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Synthesis of Novel 5-(*N*-Substituted-Anilino)-8-Hydroxyquinolines via Hartwig-Buchwald Amination Reaction

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Abstract. Three novel 5-(*N*-substituted-anilino)-8-benzyloxyquinoline derivatives were efficiently synthesized via Hartwig–Buchwald amination reaction. The new 5-(*N*-substituted-anilino)-8-benzyloxyquinolines were reduced for 1–3 h to give the corresponding 5-(*N*-substituted-anilino)-8-hydroxyquinolines. Extending the reduction reaction time to 7 h afforded the corresponding 1,2,3,4-tetrahydro-8-hydroxyquinoline derivatives.

Keywords. Hartwig–Buchwald amination; electron-rich phosphine ligands; 5-anilino-8-hydroxyquinoline; 1,2,3,4-tetrahydroquinolin-8-ol; catalytic hydrogenation.

1. Introduction

Quinolines functionalized with amino substituents are particularly important due to their wide applications especially in medicine and photovoltaics.[1–10] Hartwig–Buchwald amination is an efficient reaction for the coupling of amines with aryl halides.[11–14] The reaction is preferred over other C–N bond-forming methodologies because of the milder reaction conditions and the relatively higher yields.[15,16] In addition, the availability of the starting materials and a wide variety of ligands provide access to a range of hindered and functionalized aryl amines. The choice of the palladium/ligand combination to be used during the coupling has turned out to be problematic.[6,13,17–21] A suitable catalytic system was found to vary according to the steric and electronic requirements of both the substrate and the amine. Hence, for the amination reaction to proceed efficiently towards the formation of the desired coupling product, the reaction conditions should be optimized. In continued efforts, many research groups employed different catalytic systems (Pd/L) for this coupling and many phosphine and carbene ligands have rapidly emerged.[11,13,19–25] Among the electron rich phosphine ligands, the sterically demanding (2-biphenyl)di-*tert*-butylphosphine (Johnphos) **L1**,[6,26] tri-*tert*-butylphosphine (TTBP) **L2**,[27,28] di-*tert*-butylneopentylphosphine (DTBNpP) **L3**,[6,14,29] and tricyclohexylphosphine **L4** were effectively used in H–B amination reactions[30] (figure 1).

Although palladium catalyzed coupling of quinolines with different amines has been reported,[1,6,13,31–33] reports concerning coupling between quinoline substrates and secondary anilines are rare.[34] Herron *et al.*[10] reported that the metal complexes of 5-diphenylamino-8-hydroxyquinoline **4c** acted as an efficient material in organic electronic devices. They produced the 8-hydroxyquinoline derivative **4c** by non-optimized palladium catalyzed coupling between 5-chloro-8-hydroxyquinoline and diphenylamine under reflux for 180 h.

On the other hand, 1,2,3,4-tetrahydroquinolines are important organic synthetic intermediates and building blocks for alkaloids and biologically active compounds.[35–39] Moreover, they have been used successfully as ligands in coupling reactions.[40,41] Direct hydrogenation of quinoline derivatives is the most convenient route to synthesize tetrahydroquinoline derivatives. However, the hydrogenation reaction usually requires applying high hydrogen pressure.[42–48]

Recently, we reported the synthetic route for 5-amino-8-hydroxyquinolines equipped with alicyclic amines namely, pyrrolidine, piperidine and morpholine using optimized palladium catalyzed Hartwig–Buchwald amination.[6] In the present work, three secondary aniline substrates namely, *N*-methyaniline, 3-MeO-*N*-methylaniline and diphenylamine were coupled with 5-bromo-8-benzyloxyquinoline **2** in H–B amination reaction using commercially available ligands, **L1**, **L2**, **L3** and **L4**, to produce the corresponding 5-anilino-8-benzyloxyquinolines. The corresponding

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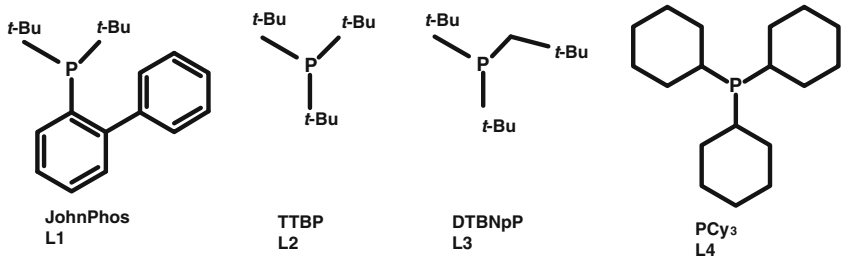


Figure 1. The commercially available ligands **L1**, **L2**, **L3** and **L4**.

5-anilino-8-hydroxyquinolines and 5-anilino-1,2,3,4-tetrahydro-8-hydroxyquinolines were prepared via mild, ligand-free catalytic hydrogenation.

2. Experimental

2.1 *General*

All reactions were carried out under argon atmosphere except the palladium catalyzed reduction reactions, which were carried out under hydrogen atmosphere. Solvents were dried by molecular sieves of proper pore size. 5-Bromo-8-hydroxyquinoline **1** was purchased from Tokyo Chemical Industry Co. (TCI). 8-(Benzyloxy)-5-bromoquinoline **2** was synthesized according to previously published procedures.[6,49] Ligands (**L1–L4**) have been used in the form of tetrafluoroborate salts and were purchased from Sigma–Aldrich Chemical Co. Palladium acetate was purchased from Fluka Chemical Co. Melting points were determined using a METTLER TOLEDO DSC821 at a heating rate of 20°C/min. NMR analyses (^{1}H and ^{13}C) were performed using Bruker DPX 200 (200 MHz) spectrometer using DMSO-d_6 or $CDCl_3$ solutions referenced internally to Me_4Si, *J* values are given in Hz. TLC were performed on dry silica gel plates and developed by using chloroform/methanol mixture as eluent.

2.2 *General procedure for the synthesis of 5-anilino-8-benzyloxyquinoline (**3a–c**) via Hartwig–Buchwald amination reaction*

In an oven-dried vessel with a magnetic stirring bar, toluene was added and bubbled with argon for 10 min. Compound **2**, $Pd(OAc)_2$ (5 mol%), ligand of choice after optimization (10 mol%), sodium *tert*-butoxide (1.25 equiv) and aniline derivative (1.25 equiv) were added and the reaction mixture was stirred under argon at optimized temperature. The reaction mixture was then allowed to cool to room temperature, filtered through a thin pad of silica gel and the solvent was evaporated under vacuum. The product was purified by flash chromatography using the proper eluent.

2.2a *5-(N-methylanilino)-8-benzyloxyquinoline **(3a)***: The title compound was prepared by following the general procedure. Specific amounts of chemicals used: Compound **2** (200 mg, 0.64 mmol), $Pd(AcO)_2$ (7.15 mg, 0.032 mmol), ligand **L**3 (19.37 mg, 0.064 mmol), sodium*tert*-butoxide (76.5 mg, 0.80 mmol) and *N*-methylaniline (0.086 mL, 0.80 mmol). The reaction was stirred for 30 min in an oil bath at 110–12°C. The crude product was purified by flash chromatography using *n*−hexane/acetone (1/1) giving **3a** as pale yellow crystals (195 mg, 90 C.^{1}H NMR (200 MHz, $CDCl_3$)δ 3.32 (s, 3H), 5.35 (s, 2H), 6.49 (d, J = 8.067 Hz, 2H), 6.66 (t, J = 7.058 Hz, 1H), 7.11 (t, J = 8.067 Hz, 2H), 7.33-7.60 (m, 8H), 8.03 (d, J = 8.47 Hz, 1H), 8.89 (d, J = 3.83 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$)δ 40.33, 70.90, 109.97, 113.229 (2C), 117.33, 121.86, 127.13 (2C), 127.56, 127.93, 128.73 (2C), 129.03 (2C), 132.32, 136.92, 137.55, 141.46, 149.59, 150.12, 153.14. HRMS $(M+H)^+$ calc for $C_{23}H_{21}N_2O$: 341.1654, found: 341.1661.

2.2b *5-(3-Methoxy-N-methylanilino)-8-benzyloxyquinoline **(3b)***: The title compound was prepared by following the general procedures. Specific amounts of chemicals used: Compound 2 (200 mg, 0.64 mmol), Pd(AcO)2 (7.15 mg, 0.032 mmol), ligand **L3** (19.37 mg, 0.064 mmol), sodium *tert*-butoxide (76.5 mg, 0.80 mmol) and 3-methoxy-*N*-methylaniline (0.10 mL, 0.80 mmol). The reaction was stirred for 5–6 h at 140–15°C. The crude product was purified by flash chromatography using *n*−hexane/acetone (1/1) giving **3b** as yellow crystals (205 mg, 87 DMSO-d_6)δ 3.28 (s, 3H), 3.60 (s, 3H), 5.32 (s, 2H), 6.04 (d, J = 5.99 Hz, 2H), 6.25 (d, J = 9.03 Hz, 1H), 6.98 (t, J = 8.20 Hz, 1H), 7.30-7.59 (m, 8H), 7.98 (d, J = 8.30 Hz, 1H), 8.89 (d, J = 3.23, 1H); ^{13}C NMR (50 MHz, $CDCl_3$)δ 40.40, 55.06, 70.82, 99.79, 101.97, 106.44, 109.88, 121.95, 126.04, 127.21 (2C), 127.51, 127.94, 128.70 (2C), 129.72, 132.30, 136.83, 137.25, 141.35, 149.57, 151.48, 153.18, 160.55. HRMS $(M+H)^+$ calc for $C_{24}H_{23}N_2O_2$: 371.1760, found: 371.1767.

2.2c *5-(N-phenylanilino)-8-benzyloxyquinoline (**3c**)*: The title compound was prepared by following the general procedure. Specific amounts of chemicals used: Compound **2** (100 mg, 0.32 mmol), $Pd(AcO)_2$ (10 mol **L4** (20 mol 0.40 mmol) and diphenylamine (2 equiv., 107.7 mg, 0.64 mmol). The reaction was stirred for 24 h at 150°C. The crude product was purified by flash chromatography using *n*−hexane/acetone (4/1) giving **3c** as bright yellow crystals (105 mg, 82 NMR (200 MHz, $CDCl_3$)δ 5.46 (s, 2H), 6.89-7.06 (m, 6H), 7.15-7.43 (m, 10H), 7.54 (d, $J = 6.81$, 2H), 8.22 (dd, $J = 8.60$ Hz, $J = 1.44$ Hz 3.60, 1H), 8.96 (dd, $J = 4.30$ Hz, $J = 1.08$ Hz, 1H); ^{13}C NMR (50 MHz, DMSO-d_6)δ 70.95, 110.0, 121.53 (4C), 121.73 (2C), 121.92, 127.22 (2C), 127.56, 127.72, 127.94, 128.71(2C), 129.15 (4C), 132.61, 135.77, 136.87, 141.50, 148.22(2C), 149.51, 153.06. HRMS $(M+H)^+$ calc for $C_{28}H_{23}N_2O$: 403.1810, found: 403.1811.

2.3 *General procedures for the synthesis of 5-anilino-8-hydroxyquinoline (**4a–c**)*

In a dry two-necked round bottom flask, 50 mg of 5-anilino-8-benzyloxyquinoline **(3a–c)** and 10 mg Pd–C (10 wt%) were stirred and refluxed in ethanol under hydrogen atmosphere for 1–3 h. The reaction mixture was filtered through a thin pad of silica gel. The filtrate was concentrated and allowed to stand at room temperature overnight. The product appeared as yellowish precipitate, which was filtered and dried in an oven at 60°C.

2.3a *5-(N-methylanilino)quinolin-8-ol (**4a**)*: Compound **4a** was prepared according to the general procedure, (31.6 mg, 86 (200 MHz, DMSO-d_6)δ 3.28 (s, 3H), 6.46 (d, $J = 7.65$ Hz, 2H), 6.61 (t, $J = 7.01$ Hz, 1H), 7.03-7.14 (m, 3H), 7.33 (d, $J = 8.29$ Hz, 1H), 7.45-7.53 (m, 1H), 7.98 (d, $J = 7.65$ Hz, 1H), 8.85 (d, $J = 2.96$ Hz, 1H), 9.96 (s, br, OH); ^{13}C NMR (50 MHz, DMSO-d_6)δ40.40, 110.25, 113.23 (2C), 117.28122.06, 126.65, 127.17, 129.02 (2C, 132.83, 136.02, 139.07, 148.10, 150.22, 150.95. HRMS $(M+H)^+$ calc for $C_{16}H_{15}N_2O$: 251.1184, found: 251.1187.

2.3b *5-(3-methoxy-N-methyl-anilino)quinolin-8-ol (**4b**)*: The title compound was prepared according to the general procedure. (30.5 mg, 81 (200 MHz, $CDCl_3$)δ 3.37 (s, 3H), 3.71 (s, 3H), 6.16 (m, 2H), 6.29 (d, $J =$ 7.93 Hz, 1H), 7.07 (t, $J = 7.21$ Hz, 1H), 7.20-7.46 (m, 3H), 8.13 (d, $J = 7.93$ Hz, 1H), 8.83 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$)δ40.50, 55.10, 99.76, 101.91, 106.43, 110.49, 121.10, 126.62, 127.47, 128.32, 129.67, 133.06, 135.77, 138.81, 150.84, 151.51, 160.66. HRMS $(M+H)^+$ calc for $C_{17}H_{16}N_2O_2$: 280.1212, found: 280.1224.

2.3c *5-(N-phenylanilino)quinolin-8-ol (**4c**)*: The title compound was prepared according to the general procedure. Bright yellow crystals (33.76 mg, 87 C. ^{1}H NMR (200 MHz, $CDCl_3$)δ 6.90-7.38 (m, 13H), 8.22 (d, $J =$ 8.14 Hz, 1H), 8.79 (d, $J = 2.9$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$)δ110.55, 121.49(4C), 121.71 (3C), 122.08, 126.77, 129.14 (4C), 133.29, 134.26, 138.94, 147.94, 148.26 (2C), 150.80. HRMS $(M+H)^+$ calc for $C_{21}H_{17}N_2O$: 313.1349, found: 313.1341.

2.4 *General procedure for the synthesis of 5-anilino-1,2,3,4-tetrahydroquinolin-8-ol **(5a-c)***

In a dry two-necked round bottom flask, 50 mg of 5-anilino-8-benzyloxyquinoline (**3a–c**) and 10 mg Pd–C (10 wt%) were stirred and refluxed in ethanol under hydrogen atmosphere for 7 h. The reaction mixture was then filtered through a thin pad of silica gel. The filtrate was concentrated and allowed to stand at room temperature overnight. The product was filtered and dried in an oven at 60°C.

2.4a *5-(N-methylanilino)-1,2,3,4-tetrahydroquinolin-8-ol (**5a**)*: Compound **5a** was prepared according to the general procedure. yellow crystals (33.24 mg, 89 121–12°C.^{1}H NMR (200 MHz, DMSO-d_6)δ 1.67 (m, 2H), 2.32 (t, $J = 6.05$ Hz, 2H), 3.06 (s, 3H), 3.15 (t, $J = 4.71$ Hz, 2H), 4.79 (s, br, NH), 6.12 (d, $J = 7.98$ Hz, 1H), 6.39-6.57 (m, 4H), 7.05 (t, $J = 7.98$ Hz, 2H), 9.12 (s, br, OH); ^{13}C NMR (50 MHz, DMSO-d_6)δ21.70, 23.02, 112.18 (2C), 112.40, 114.10, 115.90, 119.17, 129.13 (2C), 135.34, 138.19, 142.13, 149.85. HRMS $(M+H)^+$ calc for $C_{16}H_{19}N_2O$: 255.1497, found: 255.1501.

2.4b *5-(3-methoxy-N-methyl-anilino)-1,2,3,4-tetrahydroquinolin-8-ol (**5b**)*: Compound **5**b was prepared according to the general procedures. (29.17 mg, 76 C.^{1}H NMR (200 MHz, DMSO-d_6)δ 1.76 (m, 2H), 2.38 (m, 2H), 3.06 (s, 3H), 3.20 (m, 2H), 3.62 (s, 3H), 5.94-6.02 (m, 2H), 6.16-6.21 (dd, $J = 1.88$ Hz, $J =$ 8.17 Hz, 1H), 6.53 (d, $J = 8.48$ Hz, 1H), 6.72 (d, $J =$ 8.48 Hz, 1H), 6.97 (t, $J = 8.17$ Hz, 1H), 10.03 (s, br, OH); ^{13}C NMR (50 MHz, DMSO-d_6)δ20.31, 22.25, 55.12, 98.70, 101.53, 105.66, 113.45, 121.64, 125.73, 127.49, 130.04, 137.98, 145.91, 150.90, 160.67. HRMS $(M+H)^+$ calc for $C_{17}H_{21}N_2O_2$: 285.1603, found: 285.1613.

2.4c *5-(N-phenylanilino)-1,2,3,4-tetrahydroquinolin-8-ol(**5c**)*: Compound **5c** was prepared according to the general procedure; bright yellow crystals (34.6 mg, 88 20–20°C.^{1}H NMR (200 MHz, DMSO-d_6)δ 1.67 (m, 2H), 2.25 (t, $J = 6.78$ Hz, 2H), 3.12 (t, $J = 5.81$ Hz, 2H), 6.19 (d, $J = 7.75$ Hz, 1H), 6.57 (d, $J = 8.72$ Hz, 1H), 6.80-6.93 (m, 6H), 7.18 (t, $J = 7.75$ Hz, 4H), 9.38 (s, br, OH); ^{13}C NMR (50 MHz, DMSO-d_6)δ21.44, 23.56, 112.82, 117.51, 120.53 (4C), 121.14 (2C), 129.44 (4C), 133.85, 136.27, 143.08, 147.47 (3C). HRMS $(M+H)^+$ calc for $C_{21}H_{21}N_2O$: 317.1654, found: 317.1686.

3. Results and Discussion

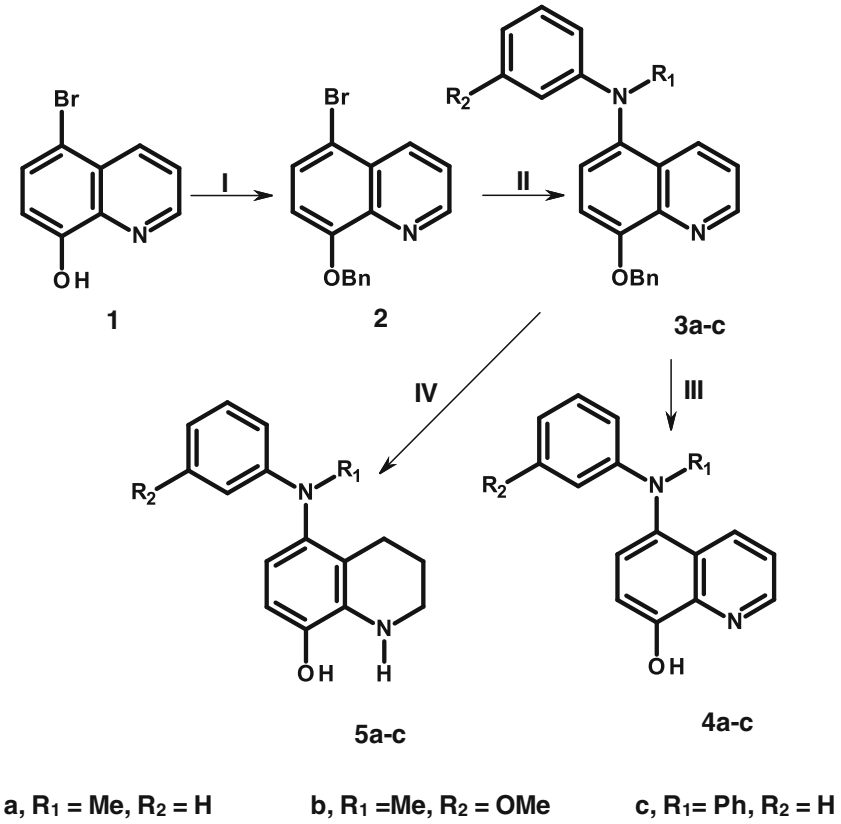
In this work, we aimed to explore the utility of commercially available phosphine ligands in Hartwig–Buchwald palladium catalyzed amination of quinoline derivative, 5-bromo-8-benzyloxyquinoline **2**, with three secondary anilines (scheme 1). For such a coupling, sterically demanding phosphine ligands, **L1**, **L2**, **L3** and **L4** have been employed (figure 1).

Previously, we investigated the H–B palladium catalyzed amination of secondary cyclic amines with 5-amino-8-benzyloxyquinoline **2**.[6] **L1**, **L2** and **L3** proved to be efficient ligands in this coupling. The cone angles of ligands play an important role in determining the catalyst system activity.[6,14,50]

A main side product that was observed during palladium catalyzed amination reactions was the arene or the reduction product of **2**.[6,51] Hartwig *et al.*[51] explained that the formation of the arene along with the desired amine during the reaction is due to competitive reductive elimination of the arylamine and β-hydrogen elimination from the amidoaryl intermediate. Moreover, the ratio of the amine to arene is controlled by steric and electronic factors of both the substrate and the ligand.

As the ligands, **L1**, **L2** and **L3** succeeded to different extents in the coupling of the secondary saturated amines, piperidine, pyrrolidine and morpholine with 5-bromo-8-benzyloxyquinolines **2**,[6] and we investigated their performance in the coupling of **2** with secondary aniline derivatives, namely *N*-methylaniline, 3-methoxy-*N*-methyl aniline and diphenylamine.

On the basis of our initial studies, the stable palladium acetate (5 mol%) proved to be a good source of palladium in H–B amination. In order to optimize the



Scheme 1. Reagents and conditions: (I) BnBr, K_2CO_3, DMF, rt, 1 h; (II) $Pd(OAc)_2$, Ligand (**L1**–**L4**), NaO-*t*-Bu (1.25 equiv.), aniline (1.25 equiv), toluene, 110–150°C, 0.5–24 h; (III): Pd–C (10 wt%), H_2, ethanol, reflux, 1–3 h; (IV): Pd–C (10 wt%), H_2, ethanol, reflux, 7 h.

reaction conditions, initially we used palladium acetate and **L1** to couple **2** with *N*-methylaniline. After 24 h of reflux at 110–120°C, ^{1}H-NMR from the crude reaction mixture revealed incomplete conversion of the starting material to products. In addition, the formation of 8-(benzyloxy)quinoline, which is the reduction product of **2**, was observed noticeably along with the desired amination product (table 1, entry 1). In contrast, the utilization of **L2** instead of **L1** (table 1, entry 2) under same conditions afforded the amination product in high yield (89%) and complete conversion was observed. The debrominated product was formed as a minor side product (11%). When **L3** was employed as the ligand (table 1, entry 3), similar to **L2**, complete conversion was observed. In addition, the highest yield of **3a** was obtained (93%) while the side reduction product was reduced noticeably to be 7%. To adjust the reaction time for the coupling of **2** with *N*-methylaniline using **L3** as the ligand, the reaction was repeated and traced with TLC. Complete conversion was observed after 30 min.

Having a defined and efficient catalytic system, the coupling of **2** with 3-MeO-*N*-methylaniline has been examined under the same reaction conditions (**L3** and 110–120°C). Surprisingly, the reaction did not proceed efficiently and only 3% of the starting material converted to products. Raising the temperature to 140–150°C afforded the desired coupling product **3b** after 6 h in high yield (89% in the crude reaction mixture). Ligand cone angle (θ) of **L3** increased with the replacement of *tert*-butyl group in **L2** with neopentyl group (**L2**, $\theta = 194^\circ <$ **L3**, $\theta = 198^\circ$).[14] The increased cone angle of **L3** allows better accommodation for the sterically hindered substrates.[30] This can explain the slightly increased efficiency of **L3** compared to **L2** during the coupling of secondary anilines.

Encouraged by the successful results we obtained using **L3** in the coupling, we were interested to investigate the coupling of **2** with diphenylamine using the same ligand. We observed very weak conversion even at high temperature as 150°C. Testing **L1** and **L2** did not lead to any improvement in the reaction. Since the phenyl is planar, diphenylamine can exhibit less steric hindrance than *N*-methylaniline, hence a less sterically demanding ligand with smaller cone angle is probably needed to couple **2** with diphenylamine. It has been reported that tricyclohexylphosphine ligand **L4** was used successfully in the coupling of substituted aryl bromides with substituted anilines giving the amination products in quantitative yields.[30] Employing tricyclohexylphosphine ligand **L4** (cone angle = 170°)[50] instead of **L3** under same reaction condition at 150°C was found to form about 70% conversion of the starting materials to products after 24 h. Raising the catalyst loading to be 10 mol% of palladium acetate resulted in a complete conversion giving the desired amination product in about 84% in the crude products mixture along with the undesired reduction product in about 16%. Herron *et al.*[10] reported the production of **4c** via palladium-catalyzed amination of 5-chloro-8-hydroxyquinoline with diphenylamine in refluxed dioxane/toluene for 180 h. The long reaction time led to catalyst deactivation and consequently decreased the yield. In this work, optimization of the reaction conditions and use of **2** as the starting material led to the production of **4c** effectively and decreased the reaction time considerably. In general, the decreased activity of diphenylamine in the coupling may be attributed to the lower nucleophilicity compared to the *N*-methylanilines. Table 2 summarizes the optimum conditions for the coupling of each aniline substrate with **2**.

After exploration of the optimal conditions for H–B amination reaction of **2** with each secondary aniline substrate, the products were purified by flash chromatography using the appropriate eluents.

The following step in this work was the deprotection of compounds **3a–c** to obtain the 5-anilino-8-hydroxyquinoline derivatives **4a–c**. The protecting benzyloxy group at 8-position in **2** tolerated the strong basic medium employed in this amination and could be smoothly removed after the coupling by catalytic hydrogenation. The deprotection took place using mild ligand-free palladium-catalyzed hydrogenation. A balloon filled with hydrogen gas fixed on top of condenser was the hydrogen source in the reaction media. The catalytic hydrogenation happened selectively on the benzyloxy group at 8-position in 1–3 h giving **4a–c** in good to high yields. Prolonged catalytic hydrogenation (6–7 h) under same condition resulted in a subsequent reduction of the pyridyl ring in the quinoline nucleus affording the corresponding 5-anilino-1,2,3,4-tetrahydro-8-hydroxyquinoline derivatives **5a–c** smoothly in high

Table 1. Pd catalyzed amination of 8-(Benzyloxy)-5-bromoquinoline **2** with *N*-methylaniline[a].

Entry	Ligand (θ)[b]	Start (%)	Red. Product (%)	Prod. **3a** (%)
1	L1 (246°)	40	32	28
2	L2 (194°)	0	11	89
3	L3 (198°)	0	7	93

[a]Reaction conditions: 50 mg of **2** , $Pd(AcO)_2$ (5mol%), Ligand (10 mol%), NaO-*t*-Bu (1.25 equiv.), amine (1.25 equiv.), Toluene at 110–120°C under argon atmosphere.
[b]Between brackets is the ligand cone angle.[14,50]
[c]isolated yield. The percentages were analyzed by ^{1}H NMR of the crude reaction mixture after reaction time 24 h.

Table 2. Optimum reaction conditions for the coupling of 8-(Benzyloxy)-5-bromoquinoline **2** with secondary aniline substrates and the yields of compounds **3a-c**.[a]

Aniline derivative	Ligand (θ)[b]	T (°C)	Reaction time	Product	Yield[c]
N-methylaniline	L3 (198°)	110-120	30 min	3a	93 (90)
3-Methoxy-*N*-methylaniline	L3 (198°)	140-150	6 h	3b	89 (87)
Diphenylamine	L4 (170°)[d]	150	24 h	3c	86 (82)

[a]Reaction conditions: 100-200 mg of **2**, $Pd(AcO)_2$ (5mol%), Ligand (10 mol%), NaO-t-Bu (1.25 equiv.), toluene under argon atmosphere.
[b]Between brackets is ligand cone angle.[14,50]
[c]Yields analzed by ^1H NMR from crude reaction mixture, number between bracket is the isolated yield after purification by flash chromatography.
[d]10 mol% of $Pd(AcO)_2$ was used in this coupling.

yields. The subsequent hydrogenation of **4a–c** to **5a–c** is attributed to the presence of the hydroxyl group in **4a-c** that facilitates the hydrogenation of quinoline nucleus.[52]

4. Conclusions

The Hartwig–Buchwald coupling reaction is an effective key step in the preparation of 5-anilino-8-benzyloxyquinoline, 5-anilino-8-hydroxyquinoline and 5-anilino-1,2,3,4-tetrahydro-8-hydroxyquinoline derivatives. Optimization of the reaction conditions and choice of a suitable catalyst/ ligand combination are prerequisites to obtain complete conversion and product yields. 5-Anilino-8-benzyloxyquinoline could be reduced smoothly by catalytic hydrogenation affording the corresponding 8-hydroxyquinoline derivatives. Once the 5-anilino-8-hydroxyquinolines were formed, the hydroxyl group facilitated further reduction of the pyridyl ring in the quinoline nucleus affording 5-anilino-1,2,3,4-tetrahydro-8-hydroxyquinolines.
Generally, all the reactions took place smoothly and under mild conditions.

Supplementary Information

^1H NMR, ^{13}C NMR spectra and HRMS for all new products are given in supplementary information, available at www.ias.ac.in/chemsci.

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