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COMMUNICATION

Regioselective synthesis of 2-(2-hydroxyaryl)pyridines from the reactions of benzynes with pyridine *N*-oxides†

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By modifying the conditions from those in Larock's reported synthesis of 3-(2-hydroxyaryl)pyridines from benzynes, and pyridine *N*-oxides, we altered the regioselectivity of the reaction toward an efficient synthesis of 2-substituted pyridines. The presence of ethyl propiolate altered the regioselectivity to afford 3-substituted pyridine products instead. We conducted appropriate control experiments that enable a full understanding of the mechanism.

Introduction

The generation of benzyne intermediates is a powerful tool for the synthesis of 1,2-difunctionalized benzenes.[1] Preparations of benzynes are commonly from *o*-(trimethylsilyl)aryl triflates and fluoride.[2] Benzynes are reactive toward 4π-electron donors through various [4 + 2]-cycloaddition reactions.[3] A more common difunctionalization of benzynes occurs through a sequential treatment with a nucleophile, followed by an electrophile, as depicted in eqn (1).[4,5] 2- and 3-Aryl-substituted pyridines are commonly used in organic light-emitting diode (OLED) materials, including green phosphorous emitters[6] and electron-transport layers.[7] The preparation of these arylpyridines relies mainly on metal-catalyzed coupling reactions.[8] Abramovitch and Shinkai reported[9] that benzynes reacted with pyridine *N*-oxides to give a mixture of 2- and 3-(2-hydroxyphenyl)pyridines, albeit in low yields. Larock developed a regioselective synthesis of 3-(2-hydroxyphenyl)pyridines using CsF in acetonitrile (eqn (2)).[10] As 2-phenylpyridine derivatives (ppy) provide an important ligand in green phosphor emitters such as $Ir(ppy)_3$,[6] a selective synthesis of 2-aryl-substituted pyridines from readily available benzyne precursors is desired. Herein, we report a chemoselectivity toward 2-(2-hydroxyphenyl)pyridines effectively through modified experimental conditions (eqn (3)); the success of this reaction enabled us to explore the behavior of key intermediates.

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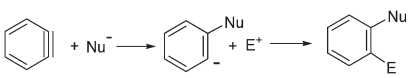
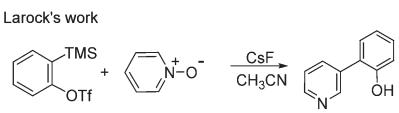
Results and discussion

Eqn (4) was our original target involving a synthesis of benzofuran derivatives through a [2 + 2 + 1]-cycloaddition among benzyne,[2] electron-deficient alkyne and organic oxides (eqn (4)). Treatment of 2-(trimethylsilyl)phenyl triflate **1a** (1.0 equiv.), pyridine *N*-oxide **2a** (1.5 equiv.), ethyl propiolate (1.0 equiv.) and Bu_4NF (1.5 equiv.) in DCM–THF (4 : 1) delivered a 3-phenylpyridine-based enol ether **3a** in 58% yield (eqn (5)). We thought that this enol ether was produced from a Michael-type reaction[11] on initial 3-(2-hydroxyphenyl)pyridine in Larock's reaction (eqn (2)). But a control experiment (eqn (6)) gave an astonishing result that 2-(2-hydroxyphenyl)pyridine **4a** was produced exclusively in the absence of ethyl propiolate; more importantly, compounds **3a** and **4a** have distinct pyridine frameworks. The regioselectivity in Larock's reaction[10] is easily affected by unknown factors.



(1)



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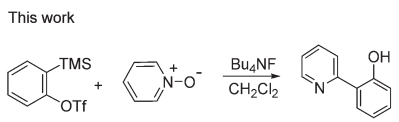

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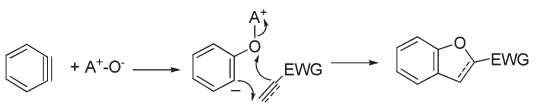

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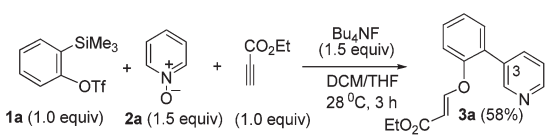
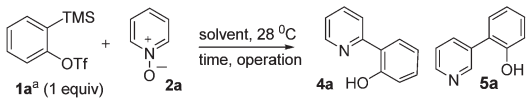


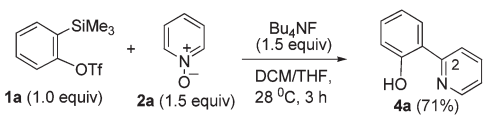
(5)

Table 1 Optimized conditions for production of 2-(2-hydroxyphenyl)pyridines



Entry	*N*-Oxide (equiv.)	Base (equiv.)	Additive	Time (h)	Solvent	Yields[b] (%) 4a	5a
1	1.5	TBAF (1.5)[c]	—	2	DCM	71	—
2	1.5	TBAF (1.5)	—	2	CH_3CN	41	12
3	1.5	TBAF (1.5)	—	2	THF	60	6
4	1.5	TBAF (1.5)	$LiPF_6$ (0.1)	18	DCM	51	13
5	0.5	TBAF (1.8)	—	24	THF	11	69
6	0.5	CsF (2.0)	—	24	CH_3CN	4	79
7	0.5	CsF (6.0)	—	3	CH_3CN	18	23
8	1.5	CsF (2.0)	—	24	CH_3CN	13	54
9	1.5	CsF (6.0)	—	24	CH_3CN	21	53
10	1.5	CsF (12)	—	24	CH_3CN	55	15
11	0.5	TBAF (5.4)	—	2	THF	31	4
12	1.5	TBAF (1.8)	—	3	THF	48	18
13	1.5	TBAF (5.4)	—	2	THF	53	12

[a] [**1a**] = 0.016 M. [b] Product yields are reported after separation from a silica column. [c] TBAF = 1 M solution in THF.



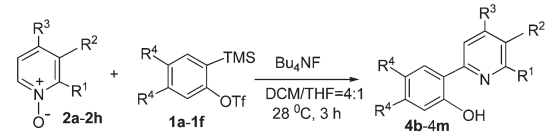
(6)

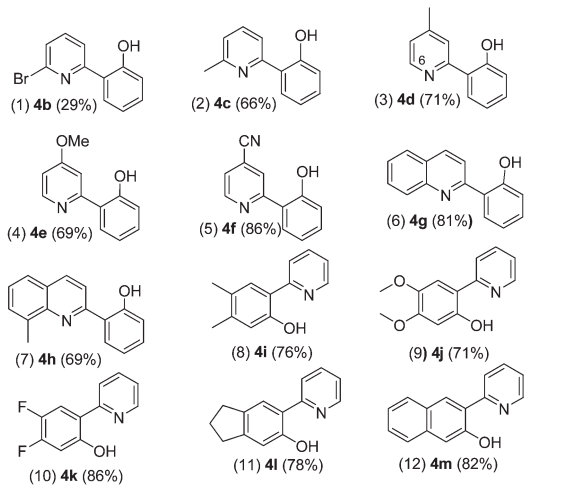
Shown in Table 1 are our efforts to understand the regiochemistry toward 2- and 3-substituted regioisomers **4a** or **5a**. The reactions were conducted according to the same procedure as described by Larock and coworkers.[10] Entry 1 depicts our success (eqn (6)) to obtain 2-substituted pyridine **4a** exclusively using a reagent ratio **1a**/**2a**/TBAF = 1 : 1.5 : 1.5 in dichloromethane/THF = 4 : 1. Entries 2–3 show the solvent effects; we obtained 2-substituted pyridine **4a** (41–60%) as the major species, together with its regioisomer **5a** (6–12%) in CH_3CN and THF. The presence of $LiPF_6$ (10 mol%) additive in dichloromethane gave 3-substituted pyridine **5a** in minor proportion (13%, entry 4). We repeated Larock's conditions using a ratio of benzyne/oxide = 2.0 (entries 5–6); we confirmed their results that 3-substituted isomer **5a** was produced predominantly from both Bu_4NF and CsF. As depicted in entries 1–4, we suspected that an excess proportion of basic *N*-oxide **2a** or fluoride (1.5 equiv.) over benzyne (1.0 equiv.) is crucial for the formation of 2-substituted regioisomer **4a**. We thus altered Larock's condition (entry 6) by steadily increasing the proportion of CsF and *N*-oxide **2a** in CH_3CN whereas benzyne **1a** was kept at 1.0 equiv. The results in entries 7–10 reveal that increasing proportions of oxide **2a** and CsF significantly enhanced 2-substituted isomer **4a**. We also observed similar phenomena in entries 11–13 that excess proportions of either *N*-oxide **2a** or TBAF gave enhanced yields of 2-substituted regioisomer **4a**. Among these parameters, the use of a less polar solvent like dichloromethane is the best choice so that a 1.5 equimolar proportion of pyridine *N*-oxide **2a** and TBAF completely alters the regioselectivity in favor of compound **4a**.

We examined the scope of this regioselective synthesis over various pyridine-based *N*-oxides **2b–2h** and benzyne precursors **1b–1f**; the results are shown in Table 2. Structural assignment of products relies on the NMR data of pyridine, in which the C(2) and C(6) protons have downfield chemical shifts (8.0–9.0 ppm). All these reactions were performed using a molar ratio *N*-oxide/Bu_4NF/benzyne = 1.5 : 1.5 : 1.0 in dichloromethane/THF = 4 : 1 (28 °C, 3 h) except entry 1 for which the reaction was run for 24 h. We obtained 2-(2-hydroxyaryl)pyridines **4b–4m** exclusively. We tested the reactions between 2-substituted pyridine *N*-oxides **2b–c** (R^1 = Br, Me; $R^2 = R^3$ = H) and benzyne precursor **1a**; the corresponding products **4b** and **4c** were obtained in 29% and 66% yields respectively. The reactions were extendable to 4-substituted pyridine oxides (R^3 = Me, OMe, CN; $R^1 = R^2$ = H), giving the desired 2-arylpyridine derivatives **4d–4f** in 69–81% yields. The structures of compounds **4d–4f** are readily assigned according to their ^{1}H NMR spectra showing only one C(6)–H proton resonance in the downfield region (8.0–9.0 ppm). The use of quinoline *N*-oxides **2g–2h** is also compatible with this reaction to give the desired products **4g–4h** in 69–81% yields (entries 6–7). Entries 8–12 show the suitability of this reaction to various benzyne precursors **2b–2f** bearing either electron-donating or withdrawing groups, giving 2-(2-hydroxyaryl) pyridines **4i–4m** in 71–86% yields.

As shown in eqn (5), the presence of ethyl propiolate (10 mol %) completely altered the regioselectivity to give enol ether **3a** exclusively. We tested this behavior on additional electron-deficient alkynes under our conditions (*N*-oxide/Bu_4NF/benzyne = 1.5 : 1.5 : 1); the results are summarized in Table 3. We selected THF as the reaction solvent because it gave a better yield (72%, entry 1) of enol ether **3a** than DCM (53%) and CH_3CN (51%). As shown in entries 2–4, we obtained similar products **3b–c** in 62–76% yields from buty-3-yn-2-one, non-1-yn-3-one, and diethyl acetylenedicarboxylate (entries 2–4). We tested the reaction on reactive alkenes including methyl acrylate

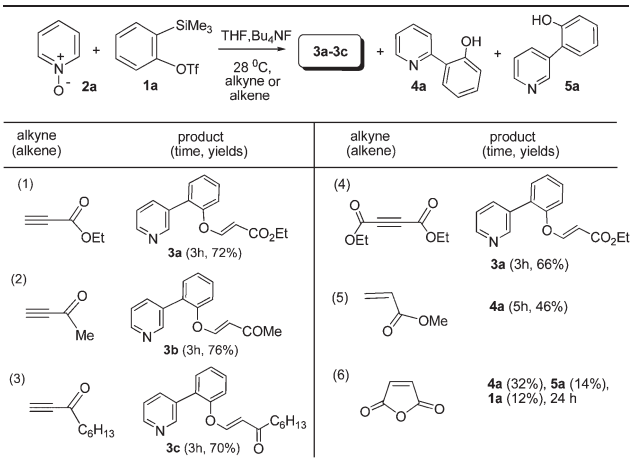
Table 2 Synthesis of 2-(2-hydroxyaryl)pyridines over various benzyne precursors and *N*-oxides[a,b]





[a] [1] = 0.016 M, **1** (1.0 equiv.), **2** (1.5 equiv.), TBAF (1.5 equiv.). [b] Product yields are reported after separation using a silica column.

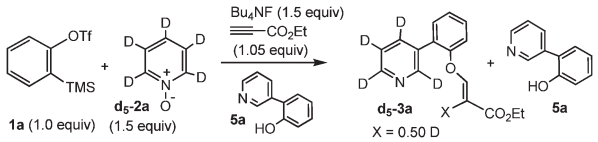
Table 3 An alteration of regioselectivity with electron-deficient alkynes[a,b]



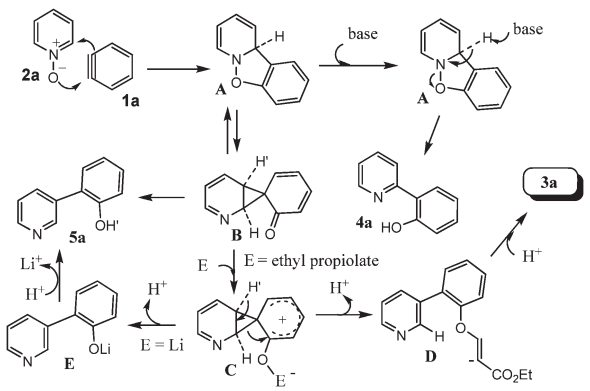
[a] [**1a**] = 0.016 M, **1a** (1 equiv.), **2a** (1.5 equiv.), alkyne or alkene (1 equiv.), Bu_4NF (1.5 equiv.). [b] Product yields are reported after separation using a silica column.

and maleic anhydride (entries 5–6), we obtained no addition products, but 2-or 3-substituted regioisomers **4a–5a**.

Shown in Scheme 1 is a deuterium-labelling experiment involving a reaction between benzyne precursor **1a** (1 equiv.), d_5 pyridine *N*-oxide (**d_5-2a**, 1.5 equiv.), TBAF (1.5 equiv.), ethyl propiolate (1.0 equiv.) and 3-(2-hydroxyphenyl)pyridine **5a** (0.5 equiv.); we found that a deuterated pyridine moiety was included only in enol ether product **d_5-3a** whereas undeuterated



Scheme 1 A deuterium-labeling experiment.



Scheme 2 Reaction routes toward 2- and 3-substituted pyridines.

compound **5a** was recovered exclusively. This observation suggests that compound **d_5-3a** was not produced from ethyl propiolate and undeuterated 3-(2-hydroxyphenyl)pyridine **5a**.

Our results provide new insight into the reaction regioselectivity. Scheme 2 shows a plausible mechanism involving well accepted intermediates **A** and **B**.[9,10] In Larock's condition, bases like pyridine *N*-oxide and fluoride were used in a deficient proportion; the transformation of intermediate **A** into 2-(2-hydroxyphenyl)pyridine **4a** is thereby unlikely to occur because there is no sufficient base to intercept species **A** through a deprotonation reaction. Thus, the regioselectivity proceeded through a rearrangement of intermediate **B** to 3-(2-hydroxyphenyl)pyridine **5a**, *via* a loss of the cyclopropyl C*H*′ proton that is more acidic than the other C–H proton.[10] We used *N*-oxide and fluorides in an excess proportion (1.5 equiv.) in dichloromethane to enable the interception of initial intermediate **A** to give 2-substituted pyridine product **4a** predominantly. This regioselectivity became invalid in the presence of ethyl propiolate or Li^+, which reacts with the carbonyl of species **B** to give cyclohexadienyl cation **C**. In this manner, the CH′ acidity of this cationic intermediate is greatly enhanced by its adjacent cationic character, thus inducing a quick proton dissociation to accelerate the **B** → **5a** (or **3a**) transformation.

Conclusions

Following Larock reporting the synthesis of 3-(2-hydroxyphenyl)pyridines from the reaction of benzynes with pyridine *N*-oxide,[10] we report here an efficient regioselective synthesis of 2-substituted pyridine isomers with *N*-oxides and fluoride in excess proportions in dichloromethane. With suitable experimental results, we postulate that the presence of *N*-oxides accelerates the formation of 2-substituted pyridine products *via* deprotonation of an initial intermediate **A** whereas an electrophile

accelerates the formation of 3-substituted pyridine *via* interception of a cyclopropyl ketone intermediate **B**. The utility of this reaction is highlighted by a widespread application of 2-phenylpyridine ligands in many green phosphor emitters.[6]

Experimental

General methods

Unless otherwise noted, all the reactions for the preparation of the substrates were performed in oven-dried glassware under a nitrogen atmosphere with freshly distilled solvents. The catalytic reactions were performed under a nitrogen atmosphere. Toluene, DCE and methanol were distilled from CaH under nitrogen. Methanol and triethylamine (Et_3N) were stored over 4 Å molecular sieves prior to use. TBAF used was a commercially available 1 M solution in THF. All other commercial reagents were used without further purification, unless otherwise indicated. ^1H NMR and ^{13}C NMR spectra were recorded on Varian 400 MHz, Bruker 400 and 600 MHz spectrometers using $CDCl_3$ as the internal standard.

Synthesis of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (1a). A mixture of 2-bromophenol (1 g, 5.7 mmol) and HMDS (1.21 g, 7.5 mmol) in THF was heated at 85 °C for 2 h. The mixture was dried in vacuum to afford the compound (2-bromophenoxy)trimethylsilane as a yellow oil (1.27 g, 94%). (2-Bromophenoxy)trimethylsilane (2.0 g, 8.6 mmol) was dissolved in THF (20 mL), and the solution was cooled to −80 °C before *n*-BuLi (2.5 M, 3.91 mL, 12.2 mmol) was added. The reaction was maintained at the same temperature for a further 20 min before Tf_2O (1.90 mL, 12.2 mmol) was added dropwise. The reaction was stirred for 30 min at room temperature. The solution was quenched with $NaHCO_3$, and extracted with ethyl acetate (2 × 20 mL). After removal of the solvent *in vacuo*, the crude material was purified by flash column chromatography on silica gel to afford 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **1a** (1.97 g, 81%) as a yellow oil.[2] IR (neat, cm^{-1}): 3078, 1621, 1335; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53–7.50 (m, 1 H), 7.44–7.40 (m, 1 H), 7.34–7.30 (m, 2 H), 0.35 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): 155.1, 136.2, 132.5, 131.2, 127.4, 119.5, 116.9, −0.87; HRMS calcd for $C_{10}H_{13}F_3O_3SSi$: 298.0307; found: 298.0310.

Synthesis of (*E*)-ethyl 3-(2-(pyridin-3-yl)phenoxy)acrylate (3a). A reaction flask was charged with pyridine *N*-oxide **2a** (47.8 mg, 0.5 mmol), followed by THF (2.0 mL) and TBAF (0.5 mL, 0.5 mmol). To this solution was added a mixture of silylaryl triflate **1a** (100 mg, 0.34 mmol) and ethyl propiolate (32 mg, 0.34 mmol) *via* a syringe pump over a period of 1 h; the resulting solution was stirred at 25 °C for 3 h. The reaction mixture was filtered over a short silica bed; the filtrate was concentrated under reduced pressure. The residue was eluted through a silica column to give the desired **3a** (65 mg, 0.24 mmol) in 72% yield. IR (neat, cm^{-1}): 3021, 1726, 1330, 795; ^1H NMR (400 MHz, $CDCl_3$): δ 8.67 (s, 1 H), 8.55 (dd, J = 4.8, 0.8 Hz, 1 H), 7.76–7.74 (m, 1 H), 7.66–7.63 (m, 1 H), 7.41–7.38 (m, 2 H), 7.33–7.26 (m, 2 H), 7.13 (d, J = 8.0 Hz, 1 H), 5.36 (d, J = 12.4 Hz, 1 H), 4.10 (q, J = 7.1 Hz, 2 H), 1.21 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 159.1, 152.5, 149.7, 148.5, 136.4, 132.5, 130.9, 129.8, 129.5, 125.7, 123.0, 119.2, 102.3, 59.9, 14.1; HRMS calcd for $C_{16}H_{15}NO_3$: 269.1052; found: 269.1046.

Synthesis of 2-(2-hydroxyphenyl)pyridine (4a). To a reaction flask were added pyridine *N*-oxide **2a** (47.8 mg, 0.5 mmol), silylaryl triflate **1a** (100 mg, 0.34 mmol), DCM (2 mL) and TBAF (0.5 mL, 0.5 mmol), and this mixture was stirred for 3 h at room temperature. The resulting solution was filtered over a short silica bed, and the filtrate was concentrated under reduced pressure. The residue was eluted through a silica column to give the desired **4a** (41 mg, 0.23 mmol) in 71% yield. IR (neat, cm^{-1}): 3039, 1750, 1338, 788; ^1H NMR (600 MHz, $CDCl_3$): δ 8.52–8.51 (m, 1 H), 7.92 (d, J = 8.2 Hz, 1 H), 7.85–7.84 (m, 1 H), 7.78 (dd, J = 8.0, 1.0 Hz, 1 H), 7.29–7.28 (m, 1 H), 7.26–7.24 (m, 1 H), 7.03 (dd, J = 8.0, 1.0 Hz, 1 H), 6.91–6.89 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 157.6, 145.5, 138.2, 131.7, 126.3, 121.6, 119.5, 118.8, 118.7 (one carbon merged to others); HRMS calcd for $C_{11}H_9NO$: 171.0684; found: 171.0687.

Spectral data for 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethane sulfonate (1b). Yellow oil, IR (neat, cm^{-1}): 3029, 1608, 1350, 1160; ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 (s, 1 H), 7.07 (s, 1 H), 2.26 (s, 3 H), 2.24 (s, 3 H), 0.32 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 140.3, 136.9, 136.0, 129.1, 120.5, 116.9, 19.9, 19.1, −0.76; HRMS calcd for $C_{12}H_{17}F_3O_3SSi$: 326.0620; found: 326.0627.

Spectral data for 4,5-dimethoxy-2-(trimethylsilyl)phenyl trifluoromethane sulfonate (1c). Pale yellow oil; IR (neat, cm^{-1}): 3068, 1610, 1335, 1236; ^1H NMR (400 MHz, $CDCl_3$): δ 6.88 (s, 1 H), 6.83 (s, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 0.33 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 148.2, 147.9, 123.1, 120.1, 116.9, 116.6, 104.2, 56.1, 56.0, −0.7; HRMS calcd for $C_{12}H_{17}F_3O_5SSi$: 358.0518; found: 358.0512.

Spectral data for 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethane sulfonate (1d). Pale yellow solid; IR (neat, cm^{-1}): 3051, 1607, 1319, 1089; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29–7.19 (m, 2 H), 0.33 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6 (dd, J = 252.8, 14.4 Hz), 149.3 (dd, J = 250.5, 11.6 Hz), 130.1, 123.5 (d, J = 17.2 Hz), 120.0, 116.8, 110.4 (d, J = 21.2 Hz), −0.823; HRMS calcd for $C_{10}H_{11}F_5O_3SSi$: 334.0118; found: 334.0113.

Spectral data for 6-(trimethylsilyl)-2,3-dihydro-1*H*-inden-5-yl trifluoromethanesulfonate (1e). Yellow oil; IR (neat, cm^{-1}): 3027, 1611, 1354, 1130; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (s, 1 H), 7.17 (s, 1 H), 2.94–2.87 (m, 4 H), 2.15–2.07 (m, 2 H), 0.34 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 148.3, 143.6, 131.3, 129.4, 115.7, 33.1, 32.1, 25.7, −0.7; HRMS calcd for $C_{13}H_{17}F_3O_3SSi$: 338.0620; found: 338.0625.

Spectral data for 3-(trimethylsilyl)naphthalen-2-yl trifluoromethanesulfonate (1f). Yellow oil; IR (neat, cm^{-1}): 3070, 1601, 1353, 1301; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1 H), 7.86–7.80 (m, 2 H), 7.78 (s, 1 H), 7.56–7.50 (m, 2 H), 0.42 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6, 137.5, 134.1, 131.8, 131.0, 127.9, 127.8, 127.7, 126.9, 120.1, 116.5, −0.75; HRMS calcd for $C_{14}H_{15}F_3O_3SSi$: 348.0463; found: 348.0467.

Spectral data for 2-(6-bromopyridin-2-yl)phenol (4b). Yellow oil; IR (neat, cm^{-1}): 3035, 1743, 1351, 754; ^1H NMR (600 MHz, $CDCl_3$): δ 7.93–7.91 (m, 1 H), 7.86–7.84 (m, 1 H), 7.79–7.77 (m, 1 H), 7.31–7.23 (m, 2 H), 7.03–7.02 (m, 1 H), 6.92–6.88 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 152.8, 139.3, 132.2, 131.2, 130.7, 127.9, 125.7, 119.6, 117.9 (one carbon merged to others); HRMS calcd for $C_{11}H_8BrNO$: 248.9789; found: 248.9795.

Spectral data for 2-(6-methylpyridin-2-yl)phenol (4c). Yellow oil; IR (neat, cm^{-1}): 3035, 1743, 1351, 754; ^1H NMR (600 MHz, $CDCl_3$): δ 7.76 (d, J = 7.8 Hz, 1 H), 7.71–7.70 (m, 1 H), 7.32–7.25 (m, 2 H), 7.08–7.06 (m, 1 H), 6.98 (d, J = 8.0 Hz, 1 H), 6.87 (t, J = 7.6 Hz, 1 H), 2.58 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 160.1, 157.3, 155.0, 138.0, 131.3, 127.4, 126.1, 121.1, 118.6, 116.0, 22.6 (one carbon merged to others); HRMS calcd for $C_{12}H_{11}NO$: 185.0841; found: 185.0845.

Spectral data for 2-(4-methylpyridin-2-yl)phenol (4d). Yellow oil; IR (neat, cm^{-1}): 3035, 1743, 1351, 754; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, J = 5.2 Hz, 1 H), 7.78 (d, J = 8.2 Hz, 1 H), 7.71 (s, 1 H), 7.28 (t, J = 7.8 Hz, 1 H), 7.05 (d, J = 5.2 Hz, 1 H), 7.00 (d, J = 8.2 Hz, 1 H), 6.88 (t, J = 7.8 Hz, 1 H), 2.43 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 157.5, 149.0, 145.4, 131.3, 125.9, 122.6, 119.6, 118.8, 118.6, 118.5, 21.6; HRMS calcd for $C_{12}H_{11}NO$: 185.0841; found: 185.0845.

Spectral data for 2-(4-methoxypyridin-2-yl)phenol (4e). Yellow oil; IR (neat, cm^{-1}): 3035, 1743, 1351, 754; ^1H NMR (600 MHz, $CDCl_3$): δ 8.32 (d, J = 5.9 Hz, 1 H), 7.72 (dd, J = 8.0, 1.4 Hz, 1 H), 7.35 (d, J = 2.4 Hz, 1 H), 7.29–7.26 (m, 1 H), 7.00 (d, J = 8.0 Hz, 1 H), 6.89–6.86 (m, 1 H), 6.77–6.76 (m, 1 H), 3.92 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.9, 160.2, 159.5, 147.2, 131.4, 125.9, 118.8, 118.7, 118.6, 108.3, 104.3, 55.3; HRMS calcd for $C_{12}H_{11}NO_2$: 201.0790; found: 201.0790.

Spectral data for 2-(4-cyanopyridin-2-yl)phenol (4f). Yellow oil; IR (neat, cm^{-1}): 3035, 1743, 1351, 754; ^1H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, J = 5.2 Hz, 1 H), 8.11 (s, 1 H), 7.73 (d, J = 7.8 Hz, 1 H), 7.43 (d, J = 5.2 Hz, 1 H), 7.36 (t, J = 7.8 Hz, 1 H), 7.03 (d, J = 7.8 Hz, 1 H), 6.95 (t, J = 7.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 159.2, 147.2, 132.9, 126.3, 122.3, 121.4, 119.4, 118.9, 117.3, 116.2 (one carbon merged to others); HRMS calcd for $C_{12}H_8N_2O$: 196.0637; found: 196.0631.

Spectral data for 2-(quinolin-2-yl)phenol (4g). Yellow oil; IR (neat, cm^{-1}): 3036, 1756, 1338, 796; ^1H NMR (600 MHz, $CDCl_3$): δ 8.23 (d, J = 8.8 Hz, 1 H), 8.03–7.98 (m, 2 H), 7.90 (dd, J = 8.0, 1.5 Hz, 1 H), 7.79 (d, J = 8.2 Hz, 1 H), 7.72–7.70 (m, 1 H), 7.53–7.50 (m, 1 H), 7.35–7.32 (m, 1 H), 7.10 (d, J = 8.2 Hz, 1 H), 6.94–6.92 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 160.9, 157.8, 144.4, 137.8, 132.1, 130.6, 127.5, 127.2, 127.0, 126.7, 126.5, 118.8, 118.6, 117.4 (one carbon merged to others); HRMS calcd for $C_{15}H_{11}NO$: 221.0841; found: 221.0839.

Spectral data for 2-(8-methylquinolin-2-yl)phenol (4h). Yellow oil; IR (neat, cm^{-1}): 3033, 1750, 1339, 758; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 8.9 Hz, 1 H), 8.04 (d, J = 8.9 Hz, 1 H), 7.96 (dd, J = 8.0, 1.6 Hz, 1 H), 7.66 (d, J = 8.1 Hz, 1 H), 7.60–7.58 (m, 1 H), 7.44 (t, J = 7.3 Hz, 1 H), 7.38–7.34 (m, 1 H), 7.09 (dd, J = 8.2, 1.2 Hz, 1 H), 6.97–6.93 (m, 1 H), 2.78 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 156.8, 143.9, 138.0, 134.9, 131.9, 130.8, 126.8, 126.4, 125.6, 118.9, 118.6, 118.5, 116.8, 18.3 (one carbon merged to others); HRMS calcd for $C_{16}H_{13}NO$: 235.0997; found: 235.0998.

Spectral data for 4,5-dimethyl-2-(pyridin-2-yl)phenol (4i). Yellow oil; IR (neat, cm^{-1}): 3034, 1748, 1336, 789; ^1H NMR (600 MHz, $CDCl_3$): δ 8.46–8.45 (m, 1 H), 7.85 (d, J = 8.2 Hz, 1 H), 7.79–7.76 (m, 1 H), 7.51 (s, 1 H), 7.18–7.16 (m, 1 H), 6.80 (s, 1 H), 2.22 (s, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 158.0, 157.9, 145.8, 140.7, 137.5, 130.6, 126.6, 120.9, 119.6, 118.6, 116.2, 19.9, 19.1; HRMS calcd for $C_{13}H_{13}NO$: 199.0997; found: 199.0994.

Spectral data for 4,5-dimethoxy-2-(pyridin-2-yl)phenol (4j). Yellow oil; IR (neat, cm^{-1}): 3036, 1752, 1339, 786; ^1H NMR (600 MHz, $CDCl_3$): δ 8.45–8.44 (m, 1 H), 7.78–7.77 (m, 1 H), 7.72–7.71 (m, 1 H), 7.24 (s, 1 H), 7.21 (s, 1 H), 6.56 (s, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 157.6, 155.9, 152.4, 145.8, 142.0, 137.6, 128.4, 123.4, 120.4, 118.2, 101.9, 56.9, 55.9 (2 C); HRMS calcd for $C_{13}H_{13}NO_3$: 231.0895; found: 231.0897.

Spectral data for 4,5-difluoro-2-(pyridin-2-yl)phenol (4k). Yellow oil; IR (neat, cm^{-1}): 3035, 1756, 1332, 788; ^1H NMR (600 MHz, $CDCl_3$): δ 8.49–8.48 (m, 1 H), 7.86–7.83 (m, 1 H), 7.73–7.72 (m, 1 H), 7.57–7.54 (m, 1 H), 7.28–7.26 (m, 1 H), 6.80–6.77 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 157.0, 156.9, 156.3, 151.8 (dd, J = 250.6, 14.1), 145.8, 143.7 (dd, J = 235.8, 13.9), 138.1, 121.9, 119.0, 113.7 (d, J = 14.1), 106.9 (d, J = 13.9); HRMS calcd for $C_{11}H_7F_2NO$: 207.0496; found: 207.0491.

Spectral data for 6-(pyridin-2-yl)-2,3-dihydro-1*H*-inden-5-ol (4l). Yellow oil; IR (neat, cm^{-1}): 3035, 1743, 1351, 754; ^1H NMR (600 MHz, $CDCl_3$): δ 8.46–8.44 (m, 1 H), 7.85 (d, J = 8.2 Hz, 1 H), 7.78–7.76 (m, 1 H), 7.62 (s, 1 H), 7.18–7.16 (m, 1 H), 6.88 (s, 1 H), 2.89–2.86 (m, 4 H), 2.09–2.04 (m, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 158.9, 158.3, 148.6, 145.7, 137.5, 134.4, 121.1, 120.8, 118.7, 116.6, 114.1, 33.1, 32.0, 25.7; HRMS calcd for $C_{14}H_{13}NO$: 211.0997; found: 211.0998.

Spectral data for 3-(pyridin-2-yl)naphthalen-2-ol (4m). Yellow oil; IR (neat, cm^{-1}): 3039, 1746, 1355, 752; ^1H NMR (400 MHz, $CDCl_3$): δ 8.42–8.41 (m, 1 H), 8.18 (s, 1 H), 7.97 (d, J = 8.2 Hz, 1 H), 7.75–7.71 (m, 1 H), 7.66 (d, J = 8.2 Hz, 1 H),7.56 (d, J = 8.2 Hz, 1 H), 7.32–7.28 (m, 2 H), 7.18–7.13 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.5, 156.8, 145.9, 137.8, 135.7, 128.3, 127.4, 127.2, 126.8, 125.8, 123.1, 122.0, 121.4, 119.9, 112.0; HRMS calcd for $C_{15}H_{11}NO$: 221.0841; found: 221.0836.

Spectral data for (*E*)-4-(2-(2,6-dimethylpyridin-3-yl)phenoxy)-but-3-en-2-one (3b). Yellow oil; IR (neat, cm^{-1}): 3021, 1726, 1330, 795; ^1H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, J = 2.2 Hz, 1 H), 8.56 (dd, J = 4.8, 1.5 Hz, 1 H), 7.78–7.75 (m, 1 H), 7.58 (d, J = 12.4 Hz, 1 H), 7.36–7.34 (m, 2 H), 7.32–7.24 (m, 2 H), 7.16–7.14 (m, 1 H), 5.73 (d, J = 12.4 Hz, 1 H), 2.13 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 196.9, 159.1, 152.4, 149.5,

148.4, 136.6, 132.6, 131.1, 130.4, 129.9, 126.0, 123.2, 119.2, 111.7, 28.2; HRMS calcd for $C_{15}H_{13}NO_2$: 239.0946; found: 239.0939.

Spectral data for (*E*)-1-(2-(pyridin-3-yl)phenoxy)non-1-en-3-one (3c). Yellow oil; IR (neat, cm^{-1}): 3021, 1726, 1330, 795; ^1H NMR (600 MHz, $CDCl_3$): δ 8.69 (s, 1 H), 8.57 (d, J = 4.3 Hz, 1 H), 7.75 (dd, J = 4.3, 1.7 Hz, 1 H), 7.60 (d, J = 12.3 Hz, 1 H), 7.43–7.40 (m, 2 H), 7.34–7.29 (m, 2 H), 7.15 (d, J = 8.3 Hz, 1 H), 5.76 (d, J = 12.3 Hz, 1 H), 2.37 (t, J = 7.4, 2 H), 1.53 (m, 2 H), 1.28–1.23 (m, 6 H), 0.85 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.8, 158.2, 152.7, 149.7, 148.6, 136.6, 132.7, 131.1, 129.9, 129.5, 125.9, 123.2, 119.1, 110.8, 41.8, 31.5, 28.8, 24.2, 22.4, 14.

Spectral data for (d_5-3a). Yellow oil; IR (neat, cm^{-1}): 3021, 1726, 1330, 795; ^1H NMR (600 MHz, $CDCl_3$): δ 7.62 (d, J = 12.3 Hz, 1 H), 7.38–7.36 (m, 2 H), 7.27–7.25 (m, 1 H), 7.13–7.11 (m, 1 H), 5.34 (d, J = 12.3 Hz, 0.5 H), 4.08 (q, J = 7.1 Hz, 2 H), 1.18 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.7, 159.1, 152.4, 149.3 (t, J = 27.4), 148.1 (t, J = 27.4), 135.9 (t, J = 24.6), 132.2, 130.9, 129.7, 129.4, 125.7, 122.5 (t, J = 24.6), 119.1, 102.3, 59.9, 14.1; HRMS calcd for $C_{16}H_{11}D_4NO_3$: 273.1303; found: 273.1295.

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