

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

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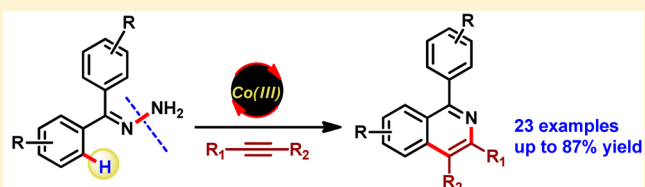
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Supporting Information

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 the presence of air.



- ✓ Co(III)-catalyzed C-H functionalization of Arylhydrazones
- ✓ Versatile isoquinoline synthesis via C-H/N-N bond activation
- ✓ Arylhydrazone as a easily synthesizable starting material
- ✓ No external oxidant, broad scope and high yield

Isoquinoline represents one of the ubiquitous structural motifs 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 for synthesizing isoquinoline such as Bischler–Napieralski, Pictet–Spengler, and Pomeranz–Fritsch reactions often suffer from a few drawbacks such as low yields, a narrow substrate scope, and harsh reaction conditions. In recent years, C–H activation reactions³ have provided an alternate route for accessing isoquinoline scaffolds with a great diversity in a concise manner.⁴ Although these methods provide straightforward access to isoquinolines; they often require the use of a precious transition metal such as Pd, Rh, or Ru. In recent years, much research has focused on the utilization of first row transition metals in the area of C–H functionalization.⁵ Because of their low toxicity, high natural abundance, and inexpensive nature, first row transition metals are now preferred over precious metals like Pd, Rh, Ru, and Ir. In this context, Kanai and Matsunaga have performed 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 intensively developed this area,⁸ including our group.⁹ Recently, several Co(III)-catalyzed isoquinoline syntheses have been reported employing different directing groups and coupling partners (Scheme 1). In this 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 isoquinolines.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 an 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 in preparing isoquinolines.¹³

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

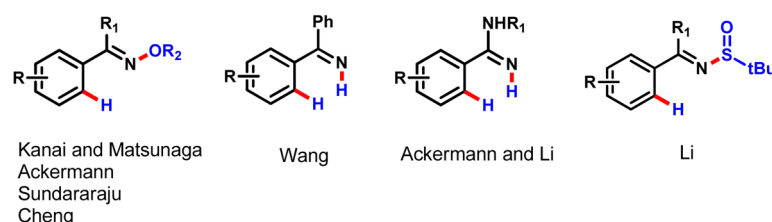
We commenced our investigation of Co(III)-catalyzed isoquinoline synthesis using benzophenone hydrazone **1a** as a starting substrate and diphenylacetylene **2a** as a coupling partner (Table 1). When benzophenone hydrazone **1a** was treated with diphenylacetylene **2a** in the presence of Cp*Co(CO)I₂ (10 mol %) and AgSbF₆ (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 an inert atmosphere,

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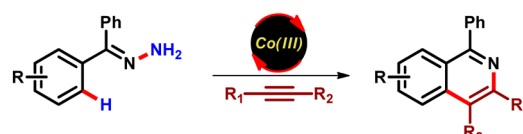
Scheme 1. Cp*Co(III)-Catalyzed Synthesis of Isoquinolines

Previous work



This work

Co(III)-catalyzed isoquinoline synthesis via C-H/N-N bond cleavage

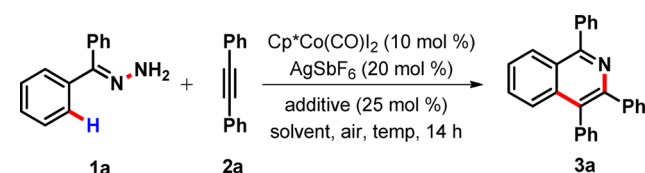


* Co(III)-catalyzed C-H functionalization of Arylhydrazones

* Versatile isoquinoline synthesis via C-H/N-N bond activation

* Aryl hydrazone as a easily synthesizable starting material

* No external oxidant, broad scope and functional group tolerance

Table 1. Optimization of Reaction Conditions^a

| 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 ₂ H | TFE | 120 | 72 |
| 7 | PivOH | TFE | 120 | 95 |
| 8 | PivOH | TFE | 120 | 77 |
| 9 | PivOH | MeOH | 120 | not detected |
| 10 | PivOH | ^t AmOH | 120 | not detected |
| 11 | PivOH | 1,2-DCE | 120 | not detected |
| 12 | PivOH | DMSO | 120 | not detected |
| 13 | PivOH | TFE | 80 | 62 |

^aReaction conditions: **1a** (0.13 mmol), **2a** (0.10 mmol), Cp*Co(CO)I₂ (10 mol %), AgSbF₆ (20 mol %), additive (25 mol %) in solvent (0.8 mL) for 14 h. ^bYields are based on crude ¹H NMR (internal standard, 1,1,2,2-tetrachloroethane) and calculated with respect to **2a**. TFE is 2,2,2-trifluoroethanol.

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, ^tAmOH, 1,2-DCE, or DMSO (Table 1, entries 9–12). A decrease in the reaction temperature resulted in a diminished yield of the product (Table 1, entry 13).

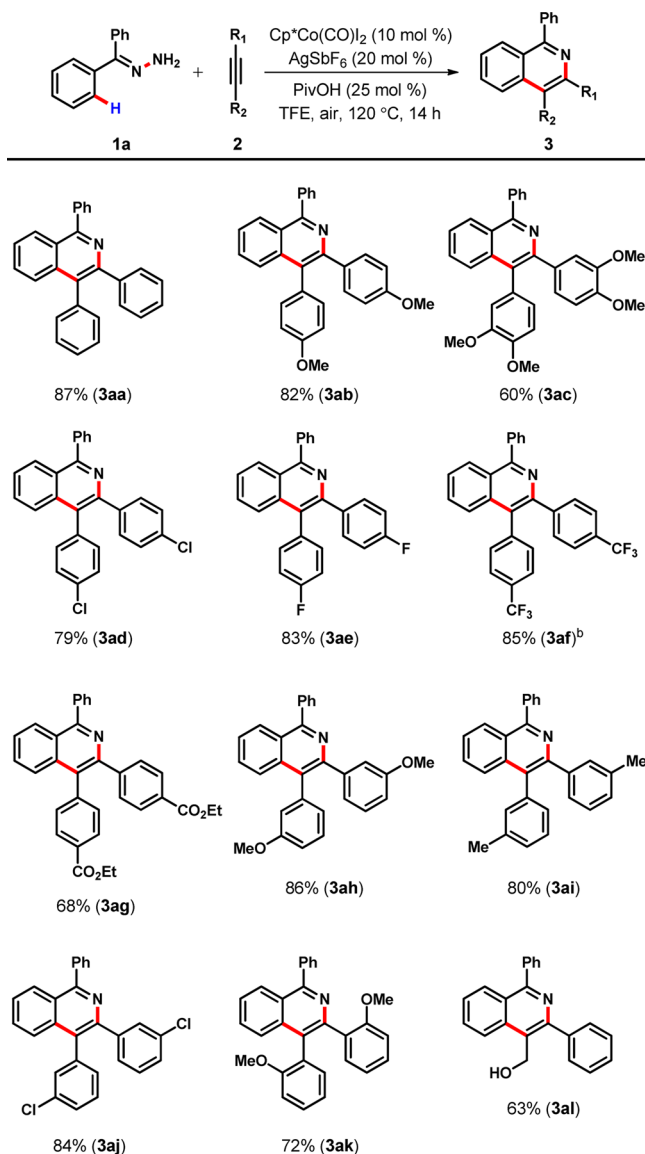
After determining the optimized condition, we investigated the scope and generality of the reaction using different internal alkynes (Scheme 2). It was found that diarylalkyne having an electron-donating functional group on the aromatic ring furnished the corresponding isoquinoline in good yield (**3ab**).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

annulation reaction, producing the corresponding product in moderate yield (**3ac**).

The alkynes bearing electron-withdrawing groups such as Cl, F, CF₃, and ester on the aromatic ring also furnished the corresponding isoquinolines in good to excellent yields (**3ad–3ag**). When meta-substituted diarylalkynes were employed, the reaction also delivered the products in high yields (**3ah–3aj**). The sterically hindered *o*-substituted diarylalkyne was also found to be compatible under our reaction conditions (**3ak**). The unsymmetrical alkyne, 3-phenylprop-2-yn-1-ol (**2l**), that possesses a free hydroxyl group also worked to furnish the corresponding product in moderate yield (**3al**), thus demonstrating functional group tolerance. The structure of **3al** was confirmed by comparing its ¹H and ¹³C NMR spectrum with that of the known compound.¹⁵ The exact reason for this selectivity is unclear; however, it may be due to intramolecular coordination of the phenyl group of 3-phenylprop-2-yn-1-ol (**2l**) with cobalt metal in intermediate C (see Scheme 5) to stabilize it.^{16,17} A terminal alkyne such as phenylacetylene turned out to be an ineffective coupling partner under our reaction conditions.

After the scope of alkynes had been examined, the 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 into the mechanism, we conducted some preliminary experiments (Scheme 4).¹⁸ When an intermolecular competitive experiment with differently functionalized hydrazones (**1c** and **1e**) was performed, we observed that electron rich hydrazone reacts preferentially. This can be rationalized in terms of intramolecular electrophilic substitution type C–H activation reaction via carboxylate

Scheme 2. Scope of Alkyne^a

^aReaction conditions: **1** (0.26 mmol), **2** (0.20 mmol), $\text{Cp}^*\text{Co}(\text{CO})_2$ (10 mol %), AgSbF_6 (20 mol %), PivOH (25 mol %) in TFE (1.5 mL) for 14 h. Isolated yields are given. ^bRun for 20 h.

assistance. Furthermore, an intermolecular competitive experiment with differently functionalized alkynes revealed the electron rich alkyne to be more reactive.

On the basis of the control experiments described above and related Rh(III)-catalyzed¹⁹ and cobalt(III)-catalyzed annulation reactions,^{10–14} a plausible mechanism is proposed as outlined in Scheme 5. Initially, $\text{Cp}^*\text{Co}(\text{CO})_2$ reacts with AgSbF_6 in the presence of PivOH to generate catalytically active complex A. Then complex A undergoes cyclometalation with **1a** to generate cobaltacycle B. This is followed by migratory insertion of alkyne **2** into B to form seven-membered cobaltacyclic intermediate C, which upon pivalic acid-assisted proton transfer²⁰ generates intermediate D, which eventually undergoes intramolecular substitution resulting in the formation of a C–N bond and the breakage of a N–N bond to furnish isoquinoline **3** with concomitant regeneration of catalytically active Co(III) species A.

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. This protocol employs simple arylhydrazones as substrates that 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 precoated silica gel 60 F₂₅₄ plates. Visualization via 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 ¹H NMR spectra and 75 or 100 MHz for ¹³C NMR spectra. Chemical shifts are quoted in parts per million 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 doublets; td, triplet of doublets; m, multiplet. Coupling constants, *J*, are reported in hertz. For ¹³C NMR, chemical shifts are reported in parts per million referenced to the center of a triplet at 77.0 ppm of chloroform-*d*. HRMS spectra were recorded using ESI-TOF techniques. $\text{Cp}^*\text{Co}(\text{CO})_2$ was synthesized according to the literature.^{7c} Arylhydrazones **1a** were prepared according to the procedure described in the literature.²¹

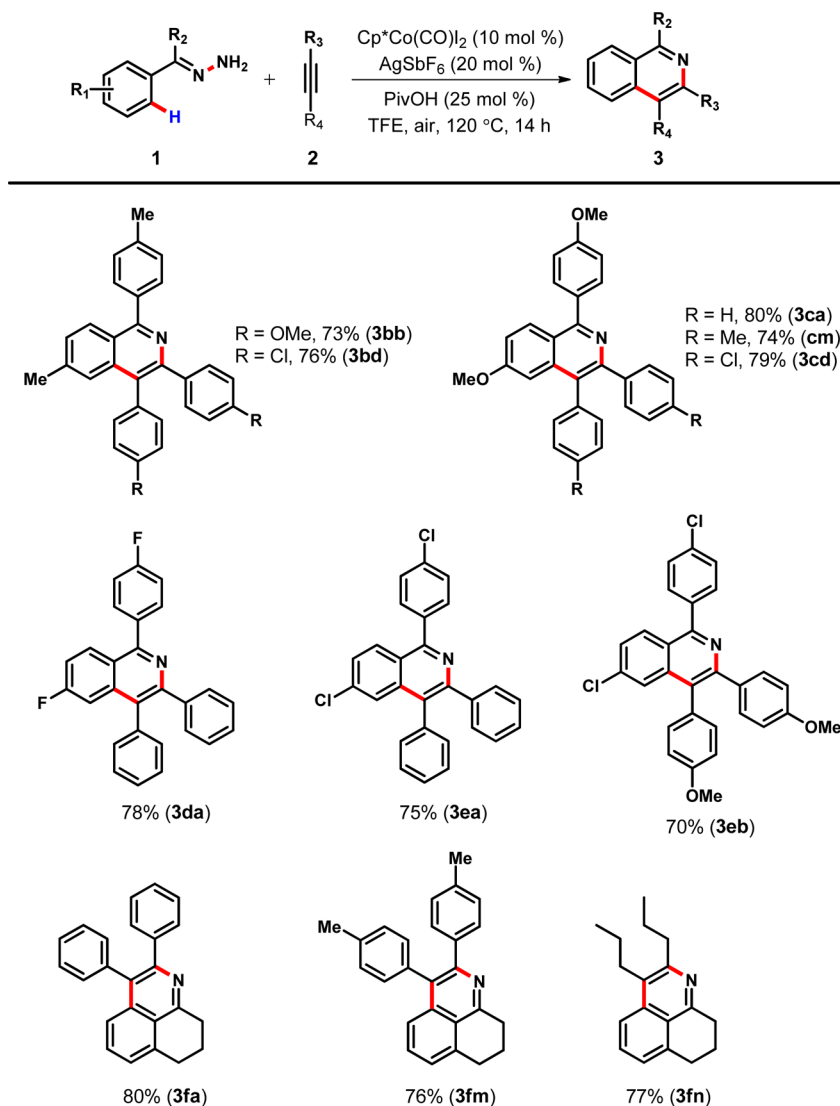
General Procedure for Co-Catalyzed Synthesis of Isoquinolines. To a screw-capped vial with a spinvane triangular-shaped Teflon stirbar were added arylhydrazone (**1a**, 0.26 mmol), diphenylacetylene (**2a**, 0.20 mmol), $\text{Cp}^*\text{Co}(\text{CO})_2$ (9.5 mg, 10 mol %), AgSbF_6 (13.8 mg, 20 mol %), PivOH (5.1 mg, 25 mol %), and TFE (1.5 mL) under an air atmosphere. The reaction mixture was stirred at 120 °C for 14 h. Afterward, it was filtered through a short pad of Celite, and the Celite pad was washed with CHCl_3 (2 × 25 mL). The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel using an *n*-hexane/EtOAc solvent (50:1) to give desired product **3aa** as a white solid (62 mg, 87%).

1,3,4-Triphenylisoquinoline (3aa).^{22a} White solid (62 mg, 87%); ¹H 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); ¹³C 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 because of overlap).

3,4-Bis(4-methoxyphenyl)-1-phenylisoquinoline (3ab).^{22b} White solid (68.5 mg, 82%); ¹H 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); ¹³C 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%); mp 199–201 °C; ¹H 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); ¹³C 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 $\text{C}_{31}\text{H}_{27}\text{NO}_4$ [*M* + *H*]⁺ 478.2013, found 478.2014.

3,4-Bis(4-chlorophenyl)-1-phenylisoquinoline (3ad).^{22a} White solid (67.0 mg, 79%); ¹H 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

Scheme 3. Scope of Arylhydrazones^a

^aReaction conditions: **1** (0.26 mmol), **2** (0.20 mmol), $\text{Cp}^*\text{Co}(\text{CO})_2$ (10 mol %), AgSbF_6 (20 mol %), PivOH (25 mol %) in TFE (1.5 mL) for 14 h. Isolated yields are given.

(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%); ^1H 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, $J_{\text{C-F}} = 245.7$ Hz), 162.0 (d, $J_{\text{C-F}} = 245.5$ Hz), 160.1, 148.8, 139.6, 136.9, 136.8 (d, $J_{\text{C-F}} = 2.8$ Hz), 133.2 (d, $J_{\text{C-F}} = 3.1$ Hz), 132.9 (d, $J_{\text{C-F}} = 7.9$ Hz), 132.1 (d, $J_{\text{C-F}} = 8.0$ Hz), 130.2, 130.1, 128.6, 128.3, 127.6, 126.8, 125.7, 125.4, 115.6 (d, $J_{\text{C-F}} = 21.3$ Hz), 114.6 (d, $J_{\text{C-F}} = 21.2$ Hz) (one carbon is missing because of overlap).

1-Phenyl-3,4-bis[4-(trifluoromethyl)phenyl]isoquinoline (3af). White solid (84.0 mg, 85%); mp 208–210 °C; ^1H 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, $J_{\text{C-F}} = 32.6$ Hz), 129.3 (q, $J_{\text{C-F}} = 32.1$ Hz), 128.9, 128.8, 128.4, 127.8, 127.4, 125.7, 125.5, 124.8 (q, $J_{\text{C-F}} = 3.6$ Hz), 124.1 (d, $J_{\text{C-F}} = 270.5$ Hz), 124.0 (d, $J_{\text{C-F}} = 270.6$ Hz) (one carbon is missing

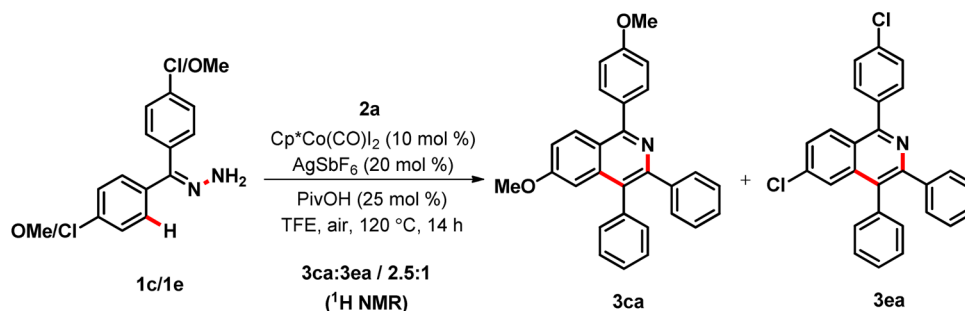
because of overlap); HRMS (ESI) m/z calcd for $\text{C}_{29}\text{H}_{17}\text{NF}_6$ [$\text{M} + \text{H}$]⁺ 494.1338, found 494.1349.

Diethyl 4,4'-(1-Phenylisoquinoline-3,4-diyl)dibenzoate (3ag). White solid (68.0 mg, 68%); mp 73–75 °C; ^1H 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 $\text{C}_{33}\text{H}_{27}\text{NO}_4$ [$\text{M} + \text{H}$]⁺ 502.2013, found 502.2019.

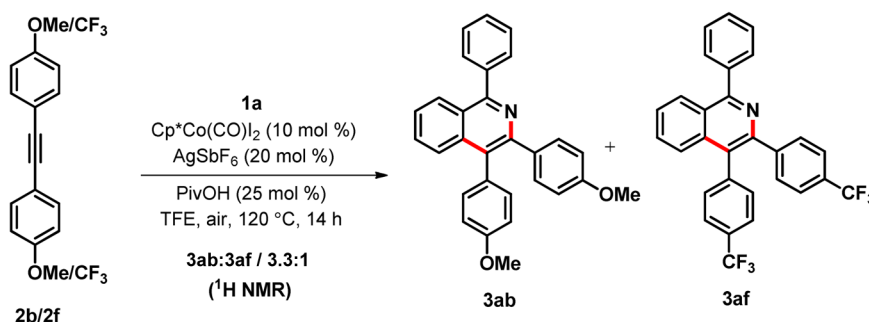
3,4-Bis(3-methoxyphenyl)-1-phenylisoquinoline (3ah).¹¹ White solid (72.0 mg, 86%); ^1H NMR (300 MHz, CDCl_3) δ 8.18 (d, $J = 8.2$ Hz, 1H), 7.82 (d, $J = 6.5$ Hz, 2H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.64–7.45 (m, 5H), 7.32 (t, $J = 7.9$ Hz, 1H), 7.18–7.06 (m, 2H), 7.00 (brs, 1H), 6.97–6.87 (m, 2H), 6.85 (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.

Scheme 4. Control Experiments

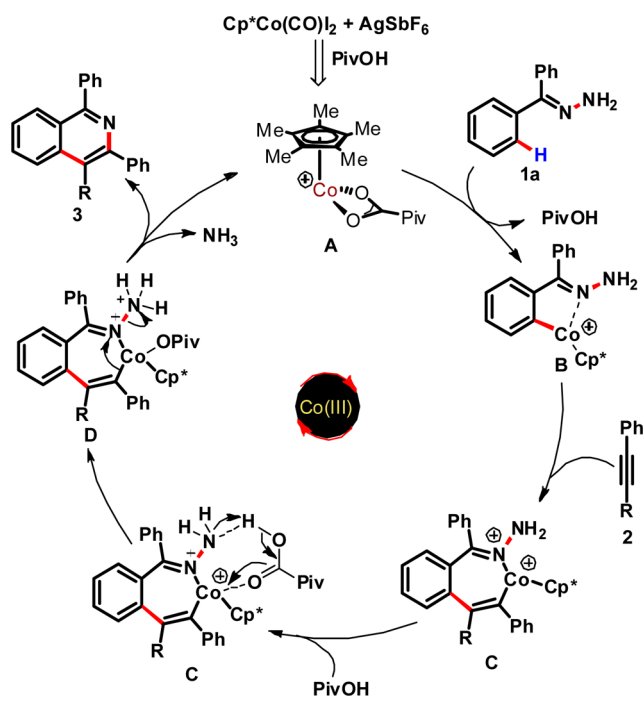
a) Intermolecular competition between hydrazones



b) Intermolecular competition between alkynes



Scheme 5. Plausible Mechanism



1-Phenyl-3,4-di-*m*-tolylisoquinoline (3ai).^{22a} White solid (61.5 mg, 80%); ^1H 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 carbons attached to the aromatic ring is missing because of overlap).

3,4-Bis(3-chlorophenyl)-1-phenylisoquinoline (3aj). White solid (71.8 mg, 84%); mp 213–215 °C; ^1H 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 because of overlap); HRMS (ESI) m/z calcd for $\text{C}_{27}\text{H}_{17}\text{NCl}_2$ [$M + \text{H}$] $^+$ 426.0811, found 426.0813.

3,4-Bis(2-methoxyphenyl)-1-phenylisoquinoline (3ak).¹⁷ White solid (60.0 mg, 72%); ^1H 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 because of overlap).

(1,3-Diphenylisoquinolin-4-yl)methanol (3al).¹⁵ Pale yellow solid (39.0 mg, 63%); ^1H 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 because of overlap).

3,4-Bis(4-methoxyphenyl)-6-methyl-1-(*p*-tolyl)isoquinoline (3bb). White solid (65.0 mg, 73%); mp 179–181 °C; ^1H 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 because of overlap); HRMS (ESI) m/z calcd for $\text{C}_{31}\text{H}_{27}\text{NO}_2$ [$M + \text{H}$] $^+$ 446.2115, found 446.2125.

3,4-Bis(4-chlorophenyl)-6-methyl-1-(*p*-tolyl)isoquinoline (3bd).^{22a} White solid (69.0 mg, 76%); ^1H 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 because of overlap).

6-Methoxy-1-(4-methoxyphenyl)-3,4-diphenylisoquinoline (3ca).¹¹ White solid (67.0 mg, 80%); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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%); ¹H NMR (300 MHz, CDCl₃) δ 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); ¹³C NMR (75 MHz, CDCl₃) 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%); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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%); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) δ 163.2 (d, *J*_{C-F} = 246.2 Hz), 163.1 (d, *J*_{C-F} = 250.7 Hz), 158.5, 150.6, 140.4, 139.0 (d, *J*_{C-F} = 9.7 Hz), 137.0, 135.6 (d, *J*_{C-F} = 3.2 Hz), 131.9 (d, *J*_{C-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 because of overlap).

6-Chloro-1-(4-chlorophenyl)-3,4-diphenylisoquinoline (3ea).^{22b} White solid (64.0 mg, 75%); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 because of overlap).

6-Chloro-1-(4-chlorophenyl)-3,4-bis(4-methoxyphenyl)-isoquinoline (3eb). Light yellow solid (68.0 mg, 70%); mp 169–171 °C; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₉H₂₁Cl₂NO₂ [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%); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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%); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 because of overlap).

2,3-Dipropyl-8,9-dihydro-7H-benzo[de]quinoline (3fn).^{22d} Colorless solid (39.0 mg, 77%); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02001.

Characterization of new compounds (¹H and ¹³C NMR spectra) (PDF)

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Notes

The authors declare no competing financial interest.

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