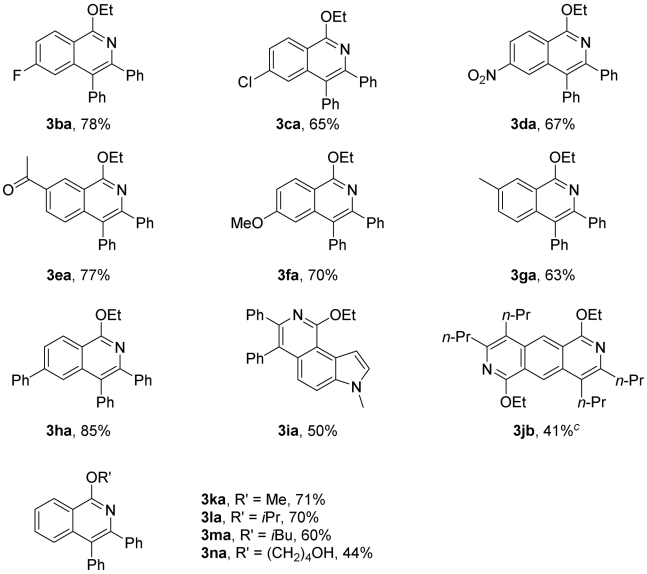
entry	catalyst	Ag(I) salt	additive	solvent	T (°C)	yield[b] (%)
1	Cp*Co(CO)I_2	$AgBF_4$	KOAc	DCE	80	22
2	Cp*Co(CO)I_2	$AgSbF_6$	KOAc	DCE	80	67
3	Cp*Co(CO)I_2	$AgPF_6$	KOAc	DCE	80	47
4	Cp*Co(CO)I_2	$AgNTf_2$	KOAc	DCE	80	75
5	Cp*Co(CO)I_2		KOAc	DCE	80	0
6	Cp*Co(CO)I_2	$AgNTf_2$		DCE	80	10
7	Cp*Co(CO)I_2	$AgNTf_2$	K_2CO_3	DCE	80	21
8	Cp*Co(CO)I_2	$AgNTf_2$	HOAc	DCE	80	81
9	Cp*Co(CO)I_2	$AgNTf_2$	HOAc	DCE	50	44
10	Cp*Co(CO)I_2	$AgNTf_2$	HOAc	DCE	25	25
11	Cp*Co(CO)I_2	$AgNTf_2$	HOAc	dioxane	80	53
12	Cp*Co(CO)I_2	$AgNTf_2$	HOAc	THF	80	51
13	Cp*Co(CO)I_2	$AgNTf_2$	HOAc	acetonitrile	80	27
14	$Co(OAc)_2$	$AgNTf_2$	HOAc	DCE	80	0
15	$CoBr_2$	$AgNTf_2$	HOAc	DCE	80	0

[a]General reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), cobalt catalyst (10 mol %), Ag(I) salt (20 mol %), additive (20 mol %), solvent (1 mL), 12 h. [b]Isolated yields.

Scheme 1. Substrate Scope of Benzimidates[a,b]

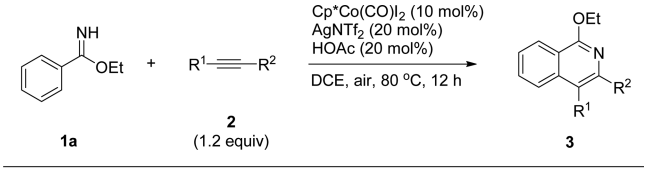


1 2a (1.2 equiv) 3

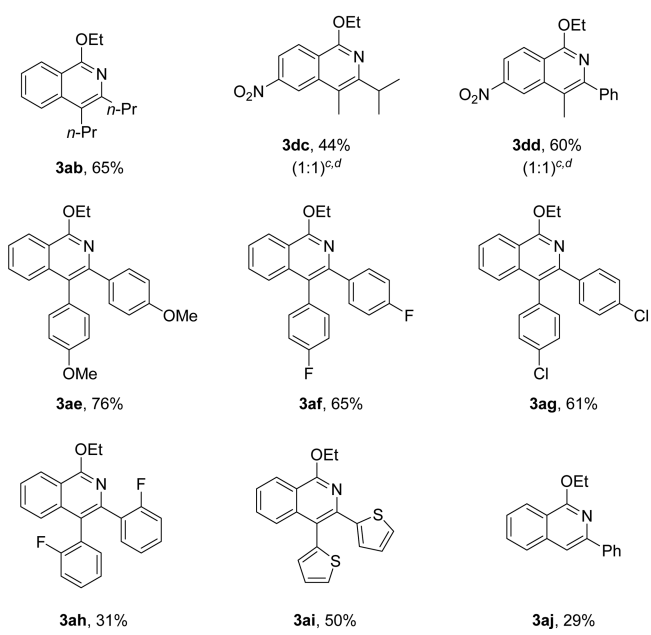


[a]Reaction performed on 0.2 mmol scale. [b]Isolated yields. [c]4-Octyne was used instead of diphenylacetylene.

Scheme 2. Substrate Scope of Alkynes[a,b]



1a 2 (1.2 equiv) 3

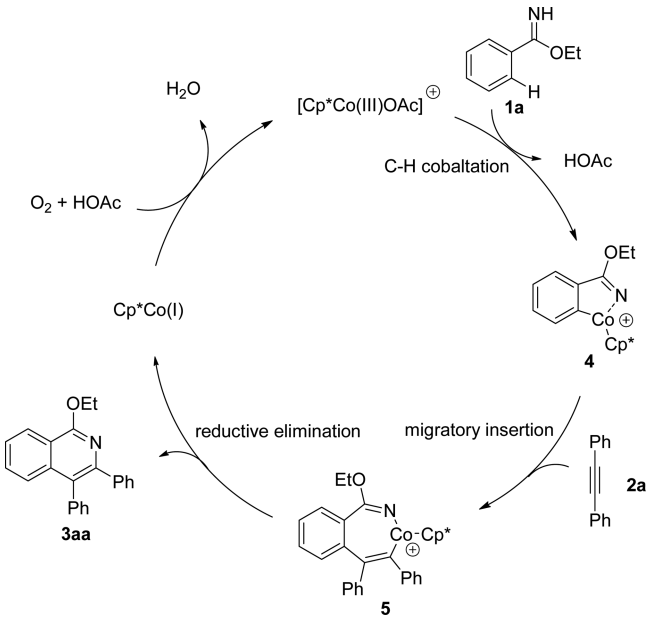


[a]Reaction performed on 0.2 mmol scale. [b]Isolated yields. [c]Ethyl 4-notrobenzimidate was used instead of ethyl benzimidate. [d]One of the isomers is shown.

substituents in the *para* position of the benzene ring were tolerated in this transformation and afforded the products **3ae**, **3af**, and **3ag** in moderate to good yields. The reaction became sluggish when arylalkyne bore a substituent at the *ortho* position because of steric hindrance (**3ah**). The reaction of heteroarylalkyne also proceeded and gave the product in moderate yield (**3ai**). The terminal alkyne participated in the reaction but with low reactivity under the present reaction conditions (**3aj**).

DOI: 10.1021/acs.joc.7b01052
J. Org. Chem. 2017, 82, 7643−7647

Scheme 3. Plausible Catalytic Cycle



According to the reported work,[9d,11] we proposed the reaction mechanism of this transformation (Scheme 3). First, acetate-assisted C−H cobaltation generates a five-membered metalacycle **4**. A subsequent migratory insertion of alkyne affords the seven-membered ring intermediate **5**. The reductive elimination of **5** generates the desired isoquinoline product along with a Co(I) species. The catalytic cycle is completed by the regeneration of the Co(III) species by oxidation of Co(I) with O_2 in air.

In summary, we have developed a cobalt(III)-catalyzed C−H functionalization of benzimidates with alkynes under air. Various benzimidates and alkynes could be applied in this reaction, and the corresponding isoquinoline products were obtained in moderate to good yields.

EXPERIMENTAL SECTION

General Experimental Methods. Unless otherwise noted, all chemicals were purchased from commercial suppliers and used without further purification. All reactions were performed by standard Schlenk techniques in oven-dried reaction vessels under air. Flash column chromatography was carried out using commercially available 300−400 mesh under pressure unless otherwise indicated. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV-300 (300 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. HRMS data were recorded on an ESI-Q-TQF mass spectrometer. Anhydrous 1,2-dichloroethane (DCE) was distilled and stored over molecular sieves. Cp*Co(CO)I_2 was prepared by following the procedure as described in the literature.[12] Benzimidate derivatives **1** were prepared by following the same procedure as described in the literature.[13]

General Procedure for the Cobalt(III)-Catalyzed Annulations. To a dried screw-capped vial were added benzimidate **1** (0.2 mmol, 1.0 equiv), alkyne **2** (0.24 mmol, 1.2 equiv), Cp*Co(CO)I_2 (9.5 mg, 10 mol %), $AgNTf_2$ (15.5 mg, 20 mol %), HOAc (2.4 mg, 20 mol %), and 1,2-dichloroethane (1.0 mL). The reaction mixture was stirred at 80 °C for 12 h. After the mixture was cooled to ambient temperature, water (2 mL) was added, the mixture was extracted with EtOAc (5 mL × 3), the combined organic layer was dried over Na_2SO_4, after filtration, solvents were removed under reduced pressure, and the residue was purified by column chromatography on silica gel (PE/EtOAc = 100/1) to give the desired product.

*1-Ethoxy-3,4-diphenylisoquinoline (**3aa**):* 52.7 mg, 81% yield; pale yellow solid; mp 126−127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37−8.33 (m, 1H), 7.55−7.53 (m, 3H), 7.42−7.31 (m, 5H), 7.24−7.21 (m, 2H), 7.18−7.16 (m, 2H), 4.68 (q, J = 7.08 Hz, 2H), 1.54 (t, J = 7.08 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 146.4, 140.5, 137.9, 137.6, 131.2, 129.8, 129.7, 127.8, 126.9, 126.5, 126.4, 125.5, 124.9, 124.1, 123.5, 118.0, 61.4, 14.2; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{20}NO$ 326.1545, found 326.1544.

*1-Ethoxy-6-fluoro-3,4-diphenylisoquinoline (**3ba**).* Purified by column chromatography on silica gel (PE/EtOAc = 200/1) to give the desired product: 53.6 mg, 78% yield; yellow solid; mp 156−157 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39−8.34 (m, 1H), 7.42−7.34 (m, 5H), 7.27−7.17 (m, 7H), 4.68 (q, J = 7.05, 2H), 1.54 (t, J = 7.08, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 161.7, 158.6, 147.8, 140.1, 139.9, 137.1, 131.0, 129.8, 128.6, 127.5, 126.9, 126.7,126.6,115.4, 115.1, 109.1, 108.8, 61.6, 14.2; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{19}FNO$ 344.1451, found 344.1447.

*1-Ethoxy-6-chloro-3,4-diphenylisoquinoline (**3ca**).* Purified by column chromatography on silica gel (PE/EtOAc = 300/1) to give the desired product: 46.8 mg, 65% yield; white solid; mp 171−172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 8.67 Hz, 1H), 7.54−7.54 (m, 1H), 7.49−7.46 (m, 1H), 7.43−7.38 (m, 5H), 7.25−7.19 (m, 5H), 4.71 (q, J = 7.05 Hz, 2H), 1.56 (t, J = 7.02 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 147.9, 140.1, 139.1, 136.9, 136.4, 131.1, 129.8, 128.0, 126.9, 126.8, 126.7, 126.3, 125.3, 123.9, 123.4, 116.2, 61.6, 14.2; HRMS (ESI-TOF) $m/$ z [M + H]$^+$ calcd for $C_{23}H_{19}ClNO$ 360.1155, found 360.1154.

*1-Ethoxy-6-nitro-3,4-diphenylisoquinoline (**3da**).* Purified by column chromatography on silica gel (PE/EtOAc = 200/1) to give the desired product: 49.6 mg, 67% yield; yellow solid; mp 151−152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48−8.43 (m, 2H), 8.23−8.19 (m, 1H), 7.39−7.36 (m, 5H), 7.21−7.17 (m, 5H), 4.69 (q, J = 7.08 Hz, 2H), 1.54 (t, J = 7.08 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 149.4, 148.9, 139.9, 138.3, 136.4, 131.5, 130.3, 129.4, 128.8, 127.8, 127.6, 126.3, 125.4, 121.6, 120.1, 119.5, 62.7, 14.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{19}N_2O_3$ 371.1396, found 371.1395.

*1-Ethoxy-7-acetyl-3,4-diphenylisoquinoline (**3ea**).* Purified by column chromatography on silica gel (PE/EtOAc = 300/1) to give the desired product: 56.6 mg, 77% yield; white solid; mp 95−96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, J = 9.03 Hz, 1H), 7.39−7.28 (m, 5H), 7.23−7.09 (m, 6H), 6.83 (d, J = 2.37 Hz, 1H), 4.65 (q, J = 7.08 Hz, 2H), 3.68 (s, 3H), 1.51 (t, J = 7.08 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 158.8, 147.3, 140.7, 140.0, 137.9, 131.1, 129.9, 127.9, 126.9, 126.4, 125.4, 123.7, 116.9, 113.0, 104.4, 61.3,54.9, 14.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{22}NO_2$ 368.1651, found 368.1648.

*1-Ethoxy-6-methoxy-3,4-diphenylisoquinoline (**3fa**).* Purified by column chromatography on silica gel (PE/EtOAc = 300/1) to give the desired product. 49.8 mg, 70% yield; pale yellow solid; mp 97−98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27−8.24 (d, J = 9.03 Hz, 1H), 7.40−7.30 (m, 5H), 7.24−7.21 (m, 2H), 7.18−7.10 (m, 4H), 6.84−6.83 (d, 1H), 4.66 (q, J = 7.08 Hz, 2H), 3.71 (s, 3H), 1.52 (t, J = 7.08 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 158.7, 147.3, 140.6, 139.9, 137.8, 131.1, 129.8, 127.9, 127.6, 126.9, 126.43, 126.36, 125.4, 123.7, 116.9, 112.9, 104.3, 61.2, 54.6, 14.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{24}H_{22}NO_2$ 356.1651, found 356.1650.

*1-Ethoxy-7-methyl-3,4-diphenylisoquinoline (**3ga**).* Purified by column chromatography on silica gel (PE/EtOAc = 300/1) to give the desired product: 42.8 mg, 63% yield; pale yellow solid; mp 119−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.46−7.31 (m, 7H), 7.19−7.15 (m, 5H), 4.54 (q, J = 7.05 Hz, 2H), 2.53 (s, 3H), 1.55 (t, J = 7.05 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 145.5, 140.5, 137.8, 136.6 (, 135.5, 131.8, 131.2, 129.8, 129.5, 127.8, 126.9, 126.4, 126.3, 124.9, 124.1, 122.5, 118.1, 61.4, 21.1,14.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{24}H_{22}NO$ 340.1701, found 340.1698.

DOI: 10.1021/acs.joc.7b01052
J. Org. Chem. 2017, 82, 7643−7647

*1-Ethoxy-3,4,6-triphenylisoquinoline (**3ha**).* Purified by column chromatography on silica gel (PE/EtOAc = 300/1) to give the desired product: 68.3 mg, 85% yield; white solid; mp 180−181 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, J = 8.34 Hz, 1H), 7.78−7.74 (m, 2H), 7.55−7.53 (m, 2H), 7.43−7.38 (m, 4H), 7.36−7.31 (m, 4H), 7.27−7.24 (m, 2H), 7.18−7.16 (m, 3H), 4.71 (q, J = 7.08 Hz, 2H), 1.56 (t, J = 7.05 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 147.5, 142.9, 140.9, 140.8, 138.8, 131.7, 130.4, 128.9, 128.4, 127.8, 127.6, 127.4, 127.0, 126.9, 125.7, 124.8, 124.6, 123.4, 117.5, 62.0, 14.8; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{29}H_{24}NO$ 402.1858, found 402.1853.

*1-Ethoxy-7-methyl-3,4-diphenyl-7H-pyrrolo [2,3-h]isoquinoline (**3ia**).* Purified by column chromatography on silica gel (PE/EtOAc = 150/1) to give the desired product: 37.8 mg, 50% yield; brown solid; mp 158−159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.52 (m, 1H), 7.47−7.41 (m, 3H), 7.35−7.33 (m, 4H), 7.27−7.15 (m, 6H), 4.79 (q, J = 7.05 Hz, 2H), 3.88 (s, 3H), 1.65 (t, J = 7.05 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 144.9, 141.5, 139.3, 134.6, 134.0, 131.9, 130.4, 128.2, 128.0, 127.3, 126.7, 126.5, 125.4, 121.6, 119.5, 114.3, 112.2, 105.1, 61.8, 33.2, 14.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{26}H_{23}N_2O$ 379.1810, found 379.1822.

*1,6-Diethoxy-3,4,8,9-tetrapropylpyrido[3,4-g]isoquinoline (**3jb**).* Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product: 35.8 mg, 41% yield; bright yellow-green solid; mp 101−102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (s, 2H), 4.62 (q, J = 7.05 Hz, 4H), 3.02 (t, J = 7.92 Hz, 4H), 2.80(t, J = 7.44 Hz, 4H), 1.89−1.79 (m, 4H), 1.75−1.65 (m,4H), 1.53 (t, J = 7.05 Hz, 6H), 1.10 (t, J = 7.38 Hz, 6H), 1.02 (t, J = 7.38 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 147.3, 133.7, 120.8, 120.3, 118.9, 61.6, 36.7, 29.5, 24.0, 22.8, 14.7, 14.5, 14.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{28}H_{41}N_2O_2$ 437.3168, found 437.3165.

*1-Methoxy-3,4-diphenylisoquinoline (**3ka**).* Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product: 44.2 mg, 71% yield; white solid; mp 166−167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33−8.30 (m, 1H), 7.55−7.46 (m, 3H), 7.44−7.40 (m, 2H), 7.37−7.29 (m, 3H), 7.23−7.14 (m, 5H), 4.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 138.4, 138.0, 131.7, 130.4, 128.4, 127.5, 127.1, 127.0, 126.2, 125.5, 124.9, 124.0, 118.5, 53.7; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{18}NO$ 312.1388, found 312.1395.

*1-Isopropoxy-3,4-diphenylisoquinoline (**3la**).* Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product: 47.6 mg, 70% yield; pale yellow solid; mp 108−109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36−8.33 (m, 1H), 7.55−7.46 (m, 3H), 7.42−7.30 (m, 5H), 7.24−7.21 (m, 2H), 7.19−7.15 (m, 3H), 5.73 (m, J = 6.18 Hz, 1H), 1.51 (d, J = 6.18 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 138.6, 138.2, 131.8, 130.5, 128.4, 127.5, 127.0, 127.0, 126.1, 125.5, 124.4, 124.2, 118.9, 68.4, 22.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{24}H_{22}NO$ 340.1701, found 340.1712.

*1-Isobutoxy-3,4-diphenylisoquinoline (**3ma**).* Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product: 42.4 mg, 60% yield; pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36−8.33 (m, 1H), 7.55−7.48 (m, 3H), 7.41−7.37 (m, 2H), 7.34−7.29 (m, 3H), 7.22−7.13 (m, 5H), 4.39 (d, J = 3.29 Hz, 2H), 2.26 (m, J = 6.66 Hz, 1H), 1.12 (d, J = 3.36 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 147.0, 140.9, 138.4, 138.1, 131.7, 130.4, 130.3, 128.3, 127.4, 127.0, 125.4, 124.6, 124.0, 118.5, 72.4, 28.3, 19.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{24}NO$ 354.1858, found 354.1868.

*4-((3,4-Diphenylisoquinolin-1-yl)oxy)butan-1-ol (**3na**).* Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product: 32.5 mg, 44% yield; yellow solid; mp 88−89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25−8.22 (m, 1H), 7.47−7.39 (m, 3H), 7.33−7.29 (m, 2H), 7.28−7.21 (m, 3H), 7.15−7.07 (m, 5H), 4.58 (t, J = 5.80 Hz, 2H), 3.59 (t, J = 6.20 Hz, 2H), 1.99 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 146.9, 140.8, 138.5, 138.0, 130.4, 130.3, 128.4, 127.5, 127.0, 126.2, 125.5, 124.6, 123.9, 118.4, 65.3, 44.9, 29.8, 26.6.

*1-Ethoxy-3,4-dipropylisoquinoline (**3ab**).* Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product: 33.5 mg, 65% yield; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J = 8.10 Hz, 1H), 7.84 (d, J = 8.49 Hz, 1H), 7.65−7.60 (m, 1H), 7.46−7.40 (m, 1H), 4.55 (q, J = 7.05 Hz, 2H), 2.92−2.87 (m, 2H), 2.82−2.77 (m, 2H), 1.87−1.75 (m, 2H), 1.69−1.58 (m, 2H), 1.48 (t, J = 7.08 Hz, 3H), 1.11−1.04 (t, J = 7.32, 3H), 1.04−0.98 (t, J = 7.41, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 148.9, 137.1, 129.3, 124.2, 123.9, 122.3, 120.5, 117.8, 60.8, 36.2, 28.9, 23.5, 22.3, 14.2, 14.0, 13.8; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{24}NO$ 258.1858, found 258.1856.

*1-Ethoxy-3-isopropyl-4-methyl-6-nitroisoquinoline (**3dc**).* Purified by column chromatography on silica gel (PE/EtOAc = 100/1) to give the desired product: 12.6 mg, 23% yield; yellow solid; mp 58−59 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (d, J = 1.71 Hz, 1H), 8.40 (d, J = 9.03 Hz, 1H), 8.14 (dd, J_1 = 2.01 Hz, J_2 = 9.06 Hz, 1H), 4.56 (q, J_1 = 7.08 Hz, J_2 = 14.16 Hz, 2H), 3.76−3.66 (m, 1H), 2.64 (s, 3H), 1.51 (t, J = 7.04 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 148.2, 148.0, 136.4, 127.8, 119.9, 117.7, 62,1, 29.7, 29.4, 28.3, 23.6, 21.9, 18.3, 14.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{19}N_2O_3$ 275.1396, found 275.1392.

*1-Ethoxy-4-isopropyl-3-methyl-6-nitroisoquinoline (**3dc′**).* Purified by column chromatography on silica gel (PE/EtOAc = 100/1) to give the desired product: 11.6 mg, 21% yield; yellow solid; mp 75−76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, J = 1.92 Hz, 1H), 8.34 (d, J = 9.00 Hz, 1H), 8.15 (dd, J_1 = 2.13 Hz, J_2 = 9.00 Hz, 1H), 4.60 (q, J_1 = 7.05 Hz, J_2 = 14.10 Hz, 2H), 3.48−3.39 (m, 1H), 2.55 (s, 3H), 1.50 (t, J = 7.05 Hz, 3H), 1.30 (d, J = 6.69 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 156.7, 148.5, 137.9, 131.1, 126.4, 124.8, 121.8, 119.4, 118.1, 115.9, 61.9, 31.4, 29.7, 21.9, 14.6, 12.7; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{19}N_2O_3$ 275.1396, found 275.1393.

*1-Ethoxy-4-methyl-6-nitro-3-phenylisoquinoline (**3dd**).* Purified by column chromatography on silica gel (PE/EtOAc = 50/1) to give the desired product: 17.9 mg, 29% yield; yellow solid; mp 103−104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, J = 8.82 Hz, 1H), 8.19−8.14 (m, 2H), 7.55−7.45 (m, 4H), 7.28−7.26 (m, 2H), 4.64 (q, J_1 = 7.08 Hz, J_2 = 14.16 Hz, 2H), 2.36 (s, 3H), 1.54 (t, J = 7.08 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 149.1, 148.8, 137.8, 136.8, 130.5, 128.9, 127.9, 126.2, 125.5, 120.9, 119.9, 118.5, 63.5, 23.0, 14.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_3$ 309.1239, found 309.1238.

*1-Ethoxy-3-methyl-6-nitro-4-phenylisoquinoline (**3dd′**).* Purified by column chromatography on silica gel (PE/EtOAc = 50/1) to give the desired product: 19.1 mg, 31% yield; yellow solid; mp 131−132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (d, J = 1.86 Hz, 1H), 8.45 (d, J = 9.00 Hz, 1H), 8.26 (q, J_1 = 2.13 Hz, J_2 = 9.00 Hz, 1H), 7.63−7.60 (m, 2H), 7.51−7.39 (m, 3H), 4.61 (q, J_1 = 7.08 Hz, J_2 = 14.16 Hz, 2H), 2.62 (s, 3H), 1.50 (t, J = 7.07 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 146.4, 140.5, 137.9, 137.6, 131.2, 129.8, 129.7, 127.8, 126.9, 126.5, 126.4, 125.5, 124.9, 124.1, 123.5, 118.0, 61.4, 15.3, 14.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{17}N_2O_3$ 309.1239, found 309.1237.

*1-Ethoxy-3,4-bis(4-methoxylphenyl)isoquinoline (**3ae**).* Purified by column chromatography on silica gel (PE/EtOAc = 300/1) to give the desired product: 58.6 mg, 76% yield; off-white solid; mp 128−129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31−8.28 (d, 1H), 7.52−7.42 (m, 3H), 7.38−7.35 (m, 2H), 7.13−7.10 (m, 2H), 6.90−6.88 (m, 2H), 6.72−6.69 (m, 2H), 4.67 (q, J = 7.08 Hz, 2H), 3.82 (s, 3H), 3.73 (s, 3H), 1.51 (t, J = 7.05 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 158.6, 158.5, 146.5, 138.9, 133.6, 132.69, 131.6, 130.5, 130.1, 125.8, 125.3, 123.9, 123.5, 118.3, 113.9, 112.9, 61.9, 55.3, 55.2, 14.8; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{24}NO_3$ 386.1756, found 386.1753.

*1-Ethoxy-3,4-bis(4-fluorophenyl)isoquinoline (**3af**).* Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product: 47.0 mg, 65% yield; white solid; mp 140−141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36−8.34 (d, 1H), 7.58−7.48 (m, 3H), 7.38−7.33 (m, 2H), 7.19−7.14 (m, 2H), 7.08−7.03 (m, 2H), 6.90−6.85 (t, 2H), 4.68 (q, J = 7.05 Hz, 2H), 1.54 (t, J = 7.05 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 163.6, 160.4, 160.3, 159.5, 146.2, 138.4, 136.8, 136.8, 133.8, 133.8, 133.3, 133.2, 132.1, 131.9, 131.7, 130.6, 130.5, 130.4, 128.5, 127.6, 127.1, 126.3, 126.2, 125.4,

DOI: 10.1021/acs.joc.7b01052
J. Org. Chem. 2017, 82, 7643−7647

125.1, 124.2, 124.2, 123.4, 118.5, 115.7, 115.5, 115.4, 115.3, 114.6, 114.2, 62.1, 14.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{18}F_2NO$ 362.1356, found 362.1353.

*1-Ethoxy-3,4-bis(4-chlorophenyl) isoquinoline (**3ag**).* Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product: 48.1 mg, 61% yield; white solid; mp 135−136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36−8.33 (d, 1H), 7.59−7.46 (m, 3H), 7.36−7.29 (m, 4H), 7.18−7.13 (m, 4H), 4.66 (q, J = 7.05 Hz, 2H), 1.52 (t, J = 7.05 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 145.9, 139.1, 138.1, 136.3, 133.3, 133.2, 132.9, 131.6, 130.7, 128.8, 127.9, 127.8, 126.5, 125.1, 124.2, 123.4, 118.6, 62.1, 14.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{18}Cl_2NO$ 394.0765, found 394.0761.

*1-Ethoxy-3,4-bis(2-fluorophenyl)isoquinoline (**3ah**).* Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product: 22.4 mg, 31% yield; white solid; mp 84−85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39−8.36 (m, 1H), 8.62−7.53 (m, 2H), 7.44−7.42 (m, 1H), 7.35−7.01 (m, 7H), 6.92−6.86 (m, 1H), 4.63 (q, J_1 = 6.99 Hz, J_2 = 12.15 Hz, 2H), 1.51 (t, J = 7.08 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 146.4, 140.5, 137.9, 137.6, 131.2, 129.8, 129.7, 127.8, 126.9, 126.5, 126.4, 125.5, 124.9, 124.1, 123.5, 118.0, 61.4, 14.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{18}F_2NO$ 362.1356, found 362.1351.

*1-Ethoxy-3,4-di(thiophene-2-yl)isoquinoline (**3ai**).* Purified by column chromatography on silica gel (PE/EtOAc = 500/1) to give the desired product: 33.7 mg, 50% yield; white solid; mp 140−141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23−8.20 (m, 1H), 7.54−7.49 (m, 2H), 7.45−7.40 (m, 2H), 7.23−7.20 (m, 2H), 7.03−7.02 (d, 1H), 6.67−6.83 (t, 1H), 6.67−6.66 (d, 1H), 4.68 (q, J = 7.08 Hz, 2H), 1.53 (t, J = 7.05 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 145.4, 142.4, 140.00, 138.4, 130.8, 129.2, 127.9, 127.7, 127.5, 127.09, 126.1, 125,3, 123.9, 118.3, 113.9, 62.5, 14.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{16}NOS_2$ 338.0673, found 338.0670.

*1-Ethoxy-3-phenylisoquinoline (**3aj**).* Purified by column chromatography on silica gel (PE/EtOAc = 300/1) to give the desired product: 14.5 mg, 29% yield; pale yellow solid; mp 41−42 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, J = 8.19, 1H), 8.17−8.14 (m, 2H), 7.76 (d, J = 8.13 Hz, 1H), 7.66−7.59 (m, 2H), 7.51−7.45 (m, 3H), 7.39−7.35 (m, 1H), 4.72 (q, J = 7.08 Hz, 2H), 1.55 (t, J = 7.08 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 147.9, 139.6, 138.8, 130.4, 128.6, 126.6, 126.3, 124.2, 119.0, 110.1, 61.9, 14.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{16}NO$ 250.1232, found 250.1229.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01052.

^{1}H NMR and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: zhding@cpu.edu.cn.

*E-mail: haiyings1969@163.com.

ORCID

Zhenhua Ding: 0000-0002-5335-3892

Author Contributions

†S.G. and W.X. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation of China (NSFC 81602952), the Natural Science Foundation of Jiangsu Province (BK20160748), the Program for Jiangsu Province Innovative Research Team, the Program for Specially Appointed Professor of Jiangsu Province and the Scientific Research Foundation of China Pharmaceutical University (3010010089, 3010010113) is acknowledged.

■ REFERENCES

(1) (a) Kletsas, D.; Li, W.; Han, Z.; Papadopoulos, V. *Biochem. Pharmacol.* **2004**, *67*, 1927. (b) Muscarella, D. E.; O'Brian, K. A.; Lemley, A. T.; Bloom, S. E. *Toxicol. Sci.* **2003**, *74*, 66. (c) Feng, J.-B.; Wu, X.-F. *Org. Biomol. Chem.* **2015**, *13*, 10656. (d) Rahnasto, M.; Raunio, H.; Poso, A.; Wittekindt, C.; Juvonen, R. O. *J. Med. Chem.* **2005**, *48*, 440.

(2) (a) Satoh, T.; Miura, M. *Chem. - Eur. J.* **2010**, *16*, 11212. (b) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (c) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281.

(3) He, R.; Huang, Z.-T.; Zheng, Q.-Y.; Wang, C. *Tetrahedron Lett.* **2014**, *55*, 5705.

(4) (a) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050. (b) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688. (c) Shi, Z.; Koester, D. C.; Boultadakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204. (d) Chu, H.; Sun, S.; Yu, J.-T.; Cheng, J. *Chem. Commun.* **2015**, *51*, 13327. (f) Chu, H.; Xue, P.; Yu, J.-T.; Cheng, J. *J. Org. Chem.* **2016**, *81*, 8009.

(5) (a) Chinnagolla, R. K.; Pimparkar, S.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 3032. (b) Chinnagolla, R. K.; Pimparkar, S.; Jeganmohan, M. *Chem. Commun.* **2013**, *49*, 3703. (c) Parthasarathy, K.; Senthilkumar, N.; Jayakumar, J.; Cheng, C.-H. *Org. Lett.* **2012**, *14*, 3478. (d) Villuendas, P.; Urriolabeitia, E. P. *J. Org. Chem.* **2013**, *78*, 5254. (e) Kornhaab, C.; Kuper, C.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1619. (f) Kornhaab, C.; Li, J.; Ackermann, L. *J. Org. Chem.* **2012**, *77*, 9190.

(6) (a) Zhu, Z.; Tang, X.; Li, X.; Wu, W.; Deng, G.; Jiang, H. *J. Org. Chem.* **2016**, *81*, 1401. (b) Rouchet, J-B. E. Y.; Schneider, C.; Fruit, C.; Hoarau, C. *J. Org. Chem.* **2015**, *80*, 5919.

(7) (a) Kulkarni, A.; Daugulis, O. *Synthesis* **2009**, 4087. (b) Nakao, Y. *Chem. Rec.* **2011**, *11*, 242. (c) Yoshikai, N. *Synlett* **2011**, *2011*, 1047. (d) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, *2013*, 19. (e) Nakamura, E.; Hatakeyama, T.; Ito, S.; Ishizuka, K.; Ilies, L.; Nakamura, M. *Org. React.* **2014**, *83*, 1. (f) Moselage, M.; Li, J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 498. (g) Liu, W.; Ackermann, L. *ACS Catal.* **2016**, *6*, 3743.

(8) (a) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2207. (b) Li, J.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 3635. (c) Lerchen, A.; Vasquez-Cespedes, S.; Glorius, F. *Angew. Chem., Int. Ed.* **2016**, *55*, 3208. (d) Boerth, J. A.; Hummel, J. R.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 12650. (e) Park, J.; Chang, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 14103. (f) Kong, L.; Yu, S.; Zhou, X.; Li, X. *Org. Lett.* **2016**, *18*, 588. (g) Prakash, S.; Muralirajan, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2016**, *55*, 1844. (h) Liu, X.-G.; Zhang, S.-S.; Jiang, C.-Y.; Wu, J.-Q.; Li, Q.; Wang, H. *Org. Lett.* **2015**, *17*, 5404.

(9) (a) Wang, H.; Koeller, J.; Liu, W.; Ackermann, L. *Chem. - Eur. J.* **2015**, *21*, 15525. (b) Sen, M.; Kalsi, D.; Sundararaju, B. *Chem. - Eur. J.* **2015**, *21*, 15529. (c) Yu, X.; Chen, K.; Yang, F.; Zha, S.; Zhu, J. *Org. Lett.* **2016**, *18*, 5412. (d) Li, J.; Tang, M.; Zang, L.; Zhang, X.; Zhang, Z.; Ackermann, L. *Org. Lett.* **2016**, *18*, 2742. (e) Kuppusamy, R.; Muralirajan, K.; Cheng, C.-H. *ACS Catal.* **2016**, *6*, 3909.

(10) (a) Wang, L.; Lorion, M. M.; Ackermann, L. *ACS Catal.* **2017**, *7*, 3430. (b) Mei, R.; Ackermann, L. *Adv. Synth. Catal.* **2016**, *358*, 2443. (c) Wang, L.; Lorion, M. M.; Ackermann, L. *Angew. Chem., Int. Ed.* **2016**, *55*, 10386. (d) Wang, F.; Wang, H.; Wang, Q.; Yu, S.; Li, X. *Org. Lett.* **2016**, *18*, 1306. (e) Wang, X.; Lerchen, A.; Glorius, F. *Org. Lett.* **2016**, *18*, 2090.

(11) (a) Li, L.; Wang, H.; Yu, S.; Yang, X.; Li, X. *Org. Lett.* **2016**, *18*, 3662. (b) Zhang, S.-S.; Liu, X.-G.; Chen, S.-Y.; Tan, D.-H.; Jiang, C.-Y.; Wu, J.-Q.; Li, Q.; Wang, H. *Adv. Synth. Catal.* **2016**, *358*, 1705. (c) Gupta, S.; Han, J.; Kim, Y.; Lee, S. W.; Rhee, Y. H.; Park, J. *J. Org. Chem.* **2014**, *79*, 9094.

(12) Sun, B.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Adv. Synth. Catal.* **2014**, *356*, 1491.

(13) Yadav, V. K.; Babu, K. G. *Eur. J. Org. Chem.* **2005**, *2005*, 452.

DOI: 10.1021/acs.joc.7b01052
J. Org. Chem. 2017, 82, 7643−7647