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4-Aryl-8-hydroxyquinolines from 4-chloro-8-tosyloxyquinoline using a Suzuki–Miyaura cross-coupling approach

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ABSTRACT

4-Chloro-8-tosyloxyquinoline was successfully cross-coupled with various arylboronic acids in anhydrous Suzuki–Miyaura conditions. The protective tosyl group was stable during the anhydrous coupling. The use of tosyl protection in association with anhydrous Suzuki–Miyaura reaction conditions allows the use of commercially available but relative inert 5-chloro-8-hydroxyquinoline for the synthesis of 5-phenyl-8-hydroxyquinoline. Deprotection could easily be made by using suitable nucleophiles to afford the final 5-phenyl and 4-aryl-8-hydroxyquinolines in high yields. Under acidic conditions the tosyloxy group is sufficiently stable to allow selective further modification of acid labile functional groups.

1. Introduction

Suzuki–Miyaura coupling is widely used in organic synthesis to create carbon–carbon bonds. The palladium catalyzed reaction can be conducted by using a wide variety of phosphine ligands in the presence of suitable bases such as carbonates, hydroxides, phosphates, or alkoxides.[1] A base is needed to accelerate the transmetallation step of the catalytic cycle.[1a,2] Brominated and iodinated aromatic compounds are favored over chlorinated counterparts due to lower reactivity of the C–Cl bond in the oxidative addition step.[3] A generally accepted reactivity order is $I \gg OTf > Br \gg Cl$.[1] Furthermore, it has also been shown that some substituted *o*-fluoronitrobenzenes can cross-couple with arylboronic acids and fluorobenzene undergoes the coupling if supported Pd catalyst is used.[4] However, the rate of the modified Suzuki–Miyaura coupling between fluorobenzene and phenylboronic acid is much lower than the rate of the corresponding cross-coupling between bromo or chlorobenzene and phenylboronic acid.[4c] Chlorinated aromatic compounds have many advantages compared to other halogenated starting materials. They are usually cheaper and they have often better commercial availability.

The reaction is usually carried out in the presence of water.[1a] Addition of water to the reaction medium has been shown to accelerate the coupling reaction considerably.[5] However, there are also some reports on the use of anhydrous conditions in successful Suzuki–Miyaura reactions. For example, aromatic iodo and bromo compounds have been coupled in benzene or in DMF with various boronic esters by using $Pd(PPh_3)_4$ as the catalyst and anhydrous Tl_2CO_3 or K_3PO_4 as the base.[6] It has also been observed that $Na_2B_4O_7$, CsF, and KF can be used as bases in Suzuki–Miyaura reactions.[7]

β-Oxo amides have been used as ligands for Pd but the yields of the coupling products have been low with chlorinated aryl reagents.[3b] On the other hand, some aryl and heteroaryl chlorides have been successfully coupled under anhydrous conditions with electron rich or electronically neutral arylboronic acids by using specially tailored phosphine ligands.[8] Recently, it has also been shown that electron-deficient chlorinated heteroaromatic compounds, such as pyridines, naphthyridones, and pyrimidines undergo Suzuki–Miyaura coupling in moderate to high yields under anhydrous conditions.[9]

2-Chloro[10] and 4-chloro[5,11] quinolines and 1-chloro isoquinoline[12] have been efficiently coupled with various arylboronic acids in the presence of water. Nakano et al. and Anzenbacher et al. have reported that 5-aryl-8-hydroxyquinolines can be synthesized by using aqueous Suzuki–Miyaura coupling between 5-bromo-8-benzyloxyquinoline and arylboronic acids.[3a,13] The products were collected in low to high (41–88%) yields. Removal of the benzyl protection by using Pd/C catalyzed hydrogenolyses with cyclohexadiene as the hydrogen source was problematic and gave the deprotected compounds in varying yields (20–95%).[3a,13]

Although a tosyloxy group is most frequently used as a good leaving group in synthetic organic chemistry, the tosyl group has also recently become an important protective group for phenolic hydroxyl groups.[14] It is stable in some acidic conditions[14a,e] and toward NaH.[15a] However, the stability is not obvious in a Suzuki–Miyaura reaction because it has previously been found that Pd catalysts may decompose tosyl groups, for example, during standard Pd/C-catalyzed hydrogenation.[14e] Pd-catalyzed lactonization

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may also lead to undesirable detosylation if it is performed in DMF in the presence of K_2CO_3.[14b]

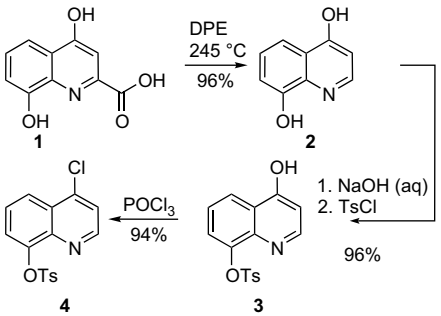
4-Arylquinolines and 8-hydroxyquinoline derivatives have interesting applications, for example, as maxi-K channel openers and as an inhibitor of mitogen-activated protein kinase.[16] Furthermore, dichloro-8-hydroxyquinolines show improved antifungal activity compared to the parent 8-hydroxyquinoline.[17] Aluminum complexes of 8-hydroxyquinolines with electron poor aryl substituents at the 5-position or an electron donating methyl substituent at the 4-position have enhanced photoluminescence (PL) quantum efficiencies compared with the PL quantum efficiency of the parent aluminum tris(8-hydroxyquinoline), Alq_3. They also exhibit enhanced electroluminescence (EL) characteristics in OLED applications.[13,18] Furthermore, the emission wavelength of Alq_3 can be tuned simply by attaching suitable substituents to the 8-hydroxyquinoline ligands.[13]

In this paper, we describe a synthetic method to produce 4-aryl-8-hydroxyquinolines and 4-hydroxypyridinoanthrene[19] from the readily available 4-chloro-8-tosyloxyquinoline.[15b] We demonstrate that the tosyl group is stable during anhydrous Suzuki–Miyaura coupling and that the electron-deficient chlorinated starting material couples efficiently with various arylboronic acids under anhydrous conditions. We also show that the commercially available 5-chloro-8-hydroxyquinoline[20] can, after tosyl protection, act as a starting material for synthesis of 5-phenyl-8-hydroxyquinoline. Removal of the tosyl group can be executed efficiently by using suitable nucleophiles in the final deprotection step.

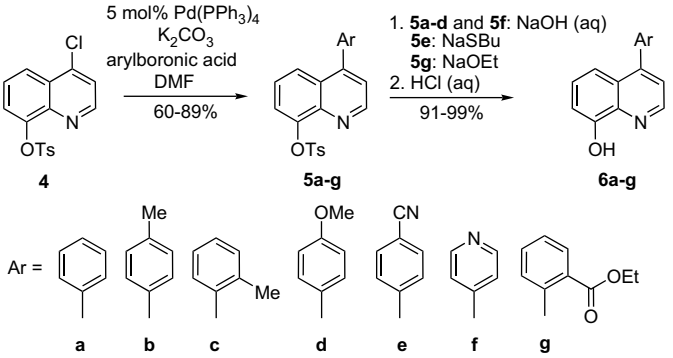
2. Results and discussion

The starting material in our synthetic route, 4-chloro-8-tosyloxyquinoline **4**,[15b] can be prepared on a large scale and in high yield from the readily available 4-hydroxy-8-tosyloxyquinoline[15a] **3** (Scheme 1). Compound **3** can be produced from commercially available xanthurenic acid **1** by decarboxylation and selective tosylation during the consequent step. Suzuki–Miyaura coupling between **4** and various arylboronic acids was made in dry DMF by using anhydrous potassium carbonate as the base (Scheme 2). The yields of the arylated 8-tosyloxyquinolines **5a–g** are presented in Table 1.

We studied the effect of catalyst loadings in the anhydrous Suzuki–Miyaura coupling. Compound **4** was treated with phenylboronic acid by using 1 mol % of $Pd(PPh_3)_4$. The low catalyst loading led to a diminished conversion of the starting material and after 2 h product **5a** was produced only in a moderate yield (45%) (Table 1, entry 1). Elevation of the catalyst loading to 5 mol % enhanced the yield of the coupling product **5a** to 75% (entry 2). Furthermore, we also observed that a doubling of the reaction time slightly improved the yield of **5a** (78%, entry 3). We were also interested to see how fluoride ion works as the base in the Suzuki–Miyaura coupling between **4** and phenylboronic acid.[21] The result was disappointing



Scheme 1.



Scheme 2.

because the reaction gave **5a** only in a moderate yield (47%) (Table 1, entry 4). A plausible explanation for the result is that some of the chlorine atoms were substituted by fluorine atoms and the resulting C–F bonds were considerably less reactive or even unreactive compared with the original C–Cl bonds in Suzuki–Miyaura couplings.[4c,22]

We also studied Suzuki–Miyaura coupling in aqueous conditions. Interestingly, the results show clearly that the Suzuki–Miyaura coupling in aqueous conditions between **4** and the especially electron poor 4-pyridylboronic acid had a deleterious effect on yield (Table 1, entry 11). The conversion of the starting material was very low and a simultaneous formation of the deprotected **5f** could be observed. The yield of **5f** was only 24%. On the other hand, 4-pyridylboronic acid and **4** undergoes Suzuki–Miyaura coupling readily if anhydrous coupling conditions are employed. 4-(4-Pyridyl)-8-tosyloxyquinoline **5f** could be isolated in 60% yield (Table 1, entry 10). The Suzuki–Miyaura coupling between **4** and phenylboronic acid was also considerably more successful in anhydrous conditions than in aqueous conditions (Table 1, entries 3 and 5, respectively).

Table 1 shows clearly that anhydrous Suzuki–Miyaura couplings between **4** and electron rich 4-methoxyphenylboronic, 4-methylphenylboronic, and 2-methylphenylboronic acids as well as the electron poor 4-cyanophenylboronic and 2-(ethoxycarbonyl)phenylboronic acids proceed efficiently. Compounds **5b–e** and **5g** were collected in medium 64% to high 89% yields (Table 1, entries 6–9 and 12).

The C–OTs bond was stable during Suzuki–Miyaura couplings. A feasible reason for the stability is that nitrogen of the quinoline ring

Table 1
Reaction times and the yields in Suzuki–Miyaura couplings of **4**

Entry	Product	Time	Yield %
1	**5a**[a]	2 h	45[b]
2	**5a**	2 h	75
3	**5a**	4 h	78
4	**5a**[c]	4 h	47[b]
5	**5a**[d]	4 h	62
6	**5b**	4 h	79
7	**5c**	4 h	89
8	**5d**	4 h	76
9	**5e**	7 h	65
10	**5f**	$8^1/_2$ h	60
11	**5f**[d]	$8^1/_2$ h	24[b]
12	**5g**	2 h	64

General reaction conditions: 5 mol % of $Pd(PPh_3)_4$, anhydrous K_2CO_3 (2.1 equiv), and $ArB(OH)_2$ (1.05 equiv).

[a] The amount of $Pd(PPh_3)_4$ was 1 mol %.

[b] The amount of the product was estimated from ^1H NMR spectrum of the crude mixture.

[c] KF (2.1 equiv) was used instead of K_2CO_3.

[d] 2 M K_2CO_3 (aq) (2.1 equiv).

Table 2
Yields of 4-aryl-8-hydroxyquinolines

Entry	Product	Yield %
1[a]	**6a**	92
2[a]	**6b**	97
3[a]	**6c**	99
4[a]	**6d**	98
5[b]	**6e**	96
6[a]	**6f**	91
7[c]	**6g**	92
8[a]	**6h**	92

[a] Deprotection reagent: NaOH (aq).
[b] Deprotection reagent: NaSBu in *t*-amylalcohol.
[c] Deprotection reagent: NaOEt in ethanol.

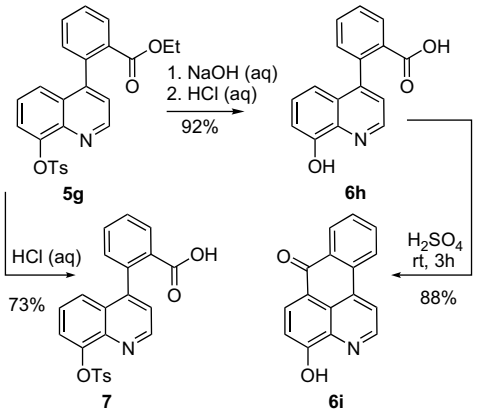
suppresses the ability of Pd(0) to oxidatively add to the C–OTs bond combined with that the C–Cl bond in the 4-position is especially weak and prone to Suzuki–Miyaura coupling due to the π-deficient quinoline ring.

Alkaline deprotection of **5a–d** and **5f** was carried out efficiently by using aqueous sodium hydroxide (Scheme 2). The final products **6a–d** and **6f** were collected by filtration from neutralized water solutions in high yields (91–98%) (Table 2, entries 1–4 and 6).

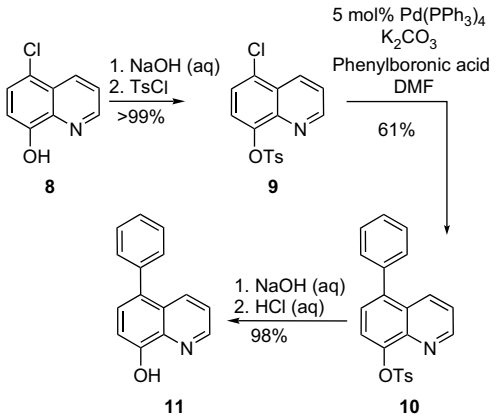
Removal of the protecting tosyl group from **5e** by alkaline hydrolysis was unsuccessful due to a simultaneous hydrolysis of the cyano group.[23a] Various nucleophilic reagents were tested and it was finally found that sodium 1-butylthiolate in 2-methyl-2-butanol cleanly removed the protective tosyl group to afford **6e** in 96% yield (Table 2, entry 5). We also observed that the reaction between **5e** and sodium 1-butylhiolate with 1-butanol as the solvent, instead of *tert*-amylalcohol, led to the formation of sodium butoxide, which then added to the cyano group.[23b]

4-*o*-Ethoxycarbonylphenyl-8-hydroxyquinoline **6g** can be prepared from **5g** by using sodium ethoxide in ethanol as the deprotecting agent instead of aqueous sodium hydroxide (Scheme 2). Compound **6g** was collected in a high 92% yield (Table 2, entry 7). It is also worthy of mention that during the deprotections of **5e** with sodium butylthiolate and **5g** with sodium ethoxide, no potential S_NAr reaction products, 4-*p*-cyanophenyl-8-butylthioquinoline and 4-*o*-ethoxycarbonylphenyl-8-ethoxyquinoline, could be detected.

Deprotection of **5g** with aqueous sodium hydroxide (Scheme 3) led to a simultaneous hydrolysis of the ethyl ester group and gave 4-*o*-carboxyphenyl-8-hydroxyquinoline **6h** in 92% yield (Table 2, entry 8). We also observed that when **5g** was treated with aqueous hydrochloric acid, the ethyl ester group was hydrolyzed selectively to give 4-*o*-carboxyphenyl-8-tosyloxyquinoline **7** in a good yield (73%) (Scheme 3).



Scheme 3.



Scheme 4.

In the case of compound **6h**, we were also interested to investigate the possibility to produce a new tetracyclic 8-hydroxyquinoline derivative **6i** from **6h** (Scheme 3). We found that **6h** underwent an intramolecular Friedel–Crafts acylation cleanly in concentrated sulfuric acid and that 4-hydroxypyridinoanthrene **6i** could be collected in a high yield (88%).

Finally, we were also keen to demonstrate the usefulness of the protective tosyl group in a Suzuki–Miyaura coupling between a relatively inert but commercially available 5-chloro-8-hydroxyquinoline **8** and phenylboronic acid. Compound **8** was tosylated by using 1 equiv of sodium hydroxide and *p*-toluenesulfonyl chloride (Scheme 4) to give 5-chloro-8-tosyloxyquinoline **9** in a quantitative yield (>99%). Compound **9** and phenylboronic acid underwent Suzuki–Miyaura coupling readily under anhydrous conditions to give 5-phenyl-8-tosyloxyquinoline **10** in 61% yield. This is an interesting result because it has been reported previously that 5-chloro-8-benzyloxyquinoline is completely inactive in an attempted Suzuki–Miyaura reaction.[3a] π-Deficient heteroaryl chlorides are known to be much more reactive in Suzuki–Miyaura couplings than the electronically neutral or electron rich aryl chlorides.[1] Compared with an electron donating benzyloxy group (Hammett $\sigma_p=-0.33$),[24a] a tosyloxy group is much more electron withdrawing (Hammett $\sigma_p=+0.28$)[24b] and 5-chloro-8-tosyloxyquinoline **9** is, therefore, more π-deficient than 5-chloro-8-benzyloxyquinoline. Apparently, a benzyloxy group deactivated 5-chloroquinoline in the attempted Suzuki–Miyaura reaction. The deprotection of **10** with aqueous sodium hydroxide occurred readily to give 5-phenyl-8-hydroxyquinoline **11** in high yield (98%).[25]

3. Conclusions

Nine 8-hydroxyquinoline derivatives have been synthesized. Readily available 4-chloro-8-tosyloxyquinoline and various arylboronic acids were efficiently coupled by using anhydrous Suzuki–Miyaura conditions and commercially available $Pd(PPh_3)_4$ as the catalyst. The protective tosyl group was stable during the coupling reactions. The use of tosyl protection in association with anhydrous Suzuki–Miyaura reaction conditions also enables the use of 5-chloro-8-hydroxyquinoline in the synthesis of 5-phenyl-8-hydroxyquinoline. Detosylation could be successfully accomplished by using various nucleophilic deprotection agents. The final 5-phenyl-8-hydroxyquinoline and 4-aryl-8-hydroxyquinolines were produced in high yields. The formation of undesired by-products during the deprotection step could be avoided by choosing the conditions and nucleophiles with care. Under acidic conditions the tosyloxy group is stable enough to allow further modification of acid labile

functionalities. Similarly, to our previous observations[15] our present work demonstrates that the tosyl group is an extremely useful protective group in the synthetic chemistry of 8-hydroxyquinolines.

4. Experimental section

4.1. General remarks

Commercially available reagents were used as received. DMF and *n*-hexane were dried with molecular sieves (4 Å). Silica gel with 0.040–0.063 mm particle size was used as a support in every flash chromatography purification procedure.

4.2. General procedure for synthesis of 5-phenyl-8-tosyloxyquinoline and 4-aryl-8-tosyloxyquinolines

Chloro-8-tosyloxyquinoline and 5 mol % $Pd(PPh_3)_4$ were dissolved in DMF (14 mL). Anhydrous K_2CO_3 (2.1 equiv) and arylboronic acid (1.05 equiv) were mixed together in DMF (6 mL). After 10 min, the two mixtures were combined. The resulting mixture was refluxed under nitrogen atmosphere. The reaction was monitored by TLC. The solvent was removed in vacuum. Chloroform (30 mL) was added and the solution was extracted with three 10 mL portions of distilled water. The organic layer was dried with Na_2SO_4 and filtered. The filtrate was concentrated in vacuum. Purification of the residue by flash chromatography afforded the coupled products.

*4.2.1. 4-Phenyl-8-tosyloxyquinoline (**5a**)*

The specific amounts of chemicals used were: 4-chloro-8-tosyloxyquinoline **4** (1.00 g, 3.00 mmol), $Pd(PPh_3)_4$ (173 mg, 0.15 mmol), anhydrous K_2CO_3 (870 mg, 6.29 mmol), phenylboronic acid (384 mg, 3.15 mmol), and DMF (20 mL). The reaction time was 4 h. Purification by flash chromatography (1:1 ethyl acetate/*n*-hexane) afforded the title compound (872 mg, 78%) as off-white crystals. Mp: 168–171 °C. IR (KBr): ν=3042 (w), 2996 (w), 2913 (w), 1590 (s). ^{1}H NMR (200 MHz, DMSO-d_6): δ=2.42 (3H, s), 7.44–7.62 (10H, m), 7.79–7.89 (3H, m), 8.89 (1H, d, J=4.3 Hz). ^{13}C NMR (50 MHz, DMSO-d_6): δ=21.7, 122.0, 122.2, 125.1, 125.7, 128.2, 128.6, 128.7, 129.4, 129.5, 133.3, 137.5, 142.1, 145.0, 145.8, 148.2, 150.3. HRMS: calcd for $C_{22}H_{18}NO_3S$ ($[M+H]^+$) 376.1007, found 376.1011.

*4.2.2. 4-p-Methylphenyl-8-tosyloxyquinoline (**5b**)*

The specific amounts of chemicals used were: 4-chloro-8-tosyloxyquinoline **4** (1.00 g, 3.00 mmol), $Pd(PPh_3)_4$ (173 mg, 0.15 mmol), anhydrous K_2CO_3 (871 mg, 6.30 mmol), 4-methylphenylboronic acid (428 mg, 3.15 mmol), and DMF (20 mL). The reaction time was 4 h. Purification by flash chromatography (1:1 ethyl acetate/*n*-hexane) afforded the title compound (920 mg, 79%) as off-white crystals. Mp: 144–147 °C. IR (KBr): ν=3030 (w), 2919 (m), 1589 (s). ^{1}H NMR (200 MHz, DMSO-d_6): δ=2.41 (6H, m), 7.36–7.49 (8H, m), 7.57 (1H, t, J=8.2 Hz), 7.81–7.88 (3H, m), 8.87 (1H, d, J=4.4 Hz). ^{13}C NMR (50 MHz, DMSO-d_6): δ=21.0, 21.4, 122.1, 122.5, 125.1, 126.5, 127.8, 128.5, 129.6, 129.7, 130.1, 132.8, 134.1, 138.6, 141.7, 145.4, 145.7, 147.7, 150.8. HRMS: calcd for $C_{23}H_{20}NO_3S$ ($[M+H]^+$) 390.1164, found 390.1173.

*4.2.3. 4-o-Methylphenyl-8-tosyloxyquinoline (**5c**)*

The specific amounts of chemicals used were: 4-chloro-8-tosyloxyquinoline **4** (502 mg, 1.50 mmol), $Pd(PPh_3)_4$ (87.4 mg, 0.076 mmol), anhydrous K_2CO_3 (436 mg, 3.15 mmol), 2-methylphenylboronic acid (215 mg, 1.05 mmol), and DMF (10 mL). The reaction time was 4 h. Purification by flash chromatography (2:5 acetone/*n*-hexane, 10 mL methanol in 1.5 L) afforded the title compound (522 mg, 89%) as off-white crystals. Mp: 146–149 °C. IR (KBr): ν=3059 (w), 2961 (w), 2923 (w), 1592 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ=1.93 (3H, s), 2.39 (3H, s), 7.22 (1H, d, J=7.2 Hz), 7.31–7.58 (9H, m), 7.83 (2H, d, J=8.3 Hz), 8.88 (1H, d, J=4.3 Hz). ^{13}C NMR (50 MHz, DMSO-d_6): δ=19.7, 21.3, 122.2, 122.8, 125.0, 126.2, 126.7, 128.2, 128.6, 128.9, 129.5, 130.0, 130.4, 132.6, 135.5, 136.7, 141.3, 145.4, 145.7, 147.6, 150.8. HRMS: calcd for $C_{23}H_{19}NO_3NaS$ ($[M+Na]^+$) 412.0983, found 412.0981.

*4.2.4. 4-p-Methoxyphenyl-8-tosyloxyquinoline (**5d**)*

The specific amounts of chemicals used were: 4-chloro-8-tosyloxyquinoline **4** (1.00 g, 3.00 mmol), $Pd(PPh_3)_4$ (173 mg, 0.15 mmol), anhydrous K_2CO_3 (872 mg, 6.31 mmol), 4-methoxyphenylboronic acid (479 mg, 3.15 mmol), and DMF (20 mL). The reaction time was 4 h. Purification by flash chromatography (1:1 ethyl acetate/*n*-hexane) afforded the title compound (924 mg, 76%) as off-white crystals. Mp: 135–138 °C. IR (KBr): ν=3039 (w), 2991 (w), 2923 (m), 2837 (w), 1657 (s), 1601 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ=2.41 (3H, s), 3.85 (3H, s), 7.14 (2H, d, J=8.7 Hz), 7.44–7.52 (6H, m), 7.57 (1H, t, J=8.3 Hz), 7.84–7.89 (3H, m), 8.86 (1H, d, J=4.4 Hz). ^{13}C NMR (50 MHz, DMSO-d_6): δ=21.4, 55.5, 114.5, 122.0, 122.5, 125.2, 126.5, 127.9, 128.5, 129.2, 130.1, 131.1, 132.8, 141.7, 145.4, 145.7, 147.5, 150.8, 159.9. HRMS: calcd for $C_{23}H_{19}NO_4NaS$ ($[M+Na]^+$) 428.0932, found 428.0917.

*4.2.5. 4-p-Cyanophenyl-8-tosyloxyquinoline (**5e**)*

The specific amounts of chemicals used were: 4-chloro-8-tosyloxyquinoline **4** (1.00 g, 3.00 mmol), $Pd(PPh_3)_4$ (173 mg, 0.15 mmol), anhydrous K_2CO_3 (871 mg, 6.30 mmol), 4-cyanophenylboronic acid (463 mg, 3.15 mmol), and DMF (20 mL). The reaction time was 7 h. Purification by flash chromatography (1:1 ethyl acetate/*n*-hexane) and recrystallization from ethanol afforded the title compound (784 mg, 65%) as off-white crystals. Mp: 164–167 °C. IR (KBr): ν=3067 (w), 2920 (w), 2227 (m), 1592 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ=2.42 (3H, s), 7.44–7.64 (5H, m), 7.70–7.78 (3H, m), 7.86 (2H, d, J=8.3 Hz), 8.06 (2H, d, J=8.2 Hz), 8.93 (1H, d, J=4.3 Hz). ^{13}C NMR (50 MHz, DMSO-d_6): δ=21.4, 111.8, 111.8, 118.8, 122.4, 122.7, 124.7, 127.1, 128.6, 130.2, 130.8, 132.7, 132.9, 141.6, 141.8, 145.4, 145.8, 146.0, 150.8. HRMS: calcd for $C_{23}H_{17}N_2O_3S$ ($[M+H]^+$) 401.0960, found 401.0957.

*4.2.6. 4-(4-Pyridine)-8-tosyloxyquinoline (**5f**)*

The specific amounts of chemicals used were: 4-chloro-8-tosyloxyquinoline **4** (1.00 g, 3.00 mmol), $Pd(PPh_3)_4$ (173 mg, 0.15 mmol), anhydrous K_2CO_3 (870 mg, 6.29 mmol), 4-pyridineboronic acid (387 mg, 3.15 mmol), and DMF (20 mL). The reaction time was $8\frac{1}{2}$ h. Purification by flash chromatography (1:9 methanol/ethyl acetate) and recrystallization from ethanol afforded the title compound (677 mg, 60%) as off-white crystals. Mp: 181–184 °C. IR (KBr): ν=3041 (m), 2914 (w), 1588 (s), 1540 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ=2.42 (3H, s), 7.44–7.65 (7H, m), 7.77 (1H, dd, J=1.5, 8.3 Hz), 7.86 (2H, dd, J=1.6, 6.7 Hz), 8.78 (2H, dd, J=1.6, 4.4 Hz), 8.94 (1H, d, J=4.4 Hz). ^{13}C NMR (50 MHz, DMSO-d_6): δ=21.4, 122.5, 122.5, 124.5, 124.6, 126.9, 127.2, 128.6, 130.2, 132.7, 141.5, 144.7, 145.1, 145.4, 145.8, 150.2, 150.9. HRMS: calcd for $C_{21}H_{17}N_2O_3S$ ($[M+H]^+$) 377.0960, found 377.0971.

*4.2.7. 4-o-Ethoxycarbonylphenyl-8-tosyloxyquinoline (**5g**)*

The specific amounts of chemicals used were: 4-chloro-8-tosyloxyquinoline **4** (502 mg, 1.50 mmol), $Pd(PPh_3)_4$ (87.5 mg, 0.076 mmol), anhydrous K_2CO_3 (436 mg, 3.15 mmol), 2-(ethoxycarbonyl)-phenylboronic acid (306 mg, 1.05 mmol), and DMF (10 mL). The reaction time was 2 h. Purification by flash chromatography (2:5 acetone/*n*-hexane, 10 mL methanol in 1.5 L) and recrystallization from ethanol afforded the title compound (433 mg, 64%) as off-white crystals. Mp: 121–123 °C. IR (KBr): ν=3075 (w), 2989 (m), 2959 (w), 1723 (s), 1593 (m), 1510 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ=0.49 (3H, t, J=7.1 Hz), 2.41 (3H, s), 3.72 (2H, q,

J=7.1 Hz), 7.31 (1H, dd, J=2.5, 7.3 Hz), 7.37–7.54 (6H, m), 7.64–7.82 (2H, m), 7.86 (2H, d, J=8.3 Hz), 8.04 (1H, dd, J=1.4, 7.5 Hz), 8.87 (1H, d, J=4.4 Hz). ^{13}C NMR (50 MHz, DMSO-d_6): δ=13.7, 22.0, 61.3, 122.5, 122.6, 125.3, 127.1, 129.2, 129.3, 129.9, 130.8, 131.0, 131.3, 131.8, 133.4, 138.2, 141.5, 145.9, 146.3, 148.9, 151.3, 166.8. HRMS: calcd for $C_{25}H_{22}NO_5S$ ([M+H]$^+$) 448.1219, found 448.1221.

*4.2.8. 5-Phenyl-8-tosyloxyquinoline (**10**)*

The specific amounts of chemicals used were: 5-chloro-8-tosyloxyquinoline **9** (502 mg, 1.50 mmol), $Pd(PPh_3)_4$ (88.0 mg, 0.076 mmol), anhydrous K_2CO_3 (436 mg, 3.15 mmol), phenylboronic acid (1.93 mg, 1.58 mmol), and DMF (10 mL). The reaction time was 4 h. Purification by flash chromatography (2:5 acetone/*n*-hexane, 10 mL methanol in 1.5 L) afforded the title compound (343 mg, 61%) as off-white crystals. Mp: 159–161 °C. IR (KBr): ν=3035 (w), 1591 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ=2.41 (3H, s), 7.44–7.60 (10H, m), 7.88 (2H, d, J=8.3 Hz), 8.18 (1H, dd, J=1.4, 8.6 Hz), 8.87 (1H, dd, J=1.4, 4.1 Hz). ^{13}C NMR (50 MHz, DMSO-d_6): δ=21.4, 121.7, 122.8, 126.9, 127.4, 128.3, 128.5, 128.9, 130.0, 130.2, 132.8, 134.1, 138.0, 139.5, 141.2, 144.4, 145.7, 151.1. HRMS: calcd for $C_{22}H_{18}NO_3S$ ([M+H]$^+$) 376.1007, found 376.1002.

4.3. General procedure for synthesis of 4- and 5-aryl-8-hydroxyquinolines (6a)–(6d), (6f), and (11)

Aryl-8-tosyloxyquinoline was dissolved in a mixture of acetone (15 mL) and ethanol (15 mL). NaOH (1 M, 3 equiv) was added. The solution was refluxed and the reaction was monitored by TLC. The solvents were removed by evaporation. Distilled water (10 mL) was added and pH was adjusted to 6.5 with 1 M HCl (aq). The product was collected by filtration and washed with distilled water to give the product.

*4.3.1. 4-Phenyl-8-hydroxyquinoline (**6a**)*

The specific amounts of chemicals used were: 4-phenyl-8-tosyloxyquinoline **5a** (800 mg, 2.13 mmol) and NaOH (1 M, 6.39 mL, 6.39 mmol). The reaction time was 2 h. The product was collected (432 mg, 92%) as a yellow powder. A small amount of the product was recrystallized from ethanol for analytical purposes. Mp: 110–112 °C. IR (KBr): ν=3332 (s), 3056 (m), 3034 (m), 1585 (m), 1560 (s), 1512 (s). ^{1}H NMR (200 MHz, DMSO-d_6): δ=7.11 (1H, d, J=7.4 Hz), 7.25 (1H, d, J=8.5 Hz), 7.40 (1H, d, J=7.7 Hz), 7.46 (1H, d, J=4.2 Hz), 7.55 (5H, m), 8.88 (1H, d, J=4.2 Hz), 9.81 (1H, s). ^{13}C NMR (50 MHz, DMSO-d_6): δ=111.3, 115.3, 122.2, 127.0, 128.0, 128.8, 128.9 129.5, 137.8, 139.1, 147.8, 147.9, 153.9. HRMS: calcd for $C_{15}H_{12}NO$ ([M+H]$^+$) 222.0919, found 222.0910.

*4.3.2. 4-p-Methylphenyl-8-hydroxyquinoline (**6b**)*

The specific amounts of chemicals used were: 4-*p*-methylphenyl-8-tosyloxyquinoline **5b** (800 mg, 2.05 mmol) and NaOH (aq) (1 M, 6.15 mL, 6.15 mmol). The reaction time was 2 h. The product was collected (468 mg, 97%) as yellow powder. A small amount of the product was recrystallized from ethanol for analytical purposes. Mp: 148–150 °C. IR (KBr): ν=3304 (s), 3024 (m), 2917 (w), 1615 (w), 1560 (m). ^{1}H NMR (200 MHz, DMSO-d_6): δ=2.41 (3H, s), 7.11 (1H, d, J=7.2 Hz), 7.27–7.45 (7H, m), 8.87 (1H, d, J=4.3 Hz), 9.85 (1H, br s). ^{13}C NMR (50 MHz, DMSO-d_6): δ=21.0, 111.2, 115.4, 122.1, 127.1, 127.9, 129.5, 134.9, 138.2, 139.1, 147.8, 147.9, 153.9. HRMS: calcd for $C_{16}H_{14}NO$ ([M+H]$^+$) 236.1075, found 236.1090.

*4.3.3. 4-o-Methylphenyl-8-hydroxyquinoline (**6c**)*

The specific amounts of chemicals used were: 4-*o*-methylphenyl-8-tosyloxyquinoline **5c** (800 mg, 2.05 mmol) and NaOH (aq) (1 M, 6.15 mL, 6.15 mmol). The reaction time was 2 h. The product was collected (480 mg, 99%) as yellow powder. A small amount of the product was recrystallized from ethanol for analytical purposes. Mp: 106–109 °C. IR (KBr): ν=3317 (s), 3049 (m), 2967 (w), 1628 (w), 1597 (w), 1565 (m), 1514 (s). ^{1}H NMR (200 MHz, DMSO-d_6): δ=1.97 (3H, s), 6.79 (1H, d, J=8.2 Hz), 7.09 (1H, d, J=7.2 Hz), 7.21 (1H, d, J=7.1 Hz), 7.30–7.46 (5H, m), 8.90 (1H, d, J=4.3 Hz), 9.91 (1H, br s). ^{13}C NMR (50 MHz, DMSO-d_6): δ=19.7, 111.4, 115.4, 122.3, 126.1, 127.6, 128.0, 128.6, 129.4, 130.3, 135.5, 137.5, 138.9, 147.8, 147.9, 153.9. HRMS: calcd for $C_{16}H_{14}NO$ ([M+H]$^+$) 236.1075, found 236.1081.

*4.3.4. 4-p-Methoxyphenyl-8-hydroxyquinoline (**6d**)*

The specific amounts of chemicals used were: 4-*p*-methoxyphenyl-8-tosyloxyquinoline **5d** (800 mg, 1.97 mmol) and NaOH (aq) (1 M, 5.91 mL, 5.91 mmol). The reaction time was 2 h. The product was collected (487 mg, 98%) as yellow powder. A small amount of the product was recrystallized from ethanol for analytical purposes. Mp: 149–151 °C. IR (KBr): ν=3310 (s), 3042 (m), 3007 (m), 2954 (m), 2928 (m), 2832 (m), 1607 (s), 1561 (m), 1502 (s). ^{1}H NMR (200 MHz, DMSO-d_6): δ=3.85 (3H, s), 7.09–7.15 (3H, m), 7.31–7.52 (5H, m), 8.86 (1H, d, J=4.3 Hz), 9.82 (1H, br s). ^{13}C NMR (50 MHz, DMSO-d_6): δ=55.5, 111.2, 114.4, 115.5, 122.1, 127.2, 127.8, 130.0, 130.9, 139.2, 147.6, 147.9, 153.9, 159.8. HRMS: calcd for $C_{16}H_{14}NO_2$ ([M+H]$^+$) 252.1025, found 252.1032.

*4.3.5. 4-(4-Pyridyl)-8-hydroxyquinoline (**6f**)*

The specific amounts of chemicals used were: 4-(4-pyridyl)-8-tosyloxyquinoline **5f** (800 mg, 2.13 mmol) and NaOH (aq) (1 M, 6.39 mL, 6.39 mmol). The reaction time was 1 h. The product was collected (430 mg, 91%) as off-white powder. A small amount of the product was recrystallized from ethanol for analytical purposes. Mp: 184–187 °C. IR (KBr): ν=3325 (s), 3035 (m), 1625 (m), 1594 (m), 1513 (s). ^{1}H NMR (200 MHz, DMSO-d_6): δ=7.13–7.23 (2H, m), 7.42–7.59 (4H, m), 8.77 (2H, d, J=5.6 Hz), 8.93 (1H, d, J=4.3 Hz), 10.00 (1H, s). ^{13}C NMR (50 MHz, DMSO-d_6): δ=111.7, 114.8, 122.0, 124.4, 126.2, 128.5, 139.0, 145.1, 145.5, 147.9, 150.2, 154.0. HRMS: calcd for $C_{14}H_{11}N_2O$ ([M+H]$^+$) 223.0871, found 223.0884.

*4.3.6. 5-Phenyl-8-hydroxyquinoline (**11**)*

The specific amounts of chemicals used were: 5-phenyl-8-tosyloxyquinoline **10** (450 mg, 1.20 mmol) and NaOH (aq) (1 M, 3.60 mL, 3.60 mmol). The reaction time was 2^1⁄$_2$ h. The product was collected (260 mg, 98%) as yellow powder. A small amount of the product was recrystallized from ethanol for analytical purposes. Mp: 96–98 °C.[26] ^{1}H NMR (200 MHz, DMSO-d_6): δ=7.16 (1H, d, J=7.9 Hz), 7.39–7.58 (7H, m), 8.20 (1H, dd, J=1.5, 8.6 Hz), 8.89 (1H, dd, J=1.5, 4.1 Hz).

4.4. 4-*p*-Cyanophenyl-8-hydroxyquinoline (6e)

NaH (108 mg, 4.50 mmol) in 60% oil dispersion was washed with *n*-hexane (5 mL). 1-Butanethiol (0.50 mL, 4.52 mmol) was added and the mixture was stirred vigorously. 4-*p*-Cyanophenyl-8-tosyloxyquinoline **5e** (600 mg, 1.50 mmol) in 2-methyl-2-butanol (20 mL) was added and the mixture was refluxed for 10 min. Formation of an extensive precipitate could be observed. *tert*-Amylalcohol was removed in vacuum and distilled water (10 mL) was added. pH was adjusted to 6.5 with hydrochloric acid (1 M) and the resulting mixture was concentrated in vacuum. The crude product was washed with distilled water to give the product (354 mg, 96%) as an off-white powder. A small amount of the product was recrystallized for analytical purposes from ethanol. Mp: 202–205 °C. IR (KBr): ν=3316 (s), 3043 (m), 2224 (s), 1607 (m), 1563 (m), 1500 (s). ^{1}H NMR (200 MHz, DMSO-d_6): δ=7.12–7.19 (2H, m), 7.43 (1H, d, J=8.1 Hz), 7.52 (1H, d, J=4.2 Hz), 7.75 (2H, d, J=7.9 Hz), 8.05 (2H, d, J=7.9 Hz), 8.92 (1H, d, J=4.2 Hz), 9.98 (1H, s). ^{13}C NMR

(50 MHz, DMSO-d_6): δ=111.6, 111.7, 114.9, 118.8, 122.2, 126.4, 128.5, 130.6, 132.8, 139.0, 142.6, 146.0, 147.9, 154.0. HRMS: calcd for $C_{16}H_{11}N_2O$ ([M+H]$^+$) 247.0871, found 247.0863.

4.5. 4-*o*-Ethoxycarbonylphenyl-8-hydroxyquinoline (6g)

NaH (114 mg, 4.75 mmol) in 60% oil dispersion was washed with *n*-hexane (5 mL) and ethanol (10 mL) was added. 4-*o*-Ethoxycarbonylphenyl-8-tosyloxyquinoline **5g** (701 mg, 1.57 mmol) was added and the reaction mixture was refluxed for 30 min. The reaction mixture was evaporated to dryness. Distilled water (5 mL) was added and pH was adjusted to 4.0 with 1 M HCl (aq). The resulting precipitate was collected by vacuum filtration and washed with distilled water. The procedure gave the product (423 mg, 92%) as a light-yellow powder. A small amount of the product was recrystallized for analytical purposes from ethanol. Mp: 100–102 °C. IR (KBr): ν=3304 (s), 3061 (w), 2980 (m), 2900 (w), 1712 (s), 1595 (m), 1566 (m), 1512 (s). ^{1}H NMR (200 MHz, DMSO-d_6): δ=0.57 (3H, t, J=7.1 Hz), 3.77 (2H, q, J=7.1 Hz), 6.78 (1H, d, J=8.1 Hz), 7.06 (1H, d, J=7.1 Hz), 7.29–7.47 (3H, m), 7.63–7.80 (2H, m), 8.01 (1H, dd, J=1.0, 7.5 Hz), 8.87 (1H, d, J=4.3 Hz), 9.87 (1H, br s). ^{13}C NMR (50 MHz, DMSO-d_6): δ=13.2, 60.6, 111.1, 115.0, 121.5, 127.8, 127.9, 129.0, 130.1, 130.8, 131.1, 132.6, 138.3, 138.5, 147.7, 148.2, 153.8, 166.4. HRMS: calcd for $C_{18}H_{16}NO_3$ ([M+H]$^+$) 294.1130, found 294.1159.

4.6. 4-*o*-Carboxyphenyl-8-hydroxyquinoline (6h)

Sodium hydroxide (2.19 g, 54.8 mmol) was dissolved in distilled water (5 mL). 4-*o*-Ethoxycarbonylphenyl-8-tosyloxyquinoline **5g** (500 mg, 1.12 mmol) and acetone (2 mL) were added. The reaction mixture was refluxed 5 h. The reaction mixture was allowed to cool to room temperature and pH was adjusted to 3.5 with HCl (aq). The water solution was extracted with four 20 mL portions of ethyl acetate. The separated organic layers were combined and evaporated to dryness. The precipitate was boiled with water (5 mL) and cooled with ice bath. The product was collected by filtration and washed with distilled water to give the product (272 mg, 92%) as a yellow powder. A small amount of the product was recrystallized from ethanol for analytical purposes. Mp: 104–105 °C. IR (KBr): ν=3251 (s), 3059 (w), 1702 (s), 1589 (s), 1530 (s). ^{1}H NMR (200 MHz, DMSO-d_6): δ=6.81 (1H, dd, J=0.9, 8.3 Hz), 7.05 (1H, dd, J=0.9, 7.5 Hz), 7.29–7.40 (3H, m), 7.59–7.76 (2H, m), 8.02 (1H, dd, J=1.4, 7.5 Hz), 8.85 (1H, d, J=4.4 Hz), 9.83 (1H, br s), 12.7 (1H, br s). ^{13}C NMR (50 MHz, DMSO-d_6): δ=111.0, 115.3, 121.6, 127.7, 128.0, 128.9, 130.2, 131.1, 131.8, 132.1, 138.5, 138.5, 147.7, 148.8, 153.8, 167.8. HRMS: calcd for $C_{16}H_{12}NO_3$ ([M+H]$^+$) 266.0817, found 266.0825.

4.7. 4-Hydroxypyridinoanthrene (6i)

4-*o*-Carboxyphenyl-8-hydroxyquinoline **6h** (200 mg, 0.75 mmol) was mixed vigorously with 96% sulfuric acid (4 mL) for 3 h at room temperature. The reaction vessel was cooled in an ice bath and distilled water (5 mL) was added slowly. pH was adjusted to 4.0 with NaOH (aq) and the resulting precipitate was collected by vacuum filtration. The precipitate was washed with distilled water to give the product (165 mg, 88%) as a red powder. A small amount of the product was recrystallized for analytical purposes from a mixture of ethyl acetate and dimethylsulfoxide (7:3). Mp: 286–289 °C. IR (KBr): ν=3237 (s), 3060 (w), 1713 (m), 1650 (s), 1592 (m), 1566 (s), 1517 (s). ^{1}H NMR (200 MHz, DMSO-d_6): δ=7.29 (1H, d, J=8.3 Hz), 7.76 (1H, dd, J=7.2 Hz), 7.89 (1H, dd, J=7.2 Hz), 8.37 (1H, d, J=7.9 Hz), 8.51 (1H, d, J=8.3 Hz), 8.64–8.72 (2H, m), 9.06 (1H, d, J=4.6 Hz). ^{13}C NMR (50 MHz, DMSO-d_6): δ=113.9, 118.6, 119.2, 124.4, 125.0, 127.5, 131.0, 132.3, 132.7, 133.5, 133.6, 134.3, 137.5, 149.0, 161.6, 180.2. HRMS: calcd for $C_{16}H_8NO_2$ ([M−H]$^-$) 246.0555, found 246.0551.

4.8. 4-*o*-Carboxyphenyl-8-tosyloxyquinoline (7)

4-*o*-Ethoxycarbonylphenyl-8-tosyloxyquinoline **5g** (601 mg, 1.34 mmol) was refluxed with a mixture of acetone (5 mL), 37% hydrochloric acid (2.5 mL), and distilled water (5 mL) for 48 h. The reaction mixture was allowed to cool to the room temperature. pH was adjusted to 3.5 with 1 M NaOH (aq). The precipitate was collected by filtration and washed with distilled water. The procedure gave the product (413 mg, 73%) as an off-white powder. A small amount of the product was recrystallized from ethanol for analytical purposes. Mp: 243–246 °C. IR (KBr): ν=3054 (w), 2871 (w), 2757 (w), 2481 (w), 1699 (s), 1621 (w), 1592 (s), 1509 (s). ^{1}H NMR (200 MHz, DMSO-d_6): δ=2.42 (3H, s), 7.33–7.53 (7H, m), 7.62–7.77 (2H, m), 7.85 (2H, d, J=8.3 Hz), 8.04 (1H, dd, J=1.2, 7.4 Hz), 8.84 (1H, d, J=4.3 Hz), 12.75 (1H, br s). ^{13}C NMR (50 MHz, DMSO-d_6): δ=21.4, 121.8, 122.0, 124.9, 126.4, 128.5, 128.7, 129.2, 130.2, 130.4, 131.2, 131.7, 132.3, 132.8, 137.7, 141.0, 145.3, 145.7, 148.8, 150.6, 167.7. HRMS: calcd for $C_{23}H_{18}NO_5S$ ([M+H]$^+$) 420.0906, found 420.0932.

4.9. 5-Chloro-8-tosyloxyquinoline (9)

A mixture of 5-chloro-8-hydroxyquinoline **8** (3.02 g, 16.8 mmol) and 1 M NaOH (aq) (16.8 mL) was refluxed for 30 min. The mixture was cooled to room temperature and *p*-toluenesulfonyl chloride (3.19 g, 16.7 mmol) in acetone (11 mL) was added. The resulting mixture was stirred for 2 h. The product was collected by filtration and washed with distilled water to give the product (5.56 g, >99%) as an off-white powder. A small amount of the product was recrystallized from ethanol for analytical purposes. Mp: 130–132 °C. IR (KBr): ν=3088 (w), 2920 (w), 1589 (s). ^{1}H NMR (200 MHz, DMSO-d_6): δ=2.37 (3H, s), 7.40 (2H, d, J=8.2 Hz), 7.49 (1H, d, J=8.4 Hz), 7.69–7.82 (4H, m), 8.54 (1H, dd, J=1.1, 8.6 Hz), 8.91 (1H, dd, J=1.1, 4.1 Hz). ^{13}C NMR (50 MHz, DMSO-d_6): δ=22.0, 123.3, 124.5, 127.3, 127.5, 129.3, 129.8, 130.8, 132.9, 133.4, 142.2, 144.9, 146.5, 152.7. HRMS: calcd for $C_{16}H_{13}NO_3SCl$ ([M+H]$^+$) 334.0305, found 334.0307.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.10.097.

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23. (a) MS data showed the formation of by-product. HRMS: calculated for $C_{16}H_{13}N_2O_2$ ($[M+H]^+$) 265.0977, found 265.0989; (b) HRMS: calculated for $C_{20}H_{21}N_2O_2$ ($[M+H]^+$) 321.1603, found 321.1594. Also clear signals from the butoxy group could be observed in the ^1H NMR spectrum.
24. (a) Ferreira, P. C.; Kiyan, N. Z.; Miyata, Y.; Miller, J. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1648–1651; (b) Stang, P. J.; Anderson, A. G. *J. Org. Chem.* **1976**, *41*, 781–785.
25. As a point of comparison: debenzylation has been reported to give 5-phenyl-8-hydroxyquinoline in 79% yield. See Ref. 3a.
26. Previously reported melting points of 5-phenyl-8-hydroxyquinolines: (88–90 °C) see reference 13; (91–92 °C) see Vorozhtsov, N. N., Jr. *J. Heterocycl. Chem.* **1938**, *8*, 431–437 (95–96 °C) see; Babudri, F.; Cardone, A.; Cioffi, C. T.; Farinola, G. M.; Naso, F.; Ragni, R. *Synthesis* **2006**, 1325–1332.