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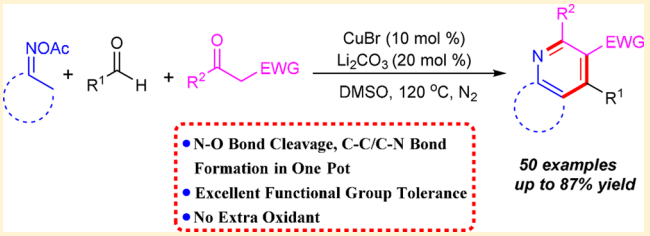
Cu-Catalyzed Three-Component Cascade Annulation Reaction: An Entry to Functionalized Pyridines

Huanfeng Jiang,* Jidan Yang, Xiaodong Tang, Jianxiao Li, and Wanqing Wu

School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, China

Supporting Information

ABSTRACT: A concise copper-catalyzed N−O bond cleavage/C−C/C−N bond formation procedure has been described for the synthesis of multisubstituted pyridines. Various oxime acetates, activated methylene compounds, and a wide range of aldehydes bearing aryl, heteroaryl, vinyl, and trifluoromethyl groups were employed to provide the tri- or tetrasubstituted pyridines with flexible substitution patterns. Moreover, this method features inexpensive catalysts, no need for extra oxidant, and high step-enconomy, which make it pratical and attractive.



INTRODUCTION

Pyridine skeletons are a class of important azaheterocyclic structures as the naturally occurring bioactive compounds,[1] pharmaceutical molecules,[2] and the fundamental part of ligands, intermediates, and building blocks in polysubstituted form.[3] For example, 3-pyridinecarboxamide derivative (nicotinamide "vitamin B_3") is widely applied in clinical practice to treat pellagra and some neurodegenerative diseases.[4] Therefore, the synthesis of pyridines has received intensive attention and encouraged the development of more valuable synthetic strategies.[5] Traditionally, pyridine synthesis relies on the condensation of amine and carbonyl compounds, including [5 + 1] condensation of 1,5-dicarbonyls with ammonia (NH_3), [2 + 2+1 + 1] Hantzsch pyridine synthesis, and [3 + 3] cyclzation of 1,3-dicarbonyl derivatives with vinylogous amides.[6] Recently, tremendous effort has been made in the field of transition-metal-catalyzed cyclizations and cross-coupling reactions to afford functionalized pyridine derivatives.[7] For example, rhodium-catalyzed-[4 + 2] cycloaddition reaction for the formation of pyridine derivatives from alkynes and α,β-unsaturated imines has been achieved by Ellman and Cheng et al.[7i,j] Despite the synthetic efficiency of these methods, the unstable nature of the precursors, expensive noble metal catalysts, and tedious operations directly limited the regioselectivity and functional diversity to afford some practical and sensitive pyridines. Thereforoe, it still remains highly desirable to develop versatile and highly chemo- and regioselective strategies starting from easily available reagents for the construction of pyridine rings under mild conditions with more flexible substitution patterns.

On the other hand, oxime derivatives used as internal oxidants have been proved to be an extremely effective method for constructing *N*-containing heterocycles by transition-metal catalysis, including ruthenium,[8] rhodium,[9] palladium,[10] and copper.[11] Recently, advancements in copper-catalyzed cyclization of oxime esters offer new routes to the synthesis of pyridine derivatives.[12] Notably, Yoshikai and co-workers described a synergistic copper/iminium-catalyzed strategy to construct pyridines from oximes and enals.[12b] In particular, copper-catalyzed three-component cascade annulations with the participation of oxime esters have emerged as pratical and convenient approaches to functionalized pyridines, which provided simpler and convergent accesses to pyridine frameworks with diverse substitution patterns in one pot from easily accessible reagents.[13] During the interests of our studies in copper-catalyzed coupling of ketoxime esters, the preparation of sulfone derivatives and a series of functionalized *N*-containing heteropolycycles has been successfully accessed.[14,11a−d] Very recently, we have developed a practical protocol for various substituted pyrazoles via copper-catalyzed cascade reactions of oxime acetates, amines, and aldehydes (Scheme 1a).[11d] Inspired by these precedents, we conceived that the Cu-

Scheme 1. Synthesis of *N*-Containing Heterocycles via Cu-Catalyzed Three-Component Reactions with the Participation of Oxime Esters

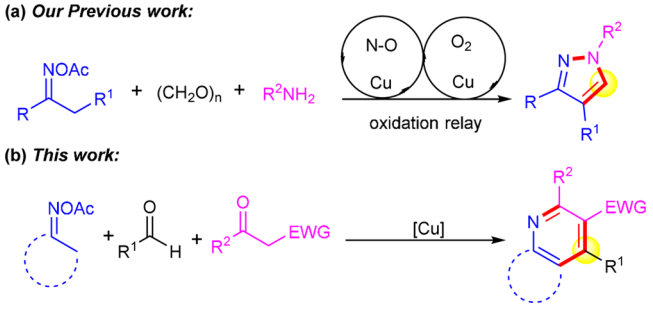


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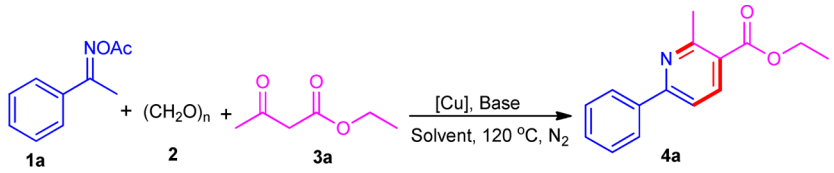
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	base	solvent	yield (%)[b]
1	CuI	Cs_2CO_3	DMSO	58
2	CuI	Li_2CO_3	DMSO	68
3	CuI	$NaHSO_3$	DMSO	60
4	CuI	Et_3N	DMSO	61
5	CuI	DBU	DMSO	57
6	CuI	*t*-BuOK	DMSO	59
7	CuI	none	DMSO	27
8	none	Li_2CO_3	DMSO	0
9	CuCl	Li_2CO_3	DMSO	67
10	**CuBr**	**Li_2CO_3**	**DMSO**	**74**
11	$CuBr_2$	Li_2CO_3	DMSO	42
12	$Cu(OAc)_2$	Li_2CO_3	DMSO	59
13	$Cu(OTf)_2$	Li_2CO_3	DMSO	56
14	CuBr	Li_2CO_3	DMF	63
15	CuBr	Li_2CO_3	toluene	25
16	CuBr	Li_2CO_3	DCE	26
17	CuBr	Li_2CO_3	CH_3CN	33

[a]Unless otherwise noted, all reactions were performed with **1a** (0.3 mmol), **2** (0.3 mmol), **3a** (1.5 equiv), catalyst (10 mol %), base (20 mol %), and solvent (2 mL) at 120 °C under a N_2 atmosphere for 6 h. [b]Determined by GC using dodecane as an internal standard.

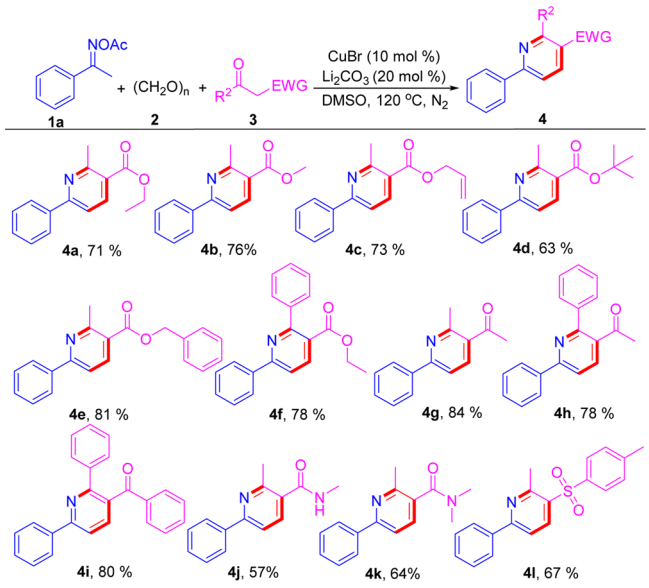
catalyzed N−O bond cleavage, C−C/C−N bond formation, and oxidative dehydrogenation process could occur in a one-pot manner. Herein, we present our recent progress in a Cu(I)-catalyzed multicomponent cascade annulation strategy with oxime acetates, activated methylene compounds, and aldehydes for the construction of tri- and tetrasubstituted pyridines (Scheme 1b).

RESULTS AND DISCUSSION

Initially, the project was carried out by investigating the reaction of acetophenone oxime acetate (**1a**), paraformaldehyde (**2**), and ethyl acetoacetate (**3a**) in the presence of CuI and Cs_2CO_3 (Table 1). To our delight, the combination of CuI and DMSO under a N_2 atmosphere afforded the desired product **4a** in 58% yield (Table 1, entry 1). Associating with previous works, the base was proved to be crucial to the interaction between copper(I) salts and oxime esters.[11a,b,12b,14] As revealed in Table 1, the other bases such as Li_2CO_3, $NaHSO_3$, Et_3N, DBU, and *t*-BuOK were investigated (entries 2−6), and Li_2CO_3 was found to be optimal, giving **4a** in 68% yield (entry 2).[15] The absence of base was ineffective for this transformation (entry 7). As expected, no product was observed without copper salts (entry 8). Subsequently, different copper salts were examined, including CuCl, CuBr, $CuBr_2$, $Cu(OAc)_2$, and $Cu(OTf)_2$, obtaining **4a** in the yields of 67, 74, 42, 59, and 56%, respectively (Table 1, entries 9−13), and CuBr was the most effective catalyst for this transformation (entry 10).[15] Replacing DMSO with other solvents, such as DMF, toluene, DCE, or CH_3CN, did not improve the yields of the desired product (entries 14−17). Thus, the optimized catalytic system for this cascade annulation reaction was: **1a** (0.3 mmol), **2** (0.3 mmol), **3a** (1.5 equiv), CuBr (10 mol %), Li_2CO_3 (20 mol %) in DMSO at 120 °C under N_2 for 6 h.

On the basis of the optimized reaction conditions, various activated methylene compounds were investigated for the preparation of 2,3,5-trisubstituted pyridines. Representative results are summarized in Table 2. Pleasingly, various substituted *β*-keto esters exhibited good functional-group tolerance to afford the desired products with high chemoselectivity in moderate to excellent yields (**4a**−**4f**). When

Table 2. Substrate Scope of Various Activated Methylene Compounds 3[a]



[a]All reactions were performed with **1a** (0.3 mmol), **2** (0.3 mmol), **3** (1.5 equiv), Li_2CO_3 (20 mol %), CuBr (10 mol %) in DMSO (2 mL) at 120 °C under a N_2 atmosphere for 6 h.

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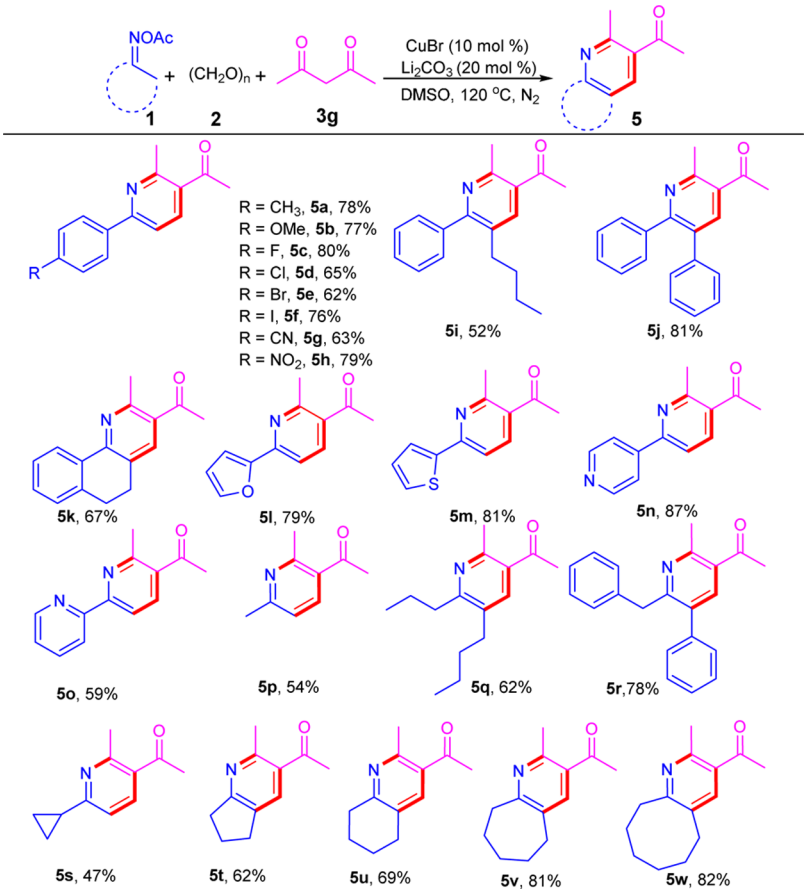
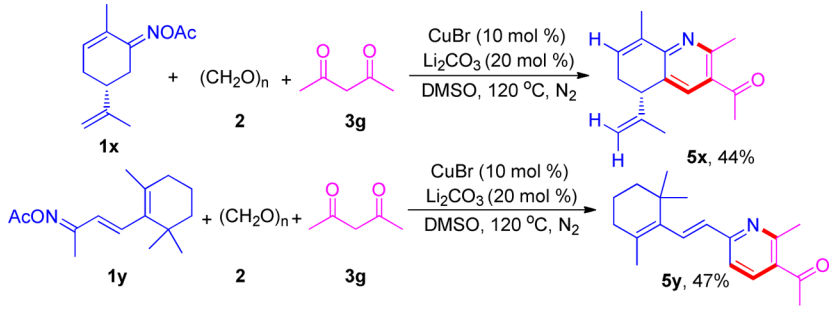
Table 3. Substrate Scope of Various Oxime Acetates 1[a]



[a]Reaction conditions: all reactions were performed with **1** (0.3 mmol), **2** (0.3 mmol), **3g** (1.5 equiv), Li_2CO_3 (20 mol %), CuBr (10 mol %) in DMSO (2 mL) at 120 °C under a N_2 atmosphere for 6 h.

Scheme 2. Synthesis of Pyridine Derivatives Derived from Natural Product Core



acetylacetone (**3g**) and dibenzoylmethane (**3i**) were employed, the corresponding pyridine derivatives **4g** and **4i** were successfully obtained in 84% and 80% yields, respectively. Moreover, the unsymmetrical 1,3-diketone **3h** could be also efficiently transferred to the desired product with good regioselectivity. The structure of **4h** has been confirmed by single-crystal X-ray analysis.[16] Notably, this strategy was available for the construction of nicotinamide derivatives **4j** and **4k** in reasonable yields, which have shown strong biological activity.[4] Additionally, 1-tosylpropan-2-one (**3l**) was also compatible in this transformation and gave the corresponding product **4l** in 67% yield.

With the positive results above, we set out to evaluate the generality of different ketone oxime acetates under the optimal reaction conditions (Table 3). A series of phenylethanone oxime acetates with an electron-donating or electron-withdrawing substituent on the arene functionality successfully participated in this transformation, providing the desired products in satisfactory yields (**5a**−**5h**). 1-Phenylhexan-1-one and 1,2-diphenylethan-1-one also proceeded smoothly to afford the 2,3,5,6-tetrasubstituted pyridines in 52% and 81% yields, respectively (**5i** and **5j**). Moreover, when polysubstituted oxime ester with a cyclic scaffold was employed, the polycyclic pyridine **5k** was successfully obtained in 67% yield. Notably, the introduction of furan, thiophene, and pyridine heterocycles into this system made this process more useful for the preparation of practical products (**5l**−**5o**). Besides, even if a series of aliphatic ketone oxime acetates were used, the reasonable yields were also obtained (**5p**−**5s**). Gratifyingly, oximes derived from cyclic aliphatic ketones such as cyclopentanone, cyclohexanone,

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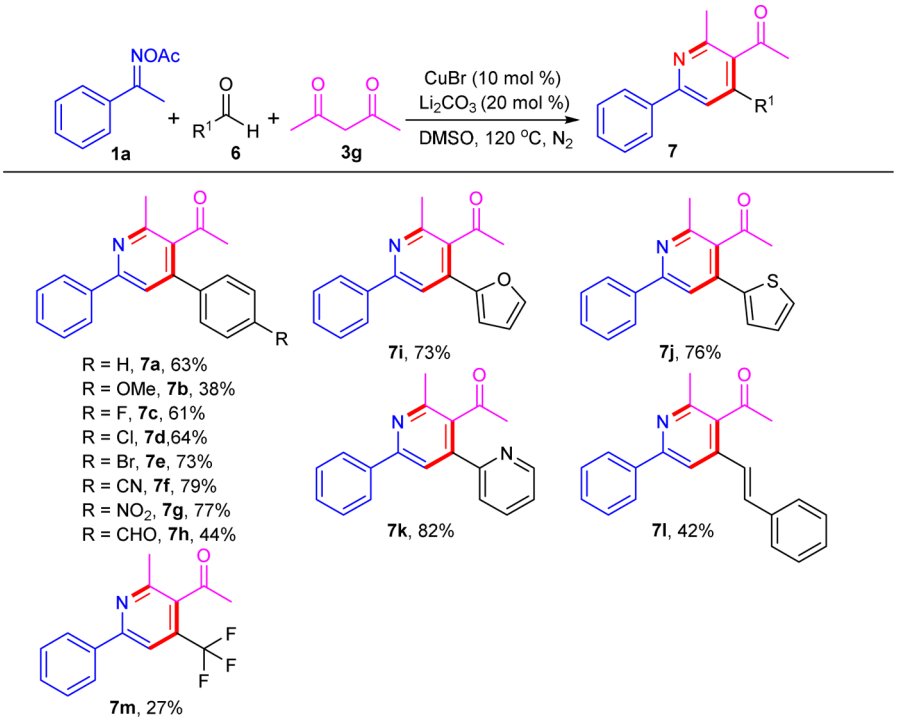
Table 4. Substrate Scope of Various Aldehydes 6[a]



[a]All reactions were performed with **1a** (0.3 mmol), **6** (0.3 mmol), **3g** (1.5 equiv), Li_2CO_3 (20 mol %), CuBr (10 mol %) in DMSO (2 mL) at 120 °C under a N_2 atmosphere for 6 h.

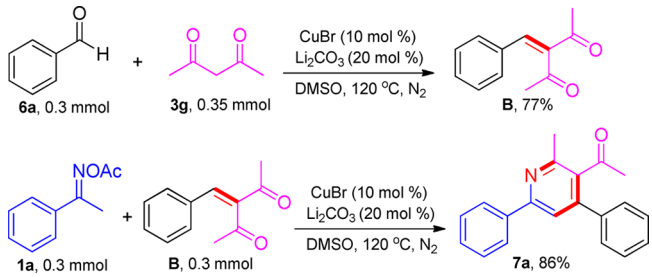
cycloheptanone, and cyclooctanone were performed well to generate the corresponding dicyclic products in the yields of 62, 69, 81, and 82%, respectively (**5t**−**5w**). Unfortunately, oxime esters with cyclopropanone and cyclobutanone failed to transfer into the corresponding products under the optimized conditions, which indicated that ring strain effects affected this transformation.

Under the optimal reaction conditions, it is delightful that oximes derived from L(−)-carvone and *β*-ionone smoothly participated in the transformation, affording the corresponding pyridine-skeleton molecules containing a natural product core in reasonable yields, respectively (Scheme 2, **5x** and **5y**).

In addition to paraformaldehyde, other aldehydes were found to be favored to afford the 2,3,4,6-tetrasubstituted pyridines with high efficiencies, and the results are summarized in Table 4. Satisfactorily, benzaldehydes with a series of valuable functional groups, such as methyl, methoxyl, halogen, cyano, nitro, and aldehyde, were successfully transferred to the desired products in moderate to excellent yields (**7a**−**7h**). Additionally, heteroaromatic aldehydes with furan, thiophene, and pyridine skeletons exhibited similar reactivity with benzaldehydes, affording the annulation products in good yields (**7i**−**7k**). The transformation of *trans*-cinnamaldehyde could proceed smoothly to give substituted pyridines **7l** in moderate yields. It is noteworthy that trifluoromethyl substituted pyridines **7m** could be separated in 27% yield when trifluoroacetaldehyde hydrate was used.[17]

To get the deep insight of the mechanism of this tranformation, we performed the reaction of benzaldehyde **6a** and acetylacetone **3g** under the standard conditions, and 3-benzylidenepentane-2,4-dione **B** was obtained in 77% yield. Notably, when we coupled oxime acetate **1a** with compound **B**, the desired product **7a** was formed in excellent yield (Scheme 3). On the basis of the above results and previous studies on

Scheme 3. Investigation of the Reaction Mechanism



oxime derivatives,[11−14,18] the plausible mechanism for this cascade annulation reaction is illustrated in Scheme 4. First, the cleavage of the N−O bond of **1** is initiated by copper salts, generating copper enamide intermediate **A** and producing another Cu^{II} species.[11a,d,14] Subsequently, the nucleophilic addition of copper(II) enamide complex **A** to intermediate **B** gives the imine intermediate **C**,[13] the tautomer of **D**. Then, the intramolecular nucleophile attack affords the dihydropyridine complex **E**. Finally, the target product is generated from oxidation of intermediate **E** by Cu(II) species and regeneration of Cu(I).

CONCLUSION

In conclusion, we have developed a Cu-catalyzed three-component cascade reaction for the synthesis of polysubstituted pyridines with high variability and impressive selectivity from ketoxime acetates, aldehydes, and activated methylene compounds under mild conditions. In this procedure, a one-pot, four-step tandem cascade annulation process was described, which has provided a potential strategy for the preparation of more complex and significant pharmaceuticals. Notably, this transformation successfully extends its application

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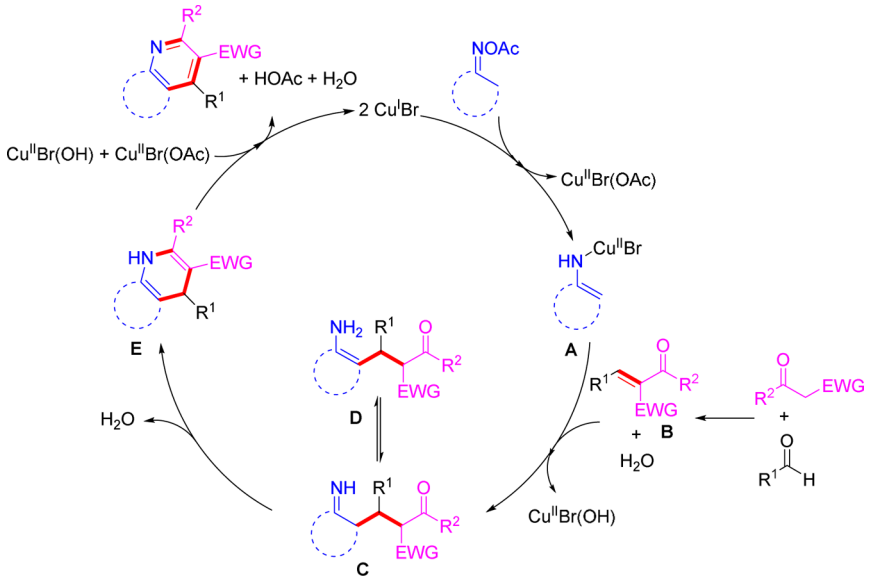
Scheme 4. Proposed Mechanism



to construct bipyridine and nicotinamide derivatives and attractive structures containing L(−)-carvone and β-ionone natural scaffolds.

EXPERIMENTAL SECTION

General Methods. Melting points were measured by a melting point instrument and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded by using a 400 MHz NMR spectrometer. ^{1}H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm) and $CHCl_3$ (77.0 ppm), respectively. IR spectra were obtained either as potassium bromide pellets or as liquid films between two potassium bromide pellets with an infrared spectrometer. GC−MS was obtained using electron ionization. The data of HRMS were carried out on a high-resolution mass spectrometer (LCMS-IT-TOF). Unless otherwise noted, all purchased chemicals were used without further purification. The ketoxime acetates were prepared according to the literature.[9a,14]

General Procedure for the Synthesis of Polysubstituted Pyridines 4, 5, and 7. The ketoxime acetates **1** (0.3 mmol), aldehydes **2** or **6** (0.3 mmol), activated methylene compound **3** (1.5 equiv), CuBr (10 mol %, 0.03 mmol, 4.26 mg), and Li_2CO_3 (20 mol %, 0.06 mmol, 4.44 mg) were stirred in DMSO (2.0 mL) at 120 °C, in a 20 mL tube under N_2 for 6 h. When the reaction was completed (detected by TLC), the mixture was cooled to room temperature. The reaction was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and then evaporated in vacuum. The residue was purified by column chromatography on silica gel to afford the corresponding pyridines with hexanes/ethyl acetate as the eluent.

*Ethyl 2-Methyl-6-phenylnicotinate (**4a**).* Yield: 71% (51.3 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.2 Hz, 1H), 8.06 (d, *J* = 7.2 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.49−7.41 (m, 3H), 4.39 (q, *J* = 7.2 Hz, 2H), 2.92 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 166.6, 159.9, 159.0, 139.3, 138.5, 129.7, 128.8, 127.3, 123.7, 117.3, 61.1, 25.3, 14.3; IR (KBr): 2982, 1719, 1585, 1540, 1268, 1085, 757, 694 cm^{-1}; MS (EI) *m*/*z* 77, 83, 115, 141, 168, 196, 213, 241; HRMS-ESI (*m*/*z*): calcd for $C_{15}H_{16}NO_2$, $[M + H]^+$: 242.1176, found, 242.1182.

*Methyl 2-Methyl-6-phenylnicotinate (**4b**).* Yield: 76% (51.8 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.2 Hz, 1H), 8.06 (d, *J* = 6.8 Hz, 2H), 7.61 (d, *J* = 9.8 Hz, 1H), 7.50−7.42 (m, 3H), 3.93 (s, 3H), 2.93 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 167.0, 160.1, 159.2, 139.4, 138.4, 129.7, 128.8, 127.3, 123.3, 117.4, 52.2, 25.2; IR (KBr): 2952, 1726, 1585, 1432, 1272, 1090, 758, 693 cm^{-1}; MS (EI) *m*/*z* 77, 83, 115, 141, 168, 196, 212, 227; HRMS-ESI (*m*/*z*): calcd for $C_{14}H_{14}NO_2$, $[M + H]^+$: 228.1019, found, 228.1025.

*Allyl 2-Methyl-6-phenylnicotinate (**4c**).* Yield: 73% (55.4 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.2 Hz, 1H), 8.07 (d, *J* = 7.2 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.50−7.42 (m, 3H), 6.11−6.01 (m, 1H), 5.43 (d, *J* = 17.2 Hz, 1H), 5.32 (d, *J* = 10.4 Hz, 1H), 4.84 (d, *J* = 5.6 Hz, 2H), 2.94 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 166.2, 160.2, 159.2, 139.4, 138.4, 132.1, 129.7, 128.8, 127.3, 123.3, 118.6, 117.4, 65.8, 25.3; IR (KBr): 3067, 2936, 1723, 1548, 1449, 1263, 1075, 757, 695 cm^{-1}; MS (EI) *m*/*z* 77, 83, 115, 141, 153, 168, 184, 196, 212, 253; HRMS-ESI (*m*/*z*): calcd for $C_{16}H_{16}NO_2$, $[M + H]^+$: 254.1176, found, 254.1181.

*tert-Butyl 2-Methyl-6-phenylnicotinate (**4d**).* Yield: 63% (50.8 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 7.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.50−7.41 (m, 3H), 2.89 (s, 3H), 1.61 (s, 9H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 166.1, 159.3, 158.6, 139.2, 138.6, 129.5, 128.8, 127.3, 125.4, 117.4, 81.8, 28.3, 25.3; IR (KBr): 2977, 2931, 1715, 1584, 1452, 1369, 1285, 1143, 848, 758 cm^{-1}; MS (EI) *m*/*z* 77, 83, 115, 141, 168, 196, 213, 269; HRMS-ESI (*m*/*z*): calcd for $C_{17}H_{20}NO_2$, $[M + H]^+$: 270.1489, found, 270.1492.

*Benzyl 2-Methyl-6-phenylnicotinate (**4e**).* Yield: 81% (73.6 mg) as a yellow solid; mp = 61.4−62.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.2 Hz, 1H), 8.02 (d, *J* = 6.8 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.43−7.40 (m, 4H), 7.38 (d, *J* = 6.8 Hz, 2H), 7.35−7.31 (m, 2H), 5.33 (s, 2H), 2.91 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 166.3, 160.3, 159.2, 139.5, 138.4, 135.9, 129.8, 128.9, 128.7, 128.5, 128.4, 127.4, 123.3, 117.4, 67.0, 25.4; IR (KBr): 3064, 3023, 2952, 1724, 1586, 1455, 1381, 1092, 1066, 756, 695 cm^{-1}; MS (EI) *m*/*z* 65, 77, 91, 115, 141, 168, 196, 226, 258, 303; HRMS-ESI (*m*/*z*): calcd for $C_{20}H_{18}NO_2$, $[M + H]^+$: 304.1332, found, 304.1338.

*Ethyl 2,6-Diphenylnicotinate (**4f**).* Yield: 78% (70.9 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 6.8 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 5.6 Hz, 2H), 7.50 (d, *J* = 6.8 Hz, 2H), 7.47 (d, *J* = 4.0 Hz, 2H), 7.45 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 168.3, 158.8, 158.4, 140.6, 138.9, 138.3, 129.8, 128.9, 128.8, 128.6, 128.0, 127.4, 125.4, 117.9, 61.4, 13.7; IR (KBr): 3061, 2929, 2853, 1717, 1582, 1436, 1380, 1291, 1144, 762, 696 cm^{-1}; MS (EI) *m*/*z* 65, 77, 91, 115, 141, 168, 196, 226, 258, 303; HRMS-ESI (*m*/*z*): calcd for $C_{20}H_{18}NO_2$, $[M + H]^+$: 304.1332, found, 304.1334.

*1-(2-Methyl-6-phenylpyridin-3-yl)ethan-1-one (**4g**).* Yield: 84% (53.2 mg) as a yellow solid; mp = 90.3−91.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (t, *J* = 7.4 Hz, 3H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.50−7.43 (m, 3H), 2.85 (s, 3H), 2.61 (s, 3H); ^{13}C {1H} NMR (100 MHz,

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$CDCl_3$) δ 199.9, 158.6, 158.6, 138.4, 138.0, 130.7, 129.8, 128.9, 127.3, 117.3, 29.3, 25.3; IR (KBr): 2965, 2927, 1682, 1583, 1555, 1457, 1260, 743, 692 cm^{-1}; MS (EI) m/z 77, 83, 115, 141, 153, 168, 184, 196, 211; HRMS-ESI (m/z): calcd for $C_{14}H_{14}NO$, $[M + H]^+$: 212.1070, found, 212.1074;

1-(2,6-Diphenylpyridin-3-yl)ethan-1-one ***(4h)***. Yield: 78% (63.9 mg) as a yellow solid; mp = 75.1−76.4 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.6 Hz, 2H), 7.83 (d, J = 7.8 Hz, 2H), 7.72 (d, J = 7.8 Hz, 1H), 7.65−7.60 (m, 2H), 7.51−7.45 (m, 5H), 2.64 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 197.2, 158.1, 157.0, 138.7, 137.4, 137.3, 133.5, 130.0, 129.5, 128.9, 128.7, 127.2, 116.9, 23.8; IR (KBr): 3061, 2925, 2852, 1663, 1581, 1448, 1275, 933, 747, 694 cm^{-1}; MS (EI) m/z 77, 105, 141, 153, 168, 184, 196, 244, 273; HRMS-ESI (m/z): calcd for $C_{19}H_{16}NO$, $[M + H]^+$: 274.1226, found, 274.1230.

(2,6-Diphenylpyridin-3-yl)(phenyl)methanone ***(4i)***. Yield: 80% (80.4 mg) as a yellow solid; mp = 101.4−103.1 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 7.2 Hz, 2H), 7.90 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 7.2 Hz, 2H), 7.62 (d, J = 6.8 Hz, 2H), 7.49 (t, J = 7.2 Hz, 2H), 7.45 (d, J = 7.2 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.27 (t, J = 7.3 Hz, 2H), 7.23 (d, J = 7.2 Hz, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 197.50, 158.04, 157.29, 139.54, 138.44, 138.32, 136.90, 133.26, 132.62, 129.89, 129.75, 129.49, 128.89, 128.38, 128.28, 127.32, 117.88; IR (KBr): 3060, 1663, 1432, 1314, 1279, 927, 749, 695 cm^{-1}; MS (EI) m/z 77, 105, 128, 167, 202, 228, 258, 306, 335; HRMS-ESI (m/z): calcd for $C_{24}H_{18}NO$, $[M + H]^+$: 336.1383, found, 336.1386.

N,2-Dimethyl-6-phenylnicotinamide ***(4j)***. Yield: 57% (38.6 mg) as a yellow solid; mp = 141.8−142.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 7.2 Hz, 2H), 7.63 (d, J = 7.2 Hz, 1H), 7.49−7.45 (m, 2H), 7.44−7.39 (m, 2H), 6.24 (s, 1H), 2.95 (d, J = 4.0 Hz, 3H), 2.68 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 169.5, 157.6, 156.1, 138.7, 135.6, 129.9, 129.4, 128.8, 127.1, 117.3, 26.8, 23.3; IR (KBr): 3066, 2927, 1646, 1551, 1307, 1163, 839, 764, 696 cm^{-1}; MS (EI) m/z 77, 105, 115, 141, 153, 168, 196, 211, 226; HRMS-ESI (m/z): calcd for $C_{14}H_{15}N_2O$, $[M + H]^+$: 227.1179, found, 227.1186.

N,N,2-Trimethyl-6-phenylnicotinamide ***(4k)***. Yield: 64% (46.1 mg) as a yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.6 Hz, 2H), 7.59−7.44 (m, 2H), 7.46 (t, J = 7.3 Hz, 2H), 7.42−7.38 (m, 1H), 3.15 (s, 3H), 2.89 (s, 3H), 2.58 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 170.1, 157.2, 154.3, 138.9, 134.9, 130.1, 129.2, 128.8, 127.0, 117.7, 38.5, 34.8, 22.5; IR (KBr): 3060, 2927, 1641, 1586, 1442, 1396, 1269, 1061, 753, 694 cm^{-1}; MS (EI) m/z 77, 83, 115, 141, 153, 168, 196, 225, 240; HRMS-ESI (m/z): calcd for $C_{15}H_{17}N_2O$, $[M + H]^+$: 241.1335, found, 241.1340.

2-Methyl-6-phenyl-3-tosylpyridine ***(4l)***. Yield: 67% (64.9 mg) as a brown solid; mp = 128.6−129.9 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 6.0 Hz, 2H), 7.79 (d, J = 7.6 Hz, 2H), 7.74 (d, J = 8.0 Hz, 1H), 7.45 (s, 3H), 7.32 (d, J = 7.6 Hz, 2H), 2.74 (s, 3H), 2.41 (s, 3H). ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 160.4, 157.4, 144.6, 138.1, 137.7, 134.3, 130.2, 129.9, 128.9, 127.9, 127.4, 126.8, 117.9, 23.9, 21.6; IR (KBr): 3062, 2925, 1565, 1440, 1310, 1151, 1038, 688, 550 cm^{-1}; MS (EI) m/z 65, 77, 91, 115, 139, 156, 167, 207, 243, 258, 323; HRMS-ESI (m/z): calcd for $C_{19}H_{18}NO_2S$, $[M + H]^+$: 324.1053, found, 324.1056.

1-(2-Methyl-6-(p-tolyl)pyridin-3-yl)ethan-1-one ***(5a)***. Yield: 78% (52.7 mg) as a yellow solid; mp = 75.8−76.7 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 7.6 Hz, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 7.6 Hz, 2H), 2.84 (s, 3H), 2.61 (s, 3H), 2.41 (s, 3H). ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 199.9, 158.6, 158.5, 140.0, 138.1, 135.5, 130.4, 129.6, 127.2, 117.0, 29.3, 25.3, 21.4; IR (KBr): 2921, 1680, 1579, 1261, 821 cm^{-1}; MS (EI) m/z 65, 91, 115, 167, 182, 210, 225; HRMS-ESI (m/z): calcd for $C_{15}H_{16}NO$, $[M + H]^+$: 226.1226, found, 226.1235.

1-(6-(4-Methoxyphenyl)-2-methylpyridin-3-yl)ethan-1-one ***(5b)***. Yield: 77% (55.7 mg) as a yellow solid; mp = 109.4−110.8 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, J = 10.8, 8.9 Hz, 3H), 7.55 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 8.0 Hz, 2H), 3.85 (s, 1H), 2.82 (s, 1H), 2.58 (s, 1H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 199.8, 161.2, 158.6, 158.2, 138.1, 130.8, 129.9, 128.7, 116.4, 114.2, 55.4, 29.2, 25.4; IR (KBr): 2968, 1684, 1606, 1576, 1510, 1434, 1259, 1026, 827 cm^{-1}; MS (EI) m/z 63, 77, 108, 113, 128, 140, 154, 171, 183, 198, 226, 241; HRMS-ESI (m/z): calcd for $C_{15}H_{16}NO_2$, $[M + H]^+$: 242.1176, found, 242.1181.

1-(6-(4-Fuorophenyl)-2-methylpyridin-3-yl)ethan-1-one ***(5c)***. Yield: 80% (55.0 mg) as a yellow solid; mp = 71.3−72.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07−8.04 (m, 3H), 7.60 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 8.4 Hz, 2H), 2.84 (s, 3H), 2.61 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 199.8, 164.0 (J = 248.4 Hz), 158.0, (J = 116.4 Hz), 138.2, 134.3, 130.7, 129.3 (J = 8.5 Hz), 127.8 (J = 8.1 Hz), 117.0, 115.8 (J = 21.6 Hz), 29.3, 25.2; IR (KBr): 2928, 1681, 1581, 1504, 1355, 1263, 1162, 823 cm^{-1}; MS (EI) m/z 63, 75, 92, 133, 159, 171, 186, 214, 229; HRMS-ESI (m/z): calcd for $C_{14}H_{13}FNO$, $[M + H]^+$: 230.0976, found, 230.0984.

1-(6-(4-Chlorophenyl)-2-methylpyridin-3-yl)ethan-1-one ***(5d)***. Yield: 65% (47.8 mg) as a yellow solid; mp = 91.5−92.8 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 2.83 (s, 3H), 2.61 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 199.8, 158.7, 157.3, 138.1, 136.7, 136.0, 131.0, 129.0, 128.6, 117.1, 29.3, 25.2; IR (KBr): 2926, 1679, 1578, 1577, 1353, 817 cm^{-1}; MS (EI) m/z 63, 75, 83, 115, 139, 167, 175, 202, 230, 245; HRMS-ESI (m/z): calcd for $C_{14}H_{13}ClNO$, $[M + H]^+$: 246.0680, found, 246.0684.

1-(6-(4-Bromophenyl)-2-methylpyridin-3-yl)ethan-1-one ***(5e)***. Yield: 62% (53.8 mg) as a yellow solid; mp = 98.0−99.3 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.62−7.59 (m, 3H), 2.83 (s, 3H), 2.61 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 199.8, 158.7, 157.3, 138.1, 137.1, 132.0, 131.0, 128.8, 124.4, 117.0, 29.3, 25.2; IR (KBr): 2925, 1677, 1578, 1430, 1260, 817, 761 cm^{-1}; MS (EI) m/z 63, 115, 140, 167, 207, 274, 289; HRMS-ESI (m/z): calcd for $C_{14}H_{13}BrNO$, $[M + H]^+$: 290.0175, found, 290.0173.

1-(6-(4-Iodophenyl)-2-methylpyridin-3-yl)ethan-1-one ***(5f)***. Yield: 76% (76.8 mg) as a yellow solid; mp = 123.1−124.3 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.0 Hz, 1H), 7.81 (s, 3H), 7.61 (d, J = 5.6 Hz, 2H), 2.83 (s, 3H), 2.61 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 199.9, 158.7, 157.5, 138.1, 138.0, 132.0, 129.0, 128.9, 117.0, 96.34, 29.4, 25.2; IR (KBr): 1676, 1575, 1431, 1260, 818 cm^{-1}; MS (EI) m/z 76, 83, 115, 140, 161, 167, 294, 322, 337; HRMS-ESI (m/z): calcd for $C_{14}H_{13}INO$, $[M + H]^+$: 338.0036, found, 338.0031.

4-(5-Acetyl-6-methylpyridin-2-yl)benzonitrile ***(5g)***. Yield: 63% (44.6 mg) as a yellow solid; mp = 169.9−170.7 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.0 Hz, 2H), 8.09 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.0 Hz, 1H), 2.84 (s, 3H), 2.63 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 199.8, 158.8, 156.2, 142.3, 138.1, 132.6, 131.9, 127.8, 118.7, 117.9, 113.1, 29.4, 25.1; IR (KBr): 2924, 2851, 2224, 1678, 1574, 1427, 1353, 1261, 822 cm^{-1}; MS (EI) m/z 63, 140, 166, 178, 193, 221, 236; HRMS-ESI (m/z): calcd for $C_{15}H_{13}N_2O$, $[M + H]^+$: 237.1022, found, 237.1021.

1-(2-Methyl-6-(4-nitrophenyl)pyridin-3-yl)ethan-1-one ***(5h)***. Yield: 79% (60.7 mg) as a yellow solid; mp = 140.1−141.2 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, J = 28.4, 8.4 Hz, 4H), 8.10 (d, J = 8.0 Hz, 1H), 7.74 (s, 1H), 2.82 (s, 3H), 2.63 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 199.9, 158.8, 155.7, 148.5, 144.2, 138.1, 132.0, 128.1, 124.0, 118.2, 29.4, 25.1; IR (KBr): 2926, 1682, 1582, 1560, 1344, 1263, 826, 742 cm^{-1}; MS (EI) m/z 70, 115, 140, 167, 196, 213, 241, 256; HRMS-ESI (m/z): calcd for $C_{14}H_{13}N_2O_3$, $[M + H]^+$: 257.0921, found, 257.0927.

1-(5-Butyl-2-methyl-6-phenylpyridin-3-yl)ethan-1-one ***(5i)***. Yield: 52% (41.7 mg) as a yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 7.6 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 7.21−7.17 (m, 2H), 2.75 (s, 3H), 2.58 (t, J = 7.7 Hz, 2H), 2.51 (s, 3H), 1.58−1.50 (m, 2H), 1.33−1.24 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 199.9, 158.8, 158.6, 144.9, 138.0, 135.8, 130.3, 129.0, 127.2, 116.9, 35.5, 33.5, 29.3, 25.4, 22.3, 14.0; IR (KBr): 2961, 2928, 2858, 1686, 1580, 1262, 825 cm^{-1}; MS (EI) m/z 89, 91, 115, 141, 153, 168, 181, 196, 209, 224, 238, 252, 267; HRMS-ESI (m/z): calcd for $C_{18}H_{22}NO$, $[M + H]^+$: 268.1696, found, 268.1704.

1-(2-Methyl-5,6-diphenylpyridin-3-yl)ethan-1-one ***(5j)***. Yield: 81% (69.7 mg) as a yellow solid; mp = 87.9−89.1 °C; ^1H NMR (400 MHz,

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$CDCl_3$) δ 7.99 (s, 1H), 7.39 (d, J = 6.0 Hz, 2H), 7.27 (s, 3H), 7.22 (d, J = 6.4 Hz, 3H), 7.19−7.17 (m, 2H), 2.86 (s, 3H), 2.62 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 200.0, 158.4, 156.8, 139.8, 139.3, 139.1, 133.3, 130.9, 130.0, 129.5, 128.6, 128.4, 128.0, 127.5, 29.4, 24.8; IR (KBr): 3058, 2926, 1690, 1579, 1530, 1424, 1250, 1214, 800, 766 cm^{-1}; MS (EI) m/z 77, 91, 115, 121, 139, 166, 202, 215, 244, 287; HRMS-ESI (m/z): calcd for $C_{20}H_{17}NO$, $[M + H]^+$: 288.1383, found, 288.1387.

1-(2-Methyl-5,6-dihydrobenzo[h]quinolin-3-yl)ethan-1-one (**5k**). Yield: 67% (47.6 mg) as a yellow solid; mp = 106.3−107.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 6.8 Hz, 1H), 7.77 (s, 1H), 7.40−7.28 (m, 2H), 7.21 (d, J = 7.2 Hz, 1H), 2.93 (s, 4H), 2.80 (s, 3H), 2.58 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 200.0, 156.6, 153.9, 138.7, 136.8, 133.8, 130.8, 129.9, 128.6, 127.9, 127.3, 125.6, 29.3, 28.0, 27.4, 25.1; IR (KBr): 2928, 2843, 1683, 1589, 1581, 1436, 1350, 1251, 748 cm^{-1}; MS (EI) m/z 96, 115, 152, 167, 178, 194, 222, 237; HRMS-ESI (m/z): calcd for $C_{16}H_{16}NO$, $[M + H]^+$: 238.1226, found, 238.1231.

1-(6-(Furan-2-yl)-2-methylpyridin-3-yl)ethan-1-one (**5l**). Yield: 79% (47.6 mg) as a red oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 6.0 Hz, 2H), 7.16 (d, J = 2.8 Hz, 1H), 6.54 (s, 1H), 2.78 (s, 3H), 2.57 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 199.4, 159.0, 153.1, 150.3, 144.3, 138.0, 130.2, 115.3, 112.4, 110.8, 29.2, 25.3; IR (KBr): 2926, 1686, 1597, 1262, 745 cm^{-1}; MS (EI) m/z 63 77, 103, 130, 140, 158, 186, 201; HRMS-ESI (m/z): calcd for $C_{12}H_{12}NO_2$, $[M + H]^+$: 202.0863, found, 202.0869.

1-(2-Methyl-6-(thiophen-2-yl)pyridin-3-yl)ethan-1-one (**5m**). Yield: 81% (52.7 mg) as a red oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 2.8 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 4.8 Hz, 1H), 7.13−7.11 (m, 1H), 2.79 (s, 3H), 2.57 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 199.3, 159.0, 153.7, 144.0, 138.1, 130.2, 129.2, 128.3, 126.1, 115.5, 29.2, 25.3; IR (KBr): 2926, 1683, 1581, 1424, 1260, 1150, 823, 707 cm^{-1}; MS (EI) m/z 63, 86, 130, 140, 147, 159, 174, 202, 217; HRMS-ESI (m/z): calcd for $C_{12}H_{12}NOS$, $[M + H]^+$: 218.0634, found, 218.0639.

1-(6-Methyl-[2,4′-bipyridin]-5-yl)ethan-1-one (**5n**). Yield: 87% (55.3 mg) as a yellow solid; mp = 78.6−79.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 2H), 8.06 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 4.4 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 2.81 (s, 3H), 2.59 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 199.9, 158.8, 155.6, 150.4, 145.4, 138.0, 132.4, 121.3, 117.8, 29.4, 25.1; IR (KBr): 2926, 1688, 1560, 1415, 1262, 958, 820, 686 cm^{-1}; MS (EI) m/z 78, 98, 115, 142, 169, 197, 212; HRMS-ESI (m/z): calcd for $C_{13}H_{13}N_2O$, $[M + H]^+$: 213.1022, found, 213.1027.

1-(6-Methyl-[2,2′-bipyridin]-5-yl)ethan-1-one (**5o**). Yield: 59% (37.5 mg) as a brown solid; mp = 77.1−78.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.49 (d, J = 7.6 Hz, 1H), 8.31 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.83 (t, J = 7.0 Hz, 1H), 7.33 (s, 1H), 2.83 (s, 3H), 2.62 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 200.2, 158.0, 157.2, 155.2, 149.3, 138.0, 137.0, 132.2, 124.3, 121.8, 118.0, 29.4, 25.2; IR (KBr): 2925, 2856, 1683, 1580, 1551, 1432, 1356, 1253, 794, 747 cm^{-1}; MS (EI) m/z 78, 117, 142, 169, 197, 212; HRMS-ESI (m/z): calcd for $C_{13}H_{13}N_2O$, $[M + H]^+$: 213.1022, found, 213.1026.

1-(2,6-Dimethylpyridin-3-yl)ethan-1-one (**5p**). Yield: 54% (24.1 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 7.2 Hz, 1H), 7.07 (d, J = 7.2 Hz, 1H), 2.73 (s, 3H), 2.56 (s, 6H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 200.0, 160.8, 158.0, 137.4, 130.0, 120.3, 29.2, 24.8, 24.6; IR (KBr): 2924, 2856, 1679, 1582, 1437, 1366, 1226, 1053 cm^{-1}; MS (EI) m/z 77, 79, 106, 134, 149 ; HRMS-ESI (m/z): calcd for $C_9H_{12}NO$, $[M + H]^+$: 150.0913, found, 150.0916.

1-(5-Butyl-2-methyl-6-propylpyridin-3-yl)ethan-1-one (**5q**). Yield: 62% (43.3 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 2.79−2.75 (m, 2H), 2.68 (s, 3H), 2.61−2.57 (m, 2H), 2.55 (s, 3H), 1.69−1.56 (m, 4H), 1.46−1.375 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 200.4, 162.9, 154.9, 137.8, 132.1, 130.3, 34.9, 33.8, 31.9, 29.3, 24.4, 23.9, 22.9, 14.0; IR (KBr): 2962, 2927, 2867, 1687, 1544, 1439, 1263, 940 cm^{-1}; MS (EI) m/z 77, 91, 163, 176, 191, 204, 218, 233; HRMS-ESI (m/z): calcd for $C_{15}H_{24}NO$, $[M + H]^+$: 234.1852, found, 234.1858.

1-(6-Benzyl-2-methyl-5-phenylpyridin-3-yl)ethan-1-one (**5r**). Yield: 78% (70.4 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.41 (s, 3H), 7.21 (d, J = 4.4 Hz, 2H), 7.18−7.11 (m, 3H), 7.01 (d, J = 7.2 Hz, 2H), 4.15 (s, 2H), 2.83 (s, 3H), 2.58 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 200.1, 159.9, 156.9, 139.3, 138.8, 134.6, 130.4, 129.3, 128.8, 128.5, 128.2, 127.7, 126.1, 41.7, 29.3, 24.7; IR (KBr): 3060, 3027, 2925, 2851, 1687, 1586, 1534, 1429, 1224, 700 cm^{-1}; MS (EI) m/z 73, 91, 207, 224, 281, 301; HRMS-ESI (m/z): calcd for $C_{21}H_{19}NNaO$, $[M + Na]^+$: 324.1359, found, 324.1363.

1-(6-Cyclopropyl-2-methylpyridin-3-yl)ethan-1-one (**5s**). Yield: 47% (24.7 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 2.68 (s, 3H), 2.54 (s, 3H), 2.07−2.01 (m, 1H), 1.06 (s, 2H), 1.02 (d, J = 8.4 Hz, 2H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 199.8, 165.5, 158.4, 137.1, 129.3, 117.7, 29.1, 25.2, 17.5, 10.6; IR (KBr): 2925, 2853, 1684, 1586, 1264, 1144, 960, 818 cm^{-1}; MS (EI) m/z 65 77, 117, 132, 160, 175; HRMS-ESI (m/z): calcd for $C_{11}H_{14}NO$, $[M + H]^+$: 176.1070, found, 176.1074.

1-(2-Methyl-6,7-dihydro-5H-cyclopenta[b]pyridin-3-yl)ethan-1-one (**5t**). Yield: 62% (32.6 mg) as a red oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 3.02 (t, J = 7.6 Hz, 2H), 2.95 (t, J = 7.4 Hz, 2H), 2.71 (s, 3H), 2.56 (s, 3H), 2.19−2.12 (m, 2H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 200.6, 167.9, 156.4, 134.4, 133.0, 130.8, 34.4, 30.2, 29.5, 24.4, 23.1; IR (KBr): 2962, 2925, 1601, 1553, 1429, 1357, 1267, 740 cm^{-1}; MS (EI) m/z 65, 77, 91, 111, 132, 160, 175; HRMS-ESI (m/z): calcd for $C_{11}H_{14}NO$, $[M + H]^+$: 176.1070, found, 176.1075.

1-(2-Methyl-5,6,7,8-tetrahydroquinolin-3-yl)ethan-1-one (**5u**). Yield: 69% (39.1 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 2.90 (t, J = 6.2 Hz, 2H), 2.76 (t, J = 5.9 Hz, 2H), 2.68 (s, 3H), 2.54 (s, 3H), 1.88 (d, J = 5.6 Hz, 2H), 1.81 (d, J = 5.6 Hz, 2H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 200.2, 159.8, 155.0, 138.0, 130.3, 129.4, 32.5, 29.2, 28.3, 24.3, 22.8, 22.6; IR (KBr): 2931, 1684, 1549, 1440, 1149, 930 cm^{-1}; MS (EI) m/z 77, 91, 119, 131, 146, 174, 189; HRMS-ESI (m/z): calcd for $C_{12}H_{16}NO$, $[M + H]^+$: 190.1226, found, 190.1232.

1-(2-Methyl-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-3-yl)-ethan-1-one (**5v**). Yield: 81% (49.3 mg) as a yellow solid; mp = 67.3−68.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 3.02 (d, J = 7.6 Hz, 2H), 2.77 (d, J = 7.2 Hz, 2H), 2.67 (s, 3H), 2.54 (s, 3H), 1.86 (s, 2H), 1.67 (s, 4H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 200.3, 165.6, 154.7, 137.6, 135.1, 130.3, 39.4, 34.8, 32.7, 29.3, 27.9, 26.3, 24.3; IR (KBr): 2924, 2851, 1685, 1590, 1549, 1436, 1283, 1254, 944 cm^{-1}; MS (EI) m/z 77, 91, 118, 133, 160, 188, 203; HRMS-ESI (m/z): calcd for $C_{13}H_{18}NO$, $[M + H]^+$: 204.1383, found, 204.1391.

1-(2-Methyl-5,6,7,8,9,10-hexahydrocycloocta[b]pyridin-3-yl)-ethan-1-one (**5w**). Yield: 82% (53.4 mg) as a yellow solid; mp = 51.2−52.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 2.96−2.93 (m, 2H), 2.78−2.75 (m, 2H), 2.68 (s, 3H), 2.55 (s, 3H), 1.78 (s, 2H), 1.69 (s, 2H), 1.37 (s, 4H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 200.4, 163.6, 155.4, 137.5, 133.2, 130.8, 34.7, 32.1, 31.5, 30.5, 29.3, 25.9, 25.8, 24.4; IR (KBr): 2925, 2853, 1688, 1591, 1548, 1436, 1356, 1264, 941, 648 cm^{-1}; MS (EI) m/z 77, 91, 117, 146, 174, 188, 202, 217; HRMS-ESI (m/z): calcd for $C_{14}H_{20}NO$, $[M + H]^+$: 218.1539, found, 218.1542.

(S)-1-(2,8-Dimethyl-5-(prop-1-en-2-yl)-5,6-dihydroquinolin-3-yl)-ethan-1-one (**5x**). Yield: 44% (31.8 mg) as a red oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 6.17 (s, 1H), 4.95 (s, 1H), 4.80−4.75 (m, 1H), 3.61 (t, J = 8.7 Hz, 1H), 2.73 (s, 3H), 2.54 (s, 3H), 2.44 (d, J = 6.0 Hz, 2H), 2.14 (s, 3H), 1.73 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 200.2, 155.8, 155.7, 145.5, 135.4, 134.5, 130.5, 130.3, 129.4, 114.3, 45.2, 29.3, 27.7, 24.8, 19.7, 18.0; IR (KBr): 3077, 2973,2924, 1686, 1586, 1437, 1357, 1265, 1230, 899, 830 cm^{-1}; MS (EI) m/z 65, 77, 91, 115, 128, 142, 158, 184, 200, 213, 236, 241; HRMS-ESI (m/z): calcd for $C_{16}H_{20}NO$, $[M + H]^+$: 242.1539, found, 242.1544.

(E)-1-(2-Methyl-6-(2-(2,6,6-trimethylcyclohex-1-en-1-yl)vinyl)-pyridin-3-yl)ethan-1-one (**5y**). Yield: 47% (39.9 mg) as a red oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 16.0

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Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 6.49 (d, J = 16.0 Hz, 1H), 2.77 (s, 3H), 2.57 (s, 3H), 2.07 (t, J = 5.8 Hz, 2H), 1.81 (s, 3H), 1.63 (d, J = 5.6 Hz, 2H), 1.50 (d, J = 5.6 Hz, 2H), 1.10 (s, 6H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 199.6, 158.6, 157.9, 137.7, 137.1, 134.8, 132.3, 131.4, 130.0, 117.8, 39.8, 34.3, 33.3, 29.2, 29.0, 25.4, 21.9, 19.1; IR (KBr): 2966, 2927, 2854, 1687, 1578, 1461, 1256, 970, 676 cm^{-1}; MS (EI) m/z 77, 91, 119, 149, 207, 260, 268, 283; HRMS-ESI (m/z): calcd for $C_{19}H_{26}NO$, $[M + H]^+$: 284.2009, found, 284.2009.

1-(2-Methyl-4,6-diphenylpyridin-3-yl)ethan-1-one (**7a**). Yield: 63% (54.2 mg) as a yellow solid; mp = 102.4−103.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 7.2 Hz, 2H), 7.58 (s, 1H), 7.50−7.44 (m, 6H), 7.43 (s, 2H), 2.64 (s, 3H), 2.02 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 206.3, 157.0, 154.1, 147.3, 138.8, 138.4, 134.5, 129.3, 129.1, 129.0, 128.8, 128.5, 127.2, 118.6, 32.1, 23.0; IR (KBr): 3061, 2925, 1696, 1578, 1539, 753, 670 cm^{-1}; MS (EI) m/z 77, 115, 143, 203, 244, 272, 287; HRMS-ESI (m/z): calcd for $C_{20}H_{18}NO$, $[M + H]^+$: 288.1383, found, 288.1385.

1-(4-(4-Methoxyphenyl)-2-methyl-6-phenylpyridin-3-yl)ethan-1-one (**7b**). Yield: 38% (36.1 mg) as a yellow solid; mp = 99.6−100.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.2 Hz, 2H), 7.55 (s, 1H), 7.47 (t, J = 6.9 Hz, 2H), 7.43 (d, J = 6.8 Hz, 1H), 7.35 (d, J = 7.2 Hz, 2H), 6.99 (d, J = 7.2 Hz, 2H), 3.86 (s, 3H), 2.62 (s, 3H), 2.03 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 206.7, 160.3, 157.0, 154.0, 147.0, 138.9, 134.4, 130.6, 129.8, 129.3, 128.8, 127.2, 118.5, 114.5, 55.4, 32.0, 23.0; IR (KBr):, 2930, 2838, 1695, 1608, 1576, 1512, 1252, 1180, 1030, 837, 764, 694 cm^{-1}; MS (EI) m/z 77, 115, 189, 233, 302, 317; HRMS-ESI (m/z): calcd for $C_{21}H_{20}NO_2$, $[M + H]^+$: 318.1489, found, 318.1494.

1-(4-(4-Fluorophenyl)-2-methyl-6-phenylpyridin-3-yl)ethan-1-one (**7c**). Yield: 61% (55.8 mg) as a yellow solid; mp = 135.7−136.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.2 Hz, 2H), 7.53 (s, 1H), 7.48−7.43 (m, 3H), 7.41−7.39 (m, 2H), 7.17 (t, J = 8.3 Hz, 2H), 2.62 (s, 3H), 2.04 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 206.1, 163.3 (J = 248.0 Hz), 157.1, 154.1, 146.1, 138.6, 134.5, 134.3 (J = 3.3 Hz), 130.4 (J = 8.3 Hz), 129.4, 128.8, 127.1, 118.5, 116.1 (J = 21.5 Hz), 32.11, 23.00; IR (KBr): 3059, 2925, 2856, 1695, 1585, 1507, 1357, 842, 765, 693 cm^{-1}; MS (EI) m/z 77, 110, 152, 221, 290, 305; HRMS-ESI (m/z): calcd for $C_{20}H_{17}FNO$, $[M + H]^+$: 306.1289, found, 306.1291.

1-(4-(4-Chlorophenyl)-2-methyl-6-phenylpyridin-3-yl)ethan-1-one (**7d**). Yield: 64% (61.3 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.2 Hz, 2H), 7.53 (s, 1H), 7.49 (d, J = 6.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 3H), 7.35 (d, J = 7.6 Hz, 2H), 2.62 (s, 3H), 2.05 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 206.0, 157.2, 154.2, 145.9, 138.6, 136.7, 135.4, 134.4, 129.9, 129.5, 129.3, 128.8, 127.1, 118.3, 32.2, 23.1; IR (KBr): 2925, 1697, 1595, 1491, 1353, 1252, 1090, 834, 694 cm^{-1}; MS (EI) m/z 77, 143, 202, 237, 306, 321; HRMS-ESI (m/z): calcd for $C_{20}H_{17}ClNO$, $[M + H]^+$: 322.0993, found, 322.0998.

1-(4-(4-Bromophenyl)-2-methyl-6-phenylpyridin-3-yl)ethan-1-one (**7e**). Yield: 73% (79.9 mg) as a yellow solid; mp = 104.6−105.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 6.8 Hz, 2H), 7.60 (d, J = 7.6 Hz, 2H), 7.52 (s, 1H), 7.49−7.43 (m, 3H), 7.28 (d, J = 7.7 Hz, 2H), 2.62 (s, 3H), 2.05 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 205.9, 157.2, 154.2, 145.9, 138.6, 137.2, 134.3, 132.3, 130.1, 129.5, 128.8, 127.1, 123.6, 118.2, 32.2, 23.0; IR (KBr): 2924, 1697, 1586, 1536, 1488, 1353, 1254, 831, 694 cm^{-1}; MS (EI) m/z 77, 120, 142, 202, 271, 350, 365; HRMS-ESI (m/z): calcd for $C_{20}H_{17}BrNO$, $[M + H]^+$: 366.0488, found, 366.0492.

4-(3-Acetyl-2-methyl-6-phenylpyridin-4-yl)benzonitrile (**7f**). Yield: 79% (73.9 mg) as a yellow solid; mp = 150.4−152.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.2 Hz, 2H), 7.75 (d, J = 7.6 Hz, 2H), 7.52 (d, J = 7.2 Hz, 3H), 7.49−7.43 (m, 3H), 2.62 (s, 3H), 2.06 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 205.4, 157.4, 154.4, 145.1, 142.9, 138.3, 134.2, 132.7, 129.7, 129.3, 128.9, 127.1, 118.2, 118.0, 113.0, 32.4, 23.1; IR (KBr): 3062, 2925, 2853, 2229, 1697, 1580, 1536, 1354, 1254, 844, 785, 695 cm^{-1}; MS (EI) m/z 77, 207, 228, 297, 312; HRMS-ESI (m/z): calcd for $C_{21}H_{17}N_2O$, $[M + H]^+$: 313.1335, found, 313.1341.

1-(2-Methyl-4-(4-nitrophenyl)-6-phenylpyridin-3-yl)ethan-1-one (**7g**). Yield: 77% (76.7 mg) as a yellow solid; mp = 130.3−131.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 7.6 Hz, 2H), 8.04 (d, J = 6.4 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 7.55 (s, 1H), 7.51−7.44 (m, 3H), 2.64 (s, 3H), 2.09 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 205.3, 157.4, 154.4, 148.2, 144.8, 138.3, 134.2, 129.7, 129.6, 128.9, 128.8, 127.1, 124.1, 118.0, 32.4, 23.1; IR (KBr): 3066, 2925, 2855, 1698, 1601, 1520, 1349, 1233, 857, 696 cm^{-1}; MS (EI) m/z 77, 139, 202, 248, 271, 317, 332; HRMS-ESI (m/z): calcd for $C_{20}H_{17}N_2O_3$, $[M + H]^+$: 333.1234, found, 333.1238.

4-(3-Acetyl-2-methyl-6-phenylpyridin-4-yl)benzaldehyde (**7h**). Yield: 44% (41.6 mg) as a yellow solid; mp = 152.2−153.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.04 (d, J = 7.2 Hz, 2H), 7.99 (d, J = 7.6 Hz, 2H), 7.61 (s, 1H), 7.58 (d, J = 7.2 Hz, 2H), 7.51−7.45 (m, 3H), 2.65 (s, 3H), 2.06 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 205.6, 191.5, 157.3, 154.3, 145.8, 144.3, 138.4, 136.4, 134.3, 130.2, 129.6, 129.3, 128.9, 127.2, 118.2, 32.3, 23.1; IR (KBr): 3680, 2924, 2854, 1698, 1577, 1359, 760, 693 cm^{-1}; MS (EI) m/z 115, 202, 207, 272, 300, 315; HRMS-ESI (m/z): calcd for $C_{21}H_{18}NO_2$, $[M + H]^+$: 316.1332, found, 316.1330.

1-(4-(Furan-2-yl)-2-methyl-6-phenylpyridin-3-yl)ethan-1-one (**7i**). Yield: 73% (60.7 mg) as a red oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.2 Hz, 2H), 7.79 (s, 1H), 7.56 (s, 1H), 7.48 (t, J = 7.0 Hz, 2H), 7.44 (d, J = 6.4 Hz, 1H), 6.80 (s, 1H), 6.53 (s, 1H), 2.58 (s, 3H), 2.44 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 206.1, 157.2, 153.8, 150.0, 144.3, 138.8, 134.5, 131.1, 129.3, 128.8, 127.1, 114.2, 112.4, 111.1, 31.8, 22.7; IR (KBr): 2926, 2853, 1700, 1596, 1568, 1354, 1254, 751, 695 cm^{-1}; MS (EI) m/z 77, 139, 193, 207, 235, 262, 277; HRMS-ESI (m/z): calcd for $C_{18}H_{16}NO_2$, $[M + H]^+$: 278.1176, found, 278.1182.

1-(2-Methyl-6-phenyl-4-(thiophen-2-yl)pyridin-3-yl)ethan-1-one (**7j**). Yield: 76% (66.8 mg) as a red oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 6.8 Hz, 2H), 7.64 (s, 1H), 7.48 (d, J = 5.6 Hz, 4H), 7.17 (s, 1H), 7.12 (s, 1H), 2.62 (s, 3H), 2.22 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 206.2, 157.1, 154.0, 139.6, 138.9, 138.3, 133. 9, 129.5, 128.8, 128.8, 128. 5, 128.2, 127.2, 118.4, 31. 8, 22.8; IR (KBr): 3066, 2925, 1696, 1578, 1542, 1429, 1355, 1249, 758, 698 cm^{-1}; MS (EI) m/z 77, 104, 165, 209, 278, 293; HRMS-ESI (m/z): calcd for $C_{18}H_{16}NOS$, $[M + H]^+$: 294.0947, found, 294,0951.

1-(2′-Methyl-6′-phenyl-[2,4′-bipyridin]-3′-yl)ethan-1-one (**7k**). Yield: 82% (70.8 mg) as a yellow solid; mp = 143.3−144.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 2H), 8.03 (d, J = 7.2 Hz, 2H), 7.53 (s, 1H), 7.47 (dd, J = 15.4, 7.4 Hz, 3H), 7.34 (s, 2H), 2.63 (s, 3H), 2.10 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 205.4, 157.5, 154.4, 150.4, 146.2, 144.3, 138.3, 134.1, 129.7, 128.9, 127.1, 123.2, 117.8, 32.4, 23.2; IR (KBr): 3064, 2925, 2583, 1697, 1574, 1509, 1353, 1299, 841, 694 cm^{-1}; MS (EI) m/z 77, 204, 245, 273, 288; HRMS-ESI (m/z): calcd for $C_{19}H_{17}N_2O$, $[M + H]^+$: 289.1335, found, 289.1338.

(E)-1-(2-Methyl-6-phenyl-4-styrylpyridin-3-yl)ethan-1-one (**7l**). Yield: 42% (39.4 mg) as a brown solid; mp = 72.4−73.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.2 Hz, 2H), 7.73 (s, 1H), 7.50−7.46 (m, 4H), 7.42 (d, J = 6.8 Hz, 1H), 7.39−7.35 (m, 2H), 7.32 (d, J = 6.4 Hz, 1H), 7.22 (s, 1H), 6.98 (d, J = 12.0 Hz, 1H), 2.57 (s, 3H), 2.54 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 206.4, 157.2, 153.4, 142.1, 139.0, 136.0, 135.5, 134.1, 129.3, 129.1, 128.9, 128.8, 127.2, 127.1, 123.3, 114.4, 32.8, 22.9; IR (KBr): 3034, 2924, 2856, 1694, 1577, 1538, 1256, 965, 912, 714, 692 cm^{-1}; MS (EI) m/z 77, 207, 228, 270, 298, 313; HRMS-ESI (m/z): calcd for $C_{22}H_{20}NO$, $[M + H]^+$: 314.1539, found, 314.1542.

1-(2-Methyl-6-phenyl-4-(trifluoromethyl)pyridin-3-yl)ethan-1-one (**7m**). Yield: 27% (22.6 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 6.4 Hz, 2H), 7.78 (s, 1H), 7.50 (d, J = 7.2 Hz, 3H), 2.63 (s, 3H), 2.60 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 202.8, 158.1, 154.7, 137.5, 133.6 (q, J = 279.6 Hz), 130.1, 129.0, 127.1, 124.2, 121.5, 113.8 (q, J = 4.3 Hz), 32.0, 22.8; IR (KBr): 2926, 2854, 1710, 1600, 1380, 1348, 1167, 690, 558 cm^{-1}; MS (EI) m/z 77, 108, 167, 216, 236, 264, 279; HRMS-ESI (m/z): calcd for $C_{15}H_{13}F_3NO$, $[M + H]^+$: 280.0944, found, 280.0945.

3-Benzylidenepentane-2,4-dione (**B**). Yield: 77% (43.4 mg) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.39 (s, 5H),

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2.41 (s, 3H), 2.27 (s, 3H); ^{13}C {1H} NMR (100 MHz, $CDCl_3$) δ 205.4, 196.5, 142.8, 139.8, 132.9, 130.6, 129.7, 129.0, 31.6, 26.4; MS (EI) *m/z* 77, 103, 115, 131, 145, 173, 188.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01621.

Spectral data for all new compounds (PDF)

Crystallographic data for **4h** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jianghf@scut.edu.cn. Fax: (+86) 20-8711-2906.

Notes

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(16) CCDC 1404112 (**4h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. A single crystal of product **4h** is in the Supporting Information.

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