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Cp*Co(III)-Catalyzed C–H/N–N Functionalization of Arylhydrazones for the Synthesis of Isoquinolines

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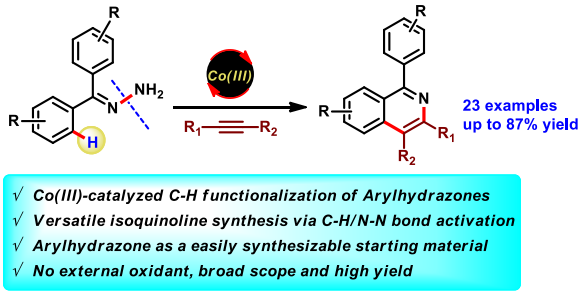
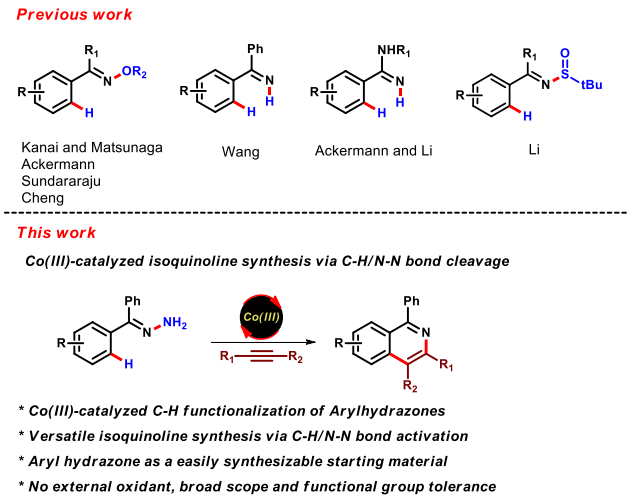


ABSTRACT: Cationic Co(III)-catalyzed C−H/N−N bond functionalization of arylhydrazones with internal alkynes has been developed for the synthesis of isoquinoline derivatives. The arylhydrazones are easy to prepare and require inexpensive and commercially available hydrazine hydrate. The reaction works well with a variety of internal alkynes and arylhydrazones and offers broad scope, good functional group tolerance and high yields under redox-neutral conditions in presence of air.

Isoquinoline represent one of the ubiquitous structural motif found in various natural products and pharmaceutical compounds.[1] In addition, isoquinoline derivatives play an important role in asymmetric catalysis and photochemistry; where they can be used as ligands.[2] Traditional methods to synthesize isoquinoline such as Bischer-Napieralski, Pictet-Spengler and Pomeranz-Fritsch often suffers from a few drawbacks such as low yields, narrow substrate scope and harsh reaction conditions. In recent years, C−H activation reactions[3] has provided an alternate route to access

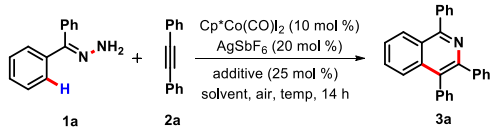
isoquinoline scaffolds with large diversity in a concise manner.[4] Although, these methods provide straightforward access to isoquinolines; they often require the use of precious transition metals such as Pd, Rh or Ru. In the recent years, a lot of research has been focused on the utilization of first row transition metals in the area of C−H functionalization.[5] Due to their low toxicity, high natural abundance and inexpensive nature, first row transition metals are now preferred over precious metals like Pd, Rh, Ru or Ir. In this context, Kanai and Matsunaga has done pioneering work in the development of Cp*Co(III) catalysis for C−H activation.[6,7] Since then, several other groups across the globe have extensively put their efforts for further development in this area,[8] including our group.[9] Recently, several Co(III)-catalyzed isoquinoline synthesis have been reported employing different directing groups and coupling partners (Scheme 1). In his context, Kanai and Matsunaga, Ackermann, Sundararaju and Cheng independently reported Co(III)-catalyzed C−H/N−O bond functionalization of oximes with alkynes for the synthesis of isoquiolines.[10] On the other hand, Wang et. al reported Cp*Co(III)-catalyzed oxidative annulation of N−H imines with alkynes in the presence of external oxidant to provide isoquinolines.[11] Ackermann and Li reported an elegant C−H/N−H bond functionalization of amidines with diazo compounds to furnish isoquinolines.[12] Very recently, Li and co-workers reported C−H/N−S bond functionalization of *N*-sulfinyl imines with alkynes to prepare isoquinolines.[13]

Scheme 1. Cp*Co(III)-Catalyzed Synthesis of Isoquinolines



To the best of our knowledge, Co(III)-catalyzed isoquinoline synthesis via C−H/N−N bond functionalization of hydrazones using N−N as an internal oxidant has not been realized.[14] In continuation of our interest in Cp*Co(III) catalysis,[9] herein, we report Cp*Co(III)-catalyzed C−H/N−N bond functionalization arylhydrazones with internal alkynes for the synthesis of highly substituted isoquinolines (Scheme 1). The major advantage of the present protocol is the use of arylhydrazones as inexpensive starting materials, which are synthesized from benzophenones and hydrazine hydrate, reagents those are commercially available and cost-effective.

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

entry	additive	solvent	temp (°C)	yield (%)[b]
1	-	TFE	120	30
2	NaOAc	TFE	120	58
3	KOAc	TFE	120	50
4	CsOAc	TFE	120	56
5	AcOH	TFE	120	70
6	$PhCO_2H$	TFE	120	72
7	**PivOH**	**TFE**	**120**	**95**
8	PivOH	TFE	120	77
9	PivOH	MeOH	120	n.d.
10	PivOH	^{t}AmOH	120	n.d.
11	PivOH	1,2-DCE	120	n.d.
12	PivOH	DMSO	120	n.d.
13	PivOH	TFE	80	62

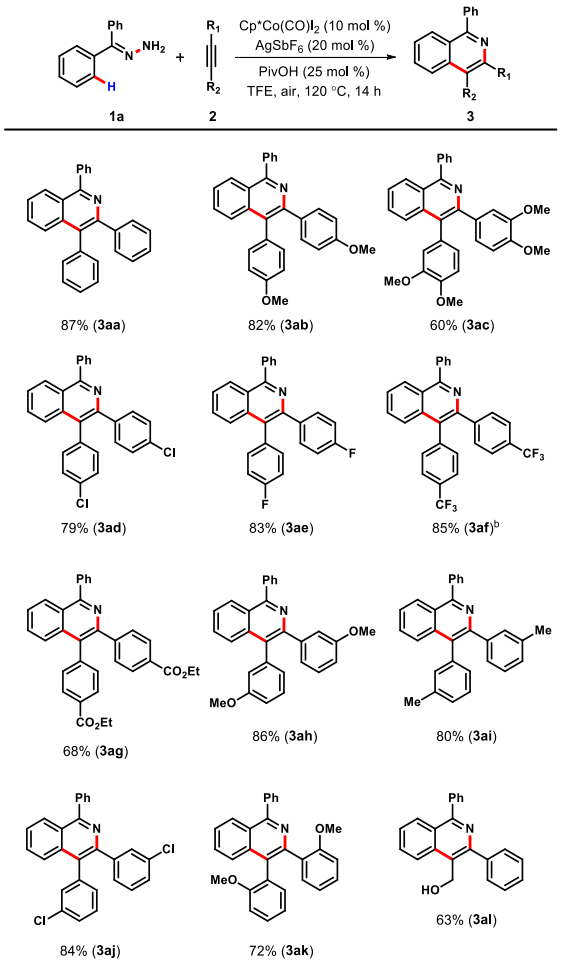
[a]Reaction conditions: **1a** (0.13 mmol), **2a** (0.10 mmol), Cp*Co(CO)I_2 (10 mol %), $AgSbF_6$ (20 mol %), additive (25 mol %) in solvent (0.8 mL) for 14 h. [b]Yields are based on crude ^{1}H NMR (internal standard: 1,1,2,2 tetrachloroethane) and calculated with respect to **2a**, n.d. = not detected. TFE = 2,2,2-Trifluoroethanol.

We commenced our investigation of Co(III)-catalyzed isoquinoline synthesis using benzophenone hydrazone **1a** as a starting substrate and diphenylacetylene **2a** as a coupling partner (Table 1). When benzophenone hydrazone **1a** was treated with diphenylacetylene **2a** in the presence of Cp*Co(CO)I_2 (10 mol %) and $AgSbF_6$ (20 mol %) in TFE at 120 °C for 14 h; it furnished desired isoquinoline **3aa** in low yield (Table 1, entry 1). Gratifyingly, introduction of acetate additives such as NaOAc, KOAc and CsOAc was found to promote the reaction (Table 1, entries 2-4). More pleasingly, when acid additives were tested (Table 1, entries 5-7), it was found that addition of pivalic acid furnished the

required isoquinoline in almost quantitative yield (Table 1, entry 7). When the reaction was performed under inert atmosphere, the yield of the product dropped to 77% (Table 1, entry 8). Surprisingly, the reaction did not work at all in other solvents like MeOH, ^{t}AmOH, 1,2-DCE and DMSO (Table 1, entries 9-12). The lowering of the reaction temperature resulted in the diminished yield of the product (Table 1, entry 13).

After having the optimized condition in hand, we investigated the scope and generality of the reaction using different internal alkynes (Scheme 2). It was found that diarylalkyne having electron donating functional group on the aromatic ring furnished the corresponding isoquinoline in good yield (**3ab**). Intriguingly, disubstituted alkyne also participated in the annulation reaction producing the corresponding product in moderate yield (**3ac**).

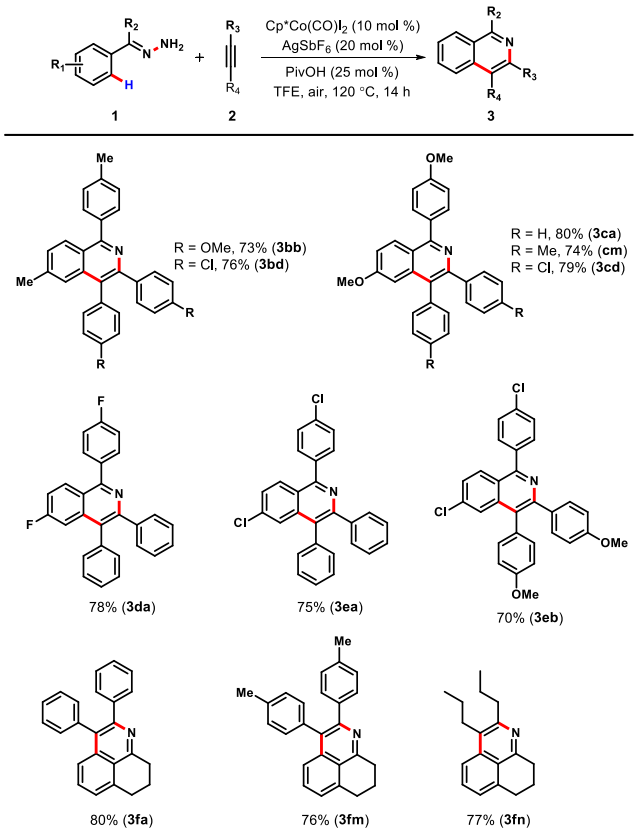
Scheme 2. Scope of Alkyne



[a]Reaction conditions: **1** (0.26 mmol), **2** (0.20 mmol), Cp*Co(CO)I_2 (10 mol %), $AgSbF_6$ (20 mol %), PivOH (25 mol %) in TFE (1.5 mL) for 14 h; isolated yields are given. [b] Run for 20 h.

The alkynes bearing electron-withdrawing groups such as Cl, F, CF_3 and ester on the aromatic ring also furnished the corresponding isoquinolines in good to excellent yields (**3ad**–**3ag**). When meta-substituted diarylalkynes were employed, it also delivered the products in high yields (**3ah**–**3aj**). The sterically hindered *o*-substituted diarylalkyne was also found to be compatible under present reaction conditions (**3ak**). The unsymmetrical alkyne, 3-phenylprop-2-yn-1-ol (**2l**) which possess free hydroxyl group also tolerated to furnish corresponding product in moderate yield (**3al**); thus demonstrating the functional group tolerance. The structure of **3al** was confirmed by comparing its ^{1}H and ^{13}C NMR spectrum with the known compound.[15] The exact reason for this selectivity is unclear, however it may be due to intramolecular coordination of phenyl group of 3-phenylprop-2-yn-1-ol (**2l**) with cobalt metal in intermediate **C** (see Scheme 5) in order to stabilize it.[16,17] The terminal alkyne such as phenylacetylene was turned out to be an ineffective coupling partner under the present reaction conditions.

Scheme 3. Scope of Arylhydrazones[a]

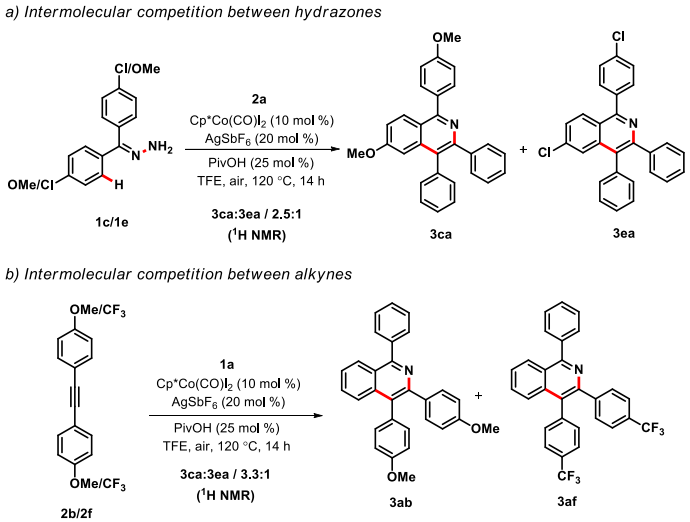


[a]Reaction conditions: **1** (0.26 mmol), **2** (0.20 mmol), Cp*Co(CO)I_2 (10 mol %), $AgSbF_6$ (20 mol %), PivOH (25 mol %) in TFE (1.5 mL) for 14 h; isolated yields are given.

After examining the scope of alkynes, scope of arylhydrazones for the synthesis of isoquinoline was tested (Scheme 3). We were delighted to see that, arylhydrazones having both electron-donating and electron-withdrawing groups such as Me, OMe, F and Cl reacted smoothly with various diarylalkynes to furnish the corresponding isoquinoline derivatives in good yields (**3bb**−**3eb**). The hydrazone derived from α-tetralone also reacted efficiently with diarylalkynes as well as with dialkylalkyne (4-octyne, **2n**) to generate tricyclic compounds in excellent yields (**3fa**−**3fn**).

To understand and gain insight the mechanism, some preliminary experiments were conducted (Scheme 4).[18] When intermolecular competitive experiment with differently functionalized hydrazones (**1c** and **1e**) was performed, it was observed that electron rich hydrazone reacts preferentially. This can be rationalized in terms of intramolecular electrophilic-substitution type C–H activation reaction via carboxylate assistance. Furthermore, intermolecular competitive experiment with differently functionalized alkynes revealed that electron rich alkyne to be more reactive.

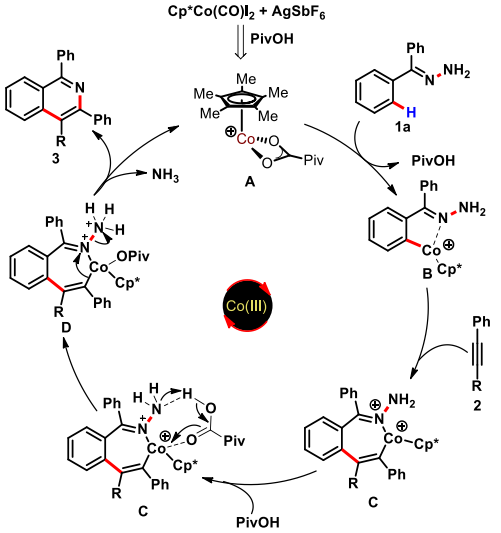
Scheme 4. Control Experiments



Based on the above control experiments and related Rh (III)[19] as well as cobalt(III)-catalyzed annulation reactions;[10-14] a plausible mechanism is proposed in as outlined Scheme 5. Initially Cp*Co(CO)I_2 react with $AgSbF_6$ in presence of PivOH to generate catalytically active complex **A**. Then complex **A** undergo cyclometalation with **1a** to generate the cobaltacycle **B**. This is followed by

migratory insertion of alkyne **2** into **B** to form seven membered cobaltacyclic intermediate **C**, which on pivalic acid-assisted proton transfer,[20] generates an intermediate **D**, which eventually undergo intramolecular substitution resulting in the formation C–N bond and the breakage of N–N bond in order to furnish isoquinoline **3** with concomitant regeneration of catalytically active Co(III) species **A**.

Scheme 5. Plausible Mechanism



In summary, we have developed Co(III)-catalyzed [4+2] annulation of arylhydrazones and internal alkynes via C–H/N–N bond functionalization. The reaction works with differently functionalized alkynes and hydrazones in good to excellent yield under redox-neutral conditions. The present protocol employs simple arylhydrazones as substrates which are easily synthesized from commercially available benzophenones and hydrazine hydrate thus making this reaction cost-effective.

EXPERIMENTAL SECTION

General Remarks

Unless otherwise stated, all commercial reagents and solvents were used without additional purification. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F_{254} plates. Visualization on TLC was achieved by the use of UV light (254 nm). Column chromatography was undertaken on silica gel (100–200 mesh) using a proper eluent system. NMR

spectra were recorded in chloroform-d at 300 or 400 MHz for ^{1}H NMR spectra and 75 MHz or 100 MHz for ^{13}C NMR spectra. Chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane. The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, dd = doublet of doublet, td = triplet of doublet, m = multiplet. Coupling constants, *J*, were reported in hertz unit (Hz). For ^{13}C NMR chemical shifts were reported in ppm referenced to the center of a triplet at 77.0 ppm of chloroform-*d*. HRMS were recorded using ESI-TOF techniques. Cp*Co(CO)I_2 was synthesized according to the literature.[7c] The arylhydrazones **1aa** were prepared according to literature procedure.[21]

General Procedure for Co-Catalyzed Synthesis of Isoquinolines

To a screw capped vial with a spinvane triangular-shaped Teflon stirbar were added arylhydrazone (**1a,** 0.26 mmol), diphenylacetylene (**2a**, 0.20 mmol), Cp*Co(CO)I_2 (9.5 mg, 10 mol %), $AgSbF_6$ (13.8 mg, 20 mol %), PivOH (5.1 mg, 25 mol %), and TFE (1.5 mL) under air atmosphere. The reaction mixture was stirred at 120 °C for 14 h. Afterwards, it was filtered through short pad of celite and celite pad was washed with $CHCl_3$ (25 mL × 2). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using *n*-hexane/EtOAc (50:1) to give the desired product **3aa** as a white solid (62 mg, 87%).

1,3,4-Triphenylisoquinoline **(3aa).**[22a] White solid (62 mg, 87%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.1 Hz, 1H), 7.82 (dd, *J* = 7.9, 1.4 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.63 – 7.46 (m, 5H), 7.46 – 7.33 (m, 5H), 7.33 – 7.25 (m, 2H), 7.24 – 7.09 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 149.6, 140.9, 139.8, 137.5, 136.9, 131.3, 130.4, 130.2, 129.9, 129.7, 128.5, 128.3, 127.50, 127.46, 127.2, 126.9, 126.5, 126.0, 125.4 (One carbon is missing due to overlap).

3,4-Bis(4-methoxyphenyl)-1-phenylisoquinoline **(3ab).**[22b] White solid (68.5 mg, 82%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.2 Hz, 1H), 7.81 (dd, *J* = 7.8, 1.3 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.62 – 7.44 (m, 5H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 158.7, 158.6, 149.3,

139.9, 137.4, 133.5, 132.4, 131.7, 130.2, 129.9, 129.7, 128.8, 128.4, 128.2, 127.4, 126.2, 125.9, 125.2, 113.9, 113.1, 55.2, 55.1.

3,4-Bis(3,4-dimethoxyphenyl)-1-phenylisoquinoline **(3ac).** White solid (57.0 mg, 60%); m.p. 199– 201 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.3 Hz, 1H), 7.86 – 7.75 (m, 3H), 7.64 – 7.44 (m, 5H), 7.16 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.99 (d, *J* = 1.8 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.90 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.83 (d, *J* = 1.5 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 3.94 (s, 3H), 3.84 (s, 3H), 3.74 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 149.1, 149.0, 148.2, 148.1, 147.8, 139.8, 137.3, 133.6, 130.3, 130.2, 129.9, 128.9, 128.5, 128.2, 127.4, 126.3, 125.9, 125.3, 123.6, 123.1, 114.5, 113.6, 111.2, 110.5, 55.94, 55.92, 55.8, 55.5; HRMS (ESI) m/z calcd. for $C_{31}H_{27}NO_4$ $[M+H]^+$: 478.2013, found: 478.2014.

3,4-Bis(4-chlorophenyl)-1-phenylisoquinoline **(3ad).**[22a] White solid (67.0 mg, 79%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.2 Hz, 1H), 7.79 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.72 – 7.47 (m, 6H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 148.5, 139.5, 139.1, 136.7, 135.8, 133.6, 133.3, 132.6, 131.7, 130.3, 130.1, 128.8, 128.7, 128.6, 128.4, 127.9, 127.7, 126.9, 125.6, 125.5.

3,4-Bis(4-fluorophenyl)-1-phenylisoquinoline (**3ae**).[22a] White solid (65.0 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.3 Hz, 1H), 7.84 – 7.75 (m, 2H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.63 – 7.57 (m, 1H), 7.57 – 7.46 (m, 4H), 7.42 – 7.33 (m, 2H), 7.28 – 7.20 (m, 2H), 7.10 (t, *J* = 8.7 Hz, 2H), 6.89 (t, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1 (d, $J_{C\text{-}F}$ = 245.7 Hz), 162.0 (d, $J_{C\text{-}F}$ = 245.5 Hz), 160.1, 148.8, 139.6, 136.9, 136.8 (d, $J_{C\text{-}F}$ = 2.8 Hz), 133.2 (d, $J_{C\text{-}F}$ = 3.1 Hz), 132.9 (d, $J_{C\text{-}F}$ = 7.9 Hz), 132.1 (d, $J_{C\text{-}F}$ = 8.0 Hz), 130.2, 130.1, 128.6, 128.3, 127.6, 126.8, 125.7, 125.4, 115.6 (d, $J_{C\text{-}F}$ = 21.3 Hz), 114.6 (d, $J_{C\text{-}F}$ = 21.2 Hz) (One carbon is missing due to overlap).

1-Phenyl-3,4-bis(4-(trifluoromethyl)phenyl)isoquinoline (**3af**). White solid (84.0 mg, 85%); m.p. 208–210 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.2 Hz, 1H), 7.85 – 7.74 (m, 2H), 7.75 – 7.63 (m, 4H), 7.63 – 7.38 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 148.1, 144.0, 141.0, 139.3, 136.5,

131.7, 130.7, 130.6, 130.1, 130.0 (q, J_{C-F} = 32.6 Hz), 129.3 (q, J_{C-F} = 32.1 Hz), 128.9, 128.8, 128.4, 127.8, 127.4, 125.7, 125.5, 124.8 (q, J_{C-F} = 3.6 Hz), 124.1 (d, J_{C-F} = 270.5 Hz), 124.0 (d, J_{C-F} = 270.6 Hz) (One carbon is missing due to overlap); HRMS (ESI) m/z calcd. for $C_{29}H_{17}NF_6$ $[M+H]^+$: 494.1338, found: 494.1349.

Diethyl 4,4'-(1-phenylisoquinoline-3,4-diyl)dibenzoate (**3ag**). White solid (68.0 mg, 68%); m.p. 73–75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.1 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 6.8 Hz, 2H), 7.71 – 7.51 (m, 6H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 166.3, 160.5, 148.5, 144.9, 142.0, 139.3, 136.5, 131.4, 130.5, 130.4, 130.2, 129.71, 129.69, 129.4, 129.1, 129.0, 128.8, 128.4, 127.8, 127.2, 125.7, 125.6, 61.1, 60.9, 14.34, 14.29; HRMS (ESI) m/z calcd. for $C_{33}H_{27}NO_4$ $[M+H]^+$: 502.2013, found: 502.2019.

3,4-Bis(3-methoxyphenyl)-1-phenylisoquinoline **(3ah).**[11] White solid (72.0 mg, 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 6.5 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.64 – 7.45 (m, 5H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.18 – 7.06 (m, 2H), 7.00 (brs, 1H), 6.97 – 6.87 (m, 2H), 6.85 (brs, 1H), 6.74 (dt, *J* = 6.9, 2.4 Hz, 1H), 3.72 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 159.6, 158.8, 149.2, 142.1, 139.8, 139.0, 136.9, 130.2, 129.9, 129.6, 129.3, 128.6, 128.5, 128.3, 127.5, 126.6, 126.1, 125.4, 123.8, 123.0, 116.7, 115.3, 113.6, 113.1, 55.3, 55.1.

1-Phenyl-3,4-di-m-tolylisoquinoline (**3ai**).[22a] White solid (61.5 mg, 80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 6.8 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.63 – 7.42 (m, 5H), 7.35 (s, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.19 – 7.10 (m, 3H), 7.10 – 6.90 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 149.6, 140.7, 139.9, 137.7, 137.5, 137.0, 136.9, 131.9, 131.2, 130.2, 129.83, 129.76, 128.42, 128.36, 128.2, 128.1, 127.9, 127.7, 127.5, 127.4, 127.2, 126.4, 126.1, 125.3, 21.4 (One of the methyl carbon attached to aromatic ring is missing due to overlap).

3,4-Bis(3-chlorophenyl)-1-phenylisoquinoline (**3aj**)**.** White solid (71.8 mg, 84%); m.p. 213– 215 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.3 Hz, 1H), 7.80 (d, *J* = 6.6 Hz, 2H), 7.72 – 7.62 (m, 2H),

7.62 – 7.47 (m, 5H), 7.43 – 7.29 (m, 3H), 7.22 – 7.13 (m, 3H), 7.13 – 7.04 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 148.1, 142.2, 139.4, 139.0, 136.6, 134.4, 133.7, 131.1, 130.5, 130.4, 130.1, 129.8, 129.5, 128.8, 128.6, 128.5, 128.4, 127.8, 127.7, 127.4, 127.1, 125.7, 125.6 (One carbon is missing due to overlap) ; HRMS (ESI) m/z calcd. for $C_{27}H_{17}NCl_2$ $[M+H]^+$: 426.0811, found: 426.0813.

3,4-Bis(2-methoxyphenyl)-1-phenylisoquinoline (**3ak**).[11] White solid (60.0 mg, 72%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 6.7 Hz, 2H), 7.68 – 7.42 (m, 6H), 7.37 – 7.23 (m, 2H), 7.22 – 7.06 (m, 2H), 6.94 – 6.79 (m, 3H), 6.68 (d, *J* = 8.3 Hz, 1H), 3.61 (s, 3H), 3.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 157.2, 156.6, 148.6, 139.4, 136.6, 132.2, 131.4, 130.6, 130.3, 129.7, 128.2, 128.8, 128.3, 128.1, 127.6, 126.4, 125.9, 125.6, 119.9, 119.8, 110.3, 55.2, 55.0 (three carbons are missing due to overlap).

(1,3-Diphenylisoquinolin-4-yl)methanol (**3al**).[15] Pale yellow solid (39.0 mg, 63%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.5 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.84 – 7.65 (m, 5H), 7.64 – 7.37 (m, 7H), 5.10 (s, 2H), 2.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 152.1, 140.4, 139.5, 136.7, 130.6, 130.1, 129.9, 128.6, 128.24, 128.16, 128.0, 126.7, 125.9, 124.7, 124.2, 59.5 (one carbon is missing due to overlap).

3,4-Bis(4-methoxyphenyl)-6-methyl-1-(p-tolyl)isoquinoline (**3bb**). White solid (65.0 mg, 73%); m.p. 179– 181 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 2H), 7.47 (s, 1H), 7.42 – 7.26 (m, 5H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.74 (s, 3H), 2.45 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 158.6, 158.5, 149.4, 139.9, 138.2, 137.6, 137.2, 133.8, 132.4, 131.7, 130.1, 128.9, 128.3, 128.1, 127.4, 124.7, 123.6, 113.8, 113.0, 55.20, 55.10, 22.1, 21.3 (one carbon is missing due to overlap); HRMS (ESI) m/z calcd. for $C_{31}H_{27}NO_2$ $[M+H]^+$: 446.2115, found: 446.2125.

3,4-bis(4-chlorophenyl)-6-methyl-1-(p-tolyl)isoquinoline **(3bd)**.[22a] White solid (69.0 mg, 76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.5 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 2H), 7.49 – 7.29 (m, 8H),

7.24 – 7.13 (m, 4H), 2.46 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 148.5, 140.7, 139.3, 138.6, 137.0, 136.8, 136.0, 133.4, 133.1, 132.6, 131.7, 130.0, 129.0, 128.8, 127.8, 127.6, 124.4, 123.9, 22.13, 21.36 (two carbons are missing due to overlap).

6-Methoxy-1-(4-methoxyphenyl)-3,4-diphenylisoquinoline (**3ca**).[11] White solid (67.0 mg, 80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J* = 9.2 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.46 – 7.32 (m, 5H), 7.32 – 7.26 (m, 2H), 7.21 – 7.10 (m, 4H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 2.3 Hz, 1H), 3.89 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 160.0, 158.8, 150.1, 141.0, 139.1, 137.9, 132.4, 131.5, 131.2, 130.4, 129.5, 128.7, 128.3, 127.4, 127.2, 126.9, 121.2, 118.7, 113.7, 104.2, 55.4, 55.2.

6-Methoxy-1-(4-methoxyphenyl)-3,4-di-p-tolylisoquinoline (**3cm**).[22c] White solid (66.0 mg, 74%); ^{1}H NMR (300 MHz, $CDCl_3$) 8.09 (d, *J* = 9.2 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.25 – 7.14 (m, 4H), 7.11 (dd, *J* = 9.3, 2.3 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 2H), 7.02 – 6.92 (m, 3H), 3.88 (s, 3H), 3.72 (s, 3H), 2.40 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4, 159.9, 158.4, 150.0, 139.3, 138.2, 136.6, 136.4, 134.9, 132.5, 131.5, 131.0, 130.3, 129.4, 129.1, 128.4, 128.2, 121.0, 118.5, 113.7, 104.3, 55.3, 55.2, 21.3, 21.1.

3,4-Bis(4-chlorophenyl)-6-methoxy-1-(4-methoxyphenyl)isoquinoline (**3cd**).[22c] White solid (76.5 mg, 79%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J* = 9.2 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.25 – 7.13 (m, 5H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 2.4 Hz, 1H), 3.90 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 160.1, 159.3, 149.1, 139.3, 138.9, 136.2, 133.4, 133.2, 132.5, 132.2, 131.7, 131.4, 129.7, 128.9, 127.8, 127.4, 121.2, 119.0, 113.8, 103.7, 55.4, 55.3.

6-Fluoro-1-(4-fluorophenyl)-3,4-diphenylisoquinoline (**3da**).[22a] White solid (61.5 mg, 78%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 9.2, 5.8 Hz, 1H), 7.79 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.47 – 7.33 (m, 5H), 7.33 – 7.11 (m, 9H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2 (d, $J_{C\text{-}F}$ = 246.2 Hz), 163.1 (d, $J_{C\text{-}F}$ = 250.7 Hz), 158.5, 150.6, 140.4, 139.0 (d, $J_{C\text{-}F}$ = 9.7 Hz), 137.0, 135.6 (d, $J_{C\text{-}F}$ = 3.2 Hz), 131.9 (d, $J_{C\text{-}F}$

= 8.3 Hz), 131.1, 130.4 (d, J_{C-F} = 9.9 Hz), 130.3, 129.6 (d, J_{C-F} = 5.8 Hz), 128.5, 127.6, 127.3, 122.6, 117.0 (d, J_{C-F} = 25.1 Hz), 115.4 (d, J_{C-F} = 21.5 Hz), 109.7 (d, J_{C-F} = 22.3 Hz) (One carbon is missing due to overlap).

6-Chloro-1-(4-chlorophenyl)-3,4-diphenylisoquinoline (**3ea**).[22b] White solid (64.0 mg, 75%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.9 Hz, 1H), 7.75 (d, *J* = 7.0 Hz, 2H), 7.70 (brs, 1H), 7.59 – 7.50 (m, 2H), 7.47 (d, *J* = 9.8 Hz, 1H), 7.44 – 7.33 (m, 5H), 7.33 – 7.23 (m, 2H), 7.23 – 7.09 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 150.9, 140.3, 138.1, 137.7, 136.7, 135.1, 131.5, 131.2, 130.4, 129.3, 128.9, 128.7, 128.6, 127.8, 127.7, 127.6, 127.4, 125.0, 123.6 (One carbon is missing due to overlap).

6-Chloro-1-(4-chlorophenyl)-3,4-bis(4-methoxyphenyl)isoquinoline **(3eb)**. Light yellow solid (68.0 mg, 70%); m.p. 169– 171 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 9.0 Hz, 1H), 7.80 – 7.65 (m, 3H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.42 (dd, *J* = 9.0, 1.8 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 158.9, 158.0, 150.5, 138.5, 137.8, 136.5, 134.9, 132.8, 132.2, 131.6, 131.5, 128.95, 128.86, 128.6, 128.4, 127.4, 124.9, 123.3, 114.2, 113.2, 55.3, 55.1; HRMS (ESI) m/z calcd. for $C_{29}H_{21}Cl_2NO_2$ $[M+H]^+$: 486.1022, found: 486.1024.

2,3-Diphenyl-8,9-dihydro-7H-benzo[de]quinoline (**3fa**).[10c] White solid (51.5 mg, 80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.43 (m, 2H), 7.41 – 7.27 (m, 6H), 7.26 – 7.12 (m, 5H), 3.41 (t, *J* = 6.2 Hz, 2H), 3.19 (t, *J* = 6.0 Hz, 2H), 2.34 – 2.19 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 149.1, 140.7, 138.5, 137.6, 136.2, 131.3, 130.2, 130.1, 129.1, 128.1, 127.5, 127.0, 126.9, 124.8, 123.8, 123.5, 34.5, 30.6, 23.3.

2,3-Di-p-tolyl-8,9-dihydro-7H-benzo[de]quinoline (**3fm**).[22b] White solid (53.0 mg, 76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.38 (m, 2H), 7.33 – 7.22 (m, 3H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 3.35 (t, *J* = 6.2 Hz, 2H), 3.15 (t, *J* = 6.0 Hz, 2H), 2.36 (s, 3H), 2.31 – 2.17 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 149.3, 138.3, 138.2, 136.4, 136.3, 134.8,

131.1, 130.1, 129.7, 128.8, 128.7, 128.2, 124.4, 123.7, 123.5, 34.6, 30.7, 23.4, 21.2, 21.1 (One carbon is missing due to overlap).

2,3-Dipropyl-8,9-dihydro-7H-benzo[de]quinoline (**3fn**).[22d] Colourless solid (39.0 mg, 77%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.6 Hz, 1H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.26 (d, *J* = 7.1 Hz, 1H), 3.28 (t, *J* = 6.2 Hz, 2H), 3.09 (t, *J* = 6.0 Hz, 2H), 3.01 – 2.88 (m, 4H), 2.22 – 2.10 (m, 2H), 1.89 – 1.57 (m, 4H), 1.19 – 0.99 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 150.6, 139.2, 135.8, 130.0, 126.6, 123.8, 123.6, 120.9, 36.8, 33.7, 30.6, 29.8, 24.0, 23.9, 23.2, 14.5, 14.3.

ASSOCIATED CONTENT

Supporting Information

characterization of new compounds (^{1}H, ^{13}C NMR spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For selected reviews, see: (a) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341. (b) Giri, P.; Kumar, G. S. *Mini-Rev. Med. Chem.* **2010**, *10*, 568.

(2) (a) Alcock, N. W.; Brown J. M.; Hulmes, G. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743. (b) Lim, C. W.; Tissot, O.; Mattison, A.; Hooper, M. W.; Brown, J. M.; Cowley, A. R.; Hulmes, D. I.; Blacker, A. J. *Org. Process Res. Dev.* **2003,** *7*, 379. (c) Sweetman, B. A.; Muller-Bunz, H.; Guiry, P. J. *Tetrahedron Lett.* **2005**, *46*, 4643. (d) Durola, F.; Sauvage, J.-P.; Wenger, O. S. *Chem. Commun.* **2006**, 171.

(3) For selected reviews on C−H bond activation, see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev*. **2010**, *110*, 624. (b) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (c) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (d) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (e) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H.; *Chem. Rev*. **2012**, *112*, 5879. (f) Wencel-Delord, J.; Glorius, F. *Nat. Chem*. **2013**, *5*, 369. (g) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040. (h) Ackermann, L. *Org. Process Res. Dev*. **2015**, *19*, 260.

(4) For review on transition metal catalyzed isoquinoline synthesis via C–H activation, see: He, R.; Huang, Z.-T.; Zheng, Q.-Y.; Wang, C. *Tetrahedron Lett.* **2014**, *55*, 5705, and references therein.

(5) For recent reviews on the first row transition metal-catalyzed C−H bond functionalization, see: (a) Kulkarni, A.; Daugulis, O. *Synthesis* **2009**, 4087. (b) Nakao, Y. *Chem. Rec.* **2011**, *11*, 242. (c) Miao, J.; Ge, H. *Eur. J. Org Chem.* **2015**, 7859. (d) Liu, W.; Ackermann, L. *ACS Catal*. **2016**, *6*, 3743.

(6) For reviews on Co-catalyzed C–H activation, see: (a) Yoshikai, N. *Synlett* **2011**, 1047. (b) Gao, K.; Yoshikai, N. *Acc. Chem. Res.* **2014**, *47*, 1208. (c) Yoshikai, N. *Bull. Chem. Soc. Jpn.* **2014**, *87*, 843. (d) Ackermann, L. *J. Org. Chem.* **2014**, *79*, 8948. (e) Moselage, M.; Li, J.; Ackermann, L. *ACS Catal*. **2015**, *6*, 498. (f) Wei, D.; Zhu, X.; Niu, L.; Song, M.-P. *ChemCatChem* **2016**, *8*, 1242.

(7) (a) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 2207. (b) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Chem.–Eur. J.* **2013**, *19*, 9142. (c) Sun, B.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Adv. Synth. Catal.* **2014**, *356*, 1491. (d) Ikemoto, H.; Yoshino,

T.; Sakata, K.; Matsunaga, S.; Kanai, M. *J. Am. Chem. Soc.* **2014**, *136*, 5424. (e) Sun, B.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Chem. Commun.* **2015**, *51*, 4659. (f) Suzuki, Y.; Sun, B.; Yoshino, T.; Kanai, M.; Matsunaga, S. *Tetrahedron* **2015**, *71*, 4552. (g) Suzuki, Y.; Sun, B.; Sakata, K.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 9944.

(8) For selected references of Cp*Co(III) catalysis, see: (a) Li, J.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 3635. (b) Mei, R.; Loup, J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 793. (c) Yu, D.-G.; Gensch, T.; de Azambuja, T.; Vasquez-Cespedes, S.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17722. (d) Zhao, D.; Kim, J. H.; Stegemann, L.; Strassert, C. A.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, (e) Pawar, A. B.; Chang, S. *Org. Lett.* **2015**, *17*, 660. (f) Patel, P.; Chang, S. *ACS Catal.* **2015**, *5*, 853. (g) Hummel, J. R.; Ellman, J. A. *J. Am. Chem. Soc.* **2015**, *137*, 490. (h) Hummel, J. R.; Ellman, J. A. *Org. Lett.* **2015**, *17*, 2400. (i) Prakash, S.; Muralirajan, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2016**, *55*, 1844.

(9) (a) Pawar, A. B.; Lade, D. M. *Org. Biomol. Chem.* **2016**, *14*, 3275. (b) Lade, D. M.; Pawar, A. B. *Org. Chem. Front.* **2016**, *3*, 836.

(10) (a) Sun, B.; Yoshino, T.; Kanai, M.; Matsunaga, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 12968. (b) Wang, H.; Koeller, J.; Liu, W.; Ackermann, L. *Chem.–Eur. J.* **2015**, *21*, 15525. (c) Sen, M.; Kalsi, D.; Sundararaju, B. *Chem.–Eur. J.* **2015**, *21*, 15529. (d) Muralirajan, K.; Kuppusamy, R.; Prakash, S.; Cheng, C.-H. *Adv. Synth. Catal.* **2016**, *358*, 774.

(11) 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.

(12) Li, J.; Tang, M.; Zang, L.; Zhang, X.; Zhang, Z.; Ackermann, L. *Org. Lett.* **2016**, *18*, 2742.

(13) Wang, F.; Wang, Q.; Bao, M.; Li, X. *Chin. J. Catal.* **2016**, *37*, 1423.

(14) During final stages of preparation of this manuscript, Zhu *et. al* reported a similar Co(III)-catalyzed isoquinoline synthesis. However, they employed N-Boc hydrazone as a substrate and HFIP as a solvent under argon atmosphere. see: Wang, J.; Zha, S.; Chen, K.; Zhu, J. *Org. Chem. Front.* **2016**, *3*, 1281.

(15) Zhang, X.; Chen, D.; Zhao, M.; Zhao, J.; Jia, A.; Li, X. *Adv. Synth. Catal.* **2011**, *353*, 719.

(16) Chinnagolla, R. K.; Pimparkar, S.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 3032.

(17) Similar kind of regioselectivity was observed with 3-phenylprop-2-yn-1-ol (**2l**) in Rh(III)-catalyzed annulation reactions. see: (a) Zheng, L.; Ju, J.; Bin, Y.; Hua, R. *J. Org. Chem.* **2012**, *77*, 5794. (b) Huang, X.-C.; Yang, X.-H.; Song, R.-J.; Li, J.-H. *J. Org. Chem.* **2014**, *79*, 1025. (c) Gupta, S.; Han, J.; Kim, Y.; Lee, S. W.; Rhee, Y. H. *J. Org. Chem.* **2014**, *79*, 9094. (d) Also see ref. 15, 22a and 22b.

(18) See the Supporting Information for details on intermolecular competitive experiments.

(19) Chuang, S.-C.; Gandeepan, P.; Cheng, C.-H. *Org. Lett.* **2013**, *15*, 5750.

(20) Please see ref. 14 and references cited therein.

(21) Hu, M.; Ni, C.; Li, L.; Han, Y.; Hu, J. *J. Am. Chem. Soc.* **2014**, *137*, 14496.

(22) (a) Zhang, S.; Huang, D.; Xu, G.; Cao, S.; Wang, R.; Penga, S.; Sun, J. *Org. Biomol. Chem.* **2015**, *13*, 7920. (b) Qiu, L.; Huang, D.; Xu, G.; Dai, Z.; Sun, J. *Org. Lett.* **2015**, *17*, 1810. (c) He, K.-H.; Zhang, W.-D.; Yang, M.-Y.; Tang, K.-L.; Qu, M.; Ding, Y.-S.; Li, Y. *Org. Lett.* **2016**, *18*, 2840. (d) Lee, H.; Sim, Y.-K.; Park, J.-W.; Jun, C.-H *Chem.–Eur. J.* **2014**, *20*, 312.