Palladium-Catalyzed Intramolecular Biaryl Coupling: A Highly Efficient Avenue for Benzannulated Pyranoquinolines and Julolidine Derivatives

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Abstract: A new efficient route to the synthesis of benzannulated pyranoquinolines has been accomplished via palladium-catalyzed intramolecular aryl–aryl cross-coupling reactions. The coupling reactions proceeded smoothly under ligand-free conditions with the catalytic system $Pd(OAc)_2/Cs_2CO_3$/TBAB in high yields. Halogen-reduced product was not obtained in optimum reaction conditions. Regioselective synthesis of 5,6-dihydro-4*H*,8*H*-pyrido[3,2,1-*de*]phenanthridine is also described. In the latter case, a pronounced effect of base (Ag_2CO_3) has been observed on the efficiency of the conversion.

Key words: biaryl coupling, Heck reaction, intramolecular cyclization, palladium catalyst, pyranoquinolines, dihydropyridophenanthridine

The importance of quinoline and its annulated derivatives is well recognized by synthetic and biological chemists.[1] Compounds possessing this ring system have wide applications in medicinal chemistry;[2] being used as antimalarial, anti-inflammatory, antiasthmatic, antibacterial, antihypertensive, and tyrosine kinase inhibiting agents.[3] Alkaloids containing the pyranoquinoline core constitute a significant group of the quinoline alkaloids and these classes of compounds have been shown to exhibit a range of biological activities.[4] Some examples of natural products containing the pyranoquinoline core structure include geibalansine (**I**), helietidine (**II**), dutadrupine (**III**), and ribalinine (**IV**) (Figure 1).[4,5] Therefore, considerable efforts have been made towards the preparation and synthetic manipulation of this class of compounds.[6] As a result, a number of compounds have been obtained with diverse biological activities. However, the corresponding benzannulated analogues of pyranoquinolines have remained unexplored for their biological activities, which may be due to the lack of general synthetic route for these classes of heteroaromatics from easily accessible precursors.

Over the past decade, palladium-catalyzed cyclization reaction has proven to be an extremely powerful and useful tool for the construction of carbon–carbon, as well as carbon–heteroatom bonds.[7] In particular, intramolecular biaryl coupling reactions involving a palladium reagent is of considerable interest due to its significant utility in the synthesis of many condensed heteroaromatic compounds.[8] Recently, we reported the synthesis of condensed heteroaromatic compounds using biaryl-coupling reactions with the palladium reagent under ligand-free conditions.[9]

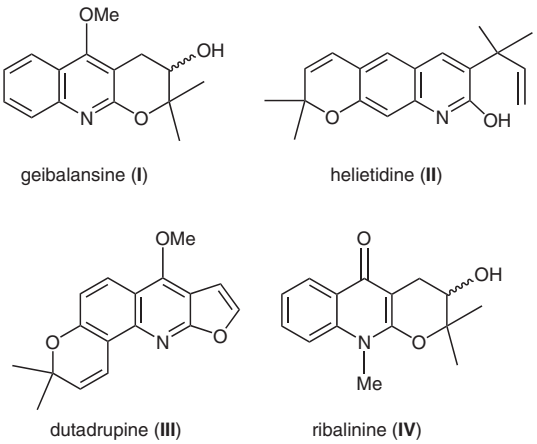

Figure 1 Examples of natural products containing the pyranoquinoline core structure

Although a number of protocols have been developed for the coupling of biaryl moieties, many of them have limited applicability in organic synthesis due to the harshness or functional group intolerance[10] and high[11] (even stoichiometric)[12] catalyst loading under optimized conditions. Use of phosphine ligand may become problematic in the separation process.[13] Overcoming these hurdles will necessarily require the discovery and development of novel catalytic systems. It has been reported that phenolates have been shown to exhibit enhanced reactivity in intramolecular arylation reactions.[14–16] However, the palladium-catalyzed biaryl-coupling reactions of ethers such as 2-bromobenzyl phenyl ether that lack a phenolate activating group proceeded poorly and gave lower yield of the product.[14,17] Rawal et al. reported[14] that in the absence of a phenolate activating group on the nucleophilic arene, less than 10% of the coupled product was obtained after prolonged reaction. Recently, Fagnou and co-workers[18] also attempted the same type of cyclization reaction, using $Pd(OAc)_2$ as catalyst and 2-(diphenylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl as ligand, for this cyclization. They obtained a significant amount of dehalogenated product in the absence of the ligand. Therefore, the above mentioned observations have prompted us to undertake a study of the Heck type of reaction on the biaryl ethers as starting materials, with a view to synthesize the condensed heteroaromatic compounds of biological interest.

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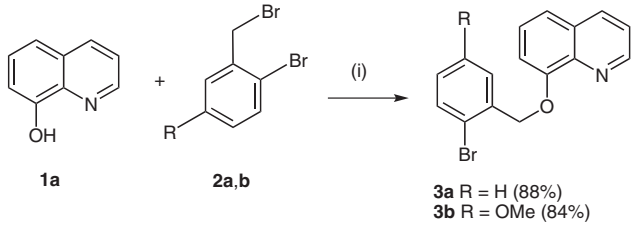
Furthermore, this coupling reaction provides a new methodology to construct the pyranoquinoline skeleton present in numerous natural alkaloids.[4,5]

Preparation of the cyclization precursors **3a–f** for the present investigations was carried out by the alkylation of different hydroxyquinolines with either 2-bromobenzyl bromide (**2a**) or 2-bromo-5-methoxybenzyl bromide (**2b**). For example, compounds **3a**,**b** were prepared by classical alkylation procedure according to which 8-hydroxyquinoline (**1a**) was dissolved in anhydrous acetone and to this 2-bromobenzyl bromide (**2a**) or 2-bromo-5-methoxybenzyl bromide (**2b**) and anhydrous K_2CO_3 were added, and the reaction mixture was refluxed for 6 hours to afford **3a**,**b** in 88 and 84% yield, respectively (Scheme 1). In a similar manner, other precursors **3c–f** were also prepared in 78–87% yields from 5-hydroxy-2,4-dimethylquinoline and 7-hydroxy-2,4-dimethylquinoline.



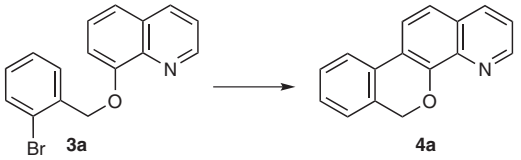
Scheme 1 *Reagents and conditions*: (i) anhyd acetone, anhyd K_2CO_3, reflux, 6 h.

When the coupling reaction was carried out with precursor **3a** in the presence of 5 mol% of $Pd(OAc)_2$ as a catalyst, Cs_2CO_3 as a base, and tetrabutylammonium bromide (TBAB) as an additive in anhydrous DMF as a solvent at 95 °C for two hours under nitrogen, the pyranoquinoline derivative **4a** was obtained in 90% yield. The optimum conditions for the cyclization were found through a series of experiments where various changes were made to the catalyst, base, additive, and solvent used in the reaction (Table 1). We found that the catalyst, base, additive, and solvent have a profound effect on the reaction yield. The use of $PdCl_2$, which is mostly used in the Heck type of reaction provides only 35% yield of the cyclized product **4a** (Table 1, entry 2)**.** The additive tetrabutylammonium chloride (TBACl) was also found to be effective in this case, but the yield of the product was reduced to 46 and 25% using $Pd(OAc)_2$ and $PdCl_2$ as catalyst, respectively (entries 3 and 4). Here, it is pertinent to note that the additive plays an important role in the cyclization. Without any additive such as TBAB or TBACl, the reactions became extremely slow and gave a significant amount of dehalogenated product (entry 5); but with the catalytic system $Pd(OAc)_2/Cs_2CO_3/Ph_3P$, the reaction did not occur (entry 6). The catalytic system $Pd(PPh_3)_2Cl_2/Cs_2CO_3$/TBAB was also inactive towards the cyclization (entry 7).

The effect of base on the reaction was also investigated. The use of KOAc as a base gave 60% and 55% of **4a** in DMF and DMSO, respectively (entries 8 and 15). Replacement of the base, KOAc with Cs_2CO_3 was found to be highly effective with the catalyst $Pd(OAc)_2$ (entries 1, 3, and 12) and excellent yield of the product was obtained in DMF (entry 1). Other inorganic bases such as K_2CO_3, Ag_2CO_3, and organic base like Et_3N were explored. The use of Ag_2CO_3 was found to be effective (entries 9 and 16); however, with K_2CO_3 and Et_3N reaction did not occur at all (entries 10 and 11).

Among the several aprotic polar solvents examined, DMF resulted to give the highest yield. Other solvent such as DMSO was also found to be effective, but gave lower yield of the product (entries 12, 15, and 16) whereas no reaction occurred in MeCN and dioxane (entries 13, 14, and 17). The reaction also did not occur at 80 °C or at lower temperature. In order to examine the versatility of this intramolecular biaryl coupling reaction, a number of pyranoquinoline derivatives **4b–f** were synthesized under the

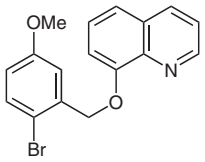
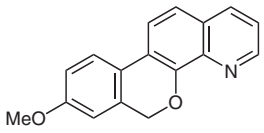
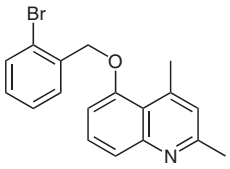
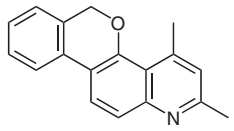
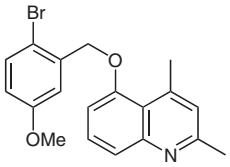
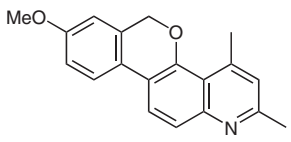
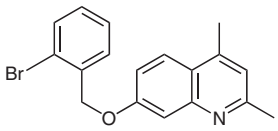
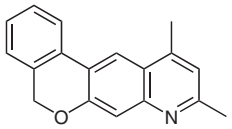
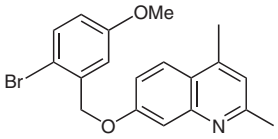
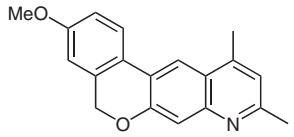
Table 1 Palladium-Catalyzed Cyclization of **3a** to **4a**[a]



Entry	Catalyst[b]	Base[c]	Additive[d]	Solvent	Yield (%)[e]
1	$Pd(OAc)_2$	Cs_2CO_3	TBAB	DMF	90
2	$PdCl_2$	Cs_2CO_3	TBAB	DMF	35
3	$Pd(OAc)_2$	Cs_2CO_3	TBACl	DMF	46
4	$PdCl_2$	Cs_2CO_3	TBACl	DMF	25
5	$Pd(OAc)_2$	Cs_2CO_3	–	DMF	15[f]
6	$Pd(OAc)_2$	Cs_2CO_3	–	DMF	NR[g]
7	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	TBAB	DMF	NR
8	$Pd(OAc)_2$	KOAc	TBAB	DMF	60
9	$Pd(OAc)_2$	Ag_2CO_3	TBAB	DMF	28
10	$Pd(OAc)_2$	K_2CO_3	TBAB	DMF	NR
11	$Pd(OAc)_2$	Et_3N	TBAB	DMF	NR
12	$Pd(OAc)_2$	Cs_2CO_3	TBAB	DMSO	70
13	$Pd(OAc)_2$	Cs_2CO_3	TBAB	MeCN	NR
14	$Pd(OAc)_2$	KOAc	TBAB	MeCN	NR
15	$Pd(OAc)_2$	KOAc	TBAB	DMSO	55
16	$Pd(OAc)_2$	Ag_2CO_3	TBAB	DMSO	35
17	$Pd(OAc)_2$	Cs_2CO_3	TBAB	dioxane	NR

[a] All reactions were carried out at 95 °C for 2 h.
[b] $Pd(OAc)_2$ and $PdCl_2$ catalyst were used in 5 mol% and 10 mol%, respectively.
[c] Amount of base used in the reaction = 1.5 equiv.
[d] Amount of additive used in the reaction = 1.5 equiv.
[e] Isolated yields; NR = no reaction.
[f] An amount of 55% of debrominated product was obtained.
[g] Amount of Ph_3P as ligand used in the reaction = 20 mol%.

Table 2 Ether Cyclization by Palladium-Catalyzed Heck Type of Reaction[a]

Entry	Starting material		Product		Yield (%)[b]
1	**3b**		**4b**		95
2	**3c**		**4c**		86
3	**3d**		**4d**		88
4	**3e**		**4e**		78[c]
5	**3f**		**4f**		84

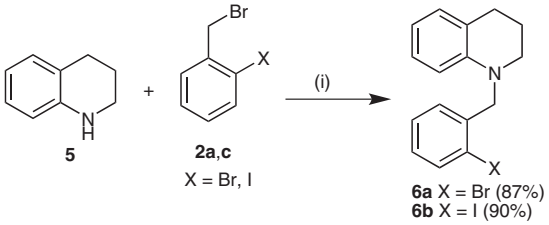
[a] All reactions were performed under optimized conditions.
[b] Isolated yields.
[c] Angular fused product was obtained in 5% yield.

optimized reaction conditions, $Pd(OAc)_2/Cs_2CO_3$/TBAB/DMF. The results are summarized in Table 2.

We next examined the palladium-catalyzed intramolecular aryl–aryl cross coupling of compounds **6a**,**b**. This coupling reaction would provide a new methodology to construct the 2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-*i*,*j*]quinoline skeleton present as a basic structural moiety in a number of alkaloids such as julolidine alkaloids.[19] Some derivatives of the latter show very interesting pharmacological properties and, as a result, synthesis has been attempted.[20]

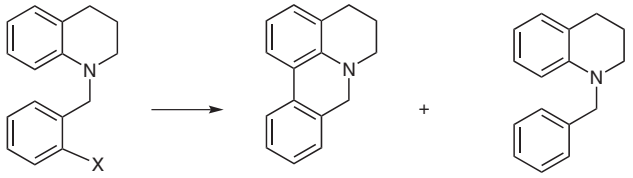
Treatment of tetrahedroquinoline (**5**) with sodium hydride followed by addition of 2-bromobenzyl bromide afforded the precursor **6a** in 87% yield. The related aryl iodide precursor **6b** was also prepared in a similar manner (Scheme 2).

Here, it is important to note that under the above optimized conditions the substrates **6a** and **6b** did not give any cyclized product; only halogen-reduced product was obtained. Flippin et al.[21] reported that the use of $Pd(OAc)_2$ as a catalyst and triethylamine as a base, and with the addition of Ph_3P as a ligand, afforded the best result for similar type of cyclization with indole derivatives. Surprisingly, use of these conditions in our system gave only 5% yield of the desired cyclized product (Table 3, entry 1). Indeed, the halogen-reduced product was isolated in 84% yield. Therefore, a further optimization study was needed. With $Pd(OAc)_2$ catalyst, variation of bases such as KOAc, Cs_2CO_3, K_2CO_3, and phosphine ligand such as triphenylphosphine, and solvents (DMF, DMSO, MeCN, dioxane) used in the reaction had little effect on the outcome of the reaction. All efforts gave mainly the dehalogenated product (Table 3). Finally, the best result was achieved after 8 hours using Ag_2CO_3 as a base, $PdCl_2$ as a catalyst along with TBAB as additive and DMSO as a solvent at 120 °C under nitrogen. This provided a 72% yield of the cyclized product **7**, and 10% of the reduced *N*-benzyltet-



Scheme 2 *Reagents and conditions*: (i) anhyd THF, NaH, reflux, 4 h.

Table 3 Palladium-Catalyzed Cyclization of **6** to **7**



6a X = Br
6b X = I

7 **8**

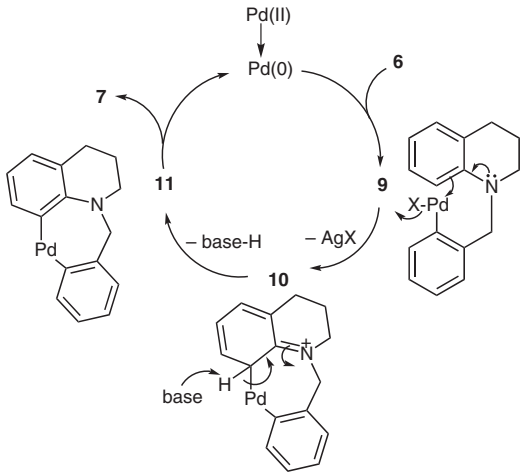
Entry	Substrate	Catalyst (mol%)	Base[a]	Additive[b]	Solvent	Yield (%) **7/8**
1	**6a**	$Pd(OAc)_2$ (10)	Et_3N	–	DMF	5:84
2	**6a**	$PdCl_2$ (10)	Ag_2CO_3	TBAB	DMSO	72:10
3[c]	**6a**	$PdCl_2$ (10)	Ag_2CO_3	–	DMSO	20:65
4	**6a**	$PdCl_2$ (10)	Cs_2CO_3	TBAB	DMSO	56:36
5	**6b**	$PdCl_2$ (10)	Ag_2CO_3	TBAB	DMSO	82:0
6	**6b**	$PdCl_2$ (10)	Cs_2CO_3	TBAB	DMSO	65:25
7	**6b**	$PdCl_2$ (10)	KOAc	TBAB	DMSO	0:95
8	**6b**	$PdCl_2$ (10)	Ag_2CO_3	TBAB	DMF	45:45
9	**6b**	$PdCl_2$ (10)	Ag_2CO_3	TBAB	MeCN	25:30
10	**6b**	$PdCl_2$ (10)	Ag_2CO_3	TBAB	dioxane	15:70
11	**6b**	$Pd(OAc)_2$ (10)	Ag_2CO_3	TBAB	DMSO	0:90

[a] Amount of base used in the reaction = 2.5 equiv.
[b] Amount of additive used in the reaction = 2.0 equiv.
[c] Amount of Ph_3P used as ligand = 20 mol%.

rahydroquinoline **8** (Table 3, entry 2). However, without TBAB the yield of the cyclized product was dramatically reduced to 20% at the expense of a significant amount of dehalogenated product (Table 3, entry 3). Use of Cs_2CO_3 as a base with catalyst $PdCl_2$ gave only 56% of the cyclized product (Table 3, entry 4). The positive effect of Ag_2CO_3 is presumably due to abstraction of halide from the arylpalladium complex[22] and formation of a cationic arylpalladium intermediate **10** (Scheme 3).

From this preliminary result, we expected that the use of *o*-iodobenzyl derivative **6b** as a starting material may decrease the yield of the reduction product and improve the yield of the cyclized product. It was indeed found that treatment of *o*-iodobenzyl derivative **6b** with the catalytic system $PdCl_2/Ag_2CO_3$/TBAB in anhyd DMSO at 120 °C for 10 hours, afforded an improved yield of **7** (82%, Table 3, entry 5). Other bases such as Cs_2CO_3 gave 65% yield of the product (entry 6) whereas KOAc afforded dehalogenated product only (entry 7). The solvents DMF, MeCN, and dioxane were also effective with the catalytic system $PdCl_2/Ag_2CO_3$, but afforded lower yield of the product (entry 8–10). However, compound **6b** with catalyst $Pd(OAc)_2/Ag_2CO_3$ gave only reduced product **8** (95%, Table 3, entry 11).

From a mechanistic point of view, the cyclization proceeds through the oxidative addition of Pd(0) to the aryl halides **3** to give a σ-arylpalladium intermediate. Electrophilic attack on the aromatic ring leads to the biarylpalladium species, which after reductive elimination of palladium affords the cyclized products **4**. A plausible catalytic cycle for the formation of the product **7** from the substrate **6** is outlined in Scheme 3. Abstraction of halide[22] by silver carbonate leads to cationic intermediate



Scheme 3

10 presumably stabilized by the nitrogen atom of the tetrahydroquinoline moiety.

It has been observed that the biaryl coupling reactions proceeded smoothly in our optimized reaction conditions and give much better yields of the cyclized products as compared to previous reports[10,14,18] under ligand-free conditions. Halogen-reduced product was not obtained at all. The use of *o*-iodobenzyl derivative and Ag_2CO_3 as base completely inhibit the formation of the undesired reduced product **8** and dramatically improve the yield of the desired product **7**.

In conclusion, we have developed a convenient and high yielding method for the synthesis of benzannulated pyranoquinolines and 2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-*i*,*j*]quinoline system, present in many biologically active alkaloids by palladium-catalyzed intramolecular Heck reaction under ligand-free conditions. The method is new, mild and highly effective for the cyclization of biaryl system, and afforded the cyclized products in high yields. The method would be applicable for several other ring systems and heteroatomic species.

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer L 120-000A spectrometer using samples as neat liquids and solid samples were recorded as KBr discs. ^{1}H NMR (300 MHz, 400 MHz, 500 MHz) spectra were recorded on a Bruker-300, Bruker DPX-400 and Bruker DRX-500 spectrometer in $CDCl_3$ (chemical shift in δ) with TMS as internal standard. Silica gel [(60–120, 230–400 mesh), Spectrochem, India] was used for chromatographic separation. Silica gel G [E-Merck (India)] was used for TLC. Petroleum ether (PE) refers to the fraction boiling between 60–80 °C.

Compounds 3a–f; General Procedure

A mixture of 8-hydroxyquinoline (**1a**; 0.20 g, 1.38 mmol), 2-bromobenzyl bromide (**2a**; 0.410 g, 1.65 mmol) or 2-bromo-5-methoxybenzyl bromide (**2b**; 0.460 g, 1.65 mmol), anhyd K_2CO_3 (3 g) was refluxed in anhyd acetone (75 mL) on a water bath for 6 h. The reaction mixture was cooled, filtered, and the solvent was removed. The residual mass was extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 extracts were washed with H_2O (3 × 30 mL) and dried (Na_2SO_4). The residual mass after removal of CH_2Cl_2 was subjected to column chromatography over silica gel (60–120 mesh) using PE–EtOAc as eluent to give compounds **3a**,**b**. Similarly other substrates **3c**–**f** were prepared from 5-hydroxy-2, 4-dimethylquinoline and 7-hydroxy-2,4-dimethylquinoline.

8-[(2-Bromobenzyl)oxy]quinoline (3a)

Eluted from the column with EtOAc–PE (3:17) as a colorless solid (88%); mp 104–106 °C ($CHCl_3$–hexane).

IR (KBr): 2852, 1571, 1107 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.49 (s, 2 H), 6.94 (dd, *J* = 2.4, 6.5 Hz, 1 H), 7.12–7.62 (m, 7 H), 8.12 (dd, *J* = 1.8, 8.3 Hz, 1 H), 8.97–8.98 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 69.8, 109.6, 115.4, 120.7, 121.6, 126.5, 127.5, 128.4, 128.9, 129.4, 132.4, 135.8, 140.2, 149.3, 153.7, 158.68.

MS: *m*/*z* = 313, 315 [M$^+$].

Anal. Calcd for $C_{16}H_{12}BrNO$: C, 61.17; H, 3.85, N, 4.46. Found: C, 61.36; H, 3.91, N, 4.49.

8-[(2-Bromo-5-methoxybenzyl)oxy]quinoline (3b)

Eluted from the column with EtOAc–PE (3:17) as a colorless solid (84%); mp 92–94 °C ($CHCl_3$–hexane).

IR (KBr): 2921, 1617, 1015 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.66 (s, 3 H), 5.46 (s, 2 H), 6.69 (dd, *J* = 3.1, 8.7 Hz, 1 H), 6.94 (dd, *J* = 2.3, 6.6 Hz, 1 H), 7.20 (d, *J* = 3.0 Hz, 1 H), 7.35–7.46 (m, 4 H), 8.12 (dd, *J* = 1.7, 8.3 Hz, 1 H), 8.96 (dd, *J* = 1.7, 4.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3, 70.1, 110.0, 111.8, 114.0, 115.1, 120.2, 121.6, 126.6, 129.4, 133.0, 135.9, 137.0, 140.2, 149.3, 153.8, 159.2.

MS: *m*/*z* = 343, 345 [M$^+$].

Anal. Calcd for $C_{17}H_{14}BrNO_2$: C, 59.32; H, 4.10, N, 4.07. Found: C, 59.43; H, 4.19, N, 4.12.

5-[(2-Bromobenzyl)oxy]-2,4-Dimethylquinoline (3c)

Eluted from the column with EtOAc–PE (1:9) as a colorless solid (80%); mp 78–80 °C ($CHCl_3$–hexane).

IR (KBr): 2928, 1615, 1236 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.63 (s, 3 H), 2.80 (s, 3 H), 5.24 (s, 2 H), 6.82 (d, *J* = 7.5 Hz, 1 H), 6.99 (s, 1 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 7.31–7.35 (m, 1 H), 7.48–7.53 (m, 2 H), 7.61–7.63 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 24.7, 70.4, 106.0, 119.1, 122.2, 122.9, 123.9, 127.5, 128.6, 129.5, 129.6, 132.8, 135.7, 145.3, 150.0, 156.2, 158.4.

MS: *m*/*z* = 341, 343 [M$^+$].

Anal. Calcd for $C_{18}H_{16}BrNO$: C, 63.17; H, 4.71, N, 4.09. Found: C, 63.38; H, 4.68, N, 4.19.

5-[(2-Bromo-5-methoxybenzyl)oxy]-2,4-dimethylquinoline (3d)

Eluted from the column with EtOAc–PE (1:9) as a colorless solid (87%); mp 120–122 °C ($CHCl_3$–hexane).

IR (KBr): 2931, 1596, 1238 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.63 (s, 3 H), 2.84 (s, 3 H), 3.76 (s, 3 H), 5.20 (s, 2 H), 6.75 (dd, *J* = 3.1, 8.7 Hz, 1 H), 6.83 (d, *J* = 7.7 Hz, 1 H), 7.00 (s, 1 H), 7.10 (d, *J* = 3.0 Hz, 1 H), 7.48–7.52 (m, 2 H), 7.61 (dd, *J* = 0.8, 8.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7, 24.8, 55.3, 70.5, 106.1, 112.8, 114.9, 115.0, 119.1, 122.2, 124.0, 128.7, 133.3, 136.6, 145.3, 149.9, 156.1, 158.5, 159.0.

MS: *m*/*z* = 371, 373 [M$^+$].

Anal. Calcd for $C_{19}H_{18}BrNO_2$: C, 61.30; H, 4.87, N, 3.76. Found: C, 61.57; H, 4.95, N, 3.90.

7-[(2-Bromobenzyl)oxy]-2,4-dimethylquinoline (3e)

Eluted from the column with EtOAc–PE (1:9) as a colorless solid (82%); mp 80–81 °C ($CHCl_3$–hexane).

IR (KBr): 2918, 1618, 1134 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.62 (s, 3 H), 2.64 (s, 3 H), 5.25 (s, 2 H), 7.01 (s, 1 H), 7.16 (td, *J* = 1.5, 7.7 Hz, 1 H), 7.24 (d, *J* = 2.6 Hz, 1 H), 7.30–7.34 (m, 1 H), 7.44 (d, *J* = 2.5 Hz, 1 H), 7.57 (dd, *J* = 1.2, 8.0 Hz, 2 H), 7.85 (d, *J* = 9.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 24.9, 69.3, 108.4, 118.1, 120.8, 121.6, 122.2, 124.8, 127.3, 128.5, 129.1, 132.5, 135.7, 144.0, 149.1, 158.9, 159.0.

MS: *m*/*z* = 341, 343 [M$^+$].

Anal. Calcd for $C_{18}H_{16}BrNO$: C, 63.17; H, 4.71, N, 4.09. Found: C, 63.03; H, 4.73, N, 4.14.

7-[(2-Bromo-5-methoxybenzyl)oxy]-2,4-dimethylquinoline (3f)
Eluted from the column with EtOAc–PE (1:9) as a colorless solid (78%); mp 99–100 °C ($CHCl_3$–hexane).

IR (KBr): 2919, 1567, 1111 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.62 (s, 3 H), 2.65 (s, 3 H), 3.77 (s, 3 H), 5.21 (s, 2 H), 6.72 (dd, *J* = 3.0, 8.7 Hz, 1 H), 7.01 (s, 1 H), 7.15 (d, *J* = 3.0 Hz, 1 H), 7.27 (d, *J* = 2.6 Hz, 1 H), 7.44–7.47 (m, 2 H), 7.85 (d, *J* = 9.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 24.9, 55.3, 69.2, 108.5, 112.1, 114.2, 114.4, 118.0, 120.8, 121.6, 124.7, 133.0, 136.7, 143.9, 149.1, 157.8, 158.9, 159.0.

MS: *m*/*z* = 371, 373 [M^+].

Anal. Calcd for $C_{19}H_{18}BrNO_2$: C, 61.30; H, 4.87, N, 3.76; found: C, 61.49; H, 4.99, N, 3.85.

Heck Reaction of Compound 3a–f; General Procedure
To a mixture of **3a–f** (0.318 mmol), Bu_4NBr (0.150 g, 0.47 mmol), and Cs_2CO_3 (0.153 g, 0.47 mmol) in anhyd degassed DMF (15 mL) in a screw-cap-sealed tube was added $Pd(OAc)_2$ (3.56 mg, 5 mol%) under an inert atmosphere and the sealed tube was placed in a pre-heated oil bath at 95 °C with stirring for 2–5 h. After completion of the reaction as monitored by TLC, the reaction mixture was cooled and diluted with H_2O (50 mL). This was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with aq 1 N HCl (25 mL), H_2O (3 × 20 mL), brine (30 mL), and dried (Na_2SO_4). The solvent was removed by distillation and the crude product was purified by column chromatography over silica gel (60–120 mesh) using PE–EtOAc mixture as eluent to give compounds **4a–f** (Table 2).

6*H*-Isochromeno[4,3-*h*]quinoline (4a)
Eluted from the column with EtOAc–PE (1:3) as a colorless solid (90%); mp 114–116 °C (MeCN–MeOH).

IR (KBr): 2919, 1624, 1556 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.43 (s, 2 H), 7.22 (d, *J* = 7.4 Hz, 1 H), 7.28–7.43 (m, 3 H), 7.47 (d, *J* = 8.6 Hz, 1 H), 7.73 (d, *J* = 7.7 Hz, 1 H), 7.90 (d, *J* = 8.6 Hz, 1 H) 8.90 (dd, *J* = 1.4, 8.3 Hz, 1 H), 8.91 (dd, *J* = 1.5, 4.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 68.9, 120.5, 120.7, 121.3, 121.5, 121.9, 124.6, 128.0, 128.4, 129.0, 129.6, 130.7, 135.7, 139.9, 149.7, 149.8.

HRMS: *m*/*z* calcd for $C_{16}H_{12}NO$: 234.0938 [M + H]; found: 234.0917 [M + H].

8-Methoxy-6*H*-isochromeno[4,3-*h*]quinoline (4b)
Eluted from the column with EtOAc–PE (1:3) as a colorless solid (95%); mp 92–94 °C (MeCN–MeOH).

IR (KBr): 2921, 1463, 1114 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 5.40 (s, 2 H), 6.94–7.06 (m, 3 H), 7.35–7.51 (m, 3 H), 8.27 (d, *J* = 8.3 Hz, 1 H), 8.51 (d, *J* = 4.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.0, 69.7, 109.7, 111.5, 113.7, 114.7, 119.9, 121.3, 126.3, 129.1, 132.8, 135.6, 136.7, 140.0, 149.0, 153.5, 158.9.

HRMS: *m*/*z* calcd for $C_{17}H_{14}NO_2$: 264.1016 [M + H]; found: 264.1017 [M + H].

2,4-Dimethyl-6*H*-isochromeno[4,3-*f*]quinoline (4c)
Eluted from the column with EtOAc–PE (1:4) as a colorless solid (86%); mp 112–114 °C (MeCN–MeOH).

IR (KBr): 2925, 1591, 1199 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.64 (s, 3 H), 2.85 (s, 3 H), 5.22 (s, 2 H), 7.01 (s, 1 H), 7.19 (d, *J* = 7.4 Hz, 1 H), 7.28 (t, *J* = 7.4 Hz, 1 H), 7.39 (t, *J* = 7.5 Hz, 1 H), 7.68–7.74 (m, 2 H), 7.98 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.3, 19.8, 63.4, 113.0, 114.1, 117.2, 118.1, 119.2, 119.3, 119.4, 122.4, 123.7, 125.4, 125.5, 140.5, 144.9, 147.2, 153.8.

MS: *m*/*z* = 261 [M^+].

Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.92; H, 5.87; N, 5.42.

8-Methoxy-2,4-dimethyl-6*H*-isochromeno[4,3-*f*]quinoline (4d)
Eluted from the column with EtOAc–PE (1:4) as a colorless solid (88%); mp 100–102 °C (MeCN–MeOH).

IR (KBr): 2920, 1595, 1184 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.63 (s, 3 H), 2.85 (s, 3 H), 3.85 (s, 3 H), 5.18 (s, 2 H), 6.74 (d, *J* = 2.1 Hz, 1 H), 6.94 (dd, *J* = 2.3, 8.5 Hz, 1 H), 6.99 (s, 1 H), 7.64 (t, *J* = 8.9 Hz, 2 H), 7.92 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 24.7, 55.3, 68.5, 110.0, 113.8, 118.1, 119.0, 122.9, 123.2, 123.5, 123.8, 124.2, 131.9, 133.3, 145.2, 149.2, 158.2, 159.3.

MS: *m*/*z* = 291 [M^+].

Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.40; H, 5.91; N, 4.86.

2,4-Dimethyl-8*H*-isochromeno[4,3-*h*]quinoline (4e)
Eluted from the column with EtOAc–PE (3:17) as a colorless solid (78%); mp 156 °C (MeCN–MeOH).

IR (KBr): 2919, 1624, 1156 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.68 (s, 3 H), 2.71 (s, 3 H), 5.20 (s, 2 H), 7.03 (s, 1 H), 7.20 (d, *J* = 7.5 Hz, 1 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.61 (s, 1 H), 7.88 (d, *J* = 7.7 Hz, 1 H), 8.26 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7, 20.2, 63.5, 109.0, 112.9, 116.5, 117.80, 117.82, 118.0, 119.9, 123.1, 123.5, 124.8, 127.5, 139.1, 144.1, 150.7, 154.4.

HRMS: *m*/*z* calcd for $C_{18}H_{16}NO$: 262.1227 [M + H]; found: 262.1228 [M + H].

10-Methoxy-2,4-dimethyl-8*H*-isochromeno[4,3-*h*]quinoline (4f)
Eluted from the column with EtOAc–PE (3:17) as a colorless solid (84%); mp 110–112 °C (MeCN–MeOH).

IR (KBr): 2921, 1606, 1165 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.71 (s, 6 H), 3.86 (s, 3 H), 5.17 (s, 2 H), 6.72 (d, *J* = 2.5 Hz, 1 H), 6.95 (dd, *J* = 2.6, 8.6 Hz, 1 H), 7.03 (s, 1 H), 7.67 (s, 1 H), 7.81 (d, *J* = 8.6 Hz, 1 H), 8.16 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.5, 24.8, 55.2, 68.3, 109.5, 113.4, 114.3, 116.5, 121.2, 122.1, 122.6, 122.7, 124.1, 133.7, 143.8, 148.1, 155.0, 158.5, 159.5.

HRMS: *m*/*z* calcd for $C_{19}H_{18}NO_2$: 292.1332 [M + H]; found: 292.1335 [M + H].

Compounds 6a,b
To a solution of tetrahydroquinoline (**5**; 133 mg, 1.0 mmol) in anhyd degassed THF (10 mL) in a two-necked flask was added NaH (48.0 mg, 2 mmol) 0–5 °C under N_2. After the evolution of H_2 had stopped, 2-bromobenzyl bromide (**2a**; 250 mg, 1.0 mmol) or 2-iodobenzyl bromide (**2c**; 297 mg, 1.0 mmol) was added and the stirring was continued at r.t for 4 h. The reaction mixture was slowly poured into a mixture of ice-cold H_2O (20 mL) and Et_2O (20 mL).

The organic layer was collected and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4). The solvent was removed by distillation and the crude product was purified by column chromatography over silica gel (60–120 mesh) using PE–EtOAc mixture as eluent to give compounds **6a** or **6b** as colorless oil.

1-(2-Bromobenzyl)-1,2,3,4-tetrahydroquinoline (6a)
Eluted from the column with EtOAc–PE (1:49) as a gummy mass (87%).

IR (KBr): 2931, 1622, 1512 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.99–2.05 (m, 2 H), 2.83 (t, *J* = 6.3 Hz, 2 H), 3.38 (t, *J* = 5.6 Hz, 2 H), 4.30 (s, 2 H), 6.27 (d, *J* = 7.9 Hz, 1 H), 6.60 (t, *J* = 6.9 Hz, 1 H), 6.99–7.30 (m, 5 H), 7.89 (d, *J* = 7.9 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.3, 28.0, 49.8, 56.1, 110.8, 115.9, 121.8, 122.0, 127.4, 127.5, 128.2, 128.6, 128.9, 136.8, 139.3, 144.9.

MS: *m*/*z* = 301, 303 [M^+].

Anal. Calcd for $C_{16}H_{16}BrN$: C, 63.59; H, 5.34; N, 4.63; Found: C, 63.76; H, 5.42; N, 4.59.

1-(2-Iodobenzyl)-1,2,3,4-tetrahydroquinoline (6b)
Eluted from the column with EtOAc–PE (1:49) as a gummy mass (90%).

IR (KBr): 2925, 1602, 1505 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.02–2.08 (m, 2 H), 2.82 (t, *J* = 6.2 Hz, 2 H), 3.38 (t, *J* = 5.6 Hz, 2 H), 4.31 (s, 2 H), 6.25 (d, *J* = 8.0 Hz, 1 H), 6.56 (t, *J* = 7.3 Hz, 1 H), 6.93–7.27 (m, 5 H), 7.84 (d, *J* = 7.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.3, 28.0, 50.0, 61.2, 97.8, 110.8, 116.0, 122.0, 127.3, 127.4, 128.3, 128.6, 128.9, 139.3, 140.5, 144.9.

MS: *m*/*z* = 349 [M^+].

Anal. Calcd for $C_{16}H_{16}IN$: C, 55.03; H, 4.62; N, 4.01. Found: C, 55.26; H, 4.76; N, 4.08.

Palladium-Catalyzed Cyclization of 6a,b to 7 and 8
The procedure for the preparation of compounds **7** and **8** from **6a** and **6b** (0.33 mmol), respectively, are same as the procedure described previously for compounds **3a–f**, except that the following reagents were used: $PdCl_2$ (10 mol%) as catalyst, Ag_2CO_3 (2.5 equiv) as base, TBAB (2 equiv) as additive, and DMSO as solvent at 120 °C for 10 h.

5,6-Dihydro-4*H*,8*H*-pyrido[3,2,1-*de*]phenanthridine (7)
Prepared from **6a**. Eluted from the column with EtOAc–PE (1:49) as a gummy mass (82%).

IR (KBr): 2928, 1611, 1115 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.78–0.88 (m, 2 H), 2.10–2.16 (5 lines, m, 2 H), 3.00 (t, *J* = 6.2 Hz, 2 H), 4.30 (t, *J* = 5.9 Hz, 2 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 7.28 (d, *J* = 6.6 Hz, 1 H), 7.55–7.59 (m, 1 H), 7.72–7.76 (m, 1 H), 8.12 (d, *J* = 7.8. Hz, 1 H), 8.26 (d, *J* = 8.2 Hz, 1 H), 8.5 (dd, *J* = 0.8, 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 28.0, 49.9, 55.9, 110.6, 115.9, 121.9, 122.7, 127.1, 127.3, 127.5, 128.1, 128.8, 132.6, 136.8, 144.9.

MS: *m*/*z* = 221 [M^+].

Anal. Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.90; H, 6.86; N, 6.35.

1-Benzyl-1,2,3,4-tetrahydroquinoline (8)
Prepared from **6b**. Eluted from the column with EtOAc–PE (1:49) as a colorless oil.

IR (KBr): 2928, 1629 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.97–2.03 (m, 2 H), 2.79 (t, *J* = 6.2 Hz, 2 H), 3.34 (t, *J* = 5.7 Hz, 2 H), 4.47 (s, 2 H), 6.48 (d, *J* = 8.4 Hz, 1 H), 6.54 (t, *J* = 7.1 Hz, 1 H), 6.94 (t, *J* = 7.0 Hz, 2 H), 7.20–7.32 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2, 28.1, 49.7, 55.1, 110.9, 115.8, 122.1, 126.5, 126.6, 127.0, 128.2, 128.4, 128.5, 128.8, 138.7, 145.4.

MS: *m*/*z* = 223 [M^+].

Anal. Calcd for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 86.31; H, 7.69; N, 6.36.

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