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Regioselective Radical Arylation of 3-Hydroxypyridines

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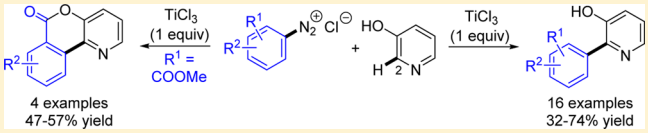
Supporting Information

ABSTRACT: The titanium(III)-mediated radical arylation of 3-hydroxypyridines was found to proceed with high regioselectivity for the 2-position. Using aryldiazonium chlorides, which were prepared from the corresponding anilines, as aryl radical sources, a range of 3-hydroxy-2-phenylpyridines were obtained in moderate to good yields under simple reaction conditions. Reactions of *ortho*-carboxylic ester substituted phenyldiazonium salts directly provided tricyclic benzopyranopyridinones.



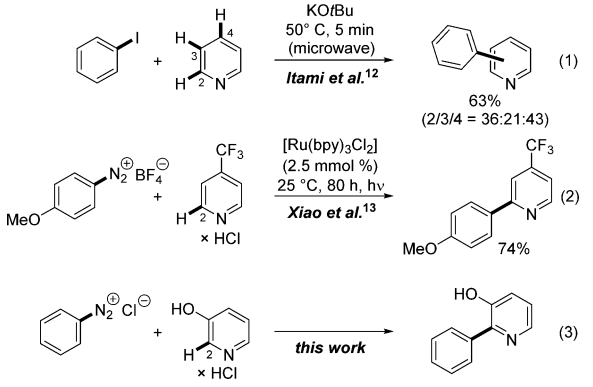
Radical arylation reactions have recently become increasingly popular for the synthesis of biaryl compounds.[1] Because of the fact that such transformations are formally comparable to aromatic C−H activation reactions, less demanding starting materials can be used than in established Suzuki-type and related transition-metal-catalyzed cross-coupling reactions. On the other hand, many radical arylations of substituted benzenes still suffer from insufficient regioselectivity,[2] so that unsubstituted benzene remains to be a commonly preferred substrate.[3,4] Notable exceptions are arylations of anilines[5] and phenols,[6] for which comparably good selectivities were recently observed. A further, and rather general, drawback of most radical arylation reactions is that the reactant acting as radical acceptor has to be employed in large excess to counterbalance the relatively low rate of addition of aryl radicals to benzenes.[7]

Regarding regioselectivity in particular, good results can be obtained in arylations of electron-rich heterocycles such as furans[8] and pyrrols,[9] which are attacked with high selectivity at the carbon atoms adjacent to the heteroatom (2- and/or 5-position). The radical arylation of pyridine, in contrast, was found to be strongly dependent on the reaction conditions. While reactions in acidic media favor arylation in the 2- and 4-positions of the pyridine core,[10] the free base is commonly converted to all three possible regioisomers in reactions proceeding via aryl radicals.[2b,11] Recent examples are shown in Scheme 1.[12−14]

Following the pH-controlled selectivity profile outlined above, all three isomers were obtained from the *tert*-butoxide-mediated reaction of iodobenzene with pyridine (Scheme 1, (1)).[12] The photocatalyzed arylation (Scheme 1, (2)),[13,15] in which a pyridinium ion assumed the role of aryl radical acceptor, proceeded with full selectivity for the 2-position due to the presence of a blocking substituent in the 4-position.

Having previously noticed the highly directing effect of hydroxy groups in titanium(III)-mediated radical arylations of phenols,[6,8] it was of interest to investigate how the regioselectivity controlling properties of this strongly electron-donating substituent would interact with those of the aromatic core of pyridine. Although basically four regioisomers can be expected from the arylation of 3-hydroxypyridine, the results of this work demonstrate that such arylations can be conducted with exceptionally high regioselectivity (Scheme 1, (3)). Until now, biaryl compounds derived from an aryl−aryl coupling of 3-hydroxypyridine at its 2-position have been performed via Negishi- or Suzuki-type cross-coupling reactions,[16,17] or via rearrangement of benzoylfurane derivatives.[18]

Scheme 1. Radical Arylation of Pyridines



3-Hydroxypyridine (**1a**) was chosen for optimization experiments since the matched effects of a protonated pyridine nitrogen and that of an *ortho*/*para*-directing hydroxy group should favor aryl radical attack in the 2-, 4-, and 6-positions of the pyridine core. Thus, basically three regioisomers were expected from the reaction of **1a** and 4-chlorophenyldiazonium chloride (**2a**) under acidic conditions, which would also be in agreement with the product distribution earlier observed in the arylations of 3-methylpyridine (2/4/6 = 30:42:28) and 3-fluoropyridine (2/4/6 = 26:50:24).[13] Selected results from a series of experiments with **1a** and **2a** are summarized in Table 1 (see also the Supporting Information).

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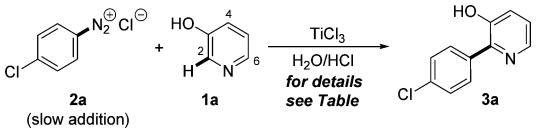
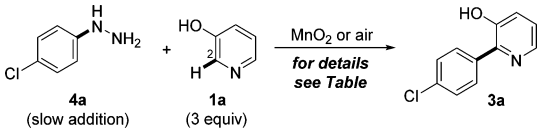
Table 1. Reductive Titanium(III)-Mediated Arylation of 3-Hydroxypyridine (1a): Optimization of Reaction Conditions



entry	pyridine **1a** (equiv)	$TiCl_3$ (equiv)	time of addition of **2a** (min)	yield **3a** (%)[a,b]
1	5	2	15	62
2	10	2	15	80
3	10	1	15	80
4	10	0.5	15	63
5	10	2	7.5	71
6	10	2	30	55

[a]General conditions: Slow addition of **2a** (1 mmol in 2.5 mL of 1.2 N HCl) to a mixture of **1a** (5−10 mmol) and $TiCl_3$ (0.5−2 mmol) over 7.5−30 min at rt. [b]Yields determined by ^{1}H NMR using maleic acid as internal standard.

Table 2. Oxidative Arylation of 3-Hydroxypyridine (1a): Optimization of Reaction Conditions



entry	time of addition of **4a** (min)	reaction conditions[a]	yield **3a** (%)[c]
1	10[b]	MnO_2 (5 equiv), NaOH (10 equiv), CH_3CN, 10 min	<10
2	60	MnO_2 (5 equiv), HOAc (2 equiv), CH_3CN, 60 min	33
3	540	air (O_2), NaOH, 24 h	11

[a]General conditions: Slow addition of **4a** to **1a** (3 equiv). [b]Hydrazine **4a** added as hydrochloride. [c]Yields determined by ^{1}H NMR using maleic acid as internal standard.

The reactions were generally performed under slow addition of a freshly prepared solution of aqueous 4-chlorophenyldiazonium chloride (**2a**) to a mixture containing pyridine **1a** and the reductant titanium(III) chloride. Slow addition of **2a** is known to be an effective measure to avoid homocoupling of aryl radicals to unreacted diazonium ions.[19] A rise in the excess of 3-hydroxypyridine (**1a**) from 5 to 10 equiv led to a significant increase in yield from 62% to 80% (entries 1 and 2). This yield fortunately remained unchanged upon reduction of the amount of titanium(III) chloride from 2 to only 1 equiv (entries 2 and 3). A further decrease to 0.5 equiv of reductant per diazonium ion led to 63% yield (entry 4). This observation shows that the arylation partially proceeds as a chain process, as the theoretical yield for a non-chain reaction with 0.5 equiv of titanium(III) chloride would be only 50%. The fact that a faster as well as a slower addition of the diazonium salt **2a** to the reaction mixture leads to decreased yields has already been observed in earlier studies (entries 5 and 6).[6b] Faster addition of **2a** can thereby be associated with increased homocoupling,[19] whereas the negative effect of a prolonged addition time again points to some participation of a radical chain process (see discussion below).

An analysis of the product mixture (entry 3, Table 1) by HPLC revealed a 10:1.4:1 ratio of regioisomers with compound **3a** as the major product (see the Supporting Information). Because of an overlap of signals, only one of the minor isomers, namely, the 6-isomer, could be detected by ^{1}H NMR of the crude reaction mixture in a comparable ratio of **3a** to 6-isomer of 8:1. While **3a** and the 6-isomer were obtained after column chromatography in 76% and 9% yield, respectively, the missing 4-isomer could not be isolated, which HPLC analysis had suggested to be formed as minor isomer as well.

In a second series of experiments, whether the regioselectivity for **3a** could also be observed in radical arylations starting from 4-chlorophenylhydrazine (**4a**) as alternative aryl radical precursor (Table 2) was evaluated. Hydrazine **4a** was again slowly added to the reaction mixture under conditions adopted from earlier studies on the radical arylation of anilines and phenols.[5b,c] The manganese(IV)-mediated reaction under strongly basic conditions, which had been successful for the arylation of phenol,[5b] gave **3a** only in a yield lower than 10% (entry 1). Weakly acidic conditions with manganese dioxide as oxidant increased the yield of **3a** to 33% (entry 2), which is, however, still significantly lower than what can be achieved in a comparable titanium(III)-mediated reaction with only 3 equiv of pyridine **1a** (50%, see the Supporting Information). The third attempt (entry 3), being basically attractive as only air is used as oxidant,[5c] was again unsuccessful, but confirmed that basic conditions are most probably unfavorable for the radical arylation of 3-hydroxypyridine (**1a**).

With these results from preliminary studies, and with optimized conditions available (Table 1, entry 3), an investigation of the scope and limitations of the regioselective radical arylation of 3-hydroxypyridine (**1a**) (Table 3) was initiated. The summarized results show that the titanium(III)-mediated reductive radical arylation of 3-hydroxypyridine (**1a**) can be carried out with a wide range of aryldiazonium salts. All halogenated and methylated derivatives **2a**−**k** (entries 1−11) gave moderate to good yields. Among the electron-donating substituents (entries 12−15), only the 4-dimethylamino compound **2o** failed to give the desired biaryl **3o** (entry 15). The fact that most electron-donating (entries 12−14) and electron-accepting substitutents (entries 16 and 17) were tolerated is in agreement with an, if at all, only minor participation of a radical chain process. Radical arylations proceeding via chain processes usually show some preference for acceptor-substituted aryldiazonium salts,[20] since the cyclohexadienyl radical adduct arising from the addition step is then more easily oxidized by the diazonium ion in the radical transfer step.[21] The lower yield obtained for **3m** (40%, entry 13) can be explained by a particular instability of diazonium salt **2m**, which partially decomposed in the syringe during addition to the reaction mixture. A short series of experiments with diazonium salts **2r**−**u** bearing a methyl ester functionality in the *ortho*-position to the diazonium unit (entries 18−21) directly provided tricyclic benzopyranopyridinones **5a**−**d** via a sequence of radical arylation and lactonization.

In the next part of the study, the applicability of the reaction conditions for the transformation of additional pyridine derivatives was investigated (Figure 1). 5-Hydroxy-2-methylpyridine (**1b**) provided the arylated product **6** in 76% yield, thereby showing that benzylic positions are tolerated, although they could basically complicate the arylation through hydrogen abstraction by the aryl radical.[1a] Arylation of 4-hydroxypyridine afforded an inseparable mixture of the two regioisomers **7a** (14%) and **7b** (6%). While the isomeric distribution of **7a** and **7b** indicates that the directing effect of the hydroxy group is

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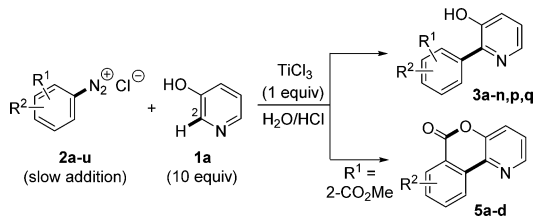
Table 3. Titanium(III)-Mediated Arylation of 3-Hydroxypyridine (1a): Scope of Diazonium Salts



entry	diazonium salt **2**: R^1, R^2 =	yield **3** or **5** (%)[a,b,c]
1	**2a**: 4-Cl, H	**3a**: 74
2	**2b**: 4-F, H	**3b**: 64
3	**2c**: 4-Br, H	**3c**: 56
4	**2d**: 3-F, H	**3d**: 52
5	**2e**: 3-Cl, H	**3e**: 50
6	**2f**: 3-Br, H	**3f**: 48
7	**2g**: 2-F, H	**3g**: 56
8	**2h**: 2-Cl, H	**3h**: 47
9	**2i**: 2-Br, H	**3i**: 43
10	**2j**: 4-Me, H	**3j**: 64
11	**2k**: 3-Me, H	**3k**: 58
12	**2l**: 4-OMe, H	**3l**: 65
13	**2m**: 3-OMe, H	**3m**: 40
14	**2n**: 4-NHAc, H	**3n**: 32
15	**2o**: 4-NMe_2, H	**3o**: --
16	**2p**: 4-CF_3, H	**3p**: 49
17	**2q**: 4-COOMe, H	**3q**: 55
18	**2r**: 2-COOMe, H	**5a**: 57
19	**2s**: 2-COOMe, 4-F	**5b**: 50
20	**2t**: 2-COOMe, 4-Cl	**5c**: 52
21	**2u**: 2-COOMe, 4-Br	**5d**: 47

[a]General conditions: Slow addition of diazonium salt **2a–u** (1 mmol, in 2.5 mL, 1 equiv) to a mixture of **1a** and $TiCl_3$ in a mixture of water (5 mL) and HCl (3 N, 2.5 mL) at rt over 15 min. [b]Yields after purification by column chromatography. [c]Minor 6-isomer detected in small amounts by TLC.

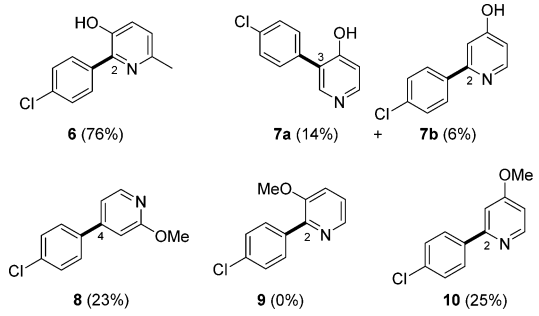
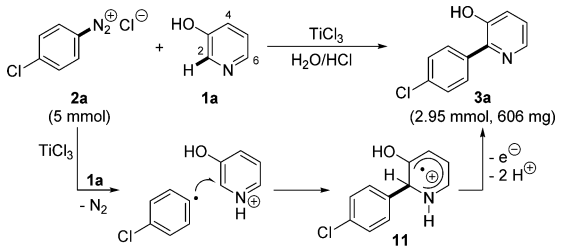


Figure 1. Arylation of hydroxy- and methoxypyridines.

stronger than that of the protonated pyridine nitrogen,[22] the low combined yield demonstrates the strong advantage of matched directing substituent effects in radical arylations. The main conclusion that can be drawn from the experiments with 2-, 3-, and 4-methoxypyridine is that a methoxy group has a significantly weaker ability to direct the radical arylation than the hydroxy functionality.[23] The structures of biaryls **8**[24] and **10**[25] clearly point to the now predominant effect of the pyridinium core on product formation, which also becomes apparent from the comparison of the structures of biaryls **7a** and **10**. The fact that a complex mixture of at least eight minor products was obtained from the arylation of 3-methoxypyridine, with biaryl **9** not being detectable after column chromatography, suggests that the radical addition step did occur, but that subsequent rearomatization might be more complicated with a methoxy than with a hydroxy group.

In the next step, the biaryl synthesis was carried out on a larger scale, leading to **3a** in a yield of 59% with regioselectivity identical to that observed on a smaller scale (Scheme 2).

Scheme 2. Large-Scale Arylation of 3-Hydroxypyridine (1a) and Possible Mode of Reaction



Regarding the overall process, it is currently assumed that the high regioselectivity of the aryl radical attack on a 3-hydroxypyridinium ion is due to a particularly good stabilization of the resulting adduct **11**. The increased importance of product stabilization in radical arylations of arenes in comparion with the aryl radical addition to alkenes has been noted previously.[26]

The exceptional capabilities of 3-hydroxypyridine (**1a**) as an aryl radical acceptor were finally confirmed in two competition experiments. The titanium(III)-mediated reaction of 4-chlorophenyldiazonium chloride (**2a**) with equal amounts of **1a** and 4-methoxyaniline (each 5 equiv) provided **3a** exclusively in a yield of 56%, which is only slightly less the yield reported in Table 1 (entry 1). Even more surprisingly, 3-hydroxypyridine (**1a**) was able to outperform furan as a radical acceptor. Conducted under identical conditions as described above, but with 5 equiv of furan instead of 4-methoxyaniline, this competition experiment led to **3a** in 58% yield and no detectable amount of 2-(4-chlorophenyl)furan.

In summary, it has been shown that the radical arylation of 3-hydroxypyridine can be carried out with high regioselectivity for the 2-position. Using titanium(III) chloride as a stoichiometric reductant under simple reaction conditions, a variety of diazonium salts could be employed for the synthesis of the corresponding biaryl compounds. Taking advantage of the high reactivity of 3-hydroxypyridine as an aryl radical acceptor, this methodology provides a new straightforward access to biaryl compounds for medicinal chemistry purposes[16b] and to benzopyranopyridinones described as ligands in organic light-emitting diodes.[27,28]

EXPERIMENTAL SECTION

General Experimental. Solvents and reagents were obtained from commercial sources and used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded using 600 MHz (^{13}C: 151 MHz), 400 MHz (^{13}C: 101 MHz), and 360 MHz (^{13}C: 91 MHz) spectrometers. For ^{1}H NMR spectra, $CDCl_3$, CD_3OD, and $(CD_3)_2SO$ were used as solvents referenced to TMS (0 ppm), $CHCl_3$ (7.26 ppm), CD_3OH (3.31 ppm), and $(CD_3)_2SO$ (2.50 ppm). Chemical shifts are reported in parts per million (ppm). Coupling constants are in hertz (Hz). The following abbreviations are used for the description of signals: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet). ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD, and $(CD_3)_2SO$ using $CDCl_3$ (77.0 ppm), CD_3OD (49.05 ppm), and $(CD_3)_2SO$

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(39.43 ppm) as standard. Chemical shifts are reported in parts per million (ppm). Mass spectra were recorded using electron spray ionization (ESI) and a sector field mass analyzer for HRMS measurements. Analytical TLC was carried out on silica gel plates using shortwave (254 nm) UV light to visualize components. Silica gel (Kieselgel 60, 40−63 mm) was used for flash column chromatography. HPLC analysis was carried out on an LC-MS system with a *C18* analytical column (4.6 × 50 mm, 3.5 μm, flow rate: 1:23 mL/min) coupled to a QDa mass detector equipped with an ESI-trap. Parameters: CH_3CN in H_2O 10−90% in 24 min, 0.1% formic acid.

General Procedure for Synthesis of 3-Hydroxy-2-phenylpyridines 3 and Benzopyrano-pyridinones 5 (GP1). To an ice-cooled degassed solution of the respective aniline (10.0 mmol) in HCl (3 N, 10 mL) and water (10 mL), a degassed solution of sodium nitrite (0.69 g, 10.0 mmol) in water (5 mL) was added dropwise by syringe pump over a period of 10 min. After stirring for an additional 20 min at 0 °C, the 0.4 M solution of diazonium chloride **2** (10 mmol/25 mL) was used for the arylation reactions. A 2.5 mL aliquot of the 0.4 M aryldiazonium chloride solution **2** (1 mmol, 1 equiv) was added dropwise by syringe pump to a vigorously stirred solution of 3-hydroxypyridine (**1a**) (10.0 mmol, 951 mg, 10 equiv) in water (5 mL), HCl (3 N, 2.5 mL), and titanium(III) chloride (1 mL, approximately 1 M solution in 3 N hydrochloric acid, 1 mmol) under a nitrogen atmosphere over 15 min. After the addition was complete, the mixture was left to stir for a further 10 min. Then, water (100 mL) and saturated sodium carbonate solution (25 mL) were added. After extraction with ethyl acetate (3 × 150 mL), the combined organic phases were washed with saturated aqueous sodium chloride (100 mL) and dried over anhydrous sodium sulfate. Concentration at reduced pressure gave the desired crude product.

General Procedure for Synthesis of 6−10 (GP2). 4-Chlorophenyldiazonium chloride (**2a**) (2.5 mL of a 0.4 M solution, 1 mmol, 1 equiv; for preparation, see GP1 above) was added dropwise by syringe pump to a vigorously stirred solution of the respective pyridine derivative (10.0 mmol, 10 equiv) in water (5 mL), HCl (3 N, 2.5 mL), and titanium(III) chloride (1 mL, approximately 1 M solution in 3 N hydrochloric acid, 1 mmol) under a nitrogen atmosphere over 15 min. After the addition was complete, the mixture was left to stir for a further 10 min. Then, water (100 mL) and saturated sodium carbonate solution (25 mL) were added. After extraction with ethyl acetate (3 × 150 mL), the combined organic phases were washed with saturated aqueous sodium chloride solution (100 mL) and dried over anhydrous sodium sulfate. Concentration at reduced pressure provided the desired crude product.

Procedure for Large-Scale Experiment. 4-Chlorophenyldiazonium chloride (**2a**) (12.5 mL of a 0.4 M solution, 5 mmol; for preparation, see GP1 above) was added dropwise by syringe pump to a vigorously stirred solution of 3-hydroxypyridine (**1a**) (50.0 mmol, 4.76 g, 10 equiv) in water (25 mL), HCl (3 N, 12.5 mL), and titanium(III) chloride (5 mL, approximately 1 M solution in 3 N hydrochloric acid, 5 mmol) under a nitrogen atmosphere within 15 min. After the addition was complete, the mixture was left to stir for a further 10 min. Then, water (500 mL) and saturated sodium carbonate solution (125 mL) were added. After extraction with ethyl acetate (3 × 300 mL), the combined organic phases were washed with saturated aqueous sodium chloride solution (200 mL) and dried over sodium sulfate. Concentration at reduced pressure afforded the desired crude product.

Procedure for Competition Experiments. 4-Chlorophenyldiazonium chloride (**2a**) (2.5 mL of a 0.4 M solution, 1 mmol, 1 equiv; for preparation, see GP1 above) was added dropwise by using a syringe pump to a vigorously stirred solution of 3-hydroxypyridine (**1a**) (476 mg, 5.0 mmol, 5 equiv) and 4-methoxyaniline (616 mg, 5.0 mmol, 5 equiv) or furan (364 μL, 5.0 mmol, 5 equiv) in water (5 mL), HCl (3 N, 2.5 mL), and titanium(III) chloride (1 mL, approximately 1 M solution in 3 N hydrochloric acid, 1 mmol) under a nitrogen atmosphere over 15 min. After the addition was complete, the mixture was left to stir for a further 10 min. Then, water (100 mL) and saturated sodium carbonate solution (25 mL) were added. After extraction with ethyl acetate (3 × 150 mL), the combined organic phases were washed with saturated aqueous sodium chloride solution (100 mL) and dried over anhydrous sodium sulfate. After concentration at reduced pressure, the product mixture was analyzed by ^{1}H NMR spectroscopy. The yields of **3a** and other products were determined by using maleic acid as internal standard.

*2-(4-Chlorophenyl)pyridin-3-ol (**3a**).* Compound **3a** was prepared according to GP1 using 4-chlorophenyldiazonium chloride (**2a**). Purification by column chromatography (chloroform/diethyl ether 10:1 to 1:1) gave **3a** (152 mg, 0.74 mmol, 74%) as a white solid. R_f = 0.4 (5:1 chloroform/diethyl ether) [UV]; mp = 231 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 1577, 1459, 1363, 1308, 1297, 1281, 1240, 1183, 1118, 1077, 1008, 831, 751; ^{1}H NMR (360 MHz, CD_3OD) δ 8.10 (dd, J = 4.6, J = 1.4 Hz, 1H), 7.91−7.84 (m, 2H), 7.47−7.39 (m, 2H), 7.33 (dd, J = 8.2, J = 1.4 Hz, 1H), 7.23 (dd, J = 8.2, J = 4.6 Hz, 1H) ; ^{13}C NMR (151 MHz, CD_3OD) δ 153.4, 146.0, 141.2, 137.5, 135.1, 131.9, 129.1, 125.3, 125.1; HRMS (ESI), calcd. for $C_{11}H_9ClNO$ [M^+ + H]: 206.0367, found: 206.0369. The melting point obtained is in agreement with the value previously reported.[29]

*2-(4-Fluorophenyl)pyridin-3-ol (**3b**).* Compound **3b** was prepared according to GP1 using 4-fluorophenyldiazonium chloride (**2b**). Purification by column chromatography (chloroform/diethyl ether 10:1 to 1:1) gave **3b** (121 mg, 0.64 mmol, 64%) as a white solid. R_f = 0.5 (5:1 chloroform/diethyl ether) [UV]; mp = 228 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 2417, 1574, 1510, 1460, 1358, 1280, 1221, 1181, 1156, 1118, 1078, 835, 797, 761; ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ 10.21 (s, 1H), 8.14 (dd, J = 4.5, J = 1.4 Hz, 1H), 8.08 (dd, J = 9.1 Hz, J_{HF} = 5.8 Hz, 2H), 7.33 (dd, J = 8.2 Hz, J = 1.5 Hz, 1H), 7.24 (t, J_{HF} = 9.0 Hz, J = 9.0 Hz, 2H), 7.20 (dd, J = 8.2, J = 4.5 Hz, 1H); ^{13}C NMR (151 MHz, $(CD_3)_2SO$) δ 161.7 (d, J_{CF} = 244.9 Hz), 151.3, 143.1, 140.1, 134.3 (d, J_{CF} = 3.0 Hz), 130.7 (d, J_{CF} = 8.2 Hz), 123.6, 123.5, 114.4 (d, J_{CF} = 21.1 Hz); HRMS (ESI), calcd. $C_{11}H_9FNO$ [M^+ + H]: 190.0663, found: 190.0662. The melting point obtained is in agreement with the value previously reported. ^{1}H NMR and ^{13}C NMR data are in agreement with those previously reported.[29]

*2-(4-Bromophenyl)pyridin-3-ol (**3c**).* Compound **3c** was prepared according to GP1 using 4-bromophenyldiazonium chloride (**2c**). Purification by column chromatography (chloroform/diethyl ether 10:1 to 1:1) gave **3c** (140 mg, 0.56 mmol, 56%) as a light yellow solid. R_f = 0.4 (5:1 chloroform/diethyl ether) [UV]; mp = 232 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 2466, 1575, 1457, 1364, 1310, 1297, 1283, 1274, 1240, 1184, 1117, 1077, 832, 761; ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (dd, J = 4.6, J = 1.4 Hz, 1H), 7.85−7.76 (m, 2H), 7.63−7.54 (m, 2H), 7.33 (dd, J = 8.2, J = 1.4 Hz, 1H), 7.23 (dd, J = 8.2, J = 4.6 Hz, 1H); ^{13}C NMR (101 MHz, CD_3OD) δ 153.5, 146.1, 141.3, 138.1, 132.2, 132.2, 125.4, 125.2, 123.4; HRMS (ESI), calcd. for $C_{11}H_9BrNO$ [M^+ + H] 249.9862; found: 249.9868.

*2-(3-Fluorophenyl)pyridin-3-ol (**3d**).* Compound **3d** was prepared according to GP1 using 3-fluorophenyldiazonium chloride (**2d**). Purification by column chromatography (chloroform/diethyl ether 10:1 to 1:1) gave **3d** (98.0 mg, 0.52 mmol, 52%) as a light brown solid. R_f = 0.4 (5:1 chloroform/diethyl ether) [UV]; mp = 193 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 2511, 1583, 1430, 1359, 1305, 1293, 1271, 1170, 1119, 1071, 874, 850, 790, 758; ^{1}H NMR (600 MHz, CD_3OD) δ 8.11 (dd, J = 4.6, J = 1.3 Hz, 1H), 7.72 (dd, J_{HF} = 7.8, J = 0.9 Hz, 1H), 7.65−7.61 (m, 1H), 7.47−7.40 (m, 1H), 7.34 (dd, J = 8.2, J = 1.3 Hz, 1H), 7.25 (dd, J = 8.2, J = 4.6 Hz, 1H), 7.15−7.07 (m, 1H); ^{13}C NMR (151 MHz, CD_3OD) δ 164.1 (d, J_{CF} = 242.9 Hz), 153.6, 145.9 (d, J_{CF} = 2.6 Hz), 141.4, 141.3, 130.7 (d, J_{CF} = 8.3 Hz), 125.6, 125.3, 126.2 (d, J_{CF} = 2.8 Hz), 117.0 (d, J_{CF} = 23.1 Hz), 115.9 (d, J_{CF} = 21.3 Hz); HRMS (ESI), calcd. for $C_{11}H_9FNO$ [M^+ + H] 190.0663; found: 190.0662.

*2-(3-Chlorophenyl)pyridin-3-ol (**3e**).* Compound **3e** was prepared according to GP1 using 3-chlorophenyldiazonium chloride (**2e**). Purification by column chromatography (chloroform/diethyl ether 10:1 to 1:1) gave **3e** (103 mg, 0.50 mmol, 50%) as a light brown solid. R_f = 0.4 (5:1 chloroform/diethyl ether) [UV]; mp = 226 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 1577, 1350, 1300, 1267, 1179, 1118, 1074, 883, 785, 750; ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (dd, J = 4.6, J = 1.4 Hz, 1H), 7.90 (t, J = 1.8 Hz, 1H), 7.82 (dt, J = 7.5, J = 1.5 Hz, 1H), 7.41 (t, J = 7.7 Hz, 1H), 7.39−7.32 (m, 2H), 7.24 (dd, J = 8.2, J = 4.6 Hz, 1H); ^{13}C NMR (101 MHz, CD_3OD) δ 153.5, 145.6, 141.3, 140.9, 134.9,

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130.5, 130.2, 129.1, 128.7, 125.5, 125.4; HRMS (ESI), calcd. for $C_{11}H_9ClNO$ [M^+ + H] 206.0367; found: 206.0369. The melting point obtained is in agreement with the value previously reported.[29]

*2-(3-Bromophenyl)pyridin-3-ol (**3f**).* Compound **3f** was prepared according to GP1 using 3-bromophenyldiazonium chloride (**2f**). Purification by column chromatography (chloroform/diethyl ether 10:1 to 1:1) gave **3f** (121 mg, 0.48 mmol, 48%) as a light brown solid. R_f = 0.4 (5:1 chloroform/diethyl ether) [UV]; mp = 220 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 2413, 1575, 1458, 1351, 1300, 1267, 1178, 1116, 1073, 795, 747; ^{1}H NMR (400 MHz, CD_3OD): δ 8.11 (dd, J = 4.6, J = 1.4 Hz, 1H), 8.05 (ddd, J = 2.1, J = 1.6, J = 0.4 Hz, 1H), 7.87 (ddd, J = 7.8, J = 1.6, J = 1.1 Hz, 1H), 7.52 (ddd, J = 8.0, J = 2.1, J = 1.1 Hz, 1H), 7.38−7.32 (m, 2H), 7.24 (dd, J = 8.2, J = 4.6 Hz, 1H); ^{13}C NMR (101 MHz, CD_3OD): δ 153.5, 145.4, 141.2, 141.1, 133.1, 132.0, 130.7, 129.0, 125.4, 125.3, 122.8; HRMS (ESI), calcd. for $C_{11}H_9BrNO$ [M^+ + H]: 249.9862, found: 249.9859.

*2-(2-Fluorophenyl)pyridin-3-ol (**3g**).* Compound **3g** was prepared according to GP1 using 2-fluorophenyldiazonium chloride (**2g**). Purification by column chromatography (chloroform/diethyl ether 10:1 to 1:1) gave **3g** (106 mg, 0.56 mmol, 56%) as a light brown solid. R_f = 0.4 (5:1 chloroform/diethyl ether) [UV]; mp = 178 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 1575, 1449, 1368, 1307, 1293, 1262, 1218, 1181, 1120, 1102, 819, 801, 755; ^{1}H NMR (600 MHz, CD_3OD) δ 8.08 (dd, J = 4.6, J = 1.1 Hz, 1H), 7.48−7.40 (m, 2H), 7.34 (dd, J = 8.3, J = 1.4 Hz, 1H), 7.29 (dd, J = 8.3, J = 4.6 Hz, 1H), 7.27−7.24 (m, 1H), 7.19−7.14 (m, 1H); ^{13}C NMR (101 MHz, CD_3OD) δ 161.8 (d, J_{CF} = 248.1 Hz), 153.9, 144.1, 140.7, 132.7 (d, J_{CF} = 3.6 Hz), 131.4 (d, J_{CF} = 8.2 Hz), 126.9 (d, J_{CF} = 15.9 Hz), 125.6, 125.0 (d, J_{CF} = 3.6 Hz), 124.9, 116.5 (d, J_{CF} = 22.2 Hz); HRMS (ESI), calcd. for $C_{11}H_9FNO$ [M^+ + H] 190.0663; found: 190.0668.

*2-(2-Chlorophenyl)pyridin-3-ol (**3h**).* Compound **3h** was prepared according to GP1 using 2-chlorophenyldiazonium chloride (**2h**). Purification by column chromatography (chloroform/diethyl ether 10:1 to 1:1) gave **3h** (96.2 mg, 0.47 mmol, 47%) as a yellow solid. R_f = 0.3 (5:1 chloroform/diethyl ether) [UV]; mp = 243 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 1559, 1456, 1434, 1367, 1303, 1283, 1245, 1181, 1114, 1085, 752, 745; ^{1}H NMR (600 MHz, CD_3OD) δ 8.06 (dd, J = 4.6, J = 1.5 Hz, 1H), 7.51−7.45 (m, 1H), 7.41−7.35 (m, 3H), 7.35−7.33 (m, 1H), 7.31 (dd, J = 8.3, J = 4.6 Hz, 1H); ^{13}C NMR (151 MHz, CD_3OD) δ 153.6, 147.0, 140.4, 138.2, 134.9, 132.5, 130.8, 130.5, 127.8, 125.8, 125.0; HRMS (ESI), calcd. for $C_{11}H_9ClNO$ [M^+ + H] 206.0367; found: 206.0367.

*2-(2-Bromophenyl)pyridin-3-ol (**3i**).* Compound **3i** was prepared according to GP1 using 2-bromophenyldiazonium chloride (**2i**). Purification by column chromatography (chloroform/diethyl ether 10:1 to 1:1) gave **3i** (107 mg, 0.43 mmol, 43%) as a light brown solid. R_f = 0.4 (5:1 chloroform/diethyl ether) [UV]; mp = 246 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 1572, 1456, 1370, 1303, 1280, 1252, 1184, 1110, 1082, 1011, 799, 773, 750, 721, ^{1}H NMR (600 MHz, CD_3OD) δ 8.05 (dd, J = 4.5, J = 1.6 Hz, 1H), 7.69−7.66 (m, 1H), 7.45−7.41 (m, 1H), 7.35−7.29 (m, 4H); ^{13}C NMR (101 MHz, CD_3OD) δ 153.3, 148.4, 140.2, 133.7, 132.4, 130.9, 128.4, 125.8, 125.0, 124.5 (one signal missing due to overlap); HRMS (ESI), calcd. for $C_{11}H_9BrNO$ [M^+ + H] 249.9862; found: 249.9857.

*2-(p-Tolyl)pyridin-3-ol (**3j**).* Compound **3j** was prepared according to GP1 using 4-methylphenyldiazonium chloride (**2j**). Purification by column chromatography (chloroform/diethyl ether 10:1 to 1:1) gave **3j** (119 mg, 0.64 mmol, 64%) as a light brown solid. R_f = 0.3 (5:1 chloroform/diethyl ether) [UV]; mp = 199 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 2919, 1577, 1454, 1300, 1280, 1242, 1183, 1109, 1017, 824, 800, 760; ^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (d, J = 4.1 Hz, 1H), 7.75−7.69 (m, 2H), 7.31 (dd, J = 8.2, J = 1.4 Hz, 1H), 7.23−7.26 (m, 2H), 7.19 (dd, J = 8.2, J = 4.7 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 153.3, 147.7, 140.8, 139.3, 136.0, 130.2, 129.6, 125.2, 124.5, 21.4; HRMS (ESI), calcd. for $C_{12}H_{12}NO$ [M^+ + H] 186.0913; found: 186.0917. The melting point obtained is in agreement with the value previously reported.[18]

*2-(m-Tolyl)pyridin-3-ol (**3k**).* Compound **3k** was prepared according to GP1 using 3-methylphenyldiazonium chloride (**2k**). Purification by column chromatography (chloroform/diethyl ether 10:1 to 1:1) gave **3k** (107 mg, 0.58 mmol, 58%) as a white solid. R_f = 0.4 (5:1 chloroform/diethyl ether) [UV]; mp = 172 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 3021.4, 2918.7, 2624.2, 1573.6, 1454.1, 1364.9, 1303.6, 1281.0, 1203.9, 1116.1, 802.2, 755.5, 698.6; ^{1}H NMR (600 MHz, CD_3OD) δ 8.07 (dd, J = 4.6, J = 1.0 Hz, 1H), 7.72−7.54 (m, 2H), 7.37- 7.25 (m, 2H), 7.21−7.17 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 153.3, 147.8, 140.8, 138.7, 138.6, 130.9, 129.9, 128.9, 127.5, 125.3, 124.7, 21.6; HRMS (ESI), calcd. for $C_{12}H_{12}NO$ [M^+ + H]; 186.0913 found: 186.0919. The melting point obtained is in agreement with the value previously reported.[29]

*2-(4-Methoxyphenyl)pyridin-3-ol (**3l**).* Compound **3l** was prepared according to GP1 using 4-methoxyphenyldiazonium chloride (**2l**). Purification by column chromatography (chloroform/diethyl ether 10:1 to 1:1) gave **3l** (131 mg, 0.65 mmol, 65%) as a light brown solid. R_f = 0.3 (5:1 chloroform/diethyl ether) [UV]; mp = 186 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 2918, 1610, 1570, 1514, 1457, 1374, 1282, 1250, 1179, 1109, 1024, 837, 799, 766; ^{1}H NMR (600 MHz, CD_3OD) δ 8.05 (dd, J = 4.7, J = 1.3 Hz, 1H), 7.84−7.77 (m, 2H), 7.32−7.27 (m, 1H), 7.17 (dd, J = 8.2, J = 4.7 Hz, 1H), 7.01−6.95 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 161.3, 153.1, 147.4, 140.8, 131.6, 131.2, 125.1, 124.2, 114.4, 55.8; HRMS (ESI), calcd. for $C_{12}H_{12}NO_2$ [M^+ + H] 202.0863; found: 202.0858. The melting point obtained is in agreement with the value previously reported.[18]

*2-(3-Methoxyphenyl)pyridin-3-ol (**3m**).* Compound **3m** was prepared according to GP1 using 3-methoxyphenyldiazonium chloride (**2m**). Purification by column chromatography (chloroform/diethyl ether 10:1 to 1:1) gave **3m** (80 mg, 0.40 mmol, 40%) as a white solid. R_f = 0.3 (5:1 chloroform/diethyl ether) [UV]; mp = 181 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 2935, 1582, 1457, 1424, 1283, 1229, 1170, 1116, 1031, 801, 760, 695; ^{1}H NMR (600 MHz, CD_3OD) δ 8.08 (dd, J = 4.7, J = 1.3 Hz, 1H), 7.44−7.38 (m, 2H), 7.36−7.30 (m, 2H), 7.22 (dd, J = 8.2, J = 4.7 Hz, 1H), 6.95 (ddd, J = 8.2, J = 2.6, J = 1.0 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 160.9, 153.3, 147.3, 140.9, 140.1, 129.9, 125.4, 124.9, 122.8, 115.8, 115.0, 55.7; HRMS (ESI), calcd. for $C_{12}H_{12}NO_2$ [M^+ + H]; 202.0863 found: 202.0866. The melting point obtained is in agreement with the value previously reported.[29]

*N-(4-(3-Hydroxypyridin-2-yl)phenyl)acetamide (**3n**).* Compound **3n** was prepared according to GP1 using 4-acetamidobenzenediazonium chloride (**2n**). Purification by column chromatography (chloroform/methanol 15:1 to 7:1) gave **3n** (73.0 mg, 0.32 mmol, 32%) as a light orange solid. R_f = 0.3 (10:1 chloroform/methanol) [UV]; mp = 106 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 3434, 1646, 1535, 1455, 1402, 1371, 1318, 1282, 1182, 1111, 1013, 767; ^{1}H NMR (600 MHz, CD_3OD) δ 8.07 (dd, J = 4.6, J = 1.1 Hz, 1H), 7.86−7.81 (m, 2H), 7.66−7.61 (m, 2H), 7.31 (dd, J = 8.2, J = 1.4 Hz, 1H), 7.19 (dd, J = 8.2, J = 4.7 Hz, 1H), 2.14 (s, 3H). ^{13}C NMR (151 MHz, CD_3OD) δ 170.3, 145.5, 139.5, 138.6, 133.1, 129.4, 123.8, 123.1, 118.9, 22.5. HRMS (ESI), calcd. for $C_{13}H_{13}N_2O_2$ [M^+ + H]: 229.0971, found: 229.0972.

*2-(4-(Trifluoromethyl)phenyl)pyridin-3-ol (**3p**).* Compound **3p** was prepared according to GP1 using 4-(trifluoromethyl)phenyldiazonium chloride (**2p**). Purification by column chromatography (chloroform/diethyl ether 10:1 to 1:1) gave **3p** (119 mg, 0.49 mmol, 49%) as a light brown solid. R_f = 0.4 (5:1 chloroform/diethyl ether) [UV]; mp = 240 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 1578, 1461, 1327, 1283, 1183, 1160, 1107, 1069, 1012, 845, 719; ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (d, J = 4.0 Hz, 1H), 8.11−8.04 (m, 2H), 7.70−7.75 (m, 2H), 7.36 (dd, J = 8.3, J = 1.4 Hz, 1H), 7.27 (dd, J = 8.3, J = 4.6 Hz, 1H); ^{13}C NMR (151 MHz, CD_3OD) δ 153.8, 145.5, 142.8, 141.4, 133.9, 130.9 (q, J_{CF} = 32.2 Hz), 130.9, 125.8 (q, J_{CF} = 3.8 Hz), 125.9 (d, J_{CF} = 271.3 Hz), 125.6, 125.5, 123.2; HRMS (ESI), calcd. for $C_{12}H_9F_3NO$ [M^+ + H] 240.0631; found: 240.0637.

*Methyl 4-(3-Hydroxypyridin-2-yl)benzoate (**3q**).* Compound **3q** was prepared according to GP1 using 4-(methoxycarbonyl)benzenediazonium chloride (**2q**). Purification by column chromatography (chloroform/diethyl ether 10:1 to 1:1) gave **3q** (126 mg, 0.55 mmol, 55%) as a light brown solid. R_f = 0.3 (5:1 chloroform/diethyl ether) [UV]; mp = 222 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 1722, 1577, 1461, 1354, 1279, 1178, 1104, 797, 744; ^{1}H NMR (600 MHz, CD_3OD) δ 8.13

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(dd, J = 4.6, J = 1.3 Hz, 1H), 8.11−8.05 (m, 2H), 8.02−7.98 (m, 2H), 7.35 (dd, J = 8.2, J = 1.4 Hz, 1H), 7.26 (dd, J = 8.2, J = 4.6 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 168.5, 153.8, 145.9, 143.7, 141.4, 130.7, 130.4, 130.1, 125.6, 125.5, 52.7; HRMS (ESI), calcd. for $C_{13}H_{12}NO_3$ [M^+ + H] 230.0812; found: 230.0815.The melting point obtained is in agreement with the value previously reported.[29]

*6H-Isochromeno[4,3-b]pyridin-6-one (**5a**).* Compound **5a** was prepared according to GP1 using 2-(methoxycarbonyl)benzenediazonium chloride (**2r**). Purification by column chromatography (chloroform/diethyl ether 10:1 to 5:1) gave **5a** (113 mg, 0.57 mmol, 57%) as a white crystalline solid. R_f = 0.8 (5:1 chloroform/diethyl ether) [UV]; mp = 138 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 1741, 1703, 1589, 1428, 1270, 1244, 1224, 1073, 1024, 772, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (dd, J = 8.0, J = 0.6 Hz, 1H), 8.61 (dd, J = 4.5, J = 1.1 Hz, 1H), 8.42−8.31 (m, 1H), 7.91 (ddd, J = 8.0, J = 7.4, J = 1.3 Hz, 1H), 7.72−7.68 (m, 1H), 7.66 (dd, J = 8.3, J = 1.4 Hz, 1H), 7.43 (dd, J = 8.3, J = 4.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 147.8, 146.0, 136.8, 135.6, 135.2, 130.6, 130.1, 124.9, 124.8, 123.4, 122.5; HRMS (ESI), calcd. for $C_{12}H_8NO_2$ [M^+ + H] 198.0550; found: 198.0555.

*8-Fluoro-6H-isochromeno[4,3-b]pyridin-6-one (**5b**).* Compound **5b** was prepared according to GP1 using 4-fluoro-2-(methoxycarbonyl)benzenediazonium chloride (**2s**). Purification by column chromatography (hexane/ethyl acetate 8:1 to 4:1) gave **5b** (108 mg, 0.50 mmol, 50%) as a white solid. R_f = 0.5 (2:1 hexane/ethyl acetate) [UV]; mp = 206 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 3086, 1740, 1503, 1447, 1407, 1331, 1265, 1236, 1066, 927, 846, 806, 752, 738; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.70 (dd, J = 8.8, J = 5.2 Hz, 1H), 8.60 (dd, J = 4.5, J = 1.4 Hz, 1H), 8.01 (dd, J = 8.4, J = 2.6 Hz, 1H), 7.67 (dd, J = 8.3, J = 1.4 Hz, 1H), 7.61 (ddd, J = 8.8, J = 8.1, J = 2.7 Hz, 1H), 7.43 (dd, J = 8.3, J = 4.5 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.72 (d, J = 252.7 Hz), 159.23 (d, J = 3.5 Hz), 147.3, 146.2, 136.2, 132.18 (d, J = 3.1 Hz), 126.36 (d, J = 8.4 Hz), 124.9, 124.8, 124.39 (d, J = 8.6 Hz), 123.47 (d, J = 22.9 Hz), 115.83 (d, J = 23.7 Hz); HRMS (ESI), calcd. for $C_{12}H_7FNO_2$ [M^+ + H] 216.0455; found: 216.0461.

*8-Chloro-6H-isochromeno[4,3-b]pyridin-6-one (**5c**).* Compound **5c** was prepared according to GP1 using 4-chloro-2-(methoxycarbonyl)benzenediazonium chloride (**2t**). Purification by column chromatography (hexane/ethyl acetate 8:1 to 4:1) gave **5c** (120 mg, 0.52 mmol, 52%) as a white solid. R_f = 0.5 (2:1 hexane/ethyl acetate) [UV]; light yellow solid, mp = 168 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 3075.9, 1744, 1591, 1443, 1289, 1253, 1239, 1223, 1100, 1073, 1020, 905, 839, 803, 750; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.63 (d, J = 8.5 Hz, 1H), 8.61 (dd, J = 4.5, J = 1.4 Hz, 1H), 8.34 (d, J = 2.2 Hz, 1H), 7.85 (dd, J = 8.5, J = 2.2 Hz, 1H), 7.67 (dd, J = 8.3, J = 1.4 Hz, 1H), 7.45 (dd, J = 8.3, J = 4.5 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.0, 147.7, 146.3, 137.0, 136.1, 135.6, 134.0, 129.6, 125.3, 125.2, 125.0, 123.7; HRMS (ESI), calcd. for $C_{12}H_7ClNO_2$ [M^+ + H]: 232.0160; found: 232.0165.

*8-Bromo-6H-isochromeno[4,3-b]pyridin-6-one (**5d**).* Compound **5d** was prepared according to GP1 using 4-bromo-2-(methoxycarbonyl)benzenediazonium chloride (**2u**). Purification by column chromatography (hexane/ethyl acetate 8:1 to 4:1) gave **5d** (129 mg, 0.47 mmol, 47%) as a white solid. R_f = 0.6 (2:1 hexane/ethyl acetate) [UV]; mp = 175 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 3071, 1733, 1588, 1440, 1390, 1315, 1289, 1253, 1239, 1223, 1194, 1098, 1080, 826, 802, 750; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.59 (dd, J = 4.5, J = 1.4 Hz, 1H), 8.52 (d, J = 8.5 Hz, 1H), 8.47 (d, J = 2.0 Hz, 1H), 7.98 (dd, J = 8.5, J = 2.1 Hz, 1H), 7.65 (dd, J = 8.3, J = 1.4 Hz, 1H), 7.45 (dd, J = 8.3, J = 4.5 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.9, 147.7, 146.3, 138.4, 136.1, 134.4, 132.6, 125.3, 125.2, 125.0, 124.9, 123.8; HRMS (ESI), calcd. for $C_{12}H_6BrNNaO_2$ [M^+ + Na]: 297.9474; found: 297.9473.

*2-(4-Chlorophenyl)-6-methylpyridin-3-ol (**6**).* Compound **6** was prepared according to GP2 using 5-hydroxy-2-methylpyridine (**1b**) (1.09 g, 10 mmol, 10 equiv). Purification by column chromatography (chloroform/diethyl ether 10:1 to 1:1) gave **6** (167 mg, 0.76 mmol, 76%) as a white solid. R_f = 0.6 (2:1 hexane/ethyl acetate) [UV]; mp = 179 °C; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 3388, 2949, 2844, 1480, 1454, 1389, 1269, 1090, 1053, 1033, 1015, 835, 773, 735; ^{1}H NMR (600 MHz, CD_3OD) δ 7.88−7.82 (m, 2H), 7.46−7.40 (m, 2H), 7.23 (d, J = 8.3 Hz, 1H), 7.09 (d, J = 8.3 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 150.9, 150.0, 145.0, 137.8, 134.9, 132.0, 129.0, 125.9, 124.6, 22.9; HRMS (ESI), calcd. For $C_{12}H_{11}ClNO$ [M^+ + H]: 220.0524; found: 220.0522.

*3-(4-Chlorophenyl)pyridin-4-ol (**7a**) and 2-(4-Chlorophenyl)-pyridin-4-ol (**7b**).* Compounds **7a** and **7b** were prepared according to GP2 using 4-hydroxypyridine (951 mg, 10 mmol, 10 equiv). Purification by column chromatography (hexane/ethyl acetate 4:1 to 1:1) gave an inseparable mixture of regioisomers **7a** and **7b** (41.0 mg, 0.20 mmol, 20% overall yield) as a light brown solid. R_f = 0.2 (2:1 hexane/ethyl acetate) [UV]; NMR analysis revealed a mixture of 14% of **7a** and 6% of **7b**. ^{1}H NMR of **7a**: (600 MHz, CD_3OD) δ 7.90 (s, 1H), 7.76 (d, J = 6.7 Hz, 1H), 7.58−7.56 (m, 2H), 7.43−7.38 (m, 2H), 6.55 (d, J = 7.1 Hz, 1H); ^{1}H NMR of **7b**: (600 MHz, CD_3OD) δ 7.88 (d, J = 7.1 Hz, 1H), 7.71−7.67 (m, 2H), 7.57−7.55 (m, 2H), 6.74 (d, J = 1.7 Hz, 1H), 6.52 (dd, J = 7.1, J = 2.4 Hz, 1H); ^{13}C NMR of mixture of both regioisomers: (151 MHz, CD_3OD) δ 138.8, 138.5, 137.8, 135.0, 134.5, 131.5, 130.5, 129.8, 129.6, 129.4, 118.7, signals missing due to overlap; HRMS (ESI), calcd. for $C_{11}H_9ClNO$ [M^+ + H] 206.0367; found: 206.0368.

*4-(4-Chlorophenyl)-2-methoxypyridine (**8**).* Compound **8** was prepared according to GP2 using 2-methoxypyridine (1.05 mL, 10 mmol, 10 equiv). Purification by column chromatography (hexane/ethyl acetate 16:1 to 4:1) gave **8** (50.3 mg, 0.23 mmol, 23%) as a yellow oil. R_f = 0.5 (8:1 hexane/ethyl acetate) [UV]; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 2945, 1609, 1546, 1476, 1405, 1386, 1326, 1252, 1209, 1093, 1056, 1033, 1023, 1012, 812, 771, ^{1}H NMR (600 MHz, CDCl3) δ 8.22 (d, J = 5.3 Hz, 1H), 7.57−7.50 (m, 2H), 7.46−7.42 (m, 2H), 7.07 (dd, J = 5.4, 1.6 Hz, 1H), 6.92 (d, J = 0.9 Hz, 1H), 3.99 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.9, 150.1, 147.3, 136.7, 135.2, 129.3, 128.3, 115.1, 108.4, 53.7; HRMS (ESI), calcd. for $C_{12}H_{11}ClNO$ [M^+ + H]: 220.0524, found: 220.0528.

*2-(4-Chlorophenyl)-4-methoxypyridine (**10**).* Compound **10** was prepared according to GP2 using 4-methoxypyridine (1.01 mL, 10 mmol, 10 equiv). Purification by column chromatography (hexane/ethyl acetate 8:1 to 2:1) gave **10** (55.8 mg, 0.25 mmol, 25%) as a light yellow oil. R_f = 0.3 (4:1 hexane/ethyl acetate) [UV]; IR (NaCl, cm^{-1}) $\tilde{\nu}$; 3011, 2969, 2940, 1597, 1577, 1562, 1496, 1472, 1442, 1312, 1216, 1091, 1033, 1012, 831; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 5.7 Hz, 1H), 7.97−7.85 (m, 2H), 7.47−7.38 (m, 2H), 7.19 (d, J = 2.2 Hz, 1H), 6.78 (dd, J = 5.7, J = 2.4 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 157.9, 150.9, 137.8, 135.2, 128.9, 128.3, 108.3, 106.9, 55.3; HRMS (ESI), calcd. for $C_{12}H_{11}ClNO$ [M^+ + H]: 220.0524, found: 220.0529. ^{1}H NMR data are in agreement with those previously reported.[25]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00894.

Optimization of reaction conditions, analysis of regioisomeric distribution, and copies of ^{1}H and ^{13}C NMR spectra of compounds **3a**−**3n**, **3p**, **3q**, **5a**−**5d**, **6**, **7a**, **7b**, **8**, and **10** (PDF)

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Notes

The authors declare no competing financial interest.

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