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PAPER

TBAF-Catalysed silver oxide-mediated cross-coupling of functional trimethysilylpyridines: access to arylpyridines and bihetaryl compounds†‡

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The concomitant use of silver oxide and catalytic amount of TBAF allowed the efficient and chemoselective coupling of readily available 4-chloro- and 4-methyl-2-trimethyl-silyl-pyridines with heteroaromatic and aromatic halides. Based on control experiments, a mechanism involving the formation of a pyridylsilver intermediate and TBAF recycling is postulated.

Introduction

The metal-catalyzed cross-coupling of aromatic and heteroaromatic derivatives[1,2] is a very important process because of the increasing demand for sophisticated functionalised biaryl compounds involved in the development of functional materials and biologically active agents. The most popular methodologies for the preparation of biaryl compounds are the Stille[3–5] and the Suzuki[6–8] reactions that, while efficient, display some drawbacks especially in terms of toxicity of released tin halides and accessibility and stability of starting boron derivatives respectively.

The cross-coupling of silicon-containing aromatics has to be considered as a valuable alternative[9–11] due to a relatively easy access to silylated derivatives and the low environmental impact of silicon. The most important issue to be addressed with this process is the very weak polarity of the carbon–silicon bond. An efficient activation mode, first disclosed by Hiyama,[12] is the addition of a nucleophilic compound to the aromatic silane to turn it into a more polarized pentacoordinate silicate able to transmetallate with the Pd(II) complex formed by reaction with an aromatic halide. The efficiency of silicon activation and subsequent cross-coupling has been found critically dependent on the silicon group substitution pattern. Halosilanes,[13–15] silanols,[16,17] siloxanes,[18–20] or silacyclobutanes[21,22] have been used with success in cross-couplings of aromatic compounds. In contrast, essentially due to synthetic and stability issues, these species have been scarcely used in heterocyclic chemistry especially in the important pyridine series for which efficient coupling methodologies are still needed. To our knowledge, only two examples of activated pyridylsilanes have been reported. Hiyama[10] introduced the instable dichloroethylsilyl group at C-2 of picoline which had to be *in situ* reacted and DeShong reported the coupling of aryltriflates with a biscatechol silicate derivative introduced only at C-3 of 2-methoxypyridine.[23] Thus the lack of stable and easily handled pyridylsilanes seriously limited the general applicability of the Hiyama cross-coupling in pyridine series. Methodologies using trimethylsilylpyridines or analogs emerged only recently.

The first palladium-catalyzed cross-coupling of 2-trimethylsilyl halogenopyridines has been reported five years ago[24] using CuI and an excess of TBAF as activating agents. Bi(het)aryl and more recently, bipyridines,[25] were obtained in excellent yields at room temperature. Since an excess of TBAF could result in purification and functional tolerance issues, methodologies have been developed to omit this salt or decrease its amount. Yoshida reported the cross-coupling of allyl(dimethyl)silyl pyridine in the presence of silver oxide. The coordination of silver by both the pyridine nitrogen and the allyl group was postulated.[26] While efficient, this process suffers from the cost of allyl(dimethyl)silyl chloride used for the preparation of starting silanes. Such Ag_2O-mediated coupling could be applied to 2-trimethylsilylpyridine provided that a catalytic amount of TBAF was used.[27] This promising reaction is still underdeveloped and really deserves deeper synthetic and mechanistic investigations. Especially the coupling of functional pyridine units and substituent tolerance has not been studied yet. The cross-coupling of the synthetically useful 4-chloro-2-trimethylsilylpyridines **1**[28] with (het)aryl halides was studied. The substrate has been chosen for several reasons. At first, it can be easily prepared by selective lithiation-silylation of the parent pyridine using the BuLi-LiDMAE superbasic reagent,[29,30] secondly the C–Cl bond is a useful reactive site for further functionalization of the bi(het)aryl product implying its retention along the coupling process.

Results and discussion

Reaction parameters were screened with **1** and using 3-bromopyridine as the coupling partner (Table 1). As a general trend, reactions containing Ag_2O produced the expected product **1a** indicating the activation of the C–Si bond of **1** using this salt

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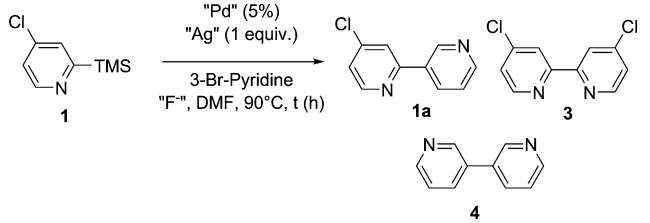
‡ Electronic supplementary information (ESI) available: Characterization data and copies of ^1H, ^{13}C spectra for new compounds. See DOI: 10.1039/c0ob00710b

Table 1 Conditions screening for cross-coupling of **1**[a]



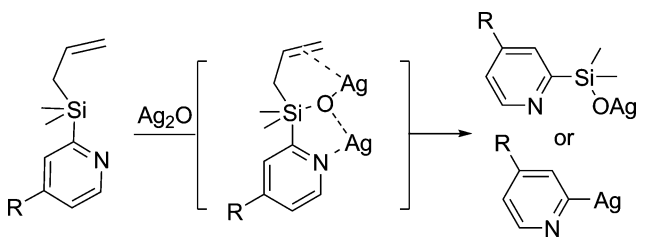
Run	BrPy (equiv.)	Pd source	"Ag"	F⁻ source (%)	Conv.%[b]	**1a**%[b]
1	1	$Pd(PPh_3)_4$	Ag_2O	TBAF (100)	50	10[d]
2	0.8	$Pd(PPh_3)_4$	Ag_2O	TBAF (100)	65	37[d]
3	0.5	$Pd(PPh_3)_4$	Ag_2O	TBAF (100)	>98	55[d]
4	0.5	$Pd(PPh_3)_4$	Ag_2O	—	50	50
5	0.5	$Pd(PPh_3)_4$	—	TBAF (100)	<5	0[e]
6	0.5	$Pd(PPh_3)_4$	Ag_2O[c]	TBAF (100)	<5	0[e]
7	0.5	$Pd(PPh_3)_4$	Ag_2O	TBAF (10)	>98	94
8	0.5	$Pd(PPh_3)_4$	AgF (100)	<5	0[e]	
9	0.5	$Pd(PPh_3)_4$	Ag_2O	AgF (10)	>98	48 (26)[d,f]
10	0.5	$Pd(PPh_3)_4$	Ag_2O	KF(10)	>98	13 (60)[d,f]
11	0.5	$Pd(PPh_3)_4$	Ag_2O	CsF(10)	>98	17 (52)[d,f]
12	0.5	$Pd(PPh_3)_4$	Ag_2O	TBAF (5)	>98	96
13	0.5	$Pd(PPh_3)_4$	Ag_2O	TBAF (5)	>98	95[g]
14	0.5	$PdCl_2(PPh_3)_2$	Ag_2O	TBAF (5)	>98	94[g]
16	0.5	$PdCl_2$dppf	Ag_2O	TBAF (5)	>98	92[g]
17	0.5	$PdCl_2(PPh_3)_2$	Ag_2O	TBAF (2)	>98	80 (20)[f,g]

[a] Reactions performed on 1 mmole of **1**. [b] Yield and conversion of 3-bromopyridine determined by GC. [c] 10% of Ag_2O were used. [d] Formation of **4**. [e] Product not detected, only degradation of **1**. [f] **3**% in brackets. [g] Reaction time was 3 h.

and subsequent transmetallation with the palladium complex. The bromopyridine stoichiometry was found to be critical. The coupling product was detected in only 10% amount using 1 equiv. of BrPy (50% conversion) besides bipyridine **4**. In contrast 0.8 equiv. of bromopyridine led to **1a** in 37% yield with incomplete conversion of bromopyridine (run 2) that was totally consumed using 0.5 equiv. affording **1a** in 55% yield (run 3). 0.5 equiv. of BrPy was then used in next experiments. When TBAF was omitted, Ag_2O allowed the cross-coupling to occur in 50% yield with 50% of unreacted BrPy and **1** was not recovered (run 4). An extended reaction time up to 72 h did not improve the yield. This result clearly illustrated the activating effect of the chlorine moiety since a separate experiment (unreported here) performed with the unsubstituted analogue did not give any coupling product under the same conditions. Yoshida also reported such an inertness in refluxing THF.[26]

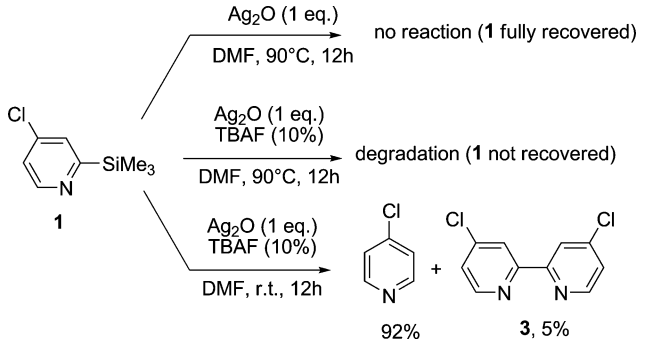
When stoichiometric TBAF was used in the absence (run 5) or with a catalytic amount of Ag_2O (run 6), only degradation of **1** was observed in both cases indicating that the formed pyridylsilicate was unable to be coupled in the absence of stoichiometric Ag_2O. We were pleased to observe that the use of a catalytic amount of TBAF (10%) in association with Ag_2O dramatically improved the cross-coupling giving exclusively bipyridine **1a** in almost quantitative yield (run 7). Other fluoride sources were also used to investigate the influence of the fluoride counterion. Since AgF was suspected to be formed upon contact between Ag_2O and TBAF, its effect was also examined (runs 8 and 9). As shown, no coupling was observed using 1 eq. of this salt but only degradation of **1** (run 7). When TBAF was replaced by AgF in the presence of Ag_2O (run 9), the yield was comparable to those obtained with Ag_2O alone (run 4) but homocoupling product 4,4′-dichlorobipyridine **3** was formed in notable amount. The other fluoride salts KF (run 10) and CsF (run 11) gave the cross-coupling product in 13 and 17% respectively with **3** as the main product besides 3,3′-bipyridine **4**. The coupling was found very efficient within a short reaction time (3 h) with 5% of TBAF and switching from $Pd(PPh_3)_4$ to other sources of Pd^0 such as $PdCl_2(PPh_3)_2$ or $PdCl_2$dppf (runs 12–16). Finally, an additional decrease of TBAF amount to 2% still gave **1a** in 80% yield (run 13) but homocoupling of **1** into **3** (20%) was obtained. Thus very efficient conditions have been found for the cross-coupling of **1** using a minimal amount of TBAF.

From the mechanistic angle, the increase in efficiency of the coupling in the presence of catalytic TBAF was intriguing. Indeed the Hiyama coupling typically involves at least 1 equiv. of TBAF to generate a pentacoordinate fluorosilicate,[10] that further releases a fluorosilane (Me_3SiF) upon the coupling step. The regeneration of fluoride ions then could be due to the reaction of Me_3SiF with Ag_2O to give AgF. Since Me_3SiF is a volatile compound (16.4 °C), its persistence in the medium under refluxing conditions (90 °C) is highly improbable. Additionally, the Si–F bond is highly stable (561 kJ/mole)[31] thus making its cleavage by a nucleophilic species unlikely in the medium. Furthermore even if AgF was formed, we have shown that this salt was unable to promote the coupling efficiently. On the other hand, **1** did not couple in the presence of TBAF alone (Table 1, run 5) while Ag_2O promoted the reaction in 50% yield (run 4). Thus, it was reasonable to propose an initial activation of the C–Si bond by Ag_2O favoured by both pyridine nitrogen coordination and silicon oxophilicity[26,32] as reported by Yoshida for allyldimethylsilylpyridine (Scheme 1). However in the case of **1**, the allyl group was not available to ensure additional coordination of the second silver and subsequent cleavage into the reactive silyloxysilver intermediate.[33] Thus the intermediate could remain as such or be turned into a pyridylsilver by cleavage of the pyridyl carbon–silicon bond.



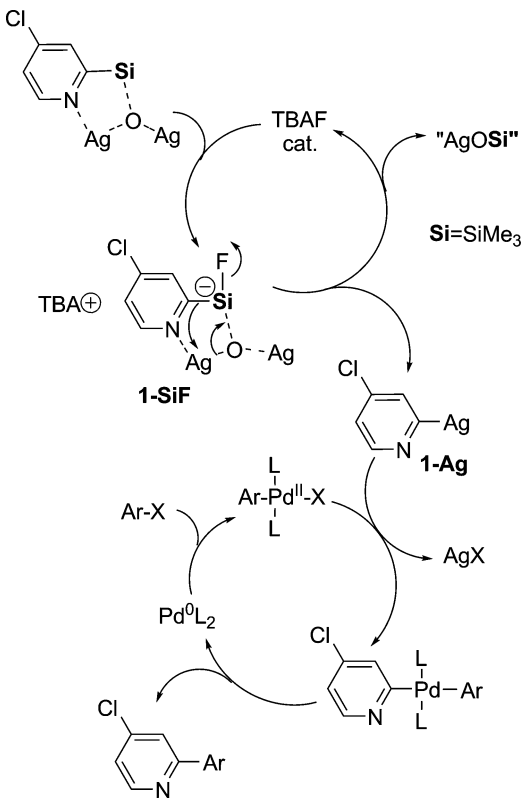
Scheme 1 Yoshida's activation of ally(dimethyl)silyl pyridine.

To check this latter hypothesis, **1** was placed in DMF in the presence of silver oxide (1 equiv.). After 24 h at 90 °C, **1** was recovered quantitatively indicating the absence of cleavage of the C–Si bond and making unlikely the formation of a pyridylsilver (Scheme 2). In contrast, when catalytic TBAF was added, **1** was fully consumed and converted into degradation products indicating the formation of an instable species in the medium. When the reaction was repeated at room temperature, 4-chloropyridine was isolated almost quantitatively besides a small amount of **3**. Thus TBAF was able to catalyse the desilylation of **1** in the presence of Ag_2O.



Scheme 2 Reaction of **1** with Ag_2O.

Fluoride release probably occurred from nucleophilic attack of the Ag_2O oxygen at the pentacoordinate fluorosilicate **1-SiF** generated in catalytic amount (Scheme 3).[34] The coordination of silver atoms by pyridine nitrogen probably favoured the process *via* proximity effects. This led us to postulate the formation of a 4-chloropyridylsilver intermediate **1-Ag**[35] giving 4-chloropyridine upon hydrolysis and able to homocouple into **3** in the presence of oxygen upon work-up. This pyridylsilver was then involved in the palladium catalytic loop. The strong affinity of silver for halides[36,37] then favoured the silver to palladium transmetallation step with the Pd^{II} complex formed after oxidative addition of Pd^0 into the C–X bond of the aromatic halide partner. The target coupling product was finally obtained after reductive elimination and regeneration of Pd^0 (Scheme 2). The need for 2 equiv. of pyridylsilane to achieve complete reaction could be result of coordination of **1** equiv of the substrate by silver or to the alternative formation of a dipyridylargentate.[38,39] At this stage despite all our efforts we have been unable to characterize pyridylsilver intermediates by NMR or mass spectroscopy due to their too high instability on standing. Such an instability is known for organosilver.[40] As shown, TBAF exhibited a unique behaviour compared with AgF, KF or CsF that, while giving the expected cross-coupling, also promoted the formation of homocoupling product **3** in notable amount (runs 9–11, Table 1). Besides possible difference of solubility, cation effect and ion-pairing could be responsible for the observed selectivities. Indeed, the organic tetrabutylammonium cation (TBA^+) is known to greatly enhance the nucleophilicity of associated anion by formation of a weak ion pair. In contrast, inorganic salts rather lead to tighter ion pairs and thus to less reactive counterions. The consequence should be a less efficient formation of **1-SiF** and then of **1-Ag** that is implied in the subsequent transmetallation process. The homocoupling product **3** then probably resulted of the competitive formation of dipyridylargentate. Alternatively, a reaction of TBAF with the palladium catalyst leading to a more electrophilic Pd^{II} fluoride complex and further fluoride release could be envisioned. However, Pd^{II} fluoride complex has been reported to be far less reactive than its iodide or bromide counterparts precluding an efficient transmetallation.[41–43]



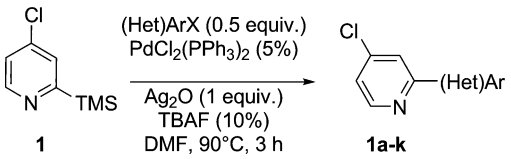
Scheme 3 Proposed catalytic loop for cross-coupling.

The scope of the reaction was next examined. The best conditions determined in Table 1 were applied to a set of heteroaromatic and aromatic partners (Table 2). As shown, 4-chloropyridine was generally efficiently reacted. The C–Cl bond was tolerated in all reactions. Good yields were obtained with heterocyclic compounds such as bromo-pyrimidine, quinoline or thiophene (runs 1–3 and 5) giving access to a range of useful bihetarylcompounds. Unfortunately we were unable to couple 2-bromopyridine and the reaction only gave reduction of the C–Br bond and silane degradation (run 4). A deactivation of the intermediate oxidative addition complex by coordination with Ag_2O could be involved in this case. Functional aromatic compounds bearing methyl, cyano acetyl and trifluoromethyl or nitro groups were coupled in moderate to excellent yields with full retention of the sensitive substituents. The reaction was found to be sensitive to steric effects since 2-iodotoluene was coupled in only 25% yield (run 6). In this case, the homocoupling product **3** was formed in 40% yield in agreement with a sluggish transmetallation of the pyridylsilver.

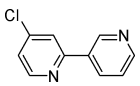
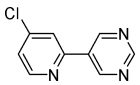
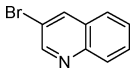
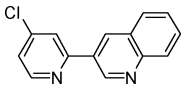
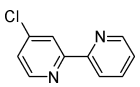
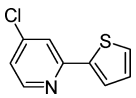
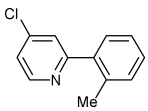
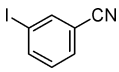
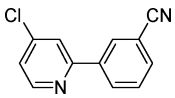
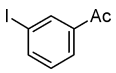
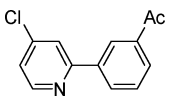
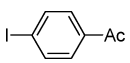
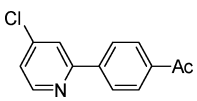
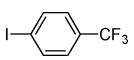
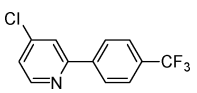
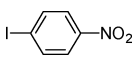
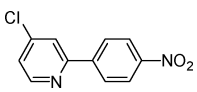
The effect of substitution on the reaction outcome was then examined. When chlorine was moved from C-4 to C-3, **2** was degradated and only traces of the expected product were detected (GC-MS) after reaction at 90 °C with 4-iodo-nitrobenzene or 5-bromopyrimidine which were excellent partners for coupling with **1** (Scheme 4). The same result was obtained when the reaction was conducted at room temperature. It is worthy of note that **2** was previously coupled in excellent yield at room temperature in copper mediated reaction.[24]

This showed the instability of the putative intermediate pyridyl silver in the presence of a leaving group at the *ortho* position. Elimination of chlorine and formation of a pyridyne intermediate probably occurred here. The reaction was also attempted with 2-chloro-6-trimethylsilylpyridine **3** (Scheme 5). In this case, traces of the expected product were obtained with recovery of the starting silane. This indicated the critical effect of the pyridine nitrogen environment. stereoelectronic effects generated by chlorine at C-2 probably impeded efficient silver coordination and subsequent coupling reaction.

Table 2 Cross-coupling of **1** with various (het)aryl halides[a]



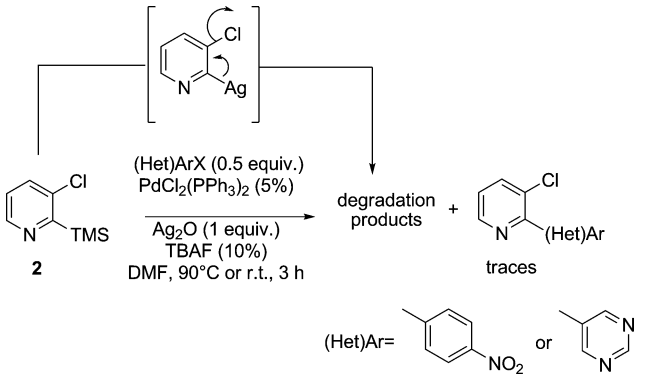
1 **1a-k**

Run	(Het)ArX (equiv.)	Product	Yield%[b]
1			**1a**, 70
2			**1b**, 85
3			**1c**, 62
4			**1d**, 0[c]
5			**1e**, 52
6			**1f**, 25[d]
7			**1g**, 80
8			**1h**, 59
9			**1i**, 60
10			**1j**, 27(62)[e]
11			**1k**, 86

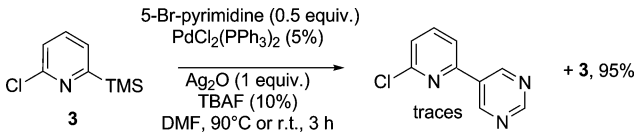
[a] Reactions performed on 1 mmole of **1**. [b] Isolated yields after column chromatography. [c] Reduction of 2-bromopyridine and degradation of **1**. [d] **3** was formed in 40% yield. [e] LC-MS yield in brackets, **1j** was difficult to separate from **3** (16%).

Then the chlorine at C-4 was changed into a methyl group to examine the influence of an electron donating group (Scheme 6).

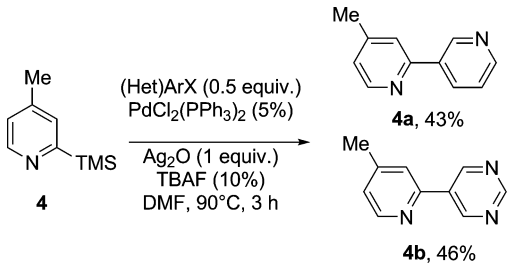
The 4-picolyl silane **4** was successfully coupled with 3-bromopyridine and 5-bromopyrimidine but in moderate 43 and 46% yields respectively. A comparison with runs 1 and 2 in Table 2



Scheme 4 Attempted cross-coupling of **2**.



Scheme 5 Attempted cross-coupling of **3**.



Scheme 6 Cross-coupling of **4**.

clearly showed the influence of electronic effects on the reaction. Indeed the electron-withdrawing chlorine group gave better yields in agreement with an increased polarization of the C–Si bond making silicon more electrophilic and thus more prone to interact with fluoride and subsquently with the oxygen of Ag_2O. As another contrast with **1**, in this case the use of Ag_2O alone did not give any coupling product.

Conclusions

In summary, an efficient cross-coupling methodology of functional 2-trimethylsilylpyridylsilane has been developed using silver oxide and a catalytic amount of TBAF. The formation of a reactive pyridylsilver intermediate is postulated to explain the regeneration of fluoride ions in the reaction medium. Heteroaromatic and aromatic halides were reacted in acceptable to excellent yields leading to a range of synthetically useful poly(hetero)aromatic compounds. The best results were obtained using an electron-withdrawing group on the pyridylsilane at C-4 while a leaving group *ortho* to the silyl group must be avoided.

Experimental section

General methods

All solvents were distilled before use. 4-chloro-2-trimethysilylpyridine **1**, 3-chloro-2-trimethysilyl-pyridine

2, 2-chloro-6-trimethysilyl-pyridine **3** and 4-methyl-2-trimethysilylpyridine **4** were prepared by lithiation-silylation of 4-chloro-, 3-chloro-, 2-chloro- and 4-methylpyridine respectively using the BuLi-LiDMAE reagent. Ag_2O was dried overnight under vacuum before use. All other reagents and catalysts were commercially available and used as such. ^1H and ^{13}C NMR spectra were performed on Bruker spectrometers at 250 or 400 MHz (^1H) and 62.5 or 100 MHz (^{13}C) in $CDCl_3$ using TMS as reference. GC experiments were performed on a Shimadzu chromatograph fitted with a 15 m capillary column. GC-MS spectra with electronic impact were performed on a Shimadzu QP 2010 apparatus. LCMS were performed on a Shimadzu LCMS-2010EV. High resolution mass spectra were performed on a Bruker microTOF-Q. Column Chromatography was performed on silica gel (70–230 mesh).

General procedure for cross-coupling reactions

To a suspension of the aryl halide (0.5 mmol) and Ag_2O (1 mmol) in degassed DMF (5 mL) under argon were added the trimethylsilylpyridine (1 mmol), $PdCl_2(PPh_3)_2$ (0.025 mmol) and TBAF (0.05 mmol, 0.05 mL of a 1 M solution in THF). The resulting suspension was stirred at 90 °C for 3h. After cooling, the reaction medium was diluted with EtOAc (5 mL), filtered, and concentrated. Column chromatography using Cyclohexane-AcOEt as eluent afforded products.

4-Chloro-2,3′-bipyridine (1a)[44]. Yield, 70%. NMR (400 MHz, $CDCl_3$): δ_H = 7.29 (dd, *J* = 5.3, 1.9 Hz, 1H), 7.40 (ddd, *J* = 8.8, 5.0, 0.9 Hz, 1H), 7.74 (dd, *J* = 1.9, 0.6 Hz, 1H), 8.28 (dt, *J* = 7.9, 1.9 Hz, 1H), 8.59 (s, 1H), 8.61 (d, *J* = 0.6 Hz, 1H), 8.67 (dd, *J* = 5.0, 1.9 Hz, 1H), 9,13 (d, *J* = 5.0, 1.9 Hz, 1H). NMR (100 MHz, $CDCl_3$): δ_C = 120.8, 123.0, 123.6, 133.6, 134.3, 145.0, 148.2, 150.5, 150.8, 156.3 ppm. FTIR (KBr): 3043, 2923, 1724, 1572, 1542, 1413, 1102, 1023, 804. MS (EI): *m/z* (%): 190[M+] (100), 164 (22).

5-(4-Chloropyridin-2-yl)-pyrimidine (1b). Yield, 85%. NMR (400 MHz, $CDCl_3$): δ_H = 7.36 (dd, *J* = 5.3, 1.9 Hz, 1H), 7.76 (d, *J* = 1.9 Hz, 1H), 8.64 (d, *J* = 5.4 Hz, 1H), 8.29 (d, *J* = 8.2 Hz, 1H), 9.30 (s, 2H). NMR (100 MHz, $CDCl_3$): δ_C = 120.8, 123.8, 131.3, 145.3, 151.2, 153.5, 155.1, 159.1 ppm. FTIR (KBr): 3045, 2923, 1564, 1376, 1185, 1056, 821. MS (EI): *m/z* (%): 191 [M+] (85), 113 (100). HRMS(ESI (M+H+)): calcd. for $C_9H_6ClN_3$ 192.0323, found 192.0330.

3-(4-Chloropyridin-2-yl)-quinoline (1c). Yield, 62%. NMR (400 MHz, $CDCl_3$): δ_H = 7.30 (dd, *J* = 5.3, 1.9 Hz, 1H), 7.57 (td, *J* = 7.6, 1.2 Hz, 1H), 7.74 (td, *J* = 8.2, 1.6 Hz, 1H), 7.86 (dd, *J* = 1.9, 0.6 Hz, 1H), 7.90 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 8.64 (d, *J* = 5.7 Hz, 1H), 8.71 (d, *J* = 2.2 Hz, 1H). NMR (100 MHz, $CDCl_3$): δ_C = 121.1, 123.0, 127.3, 127.7, 128.6, 129.4, 130.4, 130.7, 134.2, 145.1, 148.5, 149.0, 151.0, 156.4 ppm. FTIR (KBr): 3039, 1573, 1329, 1121, 966, 753. MS (EI): *m/z* (%): 240 [M+] (100), 205 (20). HRMS(ESI ($M+H^+$)): calcd. for $C_{14}H_9ClN_2$ 241.0527; found 241.0530.

4-Chloro-2-(2-thienyl)-pyridine (1e)[24]. Yield, 52%. NMR (400 MHz, $CDCl_3$): δ_H = 7.10-7.16 (m, 2H), 7.43 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.59 (dd, *J* = 3.5, 1.0 Hz, 1H), 7.65 (dd, *J* = 1.9, 0.6 Hz, 1H), 8.45 (dd, *J* = 5.3, 0.6 Hz, 1H). NMR (100 MHz, $CDCl_3$): δ_C = 118.5, 118.9, 122.0, 124.4, 125.0, 125.3, 128.1, 128.4, 150.3 ppm. FTIR (KBr): 3073, 2924, 1568, 1538, 1383, 1089, 819, 699. MS (EI); *m/z* (%): 195 [M+] (100), 160 (25).

4-Chloro-2-(2-methylphenyl)-pyridine (1f). Yield, 25%. NMR (250 MHz, CD_3OD) δ_H = 2.30 (s, 3 H), 7.27–7.37 (m, 4 H), 7.48 (dd, *J* = 5.48, 1.98 Hz, 1H), 7.57 (d, *J* = 1.98 Hz, 1 H), 8.55 (d, *J* = 5.48 Hz, 1 H). NMR (62.5 MHz, CD_3OD) δ_C = 23.3, 122.0, 124.4, 126.0, 129.0, 129.5, 130.9, 135.8, 139.1, 144.1, 150.0, 161.45 ppm. FTIR (KBr): 3050, 1567, 1540, 1149, 1353, 1114, 1087, 824, 723. LCMS (ESI): 206 (60), 204 ($M+H^+$) (100), 157 (15). HRMS (ESI ($M+H^+$)): calcd. for $C_{12}H_{10}ClN$ 204.0502, found 204.0497.

4-Chloro-2-(3-cyanophenyl)-pyridine (1g). Yield, 80%. NMR (250 MHz, $CDCl_3$) δ_H = 7.34 (dd, *J* = 5.33, 1.98 Hz, 1 H), 7.56–7.66 (m, 1 H), 7.68–7.78 (m, 2 H), 8.22 (dt, *J* = 7.92, 1.60 Hz, 1 H), 8.33 (t, *J* = 1.45 Hz, 1 H), 8.57–8.68 (m, 1 H). NMR (62.5 MHz, $CDCl_3$) δ_C = 113.2, 118.5, 121.0, 123.4, 129.7, 130.8, 131.0, 132.9, 139.2, 145.3, 150.8, 156.4 ppm. FTIR (KBr): 3050, 2227, 1573, 1549, 1458, 1367, 1058, 910, 873. LCMS (ESI): 217 (40), 215 ($M+H^+$) (100). HRMS (ESI ($M+H^+$)): calcd. for $C_{12}H_7ClN_2$ 215.0376, found 215.0371.

4-Chloro-2-(3-acetylphenyl)-pyridine (1h). Yield, 59%. NMR (250 MHz, $CDCl_3$) δ_H = 2.70 (s, 3 H), 7.31 (dd, *J* = 5.33, 1.98 Hz, 1 H), 7.61 (t, *J* = 7.77 Hz, 1 H), 7.82 (d, *J* = 1.37 Hz, 1 H), 8.05 (dt, *J* = 7.77, 1.45 Hz, 1 H), 8.21 (ddd, *J* = 7.80, 1.87, 1.14 Hz, 1 H), 8.57 (t, *J* = 1.52 Hz, 1 H), 8.62 (d, *J* = 5.33 Hz, 1 H). NMR (62.5 MHz, $CDCl_3$) δ_C = 26.8, 121.1, 122.9, 126.8, 129.2, 131.5, 137.7, 138.5, 145.1, 150.5, 157.8, 197.9 ppm. FTIR (KBr): 3100, 1674, 1571, 1554, 1458, 1360, 1300, 1245, 802. LCMS (ESI): 234 (60), 232 ($M+H^+$) (100). HRMS (ESI ($M+H^+$)): calcd. for $C_{13}H_{10}ClNO$ 232.0529, found 232.0530.

4-Chloro-2-(4-acetylphenyl)-pyridine (1i)[3]. Yield, 60%. NMR (250 MHz, $CDCl_3$) δ_H = 2.67 (s, 3 H), 7.32 (dd, *J* = 5.33, 1.83 Hz, 1 H), 7.80 (d, *J* = 1.37 Hz, 1 H), 8.09 (brs, 4 H), 8.63 (d, *J* = 5.33 Hz, 1 H). NMR (62.5 MHz, $CDCl_3$) δ_C = 26.8, 121.4, 123.1, 127.2, 128.9, 137.6, 142.2, 145.0, 150.7, 157.6, 197.7 ppm. FTIR (KBr): 3060, 1672, 1567, 1548, 1355, 1266, 967, 822. LCMS (ESI): 234 (60), 232 ($M+H^+$) (100), 157 (14).

4-Chloro-2-(4-(trifluoromethyl)phenyl)-pyridine (1j). Yield, 27%. NMR (250 MHz, $CDCl_3$) δ_H = 7.29–7.36 (m, 1 H), 7.67–7.84 (m, 3 H), 8.11 (d, *J* = 8.07 Hz, 2 H), 8.63 (dd, *J* = 5.25, 0.53 Hz, 1 H). NMR (62.5 MHz, $CDCl_3$) δ_C = 121.2, 123.1, 124.5, 124.7 (d, $^1J_{C-F}$, 272 Hz), 125.8, 126.5 (d, $^3J_{C-F}$, 5 Hz), 127.3, 131.5 (q, $^2J_{C-F}$, 33 Hz), 141.4, 145.1, 150.7, 157.3 ppm. NMR (235 MHz, $CDCl_3$) δ_F = −62.65 ppm. FTIR (KBr): 2985, 1674, 1549, 1329, 1167, 1104, 1245, 849, 827. LCMS (ESI): 260 (50), 258 ($M+H^+$) (100). HRMS(ESI ($M+H^+$)): calcd. for $C_{12}H_7ClF_3N$ 258.0219, found 258.0215.

4-Chloro-2-(4-nitrophenyl)-pyridine (1k). Yield, 86%. NMR (250 MHz, $CDCl_3$) δ_H = 7.37 (dd, *J* = 5.25, 1.90 Hz, 1 H), 7.78–7.87 (m, 1 H), 8.14–8.24 (m, 2 H), 8.30–8.43 (m, 2 H), 8.61–8.71 (m, 1H). NMR (62.5 MHz, $CDCl_3$) δ_C = 121.6, 123.8, 124.1, 127.8, 143.9, 145.2, 148.5, 150.9, 156.3. LCMS (ESI): 237 (55), 235 ($M+H^+$) (100). HRMS(ESI ($M+H^+$)): calcd. for $C_{11}H_7ClN_2O_2$ 235.0274, found 235.0266.

4-Methyl-2,3-pyridine (4a)[45]. Yield, 43%. NMR (250 MHz, $CDCl_3$) δ_H = 9.18 (m, 1H), 8.65 (m, 1H), 8.58 (d, *J* = 5.0, Hz,

1H), 8.31 (ddd, J = 8.2, 4.1, 1.9 Hz, 1H), 7.57 (m, 1H), 7.40 (dd, J = 4.9, 3.7 Hz, 1H), 7.12 (d, J = 5.1 Hz, 1H), 2.44 (s, 3H). NMR (62.5 MHz, $CDCl_3$) δ_C = 21.2, 121.6, 123.5, 123.8, 134.4, 148.1, 148.2, 149.3, 149.7, 150.0, 154.7. FTIR (KBr): 2918, 1602, 1545, 1379, 1207, 988, 829. MS (EI): m/z (%): 170 [M^+] (100), 144 (29).

5-(4-Methylpyridin-2-yl)-pyrimidine (4b)[46]. Yield, 46%. NMR (250 MHz, $CDCl_3$) δ_H = 9.31 (s, 2H), 9.25 (s, 1H), 8.60 (d, J = 5.0, Hz, 1H), 7.57 (m, 1H), 7.17 (d, J = 5.0, Hz, 1H), 2.46 (s, 3H). NMR (62.5 MHz, $CDCl_3$) δ_C = 21.2, 121.5, 124.5, 132.5, 148.4, 150.1, 151.8, 155.0, 158.5. FTIR (KBr): 2924, 2854, 1725, 1605, 1464, 14136, 1190, 1023, 869, 807. MS (EI): m/z (%): 171 [M^+] (97), 93 (100).

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