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Metal-free synthesis of 2-substituted-3-(2-hydroxyaryl)quinolines and 4-(2-hydroxyaryl)acridines *via* benzyne chemistry

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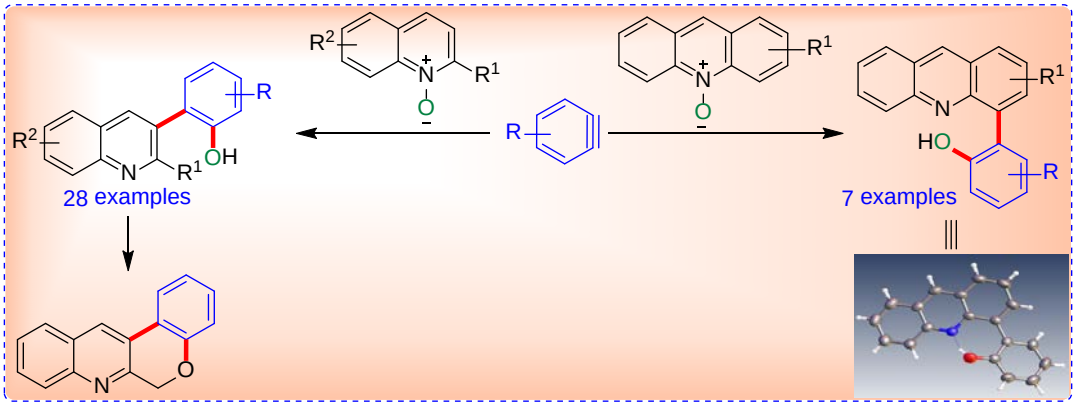
TOC graphic



ABSTRACT: A metal-free approach for the synthesis of 3-aryl-2-substituted quinolines and 4-arylacridines has been developed *via* the 1,3-dipolar cycloaddition reactions of arynes with *N*-oxides. Reactions of various 2-substitued quinoline *N*-oxides with *ortho*-(trimethylsilyl)aryltriflates in the presence of KF gave 3-(2-hydroxyaryl)quinoline derivatives in good yields. Acridine *N*-oxides also reacted with arynes to furnish 4-(2-hydroxyaryl)acridines, albeit in moderate yields.

1. INTRODUCTION

Quinoline being important heterocycle is commonly encountered in several natural products,[1] pharmaceutical agents[2] and advanced functional materials.[3] In pharmaceuticals, the substituted quinolines are known to display a broad spectrum of biological activities.[2,4] The remarkable antimalarial potential of quinolines has been well recognized for centuries[5] and these remain to be major targets as antimalarial drugs in the prevailing situation of drug resistance.[6]

Among various substituted quinolines, 2-substituted-3-arylquinolines are of significant biological importance with antiproliferative,[7] antibacterial,[8] and antitumor activity[9] and also act as selective cyclooxygenase-2 (COX-2),[10] and PI3Kδ inhibitors (Figure 1).[11] These compounds are also important materials in molecular electronics e.g. iridium complex of 2,3-diphenylquinoline (Figure 1) is an efficient red light emitting diode.[12]

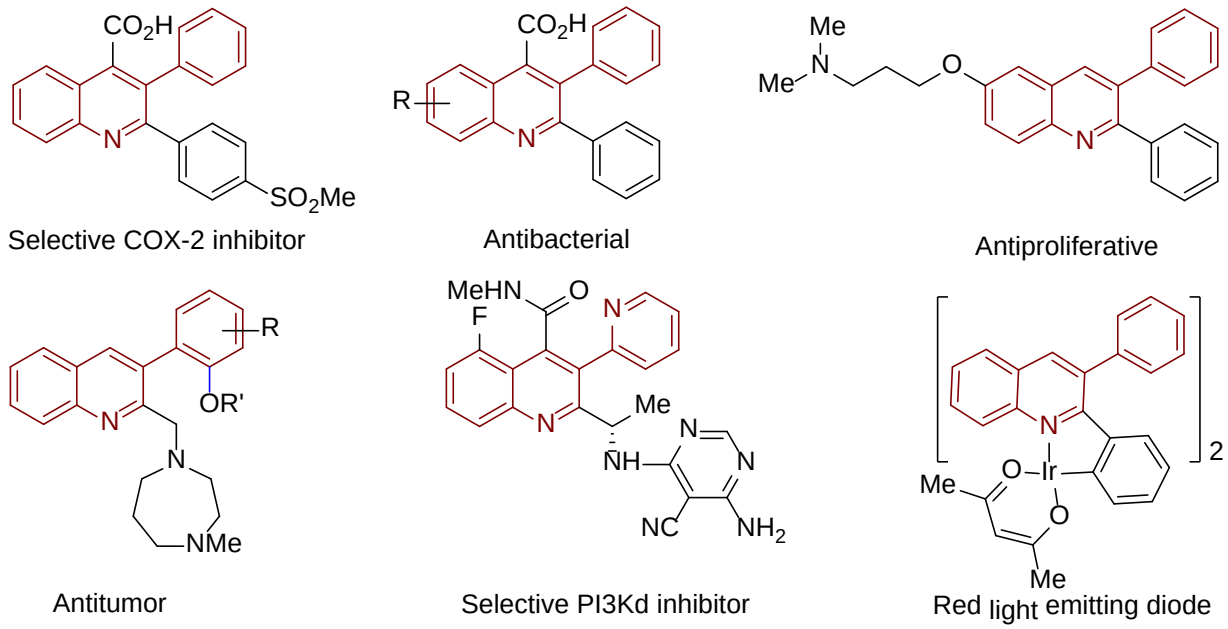
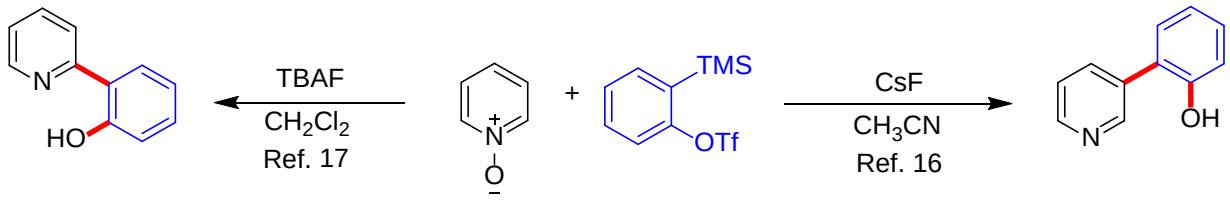


Figure 1. Selected examples of important 2-substituted 3-arylquinolines

Arynes are versatile intermediates used in organic synthesis to access diverse building blocks[13] as well as natural products.[14] Among the various reactions of arynes, 1,3-dipolar cycloadditions are of particular interest and have been explored for a large variety of organic transformations.[13,14]

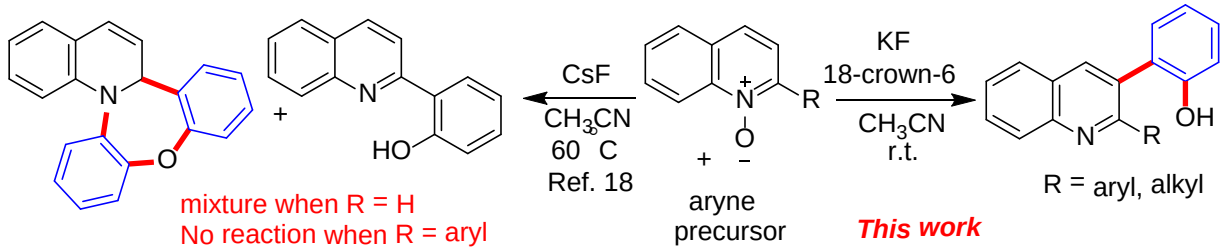
Reactions of arynes with pyridine *N*-oxide have been reported to produce 2- and 3-(2-hydroxyaryl) pyridines.[15-17] The regioselectivity of reactions depended upon the reaction conditions as well as the aryne source.[15-17] In case of ortho-(trimethylsilyl)aryl triflates as the aryne sources, the product formation depended upon the fluoride source and reaction solvent.[16,17] Use of CsF in acetonitrile produced 3-(2-hydroxyaryl)pyridines[16] whereas, Bu_4NF in CH_2Cl_2 afforded 2-(2-hydroxyaryl)pyridines (Scheme 1).[17]

Scheme 1. Reactions of pyridine *N*-oxide with arynes



We envisioned that cycloaddition reactions of arynes with 2-substituted quinolines which are rarely explored till date,[18] would furnish the corresponding 2-substituted-3-(2-hydroxyaryl)quinolines (Scheme 2). In an earlier report, no reaction was observed between benzyne and 2-substituted quinoline *N*-oxides.[18] Herein, we report the synthesis of 2-substituted-3-(2-hydroxyaryl)quinolines *via* 1,3-dipolar cycloaddition reactions of quinoline *N*-oxides with arynes. Reaction of acridine *N*-oxides with arynes for the synthesis of 4-(2-hydroxyaryl)acridines are also explored.

Scheme 2. Reactions of quinoline *N*-oxide with arynes

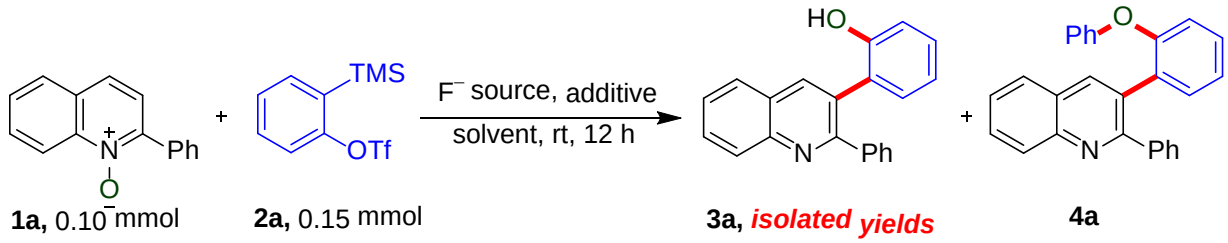


2. RESULTS AND DISCUSSIONS

For the optimization of best reaction conditions 2-phenylquinoline *N*-oxide (**1a**) was treated with *o*-(trimethylsilyl)phenyltriflate (**2a**) in presence of fluoride source for 12 h (Table 1). Reactions using

tetrabutylammonium fluoride (TBAF) in THF provided 77% isolated yield of 2-phenyl-3-(2-hydroxyphenyl)quinoline (**3a**) (entry 1). Minor side-product (**4a**), formed by reaction of **3a** with excess benzyne was also observed. Use of THF-DCM mixture lowered the product yield to 61% with a trace amount of **4a** (entry 2). Use of CsF in THF failed to provide even traces of products (entry 3). However, switching the solvent to CH_3CN resulted in 71% yield of the desired product along with traces of **4a** (entry 4). KF as F^- source in CH_3CN was unsuccessful (entry 5), however, to our delight, 2.0 equiv. of 18-crown-6 with KF as F^- source in CH_3CN afforded exclusively the desired product **3a** in 84% yield (entry 6). Further, when reaction was carried out under reported conditions, lower yield of the desired product was observed (entry 6 and 7).[18]

Table 1. Optimization of reaction conditions



1a, 0.10 mmol **2a,** 0.15 mmol **3a,** *isolated yields* **4a**

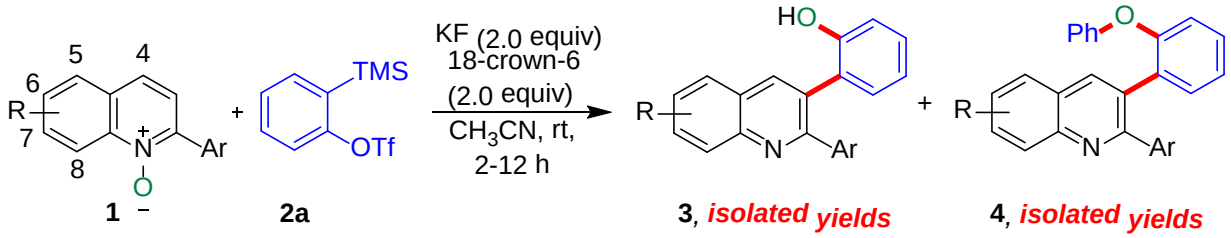
entry	F^- source[a]	additive[c]	solvent[d]	conversion (%)	yield[f] (%)	**3a**:**4a**[g]
1	$^nBu_4NF$[b]	---	THF	>99	77	97:3
2	$^nBu_4NF$[b]	---	DCM−THF[e]	>99	61	99:1
3	CsF	---	THF	0	NA	NA
4	CsF	---	CH_3CN	>99	71	98:2
5	KF	---	CH_3CN	0	NA	NA
6	KF	18-crown-6	CH_3CN	>99	84	100:0
7[h]	CsF	---	CH_3CN	>99	45%	75:25
8[i]	CsF	---	CH_3CN	>99	11%	18:82

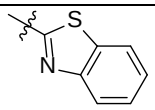
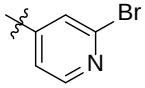
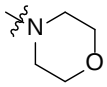
[a]0.2 mmol (2.0 equiv). [b]1.0 M solution in THF. [c]0.20 mmol (2.0 equiv). [d]1.3 mL of solvent. [e]DCM-THF ratio 4:1. [f]yield of isolated product. [g]calculated from ^1H NMR of crude reaction mixture. [h]reaction time 16h. [i]at 60 °C for 7h.

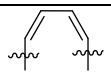
With optimal reaction conditions in hand, the scope of reactions of substituted quinoline *N*-oxides with arynes was studied (Table 2). First, 2-aryl quinoline *N*-oxides with a variety of aryl substituents were reacted with **2a**. Quinoline *N*-oxides with aryl group bearing *para*-electron donating -OMe as well as electron withdrawing -NO_2 provided moderate yields of the desired 3-arylated quinolines **3b** and **3c**, respectively. Formation of minor products **4b** (10%) and **4c** (9%), was also observed. 2-Aryl quinoline *N*-oxides with *p*-SCF_3 and *p*-Br substituents also reacted successfully to give 70% and 65% yield of products **3d** and **3e**, respectively. Presence of Br at *meta*- as well as sterically hindered *ortho*-positions did not affect the reaction outcome and provided products **3f** and **3g** in 60% and 71% yields, respectively. Formation of the minor product **4f** was also observed in 8% yield in case of reaction with **1f**. Sterically challenging *ortho*-substituted 2-phenyl quinoline *N*-oxides (**1h** and **1i**) afforded the desired products **3h** and **3i** in good yields. Further, 2-phenylquinoline *N*-oxides with various substituents in the quinoline ring were reacted with benzyne precursor **2a**. The methyl substitution on C-4 position provided good yield of the product **3j**, however in the case of -NO_2 group a lower yield of the desired product **3k** was observed, possibly due to the poor solubility of the starting material. Various substituents at C-6 position of quinoline were also well tolerated providing the desired products in 45-73 % yields (**3l-o**). In the case of C-7 derived quinoline, 4-chloro-7-trifluoromethylquinoline *N*-oxide, low yield of the desired product (**3p**) was obtained. A sterically congested, 2-phenyl-8-methylquinoline-*N*-oxide, also reacted efficiently to provide **3q** in 48% yield along with a significant amount (18 %) of the side product (**4q**). Similarly, heteroaryl substituents, benzothiazole, 2-bromopyridine and morpholine at C-2 position of quinoline moiety were also compatible and furnished product (**3r-t**) in milder to good yields. The desired products were also observed in case of benzo[*f*]quinoline (**3u**) albeit in low yield.

Formation of side products **4b**, **4c**, **4f** and **4q** arouse our interest in the synthesis of such compounds, selectively. In a model reaction, treatment of 2-phenylquinoline *N*-oxide (**1a**) with 4.0 equiv. of benzyne precursor **2a** and 5.0 equiv. of each KF and 18-crown-6 yielded 60% of product **4a** along with formation of only 20% of **3a**.

Table 2. Reactions of 2-arylquinolines with aryne[a]



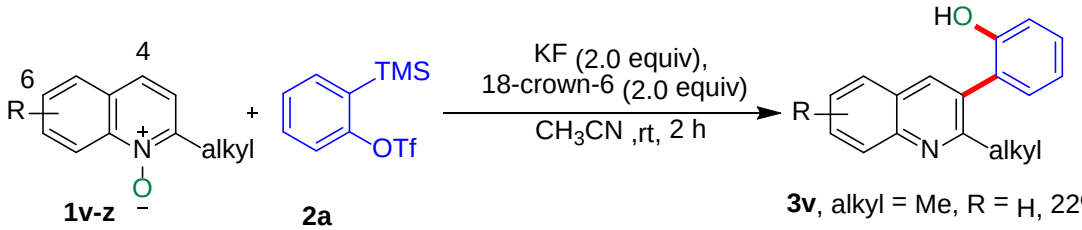
					yield (%)	
entry	**1**	Ar	R	time (h)	**3**	**4**
1	**1a**	C_6H_5	H	12h	**3a**, 84	-
2	**1b**	*p*-OMeC_6H_5	H	1h	**3b**, 50	**4b**, 10
3	**1c**	*p*-$NO_2C_6H_5$	H	3h	**3c**, 65	**4c**, 9
4	**1d**	*p*-$SCF_3C_6H_5$	H	2h	**3d**, 70	-
5	**1e**	*p*-BrC_6H_5	H	2h	**3e**, 65	-
6	**1f**	*m*-BrC_6H_5	H	2h	**3f**, 60	**4f**, 8
7	**1g**	*o*-BrC_6H_5	H	3h	**3g**, 71	-
8	**1h**	*o*-MeC_6H_5	H	6h	**3h**, 70	-
9	**1i**	*o*-PhC_6H_5	H	3h	**3i**, 56	-
10	**1j**	C_6H_5	4-Me	2h	**3j**, 74	-
11	**1k**	C_6H_5	4-NO_2	4h	**3k**, 12	-
12	**1l**	C_6H_5	6-Me	3h	**3l**, 73	-
13	**1m**	C_6H_5	6-^{i}Pr	5h	**3m**, 51	-
14	**1n**	C_6H_5	6-F	3h	**3n**, 72	-
15	**1o**	C_6H_5	6-CO_2Me	5h	**3o**, 45	-
16	**1p**	C_6H_5	4-Cl, 7-CF_3	3h	**3p**, 20	-
17	**1q**	C_6H_5	8-Me	3h	**3q**, 48	**4q**, 18
18	**1r**		H	3h	**3r**, 73	-
19	**1s**		H	6h	**3s**, 45	-
20	**1t**		H	3h	**3t**, 49	-

21	**1u**	*p*-OMeC$_6$H$_5$	5,6 = 	12h	**3u**, 45	-

[a]Reagents and conditions: **1a** (0.1−0.5 mmol), **2a** (1.5 equiv), KF (2.0 equiv), 18-crown-6 (2.0 equiv).

Replacement of the aryl substituent by methyl, proved detrimental for the reactions leading to a significant decrease in the product yields (Scheme 3). Crude mixture of the reaction of 2-methylquinoline *N*-oxide with **2a** produced a complex ^{1}H NMR which upon purification gave only 22% yield of the product **3v**. Similar results were obtained when the reaction was carried out under earlier reported reaction conditions.[18] Further methyl substitution at the C-4 and C-6 positions of the quinoline ring, significantly improved the reaction outcome and resulted in 44% and 52% yields of the 2,4-dimethyl- and 2,6-dimethyl-3-(2-hydroxyphenyl)quinolines, respectively (**3w-x**). Replacing 2-methyl with sterically challenging 2-*iso*-propyl (**1y**) and ethyl 2-hydroxypropanoate (**1z**), did not affect the outcome of the reaction and provide desired products (**3y-z**) in acceptable yields (45-55%).

Scheme 3. Reactions of 2-methylquinoline *N*-oxides with aryne[a]



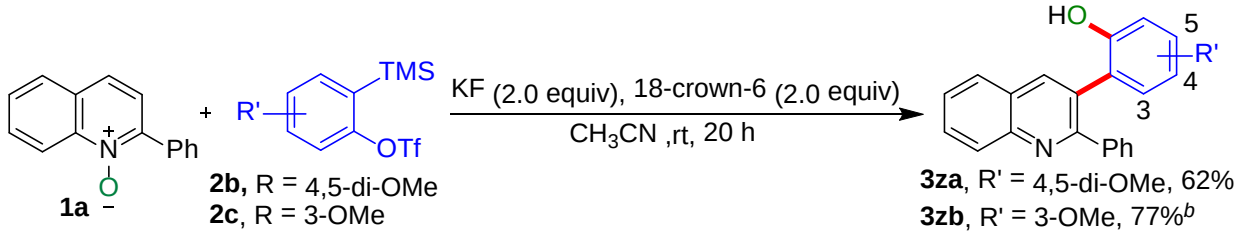
3v, alkyl = Me, R = H, 22%
3w, alkyl = Me, R = 4-Me, 44%
3x, alkyl = Me, R = 6-Me, 52%
3y, alkyl = ^{i}Pr, R = H, 46%
3z, alkyl = -$CH_2CH(OH)CO_2Et$, R = H, 55%

[a]Reagents and conditions: **1v-z** (0.1-0.5 mmol), **2a** (1.5 equiv), KF (2.0 equiv), 18-crown-6 (2.0 equiv).

The scope of reactions of 2-substituted quinoline *N*-oxides with different aryne precursors was next tested (Scheme 4). 2-Phenylquinoline *N*-oxide (**1a**) was reacted with substituted arynes generated in situ from the corresponding o-(trimethylsilyl)aryl triflates. Symmetrical, 4,5-dimethoxybenzyne precursor (**2b**) gave 62% of the product **3za**. Reaction of 3-methoxy benzyne derivative (**2c**) also afforded good

yield of **3zb** as a single isomer. Formation of a single regioisomer in the reactions of 3-methoxy benzyne follows a general trend[19] and has also been reported in reactions with pyridine *N*-oxide.[16]

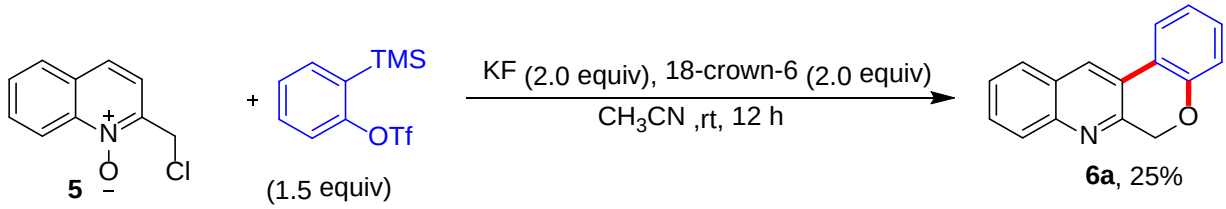
Scheme 4. Scope of reactions of 2-phenylquinoline *N*-oxide with substituted arynes[a]



[a]Reagents and conditions: **1a** (0.1 mmol), **2** (1.5 equiv), KF (2.0 equiv), 18-crown-6 (2.0 equiv). [b]Single isomer on the basis of ^{1}H NMR of crude mixture.

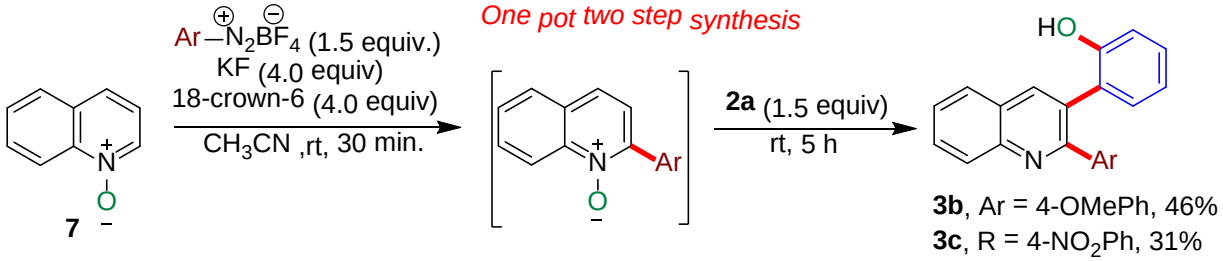
Further, when, 2-chloromethylquinoline *N*-oxide (**5**) was reacted with aryne precursor **2a** using the standard reaction conditions corresponding cyclic ether **6a** was obtained as a single product in 25% yield *via* the subsequent intramolecular S_N2 reaction of the initially formed 2-chloromethyl-3-(2-hydroxybenzene)quinoline intermediate (Scheme 5).

Scheme 5. Synthesis of a tetracyclic compound



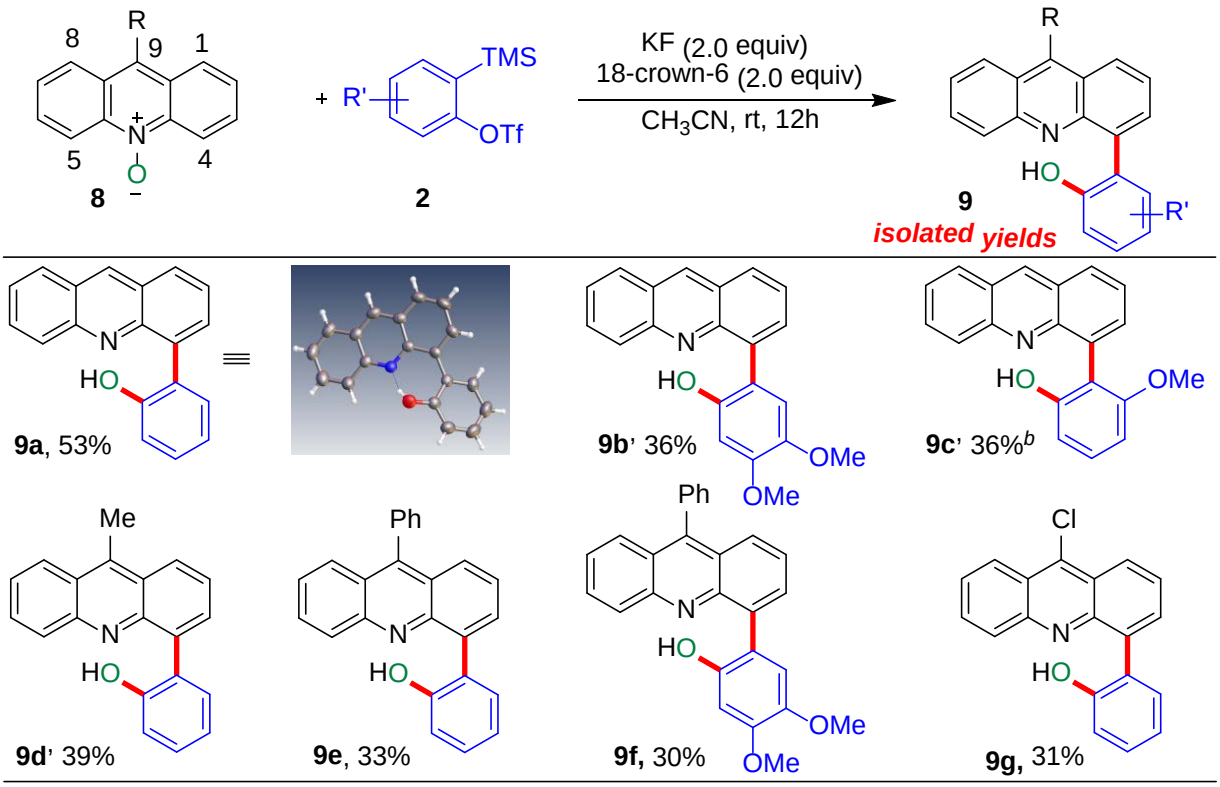
Next, a one-pot protocol for the synthesis of 2-phenyl-3-(2-hydroxyphenyl)quinolines starting from quinolines was explored. Quinoline *N*-oxide (**7**) was first reacted with commercially available aryl diazonium tetrafluoroborates (1.5 equiv)[20] in presence of KF (4.0 equiv) and 18-crown-6 (4.0 equiv) in CH_3CN for 30 minutes followed by the addition of benzyne precursor **2a** (1.5 equiv) (Scheme 6). To our delight, reaction worked well to furnish products **3b** and **3c** in 46% and 31% yields, respectively, starting from **7**. Although moderate yields of products were obtained, the one-pot strategy avoids an additional purification step and provides direct access to C-2, C-3 bis-functionalized quinolines.

Scheme 6. One-pot synthesis of 2-aryl-3-(o-hydroxyaryl)quinolines



Acridines constitute another important class of heterocycles that possess antimalarial activity,[21] and are commonly encountered in materials sciences and pharmaceuticals.[22] We wondered whether acridine *N*-oxides will undergo such reactions with arynes. To our surprise, when acridine *N*-oxide was reacted with **2a**, 4-(2-hydroxyphenyl)acridine (**9a**) was obtained in 53% yield (Table 3). The structure of **9a** was confirmed by NMR spectroscopy as well as X-ray crystallography. To test the generality of this reaction, a series of substituted acridine *N*-oxides were reacted with arynes (Table 3). All substrate reacted successfully and furnished 4-arylacridines **9a-g**, albeit in low to moderate yields. To the best of our knowledge, this is the first report for metal-free synthesis of C-4 aryl acridines using readily available acridine *N*-oxides as starting materials.

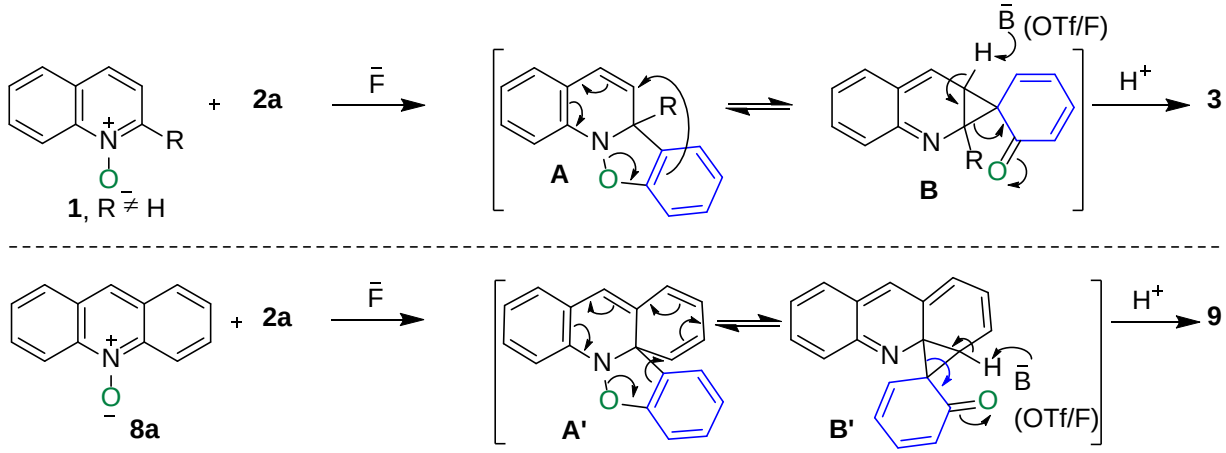
Table 3. Reactions of acridine *N*-oxides with arynes



[a]Reagents and conditions: **8** (0.1-0.3 mmol), **2** (1.5 equiv), KF (2.0 equiv), 18-crown-6 (2.0 equiv). [b]Single isomer on the basis of ^{1}H NMR of crude reaction mixture.

The reactions of pyridine-and quinoline *N*-oxides are proposed to proceed *via* pathway that involves the formation of a five membered cycloadduct.[15-18] In case of 2-substituted quinolines, the initially formed cyclo-adduct (**A**) would rearrange to quinoid form (**B**). Intermediate **B** upon deprotonation by TfO- or excess F− followed by cyclopropyl ring opening and re-aromatization would form 3-(2-hydroxyaryl)quinolines (**3**) (Scheme 7). Reactions of acridine *N*-oxides with arynes are also proposed to proceed through the formation of 5-membered cyclo-adduct **A'** (Scheme 7) *via* a [3+2] cycloaddition of acridine *N*-oxide and aryne. Similar to the quinoline *N*-oxides, the rearrangement of cycloadduct **A'** to intermediate **B'** followed by the deprotonation-re-aromatization would furnish 4-arylacridine product **9**.

Scheme 7. Proposed mechanism for the reactions of quinoline *N*-oxides and acridine *N*-oxides with arynes



3. CONCLUSIONS

In conclusion, a metal-free versatile and simple approach has been developed for the synthesis of 3-aryl-2-substituted quinolines and 4-arylacridines *via* the 1,3-dipolar cycloaddition reaction-rearrangements of arynes with *N*-oxides. Reactions proceed at room temperature with moderate to good yields of the desired products. One-pot two-step synthesis of 2,3-disubstituted quinolines was also be achieved in moderate yields, albeit with moderate yields of products. This metal-free approach offers an easy access to diverse 2,3-disubstituted quinolines for applications in pharmaceuticals and materials.

4. EXPERIMENTAL SECTION

4.1. General information

Unless otherwise stated, all reactions were carried out under air atmosphere in screw cap reaction vials. All solvents were bought from Aldrich in sure-seal bottle and used as such. All chemicals were bought from Sigma Aldrich, Alfa-aesar and TCI. Quinoline *N*-oxide[23] and 2-arylquinolines[20a] were synthesized by using literature report methods. For column chromatography, silica gel (230-400 mesh) from Merck was used. A gradient elution using *n*-hexane and ethyl acetate was performed based on Merck aluminium TLC sheets (silica gel $60F_{254}$)

4.2. Analytical information: Nuclear magnetic resonance spectra were recorded either on a Bruker-Avance 600 or 300 MHz instrument. All ^{1}H NMR experiments are reported in units, parts per million (ppm) and were measured relative to the signals for residual chloroform (7.26), DMSO-d_6 (2.50) and acetone (2.05, 2.84) in the deuterated solvents. All ^{13}C NMR spectra were reported in ppm relative to deuterated chloroform (77.16) and acetone (29.84, 206.26) and all were obtained with ^{1}H decoupling. High-resolution mass spectra (HRMS) were recorded on Waters ESI-TOF-MS. IR was analyzed by Shimadzu IR Prestige-21with ZnSe Single reflection ATR accessory. The melting points were recorded on a Bronsted Electro thermal 9100. Optimization studies were done by NMR and NMR yield were calculated by using TCE as internal standard.

4.3. General Procedure for synthesis of 2-substituted-3-(o-hydroxyaryl)quinolines and 4-(o-hydroxyaryl)acridines

To a solution of 2-substituted quinoline *N*-oxide (**1**) or acridine *N*-oxide (**8**) (1.0 molar equiv) in CH_3CN (1.3 mL per mmol) in a reaction vial equipped with magnetic stir bar, benzyne precursor, **2** (1.5 molar equiv), 18-crown-6 (2.0 molar equiv) and KF (2.0 molar equiv) were added sequentially. Reaction mixture was allowed to stir at room temperature until TLC showed disappearance of *N*-oxide. Reaction mixture was diluted with water and transferred to separating funnel with ethyl acetate. Organic layer was separated and aqueous layer was extracted three times with ethyl acetate. Combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4. Solvents were evaporated under reduced pressure and the products were isolated by column chromatography using silica gel (mesh 230-400). Eluting solvents for chromatography are indicated under the specific compound headings.

4.4 Characterization Data

2-(2-Phenylquinolin-3-yl)phenol (Table 1, entry 3a) 2-Phenylquinoline *N*-oxide **1a**: 22 mg (0.10 mmol); benzyne precursor **2a**: 44.8 mg (0.15 mmol), 18-crown-6: 52.8 mg (0.20 mmol), KF: 11.6 mg (0.20 mmol), CH_3CN: 1.3 mL. Column chromatography: eluting solvent 20% EtOAc in *n*-hexanes. Yield: 25.0 mg (84%) of white solid, m.p. 216-218 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.22 (d, J = 6.6 Hz, 2H), 7.86 (d, J = 8.4 Hz, 1H), 7.76 – 7.78 (m, 1H), 7.57 – 7.60 (m, 1H), 7.49 – 7.51 (m, 2H), 7.25 – 7.29 (m, 3H), 7.20 – 7.23 (m, 1H), 7.13 (dd, J = 7.2, 1.2 Hz, 1H), 6.91 – 6.93 (m, 1H), 6.80 (d, J = 7.8 Hz, 1H), 4.92 (br s, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 158.9, 152.7, 147.9, 140.1, 139.0, 131.5, 130.2, 129.8, 129.69, 129.66, 129.4(2C), 128.5, 128.2(2C), 127.6, 127.2, 127.1, 126.9, 121.1, 116.2.

IR (ZnSe): ν_{max} (cm^{-1}) 3055, 2922, 2852, 1589, 1487,1444, 1366, 1282, 1112, 969, 913, 829, 750, 696.

HRMS (ESI-TOF): m/z calcd for $C_{21}H_{16}NO$ $[M+H]^+$ 298.1226, found 298.1214.

2-(2-(4-Methoxyphenyl)quinolin-3-yl)phenol (Table 2, entry 3b) 2-(4-Methoxyphenyl)quinoline *N*-oxide **1b**: 126.0 mg (0.50 mmol); benzyne precursor **2a**: 224.0 mg (0.75 mmol), 18-crown-6: 264.0 mg (1.00 mmol), KF: 58.0 mg (1.00 mmol), CH_3CN: 6.5 mL. Column chromatography: eluting solvent 5-20% EtOAc in *n*-hexanes. Yield: 82.0 mg (50%) of white solid, m.p. 204-206 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.18 (d, J = 8.4 Hz, 1H), 8.16 (s, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.73 – 7.76(m, 1H), 7.54 – 7.57 (m, 1H), 7.45 – 7.48 (m, 2H), 7.21 – 7.24 (m, 1H), 7.15 – 7.16 (m, 1H), 6.93 – 6.96 (m, 1H), 6.82 (dd, J = 8.4, 0.6 Hz, 1H), 6.77 – 6.80 (m, 2H), 5.05 (br s, 1H), 3.78 (s, 3H)

^{13}C NMR (150 MHz, $CDCl_3$): δ 160.1, 158.2, 152.7, 147.9, 139.1, 132.5, 131.5, 130.9 (2C), 130.1, 129.72, 129.65, 129.5, 127.6, 127.2, 127.0, 126.8, 121.2, 116.4, 113.7(2C), 55.4.

IR (ZnSe): ν_{max} (cm^{-1}) 3060, 2921, 2852, 1605, 1589, 1512, 1487, 1441, 1418, 1371, 1244, 1178, 1106, 1020, 970, 838, 793, 754, 691, 621.

HRMS (ESI-TOF): m/z calcd for $C_{22}H_{18}NO_2$ $[M+H]^+$ 328.1332, found 328.1314.

2-(4-methoxyphenyl)-3-(2-phenoxyphenyl)quinoline (Table 2, entry 4b) Yield of **4b**: 20.6 mg (10%) of colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.16 (d, J = 8.4 Hz, 1H), 8.14 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.69 – 7.72 (m, 1H), 7.50 – 7.53(m, 1H), 7.43 – 7.45 (m, 3H), 7.24 – 7.25 (m, 1H), 7.13 – 7.16 (m, 3H), 6.96 – 6.99(m, 1H), 6.76 – 6.79(m, 2H), 6.71 (d, J = 8.4 Hz, 1H), 6.46 (d, J = 7.8 Hz, 2H), 3.80 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 159.8, 158.8, 156.2, 154.7, 147.6, 138.3, 133.9, 132.1 (2C), 131.4, 131.1, 130.9, 129.6, 129.5(2C), 129.4, 129.2, 127.6, 127.0, 126.4, 123.5, 123.1, 119.3 (2C), 117.4, 113.5 (2C), 55.5.

IR (ZnSe): ν_{max} (cm^{-1}): 3057, 2954, 2920, 2850, 1732, 1606, 1575, 1554, 1483, 1448, 1406, 1371, 1294, 1232, 1213, 1172, 1199, 1109, 1026, 792, 750, 688, 480.

HRMS (ESI-TOF): m/z calcd for $C_{28}H_{22}NO_2$ $[M+H]^+$ 404.1645 found 404.1634.

2-(2-(4-Nitrophenyl)quinolin-3-yl)phenol (Table 2, entry 3c) 2-(4-Nitrophenyl)quinoline *N*-oxide **1c**: 133.0 mg (0.50 mmol); benzyne precursor **2a**: 224.0 mg (0.75 mmol), 18-crown-6: 264.0 mg (1.00 mmol), KF: 58.0 mg (1.00 mmol), CH_3CN: 6.5 mL. Column chromatography: eluting solvent 5-20% EtOAc in *n*-hexanes. Yield: 111.0 mg (65%) of pale yellow solid, m.p. 246-248 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ 9.34 (s, 1H), 8.33 (s, 1H), 8.07 – 8.10(m, 3H), 8.04 (d, J = 7.8 Hz, 1H), 7.77 – 7.80 (m, 1H), 7.63 – 7.66(m, 3H), 7.22 – 7.24 (m, 1H), 7.14 – 7.17(m, 1H), 6.83 – 6.85 (m, 1H), 6.71 (d, J = 7.8 Hz, 1H).

^{13}C NMR (150 MHz, DMSO-d_6): δ 156.4, 154.1, 147.5, 146.8, 146.5, 138.4, 131.4, 131.1, 130.1 (2C), 130.0, 129.6, 128.8, 127.8, 127.3, 127.2, 126.0, 122.7 (2C), 119.4, 115.5.

IR (ZnSe): ν_{max} (cm^{-1}) 3423, 3347, 3064, 2923, 2852, 1724, 1592, 1515, 1485, 1458, 1345, 1277, 1217, 1177, 1137, 1107, 1014, 967, 853, 737, 700.

HRMS (ESI-TOF): m/z calcd for $C_{21}H_{15}N_2O_3$ $[M+H]^+$ 343.1077 found 343.1065.

2-(4-nitrophenyl)-3-(2-phenoxyphenyl)quinoline (Table 2, entry 4c) Yield of **4c**: 19.0 mg (9%) of pale yellow sticky solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.22 (s, 1H), 8.18 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 7.8 Hz, 1H), 7.76 – 7.78 (m, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.59 – 7.62(m, 1H), 7.50 (dd, J = 7.2, 1.8 Hz, 1H), 7.28 – 7.31(m, 1H), 7.19 – 7.22 (m, 1H), 7.11 – 7.14 (m, 2H), 6.96 – 6.99 (m, 1H), 6.73 (d, J = 7.8 Hz, 1H), 6.41 (d, J = 7.2 Hz, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 156.7, 155.8, 154.1, 147.7, 147.53, 147.49, 138.8, 131.9, 130.8, 130.4 (2C), 130.3, 130.2, 129.9, 129.7, 129.6 (2C), 127.7, 127.6, 127.5, 123.7, 123.6, 123.2 (2C), 118.6 (2C), 117.8.

IR (ZnSe): ν_{max} (cm^{-1}) 3061, 2920, 2851, 1587, 1514, 1485, 1449, 1342, 1232, 1107, 850, 795, 748, 692, 621, 590.

HRMS (ESI-TOF): m/z calcd for $C_{27}H_{19}N_2O_3$ $[M+H]^+$ 419.1390 found 419.1377.

2-(2-(4-((Trifluoromethyl)thio)phenyl)quinolin-3-yl)phenol (Table 2, entry 3d) 2-(4-Nitrophenyl)quinoline *N*-oxide **1d**: 96.0 mg (0.30 mmol); benzyne precursor **2a**: 134.0 mg (0.45 mmol), 18-crown-6: 158.0 mg (0.60 mmol), KF: 35.0 mg (0.60 mmol), CH_3CN: 3.9 mL. Column chromatography: eluting solvent 20% EtOAc in *n*-hexanes. Yield: 83.6 mg (70%) of white solid, m.p. 165-167 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.21 (s, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.75 – 7.78 (m, 1H), 7.59 – 7.61 (m, 1H), 7.50 – 7.53 (m, 4H), 7.17 – 7.20 (m, 1H), 7.10 – 7.11 (m,1H), 6.89 – 6.92 (m, 1H), 6.71 (d, J = 7.8 Hz, 1H), 5.47 (br s, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 157.6, 152.7, 147.6, 142.9, 139.1, 135.7 (2C), 131.67 (q, J_{C-F} = 307.5 Hz), 131.5, 130.5 (2C), 130.4, 130.1, 129.9, 129.5, 127.7 127.40, 127.37, 126.3, 124.4, 121.1, 116.1.

IR (ZnSe): ν_{max} (cm^{-1}) 3460, 3061, 2921, 2852, 1719, 1573, 1486, 1443, 1403, 1370, 1282, 1237, 1114, 1074, 997, 920, 889, 747, 691.

HRMS (ESI-TOF): m/z calcd for $C_{22}H_{15}F_3NOS$ $[M+H]^+$ 398.0821, found 398.0811.

2-(2-(4-Bromophenyl)quinolin-3-yl)phenol (Table 2, entry 3e) 2-(4-Bromophenyl)quinoline *N*-oxide **1e**: 150.0 mg (0.50 mmol); benzyne precursor 2a: 224.0 mg (0.75 mmol), 18-crown-6: 264.0 mg (1.00 mmol), KF: 58.0 mg (1.00 mmol), CH_3CN: 6.5 mL. Column chromatography: eluting solvent 20% EtOAc in *n*-hexanes. Yield: 122.0 mg (65%) of pale yellow solid, m.p. 173-175 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (s, 1H), 8.16 (s, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.73 – 7.78 (m, 1H), 7.56 – 7.60 (m, 1H), 7.36 (s, 4H), 7.18 – 7.23 (m, 1H), 7.11 (d, J = 7.2 Hz, 1H), 6.90 – 6.95 (m, 1H), 6.76 (d, J = 7.8 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 157.8, 152.8, 147.8, 139.2, 139.1, 131.5, 131.2 (2C), 131.1 (2C), 130.3, 129.87, 129.85, 129.5, 127.6, 127.3, 127.2, 126.6, 123.0, 121.2, 116.3.

IR (ZnSe): ν_{max} (cm^{-1}) 3425, 3436, 3247, 3062, 2923, 2853, 1720, 1634, 1588, 1534, 1485, 1452, 1414, 1372, 1280, 1198, 1072, 1009, 791, 753, 592, 535, 482, 458.

HRMS (ESI-TOF): m/z calcd for $C_{21}H_{15}BrNO$ $[M+H]^+$ 376.0332, found 376.0316.

2-(2-(3-Bromophenyl)quinolin-3-yl)phenol (Table 2, entry 3f) 2-(3-Bromophenyl)quinoline *N*-oxide **1f**: 90.0 mg (0.30 mmol); benzyne precursor **2a**: 134.0 mg (0.75 mmol), 18-crown-6: 158.0 mg (0.60 mmol), KF: 35.0 mg (0.60 mmol), CH_3CN: 3.9 mL. Column chromatography: eluting solvent 5-20% EtOAc in *n*-hexanes. Yield: 68.0 mg (60%) of light red solid, m.p. 199-201 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.21 (s, 1H), 8.20 (s, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.77 – 7.79 (m, 2H), 7.59 – 7.61 (m, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 7.2 Hz, 1H), 7.23-7.25 (m, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.07 (t, J = 7.8 Hz, 1H), 6.94 – 6.96 (m, 1H), 6.80 (d, J = 7.8 Hz, 1H), 4.96 (br s, 1H)

^{13}C NMR (150 MHz, $CDCl_3$): δ 157.3, 152.7, 147.8, 142.3, 139.0, 132.6, 131.5, 131.4, 130.3, 129.91, 129.85, 129.7, 129.4, 128.0, 127.6, 127.34, 127.32, 126.4, 122.3, 121.2, 116.1.

IR (ZnSe): ν_{max} (cm^{-1}) 3051, 2823, 2853, 1589, 1487, 1444, 1373, 1281, 1236, 1151, 1111, 1083, 1016, 969, 919, 844, 792, 750, 690, 602, 520.

HRMS (ESI-TOF): m/z calcd for $C_{21}H_{14}NaBrNO$ $[M+Na]^+$ 398.0151, found 398.0139.

2-(3-bromophenyl)-3-(2-phenoxyphenyl)-quinoline (Table 2, entry 4f): Yield: 10.6 mg (8%) of yellowish sticky solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.17 – 8.19 (m, 2H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.71 – 7.75 (m, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.43 – 7.45 (m, 2H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.27 – 7.28 (m, 1H), 7.16 – 7.19 (m, 3H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.99 – 7.02 (m, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 6.46 (d, *J* = 7.8 Hz, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 155.8, 154.5, 147.5, 143.2, 138.5, 132.8, 132.0, 131.03, 130.95, 130.6, 129.9, 129.7 (2C), 129.61, 129.56, 129.3, 128.1, 127.6, 127.4, 127.0, 123.7, 123.2, 122.3, 120.6, 119.2 (2C), 117.3.

IR (ZnSe): ν_{max} (cm^{-1}) 3059, 2922, 2850, 1587, 1575, 1554, 1485, 1469, 1446, 1367, 1230, 1211, 1199, 1161, 1116, 867, 748, 682, 601, 480.

HRMS (ESI-TOF): m/z calcd for $C_{27}H_{19}BrNO$ $[M+H]^+$ 452.0645, found 452.0634.

2-(2-(2-Bromophenyl)quinolin-3-yl)phenol (Table 2, entry 3g) 2-(2-Bromophenyl)quinoline *N*-oxide **1g**: 125.0 mg (0.42 mmol); benzyne precursor **2a**: 188.0 mg (0.63 mmol), 18-crown-6: 222.0 mg (0.84 mmol), KF: 49.0 mg (0.84 mmol), CH_3CN: 5.5 mL. Column chromatography: eluting solvent 20% EtOAc in *n*-hexanes. Yield: 112.3 mg (71%) of pale yellow solid, m.p. 217-219 °C.

^{1}H NMR (600 MHz, acetone-d_6): δ 8.33 (s, 1H), 8.13 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.60 – 7.63 (m, 1H), 7.46 – 7.49 (m, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.27 – 7.28 (m, 1H), 7.08 – 7.11 (m, 1H), 7.00 – 7.02 (m, 1H), 6.96 – 6.97 (m, 1H), 6.89 – 6.92 (m, 1H), 6.64 (d, J = 8.4 Hz, 1H), 6.53 – 6.56 (m, 1H).

^{13}C NMR (150 MHz, acetone-d_6): δ 160.0, 155.4, 147.7, 143.1, 138.7, 132.92, 132.84, 132.2(2C), 130.3, 130.01, 129.97, 129.9, 128.6, 128.4, 127.7, 127.3, 126.8, 123.3, 119.8, 116.3.

IR(ZnSe): ν_{max} (cm^{-1}) 3053, 1710, 1608, 1587, 1444, 1413, 1371, 1282, 1234, 1203, 1193, 1109, 1022, 970, 914, 750, 736.

HRMS (ESI-TOF): m/z calcd for $C_{21}H_{15}BrNO$ $[M+H]^+$ 376.0332, found 376.0323.

2-(2-(*o*-tolyl)quinolin-3-yl)phenol (Table 2, entry 3h) 2-(*o*-tolyl)quinoline *N*-oxide **1h**: 94.0 mg (0.40 mmol); benzyne precursor **2a**: 179.0 mg (0.60 mmol), 18-crown-6: 211.2 mg (0.80 mmol), KF: 46.4 mg (0.80 mmol), CH_3CN: 5.2 mL. Column chromatography: eluting solvent 7% EtOAc in *n*-hexanes. Yield: 83.0 mg (70%) of white solid, m.p. 217-218 °C.

^{1}H NMR (300 MHz, acetone-d_6): δ 8.26 (s, 1H), 8.20 (s, 1H), 7.90 – 7.97(m, 2H), 7.65 – 7.70 (m, 1H), 7.50 – 7.54 (m, 1H), 6.88 – 7.09 (m, 5H), 6.61 – 6.71 (m, 2H), 2.11 (s, 3H).

^{13}C NMR (75 MHz, acetone-d_6): δ 161.2, 155.3, 147.9, 141.9, 138.7, 137.2, 133.2, 132.3, 130.6, 130.5, 130.1, 129.9, 129.7, 128.6, 128.2, 128.0, 127.6, 127.3, 125.3, 120.0, 116.3, 20.1.

IR (ZnSe): ν_{max} (cm^{-1}) 3059.10, 2789.07, 1554.63, 1487.12, 1444.68, 1371.39, 1284.59, 1201.65, 970.19, 732.95, 628.79, 480.28.

HRMS (ESI-TOF): m/z calcd for $C_{22}H_{18}NO^+$ $(M+H)^+$ 312.1383 found 312.1390.

2-(2-([1,1'-biphenyl]-2-yl)quinolin-3-yl)phenol (Table 2, entry 3i) 2-([1,1'-biphenyl]-2-yl)quinoline *N*-oxide **1i**: 89.2 mg (0.30 mmol); benzyne precursor **2a**: 134.3 mg (0.45 mmol), 18-crown-6: 158.4 mg

(0.60 mmol), KF: 34.8 mg (0.60 mmol), CH_3CN: 3.9 mL. Column chromatography: eluting solvent 10-15% EtOAc in *n*-hexanes. Yield: 50.0 mg (56%) of brown solid, m.p. 162-164 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 8.4 Hz, 1H), 7.98 (s, 1H), 7.74 – 7.82 (m, 3H), 7.57 – 7.62 (m, 1H), 7.38 – 7.50 (m, 2H), 7.13 – 7.19 (m, 2H), 7.01 – 7.06 (m, 3H), 6.70 (d, J = 7.5 Hz, 2H), 6.58 (dd, J = 14.4, 7.5 Hz, 2H), 6.33 (d, J = 6.0 Hz, 1H).

^{13}C NMR (75 MHz, acetone-d_6) δ 161.4, 155.2, 147.9, 142.2, 141.5, 141.2, 138.3, 133.5, 132.5, 132.2(2C), 130.2, 130.0, 129.97, 129.95, 129.4, 128.8, 128.5, 128.4 (2C), 128.1, 127.23, 127.17, 127.1, 127.0, 119.8, 115.9.

IR (ZnSe): ν_{max}(cm^{-1}) 3055.24, 2924.09, 2854.65, 1587.42, 1483.26, 1446.61, 1408.04, 1371.39, 1290.38, 1105.21, 1031.92, 968.27, 740.67, 671.23.

HRMS (ESI-TOF): m/z calcd for $C_{27}H_{20}NO^+$ $(M+H)^+$ 374.1539 found 374.1544.

2-(4-Methyl-2-phenylquinolin-3-yl)phenol (Table 2, entry 3j) 4-Methyl-2-phenylquinoline *N*-oxide **1j**: 118.0 mg (0.50 mmol); benzyne precursor **2a**: 224.0 mg (0.75 mmol), 18-crown-6: 264.0 mg (1.00 mmol), KF: 58.0 mg (1.00 mmol), CH_3CN: 6.5 mL. Column chromatography: eluting solvent 20% EtOAc in *n*-hexanes. Yield: 115.0 mg (74%) of white solid. m. p. 199-201 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.21 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.74 – 7.77 (m, 1H), 7.60 – 7.63 (m, 1H), 7.38 (d, J = 6.0 Hz, 2H), 7.20 – 7.26 (m, 3H), 7.13 – 7.15 (m, 1H), 6.86 (d, J = 6.6 Hz, 1H), 6.79 (d, J = 6.6 Hz, 2H), 5.73 (br s, 1H), 2.54 (s, 3H)

^{13}C NMR (150 MHz, $CDCl_3$): δ 159.7, 153.5, 147.2, 144.9, 140.9, 131.7, 130.2, 129.8, 129.5, 129.3(2C), 128.8, 128.0, 127.8(2C), 127.2, 126.8, 125.7, 124.4, 120.6, 115.5, 16.0.

IR (ZnSe): ν_{max} (cm^{-1}) 3056, 2924, 1590, 1487, 1445, 1373, 1290, 1236, 1152, 1114, 1085, 1016, 970, 844, 793, 752, 603, 520.

HRMS (ESI-TOF): m/z calcd for $C_{22}H_{18}NO$ $(M+H)^+$ 312.1383 found 312.1361.

2-(4-Nitro-2-phenylquinolin-3-yl)phenol (Table 2, entry 3k) 4-Nitro-2-phenylquinoline *N*-oxide **1k**: 54.0 mg (0.20 mmol); benzyne precursor 2a: 90.0 mg (0.30 mmol), 18-crown-6: 106.0 mg (0.40 mmol), KF: 23.0 mg (0.40 mmol), CH3CN: 2.6 mL. Column chromatography: eluting solvent 20% EtOAc in *n*-hexanes. Yield: 8.1 mg (12%) of pale yellow solid, m. p. 150-151 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.46 (dd, J = 8.4, 0.6 Hz, 1H), 8.31 (d, J = 8.4 Hz, 1H), 7.94 – 7.96 (m, 2H), 7.79 – 7.80 (m, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.68 – 7.72 (m, 2H), 7.63 – 7.64 (m, 2H), 7.59 – 7.62 (m, 1H), 7.49 – 7.51 (m, 1H), 7.28 – 7.30 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 158.5, 156.2, 156.1, 147.3, 140.0, 130.0, 129.8, 129.5, 129.1 (2C), 128.9 (2C), 127.2, 126.8, 123.8, 123.1, 122.5, 120.9, 116.4, 114.7, 112.1.

IR (ZnSe): ν_{max} (cm^{-1}) 3049, 2956, 2920, 2850, 1726, 1579, 1556, 1535, 1508, 1492, 1458, 1444, 1438, 1361, 1192, 742, 700, 680.

HRMS (ESI-TOF): m/z calcd for $C_{21}H_{15}N_2O_3$ $[M+H]^+$ 343.1077, found 343.1065.

2-(6-Methyl-2-phenylquinolin-3-yl)phenol (Table 2, entry 3l) 6-Methyl-2-phenylquinoline *N*-oxide **1l**: 47.0 mg (0.20 mmol); benzyne precursor 2a: 90.0 mg (0.30 mmol), 18-crown-6: 106.0 mg (0.40 mmol), KF: 23.0 mg (0.40 mmol), CH3CN: 2.6 mL. Column chromatography: eluting solvent 20% EtOAc in *n*-hexanes. Yield: 45.5 mg (73%) of white solid, m. p. 195-198 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.10 (d, J = 7.8 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.47 – 7.48 (m, 2H), 7.23 – 7.28 (m, 3H), 7.18 – 7.21 (m, 1H), 7.10 – 7.11 (m, 1H), 6.89 – 6.91 (m, 1H), 6.79 (d, J = 8.4 Hz, 1H), 5.12 (br s, 1H), 2.57 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 158.0, 152.8, 146.5, 140.1, 138.4, 137.0, 132.5, 131.5, 129.7, 129.6., 129.5 (2C), 129.3, 128.4, 128.1 (2C), 127.2, 127.0, 126.4, 121.0, 116.2, 21.8.

IR (ZnSe): ν_{max} (cm^{-1}) 3431, 3347, 3245, 3061, 2921, 2852, 1666, 1590, 1487, 1452, 1424, 1369, 1287, 1198, 1024, 973, 890, 755, 725, 694, 632, 590, 573.

HRMS (ESI-TOF): m/z calcd for $C_{22}H_{18}NO$ $[M+H]^+$ 312.1383, found 312.1364.

2-(6-Isopropyl-2-phenylquinolin-3-yl)phenol (Table 2, entry 3m) 6-Isoporyl-2-phenylquinoline 1-oxide **1m**: 52.0 mg (0.20 mmol); benzyne precursor **2a**: 90.0 mg (0.30 mmol), 18-crown-6: 106.0 mg (0.40 mmol), KF: 23.0 mg (0.40 mmol), CH3CN: 2.6 ml. Column chromatography: eluting solvent 20% EtOAc in *n*-hexanes. Yield: 34.5 mg (51%) of white solid, m. p. 68-70 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.14 (d, J = 6.6 Hz, 2H), 7.68 (dd, J = 9.0, 1.8 Hz, 1H), 7.64 (s, 1H), 7.46 – 7.48 (m, 2H), 7.23 – 7.29 (m, 3H), 7.20 (td, J = 7.8, 1.2 Hz, 1H), 7.09 – 7.11 (m,1H), 6.89 – 6.91 (m, 1H), 6.79 (d, J = 8.4 Hz, 1H), 3.11 – 3.16 (m, 1H), 1.37 (d, J = 6.6 Hz, 6H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 158.1, 152.8, 147.8, 146.8, 140.2, 138.7, 131.5, 130.2, 129.7, 129.6, 129.47, 129.45 (2C), 128.4, 128.1 (2C), 127.2, 127.0, 123.6, 120.9, 116.2, 34.3, 24.0 (2C).

IR (ZnSe): ν_{max} (cm^{-1}) 3046, 2955, 2922, 2852, 1590, 1481, 1453, 1405, 1374, 1286, 1238, 1200, 1150, 1106, 1024, 972, 917, 834, 749, 692, 628, 588.

HRMS (ESI-TOF): m/z calcd for $C_{24}H_{22}NO$ $[M+H]^+$ 340.1696, found 340.1679.

2-(6-Fluoro-2-phenylquinolin-3-yl)phenol (Table 2, entry 3n) 6-Fluoro-2-phenylquinoline *N*-oxide **1n**: 48.0 mg (0.20 mmol); benzyne precursor **2a**: 90.0 mg (0.30 mmol), 18-crown-6: 106.0 mg (0.40 mmol), KF: 23.0 mg (0.40 mmol), CH3CN: 2.6 ml. Column chromatography: eluting solvent 10% EtOAc in *n*-hexanes. Yield: 45.4 mg (72%) of white solid, m. p. 163-165 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.14 – 8.16 (m, 1H), 8.12 (s, 1H), 7.48 – 7.51 (m, 1H), 7.42 – 7.46 (m, 3H), 7.26 – 7.28 (m, 1H), 7.22 – 7.24 (m, 2H), 7.14 – 7.16 (m, 1H), 7.09 – 7.10 (m, 1H), 6.87 – 6.90 (m, 1H), 6.68 (d, J = 7.8 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 160.8 (d, J = 247.5 Hz), 158.4 (d, J = 3.0 Hz), 152.9, 144.7, 139.9, 138.4 (d, J = 6.0 Hz), 131.9 (d, J = 10.5 Hz), 131.5, 131.3, 129.7, 129.4, 128.5, 128.1, 127.8 (d, J = 10.5 Hz), 126.6, 120.9, 120.4, 120.2, 116.2, 110.58, 110.43.

IR (ZnSe): ν_{max} (cm^{-1}) 3056, 2920, 2851, 1601, 1561, 1539, 1483, 1455, 1372, 1264, 1216, 1152, 1025, 957, 916, 830, 752, 704, 588, 497.

HRMS (ESI-TOF): m/z calcd for $C_{21}H_{15}FNO$ $[M+H]^+$ 316.1132, found 316.1118.

Methyl 3-(2-hydroxyphenyl)-2-phenylquinoline-6-carboxylate (Table 2, entry 3o) 6-Fluoro-2-phenylquinoline *N*-oxide **1o**: 84.0 mg (0.30 mmol); benzyne precursor **2a**: 134.0 mg (0.45 mmol), 18-crown-6: 158.0 mg (0.60 mmol), KF: 35.0 mg (0.60 mmol), CH_3CN: 3.9 mL. Column chromatography: eluting solvent 20% EtOAc in *n*-hexanes. Yield: 48.0 mg (45%) of white solid, m. p. 192-195 °C.

1H NMR (600 MHz, acetone-d_6): δ 8.71 (d, J = 1.8 Hz, 1H), 8.44 (s, 1H), 8.27 – 8.30 (m, 2H), 8.17 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 7.2 Hz, 2H), 7.24 – 7.30 (m, 3H), 7.19 – 7.22 (m, 2H), 6.85 – 6.89 (m, 2H), 3.98 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 166.8, 161.1, 152.7, 149.5, 140.1, 139.9, 131.6, 131.1, 130.8, 129.9, 129.53, 129.46 (2C), 128.9, 128.4, 128.2 (2C), 126.6, 126.3, 121.2, 116.3, 52.6, 29.4.

IR (ZnSe): ν_{max} (cm^{-1}) 3319, 3059, 2957, 1711, 1686, 1624, 1439, 1402, 1344, 1276, 1190, 1096, 1024, 925, 849, 775, 750, 696, 584.

HRMS (ESI-TOF): m/z calcd for $C_{23}H_{18}NO_3$ $[M+H]^+$ 356.1281 found 356.1270.

2-(4-Chloro-2-phenyl-7-(trifluoromethyl)quinolin-3-yl)phenol (Table 2, entry 3p) 4-Chloro-2-phenyl-7-(trifluoromethyl)quinoline *N*-oxide **1p**: 120 mg (0.37 mmol); benzyne precursor **2a**: 165.4 mg (0.56 mmol), 18-crown-6: 195.0 mg (0.74 mmol), KF: 43.0 mg (0.74 mmol), CH_3CN: 4.8 mL. Column chromatography: eluting solvent 5% EtOAc in *n*-hexanes. Yield: 62.1 mg (20%) of white solid. m. p. 155-157 °C.

1H NMR (600 MHz, $CDCl_3$): δ 8.63 (s, 1H), 8.57 (d, *J* = 9.0 Hz, 1H), 7.95 – 7.97 (m, 2H), 7.87 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.76 – 7.80 (m, 2H), 7.61 – 7.64 (m, 3H), 7.54 – 7.57 (m, 1H), 7.32 – 7.35 (m, 1H).

13C NMR (150 MHz, $CDCl_3$): δ 157.9, 157.5, 156.5, 146.1, 139.5, 131.5 (q, *J* = 33.0 Hz), 130.0, 129.1 (2C), 129.0 (2C), 128.0, 127.8 (q, *J* = 4.5 Hz), 124.2 (q, *J* = 271.5 Hz), 124.1, 122.8, 122.6, 122.5 (q, *J* = 2.7 Hz), 122.2, 118.0, 116.3, 112.3.

IR (ZnSe): ν_{max} (cm^{-1}) 3062, 2958, 2922, 2850, 1595, 1550, 1516, 1492, 1450, 1361, 1344, 1298, 1193, 1168, 1112, 1101, 750, 694.

HRMS (ESI-TOF): m/z calcd for $C_{22}H_{14}ClF_3NO$ $[M+H]^+$ 400.0711 found 400.0701.

2-(8-Methyl-2-phenylquinolin-3-yl)phenol (Table 2, entry 3q) 8-Methyl-2-phenylquinoline *N*-oxide **1q**: 48.0 mg (0.20 mmol); benzyne precursor **2a**: 90.0 mg (0.30 mmol), 18-crown-6: 106.0 mg (0.40 mmol), KF: 23.0 mg (0.40 mmol), CH_3CN: 2.6 mL. Column chromatography: eluting solvent 3-10% EtOAc in *n*-hexanes. Yield: 30.1 mg (48%) of white solid; m. p. 72-75 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.58 – 7.62 (m, 3H), 7.46 – 7.48 (m, 1H), 7.27 – 7.31 (m, 3H), 7.23 – 7.25 (m, 1H), 7.17 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.94 – 6.96 (m, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 2.89 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 157.0, 152.7, 147.0, 140.5, 139.3, 137.8, 131.4, 130.1, 129.8 (2C), 129.6, 129.2, 128.5, 128.0 (2C), 127.2, 127.1, 126.9, 125.5, 121.1, 116.2,18.0.

IR (ZnSe): ν_{max} (cm^{-1}) 3426, 3350, 3242, 3115, 2926, 2854, 1663, 1534, 1464, 1265, 1182, 1080, 967, 894, 735, 537.

HRMS (ESI-TOF): m/z calcd for $C_{22}H_{18}NO$ $[M+H]^+$ 312.1383 found 312.1369.

8-Methyl-3-(2-phenoxyphenyl)-2-phenylquinoline (Table 2, entry 4q): Yield: 14.2 mg (18%) of colourless semi solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.56-7.59 (m, 3H), 7.49 (dd, J = 7.2, 1.8 Hz, 1H), 7.42-7.44 (m, 1H), 7.30 – 7.33 (m, 1H), 7.23 – 7.27 (m, 3H), 7.13 – 7.17 (m, 3H), 6.97 – 7.00 (m, 1H), 6.63 – 6.65 (m, 1H), 6.39 – 6.40 (m, 2H), 2.87 (s, 3H, CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ 157.4, 155.9, 155.0, 146.6, 141.7, 138.6, 137.7, 132.0, 131.3, 130.6, 129.9(2C), 129.6, 129.5 (2C), 129.1, 128.0, 127.9 (2C), 127.1, 126.4, 125.5, 123.6, 122.9, 119.7 (2C), 116.9, 18.02.

IR (ZnSe): ν_{max} (cm^{-1}) 3055, 2916, 1595, 1573, 1485, 1444, 1406, 1369, 1234, 1215, 1195, 1157, 1070, 1022, 920, 867, 767, 748, 734, 601, 482.

HRMS (ESI-TOF): m/z calcd for $C_{28}H_{22}NO$ $[M+H]^+$ 388.1696 found 388.1688.

2-(2-(Benzo[d]thiazol-2-yl)quinolin-3-yl)phenol (Table 2, entry 3r) 2-(Benzo[d]thiazol-2-yl)quinoline *N*-oxide **1r**: 71.0 mg (0.25 mmol); benzyne precursor **2a**: 111.0 mg (0.37 mmol), 18-crown-6: 132.0 mg (0.50 mmol), KF: 29.0 mg (0.50 mmol), CH_3CN: 3.2 mL. Column chromatography: eluting solvent 10% EtOAc in *n*-hexanes. Yield: 64.1 mg (73%) of white solid; m. p. 190-192 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.21 (s, 1H), 7.93 – 7.96 (m, 2H), 7.89 (d, J = 7.8 Hz, 1H), 7.80 – 7.83 (m, 1H), 7.64 – 7.67 (m, 1H), 7.45 – 7.48 (m, 1H), 7.41 – 7.44 (m, 1H), 7.35 – 7.38 (m, 1H), 7.15 – 7.18 (m, 2H), 7.02 (td, J = 7.2, 1.2 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 170.4, 155.1, 152.9, 149.5, 147.1, 141.0, 136.1, 132.1, 131.5, 130.6, 130.4, 130.1, 129.7, 128.5, 128.4, 127.8, 126.5, 126.2, 123.7, 121.8, 121.6, 120.1.

IR (ZnSe): ν_{max} (cm^{-1}) 3282, 3059, 2956, 2922, 2852, 1750, 1587, 1485, 1452, 1371, 1259, 1029, 943, 748, 727, 700

HRMS (ESI-TOF): m/z calcd for $C_{22}H_{15}N_2OS$ $[M+H]^+$ 355.0900 found 355.0889.

2-(2-(2-bromopyridin-4-yl)quinolin-3-yl)phenol (Table 2, entry 3s) 2-(2-bromopyridin-4-yl)quinoline *N*-oxide **1s**: 60.0 mg (0.20 mmol); benzyne precursor **2a**: 89.5 mg (0.30 mmol), 18-crown-6: 105.6 mg (0.40 mmol), KF: 23.2 mg (0.40 mmol), CH_3CN: 2.6 mL. Column chromatography: eluting solvent 10-12% EtOAc in *n*-hexanes. Yield: 35.0 mg (45%) of brown solid, m.p. 182-183 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 5.4 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.75 – 7.81 (m, 2H), 7.59 – 7.64 (m, 1H), 7.27 – 7.33 (m, 2H), 7.25 (d, *J* = 1.5 Hz, 1H), 7.01 – 7.06 (m, 1H), 6.80 (dd, *J* = 8.1 Hz, *J* = 0.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 153.0, 151.8, 148.7, 147.3, 141.4, 138.9, 131.2, 130.7, 130.2, 130.1, 129.5, 128.4, 127.8, 127.7, 127.6, 126.2, 122.6, 121.2, 116.7.

IR (ZnSe): ν_{max}(cm^{-1}) 3051.39, 1587.42, 1529.55, 1489.05, 1450.47, 1413.82, 1367.53, 1290.38, 1271.09, 1201.65, 1076.28, 908.47, 846.75, 750.31, 576.72.

HRMS (ESI-TOF): m/z calcd for $C_{20}H_{14}BrN_2O^+$ $(M+H)^+$ 377.0284 found 377.0264.

2-(2-morpholinoquinolin-3-yl)phenol (Table 2, entry 3t) 2-morpholinoquinoline *N*-oxide **1t**: 92.0 mg (0.40 mmol); benzyne precursor **2a**: 179.0 mg (0.60 mmol), 18-crown-6: 211.2 mg (0.80 mmol), KF: 46.4mg (0.80 mmol), CH_3CN: 5.2 mL. Column chromatography: eluting solvent 6-10% EtOAc in hexanes. Yield: 60.0 mg (49%) of white solid, m.p. 118-119 °C.

^{1}H NMR (300 MHz, $CDCl_3$) *δ* 9.58 (br s, 1H), 8.12 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.67 – 7.72 (m, 1H), 7.47 – 7.52 (m, 2H), 7.34 – 7.39 (m, 1H), 7.06 – 7.11 (m, 2H), 3.86 (s, 4H), 3.32 (s, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) *δ* 156.7, 154.7, 146.3, 141.6, 130.5, 130.1, 130.0, 128.1, 127.9, 127.7, 126.0, 126.3, 125.9, 121.5, 119.2, 66.6 (2C), 50.7 (2C).

IR (ZnSe): ν_{max} (cm^{-1}) 2968.45, 2918.30, 2877.79, 1564.27, 1485.19, 1448.54, 1359.82, 1296.16, 1219.01, 1143.79, 1068.56, 987.55, 756.10, 665.44.

2-[3-(4-Methoxy-phenyl)-benzo[*f*]quinolin-2-yl]-phenol (Table 2, entry 3u): 2-[3-(4-Methoxy-phenyl)-benzo[*f*]quinolin-2-yl]-phenol **1u**: 54.0 mg (0.20 mmol); benzyne precursor **2a**: 90.0 mg (0.30 mmol), 18-crown-6: 105.6 mg (0.40 mmol), KF: 23.2 mg (0.40 mmol), CH_3CN: 2.6 mL. Column chromatography: eluting solvent 5% EtOAc in *n*-hexanes. Yield: 30.0 mg (45%) of brown solid; m. p. 72-75 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.43 (d, J = 6.9 Hz, 1H), 8.16 (d, J = 10.2 Hz, 1H), 7.89 – 7.94 (m, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.61 – 7.75 (m, 5H), 7.23 – 7.31 (m, 2H), 6.98 – 7.03 (m, 1H), 6.81 – 6.90 (m, 3H), 3.82 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.2, 156.0, 152.6, 146.2, 139.2, 134.1, 132.7, 131.7, 131.4, 131.2 (2C), 129.7, 129.5, 128.5, 128.1, 128.0, 127.4, 127.20, 127.19, 125.01, 124.97 (2C), 121.4, 116.5, 113.7 (2C).

IR (ZnSe): ν_{max} (cm^{-1}) 3051, 1605, 1587, 1510, 1439, 1287, 1246, 1172, 1152, 1026, 1017, 924, 826, 802, 772.

HRMS (ESI-TOF): m/z calcd for $C_{26}H_{19}NO_2$ $[M+H]^+$ 378.1489 found 378.1471.

2-(2-Methylquinolin-3-yl)phenol (Scheme 3, entry 3v) 2-Methylquinoline *N*-oxide **1v**: 50.0 mg (0.31 mmol); benzyne precursor **2a**: 141.0 mg (0.47 mmol), 18-crown-6: 164.0 mg (0.62 mmol), KF: 36.0 mg (0.62 mmol), CH_3CN: 4.0 mL. Column chromatography: eluting solvent 10% EtOAc in *n*-hexanes. Yield: 16.0 mg (22%) of off white solid, m. p. 190-192 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 (d, J = 8.4 Hz, 1H), 7.90 (s, 1H), 7.61 – 7.64 (m, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.39 – 7.42 (m, 1H), 7.33 – 7.36 (m, 1H), 7.15 (dd, J = 7.8, 1.2 Hz, 1H), 7.08 (d, J = 7.8 Hz, 1H), 7.03 – 7.00 (m, 1H), 2.61 (s, 3H).

^{13}C NMR (150 MHz, DMSO-d_6): δ 158.1, 154.5, 146.4, 136.0, 132.9, 130.8, 129.2, 129.0, 127.9, 127.6, 126.55, 126.58, 125.7, 119.2, 115.5, 23.6.

IR (ZnSe): ν_{max} (cm^{-1}) 3057, 2920, 2851, 1726, 1612, 1570, 1485, 1451, 1419, 1292, 1205, 1169, 983, 804, 750, 665, 583.

HRMS (ESI-TOF): m/z calcd for $C_{16}H_{14}NO$ $[M+H]^+$ 236.1070 found 236.1058.

2-(2,4-Dimethylquinolin-3-yl)phenol (Scheme 3, entry 3w) 2,4-dimethylquinoline *N*-oxide **1w**: 17.3 mg (0.10 mmol); benzyne precursor **2a**: 45.0 mg (0.15 mmol), 18-crown-6: 53.0 mg (0.20 mmol), KF: 11.6 mg (0.20 mmol), CH_3CN: 1.3 mL. Column chromatography: eluting solvent 10% EtOAc in *n*-hexanes. Yield: 12.9 mg (44%) of dirty white solid, m.p. 181-183 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.85 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.33 – 7.36 (m, 2H), 7.13 (d, J = 8.4 Hz, 1H), 6.96 – 7.01(m, 2H), 2.43 (s, 3H), 2.37 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 158.8, 153.9, 146.2, 144.2, 130.7, 130.1, 129.8, 129.3, 128.3, 126.5, 126.0, 125.1, 124.4, 120.6, 117.0, 24.9, 16.1.

IR (ZnSe): ν_{max} (cm^{-1}) 3061, 2958, 2920, 2851, 1589, 1487, 1453, 1376, 1287, 1260, 1075, 1023, 794, 749, 692, 629, 589.

HRMS (ESI-TOF): m/z calcd for $C_{17}H_{16}NO$ $[M+H]^+$ 250.1226, found 250.1219.

2-(2,6-Dimethylquinolin-3-yl)phenol (Scheme 3, entry 3x) 2,4-Dimethylquinoline *N*-oxide **1x**: 17.3 mg (0.10 mmol); benzyne precursor **2a**: 45.0 mg (0.15 mmol), 18-crown-6: 53.0 mg (0.20 mmol), KF: 11.6 mg (0.20 mmol), CH_3CN: 1.3 mL. Column chromatography: eluting solvent 10% EtOAc in *n*-hexanes. Yield: 11.0 mg (52 %) of dirty white solid, m.p. 218-220 °C.

^{1}H NMR (300 MHz, CD_3OD) δ 7.95 (s, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.64 (s, 1H), 7.56 (dd, J = 8.4, 1.8 Hz, 1H), 7.27 (td, J = 7.8, 1.8 Hz, 1H), 7.15 (dd, J = 7.5, 1.5 Hz, 1H), 6.92 – 6.97 (m, 2H), 2.53 (s, 3H), 2.52 (s, 3H).

^{13}C NMR (75 MHz, CD_3OD) δ 159.2, 155.9, 146.1, 138.0, 137.3, 134.9, 132.8, 132.0, 130.6, 128.6, 128.0, 127.7, 127.6, 120.9, 116.6, 23.2, 21.5.

IR (ZnSe): ν_{max} (cm^{-1}) 3426, 3349, 3243, 3064, 2922, 2852, 1725, 1657, 1534, 1452, 1377, 1285, 1202, 1169, 1103, 987, 922, 880, 754, 537.

HRMS (ESI-TOF): m/z calcd for $C_{17}H_{16}NO$ $[M+H]^+$ 250.1226, found 250.1220.

2-(2-isopropylquinolin-3-yl)phenol (Scheme 3, entry 3y) 2-isopropylquinoline *N*-oxide **1y**: 56.1 mg (0.30 mmol); benzyne precursor **2a**: 125.3 mg (0.45 mmol), 18-crown-6: 158.4 mg (0.60 mmol), KF: 34.8 mg (0.60 mmol), CH_3CN: 3.9 mL. Column chromatography: eluting solvent 8% EtOAc in *n*-hexanes. Yield: 36.0 mg (45%) of brown solid, m.p. 163-164 °C.

^{1}H NMR (300 MHz, acetone-d_6) δ 8.32 (br s, 1H), 7.89 – 7.94 (m, 2H), 7.80 (d, J = 8.1 Hz, 1H), 7.59 – 7.64 (m, 1H), 7.40 – 7.46(m, 1H), 7.18 – 7.24 (m, 1H), 7.13 – 7.16 (m, 1H), 6.87 – 6.95 (m, 2H), 3.13 – 3.12 (m, 1H), 1.27 (d, J = 6.3 Hz, 3H), 1.03 (d, J = 6.3 Hz, 3H).

^{13}C NMR (75 MHz, acetone-d_6) δ 167.2, 155.6, 148.4, 137.5, 132.9, 132.1, 130.1, 129.7, 129.6, 128.4, 128.0, 127.8, 126.5, 120.6, 116.5, 33.4, 23.4, 22.0.

IR (ZnSe): ν_{max} (cm^{-1}) 2964.59, 2927.94, 1589.34, 1564.27, 1489.05, 1415.75, 1448.54, 1400.32, 1377.17, 1288.45, 1217.08, 1089.78, 981.77, 750.31, 655.80, 626.87.

HRMS (ESI-TOF): m/z calcd for $C_{18}H_{18}NO^+$ $(M+H)^+$ 264.1383 found 264.1384.

Ethyl 2-hydroxy-3-(3-(2-hydroxyphenyl)quinolin-2-yl)propanoate (Scheme 3, entry 3z) 2-(3-ethoxy-2-hydroxy-3-oxopropyl)quinoline *N*-oxide **1z**: 130.5mg (0.50 mmol); benzyne precursor **2a**: 224.0 mg (0.75 mmol), 18-crown-6: 264.0 mg (1.00 mmol), KF: 58.0 mg (1.00 mmol), CH_3CN: 3.9 mL. Column chromatography: eluting solvent 12-15% EtOAc in *n*-hexanes. Yield: 93.0 mg (55%) of brown solid, m.p. 144-145 °C.

^{1}H NMR (300 MHz, acetone-d_6) δ 9.35 (br s, 1H), 8.88 (s, 1H), 8.80 (d, J = 8.4 Hz, 1H), 8.73 (d, J = 8.1 Hz, 1H), 8.51 – 8.56 (m, 1H), 8.34 – 8.38 (m, 1H), 8.03 – 8.13 (m, 2H), 7.77 – 7.86 (m, 2H), 5.49-5.52 (m, 1H), 4.81 – 4.87 (m, 2H), 4.12 (d, J = 9.6 Hz, 2H), 3.79 (br s, 1H, OH), 1.88 – 1.92 (m, 3H).

^{13}C NMR (75 MHz, acetone-d_6) δ 174.3, 159.4, 155.4, 147.3, 137.9, 134.0, 132.1, 130.4, 130.2, 129.2, 128.6, 127.9, 127.2, 127.1, 120.8, 116.7, 71.0, 61.0, 39.8, 14.4.

IR (ZnSe): ν_{max}(cm^{-1}) 3196.19, 2924.09, 1743.65, 1595.13, 1489.05, 1452.40, 1415.75, 1379.10, 1344.38, 1288.45, 1240.23, 1166.93, 1105.21, 918.12, 748.38, 721.38, 665.44.

HRMS (ESI-TOF): m/z calcd for $C_{20}H_{20}NO_4^+$ $(M+H)^+$ 338.1387 found 338.1380.

4,5-Dimethoxy-2-(2-phenylquinolin-3-yl)phenol (Scheme 4, entry 3za) 2-Phenylquinoline *N*-oxide **1a**: 22.0 mg (0.10 mmol); benzyne precursor **2b**: 53.8 mg (0.15 mmol), 18-crown-6: 53.0 mg (0.20 mmol), KF: 11.6 mg (0.20 mmol), CH_3CN: 1.3 ml. Column chromatography: eluting solvent 20% EtOAc in *n*-hexanes. Yield: 22.0 mg (62%) of white solid, m.p. 203-205 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.21 (s, 1H), 8.19 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.74 – 7.77 (m, 1H), 7.57 – 7.59 (m, 1H), 7.49 – 7.50 (m, 2H), 7.27 – 7.31 (m, 3H), 6.53 (s, 1H), 6.43 (s, 1H), 4.86 (br s, 1H), 3.84 (s, 3H), 3.65 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 159.0, 150.0, 147.7, 146.8, 143.4, 140.0, 139.0, 130.2, 129.62, 129.59, 129.4 (2C), 129.4, 128.6, 128.3 (2C), 127.5, 127.2, 127.1, 117.2, 114.4, 101.0, 56.6, 56.1.

IR (ZnSe): ν_{max} (cm^{-1}) 3426, 3347, 3245, 3062, 2923, 2853, 1720, 1665, 1528, 1462, 1410, 1370, 1278, 1202, 1151, 1005, 956, 860, 768, 737, 699, 593.

HRMS (ESI-TOF): m/z calcd for $C_{23}H_{20}NO_3$ $[M+H]^+$ 358.1438, found 358.1416.

3-Methoxy-2-(2-phenylquinolin-3-yl)phenol (Scheme 4, entry 3zb) 2-Phenylquinoline *N*-oxide **1a**: 22.0 mg (0.10 mmol); benzyne precursor **2c**: 49.3 mg (0.15 mmol), 18-crown-6: 53.0 mg (0.20 mmol),

KF: 11.6 mg (0.20 mmol), CH_3CN: 1.3 mL. Column chromatography: eluting solvent 20% EtOAc in *n*-hexanes. Yield: 25.1 mg (77 %) of white solid, m.p. 161-163 °C.

1H NMR (600 MHz, $CDCl_3$): δ 8.22 (d, J = 8.4 Hz, 1H), 8.17 (s, 1H), 7.84 (d, J = 708 Hz, 1H), 7.73 – 7.76 (m, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.44 – 7.45 (m, 2H), 7.21 – 7.25 (m, 3H), 7.13 (t, J = 8.4 Hz, 1H), 6.53 (d, J = 8.4 Hz, 1H), 6.32 (d, J = 8.4 Hz, 1H), 5.65 (s, 1H), 3.36 (s, 3H)

^{13}C NMR (150 MHz, $CDCl_3$): δ 160.6, 157.6, 154.0, 147.7, 140.5, 139.5, 130.1, 129.9, 129.5, 128.7(2C), 128.2, 127.7, 127.6, 127.3(2C), 126.8, 125.8, 115.6, 108.6, 103.2, 55.5.

IR (ZnSe): ν_{max} (cm^{-1}) 2955, 2851, 2818, 1726, 1591, 1464, 1371, 1259, 1246, 1080, 1026, 970, 914, 783, 766, 748, 725, 696, 662, 594, 480.

HRMS (ESI-TOF): m/z calcd for $C_{22}H_{18}NO_2$ $[M+H]^+$ 328.1332, found 328.1319.

4.5 Procedure for high yielding synthesis of 4a

To a solution of 2-phenylquinoline *N*-oxide **1a**: 66.0 mg (0.30 mmol, 1.0 molar equiv) in CH_3CN (3.9 mL) in a reaction vial equipped with magnetic stir bar, benzyne precursor **2a**: 358 mg (1.2 mmol, 1.5 molar equiv), 18-crown-6: 396 mg (1.5 mmol, 5.0 molar equiv) and KF: 87 mg (1.5 mmol, 5.0 molar equiv) were added sequentially. Reaction mixture was allowed to stir at room temperature for 12 h when TLC showed disappearance of *N*-oxide, 1a. Reaction mixture was diluted with 10 mL water and transferred to separatory funnel using 20 mL ethyl acetate. Organic layer was separated and aqueous layer was extracted three times with ethyl acetate (20 mL each time). Combined organic layer was washed with 10 mL brine and then dried over anhydrous Na_2SO_4. Solvents were evaporated under reduced pressure and the products were isolated by column chromatography using silica gel (mesh 230-400), eluting with 5%-20% EtOAc in *n*-hexanes. Yield of **3a**: 18.4 mg (20%) of white solid (spectral analysis, melting points and HRMS data reported above). Yield of **4a**: 66.9 mg (60%) colourless oily compound.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.19 (d, J = 9.6 Hz, 2H), 7.85 (d, J = 7.8 Hz, 1H), 7.71 – 7.74 (m, 1H), 7.53 – 7.56 (m, 1H), 7.49 – 7.50 (m, 2H), 7.44 – 7.46 (m, 1H), 7.30 (t, J = 7.2 Hz, 1H), 7.22 – 7.26 (m, 3H), 7.13 – 7.15 (m, 3H), 6.98 (t, J = 7.2 Hz, 1H), 6.64 (d, J = 8.4 Hz, 1H), 6.40 (d, J = 7.8 Hz, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 159.2, 156.0, 154.9, 147.6, 141.3, 138.4, 132.1, 131.2, 131.0, 129.7, 129.62 (2C), 129.60 (2C), 129.55 (2C), 129.3, 128.05, 128.03 (2C), 127.6, 127.2, 126.6, 123.6, 123.0, 119.6 (2C), 117.0.

IR (ZnSe): ν_{max} (cm^{-1}) 3057, 2959, 2930, 1720, 1578, 1487, 1444, 1369, 1272, 1231, 1213, 1168, 1118, 1072, 1024, 966, 916, 866, 767, 750, 692.

HRMS (ESI-TOF): m/z calcd for $C_{27}H_{20}NO$ $[M+H]^+$ 374.1539 found 374.1526.

4.6 General procedure for synthesis of cyclic ethers 6a.

To a solution of 2-(chloromethyl)quinoline *N*-oxide **5** (1.0 molar equiv) in CH_3CN (1.3 mL per mmol) in a reaction vial equipped with magnetic stir bar, benzyne precursor **2a** (1.5 molar equiv), 18-crown-6 (2.0 molar equiv) and KF (2.0 molar equiv) were added sequentially. Reaction mixture was allowed to stir at room temperature until TLC showed disappearance of *N*-oxide, **5**. Reaction mixture was diluted with water and transferred to separatory funnel with ethyl acetate. Organic layer was separated and aqueous layer was extracted three times with ethyl acetate. Combined organic layer was washed with brine and then dried over anhydrous Na_2SO_4. Solvents were evaporated under reduced pressure and the products were isolated by column chromatography using silica gel (mesh 230-400). Eluting solvents for chromatography are indicated under the specific compound headings.

6H-chromeno[3,4-b]quinoline (Scheme 5, entry 6a) 2-(chloromethyl)quinoline *N*-oxide **5**: 97.0 mg (0.50 mmol); benzyne precursor **2a**: 223.0 mg (0.75 mmol), 18-crown-6: 264.0 mg (1.00 mmol), KF: 58.0 mg (1.00 mmol), CH3CN: 6.5 mL. Column chromatography: eluting solvent 5% EtOAc in *n*-hexanes. Yield: 29.0 mg (25%) of off white solid; m. p. 84-86 °C.

^{1}H NMR (300 MHz, acetone-d_6) δ 8.71 (s, 1H), 7.99 – 8.07 (m, 3H), 7.71 – 7.76 (m, 1H), 7.57 – 7.62 (m,1H), 7.33 – 7.38 (m, 1H), 7.14 – 7.19 (m, 1H), 7.06 (d, J = 8.1 Hz, 1H), 5.32 (s, 2H).

^{13}C NMR (75 MHz, acetone-d_6) δ 155.9, 154.1, 148.2, 131.4, 130.4, 129.7, 129.5, 129.2, 128.8, 127.7, 125.2, 124.4, 123.6, 122.1, 118.6, 71.1.

IR (ZnSe): ν_{max} (cm^{-1}) 3059, 2922, 2850, 1726, 1587, 1575, 1554, 1485, 1469, 1446, 1408, 1367, 1232, 1211, 1109, 1043, 867, 781, 750, 682, 478.

HRMS (ESI-TOF): m/z calcd for $C_{16}H_{12}NO$ $[M+H]^+$ 234.0913 found 234.0902.

4.7 General procedure for one-pot synthesis of 2-aryl-3-(o-hydroxyaryl)quinolines

To a solution of quinoline *N*-oxide **7**: 36.0 mg (0.20 mmol, 1.0 molar equiv) in CH_3CN (2.5 mL) in a reaction vial equipped with magnetic stir bar, KF: 46.4 mg (0.8 mmol, 4.0 molar equiv) and 18-crown-6: 211.0 mg (0.8 mmol, 4.0 molar equiv) were added with stirring. A solution of 4-methoxyphenyl diazonium tetrafluoroborate: 67.0 mg (0.3 mmol, 1.5 molar equiv) or 4-nitrophenyl dizonium tetrafluoroborate: 71.0 mg (0.3 mmol, 1.5 molar equiv) in CH_3CN (2.5 mL) was added dropwise and reaction mixture allowed to stir at room temperature. After 30 minutes when the evolution of N_2 stopped, benzyne precursor **2a**: 90.0 mg (0.3 mmol, 1.5 molar equiv) was added directly and stirring continued at room temperature for next 5 h. Reaction mixture was then diluted with 10 mL water and transferred to separatory funnel using 10 mL ethyl acetate. Organic layer was separated and aqueous layer was extracted three times with ethyl acetate (10 mL each time). Combined organic layer was washed with 10 mL brine and then dried over anhydrous Na_2SO_4. Solvents were evaporated under reduced pressure and the products were isolated by column chromatography using silica gel (mesh 230-400), eluting with 20% EtOAc in *n*-hexanes. Yields of **3b**: 30.0 mg (46%) of white solid; Yield of **3c**: 21.0 mg (31%) of pale yellow solid.

2-(Acridin-4-yl)phenol (Table 3, entry 9a) Acridine *N*-oxide **8a**: 50.0 mg (0.26 mmol); benzyne precursor **2a**: 115.0 mg (0.38 mmol), 18-crown-6: 137.0 mg (0.52 mmol), KF: 30.0 mg (0.52 mmol), CH3CN: 3.4 ml. Column chromatography: eluting solvent 10% EtOAc in *n*-hexanes. Yield: 37.0 mg (53%) of brown solid; mp 140-142 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.70 (br s, 1H), 8.95 8.87 (s, 1H), 8.22 (d, J = 9.0 Hz, 1H), 8.00 (dd, J = 8.4, 4.5 Hz, 2H), 7.92 – 7.95 (m, 1H), 7.77 – 7.82 (m, 1H), 7.44 – 7.66 (m, 4H), 7.29 (d, J = 8.1Hz, 1H), 7.08 – 7.13 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 147.4, 146.8, 139.1, 138.7, 134.3, 132.8, 131.6, 130.1, 128.7, 128.4, 128.3, 128.1, 127.0, 126.5, 126.5, 126.4, 120.9, 119.9.

IR (ZnSe): ν_{max} (cm^{-1}) 3336, 3055, 2958, 2918, 2848, 1724, 1625, 1610, 1525, 1512, 1483, 1462, 1379, 1290, 1274,1136, 775, 758, 740.

HRMS (ESI-TOF): m/z calcd for $C_{19}H_{14}NO_3$ $[M+H]^+$ 272.1070, found 272.1058.

2-(Acridin-4-yl)-4,5-dimethoxyphenol (Table 3, entry 9b) Acridine *N*-oxide **8a**: 58.6 mg (0.30 mmol); benzyne precursor **2b**: 147.0 mg (0.45 mmol), 18-crown-6: 158.0 mg (0.60 mmol), KF: 34.8 mg (0.60 mmol), CH_3CN: 3.9 ml. Column chromatography: eluting solvent 10% EtOAc in *n*-hexanes. Yield: 35.5 mg (36%) of brown solid; mp 160-161 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.56 (br s, 1H),8.95 8.91 (s, 1H), 8.23 (d, J = 8.7 Hz, 1H), 8.01 – 8.04 (m, 2H), 7.92 (d, J = 6.7 Hz, 1H), 7.79 – 7.84 (m, 1H), 7.55 – 7.68 (m, 2H), 7.00 (s, 1H), 6.84 (s, 1H), 3.99 (s, 3H), 3.92 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 150.4, 147.4, 146.6, 143.5, 139.0, 138.8(2C), 133.5, 131.6, 128.4, 128.1, 127.7, 127.2, 126.6, 126.5, 119.1, 116.2, 103.9, 57.0, 56.1.

IR(ZnSe): ν_{max} (cm^{-1}) 3055, 2923, 2851, 1733, 1612, 1505, 1461, 1345, 1238, 1204, 1135, 1008, 862, 798, 736, 668, 614, 569.

HRMS (ESI-TOF): m/z calcd for $C_{21}H_{17}NO_3$ $[M+H]^+$ 332.1281, found 332.1270.

2-(Acridin-4-yl)-3-methoxyphenol (Table 3, entry 9c) Acridine *N*-oxide **8a**: 58.6 mg (0.30 mmol); benzyne precursor **2c**: 148.0 mg (0.45 mmol), 18-crown-6: 158.0 mg (0.60 mmol), KF: 34.8 mg (0.60 mmol), CH_3CN: 3.9 ml. Column chromatography: eluting solvent 5% EtOAc in *n*-hexanes. Yield: 32.2 mg (36%) of pale yellow solid; m. p. 219-220 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.18 (d, J = 9.0 Hz, 1H), 8.03 – 8.08 (m, 3H), 7.76 – 7.79 (m, 1H), 7.64 – 7.67 (m, 1H), 7.55 – 7.57 (m, 1H), 7.36 (t, J = 8.4 Hz, 1H), 6.91 – 6.92 (m, 1H), 6.72 (d, J = 8.4 Hz, 1H), 3.73 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 158.3, 156.4, 148.2, 147.3, 138.3, 136.4, 132.2, 131.1, 129.6, 128.9, 128.2, 128.0, 127.1, 126.3, 126.1, 125.8, 117.6, 112.5, 104.5, 56.0.

IR(ZnSe): ν_{max} (cm^{-1}) 2921, 2851, 1725, 1560, 1522, 1459, 1378, 1262, 1121, 1073, 905, 776, 740, 586.

HRMS (ESI-TOF): m/z calcd for $C_{20}H_{16}NO_2$ $[M+H]^+$ 302.1176, found 302.1165.

2-(9-Methylacridin-4-yl)phenol (Table 3, entry 9d) 9-Methylacridine *N*-oxide **8b**: 20.9 mg (0.10 mmol); benzyne precursor **2a**: 45.0 mg (0.15 mmol), 18-crown-6: 53.0 mg (0.20 mmol), KF: 11.6 mg (0.20 mmol), CH_3CN: 1.3 mL. Column chromatography: eluting solvent 10% EtOAc in *n*-hexanes. Yield: 11.0 mg (39%) of brown solid; mp 152-153 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 11.78 (br s, 1H),8.35 (d, J = 9.0 Hz, 1H), 8.30 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 7.2 Hz, 1H), 7.79 – 7.82 (m, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.60 – 7.63 (t, J = 7.8 Hz, 1H), 7.47 (d, J = 7.2 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.06–7.09 (m, 1H), 3.23 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 155.9, 146.8, 146.3, 145.5, 139.9, 134.0, 132.9, 131.1, 130.0, 129.4, 129.1, 126.3(2C), 126.1, 125.5, 124.7, 124.5, 120.8, 119.8, 14.6.

IR(ZnSe): ν_{max} (cm^{-1}) 3055, 2924, 2853, 1732, 1613, 1563, 1507, 1460, 1377, 1348, 1237, 1208, 1137, 1091, 1010, 862, 747, 694, 569, 456.

HRMS (ESI-TOF): m/z calcd for $C_{20}H_{15}NO$ $[M+H]^+$ 286.1226, found 286.1218.

2-(9-Phenylacridin-4-yl)phenol (Table 3, entry 9e) 9-Phenylacridine *N*-oxide **8c**: 27.2 mg (0.10 mmol); benzyne precursor **2b**: 45.0 mg (0.15 mmol), 18-crown-6: 53.0 mg (0.20 mmol), KF: 11.6 mg (0.20 mmol), CH_3CN: 1.3 ml. Column chromatography eluting solvent 8% EtOAc in *n*-hexanes. Yield: 11.5 mg (33%) of pale yellow solid; mp 211-212 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 11.67 (br s, 1H), 8.28 (d, J = 9.0 Hz, 1H), 7.93 (d, J = 7.2 Hz, 1H), 7.77 – 7.82 (m, 2H), 7.72 (d, J = 8.4 Hz, 1H), 7.62 – 7.65 (m, 3H), 7.55 – 7.57 (m, 1H), 7.44 – 7.51 (m, 5H), 7.29 (d, J = 8.4 Hz, 1H),7.10 (t, J = 7.2 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 155.9, 150.0, 147.2, 146.7, 139.3, 135.9, 134.1, 132.9, 131.2, 130.4 (2C), 130.0, 129.0, 128.8, 128.7 (3C), 127.1, 127.0, 126.4 (2C), 125.8, 125.2, 120.9, 119.8.

IR (ZnSe): ν_{max} (cm^{-1}) 3056, 2921, 2851, 2724, 2360, 1828, 1603, 1561, 1538, 1480, 1458, 1402, 1385, 1271, 1152, 1026, 875, 830, 752, 704, 668, 609.

HRMS (ESI-TOF): m/z calcd for $C_{25}H_{18}NO$ $[M+H]^+$ 348.1383, found 348.1369.

4,5-Dimethoxy-2-(9-phenylacridin-4-yl)phenol (Table 3, entry 9f) 9-Phenylacridine *N*-oxide **8c**: 81.6 mg (0.30 mmol); benzyne precursor **2b**: 148.0 mg (0.45 mmol), 18-crown-6: 158.0 mg (0.60 mmol), KF: 34.8 mg (0.60 mmol), CH_3CN: 3.9 ml. Column chromatography: eluting solvent 10% EtOAc in *n*-hexanes. Yield: 36.4 mg (30%) of orange solid; mp 189-190 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 11.59 (bs s, 1H), 8.28 (d, J = 9.0 Hz, 1H), 7.91 (d, J = 6.6 Hz, 1H), 7.79 – 7.82 (m, 1H), 7.70 – 7.74 (m, 2H), 7.62 – 7.66 (m, 3H), 7.54 – 7.57 (m, 1H), 7.46 -7.49 (m, 3H), 7.01 (s, 1H), 6.86 (s, 1H), 4.00 (s, 3H), 3.92 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 151.1, 150.3, 150.1, 147.2, 146.5, 143.4, 139.1, 135.9, 133.3, 131.2, 130.4(2C), 128.8, 128.70 (2C),128.68, 127.0, 126.5, 126.4(2C), 125.9, 125.2, 119.4, 116.2, 103.8, 57.0, 56.1.

IR (ZnSe): ν_{max} (cm^{-1}) 2835, 2594, 2360, 1615, 1505, 1461, 1440, 1367, 1338, 1249, 1198, 1158, 1090, 1007, 812, 749, 707, 672, 613, 565, 462.

HRMS (ESI-TOF): m/z calcd for $C_{27}H_{22}NO_3$ $[M+H]^+$ 408.1594, found 408.1588.

2-(9-Chloroacridin-4-yl)phenol (Table 3, entry 9g) 9-Chloroacridine *N*-oxide **8d**: 30.5 mg (0.10 mmol); benzyne precursor **2a**: 45.0 mg (0.15 mmol), 18-crown-6: 52.8 mg (0.20 mmol), KF: 11.6 mg (0.20 mmol), CH_3CN: 1.3 ml. Column chromatography: eluting solvent 4% EtOAc in *n*-hexanes. Yield: 9.5 mg (31%) of brown solid; mp 172 °C - 173. °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ 11.09 (br s, 1H), 8.53 (d, J = 9.0 Hz, 1H), 8.46 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 9.0 Hz, 1H), 7.97 (d, J = 7.2 Hz, 1H), 7.83 – 7.86 (m, 1H), 7.76 – 7.78 (m, 1H), 7.67 – 7.69 (m, 1H), 7.44 – 7.46 (m, 2H), 7.25 (d, J = 7.8 Hz, 1H), 7.09 (t, J = 7.2 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 155.5, 147.4, 146.8, 143.9, 139.7, 134.7, 132.9, 131.9, 130.3, 129.0, 128.4, 127.8, 127.7, 125.0, 124.8, 124.7, 124.4, 121.1, 119.8.

IR(ZnSe): ν_{max} (cm^{-1}) 3057, 2922, 2852, 1736, 1620, 1595, 1523, 1460, 1413, 1324, 1266, 1204, 1120, 870, 811, 750, 700, 606 550, 454.

HRMS (ESI-TOF): m/z calcd for $C_{19}H_{13}ClNO$ $[M+H]^+$ 306.0680, found 306.0671.

ASSOCIATED CONTENT

Supporting Information

This supporting information is available free of charge *via* internet at http://pubs.acs.org. Copy of ^{1}H and ^{13}C NMR spectra for all synthesized compounds including X-ray data for **9a** (CIF).

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Notes

The authors declare no competing financial interests.

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REFERENCES

(1) (a) Kouznetsov, V. V.; Mendez, L. Y. V.; Gomez, C. M. M. *Curr. Org. Chem*. **2005**, *9*, 141. (b) Michael, *J. P*. *Nat. Prod. Rep*., **2008**, *25*, 166.

(2) (a) Kumar, S.; Bawa, S.; Gupta, H. *Mini. Rev. Med. Chem.* **2009**, *9*, 1648. (b) Solomon, V. R.; Lee, H. *Curr. Med. Chem*. **2011**, *18*, 1488. (c) Marella, A.; Tanwar, O. P.; Saha, R.; Ali, M. R.; Srivastva, S.; Akhter, M.; Shaquiquzzaman, M.; Alam, M. M. *Saudi. Pharm. J.* **2013**, *21*, 1.

(3) (a) Jégou, G.; Jenekhe, S. A. *Macromolecules* **2001**, *34*,7926. (b) Kim, J. I.; Shin, I.-S.; Kim, H.; Lee, J. K.*J. Am. Chem. Soc*. **2005**, *127*, 1614. (c) Tokoro, Y. Nagai, A.; Kokado, K.; Chujo, Y. *Macromolecules* 2**009**, *42*, 2988.

(4) Lopez, A. E. in "Privileged scaffolds in medicinal chemistry: Design, Synthesis, Evaluation" Brase, S. (Ed.) pp 132-146, ISBN: 978-1-78262-030-3, The Royal Society of Chemistry, London, November, **2015**.

(5) (a) Foley, M.; Tilley, L. *Pharmacol. Ther*. **1998**, *79*, 55. (b) Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. *Eur. J. Med. Chem.* **2010**,*45*, 3245. (c) Vandekerckhove, S.; D'hooghe, M. *Bioorg. Med. Chem*. **2015**, *23*, 5098. (d) Rosenthal, P. J. Antimalarial Chemotherapy: Mechanisms of Action, Resistance, and New Directions in Drug Discovery, Humana Press, Totowa, N. J. **2001**. (e) Singh, S.K.; Singh, S. *Int. J. Pharm. Sci. Rev. Res.* **2014**, *25*, 295

(6) Baragana, B.; Hallyburton, I.; Lee, M. C. S.; Norcross, N. R.; Grimaldi, R.; Otto, T. D.;Proto, W. R.; Blagborough, A. M.; Meister, S.; Wirjanata, G.; Ruecker, A.; Upton, L. M.;Abraham, T. S.; Almeida, M. J.; Pradhan, A.; Porzelle, A.; Martinez, M. S.; Bolscher, J. M.;Woodland, A.; Norval, S.; Zuccotto1, F.; Thomas, J.; Simeons, F.; Stojanovski, L.;Osuna-Cabello, M.; Brock, P. M.; Churcher, T. S.; Sala, K. A.; Zakutansky, S. E.; Jimenez-Dıaz, M. B.;Sanz, L. M.; Riley, J.; Basak, R.; Campbell, M.; Avery, V. M.; Sauerwein, R. J.; Dechering, K. J.; Noviyanti, R.; Campo, B.; Frearson, J. A.; Angulo-Barturen, I.; Ferrer-Bazaga, S.;Gamo, F. J.; Wyatt, P. G.; Leroy, D.; Siegl, P.; Delves, M. J.; Kyle, D. E.; Wittlin, S.; Marfurt, J.; Price, R. N.; Sinden, R. E.; Winzeler, E. A.; Charman, S. A.; Bebrevska, L.; Gray, D. W.; Campbell, S.; Fairlamb, A. H.; Willis, P. A.; Rayner, J. C.; Fidock, D. A.; Read, K. D.; Gilbert, I. H. *Nature* **2015**, *522*, 315.

(7) Tseng, C. H.; Chen, Y. L.;Chung, K. Y.; Wang, C. H.; Peng, S. I.; Cheng, C. M.; Tzeng, C. C. *Org. Biomol.*Chem. **2011**, *9*, 3205.

(8) Saeed, A. E. M.; Elhadi, S. A. *Synth. Commun.* **2011**, *41*, 1435.

(9) Yamamoto, J.; Kinpara, K.; Fukuda, Y.; Nakasato, Y.; Uchida, K.; Nishikawa, T.PCT Int. Appl. (2011), WO 2011093365 (A1).

(10) Ghodsi, R.; Zarghi, A.; Daraei, B.; Hedayati. M. Zarghi A and Ghodsi R. *Bioorg. Med. Chem.***2010**, *18*, 5855.

(11) de Turiso, F. G. L.; Hao, X.; Shin, Y.; Bui, M.; Campuzano, I. D. G.; Cardozo, M.; Dunn, M. C.; Duquette, J.; Fisher, B.; Foti, R. S.; Henne, K.; He, X.; Hu, Y.-L.; Kelly, R. C.; Johnson, M. G.; Lucas, B. S.; McCarter, J.; McGee, L. R.; Medina, J. C.; Metz, D.; San Miguel, T.; Mohn, D.; Tran, T.; Vissinga, C.; Wannberg, S.; Whittington, D. A.; Whoriskey, J.; Yu, G.; Zalameda, L.; Zhang, X.; Cushing, T. D. *J. Med. Chem*. **2016**, *59*, 7252.

(12) Chuang, T.-H.; Yang, C.-H.; Kao, P.-C. *Inorg. Chim. Acta* **2009**, *362*, 5017.

(13) (a) Chen, Y.; Larock, R. C. *Arylation reactions involving the formation of arynes, in Modern Arylation Methods, ed*. L. Ackermann, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2009**. (b) Wenk, M.; Winkler, H. H.; Sander, W. *Angew. Chem. Int. Ed.* **2003**, *42*, 502. (c) Bhojgude, S. S.; Bhunia, A.; Biju, A. T. *Acc. Chem. Res*. 2016, 49, 1658. (d) Bhunia, A.; Yetra, S. R.; Biju, A. T.*Chem. Soc. Rev*. **2012**, *41*, 3140. (e) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701.

(14) Gampe, C. M.; Carreira, E. M. *Angew. Chem. Int. Ed*. **2012**, *51*, 3766. (b) Tadross, P. M.; Stoltz, B. M. *Chem. Rev*. **2012**, *112*, 3550.

(15) Abramovitch, R. A.; Shinkai, I. *J. Am. Chem. Soc*. **1974**, *96*, 5265.

(16) Raminelli, C.; Liu, Z.; Larock, R. C. *J. Org. Chem*. **2006**, *71*, 4689.

(17) Shaibu, B. S.; Kawade, R. K.; Liu, R. S. *Org. Biomol. Chem.***2012**, *10*, 6834.

(18) Okuma, K.; Hirano, K.; Shioga, C. Nagahora, N.; Shioji, K. *Bull. Chem. Soc. Jpn*. **2013**, *86*, 615.

(19) (a) Tadross, P. M.; Gilmore, C. D.; Bugga, P.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1224. (b) Singh, G.; Kumar, R.; Swett, G.; Zajc, B. *Org. Lett***. 2013**, *15*, 4086. (c) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (d) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C.*Org. Lett*. **2008**, *10*, 2409.

(e) Campbell-Verduyn, L. Elsinga, P. H.; Mirfeizi, L.; Dierckx, R. A.; Feringa, B. L.*Org. Biomol. Chem*. **2008**, *6*, 3461.

(20) (a) Kumar, R.; Kumar, R.; Dhiman, A.K.; Sharma, U. *Asian J. Org. Chem*. **2017**, *6*, 1043. (b) Colleville, A. P.; Richard, A. J.; Horan, R. A. J.; Olazabal, S.; Tomkinson, N. C. O. *Org. Process Res. Dev*. **2016**, *20*, 1283.

(21) Valdés, A. F. C. *Open Med. Chem. J.* **2011**, *5*, 11.

(22) Zhang, B.; Li, X.; Li, B.; Gao, C.; Jiang, Y. *Expert Opin. Ther. Patents* **2014**, *24*, 647.

(23) Hwang, H.; Kim, J.; Jeong, J.; Chang, S. *J. Am. Chem. Soc*. **2014**, *136*, 10770. (b) Jeong, J.; Patel, P.; Hwang, H.; Chang, S. *Org. Lett*. **2014**, *16*, 4598. (c) Nishikawa, M.; Saiki, S. Hamana, M.; Noda, H. *Chem. Parm. Bull.* **1980**, *28*, 2436.