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Synthesis of *N*-Pyridyl Hydroxylamines via Copper-Catalyzed Cross-Coupling

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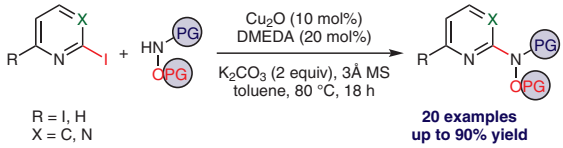

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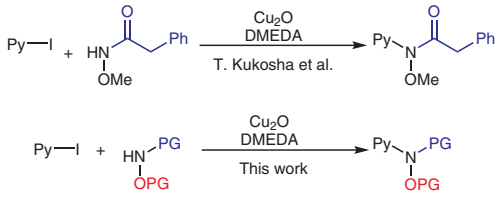
Abstract *N*-Pyridyl hydroxylamine derivatives were prepared via copper-catalyzed cross-coupling of orthogonally functionalized hydroxylamines with iodopyridines. Various amino- and hydroxyl-protecting groups were tolerated. A total of 20 examples were synthesized in 28–90% yield.

Key words copper, cross-coupling, hydroxylamines, protecting groups, pyridine

N-Pyridyl hydroxylamine scaffold is found in antibacterial,[1] antiviral,[2] anti-osteoclastogenic,[3] and anticancer agents.[4] *N*-Pyridyl hydroxylamines are conventionally prepared through palladium-catalyzed hydrogenation,[5] stoichiometric reduction of nitropyridines,[6] aromatic nucleophilic substitution,[7] *N*-alkylation of nitrosopyridines,[1a,8–10] Buchwald–Hartwig amination,[11] and *N*-arylation of hydroxylamines.[12] Kukosha et al. studied the *N*-arylation of *N*,*O*-functionalized hydroxylamines using copper(II) oxide and *N*,*N*′-dimethylethylenediamine (DMEDA).[12] This methodology provided only two examples of pyridine substrates and the hydroxamate coupling partners were limited to amides (Scheme 1). In order to expand the scope of this process, different protecting groups for the hydroxylamine coupling partner and several other *N*-heteroaromatic systems were examined using this methodology. Herein, we report our findings on copper-catalyzed coupling of iodopyridines and of *N*,*O*-protected hydroxylamines.



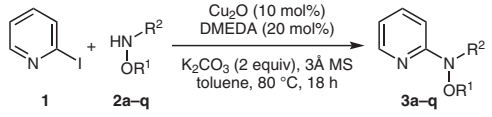
Scheme 1 Copper-catalyzed coupling of iodopyridines

The coupling of various *N*,*O*-protected hydroxamates and 2-iodopyridine was examined (Table 1). Orthogonal amino- and hydroxyl-protecting groups were chosen to allow selective deprotection using: Lewis acid, aqueous acidic hydrolysis, metal-catalyzed de-allylation, and fluoride nucleophilic attack. The reactions were carried out using 10 mol% of copper(II) oxide, DMEDA as the ligand, and potassium carbonate as the base in toluene at 80 °C. Coupling products were obtained from moderate to excellent yields (28–90%). Most protecting groups were tolerated. While *N*-arylation of *N*-tosyl-*O*-benzyl hydroxamates is inefficient via conventional coupling methods,[13] it was accomplished using 2-iodopyridine under the studied conditions (Table 1, entry 4). No coupling product was isolated from the reaction using *N*-formyl hydroxamate (entry 6) with decomposition of the hydroxylamine being observed. Similarly, no products were observed using *O*-silyl ether hydroxamates (entries 15 and 16) but starting material was recovered.

Kukosha had previously coupled 3-iodopyridine using *N*-methoxy-2-phenylacetamide as coupling partner under the studied conditions.[12] However, in our hands, no product was observed when treated with *N*-acetyl-*O*-benzyl hydroxamate. 4-Iodopyridine was also evaluated, using *N*-acetyl-*O*-benzyl hydroxylamine, and the coupling product was not observed.

Similar to Kukosha's[12] and Tomkinson's[13] results on the copper-catalyzed coupling of other aryl halides, 2-chloropyridine and 2-bromopyridine using *N*-Boc-*O*-benzyl hydroxamate did not result in the isolation of the coupling product.

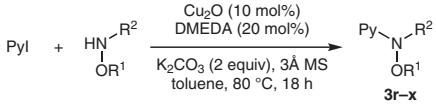
Table 1 Copper-Catalyzed Coupling of Various *N*,*O*-Protected Hydroxylamine and 2-Iodopyridine

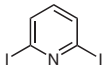
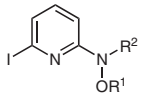
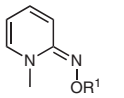
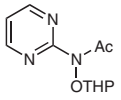


Entry	R^1	R^2	Product	Yield (%)[a]
1	Bn	Ac	**3a**	82
2	Bn	Boc	**3b**	69
3	Bn	Teoc[b]	**3c**	81
4	Bn	Ts	**3d**	83
5	Bn	Ms	**3e**	64
6	Bn	CHO	**3f**	0
7	THP	Ac	**3g**	90
8	THP	Boc	**3h**	28
9	THP	Teoc[b]	**3i**	66
10[c]	THP	Cbz	**3j**	48
11	allyl	Ac	**3k**	69
12	allyl	Boc	**3l**	50
13	allyl	Teoc[b]	**3m**	45
14	allyl	Cbz	**3n**	82
15	TBS	Ac	**3o**	0
16	TBDPS	Ac	**3p**	0
17	CH_2CH_2TMS	Ac	**3q**	43

[a] Isolated yields.
[b] Teoc: 2-(Trimethylsilyl)ethoxycarbonyl.
[c] Using 4 equiv of K_2CO_3 and heating for 42 h.

Table 2 Copper-Catalyzed Coupling of Various Iodo-Heteroaryl Substrates



Entry	Heteroaryl iodide	Product		Yield (%)[a]
1		 R^1 = Bn, R^2 = Ac	**3r**	59
2		R^1 = Bn, R^2 = Boc	**3s**	55
3		R^1 = THP, R^2 = Ac	**3u**	58
4[b]		 R^1 = Bn	**3v**	58
5[b]		R^1 = THP	**3w**	76
6			**3x**	73

[a] Isolated yields.
[b] MeCN and *N*-acetyl-*O*-protected hydroxylamine were used as solvent and coupling partner, respectively.

Exploration of several different iodo-heteroaryl partners is shown in Table 2. Selective monocouplings were achieved when coupling 2,6-diiodopyridine with 1 equivalent of *N*,*O*-protected hydroxylamines (Table 2, entries 1–3). Doubling the amount of hydroxylamine, catalyst, ligand, and base generated the corresponding bis-coupled product (see Table 1 in the Supporting Information). Interestingly, coupling of a methylated iodopyridine salt proceeded but provided only the deacetylated uncharged *O*-protected oximes (entries 4 and 5). *N*-Acetyl-*O*-THP hydroxylamine coupling with *N*-methyl pyridine salt (entry 5) as well as pyrimidine (entry 6) produced the coupling product in good yield.

In summary, Kukosha's methodology was expanded to include the coupling of 2-iodopyridines and other iodoheterocycles with protected hydroxylamines. Various *N*- and *O*-protecting groups were chosen to allow selective removal for broader synthetic versatility. This methodology is also suitable for selected iodopyridines, pyrimidines, and bifunctional substrates.

Starting materials, reagents, and solvents were purchased from commercial sources and used without further purification. The preparation of functionalized hydroxylamines **2e**,**h**,**j**,**k**,**l**,**m**,**o**,**q** is provided in the Supporting Information. All non-aqueous reactions were carried out under anhydrous conditions using oven dried glassware and an inert atmosphere of argon, unless otherwise indicated. K_2CO_3 was dried at 100 °C under vacuum prior to use. When indicated, solvents and reagents were degassed by bubbling argon through the liquids for 1 h. Flash chromatography was performed using Reveleris X2 system (Büchi Labortechnik AG; Flawil, Switzerland). Melting points were recorded on a Thomas Hoover capillary melting point apparatus (Philadelphia, PA) and reported uncorrected. ^1H and ^{13}C NMR spectra were recorded with a 400 MHz JEOL NMR spectrometer (JEOL USA, Inc.; Peabody, MA). IR spectra was recorded using a PerkinElmer FT-IR spectrophotometer (Boston, MA). High-resolution mass spectroscopy (HRMS) was measured using a ThermoFinnigan Q-Exactive instrument (Thermo Fisher Scientific; Waltham, MA) with electron spray ionization (ESI) and gas chromatography mass spectrometer chemical ionization time of flight (CI/TOF, Agilent Technologies; Santa Clara, CA).

Coupling of Iodopyridines with Functionalized Hydroxylamines; General Procedure

Hydroxamate (0.90 mmol), iodopyridine (1.34 mmol, 1.0–1.5 equiv), Cu_2O (0.90 mmol), dry K_2CO_3 (1.79 mmol), and 3 Å molecular sieves

(100% weight to the hydroxamate) were placed in a pressure tube. The tube was purged with argon three times. Degassed anhyd toluene (9.0 mL) and degassed DMEDA (0.18 mmol) were added to the flask. The vessel was sealed, and the mixture was stirred at 80 °C for 16 h. The mixture was cooled to r.t. and filtered. The filtrate was collected and eluted through a small silica plug, then concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel using a gradient of 0–20% EtOAc/CH_2Cl_2 to yield the product.

_N_-(Benzyloxy)-_N_-(pyridin-2-yl)acetamide (3a)

Tan solid; yield: 606 mg (82%); mp 81–82 °C.

IR (neat): 1673, 1570, 1462, 1428, 1371, 1331, 1278, 1147, 964, 781, 734, 697, 589 cm^{-1}.

^1H NMR (CD_3OD, 400 MHz): δ = 8.46 (m, 1 H), 7.88–7.84 (m, 1 H), 7.58 (d, *J* = 8.2 Hz, 1 H), 7.41–7.39 (m, 2 H), 7.34–7.32 (m, 3 H), 7.30–7.27 (m, 1 H), 4.96 (s, 2 H), 2.21 (s, 3 H).

^{13}C NMR (CD_3OD, 100 MHz): δ = 171.4, 151.7, 148.0, 138.5, 134.4, 129.7, 128.8, 128.3, 122.1, 118.9, 77.3, 21.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_2$: 243.1125; found: 243.1128.

***tert*-Butyl (Benzyloxy)(pyridin-2-yl)carbamate (3b)**

Brown solid; yield: 187 mg (69%); mp 51–53 °C.

IR (neat): 2974, 1702, 1582, 1466, 1432, 1339, 1289, 1252, 1117, 1020, 760, 704 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.49 (m, 1 H), 7.68–7.64 (m, 1 H), 7.49 (d, *J* = 8.3 Hz, 1 H), 7.46–7.44 (m, 2 H), 7.35–7.32 (m, 3 H), 7.09–7.04 (m, 1 H), 5.03 (s, 2 H), 1.53 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.4 (d), 148.4, 137.6, 135.1, 129.8, 128.7, 128.4, 120.6, 116.8, 82.7, 77.9, 28.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{21}N_2O_3$: 301.1547; found: 301.1543.

2-(Trimethylsilyl)ethyl (Benzyloxy)(pyridin-2-yl)carbamate (3c)

Colorless oil; yield: 489 mg (81%).

IR (neat): 2956, 1713, 1585, 1465, 1387, 1327, 1288, 1249, 1114, 1061, 858, 835, 750, 697 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.47 (m, 1 H), 7.67 (t, *J* = 8.2 Hz, 1 H), 7.50 (d, *J* = 8.2 Hz, 1 H), 7.46–7.44 (m, 2 H), 7.33–7.32 (m, 3 H), 7.08 (t, *J* = 5.5 Hz, 1 H), 5.08 (s, 2 H), 4.35–4.30 (m, 2 H), 1.11–1.07 (m, 2 H), 0.04 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.6, 153.1, 148.4, 137.8, 135.0, 129.8, 128.7, 128.4, 120.8, 116.8, 78.2, 65.3, 17.8, –1.4.

HRMS (CI/TOF): *m*/*z* [M]$^+$ calcd for $C_{18}H_{25}N_2O_3Si$: 345.1629; found: 345.1626.

***N*-(Benzyloxy)-4-methyl-*N*-(pyridin-2-yl)benzenesulfonamide (3d)**

Off-white solid; yield: 212 mg (83%); mp 73–74 °C.

IR (neat): 1582, 1428, 1360, 1169, 1087, 990, 807, 784, 708, 696, 664, 592, 567, 540 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.32–8.31 (m, 1 H), 7.57 (td, *J* = 1.8, 7.8 Hz, 1 H), 7.47 (d, *J* = 8.3 Hz, 2 H), 7.37–7.35 (m, 2 H), 7.26–7.24 (m, 3 H), 7.17 (d, *J* = 7.8 Hz, 2 H), 7.11–7.08 (m, 2 H), 5.18 (s, 2 H), 2.35 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.1, 148.5, 145.0, 137.6, 135.0, 131.0, 129.9, 129.4 (d), 128.6, 128.4, 122.5, 119.0, 79.9, 21.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{19}N_2O_3S$: 355.1111; found: 355.1106.

***N*-(Benzyloxy)-*N*-(pyridin-2-yl)methanesulfonamide (3e)**

Yellow oil; yield: 445 mg (64%).

IR (neat): 3034, 2937, 1588, 1461, 1431, 1348, 1162, 962, 767, 741, 698, 540 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.47 (m, 1 H), 7.65–7.61 (m, 1 H), 7.35–7.34 (m, 2 H), 7.26 (m, 3 H), 7.21–7.19 (m, 1 H), 7.11 (d, *J* = 6.8 Hz, 1 H), 5.16 (s, 2 H), 3.11 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.1, 149.0, 138.3, 134.9, 130.0, 128.8, 128.4, 123.4, 121.1, 79.9, 34.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}N_2O_3S$: 279.0798; found: 279.0794.

***N*-(Pyridin-2-yl)-*N*-[(tetrahydro-2*H*-pyran-2-yl)oxy]acetamide (3g)**

Yellow oil; yield: 1.31 g (91%).

IR (neat): 2941, 2869, 1686, 1585, 1466, 1431, 1366, 1320, 1276, 1035, 896, 874, 777 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.43 (m, 1 H), 7.72–7.68 (m, 1 H), 7.56–7.54 (m, 1 H), 7.13–7.11 (m, 1 H), 5.03 (s, 1 H), 3.74–3.73 (m, 1 H), 3.34–3.31 (m, 1 H), 2.30 (s, 3 H), 1.84–1.79 (m, 3 H), 1.53–1.51 (m, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.2, 153.1, 148.3, 137.8, 121.8, 119.3, 104.0, 63.6, 28.6, 24.9, 22.9, 19.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{17}N_2O_2$: 237.1234; found: 237.1230.

***tert*-Butyl Pyridin-2-yl[(tetrahydro-2*H*-pyran-2-yl)oxy]carbamate (3h)**

White solid; yield: 74.5 mg (28%); mp 59–60 °C.

IR (neat): 2970, 1709, 1585, 1567, 1461, 1439, 1329, 1279, 1155, 1114, 1096, 1024, 948, 900, 874, 795, 753 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.45–8.43 (m, 1 H), 7.65 (td, *J* = 1.88, 7.8 Hz, 1 H), 7.40 (d, *J* = 8.2 Hz, 1 H), 7.09–7.06 (m, 1 H), 5.15 (s, *J* = 3.0 Hz, 1 H), 3.79–3.73 (m, 1 H), 3.37–3.35 (m, 1 H), 1.90–1.69 (m, 3 H), 1.57–1.45 (m, 3 H), 1.47 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.2 (d), 148.3, 137.4, 121.3, 119.3, 102.7, 82.7, 62.2, 28.3, 25.2, 18.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{23}N_2O_4$: 295.1652; found: 295.1647.

2-(Trimethylsilyl)ethyl Pyridin-2-yl[(tetrahydro-2*H*-pyran-2-yl)oxy]carbamatecarbamate (3i)

Off-white solid; yield: 171 mg (66%); mp 45–46 °C.

IR (neat): 2955, 1708, 1585, 1461, 1439, 1387, 1316, 1290, 1259, 1245, 1181, 1114, 1049, 1016, 956, 904, 861, 835, 795, 769, 747, 694 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 8.43–8.41 (m, 1 H), 7.66–7.62 (m, 1 H), 7.42 (d, *J* = 8.2 Hz, 1 H), 7.07 (dd, *J* = 4.6, 7.3 Hz, 1 H), 5.13 (s, 1 H), 4.28–4.24 (m, 2 H), 3.77–3.74 (m, 1 H), 3.37–3.34 (m, 1 H), 1.90–1.69 (m, 3 H), 1.53–1.47 (m, 3 H), 1.03–0.98 (m, 2 H), –0.04 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.4, 153.9, 148.4, 137.6, 121.5, 119.2, 102.8, 65.2, 62.3, 28.2, 25.1, 18.4, 17.7, –1.5.

HRMS (CI/TOF): *m*/*z* [M]$^+$ calcd for $C_{16}H_{27}N_2O_4Si$: 339.1735; found: 339.1740.

Benzyl Pyridin-2-yl[(tetrahydro-2*H*-pyran-2-yl)oxy]carbamate (3j)

Colorless oil; yield: 125 mg (48%).

IR (neat): 3049, 2963, 2869, 1718, 1578, 1469, 1424, 1379, 1320, 1268, 1203, 1112, 1024, 941, 872, 791, 735, 556, 455 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.47 (m, 1 H), 7.71–7.67 (m, 1 H), 7.47 (d, *J* = 8.2 Hz, 1 H), 7.36–7.29 (m, 5 H), 7.12 (dd, *J* = 4.6, 7.4 Hz, 1 H), 5.25 (s, 2 H), 5.19 (m, 1 H), 3.76 (td, *J* = 3.2, 11.0 Hz, 1 H), 3.37–3.32 (m, 1 H), 1.93–1.71 (m, 3 H), 1.58–1.45 (m, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.1, 153.7, 148.5, 137.7, 135.7, 128.6, 128.3, 128.0, 121.7, 119.2, 102.9, 68.2, 62.3, 28.2, 25.1, 18.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{21}N_2O$: 329.1496; found: 329.1491.

***N*-(Allyloxy)-*N*-(pyridin-2-yl)acetamide (3k)**

Green oil; yield: 151 mg (66%).

IR (neat): 2983, 2938, 1729, 1684, 1585, 1461, 1430, 1367, 1282, 1153, 964, 909, 777 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.40 (m, 1 H), 7.65–7.61 (m, 2 H), 7.06 (s, 1 H), 5.94 (m, 1 H), 5.31–5.25 (m, 2 H) 4.45–4.43 (m, 2 H), 2.29 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.7, 151.8, 148.3, 137.9, 131.3, 121.2 (d), 117.6, 76.6, 22.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd $C_{10}H_{13}N_2O_2$: 193.0971; found: 193.0969.

***tert*-Butyl (Allyloxy)(pyridin-2-yl)carbamate (3l)**

Brown oil; yield: 59.2 mg (50%).

IR (neat): 2983, 1710, 1585, 1464, 1432, 1336, 1290, 1152, 1122, 777, 758 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.43 (s, 1 H), 7.64 (m, 1 H), 7.49–7.47 (m, 1 H), 7.04–7.03 (m, 1 H), 6.00–5.98 (m, 1 H), 5.33 (d, *J* = 8.8 Hz, 1 H), 5.22 (d, *J* = 10.0 Hz, 1 H), 4.51 (m, 2 H), 1.52 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.4, 153.3, 148.3, 137.6, 132.2, 120.5, 120.4, 116.8, 82.7, 77.1, 28.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd $C_{13}H_{19}N_2O_3$: 251.1390; found: 251.1387.

2-(Trimethylsilyl)ethyl (Allyloxy)(pyridin-2-yl)carbamate (3m)

Yellow oil; yield: 122 mg (43%).

IR (neat): 1714, 1585, 1468, 1434, 1386, 1328, 1288, 1151, 1117, 836, 777, 754 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.43 (m, 1 H), 7.66–7.63 (m, 1 H), 7.52 (d, *J* = 8.2 Hz, 1 H), 7.08–7.06 (m, 1 H), 6.02–5.94 (m, 1 H), 5.30 (d, *J* = 17.0 Hz, 1 H), 5.22 (d, *J* = 11.0 Hz, 1 H), 4.54–4.52 (m, 2 H), 4.35–4.30 (m, 2 H), 1.10–1.06 (m, 2 H), 0.02 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.6, 153.1, 148.3, 137.8, 132.0, 120.8, 120.6, 116.9, 65.3, 17.8, –1.4.

HRMS (CI/TOF): *m*/*z* [M]$^+$ calcd $C_{14}H_{23}N_2O_3Si$: 295.1473; found: 295.1467.

Benzyl (Allyloxy)(pyridin-2-yl)carbamate (3n)

Clear-blue oil; yield: 225 mg (82%).

IR (neat): 3074, 1713, 1585, 1464, 1432, 1385, 1329, 1288, 1118 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.45 (s, 1 H), 7.68–7.63 (m, 1 H), 7.54 (d, *J* = 8.2 Hz, 1 H), 7.40–7.27 (m, 5 H), 7.08–7.05 (m, 1 H), 6.01–5.91 (m, 1 H), 5.29, (s, 2 H), 5.29 (d, *J* = 6.4 Hz, 1 H), 5.20 (d, *J* = 10.1 Hz, 1 H), 4.53 (d, *J* = 6.9 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.3, 152.9, 148.4, 137.9, 135.7, 131.9, 128.6, 128.4, 128.2, 121.0, 120.8, 116.9, 77.3, 68.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd $C_{16}H_{17}N_2O_3$: 285.1234; found: 285.1299.

***N*-(Pyridin-2-yl)-*N*-(2-(trimethylsilyl)ethoxy)acetamide (3q)**

Yellow oil; yield: 124 mg (43%).

IR (neat): 1686, 1585, 1465, 1431, 1368, 1328, 1281, 1150, 943, 777, 580 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.43 (br, 1 H), 7.70–7.67 (m, 2 H), 7.09 (br, 1 H), 4.02–4.00 (m, 2 H), 2.34 (s, 3 H), 1.07–1.05 (m, 2 H), –0.01 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.4, 152.0, 148.2, 137.8, 121.0, 177.2, 73.4, 22.7, 16.8, –1.5.

HRMS (CI/TOF): *m*/*z* [M + H]$^+$ calcd $C_{12}H_{21}N_2O_2Si$: 253.1367; found: 253.1367.

***N*-(Benzyloxy)-*N*-(6-iodopyridin-2-yl)acetamide (3r)**

Off-white solid; yield: 263 mg (59%); mp 75–76 °C.

IR (neat): 3034, 1679, 1555, 1415, 1364, 1308, 1159, 1125, 780, 743, 694, 578 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.79 (d, *J* = 8.2 Hz, 1 H), 7.54–7.50 (m, 3 H), 7.40–7.38 (m, 3 H), 7.31 (t, *J* = 8.2 Hz, 1 H), 5.04 (s, 2 H), 2.35 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.0, 151.3, 139.2, 134.0, 131.7, 130.0, 129.3, 128.7, 115.5, 114.7, 78.0, 23.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd $C_{14}H_{14}IN_2O_2$: 369.0094; found: 369.0091.

***tert*-Butyl (Benzyloxy)(6-iodopyridin-2-yl)carbamate (3s)**

Yellow solid; yield: 216 mg (55%); mp 76–78 °C.

IR (neat): 2978, 1713, 1568, 1551, 1423, 1313, 1155, 1130, 747, 698 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.58 (d, *J* = 8.2 Hz, 1 H), 7.55–7.53 (m, 2 H), 7.47 (d, *J* = 7.8 Hz, 1 H), 7.40–7.30 (m, 3 H), 7.25 (t, *J* = 7.8 Hz, 1 H), 5.07 (s, 2 H), 1.55 (s, 9 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.8, 152.6, 138.8, 134.8, 131.0, 130.0, 128.9, 128.5, 114.7 (d), 83.2, 78.0, 28.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd $C_{17}H_{20}IN_2O_3$: 427.0513; found: 427.0506.

Di-*tert*-butyl Pyridine-2,6-diylbis[(benzyloxy)carbamate] (3s2)

The corresponding biscoupled product was also formed.

Yellow oil; yield: 30 mg.

IR (neat): 2978, 1711, 1582, 1439, 1313, 1152, 1121, 751, 697 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.64 (t, *J* = 8.0 Hz, 1 H), 7.44–7.42 (m, 4 H), 7.37 (d, *J* = 8.2 Hz, 2 H), 7.29–7.27 (m, 6 H), 5.10 (s, 4 H), 1.54 (s, 18 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 153.0, 151.6, 139.1, 135.2, 129.8, 128.6, 128.4, 112.4, 82.7, 77.9, 28.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd $C_{29}H_{36}N_3O_6$: 522.2599; found: 522.2591.

_N_-(6-Iodopyridin-2-yl)-_N_-[(tetrahydro-2_H_-pyran-2-yl)oxy]acetamide (3u)

Yellow solid; yield: 263 mg (58%); mp 87–90 °C.

IR (neat): 2918, 2862, 1682, 1555, 1415, 1367, 1286, 1159, 1125, 1035, 1016, 780, 723, 581 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.67 (d, *J* = 7.8 Hz, 1 H), 7.53 (d, *J* = 7.3 Hz, 1 H), 7.32 (t, *J* = 7.8 Hz, 1 H), 5.03 (m, 1 H), 3.95–3.89 (m, 1 H), 3.46–3.42 (m, 1 H), 2.38 (s, 3 H), 1.92–1.84 (m, 3 H), 1.63–1.56 (m, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.5, 152.3, 139.0, 132.0, 116.8, 114.4, 104.8, 63.9, 28.7, 25.0, 23.2, 19.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd $C_{12}H_{16}IN_2O_3$: 363.0200; found: 363.0195.

(_Z_)-1-Methylpyridin-2(1_H_)-one _O_-Benzyl Oxime (3v)

Brown oil; yield: 150 mg (58%).

IR (neat): 3030, 2911, 2851, 1644, 1556, 1454, 1347, 1045, 938, 730, 697 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.41 (d, *J* = 6.9 Hz, 2 H), 7.35–7.25 (m, 3 H), 6.86–6.83 (m, 1 H), 6.79–6.76 (m, 2 H), 5.55–5.51 (m, 1 H), 4.96 (s, 2 H), 3.22 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.9, 138.8, 137.7, 133.8, 128.3 (d), 127.5, 111.1, 100.9, 75.6, 39.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd $C_{13}H_{15}N_2O$: 215.1179; found: 215.1176.

(_Z_)-1-Methylpyridin-2(1_H_)-one _O_-Tetrahydro-2_H_-pyran-2-yl Oxime (3w)

Yellow oil; yield: 200 mg (76%).

IR (neat): 2934, 2847, 1647, 1558, 1348, 1155, 1106, 1034, 984, 945, 813, 731 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.88 (d, *J* = 9.1 Hz, 1 H), 6.84–6.78 (m, 2 H), 5.56 (td, *J* = 1.37, 6.9 Hz, 1 H), 5.13–5.12 (m, 1 H), 3.95–3.88 (m, 1 H), 3.60–3.54 (m, 1 H), 3.28 (s, 3 H), 1.99–1.71 (m, 3 H), 1.60–1.55 (m, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.4, 137.9, 134.1, 111.0, 101.3, 100.7, 63.1, 39.3, 29.6, 25.5, 20.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd $C_{11}H_{17}N_2O_2$: 209.1284; found: 209.1281.

_N_-(Pyrimidin-2-yl)-_N_-[(tetrahydro-2_H_-pyran-2-yl)oxy]acetamide (3x)

Brown oil; yield: 219 mg (73%).

IR (neat): 2938, 2866, 1695, 1564, 1405, 1368, 1298, 1245, 1034, 971, 894, 873 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.72 (m, 2 H), 7.14–7.12 (m, 1 H), 5.19 (m, 1 H), 3.93–3.90 (m, 1 H), 3.38–3.35 (m, 1 H), 2.42 (s, 3 H), 1.90–1.85 (m, 3 H), 1.62–1.55 (m, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.2, 159.8, 158.2, 118.3, 104.3, 63.2, 28.4, 24.9, 23.9, 19.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd $C_{11}H_{16}N_3O_3$: 238.1186; found: 238.1185.

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Supporting Information

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