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Iron-Catalyzed Direct Alkylamination of Phenols with *O*-Benzoyl-*N*-alkylhydroxylamines under Mild Conditions

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Abstract: A novel iron-catalyzed direct alkylamination reaction of phenols has been achieved with *O*-benzoyl-*N*-alkylhydroxylamines as aminating agents. This protocol provides a facile access to *N*-alkyl-substituted aminophenols though a radical reaction from phenols. The catalytic direct alkylamination operates at room temperature without the need of any ligands and additives to afford the desired products with excellent regioselectivity and functional group tolerance.

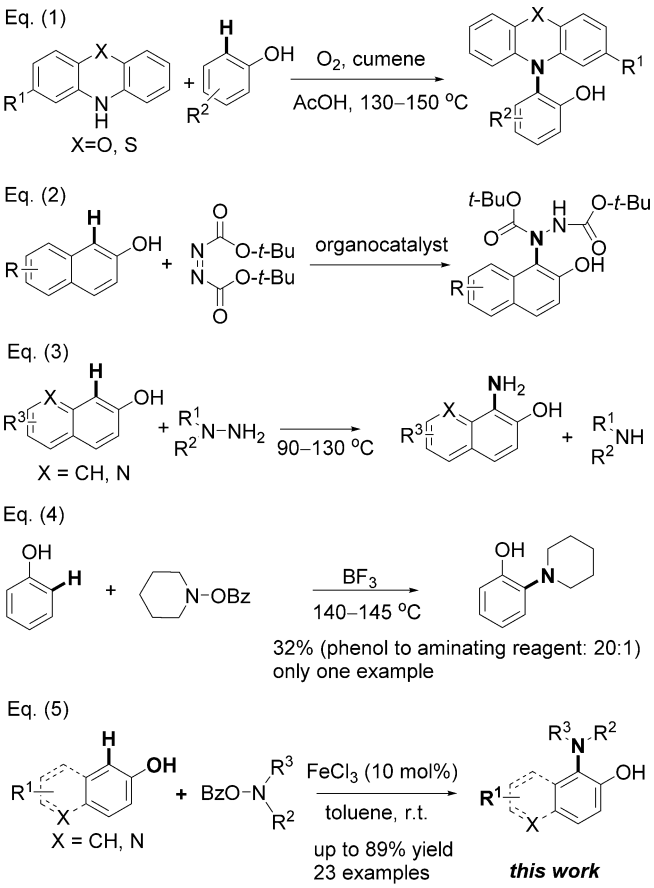
Keywords: alkylamination; C–H functionalization; iron catalysis; phenols; synthetic methods

Introduction

Arylamines are present in numerous natural products, synthetic materials and biologically active compounds, and have been greatly exploited in the area of drug discovery.[1] Among various methods for the synthesis of arylamines, the direct amination of arenes is a potentially useful synthetic tool and has received widespread interest.[2–4] One of the key advantages of the direct aromatic amination strategy, whether by oxidative C–H/N–H coupling,[2] by electrophilic attack,[3] or *via* a nitrogen radical intermediate,[4] is the absence of pre-activation steps for the aromatic C–H bonds, thus the C–N bond can be formed in a single chemical step.

N-Substituted aminophenols occur in a number of compounds which possess various biological properties.[5] They are traditionally prepared by multiple steps such as nitration and subsequent reduction, *N*-alkylation and/or *N*-arylation, which always result in low overall yields.[6] Apparently, the shortest access to *N*-substituted aminophenols is the direct amination of phenols. However, compared to other aromatic compounds, examples of the direct amination of phenols are scarce, possibly because the reaction selectivity is typically low for multiple reaction sites and concomitant homocoupling of phenols, C–O bond formation between two phenols, and complex oligo- and polyphenolic assemblies under oxidative conditions.[7,8] To date, there have been only a few examples reported for the direct amination of phenols, which often suffer from limited generality (Scheme 1).[9] Patureau and co-workers recently reported an O_2-mediated dehydrogenative amination of phenols with phenothiazines and phenoxazine in the presence of cumene [Eq. (1), Scheme 1].[9e] Bella and Jørgenson reported an organocatalytic amination of 2-naphthols by using diazodicarboxylate as aminating reagent to afford substituted hydrazines [Eq. (2), Scheme 1].[9b] We previously described the direct *ortho*-amination of naphthols using *N*,*N*-disubstituted hydrazines as aminating reagents to provide *N*-unsubstituted aminonaphthols [Eq. (3), Scheme 1].[9c] Direct introduction of an alkylamino group onto phenols to give *N*-alkylaminophenols appears to be difficult. To the best of our knowledge, there is only a single report of a direct alkylamination of phenol using *N*-benzoyloxypiperidine as the aminating reagent at 140–145 °C in the presence of excess boron trifluoride [Eq. (4), Scheme 1].[9a] A 20:1 molar ratio of phenol to *N*-benzoyloxypiperidine gave a 32% yield of *N*-(*o*- hydroxyphenyl)piperidine, and no other phenols were examined.

Thus, the direct amination of phenols still remains problematic in substrate scope and reaction conditions, and the direct alkylamination of phenols is particularly challenging. In conjunction with our recent results on direct *ortho*-amination of 2-naphthols using *N*,*N*-disubstituted hydrazines as aminating reagents,[9c] we herein present an iron-catalyzed direct alkylamination of phenols with *O*-benzoyl-*N*,*N*-dialkylhydroxylamines under mild conditions [Eq. (5), Scheme 1].

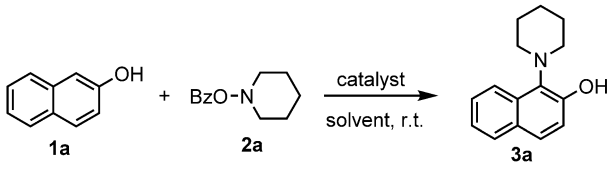


Scheme 1. Direct amination reactions of phenols.

Results and Discussion

Our initial efforts toward this goal focused on the reaction of 2-naphthol **1a** with *N*-benzoyloxypiperidine **2a** without any catalysts in dichloromethane at room temperature (Table 1). To our delight, the corresponding amination product 1-(piperidin-1-yl)-2-naphthol **3a** was obtained in 41% isolated yield after 30 h (entry 1). Encouraged by this preliminary result, we then screened different solvents and found that toluene was the most suitable for this transformation (entries 2, 3 and 4). Subsequently, a variety of metal oxides and salts like Ag_2O, MnO_2 and $Cu(OAc)_2$ were examined and shown to afford moderate yields (entries 5–7) in a shorter reaction time. Gratifyingly, when $FeCl_3$ (10 mol%) was utilized as the catalyst, a highly efficient alkylamination of **1a** with **2a** occurred, affording **3a** in an excellent isolated yield of 89% in 15 minutes (entry 8). At lower loadings of $FeCl_3$, the product was obtained in reduced yields (entries 9 and 10). Other iron catalysts such as $FeCl_2$, $Fe_2(SO_4)_3$ and Fe_2O_3 were also explored, whereby lower yields were observed (entries 11–13). It is worthy to note that iron salts have rarely been utilized as catalysts in the C–H bond amination of aromatic substrates.[4a,10] In this respect, the Fe-catalyzed highly efficient amination of phenols with *O*-benzoyl-*N*-alkylhydroxylamines at room temperature was remarkable and significant, which encouraged us to carry out further explorations.

Table 1. Optimization of the reaction conditions.[a]

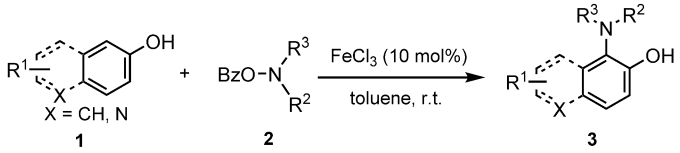


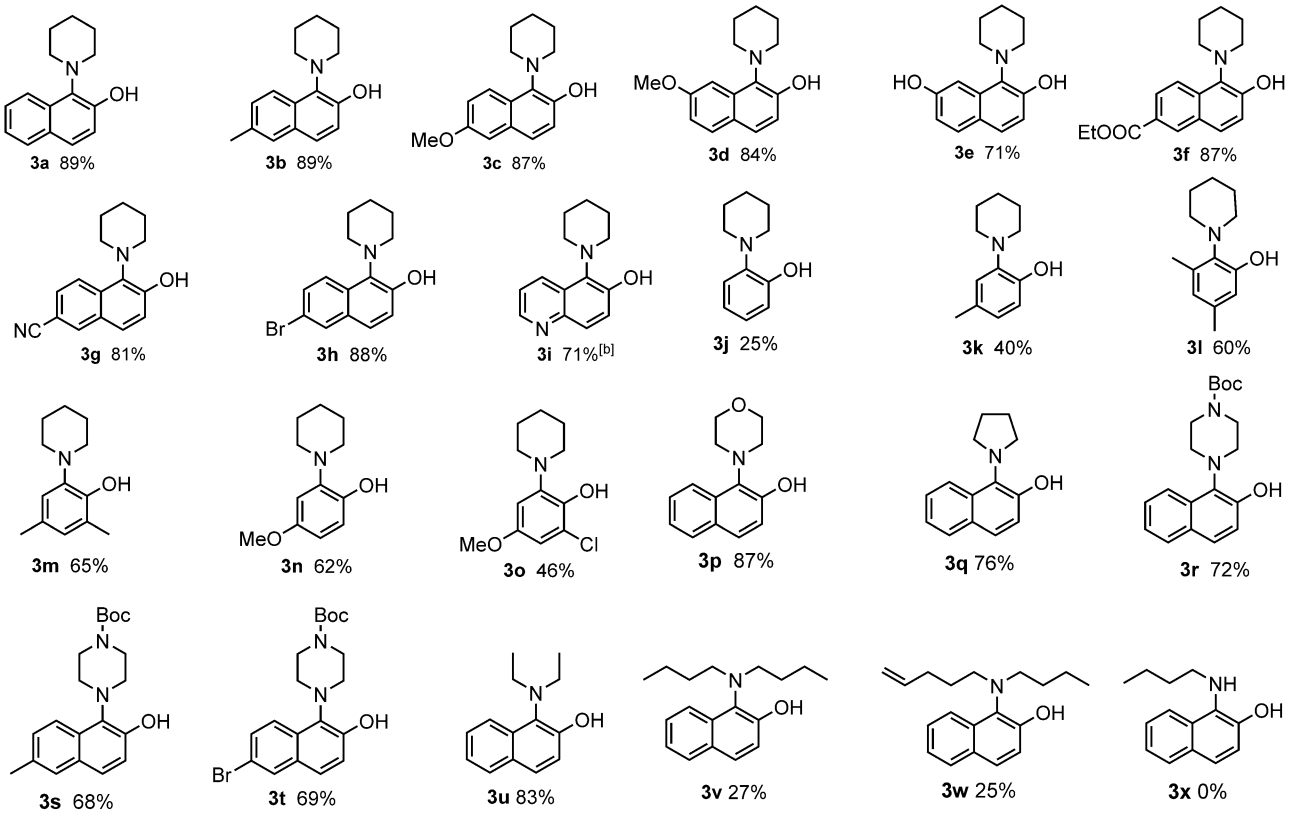
Entry	Catalyst	mol%	Solvent	Time	Yield[b]
1	–	–	DCM	30 h	41
2	–	–	MeOH	30 h	56
3	–	–	THF	30 h	32
4	–	–	toluene	30 h	84
5	Ag_2O	10	toluene	17 h	41
6	MnO_2	10	toluene	13 h	52
7	$Cu(OAc)_2$	10	toluene	24 h	69
8	**$FeCl_3$**	**10**	**toluene**	**15 min**	**89**
9	$FeCl_3$	5	toluene	1 h	76
10	$FeCl_3$	2	toluene	4 h	64
11	$FeCl_2$	10	toluene	1 h	80
12	$Fe_2(SO_4)_3$	10	toluene	7 h	81
13	Fe_2O_3	10	toluene	15 h	79

[a] *Reaction conditions:* **1a** (2.0 mmol), **2a** (2.6 mmol), solvent (4 mL), room temperature, argon.
[b] Isolated yields [%].

With the optimized conditions in hand, we further explored this $FeCl_3$-catalyzed direct alkylamination of various phenol derivatives. As shown in Table 2, several 2-naphthols were firstly tested. We were pleased to find that 2-naphthols bearing electron-donating groups such as methyl, methoxy and hydroxy were suitable substrates to afford the corresponding substituted 1-(piperidin-1-yl)-2-naphthols in good yields (**3b**–**3e**). It was noted that only one piperidin-1-yl group was introduced onto 2,7-naphthalenediol to produce **3e**. This may be attributed to the steric hindrance rising from the piperidin-1-yl group that is already situated at C-1. The mildness of the reaction conditions accommodated an electron-withdrawing bromide function as well as ester and nitrile functions (**3f**–**3h**). Moreover, 6-hydroxyquinoline also coupled with **2a** at a slightly higher temperature of 40 °C, giving the desired product **3i** in 77% yield. In addition to 2-naphthols, the reaction was also applicable to simple electron-rich phenols. Phenol (**1j**), methyl phenols (**1k**, **1l** and **1m**) and 4-methoxyphenols (**1n** and **1o**) underwent the reaction with **2a** to produce the corresponding aminophenols (**3j**–**3o**) in moderate yields along with unidentified substances of high polarity.

Table 2. Scope of direct alkylamination of phenols with *O*-benzoylhydroxylamines.[a]



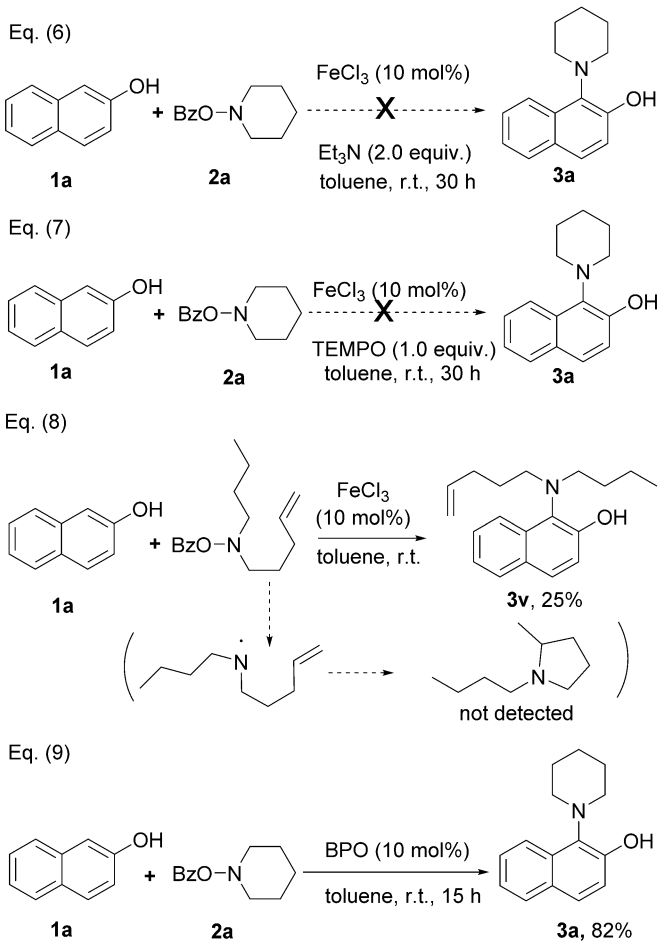


[a] *Reaction conditions:* $FeCl_3$ (0.2 mmol), **1** (2.0 mmol), **2** (2.6 mmol), toluene (4 mL), room temperature, 0.25–4.0 h, argon, isolated yields.

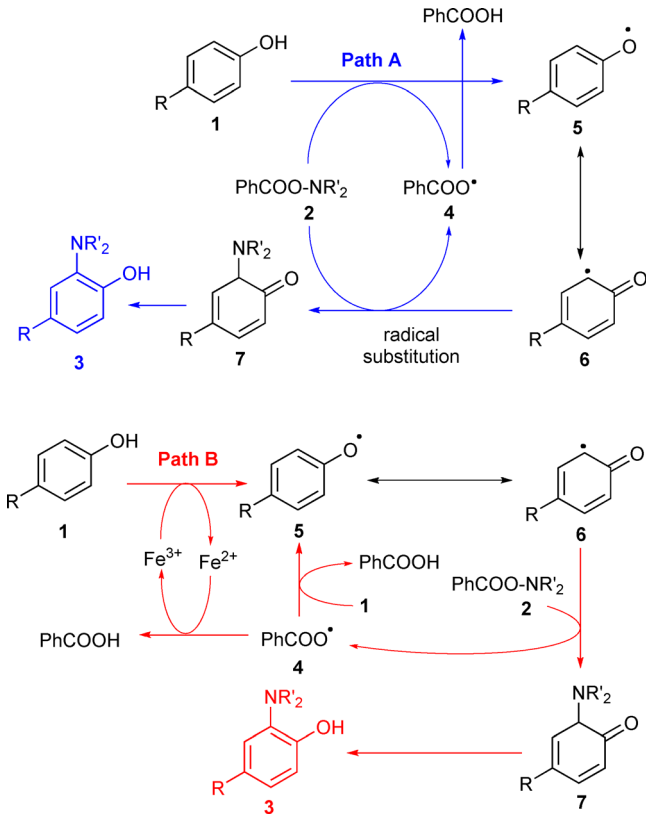
[b] *Reaction conditions:* $FeCl_3$ (0.2 mmol), **1** (2.0 mmol), **2** (5.0 mmol), 40 °C, 3.0 h, argon, isolated yields.

We further tested the direct alkylamination of 2-naphthol with various *O*-benzoylhydroxylamines. As expected, both *N*-benzoyloxymorpholine and *N*-benzoyloxypyrrolidine reacted with **1a** smoothly to generate the desired products **3p** and **3q** in 87% and 76% yields, respectively. It was noteworthy that the Boc-protected piperazine could be introduced to 2-naphthols to produce the corresponding aminated products (**3r**–**3t**) in good yields, which enable a potential application in further functionalization. While *O*-benzoyl-*N*,*N*-diethylhydroxylamine afforded product **3u** in 83% yield, *O*-benzoyl-*N*,*N*-dibutylhydroxylamine and *O*-benzoyl-*N*-butyl-*N*-(4-pentenyl)hydroxylamine gave products **3v** and **3w** in 27% and 25% yields, respectively, probably due to the steric hindrance of the two long alkyl groups. The reaction is not applicable to *N*-monosubstituted-*O*-benzoylhydroxylamine under the same reaction conditions (**3x**).

In the transition metal-catalyzed electrophilic C–H aminations of aromatic compounds other than phenols using *O*-benzoylhydroxylamines as aminating reagents, a stoichiometric amount of base was often used to regenerate the starting active catalyst to complete the catalytic cycle.[3g] It is also known that the nucleophilic activity of 2-naphthol can be further improved by the addition of a base.[7b] To our surprise, however, when the reaction between **1a** and **2a** was conducted in the presence of two equivalents of Et_3N and 10 mol% of $FeCl_3$, no desired product **3a** was obtained at all even after 30 h at room temperature [Eq. (6), Scheme 2]. This observation suggested that the present Fe-catalyzed direct alkylamination of phenols seemed not to go through an electrophilic amination process. To gain further mechanistic information about this transformation, a radical-trapping experiment was carried out. In the presence of one equiva-



Scheme 2. Control experiments for mechanism study.



Scheme 3. Proposed reaction mechanism.

lent of TEMPO, no product **3a** was obtained under the standard conditions [Eq. (7), Scheme 2], suggesting the reaction might occur *via* a radical process. We then performed the reaction of 2-naphthol with *O*-benzoyl-*N*-butyl-*N*-(4-pentenyl)hydroxylamine under the standard conditions, which gave the aminated product **3w** in 25% yield and no pyrrolidine derivatives from an aminyl radical cyclization [Eq. (8), Scheme 2].[11] This result implied that an aminyl radical-involved pathway was less likely. Finally, we found that the reaction was significantly accelerated (15 h *vs.* 30 h, Table 1, entry 4) by benzoyl peroxide (BPO, 10 mol%) [Eq. (9), Scheme 2], implicating that a radical process and benzoyloxyl radicals might be involved.

It is accepted that $FeCl_3$ can oxidize phenols to phenoxyl radicals.[12] Iron(II) can be oxidized to iron(III) by BPO [13] and *N*-benzoyloxypiperidine (see the Supporting Information).

Based on these literature results and the above-mentioned experimental observations, a putative mechanism may be proposed as shown in Scheme 3. In the absence of a catalyst, the reaction may go through path A in which the reaction is initiated by single electron transfer from phenol **1** to *O*-benzoylhydroxyamine **2** to generate benzoyloxyl radical **4** and phenoxyl radical which may be written in two resonance structures **5** and **6**. The C-radical **6** subsequently undergoes a radical substitution reaction with *O*-benzoylhydroxlamine **2** to produce benzoyloxyl radical **4** and the aminated intermediate **7** which isomerizes immediately to the final product **3**. Benzoyloxyl radical **4** can then perform the propagation by oxidizing phenol **1** to phenoxyl radical **5** or **6**. In the presence of the iron catalyst, the reaction may proceed through path B where phenoxyl radical **5** or **6** may also be produced from **1** by the oxidation of Fe(III).[12] The produced Fe(II) is reoxidized to Fe(III) by benzoyloxyl radical **4** and/or *O*-benzoylhydroxyamines **2**. Then the radical substitution reaction between radical **6** and *O*-benzoylhydroxlamine **2** produces benzoyloxyl radical **4** and the aminated intermediate **7** which isomerizes to the final product **3** just as in path A. The effect of iron catalyst as an oxidant/initiator thus significantly promotes the reaction.

Conclusions

In conclusion, a novel Fe-catalyzed direct alkylamination reaction of phenols under mild conditions has

been successfully established. The important feature of this strategy is direct furnishing *N*-alkyl-substituted aminophenols though a radical process which is accomplished *via* iron-catalyzed reaction between phenols and *O*-benzoyl-*N*- alkylhydroxylamines. The reaction proceeds smoothly at room temperature to afford a number of *N*-alkyl-substituted aminophenols in modest to excellent yields without the need of any ligands and additives. Preliminary mechanistic studies revealed that radicals were involved in the overall process and $FeCl_3$ might act as an initiator and a Lewis acid as well as to promote the transformation. The mild conditions and efficiency of the reaction render the present method attractive for future applications.

Experimental Section

General Procedure for Aminations

$FeCl_3$ (32 mg, 0.2 mmol) and phenol (**1**) (2 mmol) were placed in a 20-mL two-necked reaction flask which was filled with argon. A solution of *O*-benzoyl hydroxylamine (**2**) (2.6 mmol) in toluene (4.0 mL) was added to the flask. The solution was stirred at ambient temperature for 15 min to 3 h. Et_3N (0.5 mL) was added. The product was purified by silica gel column chromatography with hexanes/ethyl acetate (20:1) as the eluent to afford the desired target product (**3**).

1-(Piperidin-1-yl)naphthalen-2-ol (3a): Eluent: petroleum ether/ethyl acetate (20:1); yield: 89%; white solid; mp 62.0–64.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (br s, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.24 (d, J = 8.5 Hz, 2H), 3.58 (td, J = 11.7, 1.9 Hz, 2H), 2.99 (d, J = 11.2 Hz, 2H), 1.68–1.82 (m, 5H), 1.42–1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 132.2, 129.9, 129.5, 129.4, 128.1, 125.8, 122.4, 122.3, 116.0, 52.3, 27.8, 24.2; HR-MS (ESI): m/z = 228.1387, calcd. for $C_{15}H_{18}NO$ $[M+H]^+$: 228.1383.

6-Methyl-1-(piperidin-1-yl)naphthalen-2-ol (3b): Eluent: petroleum ether/ethyl acetate (20:1); yield: 89%; white solid; mp 116.0–117.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (br s, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.55(s, 1H), 7.53 (d, J = 9.8 Hz 1H), 7.26 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 8.7 Hz, 1H), 3.58 (t, J = 10.6 Hz, 2H), 2.99 (d, J = 10.9 Hz, 2H), 2.45 (s, 3H), 1.69–1.94 (m, 5H), 1.43–1.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.8, 131.7, 130.2, 129.8, 128.4, 128.0, 127.4, 122.2, 115.9, 52.3, 27.8, 24.2, 21.3; HR-MS (ESI): m/z = 242.1541, calcd. for $C_{16}H_{20}NO$ $[M+H]^+$: 242.1539.

6-Methoxy-1-(piperidin-1-yl)naphthalen-2-ol (3c): Eluent: petroleum ether/ethyl acetate (20:1); yield: 87%; white solid; mp 111.0–113.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (br s, 1H), 7.92 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.13–7.16 (m, 2H), 3.91 (s, 3H), 3.58 (t, J = 11.6 Hz, 2H), 3.02 (d, J = 11.5 Hz, 2H), 1.71–1.97 (m, 5H), 1.44–1.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 149.8, 130.4, 130.3, 127.6, 126.6, 123.8, 118.4, 116.3, 107.5, 55.3, 52.4, 27.8, 24.2; HR-MS (ESI): m/z = 258.1493, calcd. for $C_{16}H_{20}NO_2$ $[M+H]^+$: 258.1489.

7-Methoxy-1-(piperidin-1-yl)naphthalen-2-ol (3d): Eluent: petroleum ether/ethyl acetate (20:1); yield: 84%; white solid; mp 82.0–83.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (br s, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.28 (s, 1H), 7.12 (d, J = 8.7 Hz, 1H), 6.98 (dd, J = 8.9 Hz, 2.4 Hz, 1H), 3.96 (s, 3H), 3.61 (t, J = 11.7 Hz, 2H), 3.04 (d, J = 12.1 Hz, 2H), 1.72–1.99 (m, 5H), 1.43–1.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 152.1, 133.3, 130.9, 129.1, 127.9, 124.8, 114.2, 113.4, 101.9, 55.3, 51.9, 27.8, 24.3; HR-MS (ESI): m/z = 258.1493, calcd. for $C_{16}H_{20}NO_2$ $[M+H]^+$: 258.1489.

1-(Piperidin-1-yl)naphthalene-2,7-diol (3e): Eluent: petroleum ether/ethyl acetate (10:1); yield: 71%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.8 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.30 (d, J = 1.8 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 6.88 (dd, J = 8.8 Hz, 2.2 Hz, 1H), 3.54 (td, J = 11.7 Hz, 2.2 Hz, 2H), 2.95 (d, J = 11.5 Hz, 2H), 1.66–1.92 (m, 5H), 1.38–1.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.6, 152.1, 133.3, 131.3, 128.8, 128.0, 124.9, 114.1, 113.4, 104.9, 51.8, 27.8, 24.1; HR-MS (ESI): m/z = 244.1336, calcd. for $C_{15}H_{18}NO_2$ $[M+H]^+$: 244.1332.

Ethyl 6-hydroxy-5-(piperidin-1-yl)-2-naphthoate (3f): Eluent: petroleum ether/ethyl acetate (5:1); yield: 71%; white solid; mp 88.0–90.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (s, 1H), 8.52 (br s, 1H), 8.00–8.05 (m, 2H), 7.77 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2H), 3.59 (td, J = 11.7 Hz, 2.5 Hz, 2H), 3.00 (d, J = 11.1 Hz, 2H), 1.72–1.99 (m, 5H), 1.50–1.58 (m, 1H), 1.46 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 153.8, 134.4, 132.4, 130.1, 129.8, 128.4, 125.4, 124.3, 122.3, 116.7, 60.9, 52.2, 27.8, 24.1, 14.4; HR-MS (ESI): m/z = 300.1602, calcd. for $C_{18}H_{22}NO_3$ $[M+H]^+$: 300.1594.

6-Hydroxy-5-(piperidin-1-yl)-2-naphthonitrile (3g): Eluent: petroleum ether/ethyl acetate (10:1); yield: 81%; white solid; mp 112.0–114.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (br s, 1H), 8.08 (s, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.47 (d, J = 8.7 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 3.44 (t, J = 11.5 Hz, 2H), 2.90 (d, J = 11.3 Hz, 2H), 1.63–1.81 (m, 5H), 1.40–1.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 135.5, 130.3, 129.4, 128.9, 128.4, 126.4, 123.3, 119.6, 117.9, 105.6, 52.3, 27.7, 24.0; HR-MS (ESI): m/z = 253.1339, calcd. for $C_{16}H_{17}N_2O$ $[M+H]^+$: 253.1335.

6-Bromo-1-(piperidin-1-yl)naphthalen-2-ol (3h): Eluent: petroleum ether/ethyl acetate (20:1); yield: 88%; white solid; mp 103.0–105.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (br s, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.87 (d, J = 9.1 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.50 (dd, J = 9.0 Hz, 2.1 Hz, 1H), 7.28–7.30 (m, 1H), 3.54 (td, J = 11.7 Hz, 2.6 Hz, 2H), 3.00 (d, J = 12.2 Hz, 2H), 1.72–1.98 (m, 5H), 1.46–1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9, 131.2, 130.6, 130.1, 129.0, 127.2, 124.0, 117.1, 115.9, 52.3, 27.8, 24.1; HR-MS (ESI): m/z = 306.0496, calcd. for $C_{15}H_{17}BrNO$ $[M+H]^+$: 306.0488.

5-(Piperidin-1-yl)quinolin-6-ol (3i): Eluent: petroleum ether/ethyl acetate (5:1); yield: 71%; light yellow solid: mp 160.0–162.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.72 (d, J = 3.3 Hz, 1H), 8.39 (d, J = 8.6 Hz, 1H), 8.21 (br s, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.50 (d, J = 9.2 Hz, 1H), 7.35 (dd, J = 8.4 Hz, 4.3 Hz, 1H), 3.50 (t, J = 11.4 Hz, 2H), 3.03 (d, J =

11.0 Hz, 2H), 1.70–1.88 (m, 5H), 1.44–1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.8, 146.7, 144.2, 130.6, 129.5, 129.2, 127.3, 120.4, 119.4, 52.6, 27.7, 24.1; HR-MS (ESI): m/z=229.1343, calcd. for $C_{14}H_{17}N_2O$ $[M+H]^+$: 229.1335.

2-(Piperidin-1-yl) phenol (3j): Eluent: petroleum ether/ethyl acetate (10:1); yield: 25%; white solid; mp 69.0–70.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.14 (dd, J=7.8 Hz, 1.4 Hz, 1H), 7.05 (td, J=7.9, 1.5 Hz, 1H), 6.93 (dd, J=8.0 Hz, 1.4 Hz, 1H), 6.84 (td, J=7.6 Hz, 1.4 Hz, 1H), 2.80 (t, J=5.4 Hz, 4H), 1.74 (m, 4H), 1.60 (d, J=5.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.5, 140.4, 126.0, 121.3, 119.8, 113.7, 54.1, 26.8, 23.9; HR-MS (ESI): m/z=178.1230, calcd. for $C_{11}H_{16}NO$ $[M+H]^+$: 178.1226.

4-Methyl-2-(piperidin-1-yl)phenol (3k): Eluent: petroleum ether/ethyl acetate (10:1); yield: 40%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ =6.95 (s, 1H), 6.85 (t, J=2.0 Hz, 2H), 2.79 (t, J=5.6 Hz, 2H), 2.27 (s, 3H), 1.69–1.75 (m, 4H), 1.58–1.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.0, 140.1, 129.0, 126.3, 121.8, 113.3, 54.1, 26.8, 24.0, 20.8; HR-MS (ESI): m/z=192.1378, calcd. for $C_{12}H_{18}NO$ $[M+H]^+$: 192.1383.

3,5-Dimethyl-2-(piperidin-1-yl)phenol (3l): Eluent: petroleum ether/ethyl acetate (10:1); yield: 60%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.63 (s, 1H), 6.39 (s, 1H), 3.14–3.20 (m, 2H), 2.83–2.86 (m, 2H), 2.34 (s, 3H), 2.24 (s, 3H), 1.84–1.87 (m, 1H), 1.69–1.75 (m, 2H); 1.62–1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=147.2, 139.6, 128.1, 127.8, 122.6, 119.0, 54.1, 26.9, 24.0, 20.8, 15.8; HR-MS (ESI): m/z=206.1542, calcd. for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1539.

2,4-Dimethyl-6-(piperidin-1-yl)phenol (3m): Eluent: petroleum ether/ethyl acetate (20:1); yield: 65%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.80 (s, 1H), 6.75 (s, 1H), 2.77 (t, J=4.8 Hz, 4H), 2.23 (s, 6H), 1.69–1.75 (m, 4H), 1.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=147.2, 139.6, 128.1, 127.8, 122.6, 119.0, 54.1, 26.9, 24.0, 20.8, 15.8; HR-MS (ESI): m/z=206.1540, calcd. for $C_{13}H_{20}NO$ $[M+H]^+$: 206.1539.

4-Methoxy-2-(piperidin-1-yl)phenol (3n): Eluent: petroleum ether/ethyl acetate (10:1); yield: 62%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.85 (d, J=8.8 Hz, 1H), 6.73 (d, J=2.8 Hz, 1H), 6.61 (dd, J=8.8 Hz, 2.8 Hz, 1H), 3.75 (s, 3H), 2.78 (t, J=8.8 Hz, 4H), 1.70–1.74 (m, 4H), 1.58 (d, J=4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.0, 145.4, 140.9, 113.7, 110.1, 108.1, 55.8, 53.9, 26.8, 23.9; HR-MS (ESI): m/z=208.1335, calcd. for $C_{12}H_{18}NO_2$ $[M+H]^+$: 208.1332.

2-Chloro-4-methoxy-6-(piperidin-1-yl)phenol (3o): Eluent: petroleum ether/ethyl acetate (10:1); yield: 46%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.66 (s, 1H), 6.63 (s, 1H), 3.74 (s, 3H), 2.78 (t, J=5.2 Hz, 4H), 1.70–1.75 (m, 4H), 1.56–1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=152.7, 141.9, 118.6, 110.3, 107.1, 55.8, 53.8, 26.6, 23.8; HR-MS (ESI): m/z=242.0938, calcd. for $C_{12}H_{17}ClNO_2$ $[M+H]^+$: 242.0942.

1-Morpholinonaphthalen-2-ol (3p): Eluent: petroleum ether/ethyl acetate (10:1); yield: 87%; white solid; mp 162.0–164.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.11 (br s, 1H), 8.04 (d, J=8.5 Hz, 1H), 7.83 (d, J=8.1 Hz, 1H), 7.70 (d, J=8.8 Hz, 1H), 7.49 (t, J=7.0 Hz, 1H), 7.33 (t, J=7.9 Hz, 1H), 7.27–7.29 (m, 1H), 4.09 (d, J=11.7 Hz, 2H), 3.95 (td, J=11.4 Hz, 2.8 Hz, 2H), 3.85 (td, J=11.0 Hz, 2.0 Hz, 2H), 2.86 (d, J=11.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.6, 131.8, 129.6, 129.5, 128.8, 127.9, 126.2, 122.7, 121.9, 116.1, 68.5, 50.9; HR-MS (ESI): m/z=230.1182, calcd. for $C_{14}H_{16}NO_2$ $[M+H]^+$: 230.1176.

1-(Pyrrolidin-1-yl)naphthalen-2-ol (3q): Eluent: petroleum ether/ethyl acetate (10:1); yield: 76%; white solid; mp 90.0–92.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.85 (d, J=8.2 Hz, 1H), 7.73 (d, J=8.5 Hz, 1H), 7.67 (d, J=8.8 Hz, 1H), 7.46 (d, J=8.0 Hz, 1H), 7.27–7.33 (m, 3H), 3.41 (s, 4H), 2.23 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.3, 130.6, 129.8, 128.1, 126.1, 125.9, 122.4, 121.3, 115.8, 51.7, 26.5; HR-MS (ESI): m/z=214.1232, calcd. for $C_{14}H_{16}NO$ $[M+H]^+$: 214.1226.

***tert*-Butyl 4-(2-hydroxynaphthalen-1-yl)piperazine-1-carboxylate (3r):** Eluent: petroleum ether/ethyl acetate (10:1); yield: 72%; white solid; mp 164.0–166.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.10 (br s, 1H), 7.94 (d, J=8.5 Hz, 1H), 7.82 (d, J=8.1 Hz, 1H), 7.69 (d, J=8.8 Hz, 1H), 7.47 (t, J=7.4 Hz, 7.27–7.34 (m, 2H), 4.25 (s, 2H), 3.75 (t, J=11.0 Hz, 2H), 3.16 (s, 2H), 2.97 (d, J=11.0 Hz, 2H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.8, 151.4, 131.9, 129.5, 129.4, 128.8, 128.2, 126.2, 122.7, 121.9, 116.2, 80.2, 50.7, 28.5; HR-MS (ESI): m/z=329.1865, calcd. for $C_{19}H_{25}N_2O_3$ $[M+H]^+$: 329.1860.

***tert*-Butyl 4-(2-hydroxy-6-methylnaphthalen-1-yl)piperazine-1-carboxylate (3s):** Eluent: petroleum ether/ethyl acetate (10:1); yield: 68%; white solid; mp 144.0–145.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.93 (br s, 1H), 7.84 (d, J=8.7 Hz, 1H), 7.59–7.61 (m, 2H), 7.28–7.31 (m, 1H), 7.24 (d, J=8.8 Hz, 1H), 4.23 (m, 2H), 3.71 (td, J=11.6 Hz, 2.8 Hz, 2H), 3.12 (m, 2H), 2.93 (d, J=11.4 Hz, 2H), 2.48 (s, 3H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.8, 150.7, 132.1, 130.0, 129.8, 128.4, 128.2, 128.0, 121.8, 116.1, 80.1, 50.7, 28.5, 28.4, 21.2; HR-MS (ESI): m/z=343.2022, calcd. for $C_{20}H_{27}N_2O_3$ $[M+H]^+$: 343.2016.

***tert*-Butyl 4-(6-bromo-2-hydroxynaphthalen-1-yl)piperazine-1-carboxylate (3t):** Eluent: petroleum ether/ethyl acetate (10:1); yield: 69%; white solid; mp 149.0–150.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.94–7.97 (m, 2H), 7.80 (d, J=9.1 Hz, 1H), 7.57 (d, J=9.2 Hz, 1H), 7.50 (dd, J=6.8 Hz, 2.6 Hz, 1H), 7.28–7.30 (m, 1H), 4.24 (m, 2H), 3.65 (td, J=11.6 Hz, 2.9 Hz, 2H), 3.14 (m, 2H), 2.93 (d, J=11.4 Hz, 2H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.0, 151.8, 131.3, 129.7, 129.4, 128.5, 127.9, 123.6, 119.2, 117.4, 116.3, 80.6, 50.7, 28.5; HR-MS (ESI): m/z=407.0972, calcd. for $C_{19}H_{24}BrN_2O_3$ $[M+H]^+$: 407.0965.

1-(Diethylamino)naphthalen-2-ol (3u): Eluent: petroleum ether/ethyl acetate (20:1); yield: 83%; light yellow solid; mp 35.0–37.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.15 (br s, 1H), 7.72 (t, J=8.0 Hz, 2H), 7.56 (d, J=8.8 Hz, 1H), 7.33 (t, J=7.4 Hz, 1H), 7.16–7.21 (m, 2H), 3.20–3.36 (m, 4H), 0.93 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.8, 132.0, 129.7, 129.6, 128.2, 125.8, 125.6, 122.4, 121.9, 115.7, 49.3, 14.6; HR-MS (ESI): m/z=216.1388, calcd. for $C_{14}H_{18}NO$ $[M+H]^+$: 216.1383.

1-(Dibutylamino)naphthalen-2-ol (3v): Eluent: petroleum ether/ethyl acetate (20:1); yield: 27%; colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.11 (s, 1H), 7.75 (d, J=8.8 Hz, 1H), 7.72 (d, J=8.4 Hz, 1H), 7.56 (d, J=8.8 Hz, 1H), 7.34 (t, J=8.4 Hz, 1H), 7.20 (t, J=8.4 Hz, 1H), 7.18 (d, J=8.8 Hz, 1H), 3.18–3.21 (m, 4H), 1.35–1.47 (m, 2H), 1.14–1.29 (m, 6H), 0.75–0.79 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.20, 131.71, 129.77, 129.57, 128.09, 127.41,

125.83, 122.42, 122.10, 115.78, 55.82, 31.81, 20.49, 13.96; HR-MS (ESI): m/z = 272.2012, calcd. for $C_{18}H_{26}NO$ $[M+H]^+$: 272.2009.

1-[Butyl(pent-4-en-1-yl)amino]naphthalen-2-ol (3w): Eluent: petroleum ether/ethyl acetate (20:1); yield: 25%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.132 (s, 1H), 7.81 (m, 2H), 7.63 (d, J = 8.8 Hz, 1H), 7.42 (t, J = 6.8 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 5.72 (m, 1H), 4.93 (m, 2H), 3.28 (m, 4H), 2.02 (q, J = 7.2 Hz, 2H), 1.59 (m, 1H), 1.46 (m, 2H), 1.29 (m, 3H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.19, 138.09, 131.66, 129.78, 129.59, 128.18, 127.19, 125.89, 122.46, 122.04, 115.82, 114.87, 55.88, 55.43, 31.77, 31.44, 28.80, 20.48, 13.95; HR-MS (ESI): m/z = 284.2016, calcd. for $C_{19}H_{26}NO$ $[M+H]^+$: 284.2009.

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