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Iron-Catalyzed Regioselective Direct Arylation at the C-3 Position of *N*-Alkyl-2-pyridone

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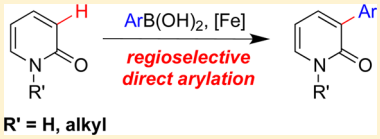
Supporting Information

ABSTRACT: A number of pharmaceutical compounds possess an arylated 2-pyridone moiety. The existing reports using expensive starting materials and/or super-stoichiometric metal salts have prompted us to explore a possible user-friendly method for their synthesis. In this report, we demonstrate an easy-to-handle reaction condition with an iron catalyst for the exclusive generation of C-3-arylated pyridone via C−H functionalization.



INTRODUCTION

Functionalization of a pyridone core has attracted a great deal of attention in recent years primarily because of its presence as a building block in a number of pharmaceutical compounds (Figure 1).[1] A regioselective direct C−H functionalization

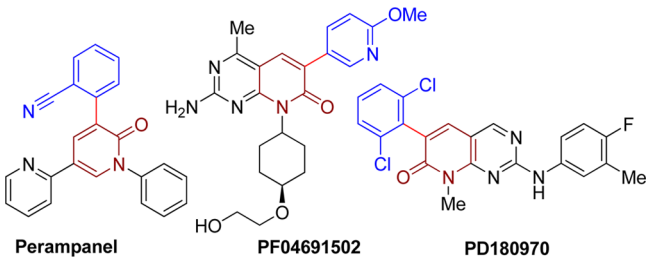


Figure 1. Drug molecules with 3-aryl-2-pyridone motifs.

protocol for the synthesis of pyridine derivatives is preferred over the conventional coupling reaction (e.g., Suzuki coupling) as it avoids the use of a prefunctionalized substrate.[2] Recently, direct olefination and arylation at the electron rich C-5 position of 2-pyridone were achieved through a palladium catalyst.[3,4] The Hiyama group reported direct alkylation and alkenylation at the electrophilic C-6 position of 2-pyridone by using a nickel catalyst in combination with a Lewis acid.[5] Miura and co-workers developed a copper-mediated selective C-6 dehydrogenative heteroarylation protocol for 1-(2-pyridyl)-2-pyridone.[6] Because the C-5 position was blocked, C-3 was alkenylated and arylated with structurally biased substrates.[4,7] Very recently, Zografos and co-workers reported a palladium-catalyzed selective C-3 arylation of N-protected pyridone, but the scope of their method was limited to only the 4-hydoxypyridone moiety.[8] Hirano and Miura reported alternative pathways for C-3 alkylation and arylation of 2-pyridone through homolytic radical aromatic substitution (HAS).[9] Although the alkylation at the C-3 position was achieved with a catalytic amount of nickel,[9a] the C-3 arylation required a superstoichiometric amount of manganese salt with boronic acid as the coupling partner.[9b]

Iron-catalyzed direct arylation of heterocycles and quinones has recently been reported by Komeyama's group using arylboronic acids.[10] We have also independently reported similar arylation reactions involving heterocycles and quinones.[11] Unfortunately, when our reaction condition was applied to *N*-methyl-2-pyridone, only 7% arylated pyridone was obtained. Notably, Wunk has recently reported two examples of Pd-catalyzed C-3-arylated pyridone starting from 3-bromopyridone (Scheme 1).[12] In this work, we demonstrate an easy-to-handle reaction condition for the generation of C-3-arylated pyridine exclusively. A notable feature of our methodology is the use of easily available pyridone precursors in combination with an iron catalyst under mild reaction protocols.

RESULTS AND DISCUSSION

Initial studies with *N*-methyl-2-pyridone and phenylboronic acid in the presence of $Fe(NO_3)_3/K_2S_2O_8$ in a α,α,α-trifluorotoluene (TFT)/H_2O solvent (1:1) at 70 °C led to the formation of only one pyridone-arylated product (isolated yield, 9%).[13]

By NMR and X-ray crystallography (*vide infra*), we confirmed that arylation was occurring exclusively at the C-3 position.[14] These promising initial results had prompted us to explore the reaction with different solvent combinations, iron sources, ligands, additives, and bases.[15] A 40% GC yield (isolated yield, 38%) of the C-3-arylated product (Table 1, entry 6) was obtained with $Fe(NO_3)_3{\cdot}9H_2O/K_2S_2O_8$. The yield of the C-3-arylated product, however, failed to improve further despite our best efforts. Starting materials mostly remained unreacted, and homocoupling of arylboronic acid was obtained as the side product.

The aforementioned optimized reaction protocol was then extended for the reaction of 4-methylphenylboronic acid (Table 2). Various *N*-alkylated pyridones gave the desired arylated product in 44−54% yield (**1**−**3**). By varying the N-protecting group from alkyl to allyl, we obtained the C-3-arylated product

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Scheme 1. Pathways for C-3 Arylation of *N*-Alkyl-2-pyridone

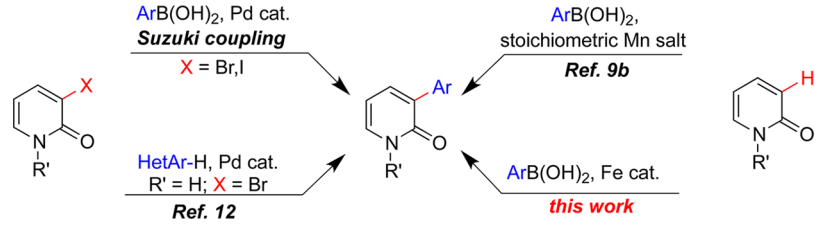
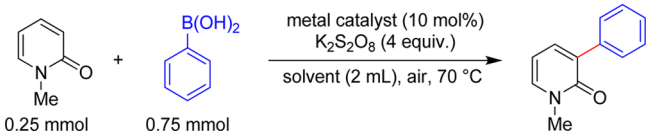


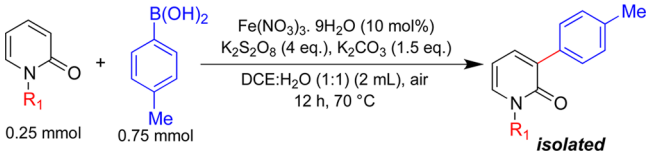
Table 1. C-3 Arylation of *N*-Methyl-2-pyridone



entry	solvent	additive	metal catalyst	time (h)	yield[a] (%)
1	TFT/H_2O (1:1)	TFA	$Fe(NO_3)_3$	24	7
2	TFT/H_2O (1:1)	–	$Fe(NO_3)_3$	24	9
3	DCE/H_2O (1:1)	–	$Fe(NO_3)_3$	24	14
4	DCE/H_2O (1:1)	K_2CO_3	$Fe(NO_3)_3$	24	40
5	DCE/H_2O (1:1)	K_2CO_3	$Fe(NO_3)_3$	24	0[b]
6	DCE/H_2O (1:1)	K_2CO_3	$Fe(NO_3)_3$	12	40
7	DCE/H_2O (1:1)	K_2CO_3	–	12	22
8	DCE/H_2O (1:1)	K_2CO_3	$AgNO_3$	12	0
9	DCE/H_2O (1:1)	K_2CO_3	$Pd(OAc)_2$	12	<1
10	DCE/H_2O (1:1)	K_2CO_3	$Cu(OAc)_2$	12	13
11	DCE/H_2O (1:1)	K_2CO_3	$Ni(acac)_2$	12	20

[a]GC yield. [b]Without $K_2S_2O_8$.

Table 2. C-3 Arylation with Various *N*-Alkyl-2-pyridones



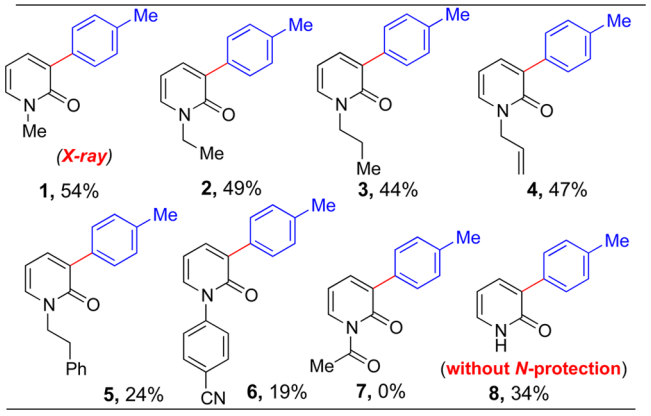
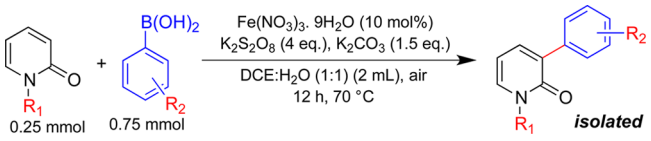
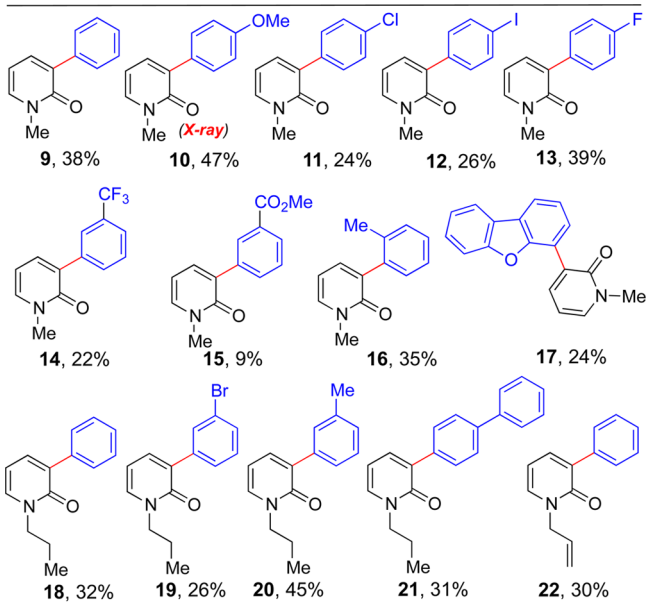


Table 3. C-3 Arylation of *N*-Alkyl-2-pyridones with Arylboronic Acids





4 in 47% yield. In the case of *N*-phenethyl-2-pyridone, the level of C-3 arylation decreased to 24% (**5**), and *N*-(4-cyanophenyl)-2-pyridone failed to increase the level of C-3 arylation (**6**). Although *N*-acyl-2-pyridone did not deliver any C-3 arylation product (**7**), the 2-pyridone moiety (without N-protection) selectively afforded a 34% yield of the C-3-arylated product (**8**).

Subsequently, the scope of the selective C-3 arylation of *N*-alkyl-2-pyridone with different arylboronic acids was investigated (Table 3). Electron rich 4-methoxyarylboronic acid provided the desired C-3-arylated product in 47% yield (**10**). Halo-aryl moieties were introduced at the C-3 position (**11**–**13** and **19**), with the intension of further functionalization. Electron poor boronic acids also afforded arylation exclusively at the C-3 position of pyridone (**13** and **14**). Additionally, sterically constrained *o*-tolylboronic acid gave the arylated pyridone **16**. Interestingly, a dibenzofuran moiety can also be coupled at the C-3 position of pyridone using dibenzofuran-4-boronic acid as a heterocyclic partner (**17**). Electron-withdrawing arylboronic acids encompassing 4-NO_2, 4-COMe, and 4-CO_2Me groups yielded very little C–C coupled product with *N*-methyl-2-pyridone. Nevertheless, 3-(methoxycarbonyl)-phenylboronic acid gave the desired product in 9% yield (**15**).

The applicability of this method with different functionalized *N*-methylpyridone entities was also tested (Table 4). The C-6-substituted (**23**–**25**) and C-5-substituted (**26**–**28**) *N*-methyl-2-pyridones were successfully arylated. Notably, various chloro-substituted pyridones could be employed for C-3 arylation (**24**, **26**, and **28**). Expectedly, methylquinolin-2(1*H*)-one moieties was arylated at the desired C-3 position (**30** and **31**).

Furthermore, a 10 mmol scale reaction under reflux conditions afforded the product in 35% yield (Scheme 2; also see entry 9 of Table 3). Anti-inflammatory agent 1-methyl-3-phenylpiperidin-2-one (**32**) was successfully prepared after

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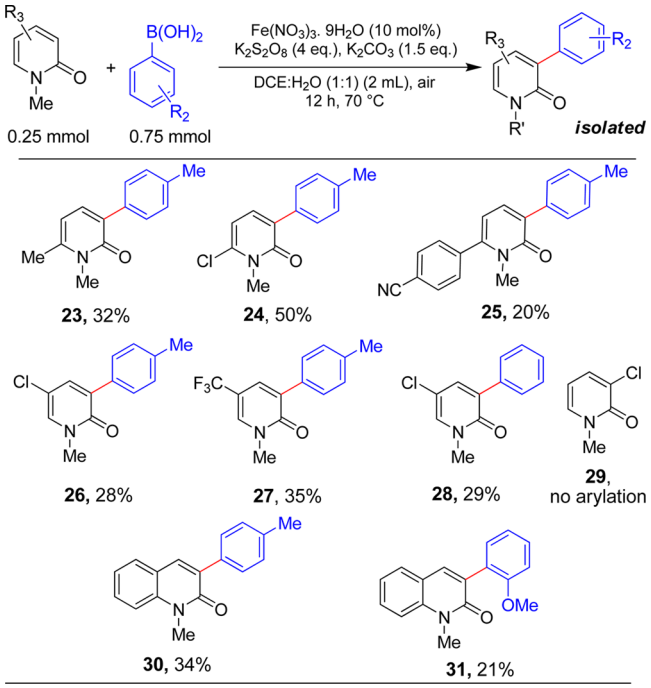
Table 4. C-3 Arylation of Substituted *N*-Methyl-2-pyridones

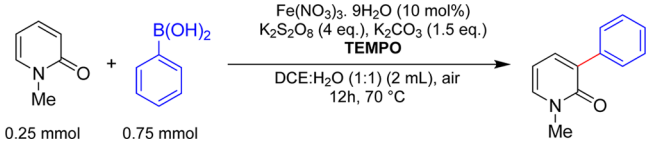


hydrogenation of **9** (Scheme 2).[15] We have also synthesized 3-(2-methoxyphenyl)quinolin-2(1*H*)-one [**33** (Scheme 2)], which can be further utilized as the precursor in generating the pharmaceutically relevant benzofuro[2,3-*b*]quinoline moiety through successive cyclization reactions.[16]

To derive mechanistic insights, we tested the standardized reaction in the presence of TEMPO (2,2,6,6-tetramethylpiperidinyloxy) as the radical scavenger. With a stoichiometric amount of TEMPO, the yield of the desired arylated product was reduced to 5% (Table 5), implying the involvement of a radical intermediate under these reaction conditions. However, when we tested a reaction with Bu_3SnPh in place of arylboronic acid, we failed to detect any arylated pyridone product.

On the basis of the literature reports as well as our experimental observations, it is proposed that $K_2S_2O_8$ thermally[17] or in the presence of iron(II)[10a,18] decomposes to sulfate radical ($SO_4^{-\bullet}$), which reacts with arylbronic acid to give aryl radical.[19] Subsequently, aryl radical reacts selectively at the C-3 position of the 2-pyridone moiety.[9,20] This is likely because the C-3 atom possesses a large coefficient of both HOMO and LUMO, and leading to a resonance-stabilized radical adduct **A**.[9] Iron(III)[21] or sulfate radical accepts one electron from **A**

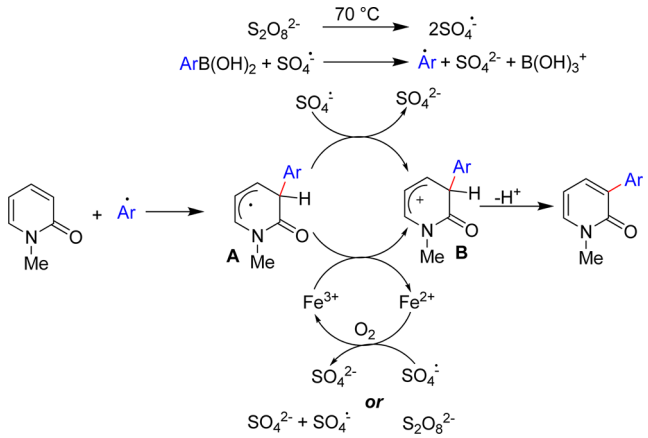
Table 5. Radical Scavenger Experiments



entry	radical scavenger	isolated yield (%)
1	no scavenger	40
2	TEMPO (1 equiv)	5

(Scheme 3) to make cationic species **B**,[10c,21,22] which facilitates the restoration of aromaticity, resulting in the desired C-3-

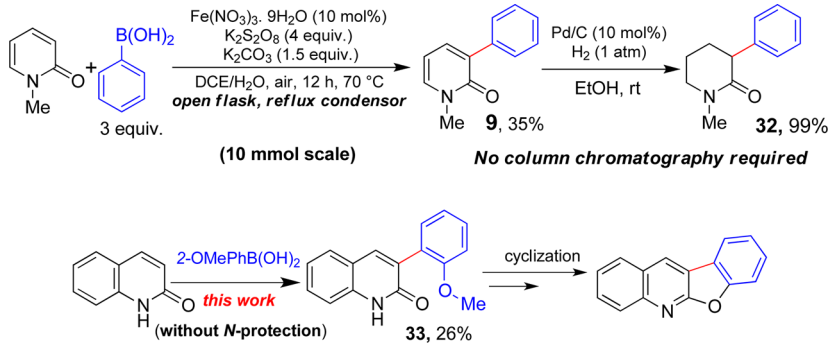
Scheme 3. Proposed Mechanism for C-3 Arylation of 2-Pyridone



arylated N-protected 2-pyridone compound.[9] Under aerobic conditions (or in the presence of sulfate radical/persulfate dianion), Fe(II) is oxidized to Fe(III). Therefore, iron may function both as a Lewis acid[19d] and as an electron transfer site.

The iron-catalyzed method described here is compatible with electron rich arylboronic acid. Such an observation is complementary to the findings of Hirano and Miura's C-3 arylation of N-protected 2-pyridone with superstoichiometric managanese.[9b] The manganese-promoted reaction gave yields with electron poor arylboronic acids (44−58%) better than those of the electron rich analogues (28%). Additionally, this iron-catalyzed protocol can be employed for the unprotected 2-pyridone moiety.

Scheme 2. Large Scale Reaction and Application in Pharmaceutically Relevant Scaffolds



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CONCLUSION

A direct C-3 arylation of the unbiased *N*-alkyl-2-pyridone moiety with an environmentally benign and abundant iron catalyst has been developed. A radical mechanism has been proposed on the basis of preliminary studies. This Fe-catalyzed method is expected to be applicable in synthetic chemistry because of its simplicity and easy-to-handle procedure.

EXPERIMENTAL SECTION

General Procedure A for Iron-Catalyzed Direct Arylation of N-Protected 2-Pyridone with Arylboronic Acid. To a clean oven-dried screw cap reaction tube charged with a magnetic stir bar were added pyridone (0.25 mmol), arylboronic acid (0.75 mmol), $K_2S_2O_8$ (1 mmol, 270 mg), K_2CO_3 (0.375 mmol, 52 mg), and $Fe(NO_3)_3 \cdot 9H_2O$ (0.025 mmol, 10 mg); 1 mL of DCE and 1 mL of H_2O were then added. Then, the reaction tube was placed in a preheated oil bath at 70 °C. The reaction mixture was stirred at that temperature for 12 h. After the reaction mixture had been cooled, a 2 N HCl solution was added dropwise to neutralize the reaction mixture. Then, 5 mL of ethyl acetate was added to the reaction mixture, and an additional 5 mL of ethyl acetate was used for washing the reaction tube. The organic portion was separated with a separating funnel and dried over anhydrous Na_2SO_4. Then, the organic solution was concentrated in a rotary evaporator, and the desired product was purified through neutral aluminum oxide using a petroleum ether/ethyl acetate mixture as the eluent.

*1-Methyl-3-p-tolylpyridin-2(1H)-one (**1**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (8:92, v/v)] to yield **1** (27 mg, 54%) as a crystalline solid: mp 130−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.60 (s, 3H), 6.23 (t, J = 6.8 Hz, 1H), 7.20 (d, J = 7.6 Hz, 2H), 7.28 (dd, J = 6.8, 2.1 Hz, 1H), 7.46 (dd, J = 7.0, 2.1 Hz, 1H), 7.59 (d, J = 7.6 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 21.4, 38.4, 106.1, 128.6, 129.0, 131.7, 134.1, 137.3, 137.4, 137.6, 162.2; HRMS (ESI-QTOF) [M + K]$^+$ calcd for $C_{13}H_{13}KNO$ m/z 238.0629, found m/z 238.0625.

*1-Ethyl-3-p-tolylpyridin-2(1H)-one (**2**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (8:92, v/v)] to yield **2** (26 mg, 49%) as a white solid: mp 81−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J = 7.2 Hz, 3H), 2.36 (s, 3H), 3.04 (q, J = 7.2 Hz, 2H), 6.24 (t, J = 6.8 Hz, 1H), 7.20 (d, J = 6.8 Hz, 2H), 7.27 (dd, J = 6.9, 2.1 Hz, 1H), 7.44 (dd, J = 6.9, 2.1 Hz, 1H), 7.59 (d, J = 6.8 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 14.8, 21.4, 45.6, 106.2, 128.7, 128.9, 131.9, 134.2, 136.1, 137.1, 137.5, 161.4; HRMS (ESI-QTOF) [M + Na]$^+$ calcd for $C_{14}H_{15}NNaO$ m/z 236.1046, found m/z 236.1046.

*1-Propyl-3-p-tolylpyridin-2(1H)-one (**3**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (8:92, v/v)] to yield **3** (25 mg, 44%) as a brown oily liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.4 Hz, 3H), 1.82 (q, J = 7.4 Hz, 2H), 2.36 (s, 3H), 3.87−4.05 (m, 2H), 6.22 (t, J = 6.8 Hz, 1H), 7.20 (d, J = 7.9 Hz, 2H), 7.25 (dd, J = 7.2, 2.6 Hz, 1H), 7.45 (dd, J = 6.9, 2.1 Hz, 1H), 7.59 (d, J = 7.9 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 11.4, 21.4, 22.6, 52.3, 105.9, 128.7, 128.9, 131.9, 134.2, 136.7, 137.1, 137.5, 161.6; HRMS (ESI-QTOF) [M + Na]$^+$ calcd for $C_{15}H_{17}NNaO$ m/z 250.1202, found m/z 250.1203.

*1-Allyl-3-p-tolylpyridin-2(1H)-one (**4**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (8:92, v/v)] to yield **4** (26 mg, 47%) as a brown oily liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 4.63 (dt, J = 5.9, 1.5 Hz, 2H), 5.20−5.32 (m, 2H), 6.00 (m, 1H), 6.26 (t, J = 6.8 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.25 (dd, J = 7.1, 2.1 Hz, 1H), 7.46 (dd, J = 6.9, 2.1 Hz, 1H), 7.59 (d, J = 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 21.4, 51.9,106.2, 118.7, 128.7, 129.0, 132.1, 132.9, 134.1, 136.1, 137.3, 137.7, 161.5; HRMS (ESI-QTOF) [M + K]$^+$ calcd for $C_{15}H_{15}KNO$ m/z 264.0785, found m/z 264.0783.

*1-Phenethyl-3-p-tolylpyridin-2(1H)-one (**5**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (8:92, v/v)] to yield **5** (17 mg, 24%) as an oily liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.10 (t, J = 7.3 Hz, 2H), 4.20 (t, J = 7.2 Hz, 2H), 6.12 (t, J = 6.8 Hz, 1H), 6.97 (dd, J = 6.7, 2.1 Hz, 1H), 7.15−7.35 (m, 7H), 7.45 (dd, J = 7.0, 2.1 Hz, 1H), 7.61 (d, J = 8.0, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 21.4, 35.3, 53.0, 105.8, 126.8, 128.7, 128.8, 129.0, 129.2, 132.0, 134.1, 136.9, 137.4, 137.7, 138.4, 161.6; HRMS (ESI-QTOF) [M + Na]$^+$ calcd for $C_{20}H_{19}NNaO$ m/z 312.1359, found m/z 312.1359.

*4-[2-Oxo-3-p-tolylpyridin-1(2H)-yl]benzonitrile (**6**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (8:92, v/v)] to yield **6** (13 mg, 19%) as a crystalline solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 6.40 (t, J = 6.9 Hz, 1H), 7.18−7.24 (m, 2H), 7.30 (dd, J = 6.9, 2.0 Hz, 1H), 7.47−7.66 (m, 5H), 7.72−7.87 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 21.5, 107.1, 112.5, 118.2, 128.0, 128.7, 129.1, 133.3, 133.3, 133.4, 135.7, 137.9, 138.3, 145.1, 161.3; HRMS (ESI-QTOF) [M + Na]$^+$ calcd for $C_{19}H_{14}N_2NaO$ m/z 309.0998, found m/z 309.1000.

*3-p-Tolylpyridin-2(1H)-one (**8**).* The title compound was purified by column chromatography [silica gel mesh 60−180, ethyl acetate/petroleum ether (50:50, v/v)] to yield **8** (16 mg, 34%) as a brown solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 6.39 (t, J = 6.7 Hz, 1H), 7.23 (d, J = 7.8 Hz, 2H), 7.37 (dd, J = 6.4, 2.0 Hz, 1H), 7.58 (dd, J = 8.5, 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 21.5, 107.9, 128.6, 129.2, 131.7, 133.5, 133.7, 138.0, 139.9, 163.9; HRMS (ESI-QTOF) [M + Na]$^+$ calcd for $C_{12}H_{11}NNaO$ m/z 208.0733, found m/z 208.0732.

*1-Methyl-3-phenylpyridin-2(1H)-one (**9**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (8:92, v/v)] to yield **7** (17 mg, 38%) as a crystalline solid: mp 128−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 6.26 (t, J = 6.8 Hz, 1H), 7.30−7.35 (m, 2H), 7.38−7.43 (m, 2H), 7.49 (dd, J = 7.0, 2.1 Hz, 1H), 7.65−7.75 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 38.4, 106.0, 127.8, 128.3, 128.8, 131.8, 137.0, 137.6, 137.8, 162.1; HRMS (ESI-QTOF) [M + H]$^+$ calcd for $C_{12}H_{11}NO$ m/z 186.0919, found m/z 186.0915.

*3-(4-Methoxyphenyl)-1-methylpyridin-2(1H)-one (**10**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (10:90, v/v)] to yield **8** (25 mg, 47%) as a crystalline solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H), 3.84 (s, 3H), 6.24 (t, J = 6.8 Hz, 1H), 6.90−6.97 (m, 2H), 7.27 (dd, J = 6.6, 2.2 Hz, 1H), 7.45 (dd, J = 7.0, 2.1 Hz, 1H), 7.62−7.72 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 38.7, 55.5, 106.1, 113.7, 129.5, 130.0, 131.4, 136. 9, 137.0, 159.4, 162.3; HRMS (ESI-QTOF) [M + Na]$^+$ calcd for $C_{13}H_{13}NNaO_2$ m/z 238.0838, found m/z 238.0834.

*3-(4-Chlorophenyl)-1-methylpyridin-2(1H)-one (**11**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (12:88, v/v)] to yield **9** (13 mg, 24%) as a white solid: mp 139−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H), 6.25 (t, J = 6.9 Hz, 1H), 7.28−7.40 (m, 3H), 7.47 (dd, J = 7.0, 2.1 Hz, 1H), 7.64 (d, J = 8.4 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 38.5, 106.1, 128.4, 130.1, 130.5, 133.7, 135.4, 137.8, 137.9, 161.9; HRMS (ESI-QTOF) [M + K]$^+$ calcd for $C_{12}H_{10}ClKNO$ m/z 258.0082, found m/z 258.0082.

*3-(4-Iodophenyl)-1-methylpyridin-2(1H)-one (**12**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (12:88, v/v)] to yield **10** (20 mg, 26%) as a yellowish-white solid: mp 144−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (s, 3H), 6.23 (t, J = 6.8 Hz, 1H), 7.31 (dd, J = 6.7, 2.1 Hz, 1H), 7.38−7.50 (m, 3H), 7.70 (d, J = 8.4 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 38.4, 93.6, 106.0, 130. 4, 130.6, 136.4, 137.3, 137.7, 138.0, 161.7; HRMS (ESI-QTOF) [M + Na]$^+$ calcd for $C_{12}H_{10}INNaO$ m/z 333.9699, found m/z 333.9698.

*3-(4-Fluorophenyl)-1-methylpyridin-2(1H)-one (**13**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (14:86, v/v)] to yield **11** (20 mg, 39%) as a brown oily liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H), 6.25 (t, J = 6.8 Hz, 1H), 7.01−7.13 (m, 2H), 7.31 (dd, J = 6.7, 2.1 Hz, 1H), 7.46 (dd, J = 7.0, 2.1 Hz, 1H), 7.63−7.72 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 38.5, 106.1, 115.2 (d, J = 21.4 Hz), 130.5, 130.6, 130.8, 133.0, 137.7, 162.1, 162.6 (d, J = 245 Hz); ^{19}F NMR

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(376 MHz, $CDCl_3$, proton-coupled) δ −114.51 (tt, J = 8.7, 5.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, proton-decoupled) δ −114.51; HRMS (ESI-QTOF) $[M + Na]^+$ calcd for $C_{12}H_{10}FNNaO$ m/z 226.0639, found m/z 226.0635.

*1-Methyl-3-[3-(trifluoromethyl)phenyl]pyridin-2(1H)-one (**14**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (16:84, v/v)] to yield **12** (14 mg, 22%) as a brown oily liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H), 6.29 (t, J = 6.9 Hz, 1H), 7.37 (dd, J = 6.7, 2.1 Hz, 1H), 7.47−7.61 (m, 3H), 7.91 (d, J = 7.7 Hz, 1H), 7.96 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 38.5, 106.1, 123.1, 124.5, 124.6, 125.6, 125.6, 128.7, 130.3, 132.1, 137.7, 138. 3, 138.4, 161. 9; ^{19}F NMR (376 MHz, $CDCl_3$, proton-coupled) δ −62.52 (t, J = 11.3 Hz); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$, proton-decoupled) δ −62.52; HRMS (ESI-QTOF) $[M+K]^+$ calcd for $C_{13}H_{10}F_3KNO$ m/z 292.0346, found m/z 292.0345.

*Methyl 3-(1-Methyl-2-oxo-1,2-dihydropyridin-3-yl)benzoate (**15**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (17:83, v/v)] to yield **15** (5 mg, 9%) as a brown oily liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (t, J = 1.6 Hz, 1H), 8.08−7.89 (m, 2H), 7.55 (dd, J = 7.0, 2.0 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.34 (dd, J = 6.7, 2.0 Hz, 1H), 6.28 (t, J = 6.9 Hz, 1H), 3.92 (s, 3H), 3.62 (d, J = 7.2 Hz, 3H); HRMS (ESI-QTOF) $[M + Na]^+$ calcd for $C_{14}H_{13}NNaO_3$ m/z 266.0788, found m/z 266.0789.

*1-Methyl-3-o-tolylpyridin-2(1H)-one (**16**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (8:92, v/v)] to yield **13** (17 mg, 35%) as a brown oily liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 3.63 (s, 3H), 6.25 (t, J = 6.8 Hz, 1H), 7.14−7.39 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 20.1, 38.3, 105.6, 125.8, 128.0, 130.1, 130.2, 133.6, 137.1, 137.8, 139.1, 161.9; HRMS (ESI-QTOF) $[M + K]^+$ calcd for $C_{13}H_{13}KNO$ m/z 238.0629, found m/z 238.0627.

*3-(Dibenzo[b,d]furan-4-yl)-1-methylpyridin-2(1H)-one (**17**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (10:90, v/v)] to yield **14** (17 mg, 24%) as a white solid: mp 88−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 6.36 (t, J = 6.8 Hz, 1H), 7.34 (td, J = 7.5, 1.0 Hz, 1H), 7.37−7.51 (m, 3H), 7.55 (dt, J = 8.3, 0.8 Hz, 1H), 7.87−8.01 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 38.6, 106.0, 111.9, 120.3, 120.8, 121.4, 122.8, 124. 6, 124.7, 126.8, 127.2, 128.7, 129.6, 138.2, 140. 2, 153.9, 156.1, 161.9; HRMS (ESI-QTOF) $[M + Na]^+$ calcd for $C_{18}H_{13}NNaO_2$ m/z 298.0838, found m/z 298.0835.

*3-Phenyl-1-propylpyridin-2(1H)-one (**18**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (8:92, v/v)] to yield **15** (17 mg, 32%) as an oily liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 7.4 Hz, 3H), 1.75−1.91 (m, 2H), 3.96 (t, J = 8.0 Hz, 2H), 6.24 (t, J = 6.8 Hz, 1H), 7.25−7.34 (m, 2H), 7.36−7.42 (m, 2H), 7.47 (dd, J = 6.9, 2.1 Hz, 1H), 7.63−7.76 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 11.4, 22.6, 52.3, 105. 9, 127.7, 128.2, 128.8, 131.9, 137.0, 137.1, 137.6, 161.5; HRMS (ESI-QTOF) $[M + H]^+$ calcd for $C_{14}H_{15}NO$ m/z 214.1232, found m/z 214.1238.

*3-(3-Bromophenyl)-1-propylpyridin-2(1H)-one (**19**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (12:88, v/v)] to yield **16** (19 mg, 26%) as an oily liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, J = 7.4 Hz, 3H), 1.83 (h, J = 7.4 Hz, 2H), 3.90−4.05 (m, 2H), 6.26 (t, J = 6.9 Hz, 1H), 7.20−7.38 (m, 2H), 7.42−7.52 (m, 2H), 7.64 (ddd, J = 7.8, 1.7, 1.0 Hz, 1H), 7.87 (t, J = 1.8 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 11.4, 22.7, 52.5, 105.9, 122.3, 127.5, 129.7, 130.4, 130.7, 131.7, 137.6, 138.0, 139.1, 161.3; HRMS (ESI-QTOF) $[M + Na]^+$ calcd for $C_{14}H_{14}BrNNaO$ m/z 314.0151, found m/z 314.0151.

*1-Propyl-3-(m-tolyl)pyridin-2(1H)-one (**20**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (8:92, v/v)] to yield **17** (26 mg, 45%) as an oily liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.4 Hz, 3H), 1.82 (q, J = 7.4 Hz, 2H), 2.38 (s, 3H), 3.89−4.02 (m, 2H), 6.23 (t, J = 6.8 Hz, 1H), 7.09−7.19 (m, 1H), 7.22−7.35 (m, 2H), 7.39−7.50 (m, 2H), 7.54 (s 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 11.3, 21.6, 22.6, 52.3, 105.9, 125.8, 128.1, 128.5, 129.5, 132.0, 136.9, 137.0, 137.5, 137.6, 161.5; HRMS (ESI-QTOF) $[M + Na]^+$ calcd for $C_{15}H_{17}NNaO$ m/z 250.1202, found m/z 250.1202.

*3-[(1,1′-Biphenyl)-4-yl]-1-propylpyridin-2(1H)-one (**21**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (8:92, v/v)] to yield **18** (22 mg, 31%) as a white solid: mp 131−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J = 7.4 Hz, 3H), 1.85 (q, J = 7.4 Hz, 2H), 3.90−4.05 (m, 2H), 6.26 (t, J = 6.8 Hz, 1H), 7.29 (dd, J = 6.8, 2.1 Hz, 1H), 7.32−7.38 (m, 1H), 7.40−7.49 (m, 2H), 7.54 (dd, J = 7.0, 2.1 Hz, 1H), 7.58−7.68 (m, 4H), 7.74−7.86 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 11.4, 22.6, 52.4, 105.9, 127.0, 127.3, 127.4, 128.9, 129.2, 131.4, 136.1, 137.0, 137.4, 140.5, 141.1, 161.6; HRMS (ESI-QTOF) $[M + Na]^+$ calcd for $C_{20}H_{19}NNaO$ m/z 312.1359, found m/z 312.1360.

*1-Allyl-3-phenylpyridin-2(1H)-one (**22**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (8:92, v/v)] to yield **19** (16 mg, 30%) as an oily brown liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (dt, J = 5.9 Hz, 2H), 5.21−5.30 (m, 2H), 6.00 (ddt, J = 17.2, 10.3, 5.9 Hz, 1H), 6.27 (t, J = 6.8 Hz, 1H), 7.24−7.36 (m, 2H), 7.36−7.42 (m, 2H), 7.48 (dd, J = 7.0, 2.1 Hz, 1H), 7.63−7.72 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 51.9, 106.2, 118.7, 127.8, 128.2, 128.8, 132.0, 132.7, 136.4, 137.0, 137.7, 161.4; HRMS (ESI-QTOF) $[M + Na]^+$ calcd for $C_{14}H_{13}NNaO$ m/z 234.0889, found m/z 234.0882.

*1,6-Dimethyl-3-p-tolylpyridin-2(1H)-one (**23**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (8:92, v/v)] to yield **20** (17 mg, 32%) as a solid: mp 134−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (d, J = 2.2 Hz, 6H), 3.58 (s, 3H), 6.11 (d, J = 7.1 Hz, 1H), 7.19 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 7.2 Hz, 1H), 7.57 (d, J = 8.2 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 21.3, 21.3, 31.8, 106.6, 128.1, 128.5, 128.9, 134.6, 136.6, 137.1, 145.3, 162.8; HRMS (ESI-QTOF) $[M + K]^+$ calcd for $C_{14}H_{15}KNO$ m/z 252.0785, found m/z 252.0786.

*6-Chloro-1-methyl-3-p-tolylpyridin-2(1H)-one (**24**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (14:86, v/v)] to yield **21** (29 mg, 50%) as a white solid: mp 118−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.75 (s, 3H), 6.39 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 7.9 Hz, 2H), 7.37 (d, J = 7.6 Hz, 1H), 7.54 (d, J = 7.9 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 21.4, 34.0, 106.8, 128.5, 129.1, 129.4, 133.6, 136.4, 136.5, 137.9, 162.3; HRMS (ESI-QTOF) $[M + Na]^+$ calcd for $C_{13}H_{12}ClNNaO$ m/z 256.0500, found m/z 256.0501.

*4-[1-Methyl-6-oxo-5-(p-tolyl)-1,6-dihydropyridin-2-yl]benzonitrile (**25**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (30:70, v/v)] to yield **26** (16 mg, 20%) as a white solid: mp >200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.43 (s, 3H), 6.18 (d, J = 7.2 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.48−7.55 (m, 3H), 7.63 (d, J = 8.1 Hz, 2H), 7.77−7.81 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 21.5, 35.3, 108.3, 113.4, 118.2, 128.7, 129.1, 129.5, 131.1, 132.8, 133.9, 136.1, 138.0, 140.1, 146.7, 162.5; HRMS (ESI-QTOF) $[M + Na]^+$ calcd for $C_{20}H_{16}N_2NaO$ m/z 323.1160, found m/z 323.1161.

*5-Chloro-1-methyl-3-p-tolylpyridin-2(1H)-one (**26**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (14:86, v/v)] to yield **22** (16 mg, 28%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.59 (s, 3H), 7.21 (d, J = 7.6 Hz, 2H), 7.33 (d, J = 2.9 Hz, 1H), 7.43 (d, J = 2.9 Hz, 1H), 7.57 (d, J = 7.6 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 21.5, 38.6, 112.3, 128.6, 129.2, 132.6, 132.9, 134.5, 137.9, 138.5, 160.8; HRMS (ESI-QTOF) $[M + Na]^+$ calcd for $C_{13}H_{12}ClNNaO$ m/z 256.0500, found m/z 256.0497.

*1-Methyl-3-p-tolyl-5-(trifluoromethyl)pyridin-2(1H)-one (**27**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (16:84, v/v)] to yield **23** (23 mg, 35%) as a white solid: mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.64 (s, 3H), 7.17−7.31 (m, 2H), 7.53−7.62 (m, 3H), 7.68 (dq, J = 2.5, 1.3 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 21.5, 38.9, 109.7 (q, J = 34.8 Hz), 123.7 (q, J = 269.7 Hz), 128.6, 129.2, 132.5, 132.8, 136.3, 136.3, 138.7, 161.7; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$, proton-decoupled) δ −62.25; HRMS (ESI-

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QTOF) [M + Na]$^+$ calcd for $C_{14}H_{12}F_3NNaO$ m/z 290.0763, found m/z 290.0761.

*5-Chloro-1-methyl-3-phenylpyridin-2(1H)-one (**28**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (6:94, v/v)] to yield **24** (16 mg, 29%) as a white solid: mp 133−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (s, 3H), 7.34−7.43 (m, 4H), 7.45 (d, J = 2.8 Hz, 1H), 7.61−7.70 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 38.6, 112.3, 128.4, 128.5, 128.8, 132.6, 134.9, 135.7, 138.4, 160.7; HRMS (ESI-QTOF) [M + H]$^+$ calcd for $C_{12}H_{10}ClNO$ m/z 220.0529, found m/z 220.0532.

*1-Methyl-3-(p-tolyl)quinolin-2(1H)-one (**30**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (16:84, v/v)] to yield **27** (21 mg, 34%) as a viscous liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.79 (s, 3H), 7.20−7.29 (m, 3H), 7.35−7.39 (m, 1H), 7.55 (ddd, J = 8.7, 7.2, 1.6 Hz, 1H), 7.58−7.63 (m, 3H), 7.78 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 21.5, 30.1, 114.1, 121.0, 122.3, 128.9, 129.0, 129.0, 130.3, 132.6, 134.1, 136.5, 138.1, 139.7, 161.8; HRMS (ESI-QTOF) [M + Na]$^+$ calcd for $C_{17}H_{15}NNaO$ m/z 272.1046, found m/z 272.1047.

*3-(2-Methoxyphenyl)-1-methylquinolin-2(1H)-one (**31**).* The title compound was purified by column chromatography [neutral alumina, ethyl acetate/petroleum ether (18:82, v/v)] to yield **29** (14 mg, 21%) as a brown oily liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.81 (s, 3H), 6.95−7.07 (m, 2H), 7.24 (td, J = 7.5, 1.0 Hz, 1H), 7.30−7.42 (m, 3H), 7.52−7.60 (m, 2H), 7.73 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 30.2, 56.0, 111.4, 114.2, 120.7, 120.8, 122.2, 126.4, 128.9, 129.7, 130.3, 131.1, 131.2, 138.5, 140.0, 157.5, 161.6; HRMS (ESI-QTOF) [M + Na]$^+$ calcd for $C_{17}H_{15}NNaO_2$ m/z 288.0995, found m/z 288.0992.

*3-(2-Methoxyphenyl)quinolin-2(1H)-one (**33**).* The title compound was purified by column chromatography [silica gel 60−120 mesh, ethyl acetate/petroleum ether (50:50, v/v)] to yield **33** (16 mg, 26%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (s, 3H), 7.03 (dd, J = 8.3, 1.0 Hz, 1H), 7.06 (td, J = 7.5, 1.1 Hz, 1H), 7.19 (ddd, J = 8.1, 7.3, 1.1 Hz, 1H), 7.29−7.33 (m, 1H), 7.40 (ddd, J = 8.3, 7.5, 1.7 Hz, 1H), 7.42−7.47 (m, 2H), 7.56 (dd, J = 7.8, 1.3 Hz, 1H), 7.84 (s, 1H), 11.52 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 56.0, 111.5, 115.8, 120.3, 120.8, 122.6, 125.7, 127.9, 130.2, 131.0, 131.4, 138.3, 140.3, 157.6, 163.0; HRMS (ESI-QTOF) [M + Na]$^+$ calcd for $C_{16}H_{13}NNaO_2$ m/z 274.0838, found m/z 274.0840.

Procedure for the Large Scale Synthesis of 1-Methyl-3-phenylpyridin-2(1*H*)-one (8). In a 250 mL round-bottom flask were placed 10.8 g (40 mmol) of $K_2S_2O_8$, 2.07 g (15 mmol) of K_2CO_3, 3.66 g (30 mmol) of phenylboronic acid, 0.403 g (1 mmol) of $Fe(NO_3)_3\cdot 9H_2O$, and 1.180 g (10 mmol) of *N*-methyl-2-pyridone, then 40 mL of H_2O and 40 mL of DCE were added. The total reaction mixture was set with a reflux condenser on a preheated 70 °C oil bath and stirred for 12 h. After the reaction mixture had cooled, a 2 N HCl solution was dropwise added to neutralize the reaction mixture. Then, 50 mL of ethyl acetate was added to the reaction mixture, and an additional 25 mL of ethyl acetate was used for washing the round-bottom flask. The organic portion was separated with a separating funnel and dried over anhydrous Na_2SO_4. Then, the organic solution was concentrated in a rotary evaporator, and the desired product was purified through neutral alumina using an ethyl acetate/petroleum ether (8:92, v/v) mixture as the eluent. The isolated yield was 0.641 g (34%).

*1-Methyl-3-phenylpiperidin-2-one (**32**).* To a clean oven-dried screw cap reaction tube charged with a magnetic stir bar were added 1-methyl-3-phenyl-2-pyridone (**9**) (0.25 mmol) and palladium in charcoal (10 mol %). Then, the reaction tube was closed tightly. The reaction tube was evacuated and filled with H_2 gas; 2 mL of H_2-purged EtOH was added, and the mixture was stirred at room temperature for 24 h.[23] After 24 h, the reaction mixture was filtered through Celite and washed with 20 mL of EtOAc. The total organic solution was concentrated and afforded 1-methyl-3-phenylpiperidin-2-one (**32**) in 99% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71−1.84 (m, 1H), 1.84−1.99 (m, 1H), 2.08−2.24 (m, 1H), 3.02 (s, 3H), 3.29−3.38 (m, 1H), 3.37−3.50 (m, 1H), 3.59−3.72 (m, 1H), 7.15−7.24 (m, 3H), 7.26−7.33 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 21.0, 30.7, 35.2, 48.7, 50.5, 126.7, 128.4, 128.6, 141.9, 170.9; HRMS (ESI-QTOF) [M + Na]$^+$ calcd for $C_{12}H_{15}NNaO$ m/z 212.1046, found m/z 212.1050.

General Procedure B for the Synthesis of *N*-Alkyl-2-pyridone from the Corresponding 2-Hydroxypyridine.[24] 2-Hydroxypyridine (5 mmol), alkyl iodide (1.5 equiv, 7.5 mmol), and K_2CO_3 (1.5 equiv, 7.5 mmol, 1.035 g) were taken in a 50 mL round-bottom flask. Then, 20 mL of MeOH was added, and the flask was set for overnight reflux in a condenser at 65 °C. After the reaction, the mixture was dried in a rotary evaporator and the residue was diluted with 20 mL of ethyl acetate. The organic part was washed with 10 mL of a brine solution and concentrated in a rotary evaporator. Desired N-protected 2-pyridone was isolated through neutral aluminum oxide using a petrolium ether/ethyl acetate mixture as the eluent.

1-Ethylpyridin-2(1H)-one. The title compound was prepared following general procedure B and purified by column chromatography (neutral alumina, ethyl acetate) to yield a brown oily liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26−1.45 (m, 3H), 3.92−4.10 (m, 2H), 6.18 (t, J = 6.7 Hz, 1H), 6.57 (d, J = 9.1 Hz, 1H), 7.20−7.40 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 14.8, 45.0, 106.3, 121.2, 137.1, 139.5, 162.7; HRMS (ESI-QTOF) [M + Na]$^+$ calcd for C_7H_9NNaO m/z 146.0576, found m/z 146.0577.

1-Propylpyridin-2(1H)-one. The title compound was prepared following general procedure B and purified by column chromatography (neutral alumina, ethyl acetate) to yield a brown oily liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 8 Hz, 3H), 1.81−1.76 (m, 2H), 3.90 (t, J = 6 Hz, 2H), 6.15 (t, J = 6 Hz, 1H), 6.57 (d, J = 7 Hz, 1H), 7.25−7.31 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 11.3, 22.7, 51.6, 106.0, 121.3, 137.8, 139.4, 162.9; HRMS (ESI-QTOF) [M + Na]$^+$ calcd for $C_8H_{11}NNaO$ m/z 160.0733, found m/z 160.0732.

1-Allylpyridin-2(1H)-one. The title compound was prepared following general procedure B and purified by column chromatography (neutral alumina, ethyl acetate) to yield a brown oily liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (dt, J = 5.8, 1.5 Hz, 2H), 5.15 (dq, J = 17.1, 1.5 Hz, 1H), 5.23 (dq, J = 10.3, 1.3 Hz, 1H), 5.93 (ddt, J = 17.1, 10.2, 5.8 Hz, 1H), 6.15 (td, J = 6.7, 1.4 Hz, 1H), 6.56 (ddd, J = 9.2, 1.3, 0.7 Hz, 1H), 7.23 (ddd, J = 6.8, 2.1, 0.7 Hz, 1H), 7.30 (ddd, J = 9.0, 6.6, 2.1 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 51.1, 106.2, 118.5, 121.2, 132.6, 137.2, 139.6, 162.5; HRMS (ESI-QTOF) [M + Na]$^+$ calcd for C_8H_9NNaO m/z 158.0576, found m/z 158.0578.

1-Phenethylpyridin-2(1H)-one. The title compound was prepared following general procedure B and purified by column chromatography (neutral alumina, ethyl acetate) to yield a crystalline solid: mp 106−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06 (t, J = 7.1 Hz, 2H), 4.14 (t, J = 7.1 Hz, 2H), 5.99 (td, J = 6.7, 1.4 Hz, 1H), 6.59 (ddd, J = 9.2, 1.4, 0.7 Hz, 1H), 6.88 (ddd, J = 6.8, 2.1, 0.7 Hz, 1H), 7.10−7.19 (m, 2H), 7.18−7.34 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 35.2, 52.3, 105.7, 121.2, 126.9, 128.8, 129.2, 138.1, 138.2, 139.7, 162.8; HRMS (ESI-QTOF) [M + Na]$^+$ calcd for $C_{13}H_{13}NNaO$ m/z 222.0889, found m/z 222.0889.

4-[2-Oxopyridin-1(2H)-yl]benzonitrile. The title compound was prepared following general procedure B and purified by column chromatography (neutral alumina, ethyl acetate) to yield a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (td, J = 6.8, 1.3 Hz, 1H), 6.67 (ddd, J = 9.4, 1.3, 0.8 Hz, 1H), 7.30 (ddd, J = 6.9, 2.1, 0.8 Hz, 1H), 7.43 (ddd, J = 9.3, 6.6, 2.1 Hz, 1H), 7.52−7.59 (m, 2H), 7.78−7.83 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 106.9, 112.6, 118.1, 122.5, 127.8, 133.5, 136.9, 140.5, 144.6, 162.0; HRMS (ESI-QTOF) [M + H]$^+$ calcd for $C_{12}H_9N_2O$ m/z 197.0709, found m/z 197.0707.

1,6-Dimethylpyridin-2(1H)-one. The title compound was prepared following general procedure B and purified by column chromatography (neutral alumina, ethyl acetate) to yield a yellow oily liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.51 (s, 3H), 5.96−6.09 (m, 1H), 6.43 (ddd, J = 9.1, 1.5, 0.7 Hz, 1H), 7.19 (dd, J = 9.1, 6.8 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 21.1, 31.3, 106.7, 117.4, 138.8, 146.5, 164.1; HRMS (ESI-QTOF) [M + H]$^+$ calcd for $C_7H_{10}NO$ m/z 124.0757, found m/z 124.0755.

6-Chloro-1-methylpyridin-2(1H)-one. The title compound was prepared following general procedure B and purified by column chromatography (neutral alumina, ethyl acetate) to yield a white

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crystalline solid: mp 59−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 3H), 6.32 (dd, J = 7.2, 1.3 Hz, 1H), 6.52 (dd, J = 9.2, 1.2 Hz, 1H), 7.15−7.32 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 33.4, 106.8, 118.4, 138.4, 138.7, 163.5; HRMS (ESI-QTOF) $[M + H]^+$ calcd for C_6H_7ClNO m/z 144.0211, found m/z 144.0210.

5-Chloro-1-methylpyridin-2(1H)-one. The title compound was prepared following general procedure B and purified by column chromatography (neutral alumina, ethyl acetate) to yield a white solid: mp 60−62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50 (s, 3H), 6.52 (dt, J = 9.6, 1.3 Hz, 1H), 7.20−7.44 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 38.0, 112.3, 121.2, 132.9, 142.6, 161.7; HRMS (ESI-QTOF) $[M + H]^+$ calcd for C_6H_7ClNO m/z 144.0211, found m/z 144.0209.

1-Methyl-5-(trifluoromethyl)pyridin-2(1H)-one. The title compound was prepared following general procedure B and purified by column chromatography (neutral alumina, ethyl acetate) to yield a white crystalline solid: mp 78−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 (s, 3H), 6.62 (dt, J = 9.5, 0.8 Hz, 1H), 7.45 (dd, J = 9.6, 2.7 Hz, 1H), 7.69 (dt, J = 3.1, 1.3 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 38.3, 109.7 (q, J = 35 Hz), 123.5 (q, J = 271 Hz), 135.4, 138.1, 162.5; ^{19}F NMR (376 MHz, $CDCl_3$, proton-decoupled) δ −62.34; HRMS (ESI-QTOF) $[M + H]^+$ calcd for $C_7H_7F_3NO$ m/z 178.0474, found m/z 178.0475.

3-Chloro-1-methylpyridin-2(1H)-one. The title compound was prepared following general procedure B and purified by column chromatography (neutral alumina, ethyl acetate) to yield a brown oily liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 6.16 (dd, J = 7.3, 6.8 Hz, 1H), 7.33 (dd, J = 6.8, 1.9 Hz, 1H), 7.54 (dd, J = 7.3, 1.9 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 38.6, 105.3, 126.1, 137.1, 137.8, 159.4; HRMS (ESI-QTOF) $[M + H]^+$ calcd for C_6H_7ClNO m/z 144.0211, found m/z 144.0211.

4-(1-Methyl-6-oxo-1,6-dihydropyridin-2-yl)benzonitrile. The title compound was prepared by C−C coupling of 6-chloro-1-methylpyridin-2(1*H*)-one (1 mmol, 143 mg) and 4-cyanophenylboronic acid (1.5 mmol, 221 mg). The reaction was conducted in a screw cap reaction tube with K_3PO_4 (3 mmol, 690 mg), $Pd(OAc)_2$ (0.03 mmol, 7 mg), X-Phos (0.03 mmol, 7 mg), and THF (3 mL). The reaction was conducted under a N_2 atmosphere at 110 °C for 24 h. After the reaction, the mixture was filtered through Celite. The pure product was isolated by column chromatography (neutral alumina, ethyl acetate) to yield a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (s, 3H), 6.08 (dd, J = 8, 2 Hz), 6.64 (dd, J = 8, 2 Hz, 1H), 7.38−7.34 (m, 1H), 7.48−7.51 (m, 2H), 7.77−7.80 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 34.6, 108.2, 113.6, 118.1, 120.4, 129.5, 132.8, 138.6, 139.9, 148.2, 163.6; HRMS (ESI) calcd for $C_{13}H_{11}N_2O$ m/z 211.0866, found m/z 211.0865.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all compounds and details of the optimization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) Experimental details of the structure determination can be found in the Supporting Information. CCDC-947672 (entry 1) and CCDC-947671 (entry 7) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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