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Copper-Catalyzed Oxidative Coupling of β-Keto Esters with N-Methylamides for the Synthesis of Symmetrical 2,3,5,6-Tetrasubstituted Pyridines

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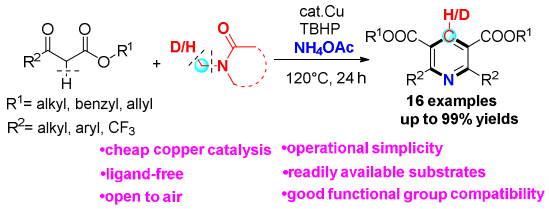


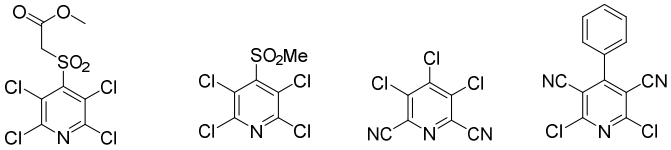
ABSTRACT: A copper-catalyzed oxidative formal [2+2+1+1] cycloaddition for the synthesis of symmetrical tetrasubstituted pyridines was first demonstrated. The reaction is involved in a domino CDC of β-keto esters and N-methylamides, C-N cleavage, Michael addition, condensation and oxidative aromatization process. Multiple C-C and C-N bonds were constructed in one pot via C-H and C-N cleavage of N-methylamides, which was employed as carbon source of pyridines. The preliminary mechanistic studies revealed that C(sp^3)-H bond cleavage of N-methylamides was the rate-determining step.

INTRODUCTION

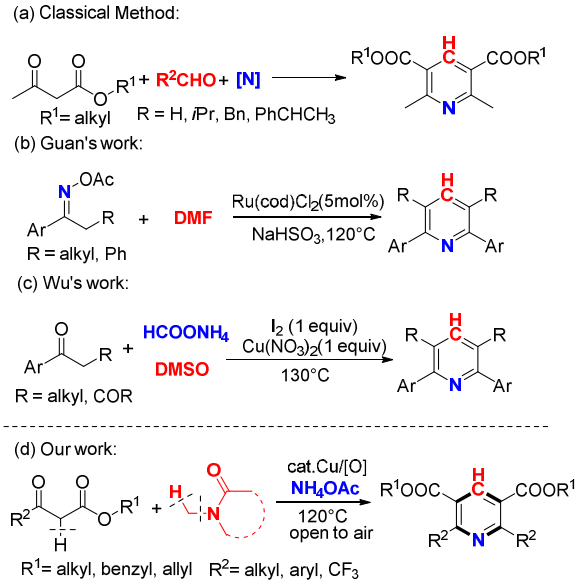
Pyridines represent an important and valuable class of nitrogen-containing heterocycles in natural products, functional materials and medicinal chemistry.[1] In particular, a variety of symmetrical multisubstituted pyridines have been employed as fungicide and herbicide because of good biological activity (Figure 1).[2] Furthermore, it was also an useful ligand in metal-catalyzed organic reactions and its hydrogenated product could be used as reducing reagents.[3] Over the past decades, symmetrical tetrasubstituted pyridines were mainly synthesized via condensation and aromatization of 1,3-dicarbonyl compounds, formaldehyde (such as formaldehyde, isobutyraldehyde 2-phenylacetaldehyde and 2-phenylacetaldehyde) and ammonium salt in two steps or in one pot (Scheme 1a).[4] However, substrate scope of reaction were narrow with only akyl group as C-2 substitution group of pyridines. In 2014, Guan's group reported a novel and efficient ruthenium-catalyzed cyclization of ketoxime acetates with DMF for the synthesis of symmetrical 2,3,5,6-tetrasubstituted pyridines (Scheme 1b).[5] In this paper, N-methyl group of DMF was employed as C-4 source of pyridine ring. However, this method required pre-synthesized substrates and expensive transition metal with only aryl group as C-2 substitution group of pyridine products. Recently, Wu's group also reported an efficient synthesis of symmetrical 2,3,5,6-tetrasubstituted pyridines via $C(sp^3)$–H oxidation and C–S cleavage of DMSO (Scheme 1c).[6a] In this reaction, S-methyl group of DMSO provided C-4 source of pyridine ring. Unfortunately, stoichiometric copper salts and iodine were added to promote this process. In addition, C-2 substituted group on pyridine ring remained limited to aryl group. At the same time, Yuan's group aslo reported a similar reaction with DMSO as C-4 source of pyridine ring promoted by NH_4I.[6b] Therefore, the

development of a simple and general protocol for symmetrical tetrasubstituted pyridines using novel C-4 source remains highly desirable.

Figure 1. Selected Examples of Symmetrical Multisubstituted Pyridines with Biological Activity



Scheme 1. Strategies for the Construction of Symmetrical 2,3,5,6-Tetrasubstituted Pyridines

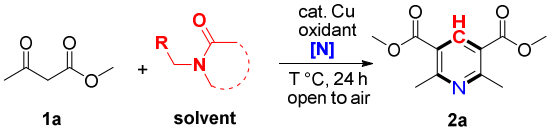


In recent years, transition-metal-catalyzed or metal-free cross dehydrogenative coupling (CDC) has emerged as an important tool for direct construction of C-C bond.[7] In particular, intermolecular CDC reaction between α-C(sp^3)-H bond of 1,3-dicarbonyl compounds and activated C(sp^3)-H bond adjacent to heteroatom could give a α-functionalized product of 1,3-dicarbonyl compounds.[8] However, to the best of our knowledge, CDC reaction between 1,3-dicarbonyl compounds and activated C-H bond for the synthesis of heterocycles has not been reported to date.

As our continuous efforts for heterocycles using novel carbon or nitrogen synthons,[9] herein we report a copper-catalyzed oxidative formal [2+2+1+1] cycloaddition for the synthesis of symmetrical tetrasubstituted pyridines (Scheme 1d). The reaction is involved in a domino CDC of β-keto esters with N-methylamides, C-N cleavage, Michael addition, condensation and oxidation process. Four chemical bonds are formed via C-H and C-N cleavage in one pot. The extra nitrogen and carbon atom of pyridines originate from ammonium acetate and N-methyl group of N-methylamides, respectively. A series of symmetrical 2,3,5,6-tetrasubstituted pyridines were obtained in moderate to excellent yields with good functional group compatibility.

RESULTS AND DISCUSSION

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	N source	oxidant	solvent	yield(%)[b]
1	$Cu(OAc)_2$	NH_4OAc	TBHP	NMP	14
2	$Cu(OAc)_2$	NH_4OAc	DTBP	NMP	13
3	$Cu(OAc)_2$	NH_4OAc	TBPB	NMP	trace
4	$Cu(OAc)_2$	NH_4OAc	DCP	NMP	trace
5	$Cu(TFA)_2$	NH_4OAc	TBHP	NMP	28
6	$Cu(OTf)_2$	NH_4OAc	TBHP	NMP	29
7	$CuBr_2$	NH_4OAc	TBHP	NMP	20
8	$CuCl_2$	NH_4OAc	TBHP	NMP	15
9	CuCl	NH_4OAc	TBHP	NMP	20
10	CuI	NH_4OAc	TBHP	NMP	24
11	CuBr	NH_4OAc	TBHP	NMP	31
12	Cu_2O	NH_4OAc	TBHP	NMP	34
13	Cu_2O	NH_4OAc	TBHP	DMF	37
14	Cu_2O	NH_4OAc	TBHP	DMA	78
15	Cu_2O	NH_4OAc	TBHP	DEA	n.d.
16	Cu_2O		TBHP	DMA	n.d.
17	Cu_2O	NH_4Cl	TBHP	DMA	11
18	Cu_2O	NH_3(aq)	TBHP	DMA	trace
19	Cu_2O	NH_4I	TBHP	DMA	12
20	Cu_2O	NH_4OAc	TBHP	DMA	56[c], 25[d]

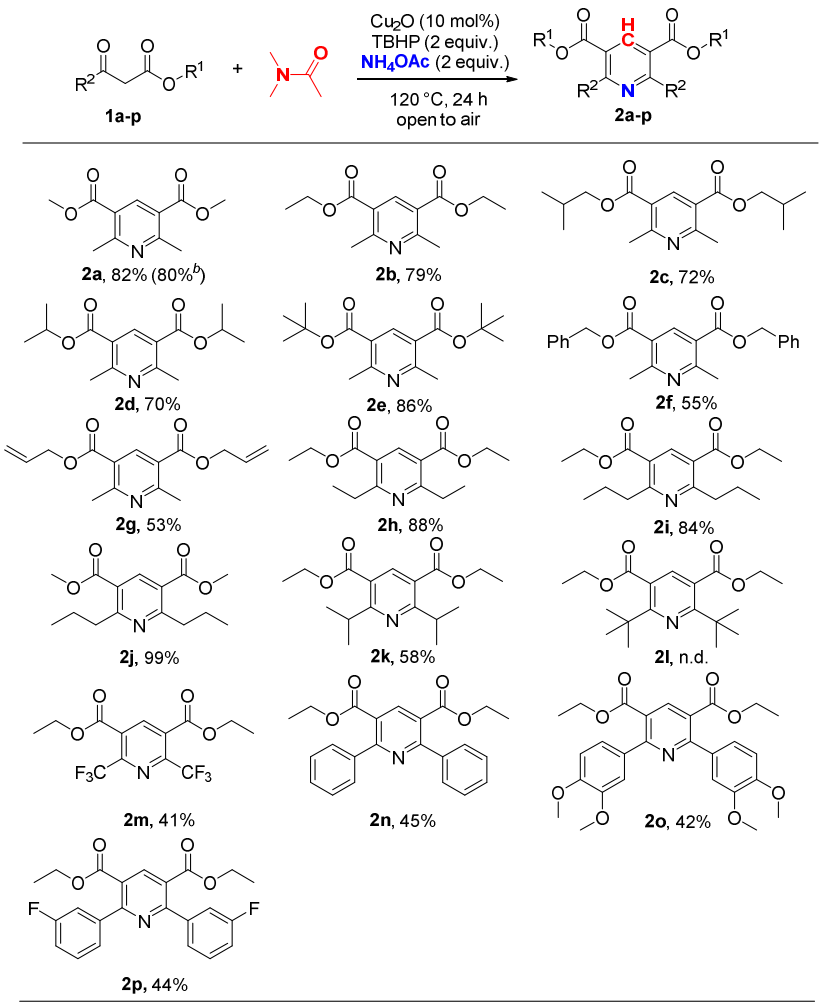
21	Cu_2O	NH_4OAc	TBHP	DMA	45[e], 40[f]
22	Cu_2O	NH_4OAc	TBHP	DMA	64[g], 67[h], 44[i], 35[j]
23[k]	Cu_2O	NH_4OAc	TBHP	DMA	32
24[l]	**Cu_2O**	**NH_4OAc**	**TBHP**	**DMA**	**82**
25[m]	Cu_2O	NH_4OAc	TBHP	DMA	68

[a] Reaction conditions: **1a** (0.4 mmol), catalyst (10 mol%), oxidant (2 equiv.), N source (1 equiv.), solvent (1 mL), 120 °C, 24 h, in air. [b] Isolated yield; n.d.= not detected. [c] 130 °C. [d] 140 °C. [e] 110 °C. [f] 100 °C. [g] DMA (0.5 mL). [h] DMA (0.8 mL). [i] DMA (1.5 mL). [j] DMA (2 mL). [k] TBHP (4 equiv.). [l] NH_4OAc (2 equiv.). [m] NH_4OAc (1 equiv.) and HOAc (1 equiv.).

Initially, we began our study with the reaction of one equivalent of methyl acetoacetate (**1a**), one equivalent of NH_4OAc, two equivalents of *tert*-butyl hydroperoxide (TBHP, 70% in aqueous) as the oxidant and 10 mol% of $Cu(OAc)_2$ as the catalyst. When the reaction mixture was heated in N-methyl pyrrolidone (NMP) at 120 °C for 24 h, dimethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**2a**) was obtained in 14% isolated yield (Table 1, entry 1). Among the examination of various per-oxidants, such as di-*tert*-butylperoxide (DTBP), *tert*-butyl peroxybenzoate (TBPB) and dicumyl peroxide (DCP), DTBP afforded **2a** in a similar yield to TBHP while TBPB and DCP gave trace amount of **2a** (Table 1, entries 2-4). When various copper salts, such as $Cu(TFA)_2$, $Cu(OTf)_2$, $CuBr_2$, $CuCl_2$, CuCl, CuBr, CuI and Cu_2O, were used as the catalyst, Cu_2O gave a highest yield of 34% (Table 1, entries 5–12). To examine the source of C-4 atom, various solvents were tested in the reaction. The use of solvents N,N-dimethylformamide (DMF) and N,N-dimethylacetamide (DMA) gave the desired product **2a**, while DMA gave a highest 78% yield (Table 1, entries 13 and 14). However, N,N-diethylacetamide (DEA) didn't give the desired product (Table 1, entry 15). These results implied that C-4 atom of **2a** was presumedly originated from the N,N-dimethyl

moiety of solvents. In the absence of NH_4OAc, no desired **2a** was detected, which indicated that NH_4OAc provided the N source of pyridine ring (Table 1, entry 16). When various nitrogen sources, such as NH_4Cl, NH_3 (aq) and NH_4I, were examined, a negative influence on reaction yields was obviouly observed (Table 1, entries 17-19). In addition, when the reaction temperature was increased from 120 °C to 130 °C or 140 °C, the reaction yields obviously decreased perhaps due to the generation of more by-products. (Table 1, entry 20). When the reaction temperature was decreased from 120 °C to 110 °C or 100 °C, the reaction yields were also decreased, which is because of low reactivity in lower temperature (Table 1, entry 21). Moreover, the reaction concentration had a significant effect on reaction yields as well (Table 1, entry 22). High concentration might result in much by-products while low concentration resulted in the reducing of reactivity. Increasing the amount of TBHP to four equivalents also decreased the reaction yield because of further oxidation of the product **2a** (Table 1, entry 23). When two equivalents of NH_4OAc was used, **2a** was isolated in 82% yield (Table 1, entry 24). Finally, when one equivalent of HOAc and one equivalent of NH_4OAc were employed together, the reaction yield decreased to 68% (Table 1, entry 25). Therefore, the optimal conditions were established as described in entry 24.

Table 2. The Substrate Scope of β-Keto Esters[a]



[a] Reaction conditions: **1** (0.4 mmol), Cu_2O (10 mol%), TBHP (2 equiv.), NH_4OAc (2 equiv.), DMA (1 mL), 120 °C, 24 h, in air; isolated yield. [b] 10 mmol scale.

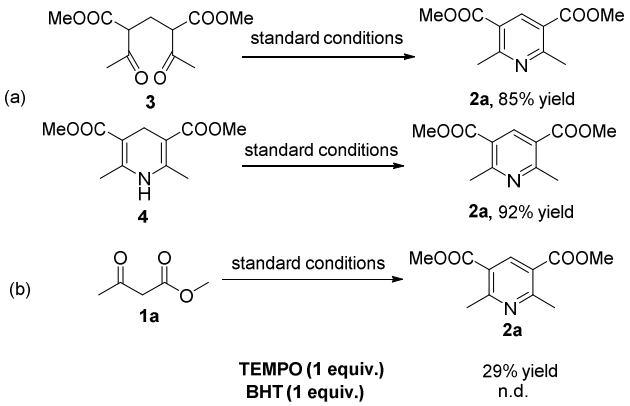
Under the optimal reaction conditions, we explored the generality of these reaction conditions for various β-keto esters (Table 2). First, various acetoacetate esters (**1a-1g**) were employed in this reaction, giving the desired products 2,6-dimethylpyridine-3,5-dicarboxylate esters (**2a-2g**) in moderate to good yields. For example, when R^1 were primary, secondary and tertiary alkyl groups, such as methyl, ethyl, isobutyl, *tert*-butyl and isopropyl, the corresponding pyridines **2a-2e** were obtained in good yields. Notably, the yields slightly decreased with the increase of carbon chain length (Table 2, **2a-2c**). Moreover, tertiary

alkyl-substitued substrate gave a higher yield than primary or secondary alkyl- substitued substrate. When R^1 was a benzyl group, the product **2f** was obtained in a moderate 55% yield. Similarly, substrate **1g** with an allyl group as R^1 substituent also gave the desired product **2g** in 53% yield. Subsequently, various substrates bearing alkyl groups as R^2 substituent were also examined in this reaction. The reaction of substrates **1h-1k** afforded the desired products **2h-2k** in high yields. However, when R^2 was a isobutyl group, the product **2k** was obtained in lower yield. Unfortunately, the reaction didn't proceed smoothly with *tert*-butyl as R^2 substituent perhaps due to steric hindrance. It is noted that **2m** having two CF_3 groups at C-2 and C-6 position was isolated with a low 41% yield when ethyl 4,4,4-trifluoro-3-oxobutanoate (**1m**) was employed as a substrate. In addition, ethyl benzoylacetates **1n-1p** also gave the corresponding products **2n-2p** in 42%-45% yields. To investigate the practicability of this method, a synthesis of **2a** could be scalable from 0.4 mmol to 10 mmol with a 80% yield, which indicated that this method could be widely applied during organic synthesis.

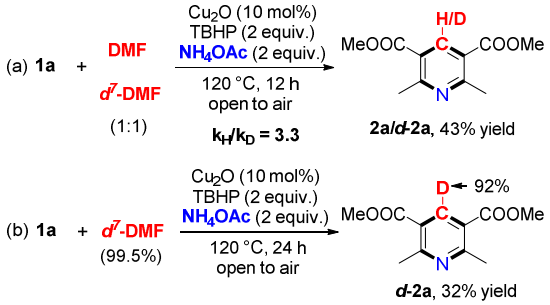
To gain an insight into the mechanism, several control experiments were carried out (Scheme 2). First, two possible intermediates dimethyl 2,4-diacetylpentanedioate (**3**) and dimethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**4**) were pre-synthesized according to known literatures.[4d,10] Then the reaction of **3** or **4** under standard conditions gave **2a** in 85% or 92% yield, respectively (Scheme 2a). This indicated that both **3** and **4** might be the reaction intermediates. Subsequently, radical trapping experiments were also carried out (Scheme 2b). It was observed that the reaction was obviously inhibited in the presence of one equivalent of radical inhibitors, such as 2,2,6,6- tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-tert-butyl-4-methylphenol (BHT). This implied that the reaction presumably underwent

a radical pathway.

Scheme 2. Control Experiments for Mechanistic Studies

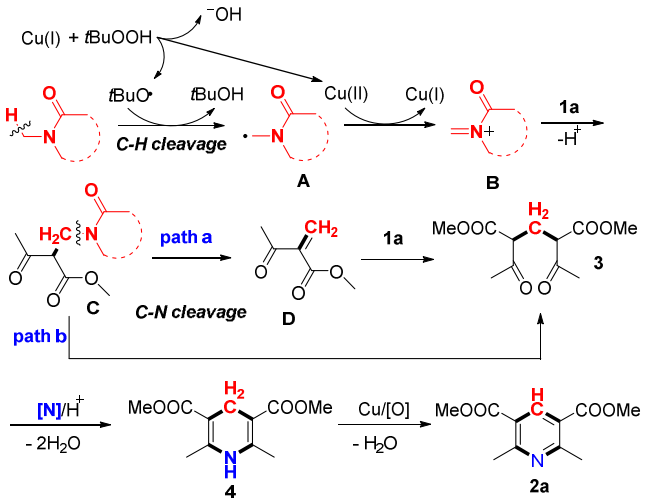


Scheme 3. KIE and D-Labeling Experiment



On the other hand, a large intermolecular kinetics isotope effect (KIE, k_H/k_D = 3.3) was observed from DMF and d^7-DMF (1:1) as co-solvents, which indicated that the C-H cleavage was a rate-determining step (Scheme 3a).[11] Moreover, 32% yield of ***d*-2a** was obtained in D-labeling experiment under standard conditions, which unambiguously established that the C-4 framework of pyridine was derived from N-methylamides (Scheme 3b). Notably, trace amount of **2a** remained obtained because hydrogen transfer probably occurs during the reaction.

Scheme 4. A Plausible Mechanism



On the basis of the results above and previous reports,[7,8,9a] a plausible mechanism was proposed (Scheme 4). Initially, the decomposition of *tert*-butyl hydroperoxide generates a *tert*-butoxy radical and a hydroxyl anion in the presence of Cu(I), which is oxidized to Cu(II). Then the *tert*-butoxy radical abstracts a hydrogen atom of C(sp^3)-H bond adjacent to nitrogen atom of N-methylamides to give a carbon radical **A**, which could generate an imine ion **B** via a single-electron-transfer (SET) process in the presence of Cu(II).[9a,12] Subsequently, the nucleophilic addition of **1a** to **B** produces an amide intermediate **C**. A sequential C-N cleavage of **C** can generate α,β-unsaturated ketone **D** (Scheme 4, path a). Then a Michael addition of **1a** to **D** provided an intermediate **3**. However, **3** could also be formed directly via a simple S_N2 substitution of **1a** to **C** (Scheme 4, path b). Finally, **3** could be converted to **2a** through tandem condensation and oxidative aromatization process.[13] Overall, the Cu(I)-Cu(II) redox process plays an important role in C-C bond construction of pyridine ring.

CONCLUSION

In summary, we have developed a copper-catalyzed oxidative coupling of β-keto esters

and N-methylamides, affording a variety of symmetrical tetrasubstituted pyridines in the presence of ammonium acetate. Compared to previous reports, this novel protocol is distinguished by 1) the use of inexpensive transition metal; 2) operational simplicity; 3) the fact that an inert atmosphere or dry solvents are not required; 4) good functional groups tolerance. Copper-catalyzed oxidative coupling reactions for the synthesis of other heterocycles using N-methylamides as carbon source are ongoing in our laboratory.

EXPERIMENTAL SECTION

Unless otherwise indicated, all commercial reagents and solvents were used without additional purification. ^{1}H-NMR spectra were recorded with a Bruker AVIII-600 spectrometer. Chemical shifts (in ppm) were referenced to tetramethylsilane (δ = 0 ppm) in $CDCl_3$ as an internal standard. ^{13}C-NMR spectra were obtained by the same NMR spectrometer and were calibrated with $CDCl_3$ (δ = 77.00 ppm). HRMS (ESI) were recorded on a Water^{TM} Q-TOF Premier Mass Spectrometer. Melting point was recorded on a Hanon MP430 Auto Melting Point System.

General Procedure for the Synthesis of Symmetrical 2,3,5,6-Tetrasubstituted Pyridines

β-keto esters **1** (0.4 mmol), Cu_2O (10 mol%, 0.04 mmol), NH_4OAc (2 equiv., 0.8 mmol) and TBHP (2 equiv., 0.8 mmol) were added to a 10 mL Schlenk tube, followed by addition of DMA (1.0 mL). The mixture was stirred was stirred at 120 °C for 24 h. The solution was then cooled to r.t., quenched by a Na_2SO_3 aqueous solution and extracted with EtOAc (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 6:1) to afford the desired products **2**.

Characterization Data for Products

dimethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**2a**)[4d]: Yield (82%, 36.5mg); White solid; mp:100-101°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.71 (s, 1H), 3.93 (s, 6H), 2.86 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.2, 162.6, 141.0, 122.6, 52.3, 24.9; GC-MS (EI): m/z 223.1, 208.1, 195.1, 178.1, 151.1, 106.1, 77.0, 63.0; IR (film, cm^{-1}): *v* 1725, 1548, 1286, 1105; UV (nm): λ_{max} 209.

diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (**2b**)[4d]: Yield (79%, 39.6mg); Yellowish solid; mp: 67-68 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.68 (s, 1H), 4.40 (q, J = 7.2 Hz, 4H), 2.85 (s, 6H), 1.42 (t, J = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 165.9, 162.2, 140.9, 123.0, 61.4, 24.9, 14.2; GC-MS (EI): m/z 251.1, 236.1, 223.1, 206.1, 195.1, 178.1, 151.1, 106.1, 77.0, 63.0; IR (film, cm^{-1}): *v* 2978, 2928, 1719, 1591, 1223, 773; UV (nm): λ_{max} 205, 207, 360.

diisobutyl 2,6-dimethylpyridine-3,5-dicarboxylate (**2c**): Yield (72%, 44.2mg); Yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.74 (s, 1H), 4.12 (d, J = 6.0 Hz, 4H), 2.87 (s, 6H), 2.10 (m, J = 6.6 Hz, 2H), 1.04 (d, J = 7.2 Hz, 12H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 165.8, 162.3, 141.0, 122.9, 71.4, 27.7, 25.0, 19.2; HRMS (ESI): calcd for $C_{17}H_{26}NO_4$ $[M+H]^+$ 308.1856, found 308.1861; IR (film, cm^{-1}): *v* 2978, 2934, 1718, 1594, 1224, 774; UV (nm): λ_{max} 208.

diisopropyl 2,6-dimethylpyridine-3,5-dicarboxylate (**2d**)[4d]: Yield (70%, 39.1mg); Yellowish solid; mp: 64-65 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.62 (s, 1H), 5.27 (hept, J = 6.3 Hz, 2H), 2.84 (s, 6H), 1.39 (d, J = 6.3 Hz, 12H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 165.6, 161.7, 140.8, 123.5, 69.1, 24.9, 21.9; GC-MS (EI): m/z 279.1, 237.1, 220.1, 195.1, 178.1, 151.1, 133.0, 105.0, 77.0, 63.0, 43.1; IR (film, cm^{-1}): *v* 2987, 2938 1715, 1224, 1107, 777; UV (nm): λ_{max} 360, 366.**di-*tert*-butyl 2,6-dimethylpyridine-3,5-dicarboxylate** (**2e**)[4d]: Yield (86%, 52.8mg); Yellow solid; mp: 107-108 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.53 (s, 1H), 2.81 (s, 6H), 1.61 (s, 18H);

^{13}C NMR (150 MHz, $CDCl_3$): δ 165.4, 161.1, 140.7, 124.6, 82.0, 28.1, 25.0; LC-MS (ESI): $[M+H]^+$ 308.2; IR (film, cm^{-1}): ν 2978 2934 1710, 1596, 1266, 1158, 847, 777; UV (nm): λ_{max} 201, 360.

dibenzyl 2,6-dimethylpyridine-3,5-dicarboxylate (**2f**)[4d]: Yield (55%, 41.2mg); White solid; mp: 83-84 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.75 (s, 1H), 7.44-7.41 (m, 4H), 7.40-7.35 (m, 6H), 5.35 (s, 4H), 2.85 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 165.6, 162.6, 141.2, 135.5, 128.7, 128.4, 128.3, 122.7, 67.1, 25.0; LC-MS (ESI): $[M+H]^+$ 376.1; IR (film, cm^{-1}): ν 2966, 2946, 1726, 1594, 1297, 1218, 733; UV (nm): λ_{max} 209.

diallyl 2,6-dimethylpyridine-3,5-dicarboxylate (**2g**)[4d]: Yield (53%, 29.2mg); Yellow solid; mp: 60-61 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.75 (s, 1H), 6.09-6.01 (m, 2H), 5.42 (dq, J_1 = 17.2 Hz, J_2 = 1.4 Hz, 2H), 5.32 (dq, J_1 = 10.4 Hz, J_2 = 1.3 Hz, 2H), 4.84 (dt, J_1 = 5.7 Hz, J_2 = 1.3 Hz, 4H), 2.86 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 165.4, 162.6, 141.1, 131.8, 122.7, 118.9, 66.0, 25.0; GC-MS (EI): m/z 275.1, 260.1, 234.1, 191.1, 178.1, 133.1, 105.1, 63.0, 41.1; IR (film, cm^{-1}): ν 2961, 2926, 1720, 1594, 1222, 771; UV (nm): λ_{max} 204, 360, 365.

diethyl 2,6-diethylpyridine-3,5-dicarboxylate (**2h**)[4d]: Yield (88%, 49.2mg); Light yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.61 (s, 1H), 4.40 (q, J = 7.1 Hz, 4H), 3.20 (q, J = 7.5 Hz, 4H), 1.41 (t, J = 7.1 Hz, 6H), 1.31 (t, J = 7.5 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.8, 166.0, 141.1, 122.6, 61.4, 30.4, 14.2, 13.8; GC-MS (EI): m/z 279.1, 264.1, 250.1, 223.1, 179.1, 134.1, 77.0, 63.0; IR (film, cm^{-1}): ν 2978, 2926, 1725, 1593, 1236, 810; UV (nm): λ_{max} 202.

diethyl 2,6-dipropylpyridine-3,5-dicarboxylate (**2i**): Yield (84%, 51.6mg); Light yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.61 (s, 1H), 4.40 (q, J = 7.2 Hz, 4H), 3.15 (t, J = 7.8 Hz, 4H), 1.78-1.70 (m, 4H), 1.41 (t, J = 7.2 Hz, 6H), 1.00 (t, J = 7.4 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$):

δ 166.2, 165.5, 141.1, 122.8, 61.3, 38.9, 23.2, 14.2, 14.1; HRMS (ESI): calcd for $C_{17}H_{26}NO_4$ $[M+H]^+$ 308.1856, found 308.1857; IR (film, cm^{-1}): *v* 2964, 2929, 1724, 1594, 1288, 1232, 1108; UV (nm): λ_{max} 360.

dimethyl 2,6-dipropylpyridine-3,5-dicarboxylate (**2j**): Yield (99%, 55.3mg); Light yellow oil; ^1H NMR (600 MHz, $CDCl_3$): δ 8.64 (s, 1H), 3.92 (s, 6H), 3.16 (t, *J* = 7.8 Hz, 4H), 1.78-1.70 (m, 4H), 1.00 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.3, 166.0, 141.2, 122.3, 52.2, 38.8, 23.1, 14.1; HRMS (ESI): calcd for $C_{15}H_{22}NO_4$ $[M+H]^+$ 280.1543, found 280.1545; IR (film, cm^{-1}): *v* 2959, 2923, 2853, 1727, 1240, 1114, 740; UV (nm): λ_{max} 213, 360.

diethyl 2,6-diisopropylpyridine-3,5-dicarboxylate (**2k**): Yield (58%, 35.6mg); Light yellow oil; ^1H NMR (600 MHz, $CDCl_3$): δ 8.44 (s, 1H), 4.38 (q, *J* = 7.2 Hz, 4H), 3.87 (t, *J* = 6.6 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 6H), 1.29 (d, *J* = 6.6 Hz, 12H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.3, 166.6, 140.1, 121.9, 61.3, 32.8, 22.1, 14.2; HRMS (ESI): calcd for $C_{17}H_{26}NO_4$ $[M+H]^+$ 308.1856, found 308.1860. IR (film, cm^{-1}): *v* 2965, 2925, 2853, 1722, 1594, 1242, 1094, 802, 741; UV (nm): λ_{max} 202, 360.

diethyl 2,6-bis(trifluoromethyl)pyridine-3,5-dicarboxylate (**2m**): Yield (41%, 29.4mg); Light yellow oil; ^1H NMR (600 MHz, $CDCl_3$): δ 8.51 (s, 1H), 4.48 (q, *J* = 7.2 Hz, 4H), 1.42 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 163.5, 146.1 (q, *J* = 37.1 Hz), 141.2, 122.9 (q, *J* = 7.2 Hz), 120.0 (q, *J* = 274.4 Hz), 63.4, 13.8; HRMS (ESI): calcd for $C_{13}H_{12}F_6NO_4$ $[M+H]^+$ 360.0665, found 360.0669. IR (film, cm^{-1}): *v* 2990, 1743, 1269, 1154, 1096, 861, 809; UV (nm): λ_{max} 209, 358.

diethyl 2,6-diphenylpyridine-3,5-dicarboxylate (**2n**)[6]: Yield (45%, 33.7mg); Colorless oil; ^1H NMR (600 MHz, $CDCl_3$): δ 8.54 (s, 1H), 7.65-7.61 (m, 4H), 7.46-7.42 (m, 6H), 4.21 (q, *J* = 7.2

Hz, 4H), 1.10 (t, J = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.4, 159.8, 140.3, 139.4, 129.2, 128.9, 128.1, 124.8, 61.7, 13.7; LC-MS (ESI): $[M+H]^+$ 376.1; IR (film, cm^{-1}): ν 2923, 1724, 1591, 1247, 699; UV (nm): λ_{max} 209, 360.

diethyl 2,6-bis(3,4-dimethoxyphenyl)pyridine-3,5-dicarboxylate (**2o**): Yield (42%, 41.6mg); Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.30 (d, J = 1.8 Hz, 2H), 7.20 (dd, J_1 = 8.3 Hz, J_2 = 2.0 Hz, 2H), 6.93 (d, J = 8.3 Hz, 2H), 4.24 (d, J = 7.2 Hz, 4H), 3.94 (s, 6H), 3.92 (s, 6H), 1.17 (t, J = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.9, 158.7, 150.2, 148.7, 140.2, 131.9, 123.9, 122.1, 112.1, 110.5, 61.6, 55.9, 13.9; HRMS (ESI): calcd for $C_{27}H_{30}NO_8$ $[M+H]^+$ 496.1966, found 496.1974. IR (film, cm^{-1}): ν 2921, 2850, 1721, 1541, 1247, 1025, 736; UV (nm): λ_{max} 209.

diethyl 2,6-bis(3-fluorophenyl)pyridine-3,5-dicarboxylate (**2p**): Yield (44%, 36.2mg); Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.57 (s, 1H), 7.43-7.35 (m, 6H), 7.18-7.14 (m, 2H), 4.21 (q, J = 7.2 Hz, 4H), 1.10 (t, J = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.8, 162.5 (d, J = 244.9 Hz), 158.4 (d, J = 2.0 Hz), 141.2 (d, J = 7.9 Hz), 140.6, 129.6 (d, J = 8.3 Hz), 125.4, 124.7 (d, J = 2.7 Hz), 116.2 (d, J = 20.9 Hz), 116.0 (d, J = 22.9 Hz), 61.9, 13.7; HRMS (ESI): calcd for $C_{23}H_{20}F_2NO_4$ $[M+H]^+$ 412.1355, found 412.1358. IR (film, cm^{-1}): ν 2923, 2853, 1726, 1584, 1251, 1106, 739; UV (nm): λ_{max} 203, 209, 360.

Kinetics Isotope Effect (KIE)

methyl acetoacetate **1a** (0.4 mmol), Cu_2O (10 mol%, 0.04 mmol), NH_4OAc (2 equiv., 0.8 mmol) and TBHP (2 equiv., 0.8 mmol) were added to a 10 mL Schlenk tube, followed by addition of DMF (0.5 mL) and d^7-DMF (0.5 mL). The mixture was stirred was stirred at 120 °C for 12 h. The solution was then cooled to r.t., quenched by a Na_2SO_3 aqueous solution and extracted with EtOAc

(3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 6:1) to afford the mixture of **2a** and ***d*-2a**. The ^{1}H NMR analysis showed that the ratio of **2a** to ***d*-2a** was 3.3:1 when compared with the standard ^{1}H NMR spectrum of **2a**, in which the integration of the peak at 9.39 ppm was 0.77 instead of 1.00.

D-Labeled Experiment

methyl acetoacetate **1a** (0.4 mmol), Cu_2O (10 mol%, 0.04 mmol), NH_4OAc (2 equiv., 0.8 mmol) and TBHP (2 equiv., 0.8 mmol) were added to a 10 mL Schlenk tube, followed by addition of d^7-DMF (0.5 mL). The mixture was stirred was stirred at 120 °C for 24 h. The solution was then cooled to r.t., quenched by a Na_2SO_3 aqueous solution and extracted with EtOAc (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 6:1) to afford ***d*-2a**. ***d*-2a** (92% deuterated): Yield (32%, 14.3mg); White solid; mp:100-101°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.73 (s, 0.08H), 3.94 (s, 6H), 2.87 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.1, 166.1, 162.6, 122.6, 52.3, 24.8.

ASSOCIATED CONTENT

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

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