# Pd-Catalyzed Carbonylative Cycloamidation of Ketoimines for Synthesis of Pyrido [1, 2-a] Pyrimidin-4-Ones

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# 1. General experimental information

## 1.1. General methods

All reactions were carried out in flame-dried sealed tubes with magnetic stirring. Unless otherwise noted, all experiments were performed under argon atmosphere. All reagents were purchased from TCI, Acros or Strem. Solvents were treated with 4 Å molecular sieves or sodium and distilled prior to use. Purifications of reaction products were carried out by flash chromatography using Qingdao Haiyang Chemical Co. Ltd silica gel (40-63 mm). Infrared spectra (IR) were recorded on a Brucker TENSOR 27 FTIR spectrophotometer and are reported as wavelength numbers (cm<sup>-1</sup>). Infrared spectra were recorded by preparing a KBr pellet containing the title compound. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded with tetramethylsilane (TMS) as internal standard at ambient temperature unless otherwise indicated on a Bruker Avance DPX 600 fourier Transform spectrometer operating at 400 MHz for <sup>1</sup>H NMR and 100 MHz for <sup>13</sup>C NMR. Chemical shifts are reported in parts per million (ppm) and coupling constants are reported as Hertz (Hz). Splitting patterns are designated as singlet (s), broad singlet (bs), doublet (d), triplet (t). Splitting patterns that could not be interpreted or easily visualized are designated as multiple (m). Low resolution mass spectra were recorded using a Waters HPLC/ZQ4000 Mass Spectrometer. High resolution mass spectra (HRMS) were recorded on an IF-TOF spectrometer (Micromass). Gas chromatograph mass spectra were obtained with a SHIMADZU model GCMS-QP5000 spectrometer. Crystal data were collected on a Bruker D8 Advance employing graphite monochromated Mo - K $\alpha$  radiation ( $\lambda = 0.71073$  Å) at 293 (2) K and operating in the  $\varphi$ - $\omega$ scan mode. The structure was solved by direct methods SHELXS-97.



	Pd catalyst (10 mol %), KI (1.0 equiv), K <sub>2</sub> CO <sub>3</sub> (1.0 equv), MnO <sub>2</sub> (1.0 equiv) DMF/CO, 80 °C, 24h			
1a		2a		
Entry	Catalyst	Yield $(\%)^{b}$		
1	Pd(TFA) <sub>2</sub>	trace		
2	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub>	trace		

3	$PdCl_2(PPh_3)_2$	5
4	PdCl <sub>2</sub>	18
5	$Pd(OAc)_2$	32

<sup>*a*</sup> The reactions were carried out using ketoimine **1a** (0.1 mmol), KI (0.1 mmol) and CO (balloon pressure) with Pd catalyst (10 mol %) in the presence of  $MnO_2$  (0.1 mmol) and  $K_2CO_3$  (0.1 mmol) in DMF (1.0 mL) at 80 °C for 24 h in a sealed reaction tube , followed by flash chromatography on SiO<sub>2</sub>. <sup>*b*</sup> Isolated yield.

1.2. Table 2. The effect of the oxidant on the Pd(II)-catalyzed carbonylative  $Csp^3$ -H amidation of ketoimines<sup>*a*</sup>



<sup>*a*</sup> The reactions were carried out using ketoimine **1a** (0.1 mmol), KI (0.1 mmol) and CO (balloon pressure) with  $Pd(OAc)_2$  (10 mol %) in the presence of oxidant (0.1 mmol) and  $K_2CO_3$  (0.1 mmol) in DMF (1.0 mL) at 80 °C for 24 h in a sealed reaction tube, followed by flash chromatography on SiO<sub>2</sub>. <sup>*b*</sup> Isolated yield.

# 1.3. Table 3. The effect of the base on the Pd(II)-catalyzed carbonylative $Csp^3$ -H amidation of ketoimines<sup>*a*</sup>

N N 1a	Pd(OAc) <sub>2</sub> (10 mol %), KI (1.0 equiv), Base (1.0 equv), Cu(OAc) <sub>2</sub> (1.0 equiv) DMF/CO, 80 °C, 24h	
Entry	Base	Yield $(\%)^{b}$
1	Cs <sub>2</sub> CO <sub>3</sub>	10
2	NaOAc	14
3	NaHCO <sub>3</sub>	31
4	$K_2CO_3$	36
	•	

5

<sup>*a*</sup> The reactions were carried out using ketoimine **1a** (0.1 mmol), KI (0.1 mmol) and CO (balloon pressure) with  $Pd(OAc)_2$  (10 mol %) in the presence of  $Cu(OAc)_2$  (0.1 mmol) and base (0.1 mmol) in DMF (1.0 mL) at 80 °C for 24 h in a sealed reaction tube, followed by flash chromatography on SiO<sub>2</sub>. <sup>*b*</sup> Isolated yield.

1.4.	Table	4.	The	effect	of	the	solvent	on	the	Pd(II)-catalyzed	carbonylative	Csp <sup>3</sup> -H
ami	dation o	of k	etoim	ines <sup>a</sup>								



Entry	Solvent	Yield $(\%)^b$		
1	toluene	nr		
2	1,4-dioxane	nr		
3	DMSO	20		
4	CH <sub>3</sub> NO <sub>2</sub>	36		
5	DCE	36		
6	CH <sub>3</sub> CN	40		
7	DMF	50		

<sup>*a*</sup> The reactions were carried out using ketoimine **1a** (0.1 mmol), KI (0.1 mmol) and CO (balloon pressure) with  $Pd(OAc)_2$  (10 mol %) in the presence of  $Cu(OAc)_2$  (0.1 mmol) and DABCO (0.1 mmol) in solvent (1.0 mL) at 80 °C for 24 h in a sealed reaction tube , followed by flash chromatography on SiO<sub>2</sub>. <sup>*b*</sup> Isolated yield.





3	100	88

<sup>*a*</sup> The reactions were carried out using ketoimine **1a** (0.1 mmol), KI (0.1 mmol) and CO (balloon pressure) with  $Pd(OAc)_2$  (10 mol %) in the presence of  $Cu(OAc)_2$  (0.1 mmol) and base (0.1 mmol) in DMF (1.0 mL) at the given temperature for 24 h in a sealed reaction tube , followed by flash chromatography on SiO<sub>2</sub>. <sup>*b*</sup> Isolated yield.

## 1.6. General procedure for the synthesis of ketoimines

The mixture of acetophenone derivatives (0.1 mmol, 1.0 equiv.) and substituted 2-aminopyridine (0.1 mmol, 1.0 equiv.) was stirred in toluene (3.0 mL) at 120 °C for 24 h in the presence of molecular sieve (4Å) (0.40 g) and a catalytic amount of concentrated H<sub>2</sub>SO<sub>4</sub> (10 mol %). The mixture was then filtered and the solvent was removed under reduced pressure to produce crude ketoimines, except that ketoimines **1a**, **1b**, **1e**, **1g**, **1h**, **1j** and **1y** could be purified by flash chromatography to get pure starting material, the other crude ketoimines including **1c**, **1d**, **1f**, **1i**, **1k**-1**x** could be directly used for synthetic purpose without further purification because these ketoimines are easily decomposed on silica gel.<sup>[1]</sup>



(*E*)-*N*-(1-phenylethylidene)pyridin-2-amine (1a)<sup>[1]</sup>: oil; 15 mg, 77% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.45 (d, *J* = 4.5 Hz, 1H), 8.00 (d, *J* = 7.7 Hz, 2H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.48 – 7.41 (m, 3H), 7.03 – 6.97 (m, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 2.27 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  167.69, 163.53, 148.86, 139.04, 137.70, 130.89, 128.33, 127.45, 118.85, 115.19, 18.15. MS (ESI): m/z = 196.09 [M]<sup>+</sup>. IR (KBr): 2917, 2850, 1609, 1555, 987, 784 cm<sup>-1</sup>.



(*E*)-*N*-(1-(p-tolyl)ethylidene)pyridin-2-amine (1b)<sup>[2]</sup>: white solid; m.p. 81-82.3 °C. 15 mg, 71% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.45 (d, *J* = 4.0 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.69 – 7.62 (m, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.04 – 6.97 (m, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 2.41 (s, 3H), 2.26 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  167.48, 163.67, 148.84, 141.22, 137.65, 136.36, 129.04, 127.46, 118.71, 115.25, 21.41, 18.07. HR-MS (ESI) calcd for [M + 1]<sup>+</sup>: C<sub>14</sub>H<sub>15</sub>N<sub>2</sub>: 211.1230, found: 211.1229; IR (KBr): 2920, 2850, 1639, 1555, 987, 784 cm<sup>-1</sup>.



(*E*)-*N*-(1-(4-methoxyphenyl)ethylidene)pyridin-2-amine (1e)<sup>[2]</sup>: oil; 14 mg, 62% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.44 (d, *J* = 4.1 Hz, 1H), 7.98 (d, *J* = 8.9 Hz, 2H), 7.66 (td, *J* = 7.8, 1.8 Hz, 1H), 6.99 (dd, *J* = 6.9, 5.4 Hz, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 3.86 (s, 3H), 2.24 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  166.66, 163.73, 161.88, 148.83, 137.63, 131.70, 129.21, 118.62, 115.33, 113.57, 55.36, 17.91. 211.1229. HR-MS (ESI) calcd for [M + 1]<sup>+</sup>: C<sub>14</sub>H<sub>15</sub>N<sub>2</sub>O: 227.1179, found: 227.1178; IR (KBr): 3077, 2962, 2837, 1635, 1583, 1462, 1234, 1114, 812 cm<sup>-1</sup>.



1g

(*E*)-*N*-(1-(4-chlorophenyl)ethylidene)pyridin-2-amine (1g)<sup>[2]</sup>: oil; 18 mg, 78% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.46 (d, *J* = 4.1 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 2H), 7.69 (td, *J* = 7.5, 1.4 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.05 – 7.01 (m, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 2.25 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  166.62, 163.20, 148.90, 137.90, 137.75, 131.54, 129.06, 125.62, 119.03, 115.15, 17.98. HR-MS (ESI) calcd for [M + 1]<sup>+</sup>: C<sub>13</sub>H<sub>12</sub>ClN<sub>2</sub>: 231.0684, found: 231.0682; IR (KBr): 3081, 3050, 1489, 1277, 1260, 799, 766 cm <sup>-1</sup>.



(*E*)-*N*-(1-(3-chlorophenyl)ethylidene)pyridin-2-amine (1h)<sup>[2]</sup>: oil; 15 mg, 65% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.46 (d, *J* = 4.7 Hz, 1H), 8.02 (s, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.07 – 7.01 (m, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 2.27 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  166.48, 163.04, 148.89, 140.78, 137.81, 134.57, 130.85, 129.60, 127.64, 125.61, 119.14, 115.16, 18.14. HR-MS (ESI) calcd for [M + 1]<sup>+</sup>: C<sub>13</sub>H<sub>12</sub>CIN<sub>2</sub>: 231.0684, found: 231.0683; IR (KBr): 3067, 3004, 1688, 1586, 1425, 1366, 1235, 815, 789 cm<sup>-1</sup>.



(*E*)-*N*-(1-(4-bromophenyl)ethylidene)pyridin-2-amine (1j)<sup>[2]</sup>: oil; 20 mg, 73% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.46 (d, *J* = 4.7 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 2H), 7.69 (t, *J* = 7.2 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.03 (t, *J* = 5.8 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 2.26 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  166.48, 163.22, 148.90, 137.75, 137.45, 137.10, 128.84, 128.56, 119.01, 115.17, 18.01. HR-MS (ESI) calcd for [M]<sup>+</sup>: C<sub>13</sub>H<sub>12</sub>BrN<sub>2</sub>: 275.0178, found: 275.0177; IR (KBr): 1277, 1260, 1053, 1032, 1010, 766, 748 cm<sup>-1</sup>.



(*E*)-*N*-(1-phenylethylidene)aniline <sup>[3]</sup>: oil; 16 mg, 82% yield. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.96 (d, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 5.6 Hz, 3H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 2H), 2.21 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  165.47, 151.77, 139.56, 130.49, 128.99, 128.56, 128.40, 127.22, 123.25, 119.41, 17.39. MS (ESI): m/z = 195.06 [M<sup>+</sup>].

## 1.7 General procedure for synthesis of pyrido [1, 2-a] pyrimidin-4-ones derivatives (2a-2w)

To the solution of ketoimines **1** (0.1 mmol) in dry DMF (1.0 mL) were added Pd(OAc)<sub>2</sub> (2.0 mg, 10 mol %), Cu(OAc)<sub>2</sub> (18 mg, 0.1 mmol), DABCO (12 mg, 0.1 mmol) and KI ( 16 mg, 0. mmol) under CO atmosphere, and then the corresponding reaction mixture was stirred in a sealed tube at 100 °C for 24 h. After the starting materials were disappeared, then the mixture was cooled down to room temperature and added 1 mL of H<sub>2</sub>O, then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). The corresponding combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum, and the resulting crude products were purified by flash chromatography on silical gel using 30% (v/v) ethyl acetate in petroleum ether as eluent to afford the desired pyrido [1, 2-a] pyrimidin-4-ones **2**.



## 2a

**2-Phenyl-4H-pyrido**[**1,2-a**]**pyrimidin-4-one** (**2a**)<sup>[4]</sup>: white solid; 19 mg, 88% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.04 (d, J = 7.1 Hz, 1H), 8.10 – 8.06 (m, 2H), 7.70 (d, J = 3.7 Hz, 2H), 7.48 (d, J = 4.9 Hz, 3H), 7.12 – 7.06 (m, 1H), 6.90 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  162.13, 158.66, 151.07, 137.31, 136.14, 130.65, 128.83, 127.45, 127.31, 126.81, 115.18, 100.13. MS (ESI): m/z = 221.98 [M]<sup>+</sup>.



#### 2b

**2-**(*p***-Tolyl)-4H-pyrido**[1,2-a]pyrimidin-4-one (2b)<sup>[4]</sup>: white solid; 21 mg, 90% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.94 (d, *J* = 7.1 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 3.2 Hz, 2H), 7.19 (d, *J* = 7.5 Hz, 2H), 7.02 – 6.95 (m, 1H), 6.79 (s, 1H), 2.32 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  161.94, 158.62, 150.95, 141.01, 136.03, 134.38, 129.52, 127.33, 127.22, 126.69, 115.01, 99.52, 21.44. MS (ESI): m/z = 235.99 [M]<sup>+</sup>.



**2-(***m***-Tolyl)-4H-pyrido[1,2-a]pyrimidin-4-one (2c)<sup>[4]</sup>:** white solid; 20 mg, 84% yield <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.04 (d, *J* = 7.1 Hz, 1H), 7.91 (s, 1H), 7.85 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 3.7 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.13 – 7.06 (m, 1H), 6.89 (s, 1H), 2.44 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  162.21, 158.58, 150.98, 138.47, 137.21, 136.09, 131.41, 128.70, 128.05, 127.23, 126.71, 124.56, 115.12, 100.08, 21.53. MS (ESI): m/z = 235.99 [M]<sup>+</sup>.





**2-(O-tolyl)-4H-pyrido[1,2-a]pyrimidin-4-one** (**2d**): white solid; 16 mg, 68% yield; m.p. 160.2-161.5 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.11 (d, *J* = 7.1 Hz, 1H), 7.73 (q, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.37 – 7.25 (m, 3H), 7.16 (t, *J* = 6.6 Hz, 1H), 6.58 (s, 1H), 2.45 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  165.54, 158.10, 150.73, 138.69, 136.23, 135.84, 131.01, 129.23, 129.10, 127.22, 126.64, 126.03, 115.42, 104.35, 20.35. HR-MS (ESI) calcd for [M + 1]<sup>+</sup>: C<sub>15</sub>H<sub>13</sub>N<sub>2</sub>O: 237.1022, found: 237.2020; IR (KBr):1978, 1929, 1717, 1650, 1121, 751 cm<sup>-1</sup>.

**2-(4-Methoxyphenyl)-4H-pyrido**[**1,2-a**]**pyrimidin-4-one** (**2e**)<sup>[4]</sup>: white solid; 23 mg, 92% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.04 (d, J = 7.1 Hz, 1H), 8.08 (d, J = 8.4 Hz, 2H), 7.74 – 7.67 (m, 2H), 7.09 (t, J = 6.4 Hz, 1H), 7.01 (d, J = 8.4 Hz, 2H), 6.85 (s, 1H), 3.88 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  161.87, 161.57, 158.63, 150.96, 136.02, 129.59, 129.01, 127.28, 126.62, 114.88, 114.18, 98.82, 55.42. MS (ESI): m/z = 251.99 [M]<sup>+</sup>.





**2-(4-Fluorophenyl)-4H-pyrido**[**1,2-a**]**pyrimidin-4-one** (**2f**)<sup>[4]</sup>: white solid; 18 mg, 75% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.07 (d, *J* = 7.1 Hz, 1H), 8.10 (dd, *J* = 8.0, 5.8 Hz, 2H), 7.79 – 7.70 (m, 2H), 7.16 (dt, *J* = 15.4, 7.7 Hz, 3H), 6.86 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  165.76, 163.26, 160.94, 158.55, 151.05, 136.30, 133.39, 129.54, 129.45, 127.32, 126.71, 115.93, 115.72, 115.23, 99.66. MS (ESI): m/z = 239.97 [M]<sup>+</sup>.



**2-(4-Chlorophenyl)-4H-pyrido**[**1,2-a**]**pyrimidin-4-one** (**2g**)<sup>[4]</sup>: white solid; 20 mg, 79% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.06 (d, *J* = 7.1 Hz, 1H), 8.10 (dd, *J* = 8.1, 5.9 Hz, 2H), 7.79 – 7.70 (m, 2H), 7.21 – 7.11 (m, 3H), 6.86 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  165.75, 160.92, 158.54, 151.04, 136.30, 133.36, 129.53, 129.45, 127.31, 126.70, 115.93, 115.71, 115.24, 99.65. MS (ESI): m/z = 255.98 [M]<sup>+</sup>.



**2-(3-Chlorophenyl)-4H-pyrido**[**1,2-a**]**pyrimidin-4-one** (**2h**)<sup>[4]</sup>: white solid; 16 mg, 62% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.05 (d, *J* = 7.1 Hz, 1H), 8.12 (s, 1H), 7.92 (d, *J* = 7.2 Hz, 1H), 7.79 – 7.70 (m, 2H), 7.46 – 7.39 (m, 2H), 7.14 (t, *J* = 6.7 Hz, 1H), 6.86 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  160.42, 158.46, 151.05, 139.07, 136.41, 134.95, 130.53, 130.00, 127.63, 127.29, 126.78, 125.40, 115.43, 100.20. MS (ESI): m/z = 255.98 [M]<sup>+</sup>.



**2-(2-Chlorophenyl)-4H-pyrido**[1,2-a]pyrimidin-4-one (2i): white solid; 14 mg, 54% yield; m.p.202.3-203.8 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.12 (d, J = 7.1 Hz, 1H), 7.82 – 7.72 (m, 2H), 7.67 – 7.61 (m, 1H), 7.49 (dd, J = 8.4, 4.4 Hz, 1H), 7.39 (dd, J = 8.9, 4.3 Hz, 2H), 7.20 (t, J = 6.7 Hz, 1H), 6.78 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  162.18, 157.94, 151.05, 137.67, 136.33, 132.20, 130.80, 130.45, 127.34, 127.03, 126.75, 115.62, 105.28. HR-MS (ESI) calcd for [M + 1]<sup>+</sup>: C<sub>14</sub>H<sub>10</sub>ClN<sub>2</sub>O: 257.0476, found: 257.0475; IR (KBr): 1902, 1674, 1415, 1190, 748 cm<sup>-1</sup>.



2j

**4-(4-Oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)benzonitrile (2j):** white solid; 16 mg, 65% yield. m.p. 232.3-234 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.02 (d, *J* = 6.7 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 2H), 7.71 (dd, *J* = 14.7, 8.4 Hz, 4H), 7.13 (t, *J* = 6.1 Hz, 1H), 6.85 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  159.75, 158.43, 151.21, 141.51, 136.75, 132.55, 128.00, 127.40, 126.88, 118.49, 115.79, 114.00, 100.86, 99.99. HR-MS (ESI) calcd for [M + 1]<sup>+</sup>: C<sub>15</sub>H<sub>10</sub>N<sub>3</sub>O: 248.0818, found: 248.0819; IR (KBr): 2221, 1733, 1559, 1250, 828 cm<sup>-1</sup>.



2k

**Methyl 4-(4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)benzoate (2k):** white solid; 21 mg, 71% yield. m.p.262.2-263.6 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.09 (d, *J* = 7.0 Hz, 1H), 8.17 (s, 3H), 7.82 – 7.75 (m, 2H), 7.18 (t, *J* = 6.4 Hz, 1H), 6.96 (s, 1H), 3.96 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  166.65, 160.86, 158.54, 151.14, 141.46, 136.45, 131.84, 130.02, 127.42, 127.36, 126.88, 115.52, 100.83, 52.30. HR-MS (ESI) calcd for [M + 1]<sup>+</sup>: C<sub>16</sub>H<sub>13</sub>N<sub>2</sub>O<sub>3</sub>: 281.0921, found: 281.0923; IR (KBr): 1868, 1629, 1578, 1190, 829 cm<sup>-1</sup>.



**2-(4-Nitrophenyl)-4H-pyrido[1,2-a]pyrimidin-4-one (21)**<sup>[3]</sup>: yellow solid; 17 mg, 64% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.02 (d, *J* = 7.1 Hz, 1H), 8.28 (d, *J* = 8.6 Hz, 2H), 8.19 (d, *J* = 8.6 Hz, 2H), 7.73 (dt, *J* = 17.4, 8.7 Hz, 2H), 7.13 (d, *J* = 6.8 Hz, 1H), 6.88 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  159.39, 158.39, 151.22, 149.10, 143.26, 136.83, 128.37, 127.41, 126.92, 123.94, 115.87, 101.16. MS (ESI): m/z = 266.94 [M]<sup>+</sup>.



2m

**2-(Benzo[d] [1, 3]dioxol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (2m):** white solid; 25 mg, 94% yield. m.p.222.3-223.8 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.98 (d, J = 7.1 Hz, 1H), 7.69 – 7.56 (m, 3H), 7.54 (s, 1H), 7.04 (t, J = 6.5 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.74 (s, 1H), 5.98 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  161.38, 158.59, 150.87, 149.92, 148.32, 136.13, 131.49, 127.29, 126.63, 122.22, 115.00, 108.51, 107.65, 101.59, 99.12. HR-MS (ESI) calcd for [M + 1]<sup>+</sup>: C<sub>15</sub>H<sub>11</sub>N<sub>2</sub>O<sub>3</sub>: 267.0764, found: 267.0764; IR (KBr): 1637, 1474, 1269, 755, 697 cm<sup>-1</sup>.



2n

**2-(Furan-2-yl)-4H-pyrido[1, 2-a]pyrimidin-4-one (2n):** white solid; 11 mg, 52% yield. m.p.152.3-153 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.97 (d, J = 7.1 Hz, 1H), 7.68 – 7.53 (m, 3H), 7.17 (d, J = 3.2 Hz, 1H), 7.02 (t, J = 6.7 Hz, 1H), 6.76 (s, 1H), 6.51 (d, J = 1.6 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  158.29, 153.07, 151.89, 151.55, 145.25, 136.32, 127.44, 126.34, 114.89, 112.75, 112.47, 97.57. HR-MS (ESI) calcd for [M + 1]<sup>+</sup>: C<sub>12</sub>H<sub>9</sub>N<sub>2</sub>O<sub>2</sub>: 213.0659, found: 213.0658; IR (KBr): 1813, 1682, 1577, 1064, 727 cm<sup>-1</sup>.



**2-(Thiophen-2-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (20):** white solid; 14 mg, 61% yield. m.p.162.3-163.9 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.96 (d, J = 7.1 Hz, 1H), 7.66 (dd, J = 11.9, 5.0 Hz, 2H), 7.59 (d, J = 8.9 Hz, 1H), 7.46 (d, J = 4.9 Hz, 1H), 7.09 (t, J = 4.3 Hz, 1H), 7.03 (t, J = 6.8 Hz, 1H), 6.73 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  158.20, 156.86, 151.16, 142.54, 136.40, 130.25, 128.46, 127.58, 127.46, 126.34, 115.02, 97.65. HR-MS (ESI) calcd for [M + 1]<sup>+</sup>: C<sub>12</sub>H<sub>9</sub>N<sub>2</sub>S: 229.0430, found: 229.0429; IR (KBr): 1636, 1545, 1038, 939 909 cm<sup>-1</sup>.



#### 2p

**2-(Pyridin-4-yl)-4H-pyrido**[1,2-a]**pyrimidin-4-one** (2**p**)<sup>[3]</sup>: white solid; 13 mg, 58% yield ;<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.02 (d, J = 7.1 Hz, 1H), 8.71 (d, J = 5.0 Hz, 2H), 7.88 (d, J = 5.0 Hz, 2H), 7.72 (dd, J = 12.8, 7.6 Hz, 2H), 7.13 (t, J = 6.7 Hz, 1H), 6.89 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  158.40, 157.44, 150.29, 149.83, 149.54, 143.63, 135.70, 126.39, 125.93, 120.30, 119.93, 114.82, 99.94. MS (ESI): m/z = 222.97 [M]<sup>+</sup>.



**2-(Pyridin-3-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (2q)**<sup>[3]</sup>: white solid; 10 mg, 45% yield. m.p.232.3-234 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.32 (s, 1H), 9.10 (d, *J* = 6.7 Hz, 1H), 8.73 (s, 1H), 8.39 (d, *J* = 7.4 Hz, 1H), 7.77 (t, *J* = 9.8 Hz, 2H), 7.45 (s, 1H), 7.19 (s, 1H), 6.93 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  159.62, 158.36, 151.31, 148.80, 136.60, 134.81, 127.38, 126.81, 123.58, 115.59, 100.28. MS (ESI): m/z = 222.96 [M]<sup>+</sup>.



**3-Methyl-2-phenyl-4H-pyrido**[**1,2-a**]**pyrimidin-4-one** (**2r**)<sup>[3]</sup>: white solid; 4 mg, 17% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.05 (d, J = 7.2 Hz, 1H), 7.66 (s, 2H), 7.59 (d, J = 6.9 Hz, 2H), 7.52 – 7.43 (m, 3H), 7.10 (d, m, 1H), 2.30 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  161.54, 159.25, 148.40, 139.27, 134.58, 128.90, 128.80, 128.32, 126.88, 126.56, 114.97, 111.87, 13.90. MS (ESI): m/z = 235.98 [M]<sup>+</sup>.



**7-Methyl-2-phenyl-4H-pyrido**[**1,2-a**]**pyrimidin-4-one** (**2s**)<sup>[3]</sup>: white solid; 19 mg, 80% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.73 (s, 1H), 7.95 (d, *J* = 5.2 Hz, 2H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.44 (d, *J* = 9.1 Hz, 1H), 7.37 (d, *J* = 5.1 Hz, 3H), 6.77 (s, 1H), 2.28 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ 161.50, 158.47, 149.89, 139.09, 137.30, 130.47, 128.74, 127.31, 126.12, 125.51, 124.64, 99.73, 18.31. MS (ESI): m/z = 235.99 [M]<sup>+</sup>.



**7-Chloro-2-phenyl-4H-pyrido**[**1,2-a**]**pyrimidin-4-one** (**2t**)<sup>[4]</sup>: white solid; 16 mg, 62% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.91 (s, 1H), 7.93 (d, *J* = 3.8 Hz, 2H), 7.51 (s, 2H), 7.40 – 7.34 (m, 3H), 6.79 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  161.69, 157.55, 149.27, 137.33, 136.67, 130.85, 128.82, 127.66, 127.34, 125.03, 123.81, 100.34. MS (ESI): m/z = 255.98 [M]<sup>+</sup>.



**9-Methoxy-2-phenyl-4H-pyrido**[1,2-a]**pyrimidin-4-one** (2u): white solid; 15 mg, 60% yield. m.p.192.3-193.9 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.71 (d, *J* = 6.3 Hz, 1H), 8.11 (d, *J* = 6.3 Hz, 2H), 7.48 (s, 3H), 7.07 – 7.01 (m, 2H), 6.95 (s, 1H), 4.07 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  161.03, 158.75, 152.53, 145.44, 137.38, 130.56, 128.80, 127.53, 119.12, 114.17, 111.13, 100.97, 56.84. HR-MS (ESI) calcd for [M + 1]<sup>+</sup>: C<sub>15</sub>H<sub>13</sub>N<sub>2</sub>O<sub>2</sub>: 253.0972, found: 253.0971; IR (KBr): 1674, 1607, 1543, 1287, 982 cm<sup>-1</sup>.



**Methyl 4-oxo-2-phenyl-4H-pyrido[1,2-a]pyrimidine-7-carboxylate (2v):** white solid; 14 mg, 50% yield. m.p. 222.3-223.5 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.72 (s, 1H), 8.20 (d, *J* = 9.2 Hz, 1H), 8.11 (s, 2H), 7.71 (d, *J* = 9.1 Hz, 1H), 7.52 (s, 3H), 6.96 (s, 1H), 4.00 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  164.14, 162.50, 158.39, 151.24, 136.75, 134.79, 131.50, 131.08, 129.92, 128.91, 127.53, 126.62, 118.67, 100.82, 52.83. HR-MS (ESI) calcd for [M + 1]<sup>+</sup>: C<sub>16</sub>H<sub>13</sub>N<sub>2</sub>O<sub>3</sub>: 281.0921, found: 281.0922; IR (KBr): 1735, 1545, 1121, 1026, 938 cm<sup>-1</sup>.

#### 2. Controlled experiments for mechanism studies

(a) Pd-catalyzed carbonylative Csp<sup>3</sup>-H amidation of ketoimines (1z) under our standard reaction conditions.



To the solution of ketoimines 1y (0.1 mmol) in dry DMF (1.0 mL) were added Pd(OAc)<sub>2</sub> (2.0 mg, 10 mol %), Cu(OAc)<sub>2</sub>(18 mg, 0.1 mmol), DABCO (12 mg, 0.1 mmol) and KI ( 16 mg, 0.

mmol) under CO atmosphere, and then the corresponding reaction mixture was stirred in a sealed tube at 100 °C for 24 h. After the starting materials were disappeared, then the reaction was cooled down to room temperature and added 1mL of H<sub>2</sub>O, then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×10 mL). The corresponding combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum, and the resulting crude products were purified by flash chromatography on silical gel using petroleum ether as eluent to afford the product **2x**.<sup>[5]</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.59 (d, *J* = 7.7 Hz, 2H), 7.39 – 7.31 (m, 4H), 7.29 (d, *J* = 6.8 Hz, 1H), 7.25 – 7.17 (m, 9H), 6.74 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  140.37, 135.19, 134.82, 132.74, 129.08, 128.72, 128.34, 128.14, 126.82, 126.56, 125.86, 125.70, 125.58, 125.15, 120.90, 108.77. MS (ESI): m/z = 295.03 [M]<sup>+</sup>.

The possible reaction mechanism of the formation of **2x** was shown as follows: At first, ketoimine (**1y**) could produce enamine **1y-a** and ketone **1y-b** *via* isomerization and hydrolysis process, respectively (Scheme a). Then ketone **1y-b** was attacked nucleophically by **1y-a** to give imine **1y-e** followed by dehydration. **1y-e** could be isomerized to alkene **1y-f** which was further converted to **2x**, possibly through Pd(II)-catalyzed C-H activation/cyclization cascade (Scheme b).



(b) H/D Exchange of N-(2-pyridyl) ketoimine (1a)



To the solution of ketoimine **1a** (0.1 mmol) in dry DMF (1.0 mL) were added CD<sub>3</sub>OD (0.5 mL) Pd(OAc)<sub>2</sub> (2.0 mg, 10 mol %) under air. The reaction mixture was stirred for 100°C and then cooled down to room temperature. After removal of solvent the resulted crude was purified by flash column chromatography to give the desired compound *d*-**1a**<sup>[2]</sup> (20% yield, as oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.46 (d, *J* = 4.1 Hz, 1H), 8.01 (d, *J* = 7.1 Hz, 2H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.49 – 7.42 (m, 3H), 7.05 – 7.00 (m, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 2.22 (dd, *J* = 16.4, 8.7 Hz, 0.54H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  167.68, 163.53, 148.85, 139.02, 137.70, 130.89, 128.33, 127.44, 118.85, 115.18.

#### (c): Kinetic isotope effect of this transformation



A sample experimental set-up is run as follows: To the solution of ketoimine (**1a**: 20 mg, 0.1 mmol; or *d*-**1a**: 20 mg, 0.1 mmol) in dry DMF (2.0 mL) were added Pd(OAc)<sub>2</sub> (2 mg, 10 mol %), Cu(OAc)<sub>2</sub> (18 mg, 0.1 mmol), DABCO (12 mg, 0.1 mmol) and KI (16 mg, 0.1 mmol) under CO atmosphere, and then the corresponding reaction mixture was stirred in a sealed tube for 100 °C. The reaction mixture (0.4 mL) was extracted at 10 minutes intervals for the first 50 minutes. After solvent of the extraction mixture (0.4 mL) was removed under reduced pressure conditions and analyzed by <sup>1</sup>H NMR spectrum (see **Figure 1** and **Figure 2**). A sample plot of the initial rate data for reactions of both **1a** and *d*-**1a** was shown in **Figure 3**. The reaction mixture was combined, added 1.0 mL of H<sub>2</sub>O. Then the mixture was extracted with DCM (3×10 mL), and the corresponding crude *d*-**2a** was purified by flash chromatography on silical gel using 30% ethyl acetate in petroleum ether as eluent. *d*-**2a**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.06 (d, *J* = 6.9 Hz, 1H), 8.09 (s, 2H), 7.72 (s, 2H), 7.48 (s, 3H), 7.11 (d, *J* = 2.8 Hz, 1H), 6.91 (s, 0.54H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  162.04, 158.62, 151.04, 137.27, 136.13, 130.63, 128.80, 127.42, 127.26, 126.77, 115.16, 100.07. HR-MS (ESI) calcd for [M + 1]<sup>+</sup>: C<sub>14</sub>H<sub>10</sub>DN<sub>2</sub>O: 224.0929, found: 224.0923.





Figure 2. The conversion of *d*-1a was monitored by <sup>1</sup>H NMR method



Figure 3. The plot of initial rates for KIE measurements.

#### 3. References

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# 4. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectrum for all isolated products.

1) (*E*)-*N*-(1-Phenylethylidene)pyridin-2-amine (**1a**) (Using CDCl<sub>3</sub> as solvent)











3) (*E*)-*N*-(1-(4-methoxyphenyl)ethylidene)pyridin-2-amine (1e): (Using CDCl<sub>3</sub> as solvent)







5) (*E*)-*N*-(1-(3-chlorophenyl)ethylidene)pyridin-2-amine (**1h**): (Using CDCl<sub>3</sub> as solvent)





6) (*E*)-*N*-(1-(4-bromophenyl)ethylidene)pyridin-2-amine (**1j**): (Using CDCl<sub>3</sub> as solvent)





8) 2-Phenyl-4H-pyrido[1,2-a]pyrimidin-4-one (**2a**) (Using CDCl<sub>3</sub> as solvent)





9) 2-(P-tolyl)-4H-pyrido[1,2-a]pyrimidin-4-one (2b) (Using CDCl<sub>3</sub> as solvent)

90 80 fl (ppm)











12) 2-(4-Methoxyphenyl)-4H-pyrido[1,2-a]pyrimidin-4-one (2e) (Using CDCl<sub>3</sub> as solvent)



13) 2-(4-Fluorophenyl)-4H-pyrido[1,2-a]pyrimidin-4-one (2f) (Using CDCl<sub>3</sub> as solvent)











16) 2-(2-Chlorophenyl)-4H-pyrido[1,2-a]pyrimidin-4-one (2i) (Using CDCl<sub>3</sub> as solvent)







18) Methyl 4-(4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)benzoate (2k) (Using CDCl<sub>3</sub> as solvent)



19) 2-(4-Nitrophenyl)-4H-pyrido[1,2-a]pyrimidin-4-one (2l) (Using CDCl<sub>3</sub> as solvent)



20) 2-(Benzo[d][1,3]dioxol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (2m) (Using CDCl<sub>3</sub> as solvent)











23) 2-(Pyridin-4-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (2p) (Using CDCl<sub>3</sub> as solvent)



24) 2-(Pyridin-3-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (2q) (Using CDCl<sub>3</sub> as solvent)









26) 7-Methyl-2-phenyl-4H-pyrido<br/>[1,2-a]pyrimidin-4-one ( $\mathbf{2s}$ ) (Using CDCl<sub>3</sub> as solvent)

27) 7-Chloro-2-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one (2t) (Using CDCl<sub>3</sub> as solvent)



28) 9-Methoxy-2-phenyl-4H-pyrido[1,2-a]pyrimidin-4-one (2u) (Using CDCl<sub>3</sub> as solvent)



29) Methyl 4-oxo-2-phenyl-4H-pyrido[1,2-a]pyrimidine-7-carboxylate (2v) (Using CDCl<sub>3</sub> as solvent)



30) H/D Exchange of *N*-pyridyl ketoimine (*d*-1a) (Using CDCl<sub>3</sub> as solvent)



31) <sup>1</sup>H and <sup>13</sup>C NMR spectrum for d-2a (using CDCl<sub>3</sub> as solvent)



32) The crude <sup>1</sup>H NMR spectrum for calculating **KIE** value (Using CDCl<sub>3</sub> as solvent) a. The crude <sup>1</sup>H NMR spectrum for the reaction of **1a** 





b. The crude <sup>1</sup>H NMR spectrum for the reaction of *d*-1a





33) 1, 2, 4-Triphenyl-1H-pyrrole (2x) (Using CDCl<sub>3</sub> as solvent)

