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Single-Step-Synthesis of 3-Iodoquinolines from 1-(2-aminophenyl)ketones through a Regioselective (6-endo dig) Electrophilic-cyclization

Srinivasarao Yaragorla,*[a,b] Abhishek Pareek,[a,b] Ravikrishna Dada[a,b] and Pyare Lal Saini[b]

Dedication (We dedicate this work to Prof. Goverdhan Mehta on the occasion of his 74th Birth Day)

Abstract: Highly facile, single-step synthetic approach of 3-iodoquinolines is developed for the first time from readily available 2-aminobenzophenones and terminal alkynes. The reaction involves a nucleophilic addition of terminal alkynes to 2-aminobenzophenones followed by intramolecular regioselective iodocyclization (6-endo dig) to furnish 2,4-disubstituted, 3-iodoquinolines in high yields. In case of 2,4-diaryl substitution, the products were isolated without a column chromatography.

Introduction

Quinolines are important heterocyclic molecules present in a large number of natural products (alkaloids), pharmaceutical and agrochemicals.[1] Quinoline moiety also serves as a key building block for the synthesis of many synthetic molecules with diverse pharmacological properties.[2] Further functionalized quinolines are widely used as organic materials[3] and catalysts.[4] Owing to their diverse applications the synthesis of quinoline and their derivatives become an active research area[5] starting from well-known classic reactions such as Combes synthesis, Conrad–Limpach–Knorr synthesis, Friedlander reaction, and Skraup–Doebner–Von Miller reaction[6] to metal catalyzed approaches .[7] Among the quinoline derivatives, in particularly halogenated quinolones are of special interest due to the reason that they provide a viable platform for further functionalization[8].

In recent years, iodine mediated electrophilic cyclization of heteroatom nucleophiles with tethered alkynes has proven to be an effective method for the synthesis of a large number of heterocyclic molecules.[9] While searching for the reported methods for the synthesis of 3-iodoquinolines,[10-13] we found that few reports are available through an iodocyclization of tethered alkynes with the amino nucleophile (Figure 1). For example, Flynn et al.[10] reported an electrophilic iodocyclization of 1-(2-N,N-dimethylaminoaryl)-2-yn-ols (Figure 1, eq 1), Liang and his co-workers[11] reported another iodocyclization of 1-(2- N-tosylaminoaryl)-2-yn-ols (Figure 1, eq 2). Later M. S. Reddy et al[12] extended the scope of this method with (unprotected) 1-(2-aminoaryl)-2-yn-ols (Figure 1, eq 3). Though the efficient methods are available, the following limitations such as a multi-step synthesis, usage of alkynylmagnesium bromide, alkynyl lithium reagents, halogenated solvents and non-readily available starting materials indicates the need to develop an efficient and eco-friendly single step synthesis. In continuation of our research aimed towards alkyne tethered inter and intramolecular annulations and sustainable chemical synthesis,[14] herein we designed a single step, green synthesis of 3-iodoquinolines from readily available 2-aminobenzophenones and terminal alkynes.

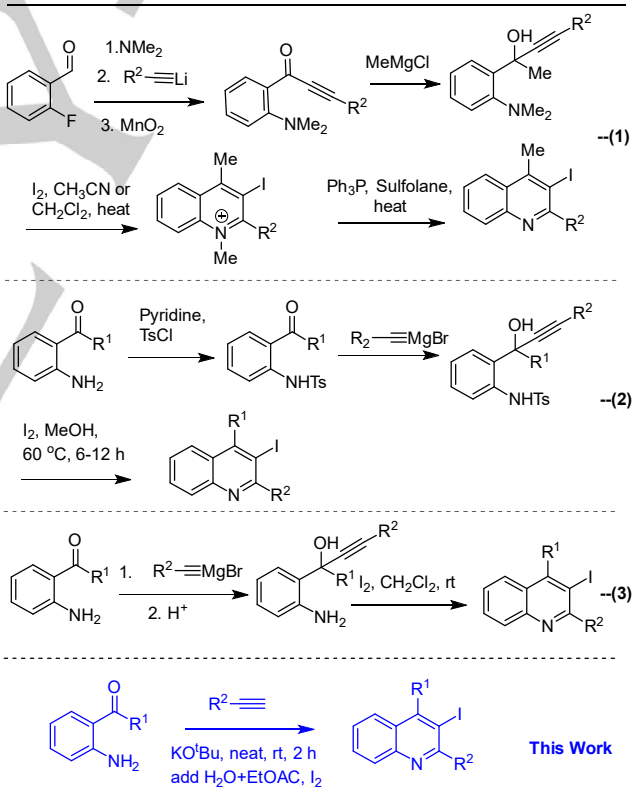

Figure 1. Comparison of iodocyclization strategies for 3-iodoquinolines

Results and Discussion

To implement our idea of single step synthesis, the in-situ generation of propargylic alcohol is a key task because all the previous approaches were involved in a multi-step synthesis and isolation of the propargylic alcohol. A thorough literature survey suggested that Chen et al reported a solvent-free synthesis of

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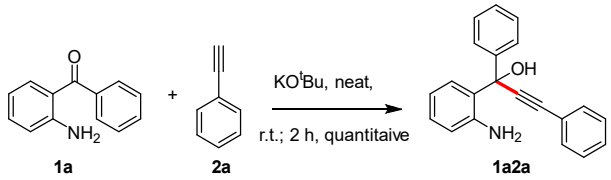
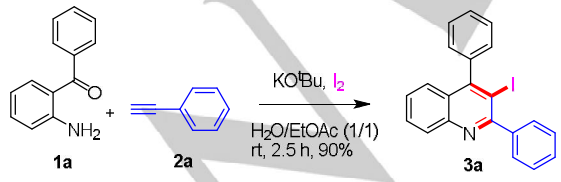
propargylic alcohols from arylacetylenes and ketones.[15] Recently our group reported the synthesis of 3-oxindolyl propargylic alcohols from readily available isatins and terminal alkynes using potassium *tert*-butoxide under neat conditions at room temperature[14a] and unlike Chen's report, our method works with aryl and aliphatic alkynes. With this background, we treated 2-aminobenzophenone (**1a**) and phenylacetylene (**2a**) with KO^{t}Bu under neat conditions at room temperature and after 2 h we were glad to isolate 1-(2-aminophenyl)-1,3-diphenylprop-2-yn-1-ol **1a2a** (Scheme 1) in quantitative yield.

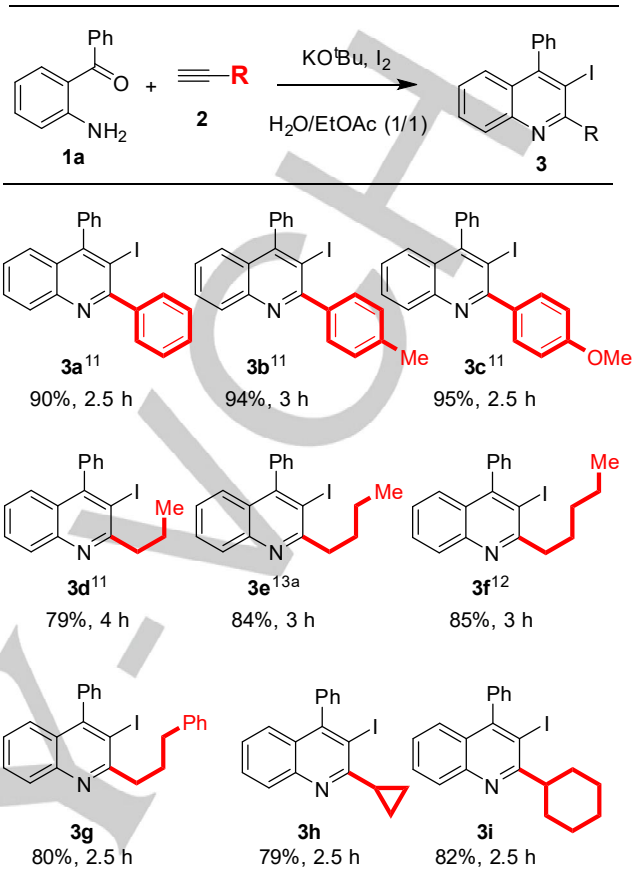


Scheme 1. Direct synthesis of **1a2a** without using organometallic reagents

Encouraged by this result, we planned to investigate a one-pot iodocyclization of **1a2a** to achieve the synthesis of 2,4-diphenyl-3-iodoquinoline (**3a**). Hence a mixture of **1a** (110 mg, 0.5 mmol), **2a** (77 mg, 076 mmol) and KO^{t}Bu (85 mg, 0.76 mmol) were slowly stirred in a round bottom flask under nitrogen atmosphere at room temperature for 2 h and then iodine was (256 mg, 1 mmol) added and the stirring continued for 6 h. However, the proposed iodocyclization could not occur and only the propargyl alcohol **1a2a** was isolated again. Agreeing that solvent is required for iodocyclization, the reaction was repeated again and water (1 mL) was added along with iodine to the reaction after 2 h, but cyclization of **1a2a** did not happen. In the next time H_2O/DCM (1:1) 2 mL was added and delightfully the reaction yielded 76% of desired product **3a** after 1 h. When the solvent combination is changed to H_2O/DCE, a slight increase in the yield was observed (82%). Encouraged by the success of a single step synthesis of 3-iodo-2,4-diphenylquinoline **3a** in 82% yield at room temperature, we further thought of making this method more environmental friendly reaction by avoiding the halogenated solvents. Hence other combinations of solvents such as MeOH/H_2O and Toluene/H_2O were tried but none of them were found effective. Nevertheless, aqueous-ethyl acetate (H_2O/EtOAc, 1:1) gave an excellent yield of **3a** (90%) in 2.5 h (Scheme 2) [refer to supporting information for the optimization Table] without a column chromatography and this made our synthetic protocol certainly a better and economic synthesis when compared to the existing methods.

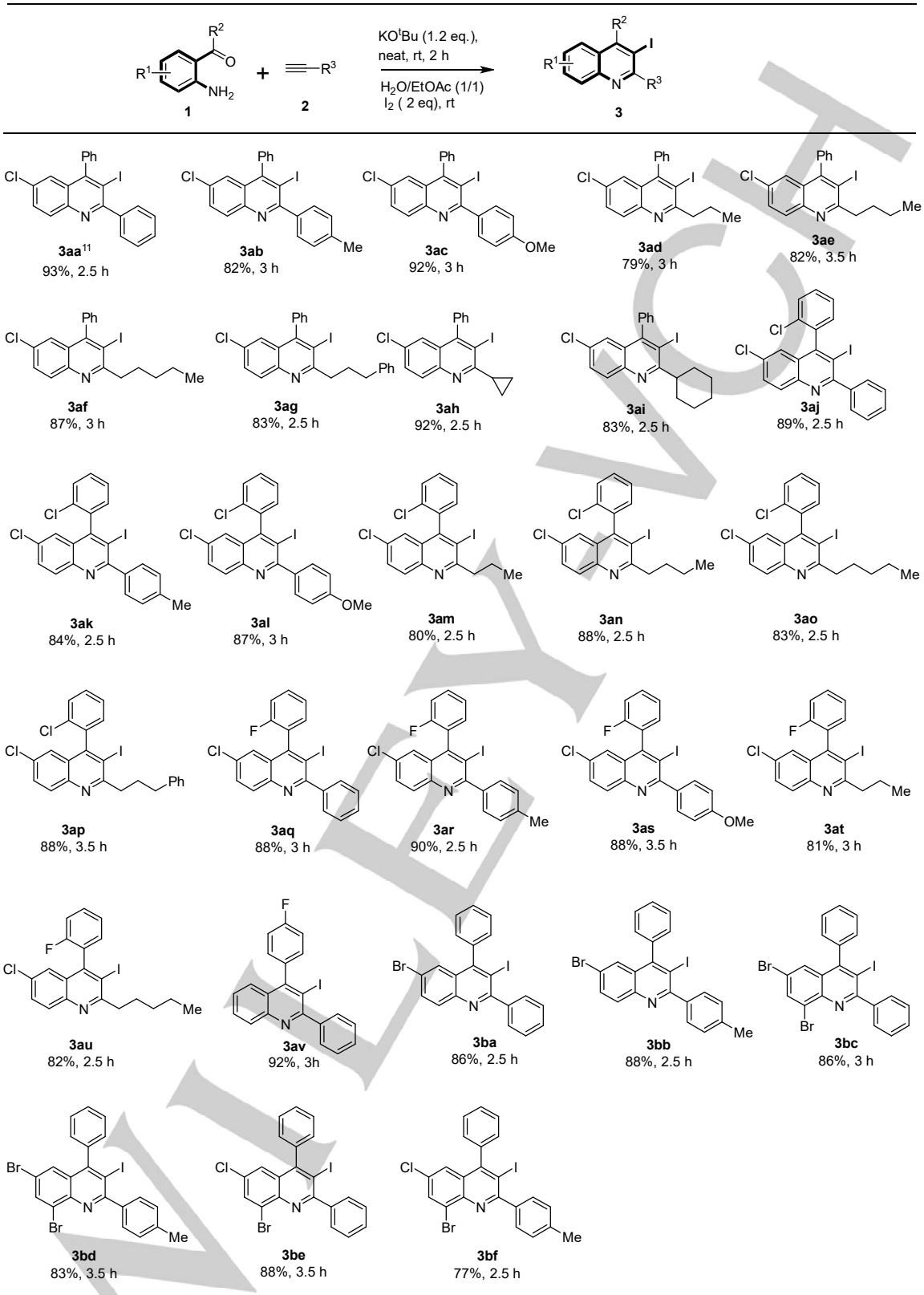


Scheme 2. Single-Step-Synthesis of **3a** (A Green Synthesis)



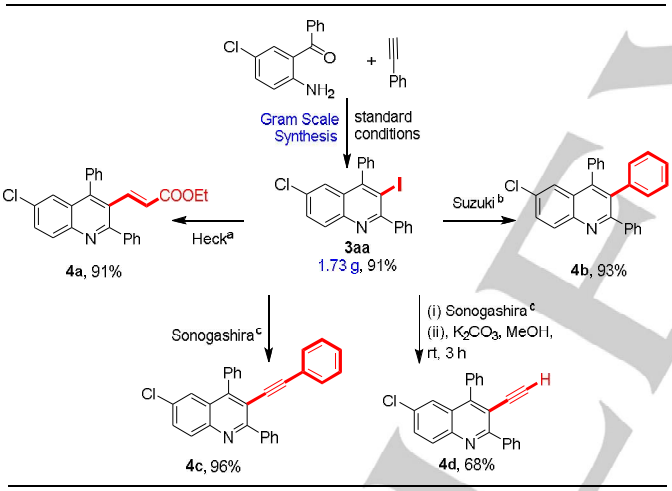
Scheme 3. Scope of various alkynes in the single step synthesis of 2,4-disubstituted, 3-iodoquinolines. *Reaction conditions*: a mixture of **1a** (1 equiv), **2** (1.5 equiv.), KO^{t}Bu (1.5 equiv) were stirred at rt for 2 h and then added aq-ethyl acetate (2 mL, 1:1) and I_2 (2 equiv.)

After developing a suitable experimental condition for a single step synthesis of 3-iodo-2,4-diphenylquinoline (**3a**) from 2-aminobenzophenone (**1a**) and phenylacetylene (**2a**), we were interested in studying the scope of different terminal alkynes in the iodocyclization reaction as depicted in the Scheme 3. Hence **1a** was treated with p-tolylacetylene (**2b**) in presence of KO^{t}Bu/I_2 in aqueous ethyl acetate (1:1) for 3 h to obtain the iodoquinoline **3b** in 94% yield. Similarly, another aryl alkyne, 4-methoxy phenylacetylene (**2c**) also gave the desired product **3c** in 95% yield after 2.5 h. Encouraged by the reactivity of aryl alkynes; we further investigated the reactivity of aliphatic alkynes. Interestingly, 1-pentyne (**2d**), 1-hexyne (**2e**), 1-heptyne (**2f**) and pent-4-yn-1-ylbenzene (**2g**) reacted with 2-aminobenzophenone (**1a**) and yielded the respective iodoquinolines **3d**, **3e**, **3f** and **3g** in high yields after the purification by column chromatography (Scheme 3). Latter cyclic alkynes such as cyclopropyl acetylene (**2h**) and ethynylcyclohexane (**2i**) also reacted with **1a** under standard optimized conditions and furnished the desired products **3h** and **3i** in 79 and 82% respective yields.



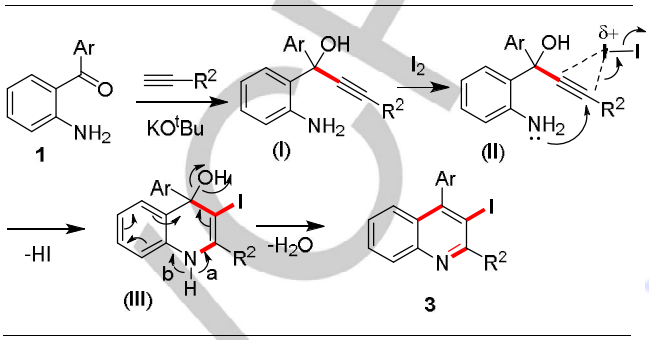
Scheme 4. Substrate scope in the single step synthesis of 2,4-disubstituted, 3-iodoquinolines. *Reaction conditions*: a mixture of **1** (1 equiv.), **2** (1.5 equiv.), KO^{t}Bu (1.5 equiv.) was stirred at rt for 2 h and then added aq-ethyl acetate (2 mL, 1:1) and I_2 (2 equiv.) at rt.

Encouraged by the participation of diverse alkynes such as aryl, acyclic and cyclic alkynes with 2-aminobenzophenone in the one pot synthesis of 3-iodo quinolines, further the generality of the synthetic protocol is expanded and described in the Scheme 4. 2-amino-5-chloro-benzophenone (**1b**) was treated with aryl alkynes such as **2a**, **2b** and **2c**, acyclic alkynes: **2d**, **2e**, **2f** and **2g** and cyclic alkynes: **2h** and **2i** under standard conditions and the respective 3-iodoquinolines **3aa-3ai** were obtained in excellent yields at room temperature. Another 2-aminophenone namely (2-amino-5-chlorophenyl)(2-chlorophenyl)methanone (**1c**) was also equally reactive towards the alkynes **2a-2g** and furnished the 2,4-disubstituted, 3-iodoquinolines **3aj-3ap** in high yields. Alkynes **2a**, **2b**, **2c**, **2d** and **2f** reacted with (2-amino-5-fluorophenyl)(2-chlorophenyl)methanone (**1d**) under the same reaction conditions to provide the respective products **3aq-3au** in good yields. Another 2-aminobenzophenone derivative **1e** yielded **3ba** and **3bb** in 86% and 88% yields. 2-amino-3,5-dibromobenzophenone (**1f**)[16] reacted with phenyl acetylene and p-tolyl acetylenes to furnish the respective 3-iodoquinolines **3bc** and **3bd** in excellent yields. Finally, 2-amino-3-bromo-5-chlorobenzophenone (**1g**)[16] also showed good reactivity towards the synthesis of **3be** and **3bf** with high yields (Scheme 4).



Scheme 5. Gram scale synthesis and synthetic utility of 3-iodoquinoline (**3aa**). *Conditions*: **Heck**[a]= ethyl acrylate (3 eq), $Pd(OAc)_2$ (5 mol%), Bu_4NBr (1 eq), Na_2CO_3 (1 eq), DMF, 80 °C, 21 h.; **Suzuki**[b]= $PhB(OH)_2$ (1.3 eq), $Pd(OAc)_2$ (5 mol%), Na_2CO_3 (1 eq), DMF/H_2O (2:1), 100 °C, 4 h.; **Sonogashira**[c]=Phenylacetylene (2 eq), $Pd(OAc)_2$ (2 mol%), DABCO (3 eq), MeCN, rt.; 12 h.

After the successful demonstration of the substrate scope, a gram scale synthesis of **3aa** (1.73 g, 91%, 3 h) is performed from **1a** (1 g, 4.32 mmol) and **2a** (0.63 g, 6.48 mmol) using KO^tBu (0.72 g, 6.48 mmol) and I_2 (1.09 g, 8.65 mmol) in aq-ethyl acetate (5 mL/5mL) at rt (Scheme 5). Then we moved to show the synthetic utility of 3-iodoquinolines and hence performed the following cross-coupling reactions (Scheme 5). 6-chloro-3-iodo-2,4-diphenylquinoline **3aa** was treated with ethyl acrylate under Heck reaction conditions[17] to yield **4a** in 91%. A Suzuki coupling[18] reaction with phenylboronic acid and iodide **3aa** furnished **4b** in excellent yield (93%). Sonogashira coupling[19] with phenylacetylene furnished **4c** in 96% yield and this reaction was also repeated with TMS-acetylene followed by silyl deprotection (K_2CO_3, MeOH, rt) furnished **4d** in 68% yield as schemed in Scheme 5.[20]



Scheme 6. Proposed mechanism for the synthesis of 3-iodoquinolines

The plausible mechanism for the single step synthesis of 3-iodoquinoline (**3**) from a simple 2-aminobenzophenone (**1**) and terminal alkyne (**2**) is described in the Scheme 6. The reaction initiated by the nucleophilic addition of acetylenic anion (generated with KO^tBu) on carbonyl carbon to furnish the corresponding akynol **I** (alkynol derivative **1a2a** was isolated and confirmed by spectral data). In the next step, cyclic iodonium ion formation (**II**) followed by a regioselective (6-endo dig), intramolecular nucleophilic attack by $–NH_2$ (S_N2) takes place to furnish intermediate **III**. Dehydration ($-H_2O$) of Quinoline **III** gives a stable 2,4-disubstituted, 3-iodoquinoline **3**.

Conclusions

In conclusion, we developed a first, single step synthesis of 2,4-disubstituted, 3-iodoquinolines from readily available 1-(2-aminophenyl)ketones and terminal alkynes in aqueous ethyl acetate using KO^tBu/I_2 at room temperature. This one pot economic synthesis proceeds through a regioselective iodocyclization and provides the large substrate scope of 3-iodoquinolines. Further 2,4-diaryl, 3-iodoquinolines were isolated without column chromatography. The synthetic utility of these compounds was demonstrated through cross-coupling reactions (Suzuki, Heck and Sonogoshira).

Experimental Section

General information: Unless otherwise noted, all reagents were used as received from commercial suppliers. Reactions were monitored using thin-layer chromatography (TLC) with aluminium sheets silica gel 60 F_{254} from Merck. TLC plates were visualized with UV light (254 nm), iodine treatment or using *p*-anisaldehyde or $KMNO_4$ stain. Column chromatography was carried out using silica gel 60-120 mesh as the stationary phase. NMR spectra were recorded at 400 & 500 MHz (Proton) and at 100 & 125 MHz (Carbon), respectively on Avance Bruker spectrometer. Chemical shifts (δ) are reported in ppm, using the residual

solvent peak in $CDCl_3$ (H: δ = 7.26 and C: δ = 77.0 ppm) as an internal standard, and coupling constants (*J*) are given in Hz. HRMS were recorded using ESI-TOF techniques. Melting points were measured with Lab India (MEPA) melting point apparatus.

General procedure for the synthesis of 3-iodo-2,4-diphenylquinoline (3): A mixture of terminal alkyne **2a** (77.6 mg, 0.76 mmol.), *t*-BuOK (85.2 mg, 0.76 mmol) and 2-aminobenzophenone **1a** (100 mg, 0.50 mmol) was placed into a reaction flask at room temperature under nitrogen atmosphere and the mixture was stirred for 2 h then 2 mL of water/EtOAc (1:1) were added to the reaction mixture along with Iodine (256 mg, 1 mmol) and further stir till completion of the reaction. The progress of reaction was monitored by TLC. After completion of the reaction, the resulting mixture was quenched with saturated solution of $Na_2S_2O_3$ (20 mL) and extracted with ethyl acetate (15 mL, thrice). Combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure and the residue was purified by washing with diethyl ether (3a-3c, 3aa-3ac, 3aj-3al and 3aq-3as) or column chromatography (3d-3i, 3ae-3ai, 3am-3ap and 3at-3au) to give of product **3a** (90%, 185 mg).

Synthesis of ethyl (E)-3-(6-chloro-2,4-diphenylquinolin-3-yl)acrylate (4a)[11] Ethyl acrylate (47 mg, 0.47 mmol), was added to a solution of 6-chloro-3-iodo-2,4-diphenylquinoline **3aa** (92 mg, 0.23 mmol) in DMF (1.8 mL) containing K_2CO_3 (53 mg, 2.5 eq) and Bu_4NBr (50 mg, 1 equiv) and stirred at room temperature for 5 min. $Pd(OAc)_2$ (5 mol %) was then added and the flask was flushed with N_2, sealed and allowed to stir at 80 °C for 22 h. The resulting mixture was filtered off, washed and extracted with diethyl ether. The combined organics were washed with water and then with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography with silica gel to give of product **4a** (95%, 91 mg).

Synthesis of 6-chloro-2,3,4-triphenylquinoline (4b)[11] $PhB(OH)_2$ (41.1 mg, 0.33 mmol) was added to a solution of 6-chloro-3-iodo-2,4-diphenylquinoline **3aa** (115.5 mg, 0.27 mmol) in 3.0 mL of DMF/H_2O (2:1) containing Na_2CO_3 (27.4 mg, 1 equiv) and stirred at room temperature for 5 min. $Pd(OAc)_2$ (5 mol %) was then added and the flask was flushed with N_2, sealed and allowed to stir at 100 °C for 4 h. The resulting mixture was filtered off, washed and extracted with diethyl ether. The combined organics were washed with water and then with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography with silica gel to give of product **4b** (91%, 92 mg).

Synthesis of 6-chloro-2,4-diphenyl-3-(phenylethynyl)quinolone (4c)[18] First $Pd(OAc)_2$ (2 mol%) was dissolved in MeCN (1mL). Then, the indicated amount of $Pd(OAc)_2$ acetonitrile solution was added to a mixure of alkyne (44.5 mg, 0.45 mmol), aryl halide **3aa** (100 mg, 0.22 mmol), DABCO (76 mg, 3 equiv), and MeCN (4 mL). Then mixure was stirred under N_2 at room temperature for 12 h. The resulting mixture was filtered off, washed and extracted with diethyl ether. The combined organics were washed with water and then with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography with silica gel to give of product **4c** (96%, 90 mg).

6-chloro-3-ethynyl-2,4-diphenylquinoline (4d) [18] First $Pd(OAc)_2$ (2 mol %) was dissolved in MeCN (1 mL). Then, the indicated amount of $Pd(OAc)_2$ acetonitrile solution was added to a mixture of tri methyl silyl acetylene (44.5 mg, 0.45 mmol), aryl halide **3aa** (100 mg, 0.26 mmol), DABCO (76 mg, 3 equiv), and MeCN (4 mL). Then mixture was stirred under N_2 at room temperature for 12 h. The resulting mixture was filtered off, washed and extracted with diethyl ether. The combined organics dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give product dissolved in 5 mL of MeOH then added was K_2CO_3 (62.7 mg, 2 equiv) stirred at rt for 3 h. The resulting mixture evaporated under reduced pressure. The Crude product extracted with EtOAc. Combined organics dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography with silica gel to give product **4d** (68%, 52 mg)

3-iodo-4-phenyl-2-(3-phenylpropyl)quinoline (3g): White solid; mp: 129-131 °C; yield: 80%; ^{1}H NMR (500 MHz, CDCl3): δ 8.12 (d, *J* = 8.5 Hz, 1H), 7.74-7.71 (m, 1H), 7.60-7.57 (m, 3H), 7.34-7.32 (m, 5H), 7.27-7.23 (m, 4H), 3.38 (t, *J* = 7.5 Hz, 2H), 2.90-2.86 (m, 2H), 2.30-2.25 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2, 153.9, 146.9, 142.3, 142.2, 129.7, 128.7, 128.6, 128.5, 128.4, 128.3, 127, 126.8, 127, 126.8, 126.5, 125.8, 100.3, 42.8, 35.8, 30.7 ppm; IR (KBr): 2939, 1649, 1443, 1375, 1122, 1090, 777 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{24}H_{20}IN$ $[M+H]^+$ 450.0718; found 450.0722.

2-cyclopropyl-3-iodo-4-phenylquinoline (3h): White solid; mp: 127-128 °C; yield: 79%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.5 Hz, 1H) 7.67-7.57 (m, 4H), 7.31-7.25 (m, 4H), 2.84-2.80 (m, 1H), 1.32-1.30 (m, 2H), 1.15-1.13 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 153.2, 146.9, 142.4, 129.6, 129.1, 128.7, 128.6, 128.3, 127.2, 126.7, 126.0, 101.8, 22.1, 11.0 ppm; IR (KBr): 1561, 1478, 1396, 1215, 1091, 982 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{18}H_{14}IN$ $[M+H]^+$ 372.0248; found 372.0248.

2-cyclohexyl-3-iodo-4-phenylquinoline (3i): Yellow solid; mp: 103-105 °C; yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12-8.05 (m, 1H), 7.95-7.69 (m, 1H), 7.60-7.54 (m, 1H), 7.39-7.33 (m, 3H), 7.29-7.24 (m, 3H), 3.56-3.53 (m, 1H), 2.17- 1.90 (m, 8H), 1.59-1.48 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.3, 153.6, 149.3, 147.1, 142.7, 138.3, 135.4, 129.5, 128.8, 128.6, 127.4, 126.8, 101.6, 49.3, 32.3, 26.6, 26.2 ppm; ESI *m/z* $[M+H]^+$ 414.2

6-chloro-3-iodo-4-phenyl-2-(p-tolyl)quinolone (3ab): Yellow solid; mp: 112-116 °C; yield: 82%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, *J* = 9 Hz, 1H), 7.67-7.64 (m, 1H), 7.61-7.56 (m, 5H), 7.37 (d, *J* = 2.5 Hz, 1H), 7.31-7.28 (m, 4H), 2.46 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.3, 153.9, 145.4, 141.6, 140.6, 138.7, 133, 131.1, 131, 129.2, 129.1, 128.9, 128.8, 128.7, 127.8, 125.6, 100.5, 21.5 ppm; HRMS (ESI) *m/z* calcd. for $C_{22}H_{15}ClIN$ $[M+H]^+$ 456.0015; found 456.0032

6-chloro-3-iodo-2-(4-methoxyphenyl)-4-phenylquinoline (3ac): Pale Yellow solid; mp: 118-122 °C; yield: 92%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, *J* = 9 Hz, 1H), 7.68-7.64 (m, 3H), 7.61-7.57 (m, 3H), 7.37 (d, *J* = 2 Hz, 1H), 7.30-7.28 (m, 2H), 7.03 (d, *J* = 9 Hz, 2H), 3.90 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.8, 160.6, 153.9, 145.4, 141.7, 135.9, 132.9, 131, 130.9, 129, 128.8, 128.7, 127.7, 125.5, 113.4, 100.2, 55.4 ppm; IR (KBr): 2946, 1642, 1439, 1126, 790 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{15}ClINO$ $[M+H]^+$ 471.9965; found 471.9948

6-chloro-3-iodo-4-phenyl-2-propylquinoline (3ad): Yellow solid; mp: 88-90 °C; yield: 79%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95-7.93 (m, 1H), 7.79 (d, *J* = 4 Hz, 1H), 7.68 (d, *J* = 2 Hz, 1H), 7.59-7.56 (m, 3H), 7.22-7.20 (m, 2H), 3.26-3.23 (m, 2H), 1.93-1.89 (m, 2H), 1.12 (t, *J* = 7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 163, 153.1, 145.3, 141.6, 132.2, 130.6, 130.4, 129, 128.8, 128.7, 127.5, 125.5, 101.7, 45.1, 22.4, 14.1 ppm; IR (KBr): 2941, 1645, 1449, 1378, 1126, 1020, 758 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{18}H_{15}ClIN$ $[M+H]^+$ 408.0015; found 408.0028

2-butyl-6-chloro-3-iodo-4-phenylquinoline (3ae): Pale White solid; mp: 128-130 °C; yield: 82%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.5 Hz, 1H), 7.62-7.54 (m, 4H), 7.28 (d, *J* = 2.5 Hz, 1H), 7.22-7.20 (m, 2H), 3.27 (t, *J* = 8 Hz, 2H), 1.88-1.84 (m, 2H), 1.57-1.52 (m, 2H), 1.02 (t, *J* = 7.5 Hz,

3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.8, 153.9, 149.9, 142.3, 129.7, 129.1, 129, 128.8, 128.7, 128.6, 128.4, 127, 126.8, 126.4, 100.3, 43, 31.4, 22.8, 14.1 ppm; HRMS (ESI) *m/z* calcd. for $C_{19}H_{17}ClIN$ $[M+H]^+$ 422.0172; found 422.0162

6-chloro-3-iodo-2-pentyl-4-phenylquinoline (3af): Yellow solid; mp: 88-90 °C; yield: 87%; ^{1}H NMR (500 MHz, CDCl3): δ 8.01 (d, *J* = 9 Hz, 1H), 7.63 (d, *J* = 2.5 Hz, 1H), 7.60-7.55 (m, 3H), 7.29 (d, *J* = 2.5 Hz, 1H), 7.23-7.21 (m, 2H), 3.29-3.26 (m, 2H), 1.90-1.87 (m, 2H), 1.53-1.42 (m, 4H), 0.96 (t, *J* = 7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.2, 153.1, 145.4, 141.6, 132.2, 130.6, 130.4, 129, 128.8, 128.7, 127.4, 125.5, 101.7, 43.2, 31.9, 28.8, 22.6, 14.2 ppm; HRMS (ESI) *m/z* calcd. for $C_{20}H_{19}ClIN$ $[M+H]^+$ 436.0328; found 436.0318

6-chloro-3-iodo-4-phenyl-2-(3-phenylpropyl)quinoline (3ag): Yellow solid; mp: 104-106 °C; yield: 83%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 9.2 Hz, 1H), 7.62-7.57 (m, 4H), 7.31-7.21 (m, 8H), 3.30 (s, 2H), 2.87-2.86 (m, 2H), 2.46-2.42 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6, 153.1, 145.3, 142.2, 141.5, 132.3, 130.7, 130.6, 130.4, 129, 128.7, 128.3, 127.5, 125.8, 125.6, 125.5, 101.7, 42.7, 35.8, 30.6 ppm; IR (KBr): 2895, 1648, 1463, 1303, 1150, 758 cm^{-1}; ESI *m/z* $[M+H]^+$ 484.02

6-chloro-2-cyclopropyl-3-iodo-4-phenylquinoline (3ah): Pale yellow solid; mp: 202-203 °C; yield: 92%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, *J* = 9.5 Hz, 1H), 7.59-7.56 (m, 4H), 7.27 (s, 1H), 7.24-7.22 (m, 2H), 2.83-2.80 (m, 1H), 1.30-1.29 (m, 2H), 1.15-1.13 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.7, 152.4, 145.4, 141.7, 131.7, 130.4, 130.3, 129.0, 128.8, 128.6, 127.6, 125.4, 102.9, 22.0, 11.2 ppm; IR (KBr): 1535, 1442, 1282, 1127, 1029 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{18}H_{13}ClIN$ $[M+H]^+$ 405.9859; found 405.9857.

6-chloro-2-cyclohexyl-3-iodo-4-phenylquinoline (3ai): Pale white solid; mp: 211-212 °C; yield: 83% ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, *J* = 9.5 Hz, 1H), 7.62-7.55 (m, 4H), 7.29 (s, 1H), 7.23-7.21 (m, 2H), 3.49-3.44 (m, 1H), 2.07-2.05 (m, 2H), 1.95-1.93 (m, 2H), 1.81-1.76 (m, 3H), 1.52-1.14 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 152.8, 145.5, 142.0, 132.0, 130.7, 130.3, 129.0, 128.7, 128.6, 127.7, 125.4, 102.7, 49.2, 32.1, 26.5, 26.1 ppm; IR (KBr): 2925, 2847, 1602, 1473, 1442, 1029 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{19}ClIN$ $[M+H]^+$ 448.0328; found 448.0328.

6-chloro-4-(2-chlorophenyl)-3-iodo-2-phenylquinoline (3aj): White solid; mp:156-157 °C; yield: 89%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, *J* = 9 Hz, 1H), 7.71-7.64 (m, 4H), 7.55-7.49 (m, 5H), 7.27 (d, *J* = 8.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.2, 151.4, 145.4, 143.0, 140.1, 133.5, 132.9, 131.3, 131.2, 130.7, 130.5, 130.2, 129.3, 128.8, 128.0, 127.5, 127.4, 124.7, 99.9 ppm; IR (KBr): 3211, 3106, 1569, 1423, 1418, 1289, 1063 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{12}Cl_2IN$ $[M+H]^+$ 475.9469; found 475.9473.

6-chloro-4-(2-chlorophenyl)-3-iodo-2-(p-tolyl)quinoline (3ak): White solid; mp: 167-168 °C; yield: 84%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, *J* = 9 Hz, 1H), 7.70-7.64 (m, 2H), 7.61 (d, *J* = 8 Hz, 2H), 7.56-7.50 (m, 2H), 7.34 (d, *J* = 8 Hz, 2H), 7.28-7.26 (m, 2H), 2.47 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.2, 151.4, 145.4, 140.2, 140.1, 138.8, 133.4, 132.9, 131.3, 131.2, 130.7, 130.4, 130.1, 129.2, 128.7, 127.4, 127.3, 124.7, 100.2, 21.4 ppm; IR (KBr): 3156, 2913, 1598, 1423, 1403, 1289 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{14}Cl_2IN$ $[M+H]^+$ 489.9654; found 489.9656.

6-chloro-4-(2-chlorophenyl)-3-iodo-2-(4-methoxyphenyl)quinolone (3al): Yellow solid; mp: 143-144 °C; yield: 87%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, *J* = 9 Hz, 1H), 7.69-7.57 (m, 4H), 7.41-7.26 (m, 4H), 7.04 (d, *J* = 9 Hz, 2H), 3.90 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.7, 160.1,159.9, 157.9, 148.6, 145.4, 135.6, 133.3, 131.2, 131.1, 130.8, 129.1, 127.6, 124.8, 124.7, 116.5, 116.3, 113.3 100.8, 55.3 ppm; IR (KBr): 3123, 2966, 1542, 1364, 1286 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{14}Cl_2INO$ $[M+H]^+$ 505.9575; found 505.9573

6-chloro-4-(2-chlorophenyl)-3-iodo-2-propylquinoline (3am): Pale Yellow solid; mp: 92-94 °C; yield: 80 %; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 9 Hz, 1H), 7.64-7.60 (m, 2H), 7.53-7.46 (m, 2H), 7.27-7.17 (m, 2H), 3.26-3.23 (m, 2H), 1.94-1.88 (m, 2H), 1.11 (t, *J* = 7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.1, 150.6, 145.4, 140.1, 133, 132.6, 130.8, 130.7, 130.6, 130.4, 130.1, 127.4, 127, 124.7, 101.8, 44.8, 22.4, 14.1 ppm; IR (KBr): 2935, 1692, 1402, 1313, 1090, 786 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{18}H_{14}Cl_2IN$ $[M+H]^+$ 441.9626; found 441.9622

2-butyl-6-chloro-4-(2-chlorophenyl)-3-iodoquinoline (3an): Pale yellow solid; mp:169-170 °C; yield: 88%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 9 Hz, 1H), 7.65-7.61 (m, 2H), 7.52-7.48 (m, 2H), 7.18 (d, *J* = 2.5 Hz, 2H), 3.30-3.27 (m, 2H), 1.89-1.86 (m, 2H), 1.58-1.53 (m, 2H), 1.03 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.2, 150.6, 145.4, 140.1, 132.9, 132.5, 130.7, 130.6, 130.6, 130.3, 130.1, 127.3, 126.9, 124.0, 101.7, 42.7, 31.1, 22.7, 14.0 ppm; IR (KBr): 2923, 1529, 1486, 1344, 1289, 1026 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{19}H_{16}Cl_2IN$ $[M+H]^+$ 455.9782; found 455.9785

6-chloro-4-(2-chlorophenyl)-3-iodo-2-pentylquinoline (3ao): Pale White solid; mp: 87-89 °C; yield: 83%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, *J* = 9 Hz, 1H), 7.57-7.54 (m, 2H), 7.39-7.33 (m, 2H), 7.29-7.24 (m, 2H) 3.56-3.53 (m, 1H), 2.17-1.89 (m, 8H), 1.59-1.48 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.3, 150.6, 145.4, 140.1, 133, 132.6, 130.8, 130.7 130.4, 130.1, 127.4, 127, 124.7, 101.8, 42.9, 31.8, 28.7, 22.6, 14.1 ppm; IR (KBr): 2902, 1702, 1586, 1324, 1140, 998, 703 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{20}H_{18}Cl_2IN$ $[M+H]^+$ 469.9939; found 469.9942

6-chloro-4-(2-chlorophenyl)-3-iodo-2-(3-phenylpropyl)quinoline (3ap): Pale Yellow solid; yield: 88%; mp: 106-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11-8.09 (d, *J* = 8.8 Hz, 1H) 7.74-7.70 (m, 1H), 7.60-7.55 (m, 3H), 7.37-7.32 (m, 1H), 7.28-7.22 (m, 6H), 3.38 (t, *J* = 8 Hz, 2H), 2.90-2.84 (m, 2H), 2.30-2.23 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 153.9, 146.9, 142.2, 142.1, 138.5, 135.3, 130.5, 129.7, 129, 128.8 128.7, 128.6, 128.5, 128.3, 127, 126.8, 126.4, 125.7, 100.3, 42.8, 35.8, 30.7 ppm; HRMS (ESI) *m/z* calcd. for $C_{24}H_{18}Cl_2IN$ $[M+H]^+$ 517.9939; found 517.9945

6-chloro-4-(2-fluorophenyl)-3-iodo-2-phenylquinoline (3aq): Pale white solid; mp:124-125 °C; yield: 88%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.5 Hz, 1H), 7.59-7.42 (m, 3H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.39-7.21 (m, 3H), 7.19 (d, *J* = 8 Hz, 2H), 7.17-7.14 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.2, 159.9, 157.9, 148.7, 145.3, 143.1, 133.5, 131.3, 131.3, 131.2, 131.1, 131.0, 129.0, 128.8, 127.7, 124.8, 124.7(2C), 116.5, 116.4, 100.4 ppm; IR (KBr): 3123, 2819, 1643, 1516, 1433, 1227 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{12}ClFIN$ $[M+H]^+$ 459.9765; found 459.9767.

6-chloro-4-(2-fluorophenyl)-3-iodo-2-(p-tolyl)quinoline (3ar): Pale yellow solid; mp: 137-138 °C; yield: 90%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 9 Hz, 1H), 7.51 (d, *J* = 8 Hz, 1H), 7.45-7.38 (m, 3H), 7.23-7.10 (m, 6H), 2.30 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.2, 159.9, 158.0, 148.6, 145.4, 140.3, 138.8, 133.4, 131.2, 131.1, 131.0, 129.3, 129.1, 129.0, 127.7, 124.8, 124.8, 124.7, 116.5, 116.4, 100.7, 21.5 ppm; IR (KBr): 3312, 3225, 1607, 1584, 1421, 1193 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{14}ClFIN$ $[M+H]^+$ 473.9921; found 473.9921

6-chloro-4-(2-fluorophenyl)-3-iodo-2-(4-methoxyphenyl)quinoline (3as): Pale yellow solid; mp: 130-132 °C; yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.4 Hz, 1H), 7.70-7.56 (m, 4H), 7.42-7.25 (m, 4H), 7.04 (d, *J* = 8.8 Hz, 2H), 3.91 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 158.8, 156.4, 147.3, 144.1, 134.3, 131.9, 129.9, 129.8, 129.7, 129.6, 127.8, 127.7, 126.3, 123.5, 123.4, 115.2, 115.0, 112.0, 99.5, 54.1 ppm; IR (KBr): 3116, 2947, 1623, 1459, 1328, 1126 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{14}ClFINO$ $[M+H]^+$ 489.9870; found 489.9867

6-chloro-4-(2-fluorophenyl)-3-iodo-2-propylquinoline (3at): Yellow solid; mp: 86-88 °C; yield: 81%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, *J* = 9 Hz, 1H), 7.55-7.53 (m, 1H), 7.50-7.45 (m, 1H), 7.26 (d, *J* = 7 Hz, 1H), 7.19-7.18 (m, 2H), 7.10-7.08 (m, 1H), 3.15 (t, *J* = 7.5 Hz, 2H), 1.86-1.80 (m, 2H), 1.03 (t, *J* = 7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 163, 159.9, 157.9, 147.8, 145.4, 132.6, 131.2, 131, 130.8, 130.7, 129, 127.4, 124.8, 116.5, 102.3, 45, 22.4, 14.1 ppm; HRMS (ESI) *m/z* calcd. for $C_{18}H_{14}ClFIN$ $[M+H]^+$ 425.9921; found 425.9924

6-chloro-4-(2-fluorophenyl)-3-iodo-2-pentylquinoline (3au): Yellow solid; mp: 91-93 °C; yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, *J* = 12 Hz, 1H), 7.7 (s, 1H), 7.56 (d, *J* = 6 Hz, 3H), 7.25 (d, *J* = 5.6 Hz, 2H), 3.30 (t, *J* = 8 Hz, 2H), 1.90 (s, 2H), 1.53-1.45 (m, 4H), 0.97 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 153.9, 146.9, 142.3, 129.8, 129.1, 129, 128.7, 128.4, 127, 126.8, 126.4, 100.3, 43.3, 31.9, 29, 22.6, 14.1 ppm; IR (KBr): 2899, 1603, 1446, 1422, 1398, 1117, 1027, 802 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{20}H_{18}ClFIN$ $[M+H]^+$ 454.0234; found 454.0222

4-(4-fluorophenyl)-3-iodo-2-phenylquinoline (3av): Pale white solid; mp: 182-183 °C; yield: 92%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, *J* = 2 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.76 (s, 1H), 7.65-7.63 (m, 2H), 7.51-7.49 (m, 3H), 7.30-7.27 (m, 5H)--- ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.5, 152.6, 145.8, 143.3, 139.0, 135.2, 131.1, 131.0, 130.9, 129.1, 128.8, 128.7, 128.0, 127.9, 116.1, 116.0, 93.4 ppm; IR (KBr): 2895, 1648, 1463, 1303, 1150, 758 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{13}FIN$ $[M+H]^+$ 426.0154 found 424.0151

6-bromo-3-iodo-2,4-diphenylquinoline (3ba): Pale yellow solid; mp: 142-145 °C; yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 9.2 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.68-7.49 (m, 9H), 7.30 (t, *J* = 8.5 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 153.9, 145.5, 143.4, 141.5, 133.7, 131.2, 129.2, 129.0, 128.9, 128.8, 128.3, 128.1, 121.5, 99.8 ppm; HRMS (ESI) *m/z* calcd. for $C_{21}H_{13}BrIN$ $[M+H]^+$ 485.9354; found 485.9353

6-bromo-3-iodo-4-phenyl-2-(p-tolyl)quinoline (3bb): White solid; mp: 156-158 °C; yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 9.2 Hz, 1H), 7.82-7.79 (m, 1H), 7.61-7.56 (m, 6H), 7.34-7.28 (m, 4H), 2.49 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 153.8, 145.6, 141.5, 140.6, 138.8, 133.6, 131.2, 129.2, 129.1, 128.9, 128.8, 128.8, 128.7, 128.2, 131.3, 100.1, 21.5 ppm; HRMS (ESI) *m/z* calcd. for $C_{22}H_{15}BrIN$ $[M+H]^+$ 499.9511; found 499.9512

6,8-dibromo-3-iodo-2,4-diphenylquinoline (3bc): Pale yellow solid; mp: 195-197 °C; yield: 86%; ^{1}H NMR (500 MHz, $CDCl_3$): 8.17 (d, *J* = 2 Hz, 1H), 7.79-7.77 (m, 2H), 7.61-7.58 (m, 3H), 7.52-7.51 (m, 4H), 7.28-7.26 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 154.4, 143.1, 142.7, 141.5, 136.4, 129.8, 129.1, 129.0, 128.9, 128.9, 128.8, 128.7, 127.8, 126.3, 120.5, 100.7 ppm; HRMS (ESI) *m/z* calcd. for $C_{21}H_{12}Br_2IN$ $[M+H]^+$ 563.8459; found 563.8462

6,8-dibromo-3-iodo-4-phenyl-2-(p-tolyl)quinoline (3bd): White solid; mp: 211-212 °C; yield: 83%; ^{1}H NMR (400 MHz, $CDCl_3$): 8.17 (d, *J* = 2 Hz, 1H), 7.72-7.70 (m, 2H), 7.61-7.59 (m, 4H), 7.51-7.27 (m, 4H), 2.48 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 154.4, 143.1, 141.6, 140, 139.1, 136.3, 129.9, 129.0, 128.9, 128.9, 128.7, 128.5, 128.5, 126.3, 120.3, 100.9, 21.5 ppm; HRMS (ESI) *m/z* calcd. for $C_{22}H_{14}Br_2IN$ $[M+H]^+$ 577.8616; found 577.8634

8-bromo-6-chloro-3-iodo-2,4-diphenylquinoline (3be): White solid; mp: 185-186 °C; yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.78 (d, *J* = 9.6 Hz, 2H), 7.61-7.58 (m, 3H), 7.52 (d, *J* = 6.8 Hz, 3H), 7.35 (s, 1H), 7.28-2.66 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3, 154.5, 142.8, 142.7, 141.5, 134.0, 132.5, 129.9, 129.8, 128.9, 128.8, 128.3, 127.8, 127.6, 126.2, 125.4, 100.7 ppm; IR (KBr): 2923, 1663, 1548, 1356, 1284, 841 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{12}BrClIN$ $[M+H]^+$ 519.8964; found 519.8959

8-bromo-6-chloro-3-iodo-4-phenyl-2-(p-tolyl)quinoline (3bf): White solid; mp: 205-206 °C; yield: 77%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 2.5 Hz, 1H), 7.71 (d, *J* = 8 Hz, 2H), 7.60-7.58 (m, 3H), 7.34-7.26 (m, 5H), 2.47 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.3, 154.4, 142.8 141.6, 139.9, 139.0, 133.9, 132.4,130.9, 129.8, 129.0, 128.9, 128.5, 128.2, 126.2, 125.4, 100.8, 21.4 ppm; IR (KBr): 2984, 1775, 1546, 1274, 1004, 780 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{14}BrClIN$ $[M+H]^+$ 533.9120; found 533.9124

Ethyl (E)-3-(6-chloro-2,4-diphenylquinolin-3-yl)acrylate (4a): Yellow solid; mp: 153-154 °C; yield: 91%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.8 Hz, 1H), 7.66-7.60 (m, 3H), 7.54-7.45 (m, 8H), 7.28 (t, *J* = 4.8 Hz, 2H), 5.40 (d, *J* = 8.8 Hz, 1H), 4.06-4.01 (m, 2H), 1.14 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 159.2, 147.8, 145.6, 141.2, 140.1, 135.5, 132.8, 131.3, 131.1, 129.7, 129.6, 128.9, 128.8, 128.7, 128.4, 127.3, 126.3, 126.0, 125.5, 60.4, 14.1 ppm; IR (KBr): 3064, 2976, 1715, 1634, 1546, 1368 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{26}H_{20}ClNO_2$ $[M+H]^+$ 414.1260; found 414.1262.

6-chloro-2,3,4-triphenylquinoline (4b): White solid; mp: 195-196 °C; yield: 93%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.8 Hz, 1H), 7.66 (dd, J_1 = 2.4, J_2= 8.8 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.23-7.25 (m, 5H) 7.21-7.19 (m, 3H), 7.12-7.09 (m, 2H), 7.01-6.99 (m, 3H), 6.87-6.85 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 146.9, 145.7, 140.8, 137.9, 136.2, 133.8, 132.4, 131.4, 131.2, 130.3, 130.2, 129.8, 128.1, 128.0, 127.8, 127.7, 127.6, 127.4, 126.5, 125.3 ppm; IR (KBr): 3471, 3014, 1654, 1501, 1319 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{27}H_{18}ClN$ $[M+H]^+$ 392.1206; found 392.1206.

6-chloro-2,4-diphenyl-3-(phenylethynyl)quinolone (4c): White solid; mp: 166-167 °C; yield: 96%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.8 Hz, 1H), 8.08 (dd, J_1 = 1.2, J_2 = 9.6 Hz, 2H), 7.65-7.53 (m, 10H), 7.24-7.22 (m, 3H), 6.97 (dd, J_1 = 1.6, J_2= 4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 151.0, 145.2, 139.8, 136.4, 132.8, 131.4, 131.1, 130.8, 129.9, 129.7, 129.1, 128.6, 128.5, 128.4, 128.2, 127.9, 126.5, 124.9, 122.8, 116.4, 99.1, 87.4 ppm; IR (KBr): 3459, 3024, 2983, 1542, 1403 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{29}H_{18}ClN$ $[M+H]^+$ 416.1205; found 416.1206.

6-chloro-3-ethynyl-2,4-diphenylquinoline (4d): Yellow sticky liquid; yield: 68%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.8 Hz, 1H), 8.08 (dd, J_1 = 1.6, J_2= 4 Hz, 2H), 7.69-7.45 (m, 10H), 3.10 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 152.6, 145.3, 139.6, 136.0, 132.9, 131.4, 131.1, 129.6, 129.1, 128.7, 128.4, 128.0, 127.9, 126.4, 125.0, 115.1, 87.2, 80.5 ppm; IR (KBr): 3398, 3136, 3083, 1642, 1592, 1403 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{23}H_{14}ClN$ $[M+H]^+$ 440.0892; found 440.0889.

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Keywords: 3-iodoquinolines •Iodocyclization •Green Synthesis • Regioselective • Cross-Coupling

[1] See for bioactivity of quinolines: a) J. P. Michael, *Nat. Prod. Rep.* **2007**, *24*, 223; b) K. Kaur, M. Jain, R. P. Reddy, R. Jain, *Eur. J. Med. Chem.* **2010**, *45*, 3245; c) N. Ahmed, K. G. Brahmbhatt, S. D. Sabde, D. Mitra, I. P. Singh, K. K. Bhutani, *Bioorg. Med. Chem.* **2010**, *18*, 2872; d) R. Musiol, M. Serda, S. Hensel-Bielowka, J. Polanski. *Curr. Med. Chem.* **2010**, *17*, 1960; e) V. R. Solomon, H. Lee, *Curr. Med. Chem.* **2011**, *18*, 1488; f) S. Jain, V. Chandra, P. K. Jain, K. Pathak, D. Pathak, A. Vaidya, Arab. *J. Chem.* **2016**, http://dx.doi.org/10.1016/j.arabjc.2016.10.009.

[2] V. V. Kouznetsov, L. Y. Vargas Mendez, C. M. M. Gomez, *Curr. Org. Chem.* **2005**, *9*, 141.

[3] a) J. L. Kim, I. S. Shin, H. Kim, *J. Am. Chem. Soc.* **2005,** *127*, 1614; b) S. Tao, L. Li, J. Yu, Y. Jiang, Y. Zhou, C. S. Lee, S. T. Lee, X. Zhang, O. Kwon, *Chem. Mater.* **2009**, *21*, 1284; c) V. Bhalla, V. Vij, M. Kumar, P. R. Sharma, T. Kaur, *Org. Lett.* **2012**, *14*, 1012.

[4] a) M. M. Biddle, M. Lin, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 3830; b) Y. Zhang, M. S. Sigman, *J. Am. Chem. Soc.* **2007**, *129*, 3076; c) B. Tan, Z. Shi, P. J. Chua, G. Zhong, *Org. Lett.* **2008**, *10*, 3425.

[5] For selected reviews on the quinoline synthesis: a) G. A. Ramann, B. J. Cowen, Molecules, 2016, 21, 986; b) S. M. Prajapati, K. D. Patel, R. H. Vekariya, S. N. Panchal, H. D. Patel, *RSC Adv.,* **2014**,4, 24463-24476; c) S. Madapa, A. Tusi, S. Batra, *Curr. Org. Chem.* **2008**, *12*, 1116; d) J. Marco-Contelles, E. Perez-Mayoral, A. Samadi, M. C. Carreiras, E. Soriano, *Chem. Rev.* **2009**, *109*, 2652. Selected recent syntheses: e) Y. Matsubara, S. Hirakawa, Y. Yamaguchi, Z.-I. Yoshida, *Angew. Chem., Int. Ed.* **2011**, *50*, 7670; f) H. Batchu, S. Bhattacharyya, S. Batra, *Org. Lett.* **2012**, *14,* 6330; g) X. Zhang, B. Liu, X. Shu, Y. Gao, H. Lv, J. Zhu, *J. Org. Chem.* **2012**, *77*, 501; h) X. Ji, H. Huang, Y. Li, H. Chen, H. Jiang, *Angew. Chem., Int. Ed.* **2012**, *51*, 7292; i) R. Yan, X. Liu, C. Pan, X. Zhou, X. Li, X. Kang, G. Huang, *Org. Lett.* **2013**, *15*, 4876; j) Y. Wang, C. Chen, J. Peng, M. Li, *Angew. Chem., Int. Ed.* **2013**, *52*, 5323; k) L. Zheng, B. Guo, R. Hua, *J. Org. Chem.* **2014**, *79*, 11541; l) K. Wu, Z. Huang, C. Liu, H. Zhang, A. Lei, *Chem. Commun.* **2015**, *51*, 2286; m) Q. Gao, S. Liu, X. Wu, A. Wu, *Org. Lett.* **2014**, *16*, 4582; n) P. Zhao, X. Yan, H. Yin, C. Xi, *Org. Lett.* **2014**, *16,* 1120.

[6] Combes synthesis: a) A. Combes, *Bull. Soc. Chim. Fr.* **1888**, *49*, 89; b) J. L. Born, *J. Org. Chem.* **1972**, *37*, 3952; c) W. S. Johnson, F. J. Mathews, *J. Am. Chem. Soc.* **1944**, *66*, 210. Skraup synthesis: d) Z. H. Skraup, *Chem. Ber.* **1880**, *13*, 2086; e) R. H. Manske, *Chem. Rev.* **1942**, *30*, 113; f) M. Warren, *Tetrahedron* **1964**, *20*, 2773. Gould−Jacobs synthesis: g) R. G. Gould, W. A. Jacob, *J. Am. Chem. Soc.* **1939**, *61*, 2890. For Conard −Limpach synthesis: h) M. Conrad, L. Limpach, *Chem. Ber.* **1887**, *20,* 944; i) F. Misani, M. T. Bogert, *J. Org. Chem.* **1945**, *10*, 347. Doebner−Von Miller synthesis: j) O. Doebner, W. V. Miller, *Chem. Ber.* **1881,** *14,* 2812; k) O. Doebner, W. V. Miller, *Chem. Ber.* **1883**, *16*, 1664. Povarov synthesis: l) L. S. Povarov, *Ser. Khim.* **1963**, 953; m) L. S. Povarov, B. M. Mikhailov, SSSR Izv. Akad. Nauk, *Ser. Khim.* **1963**, 953; n) V. V. Kouznetsov, *Tetrahedron* **2009**, *65*, 2721.

[7] For selected papers, see: a) G. S. Kumar, P. Kumar, M. Kapur, *Org. Lett.*, **2017**, 19, DOI: 10.1021/acs.orglett.7b00715.; b) A. M. Berman, J. C. Lewis, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130,* 14926; c) J. Horn, S. P. Marsden, A. Nelson, D. House, G. G. Weingarten, *Org. Lett.* **2008**, *10,* 4117; d) M. Arisawa, A. Nishida, M. Nakagawa, *J. Organomet. Chem.* **2006**, *691*, 5109; e) M. Movassaghi, M. D. Hill, *J. Am. Chem. Soc.* **2006,** 128, 4592; f) X.-Y. Liu, C.-M. Che, *Angew. Chem., Int. Ed.* **2008,** *47,* 3805. g) Z. Zhang, J. Tan, Z. Wang, *Org. Lett.* **2008**, *10*, 173; h) N. Sakai, K. Annaka, A. Fujita, A. Sato, T. Konakahara, *J. Org. Chem.* **2008,** *73*, 4160; i) A. Arcadi, M. Aschi, F. Marinelli, M. Verdecchia, *Tetrahedron.* **2008**, *64*, 5354; j) L. Li, W. D. Jones, *J. Am. Chem. Soc.* **2007,** *129*, 10707; k) B. Gabriele, R. Mancuso, G. Salerno, G. Ruffolo, P. Plastina, *J. Org. Chem.* **2007**, *72*, 6873; l) N. Sakai, K. Annaka, T. Konakahara, *J. Org. Chem.* **2006**, *71*, 3653; m) T. Godet, P. Belmont, *Synlett* **2008**, 2513.

[8] a) B. J. Newhouse, J. Bordner, D. J. Augeri, C. S. Litts, E. F. Kleinman, *J. Org. Chem.* **1992,** *57*, 6991; b) S.Torii, L. H. Xu, M. Sadakane, H. Okumoto, *Synlett.* **1992**, 513; c) M. Nobuhide, Y. Yoshinobu, I. Hiroshi, O. Yoshio, H. Tamejiro, *Tetrahedron Lett.* **1993,** *24,* 8263; d) M. Croisey-Delcey, A. Croisy, D. Carrez, C. Huel, A. Chiaroni, P. Ducrot, E Bisagni, L. Jin, G. Leclercq, *Bioorg. Med. Chem.* **2000**, *8,* 2629.

[9] a) T. Aggarwal, S. Kumar, A. K. Verma *Org. Biomol. Chem.* **2016**, *14*, 7639; b) X.-F. Ren, E. Turos, *Tetrahedron Lett.* **1993**, *34,* 1575; c) T. Kitamura, T. Takachi, H. Kawasato, H. Taniguchi, *J. Chem. Soc. Perkin Trans*. **1992,** *1*, 1969; d) T. Kitamura, S. Kobayashi, H. Taniguchi, K. Hori, *J. Am. Chem. Soc.* **1991**, *113*, 6240; e) R. W. M. Ten Hoedt, G. Van Koten, J. Noltes, *Synth. Commun.* **1977,** *7*, 61; f) T. Sonoda, M. Kawakami, T. Ikeda, S. Kobayashi, H. Taniguchi, *J. Chem. Soc. Chem. Commun*. **1976**, 612.

[10] K. O. Hessian, B. L. Flynn, *Org. Lett.* **2006,** 8, 243.

[11] S. Ali, H.-T. Zhu, X.-F. Xia, K.-G. Ji, Y.-F. Yang, X.-R. Song, Y.-M. Liang, *Org. Lett.* **2011,** *13*, 2598.

[12] M. S. Reddy, N. Thirupathi, Y. K. Kumar. *RSC Advances*, **2012,** *2*, 3986.

[13] a) X. Wang, W. Wang, D. Huang, C. Liu, X. Wang, Y. Hu, *Adv. Synth. Catal*. **2016**, *358*, 2332; b) P. J. Campos, C-Q, Tan, M. A. Rodriguez, E. Anon, *J. Org. Chem*. **1996**, *61*, 7195.

[14] a) S. Yaragorla, R. Dada, G. Singh, A. Pareek, M. Rana, A. K. Sharma, *Chemistry Select* **2016**, *1*, 6902; b) A. Pareek, R. Dada, M. Rana, A. K. Sharma, S. Yaragorla, *RSC Adv*. **2016**, *6*, 89732; c) S. Yaragorla, R. Dada, A. Pareek, G. Singh, *RSC Adv*. **2016**, *6*, 28865; d) G. Singh, S. Yaragorla, *RSC Adv.* **2017,** *7*, 18874; e) S. Yaragorla, R. Dada, G. Singh, *Synlett.* **2016**, *27*, 912; f) S. Yaragorla, G. Singh, R. Dada, *Tetrahedron Lett.* **2016**, *57*, 591; g) S. Yaragorla, G. Singh, R. Dada, *Tetrahedron Lett*. **2015**, *56,* 5924.

[15] S. Chen, F. Yuan, H. Zhao, B. Li, Res. *Chem. Intermed.* **2013**, *39,* 2391.

[16] Synthesis of **1e**, **1f** and **1g** are reported in the supporting information.

[17] a) R. F. Heck, *Palladium Reagents in Organic Synthesis*; Academic Press: San Diego, CA, 1985; pp 276-287; b) G. T. Crisp, *Chem. Soc. Rev.* **1998**, *27*, 427; c) S. Brase, A. D. Meijere, *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, **1998**; p 99.

[18] a) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147; b) A. Suzuki, *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, **1998**; 49; c) N. Miyaura, *Chem. Rev.* **1995**, 95, 2457.

[19] a) J. H. Li, Y. Liang, Y. X. Xie, *J. Org. Chem.* **2005**, *70*, 4393.

[20] Refer to the supporting information for complete experimental details of cross coupling reactions and copies of spectra for all new compounds.

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FULL PAPER

Iodocyclization*

Srinivasarao Yaragorla,[a,b] Abhishek Pareek,[a,b] Ravikrishna Dada[a,b] and Pyare Lal Saini[b]*

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Single-Step-Synthesis of 3-Iodo quinolines from 1-(2-aminophenyl) ketones through a Regioselective (6-endo dig) Electrophilic-cyclization

*A single-step-synthesis of 3-iodoquinolines is achieved through a regioselective iodocyclization. The synthesis commenced from readily available materials in aqueous-ethylacetate medium, promoted by KO^{t}Bu and I_2 at room temperature. The synthetic utility of the products in cross-coupling reactions was demonstrated.