An Efficient synthesis of Iminoisoindolione Derivatives by Cobalt-Catalyzed Oxidative Isocyanide Insertion

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ABSTRACT

A Cobalt-catalyzed oxidative isocyanide insertion of aminoquinoline benzamides has been developed. The reaction proceeded smoothly by using Ag_2CO_3 as the oxidant in PhCl at 120 °C and delivered products in moderate to excellent yields with excellent functional group tolerance. The transformation is supposed to undergo the ortho C-H activation and isocyanide insertion of C-Co species toward the benzamides. Attractive features of this system include the use of low cost cobalt catalyst, the easyhandling operation, and readily available substrates.

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During the past several decades, as a high versatile reagent, isocyanides have wide application in organic, medicinal, and combinatorial chemistry. Indeed, due to its structural and reactive properties, significant achievements have been made in isocyanide-based multicomponent reactions¹, cycloaddition reactions², heterocycle synthesis³ etc. Apart from above reactions, transition-metal-catalyzed isocyanide insertion is another kind of fundamental chemical transformation⁴, which often involved isocyanide as a powerful C1 building blocks to extend the carbon chain length. The classical isocyanide insertion is usually occurred on low-valent transition metal-catalyzed addition of halides to isocyanides, where the oxidative addition and reductive elimination is generally considered happening in the catalytic cycle⁵. However, these methods generally require multistep procedures, not-readily available starting materials, and substrate pre-functionalization. Recently, several examples have been reported via metal-catalyzed intermolecular oxidative isocyanide insertion reaction by means of C-H bond activation, which have been emerged as a conceptually new alternative to "classical isocyanide processes".⁶ For example, in 2011, Zhu and co-workers^{6a} first reported a palladium-catalyzed intramolecular C(sp²)-H amidination through oxidative isocyanide insertion. This work provides a direct access to 4-aminoquinazolines from *N*-arylamidines. In 2012, Orru and co-workers^{6b} reported another example of oxidative isocyanide insertion to get diverse cyclic guanidines. But most of these reactions are catalyzed by the noble metal such as palladium and ruthenium. So, further development of non-noble metal catalyzed oxidative isocyanide insertion is highly demanded⁷. Recently, cobalt-catalyzed C-H functionalization has attracted considerable attention due to its economy, low toxicity, and interesting reaction modes⁸. Many C-C⁹ and C-heteroatom¹⁰ bond-forming reactions have been achieved by this method. For example, Murahashi and coworkers

reported the first example of a cobalt-catalyzed chelation-assisted C-H functionalization process^{9a}. In 2014, Daugulis showed an elegant method for the annulation of benzamide using a simple, commercially available cobalt^(II) precursor along with a carboxylate base and Mn^(III) as a cocatalyst under mild conditions¹¹. More recently, Miura's group and our group have independently reported copper-catalyzed and nickel-catalyzed insertion reaction of isocyanides with aminoquinoline benzamides to construct Iminoisoindolione (Scheme 1)^{7a,12}. Although many transition-metal-catalyzed oxidative isocyanide insertion have been reported, the success of direct oxidative isocyanide insertion catalyzed by cobalt is still rare¹³. As our continuation on the development of new catalyst systems for isocyanide chemistry¹⁴, herein, we report a Co(acac)₂-catalyzed isocyanide insertion reaction of benzamides.

1) Miura's work:

2) Our previous work:

3) This work:

Scheme 1 Recent methods for the synthesis of iminoisoindoliones

We used benzamide **1a** (0.25 mol) that bears the 8-aminoquinoline-based bidentate coordination group and *t*-butyl isocyanide **2a** as substrates for the optimization of reaction conditions (Table 1). In the early experiment, the desired iminoisoindolinone **3a** was formed in 35% yield upon treatment of **1a** and **2a** in the present of a Co(acac)₂ catalyst (20 mol%) under O₂ (1 atm, balloon) in toluene at 120 °C (Table 1, entry 1). Next, different cobalt salts were screened, but the results were not satisfactory. (Table 1, entries 2-6). Some other oxidants also can promote the reaction and the result indicates the Ag₂CO₃ (3.0 eqv.) was the best choice which provided the desired product in 65% yield (table 1, entries 7-12). Different solvents were screened subsequently (Table 1, entries 13-16). From the results, it seemed that the reaction worked most efficiently when PhCl was employed as the solvent which provided the desired product in 84% yield. A lower yield was obtained when the reaction was performed at 140 or 100 °C (80%, 55% yield, Table 1, entries 17 and 18). The reaction cannot proceed when temperature lower than 80 °C (Table 1, entries 19-20).

Table 1 Optimization Studies for Cobalt-Catalyzed Oxidative Isocyanide Insertion of Benzamide **1a**^a

Entry	Catalyst	Oxidant	Solvent	Temp.(°C)	Yield ^b (%)
1	Co(acac) ₂	O ₂	Toluene	120	35
2	Co(acac) ₃	O ₂	Toluene	120	30
3	CoBr ₂	O ₂	Toluene	120	N.D.
4	CoCl ₂	O ₂	Toluene	120	N.D.
5	CoC ₂ O ₄	O ₂	Toluene	120	30
6	Co(OAc) ₂ •4H ₂ O	O ₂	Toluene	120	15
7	Co(acac) ₂	TBHP	Toluene	120	30
8	Co(acac) ₂	DTBP	Toluene	120	35
9	Co(acac) ₂	K ₂ S ₂ O ₈	Toluene	120	trace
10	Co(acac) ₂	NaIO ₄	Toluene	120	trace
11	Co(acac) ₂	BQ	Toluene	120	trace
12	Co(acac) ₂	Ag ₂ CO ₃	Toluene	120	65
13	Co(acac) ₂	Ag ₂ CO ₃	DMSO	120	N.D.
14	Co(acac) ₂	Ag ₂ CO ₃	DCE	120	57
15	Co(acac) ₂	Ag ₂ CO ₃	PhCl	120	84
16	Co(acac) ₂	Ag ₂ CO ₃	PhCF ₃	120	67
17	Co(acac) ₂	Ag ₂ CO ₃	PhCl	140	80
18	Co(acac) ₂	Ag ₂ CO ₃	PhCl	100	55
19	Co(acac) ₂	Ag ₂ CO ₃	PhCl	80	N.D.
20	Co(acac) ₂	Ag ₂ CO ₃	PhCl	r.t.	N.D.

TBHP: *tert*-butyl hydroperoxide, DTBP: *di-tert*-butyl peroxide, BQ: 1,4-Benzoquinone, DCM: Dichloromethane. [a]Reaction conditions: Benzamide **1a** (0.25mmol), isocyanide **2a** (0.5mmol), Co(acac)₂ (20 mol%), Ag₂CO₃ (3.0 eqv.) PhCl (2 mL), 120 °C. [b] Isolated yield based on benzamide **1a**.

With this optimized condition (20 mol% of Co(acac)₂, 3.0 equiv.

Table 2 Products in oxidative isocyanide insertion of various benzamides **1** and isocyanides **2**^[a]

[a]Isolated yield based on Benzamide **1a**. Q = 8-quinolynyl, Xyl = 2,6-dimethylphenyl. [b] The reaction time was 36 h.

of Ag₂CO₃, PhCl, 120 °C) in hand, we then explored the scope of the reaction of isocyanides and aminoquinoline benzamides. The results are summarized in Table 2. Various isocyanides were demonstrated to be partners in the transformation. For instance, benzamide **1a** reacted with xyl-yl-substituted isocyanide **2b** leading to the corresponding products **3b** in 49% yield. In addition to the substrate **1a**, electron-withdrawing such as trifluoromethyl, cyano, fluoro, chloro, bromo, iodo groups attached to the aromatic ring at the para position were all tolerated, and the corresponding iminoisoindolinones were obtained in moderate to good yield. The cobalt catalyst also accommodated electron-donating such as methyl, ethyl, *tert*-butyl and methoxy groups, and they showed somewhat higher efficiency and all have good yields. A similar trend was observed in the case of the substituent at the congested ortho position. However, to our surprise, the desired product could not be obtained when the methoxy group at ortho position. This may be

influenced by the steric hindrance effect. Because there are two different reaction sites, two regioisomers should be obtained from the reaction of meta-substituted substrates with isocyanide. However, what is surprising is that the the desired regioisomers of the products was not obtained when bromo, methyl groups attached the aromatic ring at the meta position. The reaction occurred exclusively at the sterically more accessible position, irrespective of electronic nature of the substituent (**3r**, **3s**). Naphthalene was also applicable to this reaction and provided the only product **3t** in 62% yield may be due to the larger steric hindrance effect at 1-position of the naphthalene ring. Moreover, heteroarene such as thiophene-fused iminoisoindolinone was also formed in acceptable yields.

Based on above result and related literature¹⁵, a proposed mechanism for the reaction of **1a** with **2a** is illustrated in **Scheme 2**. Ag_2CO_3 may oxidize the Co^{II} catalyst to the Co^{III} species, which reacts with benzamide (**1a**) to give the Co^{III} intermediate **A**. Subsequent ortho C-H activation produce the intermediate **B** followed by the insertion of the isocyanide to the C-Co bond to afford the cobalt(III) species **C**. Reductive elimination of the species **C** leads to the desired product **3a** and generating the Co^{I} catalyst. The latter was oxidized to Co^{III} species by Ag_2CO_3 again, thus completing the catalytic cycle.

Scheme 2 A plausible mechanism for the cobalt-catalyzed oxidative isocyanide insertion with aminoquinoline benzamides

In conclusion, we have developed an efficient cobalt(II)-catalyzed direct oxidative isocyanide insertion through an $\text{sp}^2\text{C-H}$ bond functionalization process. In this reaction, the ability to use isocyanides as C1 source inserting into C-H/N-H provides a convenient and alternative route for preparation of iminoisoindolinones in good yields. More transformations incorporating oxidative isocyanide insertion for the synthesis of bioactive heterocycles are currently in progress in our laboratory.

Experimental section

Synthesis and Characterization for Iminoisoindolinones via Cobalt-Catalyzed Oxidative Isocyanide Insertion

A mixture of benzamide **1** (0.25 mmol) and $\text{Co}(\text{acac})_2$ (0.2 equiv.) was added into a sealed tube under the N_2 atmosphere. Subsequently PhCl (2 mL), Ag_2CO_3 (3.0 equiv.) and isocyanide **2** (0.5 mmol) was added. Then, the sealed tube was heated at 120°C for 24 hours. After completion of reaction as indicated by TLC, the mixture was concentrated and directly purified by flash column chromatography (EtOAc /petroleum ether, 1:2) to give the desired product **3**.

(E)-3-(tert-butylimino)-2-(quinolin-8-yl)isoindolin-1-one (**3a**)

White solid; (69.2 mg, 84%); ^1H NMR (400 MHz, CDCl_3) δ 8.85 (dd, $J = 1.6, 4.0$ Hz, 1H), 8.19 (dd, $J = 1.6, 8.4$ Hz, 1H), 8.10 (d, $J = 7.6$ Hz, 1H), 8.04 (d, $J = 6.8$ Hz, 1H), 7.87 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.61-7.73 (m, 4H), 7.37 (dd, $J = 4.0, 8.0$ Hz, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.6, 150.2, 147.6, 144.9, 136.1, 134.2, 133.1, 132.3, 131.2, 131.1, 129.7, 129.0, 128.4, 127.2, 125.9, 123.9, 121.2, 53.8, 30.6.

(E)-3-((2,6-dimethylphenyl)imino)-2-(quinolin-8-yl)isoindolin-1-one (**3b**)

Black solid; (46.2 mg, 49%); ^1H NMR (400 MHz, CDCl_3) δ 8.91 (dd, $J = 1.2, 4.0$ Hz, 1H), 8.25 (dd, $J = 1.2, 8.4$ Hz, 1H), 8.00 (dd, $J = 7.6, 14$ Hz, 2H), 7.95 (d, $J = 7.2$ Hz, 1H), 7.76 (t, $J = 7.6$ Hz, 1H), 7.64 (t, $J = 7.2$ Hz, 1H), 7.42-7.48 (m, 2H), 7.06 (t, $J = 7.0$ Hz, 2H), 6.99 (t, $J = 7.2$ Hz, 1H), 6.68 (d, $J = 7.6$ Hz, 1H), 2.09 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.0, 152.5, 150.8, 146.2, 144.9, 136.3, 133.6, 132.3, 132.2, 132.0, 131.0, 130.6, 129.6, 129.5, 128.3, 128.0, 127.1, 126.6, 126.3, 124.4, 123.9, 123.6, 121.8, 18.2, 18.1.

(E)-3-(tert-butylimino)-2-(quinolin-8-yl)-5-(trifluoromethyl)isoindolin-1-one (**3c**)

White solid; (71.5 mg, 72%); ^1H NMR (400 MHz, CDCl_3) δ 8.84 (dd, $J = 1.6, 4.0$ Hz, 1H), 8.37 (s, 1H), 8.18-8.23 (m, 2H), 7.98 (d, $J = 8.0$ Hz, 1H), 7.92 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.74 (dd, $J = 1.6, 7.2$ Hz, 1H), 7.67 (t, $J = 8.0$ Hz, 1H), 7.40 (dd, $J = 8.4, 4.4$ Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.5, 150.4, 144.7, 136.8, 136.1, 134.7, 134.4, 134.1, 133.78, 132.8, 131.1, 129.1, 128.8, 128.3, 128.2, 125.9, 125.0, 124.4, 123.8, 122.3, 121.4, 119.6, 54.1, 30.7; ^{19}F NMR (CDCl_3 , 471 MHz): δ -62.47.

(E)-3-(tert-butylimino)-1-oxo-2-(quinolin-8-yl)isoindoline-5-carbonitrile (**3d**)

Yellow solid; (62.0 mg, 70%); ^1H NMR (400 MHz, CDCl_3) δ 8.83 (dd, $J = 1.6, 4.0$ Hz, 1H), 8.38 (s, 1H), 8.23 (dd, $J = 1.6, 8.0$ Hz, 1H), 8.16 (d, $J = 8.0$ Hz, 1H), 7.99 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.93 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.65-7.74 (m, 2H), 7.42 (dd, $J = 4.0, 8.0$ Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.0, 150.4, 144.8, 144.6, 137.1, 136.2, 134.8, 132.6, 131.1, 130.3, 129.1, 128.9, 125.9, 124.6, 121.5, 118.1, 116.0, 54.3, 30.8.

(E)-3-(tert-butylimino)-5-fluoro-2-(quinolin-8-yl)isoindolin-1-one (**3e**)

White solid; (62.5 mg, 72%); ^1H NMR (400 MHz, CDCl_3) δ 8.85 (dd, $J = 1.6, 4.0$ Hz, 1H), 8.21 (dd, $J = 1.6, 8.4$ Hz, 1H), 8.05 (dd, $J = 5.2, 8.4$ Hz, 1H), 7.90 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.80 (dd, $J = 2.0, 9.2$ Hz, 1H), 7.72 (dd, $J = 1.2, 6.8$ Hz, 1H), 7.66 (t, $J = 7.8$ Hz, 1H), 7.36-7.42 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 165.2 (d, $^1J_{\text{CF}} = 250$ Hz), 150.3, 144.8, 136.1, 133.0, 131.2, 129.9, 129.1, 128.6, 125.9, 125.8, 121.3, 118.3 (d, $^2J_{\text{CF}} = 23$ Hz), 114.6 (d, $^2J_{\text{CF}} = 25$ Hz), 53.9, 30.7.

(E)-3-(tert-butylimino)-5-chloro-2-(quinolin-8-yl)isoindolin-1-one (**3f**)

Yellow solid; (63.7 mg, 70%); ^1H NMR (400 MHz, CDCl_3) δ 8.85 (dd, $J = 1.6, 4.0$ Hz, 1H), 8.21 (dd, $J = 1.6, 8.4$ Hz, 1H), 8.08 (d, $J = 1.6$ Hz, 1H), 8.00 (d, $J = 8.0$ Hz, 1H), 7.91 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.64-7.73 (m, 3H), 7.40 (dd, $J = 4.0, 8.0$ Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 150.3, 145.9, 144.8, 138.7, 136.1, 133.0, 132.2, 131.3, 131.2, 129.0, 128.6, 127.2, 125.9, 125.0, 121.3, 54.0, 30.7;

(E)-5-bromo-3-(*tert*-butylimino)-2-(quinolin-8-yl)isoindolin-1-one (**3g**)

Yellow solid; (69.4 mg, 68%); ^1H NMR (400 MHz, CDCl_3) δ 8.84 (dd, $J = 1.6, 4.0$ Hz, 1H), 8.24 (d, $J = 1.6$ Hz, 1H), 8.21 (dd, $J = 1.6, 8.0$ Hz, 1H), 7.89-7.94 (m, 2H), 7.84 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.72 (dd, $J = 1.2, 7.2$ Hz, 1H), 7.66 (t, $J = 7.6$ Hz, 1H), 7.40 (dd, $J = 4.0, 8.4$ Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 150.3, 145.7, 144.8, 136.1, 134.2, 133.0, 131.2, 130.0, 129.0, 128.6, 127.0, 125.9, 125.2, 121.3, 54.0, 30.7.

(E)-3-(*tert*-butylimino)-5-iodo-2-(quinolin-8-yl)isoindolin-1-one (**3h**)

Yellow solid. (28.5 mg, 25%); ^1H NMR (400 MHz, CDCl_3) δ 8.84 (dd, $J = 1.6, 4.0$ Hz, 1H), 8.45 (s, 1H), 8.22 (dd, $J = 1.6, 8.4$ Hz, 1H), 8.05 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.91 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.71 (dd, $J = 1.2, 7.2$ Hz, 1H), 7.66 (t, $J = 7.6$ Hz, 1H), 7.41 (dd, $J = 4.0, 8.0$ Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.2, 150.3, 144.8, 140.1, 136.1, 135.9, 133.2, 132.9, 131.2, 129.0, 128.6, 125.9, 125.3, 121.3, 54.0, 30.7.

(E)-3-(*tert*-butylimino)-5-methyl-2-(quinolin-8-yl)isoindolin-1-one (**3i**)

Yellow solid; (69.5 mg, 81%); ^1H NMR (400 MHz, CDCl_3) δ 8.82 (dd, $J = 1.6, 4.0$ Hz, 1H), 8.16 (dd, $J = 1.6, 8.4$ Hz, 1H), 7.91 (d, $J = 9.6$ Hz, 1H), 7.84-7.87 (m, 2H), 7.69 (dd, $J = 5.88, 1.2, 7.2$ Hz, 1H), 7.62 (t, $J = 7.8$ Hz, 1H), 7.46 (d, $J = 7.6$ Hz, 1H), 7.35 (dd, $J = 4.0, 8.4$ Hz, 1H), 2.56 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.7, 150.2, 147.6, 145.0, 142.9, 136.0, 133.3, 131.8, 131.7, 131.2, 130.3, 129.0, 128.3, 127.8, 125.9, 123.7, 121.2, 53.7, 30.6, 22.4.

(E)-3-(*tert*-butylimino)-5-ethyl-2-(quinolin-8-yl)isoindolin-1-one (**3j**)

Yellow solid. (75.9 mg, 85%); ^1H NMR (400 MHz, CDCl_3) δ 8.86 (dd, $J = 1.2, 4.0$ Hz, 1H), 8.19 (d, $J = 8.4$ Hz, 1H), 7.96 (t, $J = 8.8$ Hz, 2H), 7.88 (d, $J = 8.0$ Hz, 1H), 7.72 (dd, $J = 1.2, 7.2$ Hz, 1H), 7.65 (t, $J = 7.8$ Hz, 1H), 7.52 (d, $J = 7.6$ Hz, 1H), 7.38 (dd, $J = 4.0, 8.4$ Hz, 1H), 2.88 (q, $J = 7.6$ Hz, 2H), 1.37 (s, 9H), 1.37 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 167.7, 150.2, 149.3, 147.8, 145.0, 136.0, 133.3, 131.9, 131.2, 130.8, 129.0, 128.3, 126.8, 125.9, 123.8, 121.2, 53.7, 30.6, 29.7, 15.8. HRMS calcd for $\text{C}_{23}\text{H}_{24}\text{N}_3\text{O}^+$ ($\text{M} + \text{H}^+$): 358.1914; Found: 358.1910.

(E)-5-(*tert*-butyl)-3-(*tert*-butylimino)-2-(quinolin-8-yl)isoindolin-1-one (**3k**)

Yellow solid; (75.2 mg, 78%); ^1H NMR (400 MHz, CDCl_3) δ 8.86 (dd, $J = 1.6, 4.0$ Hz, 1H), 8.18-8.21 (m, 2H), 7.99 (d, $J = 8.0$ Hz, 1H), 7.88 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.71-7.74 (m, 2H), 7.65 (t, $J = 7.6$ Hz, 1H), 7.39 (dd, $J = 4.0, 8.4$ Hz, 1H), 1.46 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.7, 156.1, 150.2, 145.0, 136.0, 133.3, 131.6, 131.2, 129.0, 128.3, 128.2, 127.4, 125.9, 124.6, 123.5, 121.2, 116.4, 53.6, 35.7, 31.4, 30.6.

(E)-3-(*tert*-butylimino)-5-methoxy-2-(quinolin-8-yl)isoindolin-1-one (**3l**)

Yellow solid; (65.6 mg, 73%); ^1H NMR (400 MHz, CDCl_3) δ 8.82 (dd, $J = 1.6, 4.4$ Hz, 1H), 8.17 (dd, $J = 1.6, 8.0$ Hz, 1H),

7.95 (d, $J = 8.0$ Hz, 1H), 7.85 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.69 (dd, $J = 1.2, 7.2$ Hz, 1H), 7.58-7.64 (m, 2H), 7.36 (dd, $J = 4.0, 8.0$ Hz, 1H), 7.14 (dd, $J = 2.4, 8.4$ Hz, 1H), 3.94 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.6, 163.1, 150.2, 147.1, 145.0, 136.0, 133.4, 131.3, 129.0, 128.3, 126.5, 125.9, 125.3, 121.2, 115.7, 113.8, 56.0, 53.6, 30.6.

(E)-3-(*tert*-butylimino)-7-fluoro-2-(quinolin-8-yl)isoindolin-1-one (**3m**)

Yellow solid; (43.4 mg, 50%); ^1H NMR (400 MHz, CDCl_3) δ 8.84 (dd, $J = 1.6, 4.0$ Hz, 1H), 8.19 (dd, $J = 1.6, 8.4$ Hz, 1H), 7.87-7.91 (m, 2H), 7.69-7.74 (m, 2H), 7.63 (t, $J = 7.8$ Hz, 1H), 7.38 (dd, $J = 4.4, 8.4$ Hz, 1H), 7.33 (t, $J = 8.6$ Hz, 1H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.6, 158.6 (d, $^1J_{\text{CF}} = 262$ Hz), 150.3, 145.9, 144.9, 136.1, 134.3 (d, $^3J_{\text{CF}} = 8$ Hz), 132.9, 131.3, 129.0, 128.6, 123.1, 121.3, 119.2 (d, $^2J_{\text{CF}} = 19$ Hz), 53.9, 30.5.

(E)-3-(*tert*-butylimino)-7-chloro-2-(quinolin-8-yl)isoindolin-1-one (**3n**)

Yellow solid; (47.3 mg, 52%); ^1H NMR (400 MHz, CDCl_3) δ 8.86 (dd, $J = 1.6, 4.0$ Hz, 1H), 8.21 (dd, $J = 1.6, 8.4$ Hz, 1H), 8.13 (d, $J = 7.6$ Hz, 1H), 8.07 (d, $J = 6.8$ Hz, 1H), 7.90 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.64-7.77 (m, 4H), 7.39 (dd, $J = 4.0, 8.4$ Hz, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.6, 150.2, 147.6, 144.9, 136.1, 134.2, 133.1, 132.3, 131.2, 131.1, 129.0, 128.4, 127.2, 125.9, 123.9, 121.2, 53.8, 30.6; HRMS calcd for $\text{C}_{21}\text{H}_{19}\text{ClN}_3\text{O}^+$ ($\text{M} + \text{H}^+$): 364.1211; Found: 364.1201.

(E)-3-(*tert*-butylimino)-7-methyl-2-(quinolin-8-yl)isoindolin-1-one (**3o**)

Yellow solid; (64.4 mg, 75%); ^1H NMR (400 MHz, CDCl_3) δ 8.88 (d, $J = 4.0$ Hz, 1H), 8.20 (d, $J = 8.4$ Hz, 1H), 7.97 (d, $J = 7.6$ Hz, 1H), 7.88 (d, $J = 8.0$ Hz, 1H), 7.72 (d, $J = 7.2$ Hz, 1H), 7.66 (t, $J = 7.6$ Hz, 1H), 7.59 (t, $J = 7.8$ Hz, 1H), 7.43 (d, $J = 7.6$ Hz, 1H), 7.39 (dd, $J = 4.0, 8.4$ Hz, 1H), 2.82 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.5, 150.3, 147.3, 145.1, 138.3, 136.1, 133.6, 133.4, 131.8, 131.3, 130.7, 129.0, 128.3, 125.9, 124.9, 121.2, 53.6, 30.6, 18.2.

(E)-3-(*tert*-butylimino)-4,6-dimethyl-2-(quinolin-8-yl)isoindolin-1-one (**3p**)

Yellow solid; (51.8 mg, 58%); ^1H NMR (400 MHz, CDCl_3) δ 8.87 (dd, $J = 1.6, 4.0$ Hz, 1H), 8.21 (dd, $J = 1.6, 6.8$ Hz, 1H), 7.95 (dd, $J = 1.2, 8.4$ Hz, 1H), 7.83 (dd, $J = 1.2, 7.6$ Hz, 1H), 7.69 (t, $J = 7.6$ Hz, 1H), 7.57 (s, 1H), 7.42 (dd, $J = 3.6, 8.0$ Hz, 1H), 7.30 (d, $J = 6.0$ Hz, 2H), 2.74 (s, 3H), 2.47 (s, 3H), 0.82 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.8, 151.1, 148.2, 146.0, 141.3, 140.1, 137.3, 136.7, 136.4, 136.2, 136.1, 133.2, 132.1, 130.5, 129.2, 125.9, 121.8, 121.1, 54.9, 31.5, 21.5, 19.8. HRMS calcd for $\text{C}_{23}\text{H}_{24}\text{N}_3\text{O}^+$ ($\text{M} + \text{H}^+$): 358.1914; Found: 358.1909.

(E)-3-(*tert*-butylimino)-6-fluoro-2-(quinolin-8-yl)isoindolin-1-one (**3qa**)

Yellow solid; (33.0 mg, 38%); ^1H NMR (400 MHz, CDCl_3) δ 8.85 (d, $J = 4.0$ Hz, 1H), 8.20 (d, $J = 8.0$ Hz, 1H), 8.11 (dd, $J = 4.4$ Hz, 8.4, 1H), 7.89 (d, $J = 8.0$ Hz, 1H), 7.71-7.74 (m, 2H), 7.65 (t, $J = 7.8$ Hz, 1H), 7.38-7.40 (m, 2H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.4, 164.2 (d, $^1J_{\text{CF}} = 253$ Hz), 150.3, 146.5, 144.8, 137.0 (d, $^3J_{\text{CF}} = 8$ Hz), 136.1, 132.8, 131.1, 129.2 (d, $^3J_{\text{CF}} = 8$ Hz), 129.0, 128.6, 125.9, 125.7, 121.3, 119.4 (d, $^2J_{\text{CF}} = 23$ Hz), 110.9 (d, $^2J_{\text{CF}} = 23$ Hz), 53.8, 30.6.

(E)-3-(*tert*-butylimino)-4-fluoro-2-(quinolin-8-yl)isoindolin-1-one (**3qb**)

Yellow solid; (29.5 mg, 34%); ^1H NMR (400 MHz, CDCl_3) δ 8.86 (d, $J = 4.0$ Hz, 1H), 8.23 (d, $J = 8.4$ Hz, 1H), 7.93 (d, $J = 8.4$ Hz, 1H), 7.88 (d, $J = 7.6$ Hz, 1H), 7.66–7.75 (m, 3H), 7.40–7.45 (m, 2H), 1.16 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.2, 155.8 (d, $^1J_{\text{CF}} = 258$ Hz), 150.5, 145.0, 141.2, 136.1, 135.8, 133.7, 133.6, 131.3, 129.0, 128.7, 125.9, 121.7 (d, $^2J_{\text{CF}} = 25$ Hz), 121.4, 119.9 (d, $^3J_{\text{CF}} = 4$ Hz), 54.8, 31.2.

(E)-6-bromo-3-(tert-butylimino)-2-(quinolin-8-yl)isoindolin-1-one (3r)

Yellow solid; (75.5 mg, 74%); ^1H NMR (400 MHz, CDCl_3) δ 8.84 (dd, $J = 1.6, 2.4$ Hz, 1H), 8.19–8.21 (m, 2H), 7.98 (d, $J = 8.4$ Hz, 1H), 7.85–9.91 (m, 2H), 7.72 (dd, $J = 1.6, 6.0$ Hz, 1H), 7.65 (t, $J = 7.8$ Hz, 1H), 7.40 (dd, $J = 4.0, 8.4$ Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.3, 150.3, 146.6, 144.7, 136.1, 135.9, 135.2, 132.8, 131.1, 129.0, 128.6, 128.5, 127.1, 125.9, 125.8, 121.3, 53.9, 30.6

(E)-3-(tert-butylimino)-6-methyl-2-(quinolin-8-yl)isoindolin-1-one (3s)

Yellow solid; (73.8 mg, 86%); ^1H NMR (400 MHz, CDCl_3) δ 8.85 (dd, $J = 1.6, 4.0$ Hz, 1H), 8.20 (d, $J = 8.4$ Hz, 1H), 8.00 (d, $J = 8.0$ Hz, 1H), 7.88 (d, $J = 6.8$ Hz, 2H), 7.72 (dd, $J = 1.6, 7.2$ Hz, 1H), 7.65 (t, $J = 7.2$ Hz, 1H), 7.54 (d, $J = 7.6$ Hz, 1H), 7.38 (dd, $J = 4.0, 8.0$ Hz, 1H), 2.55 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.7, 150.2, 147.9, 145.0, 141.8, 136.0, 134.5, 133.2, 133.0, 131.2, 129.0, 128.3, 127.2, 125.9, 124.3, 121.2, 53.6, 30.5, 21.6.

(E)-3-(tert-butylimino)-2-(quinolin-8-yl)-2,3-dihydro-1H-benzo[f]isoindol-1-one (3t)

Yellow solid; (58.8 mg, 62%); ^1H NMR (400 MHz, CDCl_3) δ 8.86 (dd, $J = 1.6, 4.0$ Hz, 1H), 8.57 (d, $J = 4.4$ Hz, 2H), 8.19 (dd, $J = 2.0, 8.4$ Hz, 1H), 8.07–8.11 (m, 2H), 7.89 (dd, $J = 1.2, 8.4$ Hz, 1H), 7.80 (dd, $J = 1.2, 7.2$ Hz, 1H), 7.66–7.70 (m, 3H), 7.38 (dd, $J = 4.0, 8.0$ Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.4, 150.2, 147.4, 144.8, 136.1, 135.1, 133.8, 133.3, 131.1, 130.8, 129.9, 129.5, 129.1, 128.5, 128.4, 128.4, 128.3, 126.0, 125.9, 124.3, 121.3, 53.6, 30.4.

(E)-4-(tert-butylimino)-5-(quinolin-7-yl)-4,5-dihydro-6H-thieno[2,3-c]pyrrol-6-one (3u)

Yellow liquid; (25.2 mg, 30%); ^1H NMR (400 MHz, CDCl_3) δ 8.89 (dd, $J = 1.6, 4.0$ Hz, 1H), 8.21 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.90 (dd, $J = 1.2, 6.8$ Hz, 1H), 7.76 (d, $J = 4.8$ Hz, 1H), 7.72 (dd, $J = 1.2, 9.2$ Hz, 1H), 7.66 (t, $J = 7.6$ Hz, 1H), 7.53 (d, $J = 5.2$ Hz, 1H), 7.42 (dd, $J = 4.0, 8.4$ Hz, 1H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.6, 150.3, 145.9, 145.1, 141.5, 139.8, 136.1, 134.6, 132.7, 131.4, 129.1, 128.4, 125.9, 125.2, 121.3, 54.2, 30.5.

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References and notes

- For reviews, see: (a) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210. (b) Zhu, J. P.; *Eur. J. Org. Chem.* **2003**, 1133–1144. (c) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899–907. (d) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. (e) El Kaim, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153–2171. (f) Sadjadi, S.; Heravi, M. M. *Tetrahedron* **2011**, *67*, 2707–2752. (g) van Berkel, S. S.; Bogels, B. G. M.; Wijdeven, M. A.; Westermann, B.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2012**, 3543–3559.
- (a) Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235–5331. (b) Fayol, A.; Zhu, J.; *Angew. Chem., Int. Ed.* **2002**, *41*, 3633–3635. (c) Bonne, D.; Dekhane, M.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2485–2488. (e) Yue, T.; Wang, M.; Wang, D.; Masson, G.; Zhu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6717–6721. (f) Buyck, T.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12714–12718.
- Recent reviews, see: (a) Zhang, B.; Studer, A. *Chem. Soc. Rev.* **2015**, *44*, 3505–3521. (b) Lygin, A. V. Meijere, A. D. *Angew. Chem. Int. Ed.* **2010**, *49*, 9094–9124. (c) Sharma, U. K.; Sharma, N.; Vachhani, D. D.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2015**, *44*, 1836–1860.
- Recent reviews for the isocyanide insertion: (a) Qiu, G.; Ding, Q.; Wu, J. *Chem. Soc. Rev.* **2013**, *42*, 5257–5269. (b) Vlaar, T.; Maes, B. U. W.; Ruijter, E.; Orru, R. V. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 7084–7097. (c) Lang, S.; *Chem. Soc. Rev.* **2013**, *42*, 4867–4880. (d) Lauzon, J. M. P.; Schafer, L. L. *Dalton Trans.* **2012**, *41*, 11539–11550.
- (a) Saluste, C.; Whitby, R.; Furber, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4156–4158. (c) Baelen, G.; Kuijter, S.; Rýček, L.; Sergeyev, S.; Janssen, E.; de Kanter, F.; Maes, B.; Ruijter, E.; Orru, R. *Chem.-Eur. J.* **2011**, *17*, 15039–15044. (d) Jiang, H.; Liu, B.; Li, Y.; Wang, A.; Huang, H. *Org. Lett.* **2011**, *13*, 1028–1031.
- (a) Wang, Y.; Wang, H.; Peng, J.; Zhu, Q. *Org. Lett.* **2011**, *13*, 4604–4607. (b) Vlaar, T.; Cioc, R. C.; Mampuy, P.; Maes, B. U. W.; Orru, R. V. A.; Ruijter, E. *Angew. Chem. Int. Ed.* **2012**, *51*, 13058–13061. (c) Xu, S.; Huang, X.; Hong, X.; Xu, B. *Org. Lett.* **2012**, *14*, 4614–4617. (d) Jones, W.; Kosar, W. *J. Am. Chem. Soc.* **1986**, *108*, 5640–5641. (e) Fukumoto, Y.; Hagihara, M.; Kinashi, F.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 10014–10017.
- (a) Takamatsu, K.; Hirano, K.; Miura, M. *Org. Lett.* **2015**, *17*, 4066–4069. (b) Zhu, T.; Wang, S.; Tao, Y.; Wei, T.; Ji, S. *Org. Lett.* **2014**, *16*, 1260–1263.
- (a) Cai, X.; Xie, B. *Curr. Org. Chem.* **2015**, *19*, 121–150. (b) Hyster, T. K. *Catal. Lett.* **2015**, *145*, 458–467. (c) Tilly, D.; Dayaker, G.; Bachu, P. *Catal. Sci. Technol.* **2014**, *4*, 2756–2777. (d) Yoshikai, N. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 843–857. (f) Gao, K.; Yoshikai, N. *Acc. Chem. Res.* **2014**, *47*, 1208–1219. (g) Ackermann, L. *J. Org. Chem.* **2014**, *79*, 8948–8954. (h) Yoshikai, N. *Synlett* **2011**, *2011*, 1047–1051. (i) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087–4109.
- For selected recent examples, see: (a) Zhao, D.; Kim, J. H.; Stegemann, L.; Strassert, C. A.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 4508–4511. (b) Hummel, J. R.; Ellman, J. A. *J. Am. Chem. Soc.* **2015**, *137*, 490–498. (c) Fallon, B. J.; Derat, E.; Amatore, M.; Aubert, C.; Chemla, F.; Ferreira, F.; Perez-Luna, A.; Petit, M. *J. Am. Chem. Soc.* **2015**, *137*, 2448–2451. (d) Li, J.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 3635–3638. (e) Grigorjeva, L.; Daugulis, O. *Angew. Chem., Int. Ed.* **2014**, *53*, 10209–10212. (f) Yu, D.; Gensch, T.; de Azambuja, F.; VasquezCéspedes, S.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17722–17725. (g) Ikemoto, H.; Yoshino, T.; Sakata, K.; Matsunaga, S.; Kanai, M. *J. Am. Chem. Soc.* **2014**, *136*, 5424–5431. (h) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 9279–9282. (i) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2207–2211. (j) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 775–779. (k) Song, W.; Ackermann, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 8251–8254. (l) Chen, Q.; Ilies, L.; Nakamura, E.-I. *J. Am. Chem. Soc.* **2011**, *133*, 428–429. (m) Li, B.; Wu, Z.; Gu, Y.; Sun, C.; Wang, B.; Shi, Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 1109–1113. (n) Gao, K.; Lee, P. S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249–12251. For the first example of cobalt-catalyzed C–H functionalization, see: (o) Murahashi, S. *J. Am. Chem. Soc.* **1955**, *77*, 6403–6404.
- (a) Zhang, L.; Hao, X.; Zhang, S.; Liu, Z.; Zheng, X.; Gong, J.; Niu, J.; Song, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 272–275. (b) Wu, X.; Yang, K.; Zhao, Y.; Sun, H.; Li, G.; Ge, H. *Nat. Commun.* **2015**, *6*, 6462. (c) Sun, B.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Chem. Commun.* **2015**, *51*, 4659–4661. (d) Patel, P.; Chang, S. *ACS Catal.* **2015**, *5*, 853–858. (e) Lu, H.; Li, C.; Jiang, H.; Lizardi, C.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 7028–7032. (f) Jin, L.; Lu, H.; Cui, Y.; Lizardi, C. L.; Arzua, T. N.; Wojtas, L.; Cui, X.; Zhang, X. P. *Chem. Sci.* **2014**, *5*, 2422–2427. (g) Zardi, P.; Intrieri, D.; Caselli, A.; Gallo, E. *J. Organomet. Chem.* **2012**, *716*, 269–274. (h) Kim, J.; Cho, S.; Joseph, J.; Chang, S. *Angew. Chem., Int. Ed.* **2010**,

- 49, 9899-9903. (i) Lu, H.; Jiang, H.; Wojtas, L.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2010**, *49*, 10192-10196. (j) Cenini, S.; Gallo, E.; Penoni, A.; Ragaini, F.; Tollari, S. *Chem. Commun.* **2000**, 2265-2267.
11. Grigorjeva, L.; Daugulis, O. *Angew. Chem., Int. Ed.* **2014**, *53*, 10209-10212.
12. W.Y. Hao, J. Tian, W. Li, R. Y. Shi, Z. L. Huang, A.W. Lei, *Chem.Asian J.* **2016**, *11*, 1664-1667.
13. (a) T.-H. Zhu, S.-Y. Wang, G.-N. Wang, *Chem.-Eur. J.* **2013**, *19*, 5850-5853. (b) T.-H. Zhu, S.-Y. Wang, T.-Q. Wei, S.-J. Ji, *Adv. Synth. Catal.* **2015**, *357*, 823-828; (c) T.-H. Zhu, X.-P. Xu, J. -J. Cao, T.-Q. Wei, S.-Y. Wang, S.-J. Ji, *Adv. Synth. Catal.* **2014**, *356*, 509-518.
14. (a) Hao, W. Y.; Jiang, Y. Y.; Cai, M. Z. *J. Org. Chem.*, **2014**, *79*, 3634-3640. (b) Hao, W. Y.; Zeng, J. B.; Cai, M. Z. *Chem. Commun.*, **2014**, *50*, 11686-11689. (c) Hao, W. Y.; Huang, J.; Jie, S.; Cai, M. Z. *Eur. J. Org. Chem.* **2015**, 6655.
15. (a) Zhang, J.; Chen, H.; Lin, C.; Liu, Z.; Wang, C.; Zhang, Y. *J. Am. Chem. Soc.* **2015**, *137*, 12990-12996. (b) Ma, W.; Ackermann, L. *ACS Catal.* **2015**, *5*, 2822-2825. (c) Zhang, L.; Hao, X.; Liu, Z.; Zheng, X.; Zhang, S.; Niu, J.; Song, M.; *Angew.Chem. Int. Ed.* **2015**, *54*, 10012-10015.

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