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Cp*Co(III)-catalyzed annulation of azines by C-H/N-N bond activation for the synthesis of isoquinolines†

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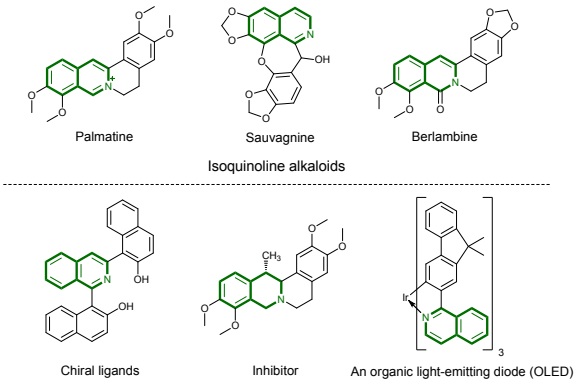
Herein, an efficient, atom economic and external oxidant free approach has been disclosed for the synthesis of isoquinolines. Azines were employed for annulation reactions with alkynes *via* sequential C-H/N-N bond activation using air-stable cobalt catalyst. The method takes advantage of incorporation of both the nitrogen atoms of azines to desired isoquinoline products, offering highest atom economy. In addition, the developed protocol works under external oxidant as well as silver salt free conditions. Further, the established methodology features relatively broad substrate scope with high product yields and scalability up to gram level.

Introduction

The beginning of twenty-first century has witnessed a revolution in the area of synthetic organic chemistry owing to advancement in transition-metal catalyzed C−H functionalization methodologies, creating new opportunities in retrosynthetic strategies.[1] It represents a powerful approach over conventional synthesis in organic chemistry in consequence of its efficiency, high atom and step economy, environmental significance and nobility. Of these processes, direct C−H bond functionalization of arenes with consequent alkyne addition has been recognized as an influential method for the development of condensed aromatics.[2] So far, the larger part of previous reports on C−H functionalization reactions have focused on complexes of noble metals like Pd, Rh, Ir, Ru, etc.[3] Nevertheless, the high cost, low abundance and toxicity of these second-row metal catalysts and selection of starting materials are definite drawbacks, and hence being limitation for its employment in the industry. Thus, in light of the economic practicality of chemistry, it is significant to have such functionalization reactions with more economical first-row transition metals.[4] Among them, cobalt seems to be a promising contender. Being inexpensive, plentiful, and less toxic than noble metal catalysts in nature, it has entered the center of attention in C−H activation chemistry.[5]

In order to regenerate the transition-metal catalysts in its active oxidation state, most of the transition-metal-catalyzed C−H bond functionalization methodologies necessitate the use of equivalent amount of external oxidants, particularly toxic metal salts, which undoubtedly concludes in lower atom economy by creating undesirable by-products and off-cycle side reactions. Therefore, for the sake of overcoming the disadvantages introduced by the external oxidant, recently, a new ideal strategy comprising simplicity, safety, and environmental friendliness has been evolved, in which an internal moiety acts as both directing group as well as oxidant for the regeneration of active catalytic species in catalytic cycle.[6] This approach can lead to improved levels of reactivity and also has clear advantages of selectivity, yield and substrate scope, moreover increasing the overall "greenness" of the process. Nevertheless, this attractive approach mostly involves the cleavage of N−N, N−O or O−O bonds for redox process, and the cleaved residue is released as a by-product.

Isoquinoline and its derivatives are key motifs ubiquitous in several natural as well as synthetic bioactive molecules (Scheme 1). The isoquinoline skeleton not only serve as privileged component in medical chemistry and pharmaceutical industry[7] but also plays an important role in the synthesis of ligands, various alkaloids, inhibitors, and organic light-emitting diodes.[8]



Scheme 1 Representative biologically active and other important molecules consist of isoquinoline skeleton.

The prevalence of this important molecule provided the driving force for synthetic chemists for the development of many useful methodologies for its synthesis. Although, many traditional

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†Electronic supplementary information (ESI) available: ^{1}H NMR and ^{13}C NMR spectra.
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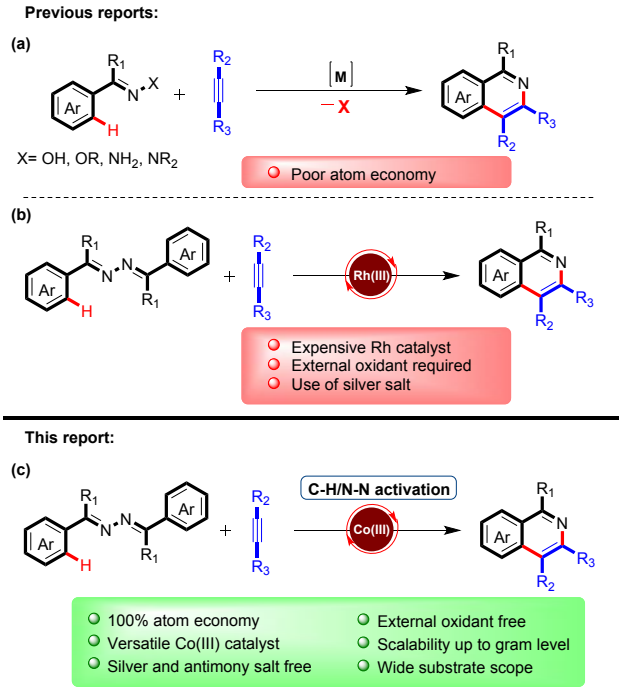
routes are reported for the synthesis of isoquinolines which are demonstrated well by Bischler-Napieralski, Pomeranz- Fritsch, and Pictet-Spengler reactions.[9] These methods are affected with few limitations such as lesser yields, limited substrate scope, tedious and harsh reaction conditions. Therefore, it is highly desirable to develop a methodology with mild reaction conditions, atom and step economy and good functional group tolerance. In this context, synthesis of isoquinolines by C–H functionalization is established as an efficient alternate pathway, which is assisted by various directing groups and catalysts.[10] These remarkable methodologies are highly efficient with several advantages. However, most of these protocols are suffered from the need of external oxidants and low atom



Scheme 2 Synthesis of isoquinolines *via* transition-metal-catalysed C–H functionalization

economy. The limitation of use of external oxidant has been overcome by installing multifunctional group that act as both, directing group as well as internal oxidant.[11] Still, these procedures have limitation of low atom economy as the directing component present in the starting substrates have never been entirely integrated to the anticipated product. Overcoming this drawback, recently, Huang group and Li group have employed ketazine as a directing group for synthesis of isoquinolines *via* annulation reaction using rhodium catalysts.[12] Despite the advantages of atom economy with ketazine as a directing group as both nitrogen atoms of the azines could be integrated to the anticipated isoquinoline products, these methods are suffered by certain limitations like use of expensive rhodium catalysts, need of external oxidant and use of silver salt or acid additive. These shortcomings led us to visualize the probability of establishing a protocol for the synthesis of isoquinolines with highest atom economy using first-row transition metal catalyst under external oxidant free and silver salt free condition. In the context of our interest in efficient construction of heterocycles,[13] herein we report cobalt catalyzed synthesis of isoquinolines by C–H/N–N bond functionalization strategy using ketazines as a directing group under silver salt as well as external oxidant free condition.

Results and discussion

We initiated our study with annulation reaction of ketazine **1a** with diphenylacetylene **2a** as model substrates using [Cp*Co(CO)I_2] as a catalyst to verify our assumption for the synthesis of 1-methyl-3,4-diphenylisoquinoline **3aa**. The reaction was attempted with sodium acetate and silver hexafluoroantimonate as additives in hexafluoroisopropanol solvent at 100 °C for 24 hours. Pleasantly, the reaction proceeded to give anticipated product 1-methyl-3,4-diphenylisoquinoline **3aa** with reasonable yield, which was confirmed by GC, GCMS and $^1H/^{13}C$ NMR analysis (Table 1, entry 1). To examine the efficiency of the proposed protocol with other cobalt salts, the reaction was performed using catalysts like [Cp*CoI_2]$_2$ and $Co(OAc)_2 \cdot 4H_2O$. Out of those [Cp*CoI_2]$_2$ could lead the product **3aa** producing 38% yield, while $Co(OAc)_2 \cdot 4H_2O$ was ineffective for the given reaction (Table 1, entries 2 and 3). Among the solvents tested, trifluoroethanol was most efficient affording product **3aa** in 81% yield (Table 1, entry 5). Among the other solvents surveyed, dichloroethane and tert-amyl alcohol could generate the product with 69% and 23% yields respectively, though methanol as a solvent was totally ineffective (Table 1, entries 4, 6 and 7). In order to make catalytic system reusable, the reaction was attempted in PEG-400 as a greener and reusable solvent. But disappointingly, the product was isolated in very low yield (Table 1, entry 8). To improve yield of the product retaining homogeneous reusable catalytic system, we next tried the reaction using PEG-400 and TFE (1:1) as a binary solvent system. Again, we obtained the product **3aa** but the yield was unsatisfactory compared with the neat TFE as a solvent (Table 1, entry 9). Considering the environmental hazards of silver hexafluoroantimonate, an attempt was made to avoid the use of silver salt, and surprisingly no effect of silver salt was found (Table 1, entry 10). Next, performing the temperature studies, the increase of yield was observed when the reaction was done at 110 °C, while further increase in temperature to 120 °C, could not improve the product yield (Table 1, entries 11 and 12). On lowering the reaction duration to 12 hours, gratifyingly the reaction furnished efficiently producing an equal amount of yield, while further decrease in time affected the reaction productively, giving 67% product yield (Table 1, entries 13 and 14). A series of additives like KOAc, AgOAc, CsOAc, $Cu(OAc)_2$, $Mn(OAc)_2$ and KOPiv was examined to study the effect of additives on the reaction. However, replacement of the NaOAc with these additives lead to product **3aa** with lesser yields (Table 1, entries 15–20). Studying the catalyst loading for the proposed reaction, 5 mol% of [Cp*Co(CO)I_2] could lead the product with 62% yield, while with 15 mol% of [Cp*Co(CO)I_2] catalyst no significant increase in the yield was observed (Table 1, entries 21 and 22). Thus, the optimized reaction conditions are: ketazine **1a** (0.2 mmol), diphenylacetylene **2a** (0.5 mmol), [Cp*Co(CO)I_2] catalyst (10 mol%), NaOAc (20 mol%), TFE (2 mL), 110 °C, 12 h.

Under the optimized reaction conditions, we then explored the substrate scope and limitations of the reaction. A broad range of aromatic ketazines with electron donating and electron withdrawing groups at different positions of phenyl rings was well tolerated for the annulation reaction with internal alkynes to deliver the desired isoquinoline products in good to excellent yields showing good generality of the proposed methodology (Table 2). Initially,

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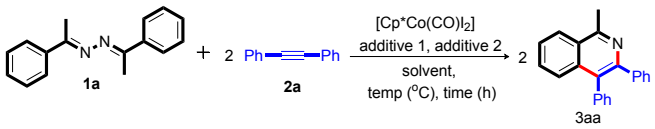
Table 1 Optimization of reaction parameters[a]



Entry	Additive 1	Additive 2	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	NaOAc	$AgSbF_6$	HFIP	100	24	76
2[c]	NaOAc	$AgSbF_6$	HFIP	100	24	38
3[d]	NaOAc	$AgSbF_6$	HFIP	100	24	nd
4	NaOAc	$AgSbF_6$	DCE	100	24	69
5	NaOAc	$AgSbF_6$	TFE	100	24	81
6	NaOAc	$AgSbF_6$	MeOH	100	24	nd
7	NaOAc	$AgSbF_6$	*t*-AmOH	100	24	23
8	NaOAc	$AgSbF_6$	PEG-400	100	24	38
9	NaOAc	$AgSbF_6$	PEG-400 + TFE (1:1)	100	24	57
10	NaOAc	-	TFE	100	24	79
11	NaOAc	-	TFE	110	24	87
12	NaOAc	-	TFE	120	24	88
13	**NaOAc**	**-**	**TFE**	**110**	**12**	**86**
14	NaOAc	-	TFE	110	10	67
15	KOAc	-	TFE	110	12	81
16	AgOAc	-	TFE	110	12	29
17	CsOAc	-	TFE	110	12	68
18	$Cu(OAc)_2$	-	TFE	110	12	15
19	$Mn(OAc)_2$	-	TFE	110	12	18
20	KOPiv	-	TFE	110	12	79
21[e]	NaOAc	-	TFE	110	12	62
22[f]	NaOAc	-	TFE	110	12	88

[a] Reaction condition: ketazine **1a** (0.2 mmol), diphenylacetylene **2a** (0.5 mmol), [$Cp^*Co(CO)I_2$] (10 mol%), additive 1 (20 mol%), additive 2 (20 mol%), solvent (2 mL), temp, time; [b] gc yield; [c] $[Cp^*CoI_2]_2$ was used as a catalyst; [d] $Co(OAc)_2{\cdot}4H_2O$ was used as a catalyst; [e] 5 mol% [$Cp^*Co(CO)I_2$] was used; [f] 15 mol% [$Cp^*Co(CO)I_2$] was used.

acetophenonazine **1a** afforded the product 1-methyl-3,4-diphenylisoquinoline **3aa** with 86% yield. Acetophenonazine with electron donating groups (e.g. methyl and methoxy) at *para* position of phenyl rings produced the anticipated products **3ba** and **3ca** in 88% and 91% yields, respectively. In addition, electron withdrawing groups (e.g. bromo, chloro, fluoro and nitro) at *para* position of phenyl rings of acetophenonazine affected the yields of desired products **3da**, **3ea**, **3fa** and **3ga**, which were observed in 76%, 79%, 78% and 68% yields, respectively. The position of methyl, methoxy, nitro and chloro groups at phenyl rings of acetophenonazine marginally affected the yields of the respective products. It is noteworthy that acetophenonazine with methyl, nitro and chloro substituents at *meta* position of phenyl rings provided the single regioselective products **3ha**, **3ja** and **3ka** with 85%, 61% and 71% yields, respectively, while azine with methoxy functionality at *meta* position of phenyl rings i. e. (1E,2E)-1,2-bis(1-(3-methoxyphenyl)ethylidene)hydrazine could produce two positional isomeric products **3ia** and **3ia'** with 53% and 32% yields, respectively. This may be due to the more steric hindrance produced by methyl, nitro and chloro substituents as compared to methoxy group. Disubstituted acetophenonazine also proceeded for the given reaction, producing 80% yield of the product **3la**. In addition, ketazines derived from propiophenone, cyclopropyl phenyl ketone and benzophenone were also screened for the annulation reaction under the given methodology and pleasantly all of these derivatives proceeded smoothly to generate desired products **3ma**, **3na** and **3oa** with product yields 89%, 81% and 93%, respectively. Furthermore, studying ketazine derived from fused ketone (e.g. 1-acetonaphthone), it was found that the benzene ring could also be effectively replaced by naphthalene moiety to provide the expected product **3pa** with 70% yield. Next, we evaluated the potential of ketazines prepared from heterocyclic ketones (e.g. 2-acetylthiophene and 4-acetylpyridine) for the proposed protocol. Out of which, to our delight, ketazine from 2-acetylthiophene could produce the desired product **3qa** in 76% yield. Unfortunately, heteroaromatic ketazine synthesized from 4-acetylpyridine failed to provide any isoquinoline product. Next, we attempted the azine synthesized from benzaldehyde for the proposed protocol. Disappointingly, we found that this azine was ineffective for annulation reaction under the given conditions.

After extensive screening with the azines and encouraged by these results, we next moved to test the potential of different internal and terminal alkynes for the given reaction (Table 3). With internal alkynes such as 1–phenyl–1–propyne, 1–phenyl–1–butyne and 3–

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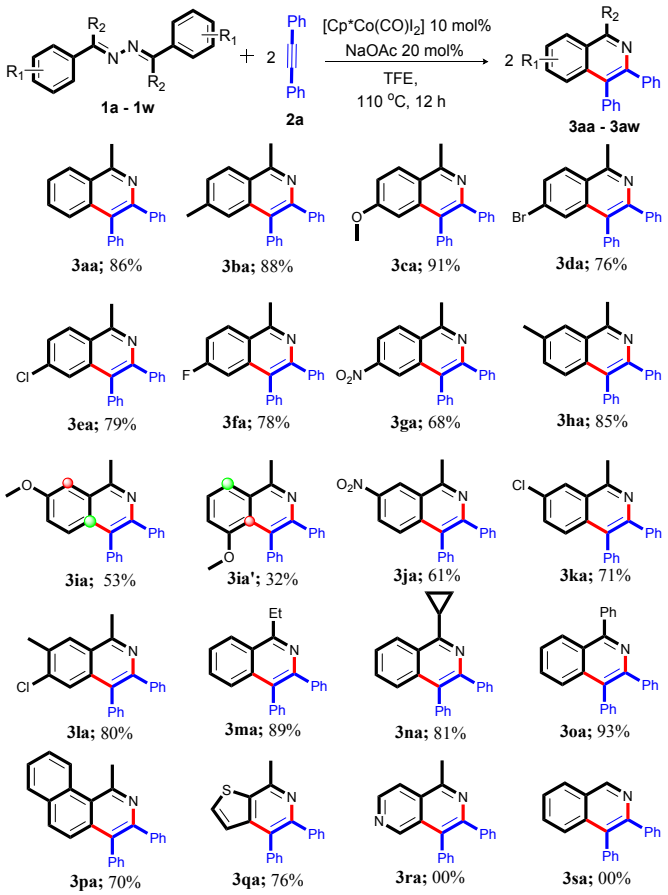
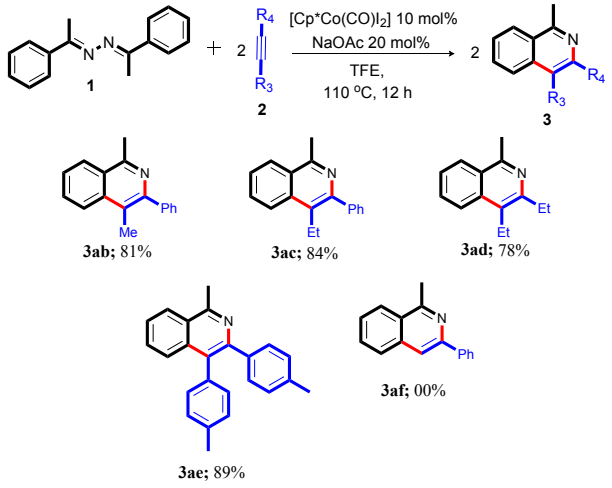
Table 2 Cobalt catalysed annulations of ketazines with diphenylacetylene[a]



[a]Reaction conditions: azine **1** (0.2 mmol), phenylacetylene **2** (0.5 mmol), [Cp*Co(CO)I$_2$] (10 mol%), NaOAc (20 mol%), TFE (2 mL), 110 °C, 12 h, isolated yield.

Table 3 Cobalt catalysed annulations of acetophenonazine with alkynes[a]

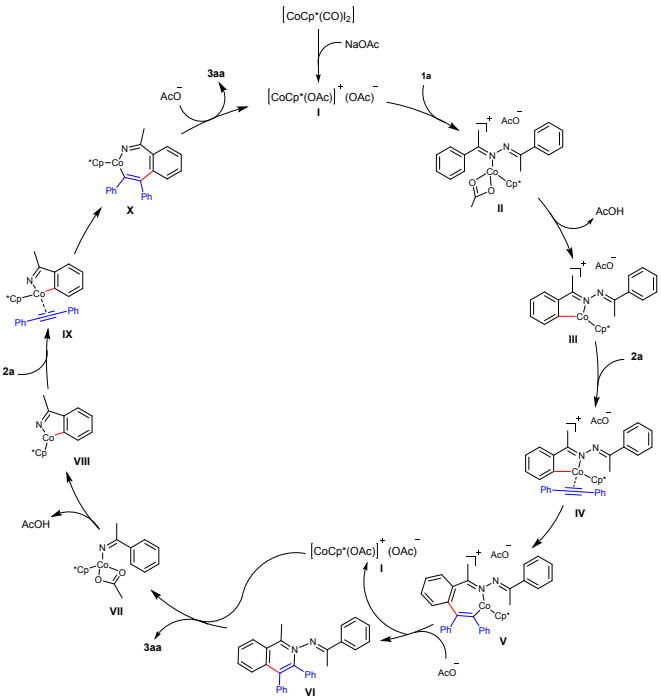


[a]Reaction conditions: acetophenonazine **1** (0.2 mmol), alkyne **2** (0.5 mmol), [Cp*Co(CO)I$_2$] (10 mol%), NaOAc (20 mol%), TFE (2 mL), 110 °C, 12 h, isolated yield.

hexyne, products **3ab**, **3ac** and **3ad** could be effectively achieved with 81%, 84% and 78% yields, respectively. Also, diphenylacetylene with methyl substituents at *para* positions of phenyl rings could generate the desired product **3ae** with 89% yield. While disappointingly, the terminal alkyne, phenylacetylene was ineffective for the annulation with acetophenonazine.

The developed synthetic methodology was then attempted for the gram scale synthesis of isoquinolines and pleasantly we could achieve its gram level synthesis with no hassle. For example, under the optimized reaction parameters, **1a** (5 mmol/1.18 g) was reacted with **2a** (12.5 mmol/2.22 g) to give the desired product **3aa** in 82% yield.

On the basis of mechanistic studies (please see supplementary information) and previous reports on Co and Rh catalyzed annulation reactions, a plausible mechanism for the present annulation *via* oxidative C−H and N−N bond activation is formulated in Scheme 3 using **1a** and **2a** as model substrates. [Cp*Co(CO)I$_2$] readily undergoes decarbonylation in the presence of NaOAc to possibly give monocationic complex [CoCp*(OAc)]$^+$ (**I**).[11b,11j] Initial coordination of nitrogen atom of ketazine **1a** to the Cp*Co centre followed by arene *ortho* C−H bond cleavage and cyclometallation leads to five-membered cobaltacycle **III** (identified by ESI-MS analysis).[14] Further, coordination of alkyne **2a** *p*-bond to cobaltacycle followed by its subsequent insertion into the Co−C bond of intermediate **IV** gives a seven membered cobaltacyclic key alkenyl intermediate **V**.[11b,11j,12a] Next, catalytic complex (**I**) is regenerated assisted by acetate ion giving intermediate **VI** (identified by ESI-MS analysis).[14] The catalytic complex **I** again bind with the intermediate **VI** cleaving the labile N−N bond to produce product **3aa** and complex **VII**. Further, acetate assisted *ortho* C−H bond cleavage of arene followed by cyclometallation gives five-membered cobaltacycle complex **VIII**.[11b,11j,12a] Successive coordination of other molecule of **2a** to complex **VIII** followed by insertion into the Co−C bond of complex **IX** generates seven membered cobaltacycle **X**.[11b,11j,12a] Finally, cobalt



Scheme 3 Plausible reaction mechanism

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catalytic complex **I** is regenerated in presence of acetate ion along with the formation of other **3aa** molecule.

Conclusions

In conclusion, azines were successfully employed for the sequential oxidative annulation reaction *via* C-H/N-N activation using cobalt catalyst for the synthesis of isoquinolines. Both the nitrogen atoms of azines could be incorporated to the anticipated isoquinoline products. Azines worked as a directing as well as oxidizing group for the proposed protocol. So, no external oxidant or silver salt needed for the completion of reaction. The developed methodology is efficient, cost effective and atom economic. Further, the reaction has higher functional group tolerance with good yields and applicability to gram scale.

Experimental

General experimental details and materials

All chemicals and solvents were purchased with high purities and used without further purification. Cobalt catalysts were prepared by the reported methods in literature. The progress of the reaction was monitored by gas chromatography (GC) with a flame ionization detector (FID) with a capillary column (30 m × 0.25 mm × 0.25 μm) and thin layer chromatography (using silica gel 60 F-254 plates). The products were visualized with a 254 nm UV lamp. GC-MS (Rtx- 17, 30 m × 25 mm ID, film thickness (df = 0.25 μm) (column flow 2 mL min^{-1} , 80 °C to 240 °C at 10 °C min^{-1} rise) was used for the mass analysis of the products. Products were purified by column chromatography on 100-200 mesh silica gel. The ^1H NMR spectras were recorded on 400 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. The ^{13}C NMR spectras were recorded on 100 MHz spectrometer and Chemical shifts were reported in parts per million (δ) relative to tetramethylsilane (TMS) as an internal standard. Coupling constant (*J*) values were reported in hertz (Hz). Splitting patterns of proton are described as s (singlet), d (doublet), dd (doublet of doublet), t (triplet) and m (multiplet) in ^1H NMR spectroscopic analysis. The products were confirmed by GCMS, ^1H and ^{13}C NMR spectroscopy analysis. ESI-MS analysis was performed by using an Agilent Triple-Quad LC MS 6520 spectometer.

General procedure of formation of substituted isoquinoline by annulation of ketazines and alkynes

An oven-dried tube equipped with a magnetic stirrer bar was charged with ketazine **1** (0.2 mmol), alkyne **2** (0.5 mmol), [$Cp^*Co(CO)I_2$] (10 mol%) and sodium acetate (NaOAc) (20 mol%). Subsequently, the tube was evacuated, purged with nitrogen gas three times and sealed. Then, TFE (2 mL) was added using syringe under nitrogen atmosphere and the sealed tube was placed in a preheated oil bath at 110 °C for 12 h. After the completion of reaction, reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure to get the crude residue which was then purified by silica gel column chromatography using pet ether/ethyl acetate as eluent to afford the desired pure product **3**.

Experimental characterization data for isoquinoline products

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1-Methyl-3,4-diphenylisoquinoline (3aa)[10c,11c]**:** Pale yellow solid; m.p. 154-156 °C; ^1H NMR (400 MHz, CDCl3) δ 8.20 – 8.18 (m, 1H), 7.66 – 7.64 (m, 1H), 7.59 – 7.56 (m, 2H), 7.36 – 7.32 (m, 5H), 7.24 – 7.16 (m, 5H), 3.07 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.69, 149.40, 140.98, 137.56, 135.99, 131.37, 130.23, 129.87, 129.16, 128.14, 127.55, 127.08, 126.88, 126.48, 126.21, 126.13, 125.49, 22.67; GCMS (EI 70 eV) m/z (% rel. inten.) 295 (M+), 294, 252, 146.

1,6-Dimethyl-3,4-diphenylisoquinoline (3ba)[11c,12a]**:** White solid; m.p. 159-161 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.9 Hz, 1H), 7.42 – 7.30 (m, 7H), 7.24 – 7.16 (m, 5H), 3.05 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.34, 149.47, 141.00, 140.28, 137.69, 136.24, 131.42, 130.24, 128.79, 128.71, 128.14, 127.53, 127.01, 126.84, 125.45, 125.08, 124.54, 22.55, 22.11; GCMS (EI 70 eV) m/z (% rel. inten.) 309 (M+), 308, 252, 146.

6-Methoxy-1-methyl-3,4-diphenylisoquinoline (3ca)[11c,12a]**:** Pale yellow solid; m.p. 179-181 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.1 Hz, 1H), 7.40 – 7.31 (m, 5H), 7.22 – 7.16 (m, 6H), 6.91 (d, *J* = 4.2 Hz, 1H), 3.71 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.55, 156.96 , 150.08, 141.14, 138.06, 137.85, 131.27, 130.19, 128.58, 128.23, 127.52, 127.43, 127.05, 126.84, 121.86, 118.66, 104.50, 55.17, 22.56; GCMS (EI 70 eV) m/z (% rel. inten.) 325 (M+), 324, 281, 154, 146.

6-Bromo-1-methyl-3,4-diphenylisoquinoline (3da)[11c,12a]**:** Slightly yellow solid; m.p. 192-194 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 1.5 Hz, 1H), 7.65 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.42 – 7.29 (m, 5H), 7.24 – 7.14 (m, 5H), 3.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.74, 150.59, 140.59, 137.39, 136.80, 131.26, 130.17, 129.99, 128.39, 128.34, 128.29, 127.61, 127.43, 127.27, 127.15, 125.03, 124.57, 22.62; GCMS (EI 70 eV) m/z (% rel. inten.) 375 (M+2), 373 (M+), 374, 372, 293, 292, 252, 147, 139, 125.

6-Chloro-1-methyl-3,4-diphenylisoquinoline (3ea)[11c,12a]**:** Pale yellow solid; m.p. 171–173 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.8 Hz, 1H), 7.62 (s, 1H), 7.52 (d, *J* = 8.9 Hz, 1H), 7.38 – 7.29 (m, 5H), 7.22 – 7.13 (m, 5H), 3.05 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.63, 150.48, 140.42, 137.14, 136.78, 136.46, 131.24, 130.18, 128.51, 128.40, 127.63, 127.47, 127.44, 127.34, 127.20, 125.10, 124.38, 22.60; GCMS (EI 70 eV) m/z (% rel. inten.) 331 (M +2), 329 (M+), 330, 328, 252, 146.

6-Fluoro-1-methyl-3,4-diphenylisoquinoline (3fa)[11c,12a]**:** White solid; m.p. 145–147 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 9.1, 5.6 Hz, 1H), 7.38 – 7.30 (m, 5H), 7.26 – 7.23 (m, 1H), 7.18 – 7.14 (m, 5H), 3.06 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.46, 161.97, 157.48, 150.26, 140.46, 138.07, 137.04, 131.16, 130.18, 128.67, 128.57, 128.38, 127.62, 127.37, 127.16, 123.41, 116.84, 116.59, 109.99, 109.77, 22.69; GCMS (EI 70 eV) m/z (% rel. inten.) 313 (M+), 312, 270.

1-Methyl-6-nitro-3,4-diphenylisoquinoline (3ga)[11c,11j]**:** Yellow solid; m. p 169–171 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.34 (q, *J* = 9.1 Hz, 2H), 7.40 – 7.37 (m, 5H), 7.26 – 7.22 (m, 5H), 3.14 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.07, 151.57, 148.24, 139.95, 135.96, 135.83, 131.19, 130.45, 130.19, 128.72, 128.02,

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127.80, 127.73, 127.71, 127.59, 122.69, 119.90, 22.97; GCMS (EI 70 eV) m/z (% rel. inten.) 340 (M+), 339, 293, 292, 189, 154, 139.

1,7-Dimethyl-3,4-diphenylisoquinoline (3ha)[11c,12a]**:** Slightly yellow solid; 131-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.42 – 7.30 (m, 6H), 7.24 – 7.14 (m, 5H), 3.04 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.96, 148.62, 141.07, 137.75, 136.35, 134.17, 132.01, 131.36, 130.23, 129.03, 128.10, 127.52, 127.00, 126.76, 126.32, 126.08, 124.46, 22.67, 21.83; GCMS (EI 70 eV) m/z (% rel. inten.) 309 (M+), 308, 252, 146, 139.

7-Methoxy-1-methyl-3,4-diphenylisoquinoline (3ia)[10f,11j]**:** Yellow solid; m.p. 121-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 9.2 Hz, 1H), 7.38 – 7.31 (m, 6H), 7.25 – 7.13 (m, 6H), 3.97 (s, 3H), 3.02 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.84, 155.96, 147.71, 141.03, 137.72, 131.42, 131.32, 130.19, 129.13, 128.11, 127.98, 127.51, 127.29, 127.04, 126.68, 122.17, 103.54, 55.46, 22.81; GCMS (EI 70 eV) m/z (% rel. inten.) 325 (M+), 324, 281, 140, 139.

5-Methoxy-1-methyl-3,4-diphenylisoquinoline (3ia')[11h,12b]**:** White solid; m.p. 145-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 8.1 Hz, 1H), 7.23 – 7.20 (m, 2H), 7.13 – 7.10 (m, 8H), 6.94 (d, *J* = 7.1 Hz, 1H), 3.39 (s, 3H), 3.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.20, 157.03, 151.23, 141.75, 141.58, 130.53, 130.35, 127.90, 127.62, 127.41, 127.24, 127.16, 126.58, 125.74, 118.18, 110.26, 55.68, 23.48; GCMS (EI 70 eV) m/z (% rel. inten.) 325 (M+), 324, 308, 154.

1-Methyl-7-nitro-3,4-diphenylisoquinoline (3ja)[10h]**:** Yellow solid; m.p. 182–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (d, *J* = 3.2 Hz, 1H), 8.30 (dd, *J* = 6.6, 2.7 Hz, 1H), 7.79 (d, *J* = 9.2 Hz, 1H), 7.41 – 7.33 (m, 5H), 7.23 – 7.16 (m, 5H), 3.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.88, 152.97, 145.34, 139.92, 138.96, 136.37, 131.14, 130.19, 129.10, 128.56, 128.28, 127.75, 127.71, 124.98, 123.03, 122.38, 22.76; GCMS (EI 70 eV) m/z (% rel. inten.) 340 (M+), 339, 293, 292, 146, 139.

7-Chloro-1-methyl-3,4-diphenylisoquinoline (3ka)[11b,11c]**:** White solid; m.p. 143–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.61 – 7.59 (m, 1H), 7.55 – 7.49 (m, 1H), 7.40 – 7.29 (m, 5H), 7.24 – 7.13 (m, 5H), 3.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.81, 149.69, 140.44, 137.00, 134.42, 132.30, 131.25, 130.72, 130.18, 129.03, 128.31, 128.15, 127.63, 127.36, 127.13, 126.82, 124.50, 22.60; GCMS (EI 70 eV) m/z (% rel. inten.) 331 (M +2), 329 (M+), 330, 328, 252, 146.

6-Chloro-1,7-dimethyl-3,4-diphenylisoquinoline (3la)[13b]**:** Slightly yellow solid; m.p. 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.48 (s, 1H), 7.38 – 7.29 (m, 5H), 7.23 – 7.13 (m, 5H), 3.03 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.50, 149.39, 140.29, 138.99, 137.05, 134.81, 133.89, 131.26, 130.19, 128.64, 128.27, 127.59, 127.52, 127.29, 127.10, 125.65, 125.10, 22.32, 20.93; GCMS (EI 70 eV) m/z (% rel. inten.) 345 (M +2), 343 (M+), 342, 307, 265, 154 ,146.

1-Ethyl-3,4-diphenylisoquinoline (3ma)[11c,12a]**:** White solid; m.p. 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.24 (m, 1H), 7.68 – 7.66 (m, 1H), 7.60 – 7.56 (m, 2H), 7.41 – 7.32 (m, 5H), 7.25 – 7.17 (m, 5H), 3.46 (q, *J* = 7.5 Hz, 2H), 1.55 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.23, 149.21, 141.04, 137.71, 136.35, 131.38, 130.34, 129.71, 128.97, 128.20, 127.53, 127.09, 126.89, 126.43, 126.40, 125.28, 125.12, 28.74, 13.94; GCMS (EI 70 eV) m/z (% rel. inten.) 309 (M+, 55), 308, 293, 154, 146.

1-Cyclopropyl-3,4-diphenylisoquinoline (3na)[10e,13b]**:** White solid; m.p. 149-151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 – 8.47 (m, 1H), 7.65 – 7.64 (m, 1H), 7.63 – 7.55 (m, 2H), 7.39 –7.33 (m, 5H), 7.24 – 7.21 (m, 2H), 7.17 – 7.15 (m, 3H), 2.85 –2.78 (m, 1H), 1.41 – 1.38 (m, 2H), 1.15 –1.11 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.53, 148.68, 141.15, 137.98, 136.14, 131.42, 130.40, 129.56, 128.22, 128.01, 127.30, 127.02, 126.78, 126.30, 126.24, 126.21, 124.81, 13.60, 9.35; GCMS (EI 70 eV) m/z (% rel. inten.) 321 (M+), 320, 243, 152.

1,3,4-Triphenylisoquinoline (3oa)[10c,12a]**:** Yellow solid; m.p. 169–171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.4 Hz, 1H), 7.84 – 7.82 (m, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.61 – 7.49 (m, 5H), 7.45 – 7.36 (m, 5H), 7.32 – 7.30 (m, 2H), 7.19 – 7.13 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.77, 149.59, 140.80, 139.72, 137.52, 136.99, 131.34, 130.45, 130.23, 129.97, 129.81, 128.55, 128.31, 128.29, 127.53, 127.29, 127.00, 126.59, 126.02, 125.44; GCMS (EI 70 eV) m/z (% rel. inten.) 357 (M+), 171, 118.

1-Methyl-3,4-diphenylbenzo[h]isoquinoline (3pa)[10h,11j]**:** Slightly yellow solid; m.p. 142–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, *J* = 9.3 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.78 – 7.71 (m, 2H), 7.66 – 7.63 (m, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 2H), 7.38 – 7.31 (m, 3H), 7.27 – 7.19 (m, 5H), 3.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.39, 150.88, 140.59, 138.02, 137.21, 132.96, 131.64, 131.09, 130.18, 129.64, 128.71, 128.23, 127.61, 127.29, 127.27, 127.15, 126.82, 126.59, 124.20, 123.94, 30.49; GCMS (EI 70 eV) m/z (% rel. inten.) 345 (M+), 344, 302, 164.

7-Methyl-4,5-diphenylthieno[2,3-c]pyridine (3qa)[10f,11j]**:** White solid; m.p. 145–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 5.3 Hz, 1H), 7.34 – 7.26 (m, 5H), 7.24 – 7.15 (m, 6H), 2.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.37, 150.92, 145.67, 140.45, 138.26, 134.20, 133.75, 130.86, 130.52, 130.27, 128.21, 127.67, 127.10, 127.01, 124.22, 23.63; GCMS (EI 70 eV) m/z (% rel. inten.) 301 (M+), 300, 258, 150, 149.

1,4-Dimethyl-3-phenylisoquinoline (3ab)[11c,11j]**:** Off white solid; m.p. 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 7.6 Hz, 1H), 7.75 – 7.72 (m, 1H), 7.63 – 7.55 (m, 3H), 7.47 – 7.44 (m, 2H), 7.39 – 7.35 (m, 1H), 2.98 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.85, 150.60, 141.52, 136.25, 129.84, 129.18, 128.06, 127.39, 126.23, 126.16, 126.05, 124.11, 122.17, 22.40, 15.37; GCMS (EI 70 eV) m/z (% rel. inten.) 233 (M+), 232, 217, 189, 115, 109.

4-Ethyl-1-methyl-3-phenylisoquinoline (3ac)[10f,11j]**:** White solid; m.p. 121–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.3 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.72 (t, *J* = 7.0 Hz, 1H), 7.58 (t, *J* = 7.9 Hz, 1H), 7.51 – 7.38 (m, 5H), 3.05 – 2.96 (m, 5H), 1.25 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.81, 150.69, 141.83, 135.13, 129.80, 129.17, 128.53, 128.12, 127.37, 126.69, 126.28, 126.14, 124.12, 22.45, 21.64, 15.66; GCMS (EI 70 eV) m/z (% rel. inten.) 247 (M+), 246, 232, 231, 230, 115.

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3,4-Diethyl-1-methylisoquinoline (3ad)[10f,13b]**:** Yellow liquid; b. p. 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 3.06 – 2.90 (m, 7H), 1.35 – 1.25 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.72, 152.47, 135.14, 129.48, 127.19, 126.11, 126.05, 125.25, 123.32, 28.40, 22.26, 20.64, 15.20, 14.88; GCMS (EI 70 eV) m/z (% rel. inten.) 199 (M+), 198, 184, 170, 128, 91.

1-Methyl-3,4-di*p*-tolylisoquinoline (3ae)[11c,11j]**:** White solid; m. p. 134-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.15 (m, 1H), 7.66 – 7.63 (m, 1H), 7.56 – 7.53 (m, 2H), 7.27 – 7.24 (m, 2H), 7.16 – 7.09 (m, 4H), 7.00 – 6.98 (m, 2H), 3.06 (s, 3H), 2.38 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.37, 149.16, 137.96, 136.61, 136.49, 136.29, 134.53, 131.16, 130.12, 129.79, 128.92, 128.31, 126.30, 126.26, 126.01, 125.46, 22.55, 21.26, 21.14; GCMS (EI 70 eV) m/z (% rel. inten.) 323 (M+), 322, 307, 265, 153, 146, 132.

Conflicts of interest

There are no conflicts to declare.

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