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Synthesis of Functionalized Pyridines via Cu(II)-Catalyzed One-Pot Cascade Reactions of Inactivated Saturated Ketones with Electron-Deficient Enamines

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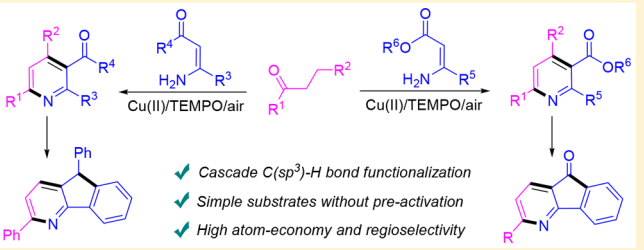
Supporting Information

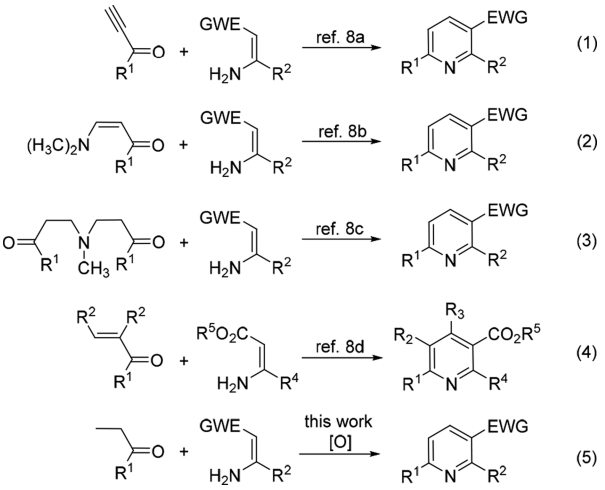
ABSTRACT: In this paper, a novel and efficient synthesis of 3-acylpyridines and pyridine-3-carboxylates through the oxidative one-pot sequential reactions of inactivated saturated ketones with electron-deficient enamines is presented. Mechanistically, the formation of the title compounds involves the in situ formation of an enone intermediate through an oxidative dehydrogenation of the saturated ketone substrate, followed by its [3+3] annulation with β-enaminone or β-enaminoester via a cascade process, including Michael addition, aldol type condensation, and oxidative aromatization.



Pyridine is an essential building block and privileged scaffold embedded in numerous natural products, pharmaceuticals, functional materials, and fine chemicals.[1,2] Many pyridine derivatives are also efficient bases and ligands routinely utilized in chemical catalysis.[3] In particular, pyridines bearing one or more carbonyl unit(s) have been frequently used as versatile substrates in the preparation of fused N-heterocycles and other structurally advanced organic molecules.[4] Unsurprisingly, the tremendous importance of pyridine derivatives has stimulated enormous efforts in developing efficient and practical methods for their preparation.[5,6]

As the unique chimera of "enamine" and "enone", electron-deficient enamines (EDEs) such as β-enaminones and β-enaminoesters not only possess the ambident nucleophilicity of enamines but also have the ambident eletrophilicity of enones. Because of their diverse and rich reactivity, EDEs are valuable substrates in the preparation of various N-heterocycles and functionalized benzenes.[7] Specifically, a number of elegant methods for the preparation of functionalized pyridines by using EDEs as the building blocks have been reported, which mainly include condensation of primary enaminone/esters with alkynone (Scheme 1, eq 1),[8a] reaction of tertiary enaminones with enaminone/esters (Scheme 1, eq 2),[8b] cyclization of the in situ-generated primary enaminones/esters with Mannich bases (Scheme 1, eq 3),[8c] $FeCl_3$-mediated condensation of enaminoesters with enones (Scheme 1, eq 4),[8d] and many others.[8e−i] Despite these advances, the development of more flexible and operationally simple methods for preparing functionalized pyridines starting from readily available and economical substrates remains a challenging task in organic synthesis.

Scheme 1. Various Versions of Pyridine Synthesis from Electron-Deficient Enamines



Meanwhile, the oxidative dehydrogenation of inactivated saturated ketones (IASKs) to give the corresponding enone derivatives is currently of interest because of the cheap price and rich source of IASKs, and the versatile reactivity and diverse utility of the enone products.[9] Moreover, some elegantly designed one-pot cascade procedures combining the oxidative dehydrogenation of IASKs with other kinds of transformations leading to the formation of complex synthetic

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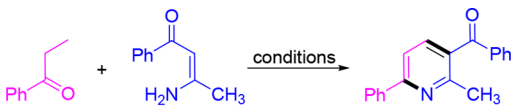
targets have also been realized in previous studies.[10] Inspired by those pioneering contributions and as a continuation of our own interest in this aspect,[11] we have designed an alternative synthesis of diversely functionalized pyridines from simple substrates by taking advantage of the direct C(sp^3)−H bond oxidative functionalization and the rich reactivity of EDEs (Scheme 1, eq 5). Herein, we report the results we obtained in this regard.

Our study was initiated by choosing propiophenone (**1a**) and 3-amino-1-phenylbut-2-en-1-one (**2a**) as model substrates and treating them with $Cu(OAc)_2$, TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl), and bpy (2,2′-bipyridine) in toluene at 120 °C for 20 h. The desired (2-methyl-6-phenylpyridin-3-yl)(phenyl)methanone (**3a**) was obtained in 68% yield (Table 1, entry 1). To improve the efficiency, various solvents,

Table 1. Optimization Studies for the Synthesis of 3a[a]



1a **2a** **3a**

entry	catalyst	oxidant (equiv)	solvent	T (°C)	yield (%)[b]
1	$Cu(OAc)_2$	TEMPO (1)	toluene	120	68
2	$Cu(OAc)_2$	TEMPO (1)	PhCl	120	66
3	$Cu(OAc)_2$	TEMPO (1)	DCE	120	46
4	$Cu(OAc)_2$	TEMPO (1)	CH_3CN	120	43
5	$Cu(OAc)_2$	TEMPO (1)	DMF	120	77
6	$Cu(OAc)_2$	TEMPO (1)	DMSO	120	60
7	$Cu(OTf)_2$	TEMPO (1)	DMF	120	53
8	$CuBr_2$	TEMPO (1)	DMF	120	52
9	$CuCl_2$	TEMPO (1)	DMF	120	43
10	–	TEMPO (1)	DMF	120	–
11	$Cu(OAc)_2$	–	DMF	120	–
12	$Cu(OAc)_2$	TEMPO (2)	DMF	120	78
13	$Cu(OAc)_2$	TEMPO (0.5)	DMF	120	42
14	$Cu(OAc)_2$	TEMPO (0.2)/O_2	DMF	120	18
15	$Cu(OAc)_2$	IBX (1)	DMF	120	8
16	$Cu(OAc)_2$	TBP (1)	DMF	120	7
17	$Cu(OAc)_2$	TBHP (1)	DMF	120	trace
18	$Cu(OAc)_2$	TEMPOH (1)	DMF	120	69
19	$Cu(OAc)_2$	TEMPO (1)	DMF	130	75
20	$Cu(OAc)_2$	TEMPO (1)	DMF	110	66
21[c]	$Cu(OAc)_2$	TEMPO (1)	DMF	120	76
22[d]	$Cu(OAc)_2$	TEMPO (1)	DMF	120	68

[a]Reaction conditions: 0.6 mmol of **1a**, 0.5 mmol of **2a**, 0.05 mmol of catalyst, 0.1 mmol of bpy, oxidant, 2 mL of solvent, air, 20 h. [b]Isolated yield. [c]Period of 24 h. [d]Period of 16 h.

including PhCl, DCE, CH_3CN, DMF, and DMSO, were used (entries 2−6, respectively). Among them, DMF was the most efficient and gave **3a** in 77% yield (entry 5). Then, $Cu(OTf)_2$, $CuBr_2$, and $CuCl_2$ were tried as the catalyst, and they were found to be less efficient than $Cu(OAc)_2$ (entries 7−9, respectively, vs entry 5). Subsequent studies showed that in the absence of either Cu(II) salt or TEMPO, the formation of **3a** was not observed (entry 10 or 11, respectively). Furthermore, increasing the amount of TEMPO from 1 to 2 equiv did not improve the yield of **3a** obviously (entry 12), while reducing this amount to 0.5 equiv resulted in diminished efficiency (entry 13). A combination of a catalytic amount of TEMPO with O_2 gave a low yield of **3a** (entry 14). Moreover, when *o*-iodoxybenzoic acid (IBX), *tert*-butyl peroxide (TBP), *tert*-butyl hydroperoxide (TBHP), or 4-hydroxy-2,2,6,6-tetramethylpiperidinooxy (TEMPOH) was used to replace TEMPO, no improvement in the yield of **3a** was observed (entries 15−18). Running the reaction at a temperature above or below 120 °C did not result in a better yield of **3a** (entry 19 or 20, respectively). Prolonging the reaction period to 24 h gave **3a** in a yield similar to that of 20 h (entry 21). On the other hand, changing the reaction period from 20 to 16 h showed an adverse effect (entry 22).

With the established optimal reaction conditions, the suitability of a range of IASKs (**1**) for this new reaction was studied by using **2a** as a model substrate. It was first observed that several propiophenones reacted smoothly with **2a** to give **3a**−**k** in good to excellent yields. Meanwhile, various functional groups such as methyl, methoxy, fluoro, chloro, bromo, or trifluoromethyl attached on the phenyl ring were well tolerated. Notably, the electronic nature of the phenyl unit did not show any obvious effect on the outcome of this reaction in that substrates bearing electron-withdrawing group(s) and those with electron-donating group(s) afforded the corresponding products in almost equally good efficiencies. Interestingly, 2-propionylthiophene took part in this reaction smoothly to give **3l** in 82% yield. Two aliphatic ketones, 1-cyclohexylpropan-1-one and 2-methylpentan-3-one, were compatible, although the yields of **3m** and **3n** were lower. 3-Phenylpropanal could also react with **2a** to give **3o**. As for the scope of enaminones (**2**), in addition to those derived from 1-phenylbutane-1,3-diones, enaminones (**2**) prepared from 1,3-diphenylpropane-1,3-dione, pentane-2,4-dione, and cyclohexane-1,3-dione could also react with various ketones (**1**) to give **3p**−**t** in moderate to good yields (Table 2).

Accomplishing the efficient synthesis of 3-acylpyridines (**3**) from **1** and **2** encouraged us to extend the scope of EDEs from enaminones (**2**) to enaminoesters (**4**), from which the biologically and synthetically significant pyridine-3-carboxylates[12,13] (**5**) should be obtained. Thus, a mixture of **1a** and ethyl 3-amino-3-phenylacrylate (**4a**) was subjected to the standard reaction conditions used for the preparation of **3** (Table 1, entry 5). To our delight, the desired ethyl 2,6-diphenylnicotinate (**5a**) was formed in 76% yield. Then, the suitability of different IASKs (**1**) was studied by using **4a** as a model substrate. It turned out that propiophenones with various functional groups attached on the phenyl ring, 2-propionylthiophene, 1-cyclohexylpropan-1-one, and 2-methylpentan-3-one, took part in this reaction smoothly to afford **5a**−**g** in moderate to good yields (Table 3). In addition, 3-phenylpropanal worked well to give **5h** in 32% yield. In addition to **4a**, several other enaminoesters (**4**) were also tried using **1a** as a model substrate. It was found that a series of 3-phenyl-substituted enaminoesters bearing a methyl, methoxy, chloro, or fluoro unit on the phenyl ring reacted with **1a** efficiently to give **5i**−**l** in 70−81% yields. Interestingly, the reaction of ethyl 3-amino-3-(thiophen-2-yl)acrylate proceeded smoothly to give **5m** in 61% yield. In addition to 3-arylenaminoesters, 3-alkyl-substituted enaminoesters were found to be suitable partners for this reaction to give **5n**−**p** in moderate yields.

On the basis of the aforementioned observations and previous reports,[7,10] a tentative mechanism accounting for the formation of **3a** is proposed in Scheme 2. First, an oxidative dehydrogenation occurs with **1a** to give enone **A**, which then undergoes a conjugate addition with **2a** to afford adduct **B**.

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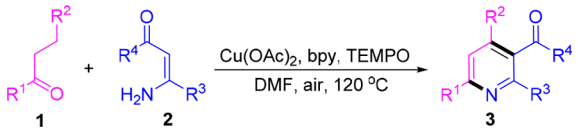
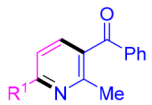
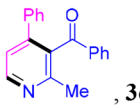
Table 2. Substrate Scope for the Synthesis of 3[a,b]

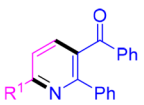




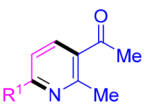
R^1 = Ph, **3a**, 77%
R^1 = (4-Me)Ph, **3b**, 70%
R^1 = (4-MeO)Ph, **3c**, 80%
R^1 = (4-F)Ph, **3d**, 84%
R^1 = (4-Cl)Ph, **3e**, 76%
R^1 = (4-Br)Ph, **3f**, 64%
R^1 = (4-F_3C)Ph, **3g**, 67%
R^1 = (3-MeO)Ph, **3h**, 68%
R^1 = (3-Cl)Ph, **3i**, 77%
R^1 = (3-Br)Ph, **3j**, 68%
R^1 = Benzo[*d*][1,3]dioxol-5-yl, **3k**, 79%
R^1 = thiophen-2-yl, **3l**, 82%
R^1 = cyclohexyl, **3m**, 46%
R^1 = isopropyl, **3n**, 44%



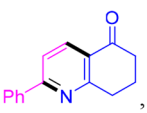
, **3o**, 28%



R^1 = Ph, **3p**, 75%
R^1 = pyridin-3-yl, **3q**, 80%



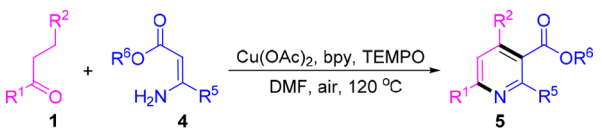
R^1 = Ph, **3r**, 64%
R^1 = (4-F)Ph, **3s**, 69%

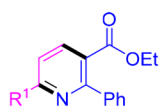


, **3t**, 66%

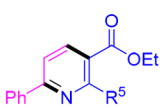
[a]Reaction conditions: 0.6 mmol of **1**, 0.5 mmol of **2**, 0.05 mmol of $Cu(OAc)_2$, 0.1 mmol of bpy, 0.5 mmol of TEMPO, 2 mL of DMF, air, 120 °C, 20 h. [b]Isolated yield.

Table 3. Substrate Scope for the Synthesis of 5[a,b]

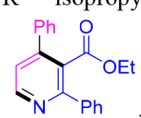




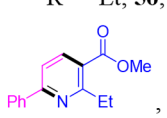
R^1 = Ph, **5a**, 76%
R^1 = (4-Me)Ph, **5b**, 78%
R^1 = (4-F_3C)Ph, **5c**, 73%
R^1 = (3-MeO)Ph, **5d**, 77%
R^1 = thiophen-2-yl, **5e**, 72%
R^1 = cyclohexyl, **5f**, 53%
R^1 = isopropyl, **5g**, 57%



R^5 = (4-Me)Ph, **5i**, 73%
R^5 = (4-MeO)Ph, **5j**, 81%
R^5 = (4-Cl)Ph, **5k**, 72%
R^5 = (4-F)Ph, **5l**, 70%
R^5 = thiophen-2-yl, **5m**, 61%
R^5 = Me, **5n**, 57%
R^5 = Et, **5o**, 55%



, **5h**, 32%



, **5p**, 60%

[a]Reaction conditions: 0.6 mmol of **1**, 0.5 mmol of **4**, 0.05 mmol of $Cu(OAc)_2$, 0.1 mmol of bpy, 0.5 mmol of TEMPO, 2 mL of DMF, air, 120 °C, 20 h. [b]Isolated yield.

Isomerization of **B** affords **B′**. Next, an intramolecular nucleophilic addition occurs with **B′** to afford dihydropyridine **D** via **C**. Finally, an oxidative dehydrogenation of **D** affords **3a** (Scheme 2). Meanwhile, an alternative pathway involving the formation of an imine (**E**) through the condensation between **A** and **2a**, oxidative dehydrogenation of **E** to give **F**, followed by a six-π-electron cyclization of **F** to give **3a** could not be eliminated at this stage.

To verify the reaction mechanism as described in Scheme 2, pre-prepared enone **A** was treated with **2a** under standard conditions to give **3a** in 85% yield (Scheme 3). This result indicated that enone **A** should be a key intermediate in the formation of **3a** from **1a** and **2a**.

Notably, the nucleophilic amino group of **2a** has the potential to be added via an aza-Michael addition onto the in situ-formed enone **A** to give intermediate **M**,[7] from which **3a′**, the regioisomer of **3a**, might be formed through an intramolecular enamine−carbonyl condensation followed by an oxidative aromatization via intermediates **N** and **O** (Scheme 4). In our study, however, the formation of **3a′** was not observed, indicating this reaction is highly regioselective.

In addition, many azafluoren(on)e derivatives are endowed with significant biological and medicinal activities.[14] In spite of their importance, efficient methods for their preparation are still limited.[15] To provide an alternative synthetic approach to 4-azafluoren(on)e derivatives and to showcase the usability of the products obtained, **3p** was first treated with $NaBH_4$ in methanol to give **6**. Treatment of **6** with TfOH led to the formation of **7** (Scheme 5, eq 1). Next, **5a** was treated with polyphosphoric acid (PPA) to give **8a** in an excellent yield of 87% (Scheme 5, eq 2). Similarly, **8b** could be obtained from **5g** in 78% yield. Given the high efficiency and easy-to-obtain substrates, these transformations hold great potential in the synthesis of azafluorene and azafluorenone derivatives.

Finally, to demonstrate the newly developed method for the preparation of functionalized pyridines is suitable for large-scale synthetic missions, the preparation of **3a** was performed on an enlarged scale of 5 mmol. It turned out that the corresponding reaction proceeded smoothly to afford **3a** in 65% yield (Scheme 6).

In summary, we have developed a novel and easy-to-run synthetic approach toward diversely functionalized pyridines through Cu-catalyzed one-pot cascade reactions of inactivated saturated ketones with electron-deficient enamines via inert $C(sp^3)$−H bond functionalization under an air atmosphere. To the best of our knowledge, this should be the first example in which 3-acylpyridines and pyridine-3-carboxylates are directly prepared from inactivated ketones and *β*-enaminone or *β*-enaminoester. With notable features such as a broad substrate scope, simple reaction conditions, excellent regioselectivity, and atom economy, the synthetic protocol developed herein is expected to find wide applications in related areas.

EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, all of the commercial reagents were used without further purification. The solvents were dried prior to use. *β*-Enaminones (**2**) and *β*-enaminoesters (**4**) were prepared on the basis of a literature procedure.[16] Melting points were recorded with a micro melting point apparatus and are uncorrected. The ^1H NMR spectra were recorded at 400 or 600 MHz. The ^{13}C NMR spectra were recorded at 100 or 150 MHz. Chemical shifts are expressed in parts per million (δ) downfield from the internal standard tetramethylsilane and are reported as s (singlet), d (doublet), t (triplet), dd (doublet of doublets), m (multiplet), br s (broad singlet), etc. Coupling constants *J* are given in hertz. High-resolution mass spectra (HRMS) were obtained in ESI mode by using a MicrOTOF mass spectrometer. The conversion of starting materials was

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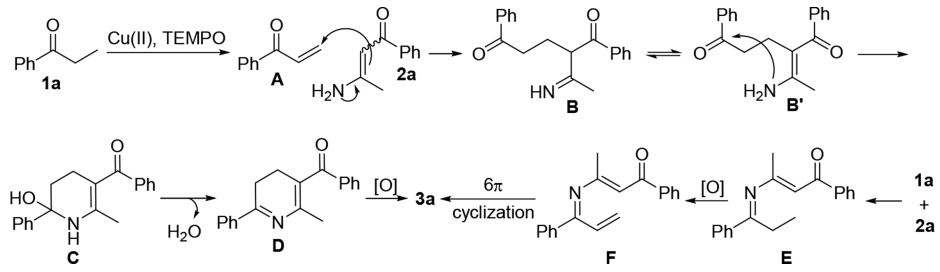
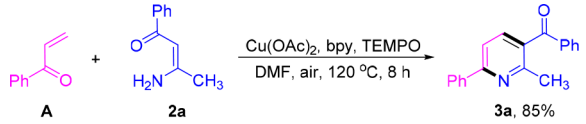
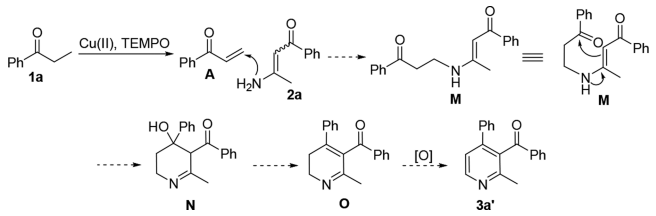
Scheme 2. Plausible Reaction Pathways Accounting for the Formation of 3a



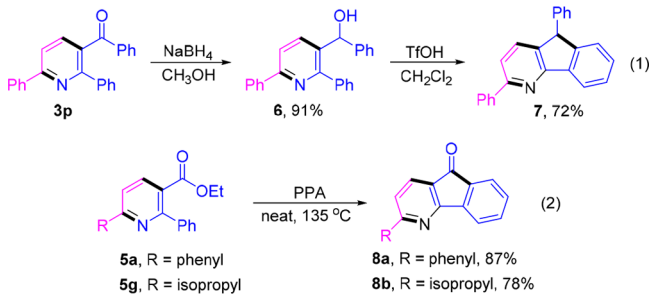
Scheme 3. Control Experiment



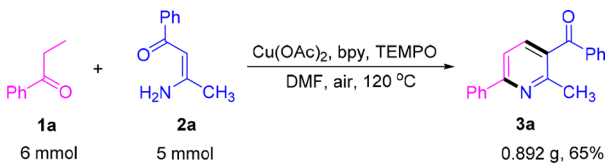
Scheme 4. Theoretically Plausible but Not Observed Formation of 3a′



Scheme 5. Synthesis of 4-Azafluorene and 4-Azafluorenones



Scheme 6. Gram-Scale Synthesis of 3a



monitored by thin layer chromatography (TLC) using silica gel plates (silica gel 60 F254 0.25 mm), and components were visualized by observation under ultraviolet light (254 and 365 nm).

Experimental Procedures. *Typical Procedure for the Synthesis of **3a** and Spectroscopic Data of **3a–t** and **5a–p**.* To a 15 mL reaction tube equipped with a stir bar containing a solution of 3-amino-1-phenylbut-2-en-1-one (**2a**, 80.6 mg, 0.5 mmol) in DMF (2 mL) were added propiophenone (**1a**, 80 μL, 0.6 mmol), $Cu(OAc)_2$ (9.1 mg, 0.05 mmol), 2,2′-bipyridine (15.6 mg, 0.1 mmol), and TEMPO (78.1 mg, 0.5 mmol). The tube was then sealed, and the mixture was stirred at 120 °C under an air atmosphere for 20 h. After the mixture had been cooled to room temperature, the reaction was quenched with water, and the mixture was extracted with ethyl acetate (3 × 8 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with a petroleum ether/ethyl acetate (20:1) eluent to give **3a**. **3b–t** and **5a–p** were obtained in a similar manner.

*(2-Methyl-6-phenylpyridin-3-yl)(phenyl)methanone (**3a**).* Eluent: petroleum ether/ethyl acetate (20:1); white solid (105 mg, 77%); mp 70–71 °C (lit.[8c] 73–74 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (s, 3H), 7.42–7.50 (m, 5H), 7.59–7.64 (m, 2H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 2H), 8.07 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 117.0, 127.3, 128.8, 128.9, 129.6, 130.1, 132.1, 133.6, 137.5, 138.8, 157.1, 158.2, 197.3; MS *m*/*z* 274 $[M + H]^+$.

*[2-Methyl-6-(p-tolyl)pyridin-3-yl](phenyl)methanone (**3b**).* Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (101 mg, 70%); mp 80–81 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.62 (s, 3H), 7.27 (d, *J* = 7.2 Hz, 2H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.58 (d, *J* = 7.2 Hz, 2H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 2H), 7.97 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4, 24.0, 116.6, 127.2, 128.8, 129.7, 130.1, 131.7, 133.6, 136.0, 137.5, 137.6, 139.7, 157.1, 158.2, 197.3; HRMS calcd for $C_{20}H_{18}NO$ 288.1383 $[M + H]^+$, found 288.1388.

*[6-(4-Methoxyphenyl)-2-methylpyridin-3-yl](phenyl)methanone (**3c**).* Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (121 mg, 80%); mp 81–82 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.62 (s, 3H), 3.85 (s, 3H), 7.00 (d, *J* = 7.8 Hz, 2H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 7.2 Hz, 2H), 8.04 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.9, 55.4, 114.2, 116.0, 128.6, 128.7, 130.0, 131.2, 131.3, 133.4, 137.5, 137.6, 157.1, 157.8, 161.0, 197.3; HRMS calcd for $C_{20}H_{18}NO_2$ 304.1332 $[M + H]^+$, found 304.1334.

*[6-(4-Fluorophenyl)-2-methylpyridin-3-yl](phenyl)methanone (**3d**).* Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (122 mg, 84%); mp 77–78 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.62 (s, 3H), 7.15 (t, *J* = 7.8 Hz, 2H), 7.47 (t, *J* = 7.2 Hz, 2H), 7.56–7.61 (m, 2H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.81 (d, *J* = 7.2 Hz, 2H), 8.06 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.9, 115.8 ($^2J_{C-F}$ = 21.9 Hz), 116.6, 128.8, 129.2 ($^3J_{C-F}$ = 8.7 Hz), 130.0, 132.0, 133.6, 134.9 ($^4J_{C-F}$ = 2.3 Hz), 137.4, 137.5, 157.0, 157.1, 163.9 ($^1J_{C-F}$ = 248.3 Hz), 197.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.09; HRMS calcd for $C_{19}H_{15}FNO$ 292.1132 $[M + H]^+$, found 292.1128.

*[6-(4-Chlorophenyl)-2-methylpyridin-3-yl](phenyl)methanone (**3e**).* Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (117 mg, 76%); mp 105–106 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.61 (s, 3H), 7.43–7.49 (m, 4H), 7.58–7.61 (m, 2H), 7.70 (d, *J* = 6.6 Hz, 1H), 7.81 (d, *J* = 7.2 Hz, 2H), 8.01 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.9, 116.8, 128.6, 128.9, 129.1, 130.1, 132.3, 133.7, 135.8, 137.1, 137.4, 137.5, 156.8, 157.2, 197.0; HRMS calcd for $C_{19}H_{15}ClNO$ 308.0837 $[M + H]^+$, found 308.0833.

*[6-(4-Bromophenyl)-2-methylpyridin-3-yl](phenyl)methanone (**3f**).* Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (112 mg, 64%); mp 115–116 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.61 (s, 3H), 7.48 (t, *J* = 7.2 Hz, 2H), 7.60–7.61 (m, 4H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 7.2 Hz, 2H), 7.95 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.9, 116.7, 124.2, 128.8, 128.9, 130.1, 132.1, 132.4, 133.7, 137.3, 137.5, 137.6, 156.8, 157.2, 197.0; HRMS calcd for $C_{19}H_{15}BrNO$ 352.0332 $[M + H]^+$, found 352.0359.

*{2-Methyl-6-[4-(trifluoromethyl)phenyl]pyridin-3-yl}(phenyl)-methanone (**3g**).* Eluent: petroleum ether/ethyl acetate (20:1);

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yellow solid (114 mg, 67%); mp 72−73 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.63 (s, 3H), 7.49 (t, J = 7.2 Hz, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.73−7.74 (m, 3H), 7.83 (d, J = 7.2 Hz, 2H), 8.18 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 117.4, 124.2 ($^1J_{C-F}$ = 270.8 Hz), 125.9 ($^3J_{C-F}$ = 3.5 Hz), 127.6, 128.9, 130.1, 131.3 ($^2J_{C-F}$ = 32.0 Hz), 133.0, 133.9, 137.2, 137.5, 142.1, 156.4, 157.3, 196.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.63; HRMS calcd for $C_{20}H_{15}F_3NO$ 342.1100 $[M + H]^+$, found 342.1094.

[6-(3-Methoxyphenyl)-2-methylpyridin-3-yl](phenyl)methanone (**3h**). Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (103 mg, 68%); mp 89−90 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.53 (s, 3H), 3.79 (s, 3H), 6.89 (d, J = 7.8 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 7.38 (t, J = 7.2 Hz, 2H), 7.51 (t, J = 7.8 Hz, 3H), 7.57−7.60 (m, 2H), 7.72 (d, J = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.8, 55.4, 112.6, 115.4, 117.1, 119.6, 128.7, 129.9, 130.0, 132.2, 133.6, 137.36, 137.39, 140.2, 157.0, 157.9, 160.2, 197.2; HRMS calcd for $C_{20}H_{18}NO_2$ 304.1322 $[M + H]^+$, found 304.1332.

[6-(3-Chlorophenyl)-2-methylpyridin-3-yl](phenyl)methanone (**3i**). Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (118 mg, 77%); mp 78−79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 3H), 7.39−7.40 (m, 2H), 7.48 (t, J = 7.6 Hz, 2H), 7.61 (t, J = 8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 7.6 Hz, 2H), 7.92 (s, 1H), 8.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 117.0, 125.3, 127.4, 128.8, 129.5, 130.05, 130.14, 132.6, 133.7, 135.0, 137.3, 137.5, 140.5, 156.5, 157.2, 197.0; HRMS calcd for $C_{19}H_{15}ClNO$ 308.0837 $[M + H]^+$, found 308.0847.

[6-(3-Bromophenyl)-2-methylpyridin-3-yl](phenyl)methanone (**3j**). Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (119 mg, 68%); mp 67−68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 3H), 7.35 (t, J = 8.0 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.56 (d, J = 8.0 Hz, 1H), 7.59−7.64 (m, 2H), 7.71 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 7.6 Hz, 2H), 7.97 (d, J = 8.0 Hz, 1H), 8.25 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.8, 117.0, 123.2, 125.7, 128.8, 130.0, 130.3, 130.4, 132.4, 132.6, 133.7, 137.2, 137.4, 140.7, 156.4, 157.1, 197.0; HRMS calcd for $C_{19}H_{15}BrNO$ 352.0332 $[M + H]^+$, found 352.0345.

[6-(Benzo[d][1,3]dioxol-5-yl)-2-methylpyridin-3-yl](phenyl)-methanone (**3k**). Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (125 mg, 79%); mp 136−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (s, 3H), 6.02 (s, 2H), 6.91 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.52 (d, J = 8.0 Hz, 1H), 7.57−7.63 (m, 3H), 7.67 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 101.4, 107.6, 108.5, 116.2, 121.5, 128.7, 130.0, 131.5, 133.1, 133.5, 137.5, 148.4, 149.0, 157.0, 157.5, 197.2; HRMS calcd for $C_{20}H_{16}NO_3$ 318.1125 $[M + H]^+$, found 318.1132.

[2-Methyl-6-(thiophen-2-yl)pyridin-3-yl](phenyl)methanone (**3l**). Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (114 mg, 82%); mp 57−58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (s, 3H), 7.11 (t, J = 4.4 Hz, 1H), 7.41−7.52 (m, 4H), 7.57−7.64 (m, 3H), 7.78 (d, J = 7.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.7, 115.1, 125.7, 128.3, 128.71, 128.73, 130.0, 131.6, 133.5, 137.48, 137.52, 144.3, 153.2, 157.4, 196.8; HRMS calcd for $C_{17}H_{14}NOS$ 280.0791 $[M + H]^+$, found 280.0793.

(6-Cyclohexyl-2-methylpyridin-3-yl)(phenyl)methanone (**3m**). Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (64 mg, 46%); mp 50−51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27−1.35 (m, 1H), 1.39−1.57 (m, 4H), 1.77 (d, J = 12.8 Hz, 1H), 1.87 (d, J = 12.4 Hz, 2H), 2.00 (d, J = 12.4 Hz, 2H), 2.54 (s, 3H), 2.72−2.79 (m, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.56−7.61 (m, 2H), 7.79 (d, J = 7.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.6, 26.0, 26.5, 32.9, 46.7, 117.0, 128.6, 130.0, 131.2, 133.4, 137.0, 137.5, 156.1, 168.0, 197.4; HRMS calcd for $C_{19}H_{22}NO$ 280.1696 $[M + H]^+$, found 280.1696.

(6-Isopropyl-2-methylpyridin-3-yl)(phenyl)methanone (**3n**). Eluent: petroleum ether/ethyl acetate (20:1); yellow liquid (53 mg, 44%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, J = 6.8 Hz, 6H), 2.54 (s, 3H), 3.07−3.14 (m, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.57−7.62 (m, 2H), 7.79 (d, J = 7.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.5, 23.6, 36.6, 116.7, 128.6, 130.0, 131.2, 133.4, 137.0, 137.5, 156.2, 168.9, 197.4; HRMS calcd for $C_{16}H_{18}NO$ 240.1383 $[M + H]^+$, found 240.1389.

(2-Methyl-4-phenylpyridin-3-yl)(phenyl)methanone (**3o**). Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (38 mg, 28%); mp 112−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 7.21−7.26 (m, 6H), 7.30 (t, J = 7.6 Hz, 2H), 7.45 (t, J = 7.6 Hz, 1H), 7.60 (d, J = 8.0 Hz, 2H), 8.65 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 121.7, 128.46, 128.48, 128.58, 128.64, 129.3, 133.6, 133.7, 136.9, 137.8, 147.8, 149.5, 155.2, 198.1; HRMS calcd for $C_{19}H_{16}NO$ 274.1226 $[M + H]^+$, found 274.1244.

(2,6-Diphenylpyridin-3-yl)(phenyl)methanone (**3p**). Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (126 mg, 75%); mp 102−103 °C (lit.[6c] 101.4−103.1 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16−7.24 (m, 5H), 7.35−7.40 (m, 1H), 7.41−7.48 (m, 3H), 7.62 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 2H), 7.66−7.68 (m, 2H), 7.77 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 8.16−8.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.8, 127.3, 128.25, 128.33, 128.9, 129.5, 129.7, 129.9, 132.6, 133.2, 136.9, 138.3, 138.5, 139.5, 157.3, 158.1, 197.5; MS m/z 336 $[M + H]^+$.

Phenyl(6-phenyl-[2,3′-bipyridin]-5-yl)methanone (**3q**). Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (134 mg, 80%); mp 119−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.28 (m, 3H), 7.31 (t, J = 8.0 Hz, 2H), 7.43−7.46 (m, 2H), 7.61−7.63 (m, 2H), 7.69−7.71 (m, 2H), 7.86 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 8.51 (dt, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 8.70 (dd, J_1 = 4.4 Hz, J_2 = 1.2 Hz, 1H), 9.37 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 118.0, 123.7, 128.37, 128.45, 129.1, 129.4, 129.9, 133.3, 133.5, 134.0, 134.7, 136.6, 138.5, 139.1, 148.6, 150.5, 155.5, 157.6, 197.2; HRMS calcd for $C_{23}H_{17}N_2O$ 337.1335 $[M + H]^+$, found 337.1336.

1-(2-Methyl-6-phenylpyridin-3-yl)ethanone (**3r**). Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (67 mg, 64%); mp 87−88 °C (lit.[6c] 90.3−91.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (s, 3H), 2.84 (s, 3H), 7.43−7.49 (m, 3H), 7.62 (d, J = 8.0 Hz, 1H), 8.01−8.06 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 29.3, 117.3, 127.3, 128.9, 129.8, 130.6, 138.1, 138.4, 158.61, 158.63, 200.0; MS m/z 212 $[M + H]^+$.

1-[6-(4-Fluorophenyl)-2-methylpyridin-3-yl]ethanone (**3s**). Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (79 mg, 69%); mp 69−70 °C (lit.[6c] 71.3−72.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 3H), 2.77 (s, 3H), 7.09 (t, J = 8.4 Hz, 2H), 7.52 (d, J = 8.0 Hz, 1H), 7.96−8.01 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 29.3, 115.8 ($^2J_{C-F}$ = 21.9 Hz), 116.8, 129.2 ($^3J_{C-F}$ = 8.7 Hz), 130.6, 134.5 ($^4J_{C-F}$ = 3.6 Hz), 138.1, 157.5, 158.6, 164.0 ($^1J_{C-F}$ = 248.0 Hz), 199.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.68; MS m/z 230 $[M + H]^+$.

2-Phenyl-7,8-dihydroquinolin-5(6H)-one (**3t**). Eluent: petroleum ether/ethyl acetate (20:1); white solid (74 mg, 66%); mp 126−127 °C (lit.[6a] 128.5−130 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18−2.25 (m, 2H), 2.71 (t, J = 7.2 Hz, 2H), 3.21 (t, J = 6.4 Hz, 2H), 7.43−7.51 (m, 3H), 7.69 (d, J = 8.4 Hz, 1H), 8.04−8.06 (m, 2H), 8.31 (d, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 32.9, 38.6, 118.9, 126.6, 127.5, 128.9, 130.0, 135.8, 138.5, 160.8, 163.8, 197.9; MS m/z 224 $[M + H]^+$.

Ethyl 2,6-Diphenylnicotinate (**5a**).[6b] Eluent: petroleum ether/ethyl acetate (20:1); colorless oil (115 mg, 76%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.05 (t, J = 7.2 Hz, 3H), 4.16 (q, J = 7.2 Hz, 2H), 7.41−7.46 (m, 6H), 7.64 (d, J = 6.6 Hz, 2H), 7.72 (d, J = 7.8 Hz, 2H), 8.10−8.15 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.7, 61.4, 117.9, 125.4, 127.4, 128.1, 128.7, 128.85, 128.94, 129.8, 138.4, 139.0, 140.7, 158.5, 158.8, 168.3; MS m/z 304 $[M + H]^+$.

Ethyl 2-Phenyl-6-(p-tolyl)nicotinate (**5b**). Eluent: petroleum ether/ethyl acetate (20:1); white solid (124 mg, 78%); mp 63−64 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.05 (t, J = 7.2 Hz, 3H), 2.38 (s, 3H), 4.15 (q, J = 7.2 Hz, 2H), 7.25 (d, J = 7.8 Hz, 2H), 7.42 (d, J = 7.2 Hz, 3H), 7.63 (d, J = 6.6 Hz, 2H), 7.69 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 7.8 Hz, 2H), 8.12 (d, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.8, 21.5, 61.4, 117.6, 125.1, 127.3, 128.1, 128.6, 129.0, 129.6, 135.6, 138.9, 140.0, 140.8, 158.5, 158.8, 168.4; HRMS calcd for $C_{21}H_{20}NO_2$ 318.1489 $[M + H]^+$, found 318.1474.

Ethyl 2-Phenyl-6-[4-(trifluoromethyl)phenyl]nicotinate (**5c**). Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (135 mg, 73%); mp 60−61 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.07 (t, J = 7.2

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Hz, 3H), 4.18 (q, J = 7.2 Hz, 2H), 7.44 (d, J = 5.4 Hz, 3H), 7.63 (d, J = 6.0 Hz, 2H), 7.70 (d, J = 7.8 Hz, 2H), 7.74 (d, J = 8.4 Hz, 1H), 8.16−8.21 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.7, 61.6, 118.2, 124.2 ($^1J_{C-F}$ = 270.2 Hz), 125.7 ($^3J_{C-F}$ = 4.4 Hz), 126.4, 127.7, 128.1, 128.9, 131.4 ($^2J_{C-F}$ = 31.7 Hz), 139.1, 140.2, 141.6, 156.7, 158.9, 168.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.68; HRMS calcd for $C_{21}H_{17}F_3NO_2$ 372.1206 $[M + H]^+$, found 372.1221.

*Ethyl 6-(3-Methoxyphenyl)-2-phenylnicotinate (**5d**).* Eluent: petroleum ether/ethyl acetate (20:1); pink oil (128 mg, 77%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.06 (t, J = 7.2 Hz, 3H), 3.85 (s, 3H), 4.16 (q, J = 7.2 Hz, 2H), 6.97 (d, J = 8.4 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.42−7.44 (m, 3H), 7.63−7.66 (m, 3H), 7.71−7.73 (m, 2H), 8.14 (d, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.7, 55.4, 61.4, 112.9, 115.5, 118.0, 119.8, 125.6, 128.0, 128.6, 128.9, 129.8, 138.9, 139.8, 140.6, 158.2, 158.7, 160.1, 168.3; HRMS calcd for $C_{21}H_{19}NNaO_3$ 356.1257 $[M + Na]^+$, found 356.1256.

*Ethyl 2-Phenyl-6-(thiophen-2-yl)nicotinate (**5e**).* Eluent: petroleum ether/ethyl acetate (20:1); light pink solid (111 mg, 72%); mp 46−47 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.05 (t, J = 7.2 Hz, 3H), 4.15 (q, J = 7.2 Hz, 2H), 7.10 (s, 1H), 7.42 (s, 1H), 7.60−7.62 (m, 3H), 7.68 (s, 1H), 8.08 (d, J = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.7, 61.4, 116.2, 124.9, 126.1, 128.0, 128.2, 128.7, 128.9, 129.1, 138.9, 140.1, 144.1, 153.8, 158.9, 168.1; HRMS calcd for $C_{18}H_{15}NNaO_2S$ 332.0716 $[M + Na]^+$, found 332.0716.

*Ethyl 6-Cyclohexyl-2-phenylnicotinate (**5f**).* Eluent: petroleum ether/ethyl acetate (20:1); yellow oil (82 mg, 53%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 3H), 1.18−1.25 (m, 1H), 1.29−1.39 (m, 1H), 1.47 (qd, J_1 = 12.4 Hz, J_2 = 2.8 Hz, 2H), 1.67 (d, J = 12.8 Hz, 1H), 1.78 (d, J = 12.8 Hz, 2H), 1.92 (d, J = 12.0 Hz, 2H), 2.75 (tt, J_1 = 11.6 Hz, J_2 = 3.6 Hz, 1H), 4.05 (q, J = 7.2 Hz, 2H), 7.10 (d, J = 8.0 Hz, 1H), 7.31−7.35 (m, 3H), 7.45−7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 26.0, 26.4, 32.7, 46.6, 61.2, 118.6, 124.6, 128.0, 128.4, 128.7, 138.3, 140.8, 158.2, 168.5, 168.7; HRMS calcd for $C_{20}H_{24}NO_2$ 310.1802 $[M + H]^+$, found 310.1804.

*Ethyl 6-Isopropyl-2-phenylnicotinate (**5g**).*[8i] Eluent: petroleum ether/ethyl acetate (20:1); yellow oil (77 mg, 57%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (td, J_1 = 7.2 Hz, J_2 = 2.8 Hz, 3H), 1.34 (dd, J_1 = 6.4 Hz, J_2 = 2.8 Hz, 6H), 3.13−3.21 (m, 1H), 4.13 (qd, J_1 = 7.2 Hz, J_2 = 2.8 Hz, 2H), 7.21 (dd, J_1 = 8.0 Hz, J_2 = 2.8 Hz, 1H), 7.41−7.42 (m, 3H), 7.54−7.56 (m, 2H), 8.03 (dd, J_1 = 8.0 Hz, J_2 = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 22.4, 36.5, 61.2, 118.2, 124.7, 128.0, 128.4, 128.8, 138.3, 140.7, 158.1, 168.5, 169.5; MS m/z 270 $[M + H]^+$.

*Ethyl 2,4-dDiphenylnicotinate (**5h**).*[6e] Eluent: petroleum ether/ethyl acetate (20:1); yellow oil (48 mg, 32%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J = 7.2 Hz, 3H), 3.95 (q, J = 7.6 Hz, 2H), 7.29 (d, J = 4.8 Hz, 2H), 7.42 (s, 8H), 7.63 (d, J = 6.8 Hz, 2H), 8.74 (d, J = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 61.4, 122.8, 128.1, 128.3, 128.4, 128.6, 128.7, 128.8, 138.1, 139.7, 148.6, 149.8, 156.9, 168.4; MS m/z 304 $[M + H]^+$.

*Ethyl 6-Phenyl-2-(p-tolyl)nicotinate (**5i**).* Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (116 mg, 73%); mp 46−47 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, J = 7.2 Hz, 3H), 2.41 (s, 3H), 4.20 (q, J = 7.2 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.41−7.49 (m, 3H), 7.55 (d, J = 7.6 Hz, 2H), 7.73 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.4, 61.4, 117.6, 125.2, 127.3, 128.7, 128.78, 128.83, 129.7, 137.7, 138.4, 138.6, 138.8, 158.4, 158.7, 168.4; HRMS calcd for $C_{21}H_{20}NO_2$ 318.1489 $[M + H]^+$, found 318.1489.

*Ethyl 2-(4-Methoxyphenyl)-6-phenylnicotinate (**5j**).*[6b] Eluent: petroleum ether/ethyl acetate (20:1); yellow oil (135 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (t, J = 7.2 Hz, 3H), 3.80 (s, 3H), 4.19 (q, J = 7.2 Hz, 2H), 6.96 (d, J = 8.2 Hz, 2H), 7.38−7.45 (m, 3H), 7.61−7.66 (m, 3H), 8.09 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 55.4, 61.4, 113.6, 117.3, 125.0, 127.3, 128.8, 129.7, 130.4, 133.0, 138.4, 138.9, 158.1, 158.2, 160.3, 168.6; HRMS calcd for $C_{21}H_{19}NNaO_3$ 356.1257 $[M + Na]^+$, found 356.1259.

*Ethyl 2-(4-Chlorophenyl)-6-phenylnicotinate (**5k**).* Eluent: petroleum ether/ethyl acetate (20:1); white solid (121 mg, 72%); mp 68−69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, J = 7.2 Hz, 3H), 4.20 (q, J = 7.2 Hz, 2H), 7.41−7.49 (m, 5H), 7.58 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 6.8 Hz, 2H), 8.18 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 61.5, 118.1, 125.1, 127.3, 128.2, 128.9, 130.0, 130.3, 134.8, 138.1, 139.1, 139.2, 157.7, 158.6, 167.8; HRMS calcd for $C_{20}H_{16}ClNNaO_2$ 360.0762 $[M + Na]^+$, found 360.0761.

*Ethyl 2-(4-Fluorophenyl)-6-phenylnicotinate (**5l**).* Eluent: petroleum ether/ethyl acetate (20:1); white solid (112 mg, 70%); mp 67−68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (t, J = 7.2 Hz, 3H), 4.18 (q, J = 7.2 Hz, 2H), 7.12 (t, J = 8.4 Hz, 2H), 7.40−7.45 (m, 3H), 7.60−7.63 (m, 2H), 7.70 (d, J = 8.0 Hz, 2H), 8.08 (d, J = 6.8 Hz, 2H), 8.13 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 61.6, 115.1 ($^2J_{C-F}$ = 21.1 Hz), 118.1, 125.2, 127.5, 129.0, 130.0, 130.9 ($^3J_{C-F}$ = 8.8 Hz), 136.8 ($^4J_{C-F}$ = 2.9 Hz), 138.3, 139.3, 157.8, 158.6, 163.3 ($^1J_{C-F}$ = 246.6 Hz), 168.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.33; HRMS calcd for $C_{20}H_{16}FNNaO_2$ 344.1057 $[M + Na]^+$, found 344.1070.

*Ethyl 6-Phenyl-2-(thiophen-2-yl)nicotinate (**5m**).*[6b] Eluent: petroleum ether/ethyl acetate (20:1); colorless oil (94 mg, 61%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J = 7.2 Hz, 3H), 4.36 (q, J = 7.2 Hz, 2H), 7.08 (t, J = 4.8 Hz, 1H), 7.44−7.50 (m, 5H), 7.65 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 61.8, 117.3, 124.0, 127.2, 127.6, 127.9, 128.6, 128.9, 129.9, 137.9, 138.6, 143.5, 150.5, 157.9, 168.4; HRMS calcd for $C_{18}H_{16}NO_2S$ 310.0896 $[M + H]^+$, found 310.0896.

*Ethyl 2-Methyl-6-phenylnicotinate (**5n**).*[8c] Eluent: petroleum ether/ethyl acetate (20:1); colorless oil (69 mg, 57%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.2 Hz, 3H), 2.92 (s, 3H), 4.40 (q, J = 7.2 Hz, 2H), 7.44−7.50 (m, 3H), 7.62 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 7.2 Hz, 2H), 8.26 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 25.3, 61.1, 117.4, 123.7, 127.3, 128.8, 129.7, 138.6, 139.3, 159.1, 160.0, 166.7; MS m/z 242 $[M + H]^+$.

*Ethyl 2-Ethyl-6-phenylnicotinate (**5o**).* Eluent: petroleum ether/ethyl acetate (20:1); white solid (70 mg, 55%); mp 57−58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36−1.43 (m, 6H), 3.26 (q, J = 7.6 Hz, 2H), 4.39 (q, J = 7.6 Hz, 2H), 7.41−7.50 (m, 3H), 7.61 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 6.8 Hz, 2H), 8.21 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 14.3, 30.5, 61.2, 117.0, 123.4, 127.3, 128.8, 129.6, 138.7, 139.3, 158.9, 164.4, 166.8; HRMS calcd for $C_{16}H_{18}NO_2$ 256.1332 $[M + H]^+$, found 256.1352.

*Methyl 2-Ethyl-6-phenylnicotinate (**5p**).* Eluent: petroleum ether/ethyl acetate (20:1); white solid (72 mg, 60%); mp 54−55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.6 Hz, 3H), 3.26 (q, J = 7.6 Hz, 2H), 3.88 (s, 3H), 7.38−7.46 (m, 3H), 7.55 (d, J = 8.4 Hz, 2H), 8.07 (d, J = 7.2 Hz, 2H), 8.16 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 30.4, 52.1, 117.0, 123.0, 127.3, 128.8, 130.0, 138.6, 139.4, 158.9, 164.5, 167.1; HRMS calcd for $C_{15}H_{16}NO_2$ 242.1176 $[M + H]^+$, found 242.1196.

*Procedures for the Synthesis of **6** and **7** and Spectroscopic Data of **6** and **7**.* To a solution of (2,6-diphenylpyridin-3-yl)(phenyl)-methanone (**3p**, 167.5 mg, 0.5 mmol) in methanol (3 mL) was slowly added $NaBH_4$ (18.9 mg, 0.5 mmol). The resulting mixture was stirred at room temperature. Upon completion as indicated by TLC, the reaction was quenched with water and the mixture was extracted with ethyl acetate (3 × 8 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with a petroleum ether/ethyl acetate (10:1) eluent to give **6**.

*(2,6-Diphenylpyridin-3-yl)(phenyl)methanol (**6**).* Eluent: petroleum ether/ethyl acetate (10:1); yellowish solid (153 mg, 91%); mp 148−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (d, J = 4.0 Hz, 1H), 5.98 (d, J = 2.8 Hz, 1H), 7.14−7.16 (m, 2H), 7.21−7.34 (m, 3H), 7.36−7.43 (m, 6H), 7.47−7.49 (m, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.0 Hz, 1H), 8.00−8.02 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.9, 119.4, 126.7, 127.1, 127.6, 128.2, 128.3, 128.5, 128.7, 129.0, 129.3, 135.1, 136.8, 139.1, 140.0, 143.2, 156.0, 157.8; HRMS calcd for $C_{24}H_{20}NO$ 338.1539 $[M + H]^+$, found 338.1540.

To a flask containing (2,6-diphenylpyridin-3-yl)(phenyl)methanol (**6**, 67.4 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was added TfOH (35 μL, 0.4 mmol). Then, the mixture was stirred at room temperature. Upon

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completion, the reaction was quenched with aqueous $NaHCO_3$ (5 mL) and the mixture was extracted with ethyl acetate (3 × 6 mL). The combined organic layers were washed with water and brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by column chromatography on silica gel with a petroleum ether/ethyl acetate (10:1) eluent to afford **7**.

*2,5-Diphenyl-5H-indeno[1,2-b]pyridine (**7**).* Eluent: petroleum ether/ethyl acetate (10:1); white solid (46 mg, 72%); mp 144−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (s, 1H), 7.11−7.13 (m, 2H), 7.26−7.32 (m, 3H), 7.37−7.45 (m, 3H), 7.47−7.52 (m, 3H), 7.59 (d, J = 8.0 Hz, 1H), 7.64 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 8.12−8.14 (m, 2H), 8.23 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.0, 118.8, 121.2, 125.3, 127.1, 127.2, 127.8, 128.3, 128.75, 128.81, 128.9, 129.3, 133.1, 139.8, 140.0, 140.49, 140.51, 148.7, 156.9, 160.1; HRMS calcd for $C_{24}H_{18}N$ 320.1434 $[M + H]^+$, found 320.1441.

*Typical Procedure for the Synthesis of **8a** and Spectroscopic Data of **8a** and **8b**.* To a flask containing ethyl 2,6-diphenylnicotinate (**5a**, 151.5 mg, 0.5 mmol) was added polyphosphoric acid (1 mL). The mixture was then stirred at 135 °C. Upon completion, it was cooled to room temperature, treated with a saturated aqueous solution of $NaHCO_3$ (5 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with a petroleum ether/ethyl acetate (20:1) eluent to give **8a**. **8b** was obtained in a similar manner.

*2-Phenyl-5H-indeno[1,2-b]pyridin-5-one (**8a**).* Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (112 mg, 87%); mp 149−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, J = 7.6 Hz, 1H), 7.46−7.51 (m, 3H), 7.57 (t, J = 8.0 Hz, 2H), 7.69 (d, J = 7.2 Hz, 1H), 7.87−7.9 (m, 2H), 8.10 (d, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.7, 121.0, 123.9, 126.7, 127.4, 128.9, 130.1, 130.9, 132.0, 135.1, 135.5, 138.4, 143.6, 161.8, 165.4, 191.7; HRMS calcd for $C_{18}H_{11}NNaO$ 280.0733 $[M + Na]^+$, found 280.0754.

*2-Isopropyl-5H-indeno[1,2-b]pyridin-5-one (**8b**).* Eluent: petroleum ether/ethyl acetate (20:1); yellow solid (87 mg, 78%); mp 58−59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, J = 6.8 Hz, 6H), 3.08−3.19 (m, 1H), 7.06 (d, J = 7.6 Hz, 1H), 7.39 (t, J = 7.2 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.79 (d, J = 7.2 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 36.9, 120.0, 120.9, 123.9, 126.1, 130.6, 131.7, 134.9, 135.3, 143.9, 165.0, 173.6, 192.0; HRMS calcd for $C_{15}H_{13}NNaO$ 246.0889 $[M + Na]^+$, found 246.0914.

*Gram-Scale Synthesis of **3a**.* To a reaction tube equipped with a stir bar containing a solution of 3-amino-1-phenylbut-2-en-1-one (**2a**, 805 mg, 5 mmol) in DMF (15 mL) were added propiophenone **1a** (0.80 mL, 6 mmol), $Cu(OAc)_2$ (91 mg, 0.5 mmol), 2,2′-bipyridine (156 mg, 1 mmol), and TEMPO (781 mg, 5 mmol). The tube was then sealed, and the mixture was stirred at 120 °C under an air atmosphere for 20 h. After the mixture had been cooled to room temperature, the reaction was quenched with water, and the mixture was extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with a petroleum ether/ethyl acetate (20:1) eluent to give **3a** (0.892 g, 65%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01901.

Copies of ^{1}H and ^{13}C NMR spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

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