Note

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Metal-free synthesis of fully substituted pyridines via ring construction based on the domino reactions of enaminones and aldehydes

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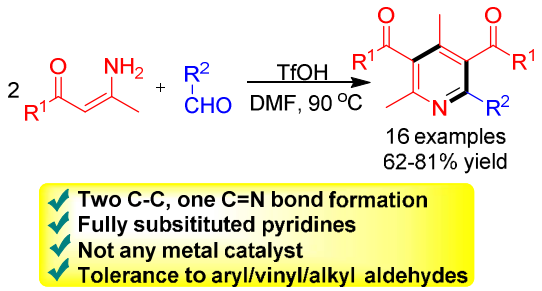


Abstract

An unprecedented domino reaction involving primary enaminones/enaminoesters and aldehydes has been developed for the synthesis of fully substituted pyridines. The construction of the products has been accomplished via the cascade generation of two C-C and one C-N bonds by simply using TfOH as a promoter.

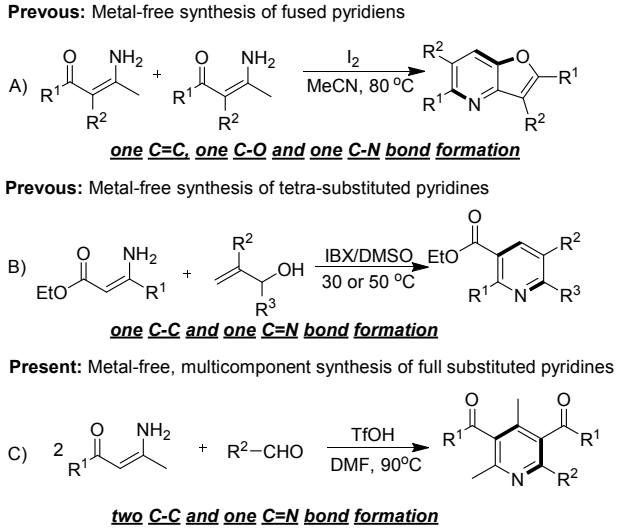
Throughout the history of synthetic science, the synthesis of pyridines occupies significant position as a fundamental heterocyclic entity. The widespread applications of pyridines in pharmaceutical, agricultural, materials and synthetic organic fields have revealed the irreplaceable merits of these compounds.[1] Classically, the Hantzsch reaction involving the condensation annulations of aldehydes, methylene dicarbonyl compounds and ammonia combining a subsequent oxidation,[2] the Kröhnke pyridine synthesis using phenacyl isoquinolinium bromides, benzalacetophenone and

ammonium,[3] the multimolecular Chichibabin reactions[4] and the [2+2+2] cycloaddition-based ring formation[5] have been predominantly utilized for pyridine synthesis. During the past decades, impressive advances have occurred in the chemistry of pyridine synthesis and a large number of alternative tactics have been successfully established to access pyridine with unprecedentedly high molecular diversity.[6] The protocols of metal-catalyzed cycloaddition reactions,[7] the multicomponent assemblies of acetophenone, aldehyde and ammonium,[8] the transition metal-catalyzed reactions of ketoxime actates with carbon electrophiles,[9] among others,[10] have constituted the representative model of new pyridine synthesis. In despite the enriched availability on the synthetic methodologies, however, one or more of the restrictions such as reliance on transition metal catalyst, stepwise operation and/or utilization of sensitive reactants remain as challenges in pyridine synthesis. In this context, extensive efforts in devising new synthetic routes of high sustainability such as metal-free methods[6,11] for the synthesis of pyridine, especially those densely or fully substituted pyridines, is present an issue of high desirability.

Enaminones are useful synthons showing prevalent application in organic synthesis.[12] Particularly, enaminones have been discovered with widespread application in the construction of heterocyclic molecules of different types,[13] including the known protocols for pyridines synthesis.[14] However, the survey on related known literatures indicates that most enaminone-based heterocycle syntheses employ tertiary or secondary enaminones. The reactions employing primary enaminones containing free NH_2 group, on the other hand, have been much less

explored. Recently, Yan, Huang and co-workers have reported an interesting dimerization reactions of primary enaminones which lead to the synthesis of various pyridine fused heterocyclic products (A in Scheme 1).[15] On the other hand, Pal, Iqbal and co-workers have reported that the reactions of primary enaminones with allylic alcohols provides 1,2,5,6-tertrasubstituted pyridines with the catalysis of IBX (B in Scheme 1).[16] During our continuous research in designing new synthetic approaches using enaminones and related electron deficient enamines, we report herein a metal-free, primary enaminone-based reaction for the synthesis of fully substituted pyridines via cascade formation of two C-C and one C=N bonds (C in Scheme 1).

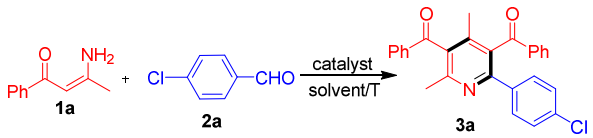
Scheme 1 Synthesis of pyridines and ring fused pyridines using enaminones



The investigation started from the condition optimization on the model reaction of primary enaminone **1a** and *p*-chlorobenzaldehyde **2a**. The reaction conducted in the presence of different Brønsted and Lewis acids was found to be capable of providing pyridine **3a**, and TfOH displayed amongst the best effect (entries 1-7, Table 1). On the other hand, the examination on entries using different media suggested that DMF was

the most proper polar organic solvent (entries 8-13, Table 1). Subsequent investigation on the effect of the reaction temperature disclosed that heightening or lowering the temperature was neither positive to the result (entries 14-15, Table 1). Finally, reducing the loading of TfOH led to the decrease on the product yield although increasing the amount of TfOH didn't gave further enhancement of the yield (entries 16-18, Table 1). The requirement of stoichiometric acid in the reaction might be attributed to the generation of the ammonium side product in the reaction which deactivated part of acid (See also the reaction mechanism in Scheme 2). Finally, a control experiment performed under argon showed the formation only trace product (entry 19, Table 1), indicating the indispensable function of air for the reaction.

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Solvent	T (^{o}C)	Yield (%)b
1	TMSCl	DMF	90	52
2	TfOH	DMF	90	81
3	PhCOOH	DMF	90	38
4	$FeCl_3$	DMF	90	45
5	$AlCl_3$	DMF	90	55
6	AcOH	DMF	90	43
7	TsOH	DMF	90	50
8	TfOH	DMSO	90	55
9	TfOH	H_2O	90	nr[c]
10	TfOH	EtOH	reflux	46
11	TfOH	CH_3CN	reflux	37
12	TfOH	THF	reflux	nr
13	TfOH	1,4-dioxane	90	34

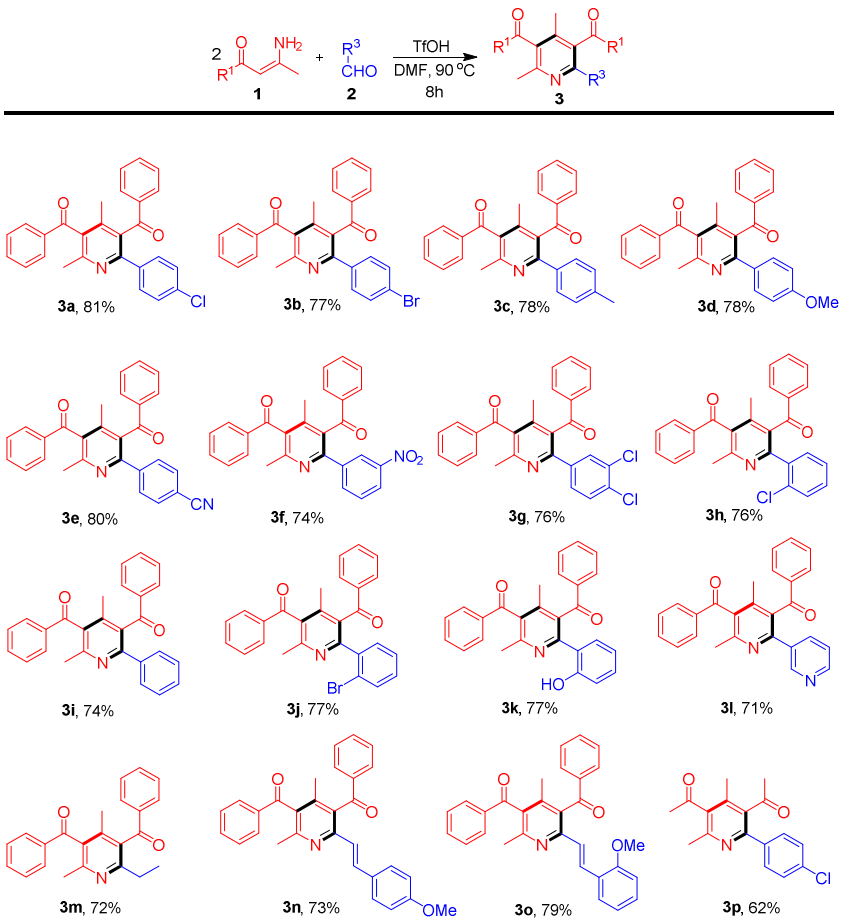
14	TfOH	DMF	80	67
15	TfOH	DMF	100	75
16[c]	TfOH	DMF	90	45
17[d]	TfOH	DMF	90	58
18[e]	TfOH	DMF	90	80
19[f]	TfOH	DMF	90	trace

[a]General conditions:**1a** (0.6 mmol), **2a** (0.3 mmol), acid promoter (0.3 mmol), stirred for 8 h. NR = no reaction. [b]Yield of isolated product. [c]The TfOH was 0.15 mmol. [d]The TfOH was 0.21 mmol. [e]The TfOH was 0.39 mmol. [f]Reaction under argon.

Based on the in hand results from the optimization experiments, the scope of the pyridine synthesis was then investigated. The results in the synthesis of various full substituted pyridines were provided in Table 2. Based on these synthesized products, it was demonstrated that the present synthetic approach was generally applicable for the synthesis of these full substituted pyridines. The tolerance of the reaction to diverse aryl aldehydes (**3a-l**, Table 2) vinyl aldehydes (**3n-o**, Table 2) and alkyl aldehyde (**3m**, Table 2) demonstrated the broad application scope of the present method in the preparation of pyridines with flexible C2-substitution. As for the enaminone component, the alkyl functionalized enaminone also exhibited practical application in the synthesis of corresponding pyridine product (**3p**, Table 2). However, the entry employing two different enaminones **1a** and **1b** (the alkyl-based enaminone) proved that complex mixture was formed.

All the products were obtained in generally good yield, and no substantial effect of the functional group to yield of products was indicated with the present data. The structure of the novel pyridine products were clearly assigned by full spectroscopic analysis and X-ray single crystal of **3i** (see SI).[17]

Table 2 Scope for the synthesis of fully substituted pyridines[a]

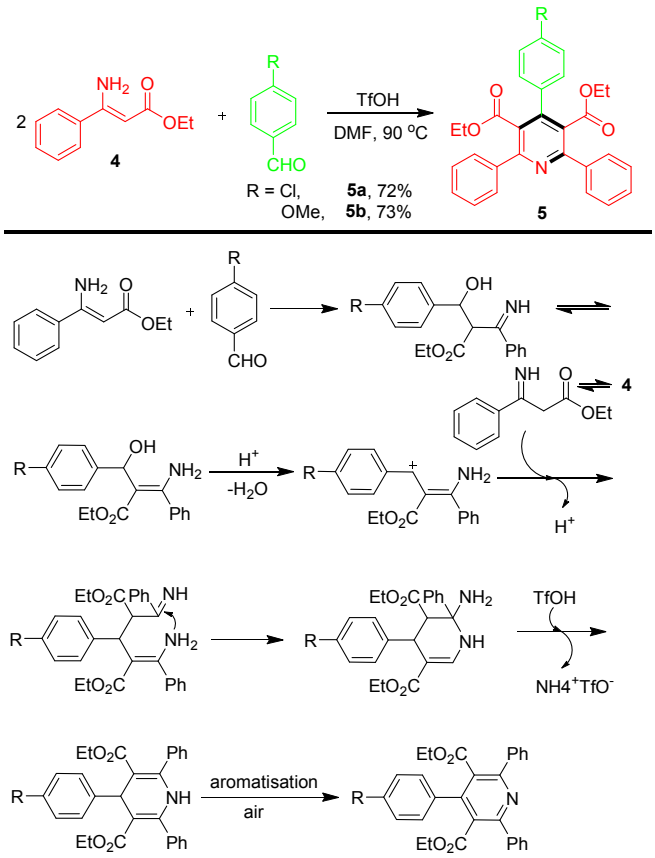


[a]Yield of isolated product based on **2** was reported.

Interestingly, when enaminoesters **4** were subjected as alternative substrates of enaminones to the catalytic system, unexpected production of symmetrical pyridines **5** were observed, revealing the novel application of the present catalytic method for the synthesis of diverse pyridines (Scheme 2). According to the structure of the products, it was possible the Hantzsch-type reaction pathway was selectively involved to provide the symmetrical pyridines with the promotion of TfOH. Based on our previous works on the switchable relative nucleophilicity of the amino group and the α-carbon in the enaminones and enaminoesters,[18] the outcome of the selective formation of symmetrical pyridines **5** might be ascribed to the electron withdrawing

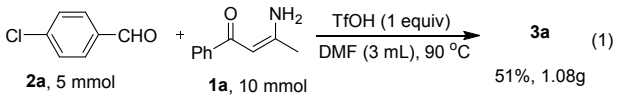
effect produced by the conjugate styrene fragment, which reduced the nucleophilic strength of the amino group in **4**, and thereafter prevented its direct condensation with the aldehyde (see also Scheme 3). Instead, the nucleophilic α-carbon in **4** acted as the initial site to incorporate the aldehyde and finally led to the formation of products **5** (Scheme 2).

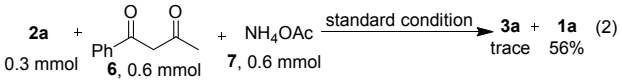
Scheme 2 Formation of symmetrical pyridines with enaminoester



To further illustrate the application potential of the method, we attempted the scaled up synthesis of pyridine **3a**, and it was found that the gram scale synthesis provided practical result with 51% yield (Eq 1). On the other hand, a control experiment using aldehyde **2a**, 1-phenylbutane-1,3-dione **6** and ammonium acetate **7** failed to afforded pyridine product **3a** under standard reaction conditions, instead, the

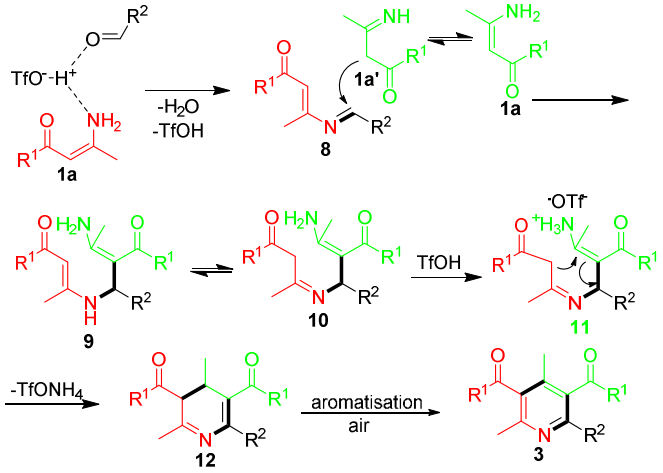
NH_2-enaminone **1a** was acquired as the main product (Eq 2), suggesting the irreplaceable role of enaminones **1** in the synthesis of these unprecedented pyridines.





According to the reaction results, a mechanism for the formation of these pyridines has been tentatively proposed in Scheme 3. Firstly, the activation of TfOH to the enaminone **1** promoted the condensation of the amino group with the aldehyde and yield imine intermediate **8**, and the nucleophilic addition of **1'**, the isomeric version of **1**, to the imine gives intermediate **9**. The tautomerization of **9** gives **10** which subsequently incorporate TfOH to access ammonium intermediate **11**. The intramolecular annulation on **11** initiated by a nucleophilic substitution yields dihydropyridine intermediate **12** and $TfONH_4$. The pyridine products **3** were then generated via the aromatization of **12** via the aerobic oxidation.

Scheme 3 The postulated reaction mechanism



In conclusion, we have established an unprecedented cascade reaction involving the dimerization of primary enaminones for the synthesis of full substituted pyridines with unprecedented pattern. Without using any metal catalyst, the construction of pyridine has been achieved through the generation of two new C-C and a C=N bonds. The easy availability and high stability of the starting materials, simple operation and novelty in both the reaction model as well as products features the high application potential of the present method.

Experimental section

General procedure for the synthesis of pyridines 3 and 5. In a 25 mL round bottom flask were charged with enaminone **1** or enaminoester **4** (0.6 mmol), aldehyde **2** (0.3 mmol), triflic acid (TfOH) (0.3 mmol) and DMF (2.0 mL). The vessel was then heated at 90 °C for 8 h (TLC) under air atmosphere. Upon completion, 10 mL water was added, and resulting mixture was extracted with ethyl acetate (3×10 mL). The organic phase was collected and dried with anhydrous Na_2SO_4. After filteration, the solution was evaporated at reduced pressure to remove the solvent, and the residue was subjected to silica gel column chromatography to give pure product using mixed petroleum ether / ethyl acetate as eluent (v / v = 15:1).

(2-(4-Chlorophenyl)-4,6-dimethylpyridine-3,5-diyl)bis(phenylmethanone) (**3a**). Yield: 103 mg; 81%; white solid; mp 189-190 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 7.2 Hz, 2 H), 7.65 (d, *J* = 8.0 Hz, 3 H), 7.55-7.47 (m, 5 H), 7.33 (t, *J* = 8.0 Hz, 2 H), 7.22 (d, *J* = 8.8 Hz, 2 H), 2.49 (s, 3 H), 2.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 197.7, 154.7, 154.3, 142.7, 137.7, 136.8, 136.4, 135.0, 134.5, 134.2, 134.0,

132.4, 130.5, 129.5, 129.4, 129.3, 128.8, 128.5, 23.1, 16.9; ESI-HRMS: Calcd for $C_{27}H_{21}ClNO_2$ $[M + H]^+$ 426.1255, found 426.1259.

(2-(4-Bromophenyl)-4,6-dimethylpyridine-3,5-diyl)bis(phenylmethanone) (**3b**). Yield: 108 mg; 77%; white solid; mp 198-199 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 7.2 Hz, 2 H), 7.66-7.63 (m, 3 H), 7.55-7.47 (m, 3 H), 7.43-7.32 (m, 6 H), 2.48 (s, 3 H), 2.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 197.7, 154.7, 154.3, 142.7, 138.1, 136.8, 136.3, 134.6, 134.2, 134.1, 132.3, 131.5, 130.8, 129.5, 129.4, 129.3, 128.8, 123.4, 23.1, 16.9; ESI-HRMS: Calcd for $C_{27}H_{21}BrNO_2$ $[M + H]^+$ 470.0750, found 470.0750.

(2,4-Dimethyl-6-(p-tolyl)pyridine-3,5-diyl)bis(phenylmethanone) (**3c**). Yield: 95 mg; 78%; white solid; mp 223-224 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.2 Hz, 2 H), 7.65 (t, *J* = 8.0 Hz, 3 H), 7.52 (t, *J* = 8.0 Hz, 2 H), 7.43 (t, *J* = 8.0 Hz, 3 H), 7.31 (t, *J* = 8.0 Hz, 2 H), 7.03 (d, *J* = 8.0 Hz, 2 H), 2.48 (s, 3 H), 2.24 (s, 3 H), 2.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 198.0, 155.7, 154.4, 142.4, 138.6, 137.0, 136.5, 136.4, 134.4, 133.6, 132.6, 132.2, 129.5, 129.4, 129.2, 129.1, 129.0, 128.6, 23.2, 21.2, 16.9. ESI-HRMS: Calcd for $C_{28}H_{24}NO_2$ $[M + H]^+$ 406.1802, found 406.1805.

(2-(4-Methoxyphenyl)-4,6-dimethylpyridine-3,5-diyl)bis(phenylmethanone) (**3d**). Yield: 99 mg; 78%; white solid; mp 195-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.6 Hz, 2 H), 7.65 (t, *J* = 7.6 Hz, 3 H), 7.54 - 7.43 (m, 5 H), 7.31 (t, *J* = 7.6 Hz, 2 H), 6.76 (d, *J* = 8.8 Hz, 2 H), 3.71 (s, 3 H), 2.48 (s, 3 H), 2.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1 (2C), 160.1, 155.2, 154.4, 142.4, 137.0, 136.6, 134.4, 133.7, 133.4, 131.9, 131.8, 130.6, 129.5, 129.3, 129.2, 128.6, 113.8, 55.1, 23.2, 16.9.

ESI-HRMS: Calcd for $C_{28}H_{24}NO_3$ $[M + H]^+$ 422.1751, found,422.1755.

4-(3,5-Dibenzoyl-4,6-dimethylpyridin-2-yl)benzonitrile (**3e**). Yield: 100 mg; 80%; white solid; mp 203-204 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.6 Hz, 2 H), 7.70-7.63 (m, 5 H), 7.57-7.49 (m, 5 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 2.50 (s, 3 H), 2.05 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 197.3, 155.1, 153.5, 143.5, 143.0, 138.6, 136.1, 134.9, 134.7, 134.3, 132.7, 132.0, 129.8, 129.5, 129.4, 128.9, 118.5, 112.4, 23.1, 17.0; ESI-HRMS: Calcd for $C_{28}H_{21}N_2O_2$ $[M + H]^+$ 417.1598, found 417.1596.

(2,4-Dimethyl-6-(3-nitrophenyl)pyridine-3,5-diyl)bis(phenylmethanone) (**3f**). Yield: 97 mg; 74%; yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 8.47 (s, 1 H), 8.09 (d, *J* = 9.6 Hz, 1 H), 7.91 (d, *J* = 7.2 Hz, 2 H), 7.86 (d, *J* = 7.6 Hz, 1 H), 7.67 (d, *J* = 7.6 Hz, 3 H), 7.56 (t, *J* = 7.6 Hz, 2 H), 7.52 - 7.41 (m, 2 H), 7.36 (t, *J* = 7.6 Hz, 2 H), 2.52 (s, 3 H), 2.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5 , 197.3, 155.2, 152.9, 148.1, 143.1, 140.7, 136.6, 136.2, 134.9, 134.8, 134.4, 132.7, 130.0, 129.5, 129.4, 129.3, 129.0, 128.4, 124.3, 123.5, 23.1, 17.0; ESI-HRMS: Calcd for $C_{27}H_{21}N_2O_4$ $[M + H]^+$ 437.1496, found, 437.1498.

(2-(3,4-Dichlorophenyl)-4,6-dimethylpyridine-3,5-diyl)bis(phenylmethanone) (**3g**). Yield: 105 mg; 76%; yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.6 Hz, 2 H), 7.70 (s, 1 H), 7.66 (d, *J* = 7.6 Hz, 3 H), 7.53 (q, *J* = 7.6 Hz, 3 H), 7.39 - 7.33 (m, 3 H), 7.29 (d, *J* = 8.8 Hz, 1 H), 2.49 (s, 3 H), 2.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 197.4, 154.9, 152.9, 142.9, 139.0, 136.8, 136.3, 134.62, 134.57, 134.2, 133.2, 132.6, 132.5, 131.2, 130.2, 129.4, 129.32, 129.29, 128.9, 128.3, 23.1, 16.9; ESI-HRMS: Calcd for $C_{27}H_{20}Cl_2NO_2$ $[M + H]^+$ 460.0866, found 460.0869.

(2-(2-Chlorophenyl)-4,6-dimethylpyridine-3,5-diyl)bis(phenylmethanone) (**3h**). Yield: 97 mg; 76%; white solid; mp 121-122 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.2 Hz, 2 H), 7.60 (d, *J* = 7.6 Hz, 3 H), 7.54 (t, *J* = 7.2 Hz, 2 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 7.32 (d, *J* = 7.2 Hz, 2 H), 7.24 (d, *J* = 7.6 Hz, 2 H), 7.11 (brs, 2 H), 2.49 (s, 3 H), 2.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 196.6, 154.3, 153.9, 142.5, 137.2, 136.8, 136.2, 134.62, 134.58, 133.8, 133.6, 132.9, 131.4, 129.9, 129.8, 129.5, 129.3, 129.2, 128.5, 126.2, 23.0, 17.0; ESI-HRMS: Calcd for $C_{27}H_{21}ClNO_2$ $[M + H]^+$ 426.1255, found 426.1257.

(2,4-Dimethyl-6-phenylpyridine-3,5-diyl)bis(phenylmethanone) (**3i**). Yield: 87 mg; 74%; white solid; mp 154-155 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.0 Hz, 2 H), 7.64 (d, *J* = 7.2 Hz, 3 H), 7.52 (t, *J* = 7.6 Hz, 4 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 7.29 (t, *J* = 7.6 Hz, 2 H), 7.22 (d, *J* = 7.2 Hz, 3 H), 2.50 (s, 3 H), 2.05 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 197.9, 155.7, 154.6, 142.6, 139.2, 136.9, 136.4, 134.6, 133.9, 133.8, 132.3, 129.5, 129.4, 129.3, 129.2, 128.8, 128.6, 128.3, 23.2, 17.0; ESI-HRMS: Calcd for $C_{27}H_{22}NO_2$ $[M + H]^+$ 392.1645, found 392.1650.

(2-(2-Bromophenyl)-4,6-dimethylpyridine-3,5-diyl)bis(phenylmethanone) (**3j**). Yield: 108 mg; 77%; yellow solid; mp 76-77 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.6 Hz, 2 H), 7.67 (d, *J* = 7.6 Hz, 3 H), 7.55 (t, *J* = 7.2 Hz, 2 H), 7.47-7.41 (m, 2 H), 7.33 (t, *J* = 7.6 Hz, 2 H), 7.25 (d, *J* = 7.2 Hz, 1 H), 7.16 (t, *J* = 7.2 Hz, 1 H), 7.04 (d, *J* = 7.6 Hz, 1 H), 2.49 (s, 3 H), 2.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 196.7, 155.0, 154.2, 142.4, 138.9, 136.9, 136.3, 134.6, 134.5, 133.8, 133.4, 133.1, 131.4, 129.9, 129.5, 129.29, 129.27, 128.5, 126.7, 122.8, 23.0, 17.0; ESI-HRMS:

Calcd for $C_{27}H_{21}BrNO_2$ $[M + H]^+$ 470.0750, found, 470.0754.

(2-(2-Hydroxyphenyl)-4,6-dimethylpyridine-3,5-diyl)bis(phenylmethanone) (**3k**). Yield: 94 mg; 77%; white solid; mp 164-165 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 12.43 (brs, 1 H), 7.87 (d, *J* = 8.0 Hz, 2 H), 7.70 - 7.65 (m, 3 H), 7.55 - 7.47 (m, 3 H), 7.40 - 7.32 (m, 3 H), 7.13 (t, *J* = 8.0 Hz, 1 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 6.61 (d, *J* = 7.6 Hz, 1 H), 2.49 (s, 3 H), 2.06 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 197.0, 157.9, 154.4, 152.4, 144.9, 136.6, 136.2, 134.7, 134.1, 133.9, 132.0, 131.6, 129.9, 129.5, 129.34, 129.29, 128.9, 120.3, 119.1, 118.0, 22.6, 17.4; ESI-HRMS: Calcd for $C_{27}H_{22}NO_3$ $[M + H]^+$ 408.1594, found, 408.1597.

(4,6-Dimethyl-[2,3'-bipyridine]-3,5-diyl)bis(phenylmethanone) (**3l**). Yield: 84 mg; 71%; yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 8.80 (brs, 1 H), 8.47 (brs, 1 H), 7.89 (q, *J* = 8.4 Hz, 3 H), 7.67 (d, *J* = 7.6 Hz, 3 H), 7.57 - 7,.47 (m, 3 H), 7.34 (d, *J* = 7.6 Hz, 2 H), 7.19 (d, *J* = 6.8 Hz, 1 H), 2.51 (s, 3 H), 2.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 197.3, 155.0, 152.4, 149.6, 149.4, 142.8, 136.7, 136.5, 136.2, 135.0, 134.65, 134.56, 134.2, 132.8, 129.4, 129.35, 129.30, 128.9, 123.0, 23.0, 16.9; ESI-HRMS: Calcd for $C_{26}H_{21}N_2O_2$ $[M + H]^+$ 393.1598, found, 393.1601.

(2-Ethyl-4,6-dimethylpyridine-3,5-diyl)bis(phenylmethanone) (**3m**). Yield: 74 mg; 72%; yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.0 Hz, 4 H), 7.66-7.62 (m, 2 H), 7.53-7.49 (m, 4 H), 2.65 (q, *J* = 7.6 Hz, 2 H), 2.42 (s, 3 H), 1.92 (s, 3 H) 1.22 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 198.0, 158.9, 154.1, 141.3, 136.8, 136.5, 134.4, 132.9, 132.4, 130.0, 129.5, 129.2, 129.1, 128.3, 29.6, 22.8, 16.8, 14.1; ESI-HRMS Calcd: for $C_{23}H_{22}NO_2[M + H]^+$ 344.1645, found

344.1655.

(E)-(2-(4-Methoxystyryl)-4,6-dimethylpyridine-3,5-diyl)bis(phenylmethanone) (**3n**). Yield: 98 mg; 73%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 15.6 Hz, 1 H), 7.88 (t, *J* = 7.6 Hz, 4 H), 7.63 (q, *J* = 7.6 Hz, 2 H), 7.50 (q, *J* = 7.6 Hz, 4 H), 7.31 (d, *J* = 7.2 Hz, 1 H), 7.21 (t, *J* = 7.2 Hz, 1 H), 6.95 (d, *J* = 15.2 Hz, 1 H), 6.84 (q, *J* = 8.0 Hz, 2 H), 3.75 (s, 3 H), 2.46 (s, 3 H), 1.94 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3 , 198.1, 160.1, 154.4, 151.4, 141.7, 137.1, 136.6, 135.2, 134.4, 133.3, 131.7, 130.4, 129.7, 129.5, 129.2, 128.9, 126.5, 121.8, 114.6, 114.1, 55.3, 23.3, 16.8; ESI-HRMS: Calcd for $C_{30}H_{26}NO_3$ $[M + H]^+$ 448.1907, found 448.1915.

(E)-(2-(2-Methoxystyryl)-4,6-dimethylpyridine-3,5-diyl)bis(phenylmethanone) (**3o**). Yield: 106 mg; 79%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.85 (m, 5 H), 7.63 (q, *J* = 8.0 Hz, 2 H), 7.50 (q, *J* = 7.6 Hz, 4 H), 7.33 (d, *J* = 7.6 Hz, 2 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 6.69 (d, *J* = 15.2 Hz, 1 H), 3.79 (s, 3 H), 2.46 (s, 3 H), 1.93 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 198.2, 157.8, 154.5, 151.7, 141.7, 137.1, 136.6, 134.4, 134.3, 133.4, 132.0, 130.9, 129.7, 129.5, 129.2, 129.1, 128.3, 125.4, 125.1, 120.5, 110.9, 55.3, 23.3, 16.8; ESI-HRMS: Calcd for $C_{30}H_{26}NO_3$ $[M + H]^+$ 448.1907, found, 448.1915.

2,4-Dimethyl-3,5-diacetyl-6-(4-chlorophenyl) pyridine (**3p**). Yield: 62 mg; 69%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2 H), 2.47 (s, 3 H), 2.45 (s, 3 H), 2.11 (s, 3 H), 1,94 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.5, 205.3, 153.0,. 152.6, 139.3, 137.5, 136.8, 135.6, 134.8, 130.4, 129.0, 32.3, 32.2, 22.6, 16.1; ESI-HRMS: Calcd for $C_{17}H_{17}ClNO_2$ $[M + H]^+$ 302.0942,

found, 302.0942.

Diethyl 4-(4-chlorophenyl)-2,6-diphenylpyridine-3,5-dicarboxylate (**5a**). Yield: 105 mg; 72%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73-7.70 (m, 4 H), 7.44-7.38 (m, 8 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 3.90 (q, *J* = 7.2 Hz, 4 H), 0.86 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 156.4, 146.3, 139.1, 135.0, 134.1, 130.0, 129.3, 128.7, 128.5, 128.4, 127.6, 61.7, 13.5; ESI-HRMS: Calcd for $C_{29}H_{25}ClNO_4$ $[M + H]^+$ 486.1467, found 486.1471.

Diethyl 4-(4-methoxyphenyl)-2,6-diphenylpyridine-3,5-dicarboxylate (**5b**). Yield: 106 mg; 73%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73-7.70 (m, 4 H), 7.44-7.40 (m, 6 H), 7.31 (d, *J* = 8.8 Hz, 2 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 3.90 (q, *J* = 7.2 Hz, 4 H), 3.82 (s, 3 H), 0.86 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8 , 159.9, 156.1, 147.2, 139.3, 129.8, 129.1, 128.7, 128.4, 128.1, 127.8, 113.5, 61.5, 55.3, 13.5; ESI-HRMS: Calcd for $C_{30}H_{28}NO_5$ $[M + H]^+$ 482.1962, found 482.1964.

Supporting Information

General experimental information, ^{1}H/^{13}C NMR spectra for all products and the crystallographic data of **3i**. This material is available free of charge via the Internet at http:

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Notes

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17. CCDC 1464635 contains the supplementary crystallographic data for this paper (**3i**).These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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