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Note

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Chelation-Assisted Copper-Mediated Direct Acetylamination of 2-Arylpyridine C-H Bonds with Cyanate Salts

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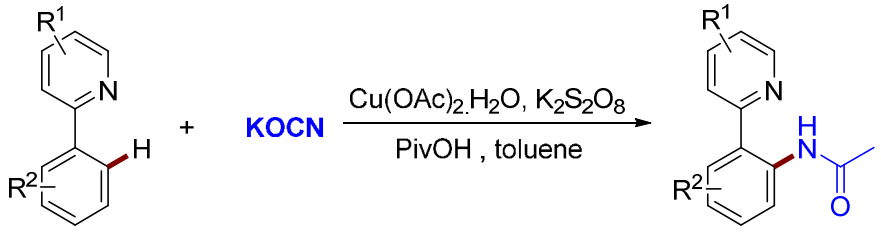


ABSTRACT: In this study, the coupling of 2-phenylpyridine derivatives and potassium cyanate through C-H bond functionalization in the presence of a copper salt is developed for the first time. By this protocol, various heteroarylated acetanilide derivatives are synthesized in good yields. 2-phenylpyridines containing electron-donating and electron-withdrawing groups appear to be well tolerated by this transformation.

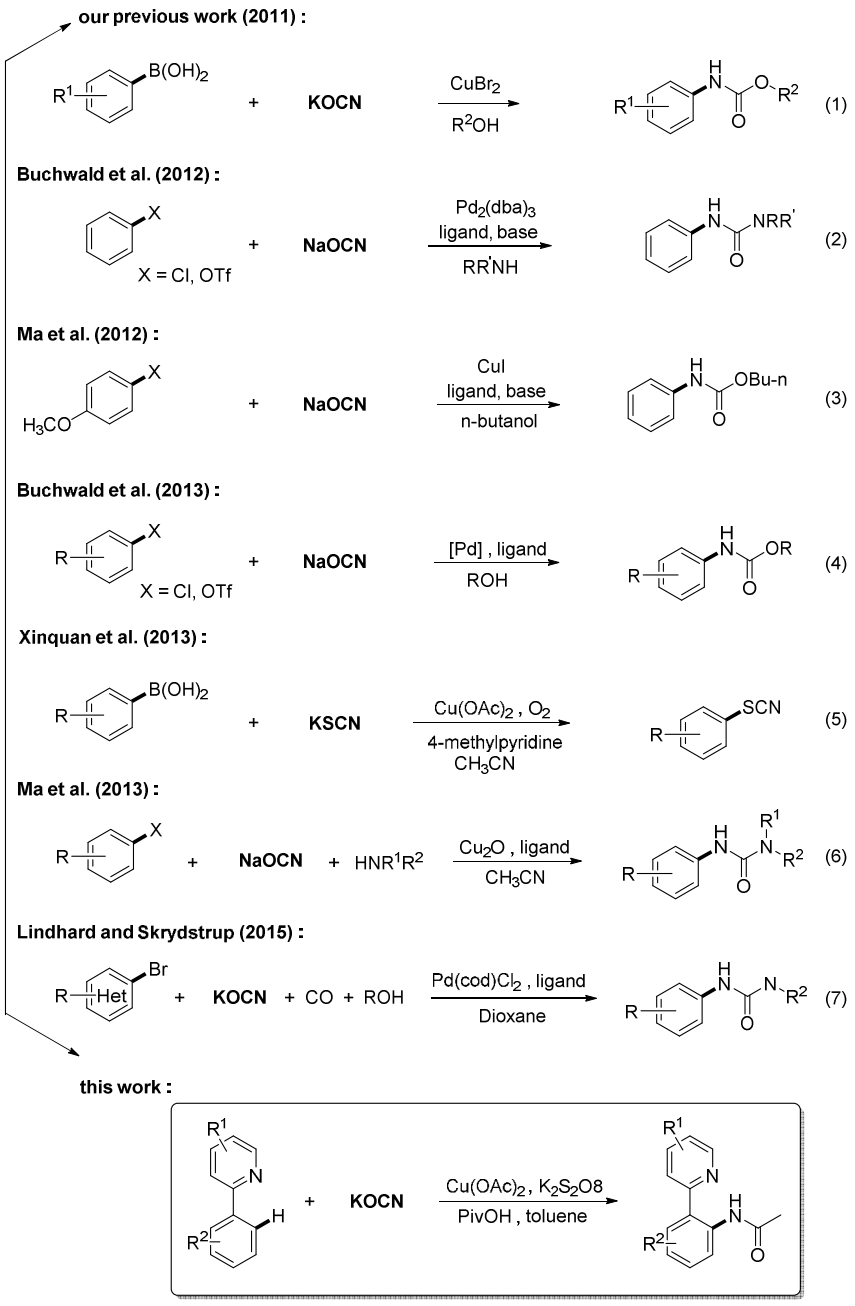
Aryl pyridine derivatives are important building blocks in organic synthesis.[1] They have found widespread application in natural products, herbicides, surfactants, insecticides, pharmaceuticals and biologically active compounds.[2] The C–N bond forming reactions through C-H functionalization have emerged as one of the most important strategy in synthetic chemistry due to elimination of prefunctionalization step of the coupling partners.[3] Buchwald and co-workers developed tandem directed C−H functionalization and amide arylation for the efficient

construction of substituted carbazoles as the pioneering study in this area.[4] Based on Buchwald's study, Inamoto reported a palladium-catalyzed C−H activation/intramolecular amination reaction to obtain 3-aryl/alkylindazoles.[5] In 2008, the Pd(II)-catalyzed intramolecular amination of sp^2 and sp^3 C−H bonds was developed by Yu's group.[6]

Direct C-H bond amidation reaction has also been investigated[7] and nitrogen sources such as aroyloxy- or acyloxycarbamates, 1,4,2-dioxazol-5-ones, N-hydroxycarbamates, dioxazolones have been used as amidation reagents. The use of cyanate salts as a coupling partner to form C-N bond have been rarely reported.[8] We reported the copper-catalyzed coupling of arylboronic acids with potassium cyanate as a new approach to the synthesis of aryl carbamates in 2011 as the first example of the use of potassium cyanate in the Chan-Lam-Evans type coupling reaction.[8a] (Scheme 1, eq. 1) The reaction was performed in air, at room temperature and, importantly, no base, ligand, or additive was required. Since then. the use of cyanate salts in metal catalyzed C-N bond forming reactions has been investigated and improved by others (Scheme 1). In 2012, Zhang and Ma reported copper-catalyzed coupling of aryl halides with potassium cyanate as affording the corresponding aryl carbamates.[8b] (Scheme 1, eq. 3) An efficient protocol for the synthesis of unsymmetrical ureas that proceeds via palladium-catalyzed cross-coupling of aryl chlorides and triflates with sodium cyanate was reported by Buchwald's group in the same year. [8c] (Scheme 1, eq. 2) A palladium-catalyzed cross-coupling reaction of aryl chlorides and triflates with sodium cyanate in the presence of alcohols as the nucleophiles was reported by the same group in 2013.[8d] (Scheme 1, eq. 4) Synthesis of aryl thiocyanates via copper-catalyzed aerobic oxidative cross-coupling between arylboronic acids and KSCN was reported by Hu in the same year.[8e] (Scheme 1, eq. 5). Assembly of N,N-disubstituted-N-arylureas via a copper-catalyzed one-pot three-component reaction of aryl bromides, potassium cyanate, and secondary amines

was also reported in the same year.[8f] (Scheme 1, eq. 6) Synthesis of acyl carbamates via four component Pd-catalyzed carbonylative coupling of aryl halides, potassium cyanate, and alcohols was reported by Skrydstrup and Lindhardt in 2015.[8g] (Scheme 1, eq. 7).

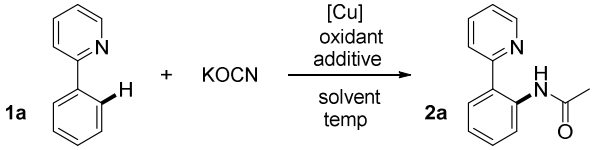
Scheme 1. Synthetic strategies using cyanate salts.



The use of prefunctionalized substrates such as arylboronic acids, halides and triflates as coupling partners along with cyanate salts is essential in all the previous reports. To the best of our knowledge, direct C-H functionalization through C-N bond formation using a cyanate salt as the coupling partner has not been reported yet. As a continuation of our interest in the field of C-

H functionalization reactions,[9] we herein report the first example of a chelation-assisted, copper-mediated, direct and regioselective acetylamination of C-H bonds of 2-arylpyridines using a cyanate salt as a coupling partner. We began our study with the selection of 2-phenylpyridine (**1a**) and potassium cyanate as a model (Table 1). Various conditions were screened to optimize the reaction condition. After preliminary screening of solvents, the results revealed that toluene was the best choice (Table 1, entries 1-4), which was then used to optimize the reaction conditions.

Table 1. Optimization of the Reaction Conditions.[a]

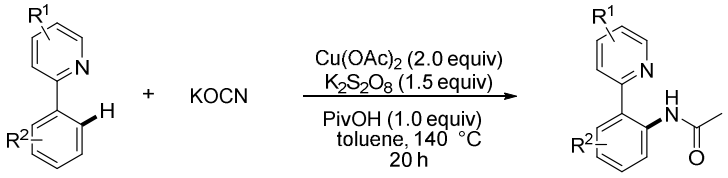


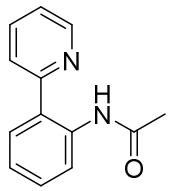
Entry	Copper-salt (equiv.)	co-oxidant[b]	Solvent	Additive	Temp (°C)	Yield (%)
1	$Cu(OAc)_2.H_2O$ (2)	air	DMF	PivOH	125	0
2	$Cu(OAc)_2.H_2O$ (2)	air	PhCl	PivOH	125	11
3	$Cu(OAc)_2.H_2O$ (2)	air	toluene	PivOH	125	43
4	$Cu(OAc)_2.H_2O$ (2)	air	*p*-xylene	PivOH	125	23
5	CuI (2)	air	toluene	PivOH	125	0
6	$CuBr_2$ (2)	air	toluene	PivOH	125	0
7	CuBr (2)	air	toluene	PivOH	125	0
8	CuO (2)	air	toluene	PivOH	125	0
9	$Cu(OAc)_2.H_2O$ (3)	air	toluene	PivOH	125	38
10	$Cu(OAc)_2.H_2O$ (1)	air	toluene	PivOH	125	32
11	$Cu(OAc)_2.H_2O$ (2)	air	toluene	PivOH	100	trace
12	$Cu(OAc)_2.H_2O$ (2)	air	toluene	PivOH	140	51
13	$Cu(OAc)_2.H_2O$ (2)	$Na_2S_2O_8$	toluene	PivOH	140	65
14	$Cu(OAc)_2.H_2O$ (2)	Ag_2CO_3	toluene	PivOH	140	23
15	$Cu(OAc)_2.H_2O$ (2)	$K_2S_2O_8$	toluene	PivOH	140	78
16	$Cu(OAc)_2.H_2O$ (2)	-	toluene	PivOH	140	0[c]
17	$Cu(OAc)_2.H_2O$ (2)	$K_2S_2O_8$	toluene	TFA	140	26
18	$Cu(OAc)_2.H_2O$ (2)	$K_2S_2O_8$	toluene	AcOH	140	14
19	$Cu(OAc)_2.H_2O$ (2)	$K_2S_2O_8$	toluene	-	140	24

[a]The reaction was performed on a 0.25 mmol scale for 20 hours. [b] Co-oxidant : 1.5 equiv. [c] Under an argon atmosphere.

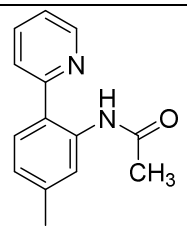
The control experiment showed that copper acetate is crucial for this reaction and the desired product **2a** was not obtained using other copper salts (Table 1, entries 5-8). The amount of the copper acetate was also examined and the best result was obtained with 2.0 equiv. of this salt (Table 1, entries 3, 9 and 10). Unfortunately, the reaction was not successful with the catalytic amounts of the copper salt (please see the supporting information).The yield of the reaction was satisfyingly increased with the increase of the reaction temperature from 100 to 140 °C (Table 1, entries 3, 11 and 12). To our delight, when the reaction was performed under 1.5 equiv of potassium persulfate as a co-oxidant with the combination of air atmosphere at 140°C, the yield of **2a** was increased to 78% (Table 1, entry 15). It is worth noting that the reaction was suppressed under an argon atmosphere (Table 1, entry 16).

Table 2. substrate scope[a]

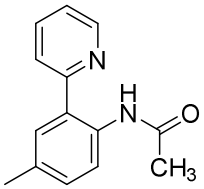




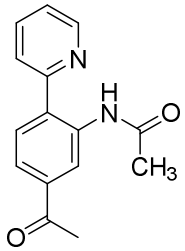
2a (78%)



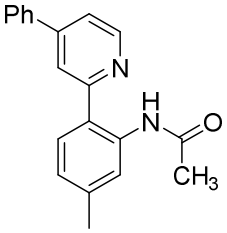
2b (83%)



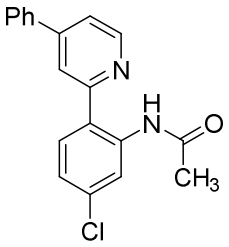
2c (74%)



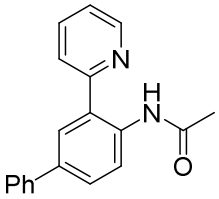
2d (49%)



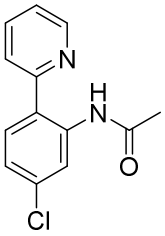
2e (81%)



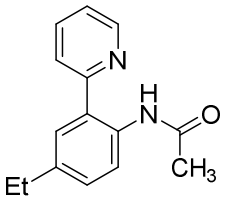
2f (47%)



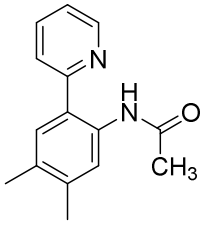
2g (58%)



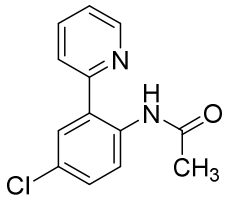
2h (53%)



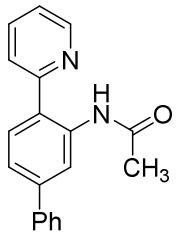
2i (76%)



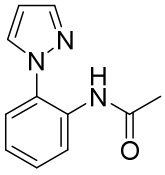
2j (68%)



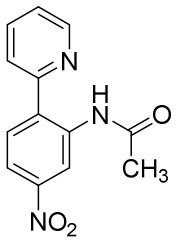
2k (45%)



2l (54%)



2m (31%)

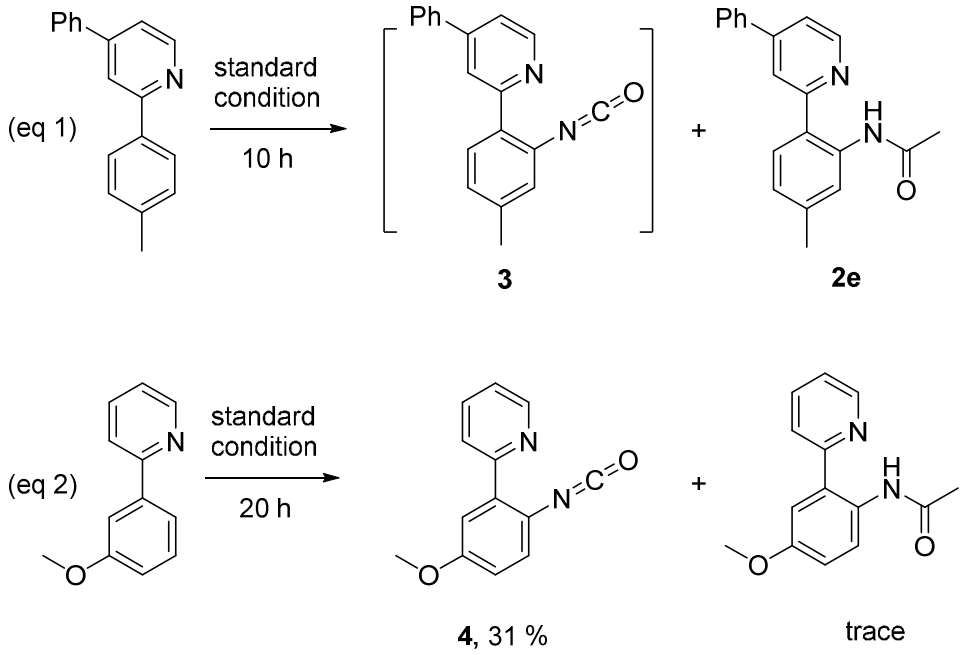


2o, n.d

[a]Reaction conditions: 2-phenylpyridines (0.25 mmol), $Cu(OAc)_2.H_2O$ (2.0 equiv), PivOH (1.0 equiv), $K_2S_2O_8$ (1.5 equiv) in toluene at 140 °C for 20 h.

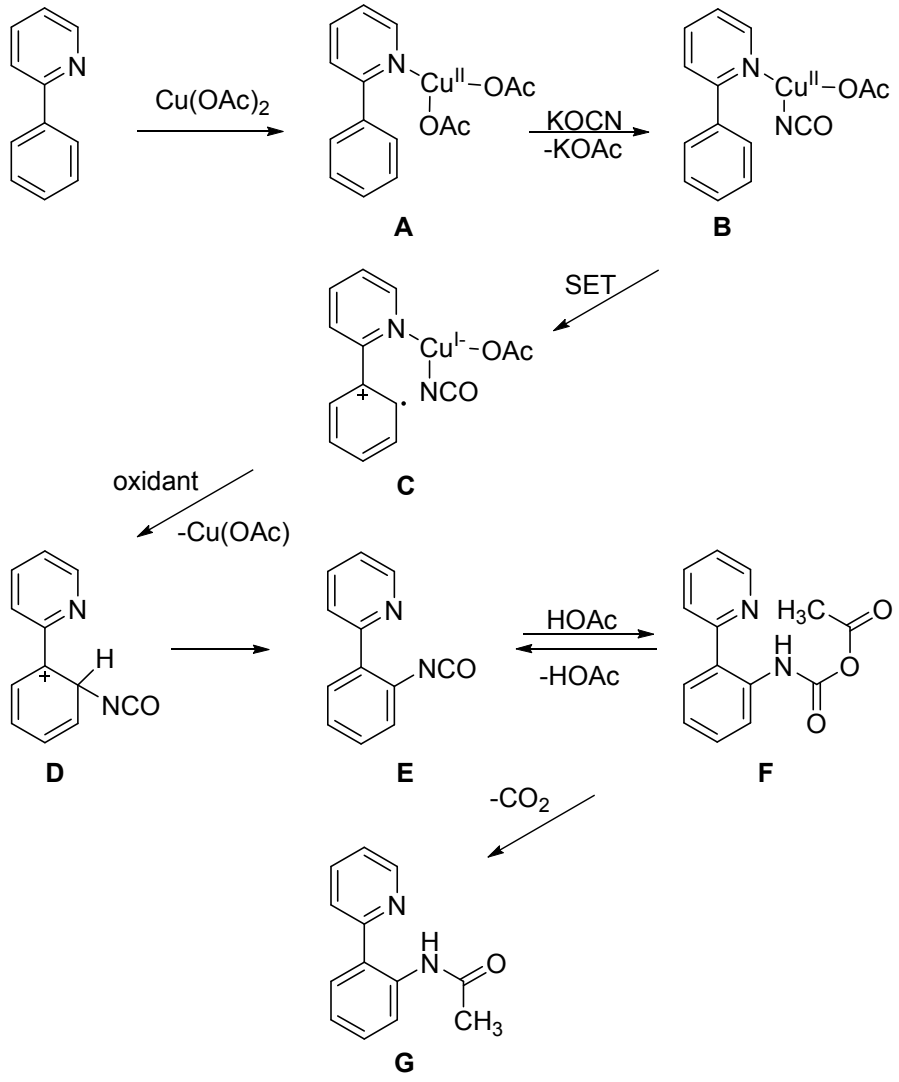
Finally, the results showed that pivalic acid was the best additive to obtain the desired products (Table 1, entries 15, 17 and 18). The best yield was achieved under the following optimal conditions: 2.0 equiv. of $Cu(OAc)_2.H_2O$, 1.5 equiv. of $K_2S_2O_8$ and 1.0 equiv. of PivOH in toluene (2.0 ml) under an air atmosphere at 140 °C for 20 h (Table 1, entry 15). The yield of the reaction was not improved by increasing the reaction time beyond 20 h. Having identified the optimized reaction conditions, we next examined the scope of this reaction (Table 2). It could be seen that electron-donating substituents on the aryl ring of 2-phenylpyridines were more compatible with this protocol and gave a higher yield relative to the substrates containing electron-withdrawing substituents such as **2d** and **2o**. It can also be observed from Table 2 that the alkyl group at the para position of the phenyl ring provided the desired product in higher yield, whereas meta-alkyl groups somehow decreased the reactivity of the reaction (Table 2, **2b**, **2c**, **2e** and **2i**). Gratifyingly, we have been able to isolate the reaction intermediate, during the investigation of the reaction scope, to gain further insight into the reaction mechanism. When the reaction of 2-(4-methylphenyl)-4-phenylpyridine was suppressed after 10 hours, 2-(2-isocyanato-4-methylphenyl)-4-phenylpyridine (**3**) was isolated from the reaction mixture. (Scheme 2, equation 1). Surprisingly, when the reaction of 2-(3-methoxyphenyl)pyridine was investigated under the optimized conditions the reaction did not lead to the desired acetylamination product and 2-(2-isocyanato-5-methoxyphenyl)-4-phenylpyridine (**4**) was isolated as the major product.

Scheme 2. Exploring the mechanistic study.



On the basis of the above results and the previous reports, a plausible mechanism for the reaction is proposed in Scheme 3.[10] Initially, copper acetate is coordinated to 2-phenylpyridine to give intermediate **A**. Subsequent ligand exchange between acetate and the isocyanate anion gives intermediate **B**. A single electron transfer (SET) from the aryl ring to the coordinated Cu(II) leads to the formation of a radical cation intermediate **C** in the next step. Subsequent trapping of the radical cation part of the substrate with the nearby isocyanate in the presence of the oxidants accounts for the ortho regioselection and gives the cationic species **D**. Deprotonation of the intermediate **D** affords the isocyanate derivative **E** which in the presence of copper acetate and pivalic acid leads to the formation of **F**. Decarboxylation of **F** under the reaction conditions gives the product **G**.[11]

Scheme 3. Plausible reaction mechanism



In summary, we have developed a one-pot, efficient and practical copper-mediated direct acetylamination of C-H bonds of 2-phenylpyridine derivatives by potassium cyanate for the first time to access a variety of new heteroarylated acetanilide compounds. $K_2S_2O_8$ and pivalic acid, which serve as co-oxidant and additive respectively, were of crucial importance and the reaction led to considerably lower yields in the absence of each. The regioselectivity of the reaction was also very high and all the products were formed in the ortho position of the phenyl ring.

EXPERIMENTAL SECTION

General Information. Solvents, $Cu(OAc)_2.H_2O$, $K_2S_2O_8$, , KOCN, PivOH and toluene were purchased from the market. 2-Arylpyridine derivatives were synthesized via Suzuki-Miyaura coupling of the corresponding aryl boronic acids with 2-bromopyridine and 2-chloropyrimidine, respectively.[12] Other reagents were purchased from commercial distributors and used without further purification. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates. The products were purified by preparative column chromatography on silica gel (0.063-0.200 mm). ^{1}H and ^{13}C-NMR Spectra: were recorded on 500, 400 or 300 MHz spectrometers in $CDCl_3$; δ in ppm, *J* in Hz. High resolution mass spectra were recorded with a Q-TOF mass spectrometer, equipped with an ESI source.

General Procedure.

A 10 mL microwave vial was charged with 2-phenylpyridines (1.0 equiv), $Cu(OAc)_2.H_2O$ (2 equiv), $K_2S_2O_8$ (1.5 equiv), PivOH (1.0 equiv) and toluene (2 ml). The vial was then sealed and immersed in an oil bath, which was preheated at 140 °C, for 20 h. After this time the reaction mixture was cooled to room temperature and then diluted with DCM and filtered. The residue was then purified by using column chromatography (n-hexane/EtOAc, 1/1) to yield the desired products.

N-(2-(pyridin-2-yl)phenyl)acetamide (2a).[8a,b] The general procedure was followed using 2-phenylpyridine (0.25 mmol, 39 mg), $K_2S_2O_8$ (102 mg, 0.38 mmol), KOCN (40 mg, 0.50 mmol), $Cu(OAc)_2.H_2O$ (100 mg, 0.50 mmol), PivOH (25 mg, 0.25 mmol), and toluene (2 mL). Purification by column chromatography (silica gel, n-hexane/ EtOAc 1:1) gave the final product 2a (41 mg, 78% yield) as a brown oil; **^{1}HNMR** (500 MHz, , $CDCl_3$) δ 11.99 (s, 1H), 8.66 (s, 1H), 8.49 (d, *J* = 8.2 Hz, 1H), 7.88 (t, *J* = 7 Hz, 1H), 7.75 (d, *J* = 8 Hz, 1H), 7.64 (d, *J* = 8 Hz, 1H), 7.43 (t, *J* = 8 Hz, 1H), 7.32 (t, *J* = 6.3 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 2.186 (s, 3H) **^{13}CNMR** (125 MHz, $CDCl_3$) δ 168.6, 158.2, 147.2, 137.9 137.5, 130.1, 128.9, 125.7, 123.6, 123.3, 122.1, 122.0, 25.1; **IR**(Film) 3178, 3059, 1686, 1589, 1529, 1435, 1311, 756 cm^{-1} ; **HRMS** (EI) m/z calculated for $C_{13}H_{12}ON_2$ (M+): 212.0950 found: 212.0950.

N-(5-methyl-2-(pyridin-2-yl)phenyl)acetamide (2b). The general procedure was followed using 2-(p-tolyl)pyridine (0.25 mmol, 42 mg), $K_2S_2O_8$ (102 mg, 0.38 mmol), KOCN (40 mg, 0.50 mmol), $Cu(OAc)_2.H_2O$ (100 mg, 0.50 mmol), PivOH (25 mg, 0.25 mmol), and toluene (2 mL). Purification by column chromatography (silica gel, n-hexane/ EtOAc 1:1) gave the final product 2b (47 mg, 83% yield) as a white solid; **mp**: 81 °C; **^{1}HNMR** (400 MHz, , $CDCl_3$) δ 12.03 (s, 1H), 8.60 (d, *J* = 4.4Hz, 1H), 8.29 (s, 1H), 7.83 (t, *J* = 7.8Hz, 1H), 7.70 (d, *J* = 8Hz, 1H), 7.50 (d, *J* = 8 Hz, 1H), 7.26 (t, *J* = 3.4 Hz, 1H), 6.97 (d, *J* = 8 Hz, 1H), 2.36 (s, 3H), 2.15 (s, 3H) ; **^{13}CNMR** (100 MHz, $CDCl_3$) δ 168.7, 146.8, 140.7, 138.2, 137.2, 128.7, 124.6, 123.1, 122.8, 121.7, 25.1, 21.6; **IR**(Film) 3055, 1680, 1585, 1539, 1471, 1419, 783; **HRMS** (EI) m/z calculated for $C_{14}H_{14}ON_2$ (M+): 226.1106. found: 226.1112.

N-(4-methyl-2-(pyridin-2-yl)phenyl)acetamide (2c). The general procedure was followed using 2-(m-tolyl)pyridine (0.25 mmol, 42 mg), $K_2S_2O_8$ (102 mg, 0.38 mmol), KOCN (40 mg, 0.50 mmol), $Cu(OAc)_2.H_2O$ (100 mg, 0.50 mmol), PivOH (25 mg, 0.25 mmol), and toluene (2 mL). Purification by column chromatography (silica gel, n-hexane/ EtOAc 1:1) gave the final product 2c (42 mg, 74% yield) as a pale yellow oil; **^{1}HNMR** (400 MHz, , $CDCl_3$) δ 11.74 (s, 1H), 8.61 (d, *J* = 4.4 Hz, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 7.84 (t, *J* = 8 Hz, 1H), 7.71 (d, *J* = 8 Hz, 1H), 7.39 (s, 1H), 7.27 (t, *J* = 6.2 Hz, 1H), 7.20 (d, *J* = 8.4Hz, 1H), 2.35 (s, 1H), 2.12 (s, 1H); **^{13}CNMR** (100 MHz, $CDCl_3$) δ 168.5, 158.2, 147.2, 138.0, 134.8, 133.1, 130.8, 129.4, 125.9, 123.3, 122.3, 121.9, 25.1, 21.0; **IR**(Film) 3244, 2972, 1720, 1684, 1593, 1522, 1413, 791; **HRMS** (EI) m/z calculated for $C_{14}H_{14}ON_2$ (M+): 226.1106. found: 226.1109.

N-(5-acetyl-2-(pyridin-2-yl)phenyl)acetamide (2d). The general procedure was followed using 1-(4-(pyridine-2-yl)phenyl)ethan-1-one (0.25 mmol, 49 mg), $K_2S_2O_8$ (102 mg, 0.38 mmol), KOCN (40 mg, 0.50 mmol), $Cu(OAc)_2.H_2O$ (100 mg, 0.50 mmol), PivOH (25 mg, 0.25 mmol), and toluene (2 mL). Purification by column chromatography (silica gel, n-hexane/ EtOAc 1:1) gave the final product 2d (31 mg, 49% yield) as a yellow oil; **mp**: 99 °C; **1HNMR** (300 MHz, , $CDCl_3$) δ 12.19 (s, 1H), 9.15 (s, 1H), 8.66 (d, *J* = 4.2 Hz, 1H), 7.87 (td, *J* = 6.5 Hz & *J* = 1.8 Hz, 1H), 7.79-7.70 (m, 3H), 7.34 (td, *J* = 6.2Hz & *J* = 1 Hz, 1H), 2.64 (s, 3H), 2.19 (s, 3H); **^{13}CNMR** (100 MHz, $CDCl_3$) δ; 197.7, 169.1, 156.4, 146.6, 139.1, 138.3, 137.6, 131.9, 129.3, 124.2, 123.6, 123.1 **HRMS** (EI) m/z calculated for $C_{15}H_{14}O_2N_2$ (M+): 254.1055. found: 254.1060.

N-(5-methyl-2-(4-phenylpyridin-2-yl)phenyl)acetamide(2e). The general procedure was followed using 4-phenyl-2-(p-tolyl)pyridine (0.25 mmol, 61 mg), $K_2S_2O_8$ (102 mg, 0.38 mmol), KOCN (40 mg, 0.50 mmol), $Cu(OAc)_2.H_2O$ (100 mg, 0.50 mmol), PivOH (25 mg, 0.25 mmol), and toluene (2 mL). Purification by column chromatography (silica gel, n-hexane/ EtOAc 1:1) gave the final product 2e (61 mg, 81% yield) as a yellow oil; **^{1}HNMR** (400 MHz, , $CDCl_3$) δ 11.35 (s, 1H), 8.69 (s, 1H), 7.95 (s, 1H), 7.71 (d, *J* = 6 Hz, 2H), 7.63 (s, 1H), 7.55 (m, 5H), 7.09 (d, *J* = 8.1 Hz, 1H), 2.42 (s, 3H), 2.16 (s, 3H); **^{13}CNMR** (100 MHz, $CDCl_3$) δ 169.3, 141.9, 136.5, 130.9, 130.4, 130.1, 129.5, 129.4, 129.0, 128.8, 128.6, 128.1, 127.4, 126.1, 120.5, 23.7, 21.6; **IR**(Film) 2927, 2864, 1720, 1591, 1539, 1470, 1417, 1379, 1238, 761, 700; **HRMS** (EI) m/z calculated for $C_{20}H_{18}ON_2$ (M+): 302.1419. found: 302.1416.

N-(5-chloro-2-(4-phenylpyridin-2-yl)phenyl)acetamide (2f). The general procedure was followed using 2-(4-chlorophenyl)-4-phenylpyridine (0.25 mmol, 66 mg), $K_2S_2O_8$ (102 mg, 0.38 mmol), KOCN (40 mg, 0.50 mmol), $Cu(OAc)_2.H_2O$ (100 mg, 0.50 mmol), PivOH (25 mg, 0.25 mmol), and toluene (2 mL). Purification by column chromatography (silica gel, n-hexane/ EtOAc 1:1) gave the final product 2f (38 mg, 47% yield) as a white solid; **mp**: 136 °C; **^{1}HNMR** (300 MHz, , $CDCl_3$) δ 11.69 (s, 1H), 8.67 (d, *J* = 5.4 Hz, 1H), 8.38 (s, 1H), 7.91 (s 1H), 7.70-7.67 (m, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.55-7.51 (m, 3H), 7.20 (d, *J* = 8.4 Hz, 1H), 2.16 (s, 3H); **^{13}CNMR** (75 MHz, $CDCl_3$) δ 169.3, 145.1, 137.8, 130.6, 130.4, 129.5, 127.4, 125.2, 122.6, 121.1, 24.5; **HRMS** (EI) m/z calculated for $C_{19}H_{15}ON_2Cl$ (M+): 322.0873. found: 322.0876.

N-(3-(pyridin-2-yl)biphenyl-4-yl)acetamide (2g). The general procedure was followed using 2-(biphenyl-3-yl)pyridine (0.25 mmol, 58 mg), $K_2S_2O_8$ (102 mg, 0.38 mmol), KOCN (40 mg, 0.50 mmol), $Cu(OAc)_2.H_2O$ (100 mg, 0.50 mmol), PivOH (25 mg, 0.25 mmol), and toluene (2 mL). Purification by column chromatography (silica gel, n-hexane/ EtOAc 1:1) gave the final product 2g (42 mg, 58% yield) as a yellow solid; **mp**: 144 °C; **^{1}HNMR** (400 MHz, , $CDCl_3$) δ 11.86 (s, 1H), 8.66 (dd, *J* = 4.8Hz & *J* = 0.8 Hz, 1H), 8.50 (d, *J* = 8.8 Hz, 1H), 7.88 (td, *J* = 7.8 Hz & *J* = 1.6 Hz, 1H), 7.82-7.79 (m, 2H), 7.64 (dd, *J* = 8.8 Hz & *J* = 2.2 Hz, 1H) 7.60-7.58 (m, 2H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.35-7.31 (m, 2H), 2.17 (s, 3H); **^{13}CNMR** (100 MHz, $CDCl_3$) δ 168.7, 157.8, 146.9, 140.3, 138.4, 136.7, 128.7, 127.7, 127.2, 126.8, 126.1, 123.6, 122.9, 122.2, 25.1; **IR**(Film) 3236, 3051, 1681, 1587, 1506, 1442, 1392, 1294, 765, 596; **HRMS** (EI) m/z calculated for $C_{19}H_{16}ON_2$ (M+): 288.1263. found: 288.1271.

N-(5-chloro-2-(pyridin-2-yl)phenyl)acetamide(2h). The general procedure was followed using 2-(4-chlorophenyl)pyridine (0.25 mmol, 47 mg), $K_2S_2O_8$ (102 mg, 0.38 mmol), KOCN (40 mg, 0.50 mmol), $Cu(OAc)_2.H_2O$ (100 mg, 0.50 mmol), PivOH (25 mg, 0.25 mmol), and toluene (2 mL). Purification by column chromatography (silica gel, n-hexane/ EtOAc 1:1) gave the final product 2h (33 mg, 53% yield) as a white solid; **mp**: 127 °C; **^{1}HNMR** (300 MHz, , $CDCl_3$) δ 11.75 (s, 1H), 8.65 (d, *J* = 4.2 Hz, 1H), 8.39 (s, 1H), 7.96 (t, J = 7.5 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.40 (t, *J* = 6 Hz, 1H), 7.17 (dd, *J* = 8.4 Hz & *J* = 2.4 Hz, 1H), 2.14 (s, 3H);**^{13}CNMR** (75 MHz, $CDCl_3$) δ 168.9, 145.9, 139.6, 138.2, 136.6, 130.0, 124.4, 124.0, 123.3, 122.7, 24.8; **IR**(Film) 3417, 2925, 1685, 1587, 1523, 1469, 1367, 1278, 783, 665; **HRMS** (EI) m/z calculated for $C_{13}H_{11}ON_2Cl$ (M+): 246.0560. found: 246.0547.

N-(4-ethyl-2-(pyridin-2-yl)phenyl)acetamide(2i). The general procedure was followed using 2-(3ethylphenyl)pyridine (0.25 mmol, 46 mg), $K_2S_2O_8$ (102 mg, 0.38 mmol), KOCN (40 mg, 0.50 mmol), $Cu(OAc)_2.H_2O$ (100 mg, 0.50 mmol), PivOH (25 mg, 0.25 mmol), and toluene (2 mL). Purification by column chromatography (silica gel, n-hexane/ EtOAc 1:1) gave the final product 2i (46 mg, 76% yield) as a yellow oil; **^{1}HNMR** (300 MHz, , $CDCl_3$) δ 11.76 (s,1H), 8.61 (d, *J* = 4.2 Hz, 1H), 8.33 (d, *J* = 8.4 Hz, 1H), 7.83 (td, *J* = 7.8 Hz, *J* = 1.8 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 1.8 Hz, 1H), 7.27 (td, *J* = 3.7 Hz, *J* = 1.2 Hz, 1H), 7.21 (d, *J* = 1.8 Hz, 1H), 2.67 (q, *J* = 6.0 Hz , 2H), 2.12 (s,3H), 1.23 (t, *J* = 7.8 Hz,3H); **^{13}CNMR** (75 MHz, $CDCl_3$) δ 168.5, 158.3, 147.2, 139.5, 138.0, 135.0, 129.6, 128.3, 125.9, 123.3, 122.4, 121.9, 28.4, 25.0, 15.7; **IR**(Film) 3170, 2966, 1683, 1591, 1523, 1473, 1413, 1301, 790, 596; **HRMS** (EI) m/z calculated for $C_{15}H_{16}ON_2$ (M+): 240.1263. found: 240.1253.

N-(4,5-dimethyl-2-(pyridin-2-yl)acetamide (2j). The general procedure was followed using 2-(3,4-dimethylphenyl)pyridine (0.25 mmol, 46 mg), $K_2S_2O_8$ (102 mg, 0.38 mmol), KOCN (40 mg, 0.50 mmol), $Cu(OAc)_2.H_2O$ (100 mg, 0.50 mmol), PivOH (25 mg, 0.25 mmol), and toluene (2 mL). Purification by column chromatography (silica gel, n-hexane/ EtOAc 1:1) gave the final product 2j (41 mg, 68% yield) as a white solid; **mp**: 111 °C; **^{1}HNMR** (300 MHz, , $CDCl_3$) δ 11.62 (s, 1H), 8.61 (d, *J* = 4.2 Hz, 1H), 8.13 (s, 1H), 7.87 (td, *J* = 7.8 Hz & *J* = 1.5Hz, 1H), 7.72 (d, *J* = 8.1Hz, 1H), 7.35 (s, 1H), 7.29 (t, *J* = 6.2Hz, 1H), 2.29 (s, 3H), 2.26 (s, 3H), 2.12 (s, 3H); **^{13}CNMR** (75 MHz, $CDCl_3$) δ 168.7, 157.5, 146.3, 139.4, 138.7, 134.9, 132.4, 129.9, 124.1, 123.7, 123.4, 121.8, 24.9, 19.9, 19.3; **IR**(Film) 3236, 2923, 1678, 1585, 1521, 1448, 1396, 1290, 790, 590; **HRMS** (EI) m/z calculated for $C_{15}H_{16}ON_2$ (M+): 240.1263. found: 240.1266.

N-(4-chloro-2-(pyridin-2-yl)phenyl)acetamide(2k). The general procedure was followed using 2-(3-chlorophenyl)pyridine (0.25 mmol, 47 mg), $K_2S_2O_8$ (102 mg, 0.38 mmol), KOCN (40 mg, 0.50 mmol), $Cu(OAc)_2.H_2O$ (100 mg, 0.50 mmol), PivOH (25 mg, 0.25 mmol), and toluene (2 mL). Purification by column chromatography (silica gel, n-hexane/ EtOAc 1:1) gave the final product 2k (28 mg, 45% yield) as a white solid; **mp**:103 °C; **^{1}HNMR** (400 MHz, , $CDCl_3$) 12.10 (s, 1H), 8.59 (d, *J* = 4.0 Hz, 1H), 8.49 (d, *J* = 8.0Hz, 1H), 7.77 (td, *J* = 4.0 Hz & *J* = 1.6Hz, 1H), 7.62 (d, *J* = 8.0Hz, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.25 (m, 2H), 2.12 (s, 3H); **^{13}CNMR** (100 MHz, $CDCl_3$) δ 168.5, 156.8, 147.5, 137.9, 136.2, 129.9, 129.5, 128.3, 128.1, 123.0, 122.9, 121.7, 25.1; **IR**(Film) 3416, 2928, 1689, 1587, 1526, 1473, 1369, 1281, 784, 666; **MS**(EI) m/z (relative intensity) 246 (M+ , 52), 231 (100), 203 (92), 168 (39), 140 (15), 79 (23). Anal. Calcd. for $C_{13}H_{11}ClN_2O$: C, 63.40; H, 4.51; N, 11.38; found: C, 63.35; H, 4.49; N, 11.36.

N-(4-(pyridin-2-yl)biphenyl-3-yl)acetamide (2l). The general procedure was followed using 2-(biphenyl-4-yl)pyridine (0.25 mmol, 58 mg), $K_2S_2O_8$ (102 mg, 0.38 mmol), KOCN (40 mg, 0.50 mmol), $Cu(OAc)_2.H_2O$ (100 mg, 0.50 mmol), PivOH (25 mg, 0.25 mmol), and toluene (2 mL). Purification by column chromatography (silica gel, n-hexane/ EtOAc 1:1) gave the final product 2l (39 mg, 54% yield) as a brown oil; **^{1}HNMR** (400 MHz, , $CDCl_3$) 12.30 (s, 1H), 8.90 (s, 1H), 8.69 (d, *J* = 4.8 Hz, 1H), 7.89 (td, *J* = 8.0 Hz & *J* = 1.6Hz, 1H), 7.82 (d, *J* = 8.0Hz, 1H), 7.74 (t, *J* = 8.4 Hz, 2H), 7.47 (m, 3H), 7.39 (m, 2H), 7.32 (td, *J* = 5.2 Hz & *J* = 1.2 Hz, 1H), 2.25 (s, 3H); **^{13}CNMR** (100 MHz, $CDCl_3$) δ 168.7, 158.1, 147.5, 142.7, 137.7, 129.1, 128.8, 128.7, 128.3, 127.7, 127.2, 127.1, 122.9, 121.9, 121.8, 120.4, 25.3; **IR**(Film) 3235, 3047, 1677, 1586, 1505, 1438, 1390, 1291, 764, 595; **MS**(EI) m/z (relative intensity) 288 (M+ , 41), 273 (100), 245 (71), 217 (23), 178 (39), 78 (18). Anal. Calcd. for $C_{19}H_{16}N_2O$: C, 79.13; H, 5.60; N, 9.72; found: C, 79.16; H, 5.59; N, 9.70

N-(2-(1H-pyrazol-1-yl)phenyl)acetamide (2m). The general procedure was followed using 1-phenyl-1H-pyrazole (0.25 mmol, 36 mg), $K_2S_2O_8$ (102 mg, 0.38 mmol), KOCN (40 mg, 0.50 mmol), $Cu(OAc)_2.H_2O$ (100 mg, 0.50 mmol), PivOH (25 mg, 0.25 mmol), and toluene (2 mL). Purification by column chromatography (silica gel, n-hexane/ EtOAc 1:1) gave the final product 2m (16 mg, 31% yield) as a yellow oil; **^{1}HNMR** (500 MHz, , $CDCl_3$) δ 10.23 (s, 1H), 8.44 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 2 Hz, 1H), 7.64 (d, *J* = 3 Hz, 1H), 7.34 (m, 2H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.49 (t, *J* = 2.2 Hz, 1H), 2.12 (s, 3H); **^{13}CNMR** (125 MHz, $CDCl_3$) δ 168.5, 141.4, 131.6, 130.2, 128.1, 127.1, 122.9, 122.4, 122.1, 107.2, 25.1; **IR**(Film) 3441, 2924, 2856, 1691, 1597,

1515, 1461, 1394, 1047, 752; **HRMS** (EI) m/z calculated for $C_{11}H_{11}ON_3$ (M+): 201.0902. found: 201.0895

2-(2-isocyanato-4-methylphenyl)-4-phenylpyridine(3). The general procedure was followed using 4-phenyl-2-(p-tolyl)pyridine (0.25 mmol, 61 mg), $K_2S_2O_8$ (102 mg, 0.38 mmol), KOCN (40 mg, 0.50 mmol), $Cu(OAc)_2.H_2O$ (100 mg, 0.50 mmol), PivOH (25 mg, 0.25 mmol), and toluene (2 mL). Purification by column chromatography (silica gel, n-hexane/ EtOAc 1:1) gave the final product 3 (25 mg, 35% yield) as a yellow solid; **mp**:82 °C; **^{1}HNMR** (500 MHz, $CDCl_3$) δ 8.81 (d, *J* = 5 Hz, 1H), 8.07 (s, 1H), 7.90 (d, *J* = 8 Hz, 1H), 7.72 (dd, *J* = 8 Hz & J = 1 Hz, 2H), 7.63 (s, 1H), 7.55- 7.48 (m, 5H), 2.45 (s, 3H); **^{13}CNMR** (100 MHz, $CDCl_3$) δ 155.7, 150.3, 149.4, 140.8, 139.2, 138.0, 134.4, 133.8, 129.9, 129.3, 129.2, 127.2, 121.4, 121.1, 119.0, 110.9, 20.9; **IR**(Film) 2466, 1595, 1461, 1383, 831, 767, 694; **HRMS** (EI) m/z calculated for $C_{19}H_{14}ON_2$ (M+): 286.1106, found: 286.1115.

2-(2-isocyanato-5-methoxyphenyl)pyridine(4). The general procedure was followed using 2-(3-methoxyphenyl)pyridine (0.25 mmol, 46 mg), $K_2S_2O_8$ (102 mg, 0.38 mmol), KOCN (40 mg, 0.50 mmol), $Cu(OAc)_2.H_2O$ (100 mg, 0.50 mmol), PivOH (25 mg, 0.25 mmol), and toluene (2 mL). Purification by column chromatography (silica gel, n-hexane/ EtOAc 1:1) gave the final product 4 (17 mg, 31% yield) as a yellow oil; **^{1}HNMR** (400 MHz, , $CDCl_3$) δ 8.84 (s, 1H), 8.06 (t, *J* = 8 Hz, 1H), 7.99 (d, *J* = 8 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.56 (t, *J* = 6.2 Hz, 1H), 7.52 (d, *J* = 2 Hz, 1H), 7.06 (dd, *J* = 8.4 Hz & *J* = 2.2 Hz, 1H), 3.97 (s, 3H); **^{13}CNMR** (100 MHz, $CDCl_3$) δ 163.1, 153.2, 147.4, 135.9, 124.9, 124.4, 121.7, 119.6, 118.5, 116.9, 115.5, 102.6, 56.1; **IR**(Film) 2938, 2839, 2219, 1604, 1562, 1491, 1465, 1305, 1225, 1029, 790; **HRMS** (EI) m/z calculated for $C_{13}H_{10}O_2N_2$ (M+): 226.0742. found: 226.0768.

ASSOCIATED CONTENT

Supporting Information

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

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REFERENCES

(1) (a) Wang, X.; Truesdale, L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010,** *132*, 3648. (b) Wang, W.; Luo, F.; Zhang, S.; Cheng, J. *J. Org. Chem.* **2010,** *75*, 2415. (c) Tsai, A. S.; Tauchert, M. E.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011,** *133*, 1248. (d) Xiao, F.; Shuai, Q.; Zhao, F.; Baslé, O.; Deng, G.; Li, C.-J. *Org. Lett.* **2011,** *13*, 1614. (e) Zhang, L.; Liu, Z.; Li, H.; Fang, G.; Barry, B.-D.; Belay, T. A.; Bi, X.; Liu, Q. *Org. Lett.* **2011,** *13*, 6536. (f) Ye, Z.; Wang, W.; Luo, F.; Zhang, S.; Cheng, J. *Org. Lett.* **2009,** *11*, 3974. (g) Saidi, O.; Marafie, J.; Ledger, Araminta E. W.; Liu, P. M.; Mahon, M. F.; Kociok-Köhn, G.; Whittlesey, M. K.; Frost, C. G. *J. Am. Chem. Soc.* **2011,** *133*, 19298.

(2) (a) Kim, S.-H.; Rieke, R. D. *Tetrahedron Lett.* **2009,** *50*, 6985. (b) Nishiyama, R.; Fujikawa, K.; Haga, T.; Toki, T.; Nagatani, K.; Imai, O. *Pyridylanilines;* Google Patents, 1982. (c) Fang, A. G.; Mello, J. V.; Finney, N. S. **2003,** *5*, 967. (d) Helmut, W.; Karl-Otto, W, W.; Ulf, M.; Peter, S. Peter, S.; Gerhard, H.; Elisabeth, H.; Ralf, K.; Hartmann, K.; Albrecht, H.; Norbert,G.; . US Pat. . 1998. US 5 733850. (e) Bagley, M. C.; Glover, C.; Merritt, E. A. **2007**, 2459. (f) Butler, D. E.; Bass, P.; Nordin, I. C.; Hauck, F. P., JR; L'Italien, Y. J. *J. Med. Chem.* **1971,** *14*, 575. (g) Deprez, N. R.; Sanford, M. S. **2009,** *131*, 11234.

(3) (a) Olson, D. E.; Du Bois, J. *J. Am. Chem. Soc.* **2008,** *130*, 11248. (b) John, A.; Nicholas, K. M. *J. Org. Chem.* **2011,** *76*, 4158. (c) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008,** *130*, 14058. (d) Thansandote, P.; Lautens, M. *Chem. Eur. J.* **2009,** *15*, 5874. (e) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061. (f) Bergman, R. G. *Nature*. **2007,** *446*, 391. (g) Godula, K.; Sames, D. *Science (New York, N.Y.)*. **2006,** *312*, 67. (h) Espino, C. G.; Du Bois, J. *Angew. Chem. Int. Ed.* **2001,** *40*, 598.

(4) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005,** *127*, 14560.

(5) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007,** *9*, 2931.

(6) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008,** *47*, 6452.

(7) (a) Wan, J.-P.; Jing, Y. *Beilstein J Org Chem.* **2015**, *11*, 2209 and references cited therein; (b) Patel, P.; Chang, S. *Org. Lett.* **2014**, *16*, 3328; (c) Zhou, B.; Du, J.; Yang, Y.; Feng, H.; Li, Y. *Org. Lett.* **2014**, *16*, 592; (d) Park, J.; Chang, S. *Angew. Chem. Int. Ed.* **2015**, *54*, 14103; (e)

Liang, Y.; Liang, Y.-F.; Tang, C.; Yuan, Y.; Jiao, N. *Chem. Eur. J.* **2015**, *21*, 16395; (f) Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4534.

(8) (a) Kianmehr, E.; Baghersad, M. H. *Adv. Synth. Catal.* **2011,** *353*, 2599. (b) Yang, X.; Zhang, Y.; Ma, D. *Adv. Synth. Catal.* **2012,** *354*, 2443. (c) Vinogradova, E. V.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012,** *134*, 11132. (d) Vinogradova, E. V.; Park, N. H.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2013,** *15*, 1394. (e) Sun, N.; Zhang, H.; Mo, W.; Hu, B.; Shen, Z.; Hu, X. *Synlett*. **2013,** *24*, 1443. (f) Yin, H.; Chen, B.; Zhang, X.; Yang, X.; Zhang, Y.; Jiang, Y.; Ma, D. *Tetrahedron*. **2013,** *69*, 5326 (g) Yin, H.; Almeida, A. M. de; Almeida, M. V. de; Lindhardt, A. T.; Skrydstrup, T. *Org. Lett.* **2015,** *17*, 1248.

(9) (a) Kianmehr, E.; Khalkhali, M. R.; Rezaeefard, M.; Khan, K. M.; Ng, S. W. *Aust. J. Chem.* **2015,** *68*, 165. (b) Kianmehr, E.; Rezaeefard, M.; Rezazadeh Khalkhali, M.; Khan, K. M. *RSC Adv.* **2014,** *4*, 13764. (c) Kianmehr, E.; Torabi, M.; Rezazadeh Khalkhali, M.; Faghih, N.; Khan, K. M. *Eur. J. Org. Chem.* **2015,** *2015*, 2796. (d) Kianmehr, E.; Faghih, N.; Khan, K. M. *Org. Lett.* **2015,** *17*, 414. (e) Kianmehr, E.; Ghanbari, M. *Eur. J. Org. Chem.* **2012,** *2012*, 256. (f) Kianmehr, E.; Kazemi, S.; Foroumadi, A. *Tetrahedron*. **2014,** *70*, 349.

(10) (a) Coward, J. K.; Sweet, W. D. *J. Org. Chem.* **1971,** *36*, 2337. (b) Chu, L.; Yue, X.; Qing, F.-L. *Org. Lett.* **2010,** *12*, 1644. (c) Kochi, J. K.; Tang, R. T.; Bernath, T. *J. Am. Chem. Soc*. **1973**, *95*, 7114. (d) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981; pp 7-8.

(11) Belforte, A.; Dell'Amico, D. B.; Calderazzo, F. *Chem. Ber.* **1988,** *121*, 1891.

(12) Guram, A. S.; Wang, X.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J. *J. Org. Chem.* **2007**, 72, 5104–5112.