Highly Regioselective Palladium-Catalyzed C2-Amination of 2,4-Dichloropyridines: Scope and Limitations

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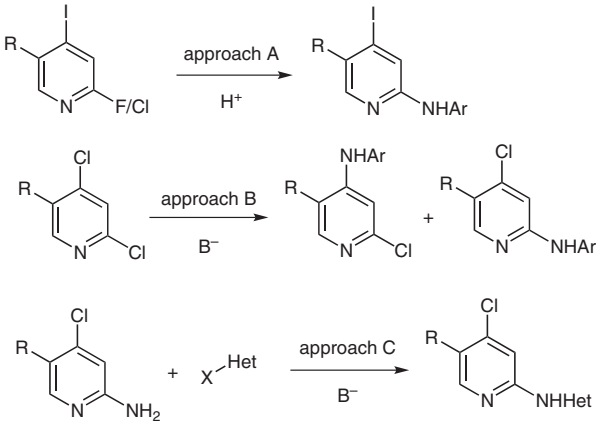
Abstract: The use of palladium(0) enables a highly regioselective C-2 amination of 4,6-dichloronicotinonitrile. Coupling with aminoarenes that are *N*-acetyl-masked to limit cross-coupling overreaction, leads to 4-chloro-6-anilino nicotinonitrile compounds after deprotection in situ. The scope of these original conditions was evaluated.

Key words: regioselectivity, palladium, amination, pyridines, cross-coupling

Several examples of 2,4-bis-anilino pyridines have been developed as very potent kinase inhibitors. Due to the broad range of substituents required to enable extensive exploration of structure–activity relationships, flexible synthetic routes to these compounds are required. Literature methods for accessing 2,4-bis-anilinopyridyl compounds usually start with functionalization at the C4-position of a 2,4-dihalopyridine ring. Some examples have involved direct functionalization at the C2-position either by differentiating two halogen atoms of the starting material (i.e., 4-iodo-2-fluoro/chloropyridine derivatives) or by introducing groups by anionic displacement on 2,4-dichloropyridines derivatives (Scheme 1).[1]



Scheme 1 Different approaches reported in the literature

Nevertheless, the first method (approach A) can be less convenient because not all the possible starting materials are commercially available. The second method (approach B) can give low yields due to imperfect levels of C2/C4 regioselectivity. A third method (approach C) to make 4-chloro-2-aminoarene pyridines **A** (see Figure 1 below) could involve a reversal of reactivity by carrying out an S_NAr reaction on activated haloheteroarenes through the anion of 2-amino-4-chloropyridine, however, this approach is limited to activated haloheteroarenes (e.g., 2-chlorothioazole).[2] For our SAR studies, access to 2-anilino-4-chloropyridines was required so that we could then create diversity at the C4-position of the pyridine ring. To the best of our knowledge, there are very few literature examples where a 2,4-dichloropyridine is first functionalized at the C2-position.[3] Herein, we report a highly regioselective palladium-catalyzed C2-amination of 2,4-dichloropyridine derivatives using Buchwald–Hartwig conditions and *N*-acetyl-masked aminoarenes.

Firstly, 4-chloro-6-anilino nicotinonitrile derivatives (**A**) were required as intermediates in our research, therefore, 4,6-dichloronicotinonitrile (**1**) was subjected to different reaction conditions in the presence of an aniline. Palladium-mediated conditions have previously been used,[3] however, for substrate **1**, overreaction occurred under these conditions leading to the formation of product **B**. C4-Substitution was predominant under basic conditions (e.g., sodium hydride) to give product **C** and other by-products (Figure 1).

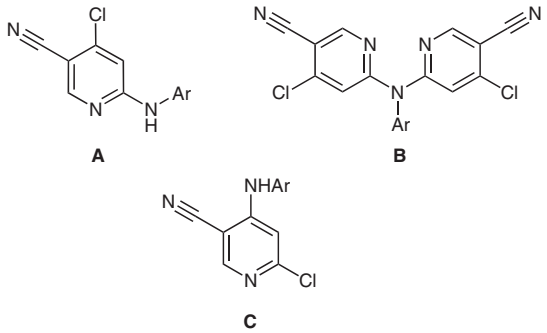


Figure 1 Target products **A** and the main by-products formed under palladium-catalyzed (**B**) and basic conditions (**C**)

From previous observations made within our group,[4] the use of an *N*-acetyl aniline derivative instead of the aniline derivative itself could lead to displacement of the C2-chlorine atom from 2-chloro-4-iodo-5-(trifluoromethyl)pyridine under basic conditions in moderate to good yields. Deacetylation then afforded the desired product.

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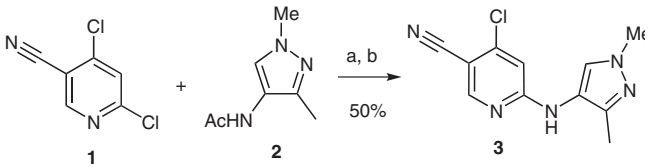
Thus, the reaction between the 4,6-dichloronicotinonitrile (**1**) and *N*-(1,3-dimethyl-1*H*-pyrazol-4-yl)acetamide (**2**) was explored as a model. Basic conditions (sodium 2-methylbutan-2-olate, dioxane, tetrahydrofuran, or sodium hydride in *N*,*N*-dimethylformamide) gave the desired major product **3** but with moderate C2/C4 regioselectivity and were formed together with polymeric products (**A**/**B**/**C** = 65:15:20). The acetyl group was cleaved during the reaction, probably due to the harsh conditions. Palladium-catalyzed conditions were then tried using 3 mol% palladium(II) acetate, 6 mol% Xantphos, and 1.5 equivalents of cesium carbonate in dioxane at 90 °C for four hours. This furnished the expected product **3** in acceptable yield, with very little by-product **B** being formed. Total regioselectivity occurred and none of the C4 product type **C** was observed.[5] Acetyl deprotection was carried out by addition of 1 M aqueous lithium hydroxide (Scheme 2).

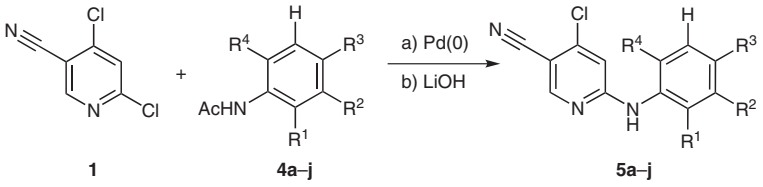


Scheme 2 *Reagents and conditions* (0.58 mmol of **1** and **2**): (a) $Pd(OAc)_2$ (3 mol%), Xantphos (6 mol%), Cs_2CO_3 (1.5 equiv), dioxane (0.3 M), 90 °C, 4 h; (b) 1 M aq LiOH (3 equiv), r.t., 30 min.

The C2-regioselective palladium-catalyzed cross-coupling reaction between 2-chloropyridine and ureas has already been reported,[6] but, to the best of our knowledge, acetamides have never been used in this kind of chemistry with the aim of using the *N*-acetyl group as a protecting group, coupled with palladium-catalyzed chemistry to enhance regioselectivity and limit overreaction. In an attempt to improve conditions for this reaction, several parameters were explored. Initially, the influence of the acetyl group was evaluated; Boc, trifluoroacetyl and formyl groups were tried in place of the acetyl group, but none gave the expected product **A** and use of the acetyl remained the preferred choice. Various palladium-catalyzed coupling conditions were then screened. A range of different bases, palladium sources, ligands and solvents were explored, but these alternative conditions did not lead to an improvement over the first results (detailed in Scheme 2), therefore, our preferred reagent mixture remained as palladium(II) acetate, Xantphos, and cesium carbonate in dioxane. The palladium was a key component in this coupling. Indeed, treating pyridine **1** and acetyl 4-amino-pyrazole **2** with no palladium source, in the presence of Xantphos and cesium carbonate in dioxane, led to less regioselectivity and the formation of more by-products.

To evaluate the scope of this reaction, pyridine **1** was reacted with a range of *N*-acetyl anilines; the results are summarized in Table 1.

Table 1 Scope of the Reaction[a]



Entry	R^1	R^2	R^3	R^4	Product	Yield (%)[b]
1	H	H	H	H	**5a**	75
2	NO_2	H	H	Me	**5b**	31[c]
3	OMe	H	H	H	**5c**	69
4	H	H	CN	H	**5d**	31[c]
5	H	H	Ac	H	**5e**	32[c]
6	Me	H	OMe	H	**5f**	85
7	$CH_2N(Me)CH_2$		H	H	**5g**	45
8	H	Cl	H	H	**5h**	54[d]
9	H	H	Br	H	**5i**	66
10	H	H	NO_2	H	**5j**	27[c]

[a] Reaction conditions: **1** (0.58 mmol) and **4** (0.58 mmol), $Pd(OAc)_2$ (3 mol%), Xantphos (6 mol%), Cs_2CO_3 (1.5 equiv), dioxane (0.3 M), 90 °C, 4 h, then 1 M aq LiOH (3 equiv), r.t., 30 min.
[b] Isolated yield after preparative HPLC/MS purification.[7]
[c] Required overnight heating for the coupling reaction and overreaction by-product type **B** was formed.
[d] Some hydrolysis product of starting pyridine **1** was formed.

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Anilines bearing electron-donating groups gave the highest yields (Table 1, entries 3 and 6), comparable to the standard aniline (entry 1), whereas electron-withdrawing groups such as nitro (entries 2 and 10), cyano (entry 4), and 4-acetyl (entry 5) led to lower yields. For these latter cases, longer reaction times were required, presumably due to their weak nucleophilicity, compared to the use of electron-rich *N*-acetyl anilines (e.g., **4c** and **4f**). Furthermore, the *N*-acetyl group on the formed C6 aniline intermediate is probably more labile and is partially cleaved during the first step (amination reaction), which might explain the more extensive formation of by-products **B**. Our conditions may not be optimal for electron-deficient anilines and further investigation would be necessary to achieve improved yields.

Hindrance of the amino group seemed to have little effect on the rate of the reaction (Table 1, entries 2, 3 and 6). Weakly basic aliphatic amine side-chains seemed to give good conversion in the cross-coupling reaction (entry 7); however, this substrate was also not very stable under in situ acetyl deprotection conditions. Complete chemoselectivity was observed for halogen-bearing anilines (entries 8 and 9).

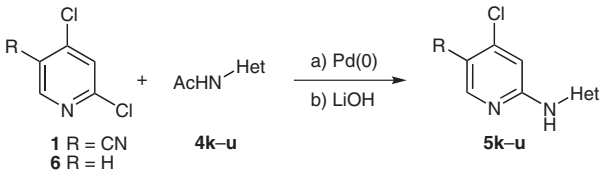
Because the versatility of these conditions looked useful for parallel synthesis, the standard protocol developed in Table 1 was applied with a wider range of *N*-acetyl amino heterocycles; the results are summarized in Table 2.

For these examples, the cross-coupling reaction required a higher temperature (110 vs. 90 °C) and longer reaction time (15 vs. 4 h) when 2,4-dichloropyridine (**6**) was used instead of pyridine **1** (Table 2, entries 8, 10 and 11 vs. Table 1, entries 8, 3 and 1, respectively). Some C4-regioisomer (type **C**) could be formed with increasing nucleophilicity of the *N*-acetyl aminoarene **4** when pyridine **6** was employed as starting material. This may be due to the higher temperature and longer reaction time required (entries 7, 9 and 11), although no C4-regioisomer (type **C**) was observed in the case of aniline **4t**, bearing an *ortho*-methoxy group (entry 10). Additionally, an *ortho*-cyano group may hinder the 4-chloro substituent of pyridine **1**. Its absence in pyridine **6** may explain the reduced regioselectivity. An encouraging result also came from the use of 2-amino-6-methylpyridine (**4l**; entry 2) and acetyl 5-aminopyrazole (**4k**; entry 1), giving the desired products in 72 and 38% yields, respectively. On the other hand, results obtained with a number of other heterocycles (entries 3–6) under these reaction conditions led to the formation of complex product mixtures, which were not purified.

On a larger scale (55 mmol), the reaction was quite reproducible, and the desired product **3** was obtained in an acceptable 44% yield (Scheme 1).

In summary, we have shown that the palladium-catalyzed amination of 4,6-dichloronicotinonitrile (**1**) can be regioselectively performed in acceptable yields with *N*-acetyl electron-rich anilines and some aminoheterocycles (e.g., 3-aminopyrazole and 2-aminopyridine), using Xantphos, palladium(II) acetate, and cesium carbonate in dioxane at 90 °C. A high preference for coupling at C2 was observed, but fine-tuning of the reaction conditions is required to achieve better yields with 2,4-dichloropyridine (**6**) or with electron-poor *N*-acetyl aminoarenes, which was beyond the scope of this study. The strategy was based on masking the amine group as an acetamide to avoid arylation

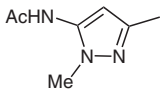
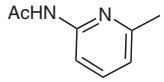
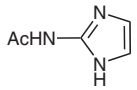
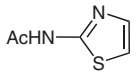
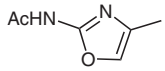
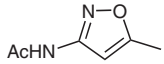
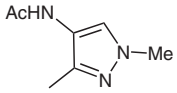
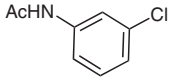
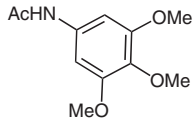
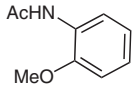
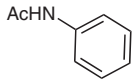
Table 2 Extending the Scope of the Reaction[a]



1 R = CN
6 R = H

4k–u

5k–u

Entry	Substrate	**4**	Product	Yield (%)[b]
1	**1**		**5k**	38
2	**1**		**5l**	72[c]
3	**1**		**5m**	n/a
4	**1**		**5n**	n/a
5	**1**		**5o**	n/a
6	**1**		**5p**	n/a
7	**6**		**5q**	65[d]
8	**6**		**5r**	45
9	**6**		**5s**	51[e]
10	**6**		**5t**	44
11	**6**		**5u**	42[f]

[a] Reaction conditions: **1** (0.58 mmol) or **6** (0.68 mmol), **4** (1 equiv), $Pd(OAc)_2$ (3 mol%), Xantphos (6 mol%), Cs_2CO_3 (1.5 equiv), dioxane (0.3 M), 90 °C (110 °C for **6**), overnight, then 1 M aq LiOH (3 equiv), r.t., 30 min.

[b] Yield (where purified) after preparative HPLC/MS.[7]

[c] Obtained as a mixture with 5 mol% 4,6-bis(6-methylpyridin-2-ylamino)nicotinonitrile.

[d] A 95:5 ratio of **5q/B** was observed during the coupling reaction.

[e] A 8:2 ratio **5s/B** was observed during the coupling reaction.

[f] A 9:1 ratio of **5u/B** was observed during the coupling reaction.

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side-reactions that lead to the formation of product **B**. The good stability of the *N*-acetyl group under the reaction conditions minimizes the formation of products of type **B**.

All starting *N*-acetyl aminoarenes **4** were purchased from commercial sources or synthesized by known procedures.[8] All other reagents were purchased from commercial sources and used without further purification. All reactions were performed in sealed microwave vials under an inert atmosphere of argon, except for the 55 mmol-scale reaction, which was performed in standard glassware. Preparative HPLC/MS was carried out with a Waters autopurification system (injector/collector 2767; pump 2525; MS detector ZQ) using a Waters XBridge 5 µm, reverse-phase column (19 × 100 mm or 30 × 150 mm) and decreasingly polar mixtures of H_2O (containing 0.2% ammonium carbonate) and MeCN as eluent. Elemental analyses were performed with a Carlo Erba CHNS EA 1108. High-resolution mass spectra were performed with a Thermo FT-ICR instrument. NMR spectra were recorded with a Bruker Avance 500 spectrometer (500 MHz for ^1H and 125 MHz for ^{13}C) relative to TMS as an internal standard. Chemical shifts are expressed in δ units (ppm). Mass spectrometry and purity assessment at two wavelengths (254 and 310 nm) were carried out with an analytical Waters HPLC/MS system, with positive and negative ion data collected automatically.

N-(1,3-Dimethyl-1*H*-pyrazol-4-yl)acetamide (2)

Acetyl chloride (4.2 mL, 60 mmol) was added dropwise to a suspension of 1,3-dimethyl-1*H*-pyrazol-4-amine dihydrochloride salt (10 g, 54 mmol) and Et_3N (18.9 mL, 136 mmol) in CH_2Cl_2 (120 mL) over a period of 15 min at 25 °C. The resulting suspension was stirred at 25 °C for 3 h, then the mixture was concentrated and the residue was taken up in a minimum of CH_2Cl_2 (ca. 35 mL), the triethylammonium chloride was removed by filtration and washed with CH_2Cl_2 (2 × 15 mL). The filtrate was concentrated in the presence of silica gel and purified by flash chromatography on silica gel (MeOH–EtOAc, 2→7%). The solvent was evaporated to dryness to afford **2**.

Yield: 6.2 g (74.5%); pink solid.

^1H NMR (700 MHz, DMSO-d_6): δ = 2.00 (s, 3 H), 2.10 (s, 3 H), 3.70 (s, 3 H), 7.80 (s, 1 H), 9.26 (br s, 1 H).

^{13}C NMR (176 MHz, DMSO-d_6): δ = 11.58, 23.19, 38.74, 119.08, 124.07, 138.29, 167.50.

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_7H_{12}N_3O$: 154.09749; found: 154.09741.

4-Chloro-6-(1,3-dimethyl-1*H*-pyrazol-4-ylamino)nicotinonitrile (3)

4,6-Dichloronicotinonitrile (**1**; 9.6 g, 55 mmol), *N*-(1,3-dimethyl-1*H*-pyrazol-4-yl)acetamide (**2**; 8.5 g, 55 mmol), diacetoxypalladium (0.374 g, 1.7 mmol), Xantphos (1.9 g, 3.3 mol) and Cs_2CO_3 (27.1 g, 83 mmol) were weighed out in a flask. Dioxane (110 mL) was added and argon was allowed to bubble through the reaction mixture for 5 min at r.t. The resulting suspension was stirred at 90 °C for 2 h, then the reaction mixture was allowed to cool to r.t. under stirring. H_2O (275 mL) was added, followed by portionwise addition of $LiOH·H_2O$ (7 g, 0.17 mol). The resulting solution was stirred at r.t. for 30 min and the resulting precipitate was collected by filtration, washed with H_2O (2 × 30 mL) and dried to give the crude product (24 g), which was purified by flash chromatography on silica gel (0→5% MeOH in EtOAc–CH_2Cl_2, 1:1). The solvent was evaporated to dryness and the residue was triturated in Et_2O. The resulting precipitate was collected by filtration, washed with Et_2O and dried to a constant weight to afford 4-chloro-6-(1,3-dimethyl-1*H*-pyrazol-4-ylamino)nicotinonitrile.

Yield: 13.7 g (44%); pale-yellow solid.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.15 (s, 1 H), 3.87 (s, 3 H), 6.45 (br s, 1 H), 6.49 (br s, 1 H), 7.44 (br s, 1 H), 8.35 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.0, 39.3, 100.0, 106.3, 115.43, 117.2, 127.4, 144.7, 146.7, 154.1, 160.6.

MS (ESI): *m*/*z* = 248 and 250 $[M + H]^+$.

Anal. Calcd for $C_{11}H_{10}ClN_5$: C, 53.34; H, 4.07; N, 28.27. Found: C, 53.11; H, 3.95; N, 27.83.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{11}ClN_5$: 248.06976; found: 248.06975.

Palladium-Mediated Amination of Pyridine 1; Typical Procedure

4,6-Dichloronicotinonitrile (**1**; 100 mg, 0.58 mmol), *N*-acetyl aminoarene **4** (0.58 mmol), Xantphos (20 mg, 0.06 mmol), diacetoxypalladium (3.9 mg, 0.02 mmol) and Cs_2CO_3 (283 mg, 0.87 mmol) were weighed out and sealed in a microwave vial. Argon-degassed dioxane (2 mL) was added and the resulting mixture was stirred at 90 °C for 2–6 h. The reaction mixture was allowed to cool to r.t., diluted with 1 M aq LiOH (1.8 mL) and stirred at r.t. for 30 min. The reaction mixture was concentrated, diluted with DMF (1.5 mL), centrifuged, and the filtrate was purified by preparative HPLC/MS. The fractions were evaporated to dryness and, depending on the solubility of the final compound, the residue was triturated in either EtOAc, pentane, Et_2O or a 1:1 mixture of pentane and Et_2O. The resulting solid was collected by filtration and dried to afford the title compound as a solid. Yields are summarized in Table 1.

4-Chloro-6-(phenylamino)nicotinonitrile (5a)

^1H NMR (500 MHz, $CDCl_3$): δ = 6.82 (s, 1 H, H5), 7.04 (br s, 1 H), 7.25 (t, *J* = 7.8 Hz, 1 H), 7.32 (dd, *J* = 7.6, 7.8 Hz, 2 H), 7.43 (t, *J* = 7.8 Hz, 2 H), 8.40 (s, 1 H, H2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 100.6, 107.0, 115.3, 123.0, 126.0, 129.9, 137.3, 146.7, 154.0, 158.8.

MS (ESI): *m*/*z* = 230 and 232 $[M + H]^+$.

Anal. Calcd for $C_{12}H_8ClN_3$: C, 62.76; H, 3.51; N, 18.30. Found: C, 62.99; H, 3.59; N, 18.26.

4-Chloro-6-(2-methyl-6-nitrophenylamino)nicotinonitrile (5b)

^1H NMR (500 MHz, $CDCl_3$): δ = 2.27 (s, 3 H), 6.55 (s, 1 H, H5), 7.38 (dd, *J* = 7.8, 8.0 Hz, 1 H), 7.60 (d, *J* = 7.8 Hz, 1 H), 7.85 (br s, 1 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 8.38 (s, 1 H, H2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.0, 102.1, 108.9, 114.8, 123.5, 126.9, 130.4, 136.5, 138.3, 143.8, 146.9, 153.9, 158.0.

MS (ESI): *m*/*z* = 330 and 332 $[MH + CH_3CN]^+$.

MS (ESI): *m*/*z* = 287 and 289 $[M - H]^-$.

4-Chloro-6-(2-methoxyphenylamino)nicotinonitrile (5c)

^1H NMR (500 MHz, $CDCl_3$): δ = 3.90 (s, 3 H), 6.84 (s, 1 H, H5), 6.96 (dd, *J* = 8.2, 0.9 Hz, 1 H), 7.01 (ddd, *J* = 8.2, 7.6, 0.9 Hz, 1 H), 7.14 (ddd, *J* = 7.6, 7.8, 0.9 Hz, 1 H), 7.28 (br s, 1 H), 7.89 (d, *J* = 7.8 Hz, 1 H), 8.44 (s, 1 H, H2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.7, 100.5, 108.5, 110.9, 115.4, 121.0, 121.3, 125.0, 127.2, 145.9, 150.1, 153.9, 158.1.

MS (ESI): *m*/*z* = 260 and 262 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{10}ClN_3O$ (10 mol% Et_2O): C, 60.26; H, 4.15; N, 15.73. Found: C, 60.64; H, 3.99; N, 15.88.

4-Chloro-6-(4-cyanophenylamino)nicotinonitrile (5d)

^1H NMR (500 MHz, DMSO-d_6): δ = 6.94 (s, 1 H, H5), 7.11 (br s, 1 H), 7.80 (d, *J* = 8.9 Hz, 2 H), 7.87 (d, *J* = 8.9 Hz, 2 H), 8.75 (s, 1 H, H2).

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^{13}C NMR (125 MHz, DMSO-d_6): δ = 100.0, 103.9, 111.2, 115.3, 119.1, 119.2, 133.2, 143.6, 143.8, 154.1, 157.3.

MS (ESI): *m*/*z* = 253 and 255 [M – H]$^-$.

Anal. Calcd for $C_{13}H_7ClN_4$ (30 mol% H_2O): C, 60.67; H, 2.86; N, 21.72. Found: C, 60.46; H, 2.59; N, 21.49.

6-(4-Acetylphenylamino)-4-chloronicotinonitrile (5e)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.60 (s, 3 H), 6.95 (s, 1 H, H5), 7.10 (br s, 1 H), 7.51 (d, *J* = 8.6 Hz, 2 H), 8.01 (d, *J* = 8.6 Hz, 2 H), 8.50 (s, 1 H, H2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.5, 102.1, 109.0, 114.9, 120.0, 130.2, 133.2, 142.3, 146.7, 154.0, 157.3, 196.6.

HRMS-ESI: *m*/*z* = 272 and 274 [M + H]$^+$ calcd for $C_{14}H_{11}ClN_3O$: 272.05852; found: 272.05865.

4-Chloro-6-(4-methoxy-2-methylphenylamino)nicotinonitrile (5f)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.22 (s, 3 H), 3.83 (s, 3 H), 6.32 (s, 1 H, H5), 6.73 (br s, 1 H), 6.81 (dd, *J* = 2.6, 8.6 Hz, 1 H), 6.86 (d, *J* = 2.6 Hz, 1 H), 7.16 (d, *J* = 8.6 Hz, 1 H), 8.35 (s, 1 H, H2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.2, 55.5, 99.7, 105.9, 112.6, 115.5, 116.6, 127.9, 128.3, 136.7, 146.7, 154.1, 159.0, 160.6.

MS (ESI) *m*/*z* = 274 and 276 [M + H] $^+$.

Anal. Calcd for $C_{14}H_{12}ClN_3O$ (70 mol% H_2O): C, 58.72; H, 4.72; N, 14.67. Found: C, 58.54; H, 4.39; N, 14.42.

4-Chloro-6-(2-methylisoindolin-4-ylamino)nicotinonitrile (5g)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.62 (s, 3 H), 3.80 (s, 2 H), 3.98 (s, 2 H), 6.60 (s, 1 H, H5), 6.98 (br s, 1 H), 7.14 (d, *J* = 7.8 Hz, 1 H), 7.16 (d, *J* = 8.2 Hz, 1 H), 7.29 (dd, *J* = 7.8, 8.2 Hz, 1 H), 8.38 (s, 1 H, H2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 42.2, 59.1, 61.2, 100.4, 106.7, 115.3, 120.8, 122.7, 128.5, 131.6, 136.0, 143.3, 146.7, 154.2, 159.0.

HRMS (ESI): *m*/*z* 285 and 287 [M + H]$^+$ calcd for $C_{15}H_{14}ClN_4$: 285.09015; found: 285.09018.

4-Chloro-6-(3-chlorophenylamino)nicotinonitrile (5h)

^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.83 (s, 1 H), 7.06 (s, 1 H), 7.19 (d, *J* = 6.9 Hz, 1 H), 7.24 (d, *J* = 7.6 Hz, 1 H), 7.34 (dd, *J* = 7.6, 6.9 Hz, 1 H), 7.45 (s, 1 H), 8.43 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 101.5, 108.1, 115.3, 120.3, 122.4, 125.7, 130.8, 135.5, 139.1, 146.8, 154.2, 158.3.

MS (ESI): *m*/*z* = 262 and 264 [M – H]$^-$.

Anal. Calcd for $C_{12}H_7Cl_2N_3$ (10 mol% pentane): C, 55.33; H, 3.05; N, 15.49. Found: C, 55.57; H, 2.73; N, 15.18.

6-(4-Bromophenylamino)-4-chloronicotinonitrile (5i)

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.00 (s, 1 H, H5), 7.52 (d, *J* = 8.9 Hz, 2 H), 7.63 (d, *J* = 8.9 Hz, 2 H), 8.66 (s, 1 H, H2), 10.07 (br s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 98.7, 110.1, 114.5, 115.6, 121.7, 131.5, 138.5, 143.3, 154.2, 157.7.

MS (ESI): *m*/*z* = 306, 308 and 310 [M – H]$^-$.

Anal. Calcd for $C_{12}H_7BrClN_3$: C, 46.71; H, 2.29; N, 13.62. Found: C, 46.75; H, 2.08; N, 13.48.

4-Chloro-6-(4-nitrophenylamino)nicotinonitrile (5j)

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.16 (s, 1 H, H5), 7.94 (d, *J* = 8.9 Hz, 2 H), 8.25 (d, *J* = 8.9 Hz, 2 H), 8.79 (s, 1 H, H2), 10.60 (br s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 100.6, 111.6, 115.2, 118.6, 125.1, 141.3, 144.0, 145.7, 154.1, 157.1.

MS (ESI): *m*/*z* = 273 and 275 [M – H]$^-$.

Anal. Calcd for $C_{12}H_7ClN_4O_2$ (5 mol% pentane): C, 52.87; H, 2.75; N, 20.13. Found: C, 53.26; H, 2.73; N, 20.34.

Palladium-Mediated Amination with Pyridine 6; Typical Procedure

2,4-Dichloropyridine (**6**; 100 mg, 0.68 mmol), *N*-acetyl aminoarene **4** (0.68 mmol), Xantphos (23.5 mg, 0.06 mmol), diacetoxypalladium (4.5 mg, 0.02 mmol) and Cs_2CO_3 (330 mg, 1.01 mmol) were weighed out and sealed in a microwave vial. Argon-degassed dioxane (2 mL) was added and the resulting mixture was stirred at 110 °C overnight. The reaction mixture was allowed to cool to r.t., diluted with a 1 M aq LiOH (2 mL) and stirred at r.t. for 30 min. The reaction mixture was concentrated, diluted with DMF (1.5 mL), centrifuged, and the filtrate was purified by preparative HPLC/MS. The fractions were evaporated to dryness and, depending on the solubility of the final compound, the residue was triturated in either EtOAc, pentane, Et_2O or a 1:1 mixture of pentane and Et_2O. The resulting solid was collected by filtration and dried to afford the title compound as a solid. Yields are summarized in Table 2.

4-Chloro-6-(1,3-dimethyl-1*H*-pyrazol-5-ylamino)nicotinonitrile (5k)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.29 (s, 3 H), 3.69 (s, 3 H), 6.01 (s, 1 H), 6.58 (s, 1 H, H5), 6.68 (br s, 1 H), 8.41 (s, 1 H, H2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 35.0, 101.3, 102.1, 107.0, 114.8, 135.6, 147.5, 148.2, 154.0, 159.3.

MS (ESI): *m*/*z* = 248 and 250 [M + H]$^+$.

Anal. Calcd for $C_{11}H_{10}ClN_5$: C, 53.34; H, 4.07; N, 28.27. Found: C, 53.05; H, 3.94; N, 28.15.

4-Chloro-6-(6-methylpyridin-2-ylamino)nicotinonitrile (5l)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.54 (s, 3 H), 6.87 (d, *J* = 7.3 Hz, 1 H), 7.13 (d, *J* = 7.6 Hz, 1 H), 7.59 (dd, *J* = 7.6, 7.3 Hz, 1 H), 7.71 (br s, 1 H), 8.16 (s, 1 H), 8.46 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.0, 102.3, 109.8, 111.3, 115.1, 117.8, 138.8, 146.6, 151.4, 151.5, 153.1, 156.3.

HRMS (ESI): *m*/*z* 245 and 247 [M + H]$^+$ calcd for $C_{12}H_{10}ClN_4$: 245.05885; found: 245.05893.

4-Chloro-*N*-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridin-2-amine (5q)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.15 (s, 3 H), 3.85 (s, 3 H), 6.11 (br s, 1 H), 6.38 (s, 1 H), 6.65 (d, *J* = 4.6 Hz, 1 H), 6.41 (s, 1 H), 8.01 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.0, 39.24, 106.3, 114.5, 119.1, 127.2, 144.8, 145.4, 149.1, 159.3.

MS (ESI): *m*/*z* = 223 and 225 [M + H]$^+$.

Anal. Calcd for $C_{10}H_{11}ClN_4$ (10 mol% EtOAc): C, 53.96; H, 5.14; N, 24.20. Found: C, 54.14; H, 4.95; N, 24.28.

4-Chloro-6-(6-methylpyridin-2-ylamino)nicotinonitrile (5r)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.66 (br s, 1 H), 6.78 (dd, *J* = 1.8, 5.4 Hz, 1 H), 6.82 (d, *J* = 1.6 Hz, 1 H), 7.05 (d, *J* = 7.8 Hz, 1 H), 7.20 (d, *J* = 8.0 Hz, 1 H), 7.26 (d, *J* = 7.8, 8.0 Hz, 1 H), 7.44 (dd, *J* = 1.8, 1.6 Hz, 1 H), 8.11 (d, *J* = 5.4 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.9, 116.5, 118.8, 120.7, 123.7, 130.7, 135.4, 141.4, 145.6, 149.7, 156.7.

MS (ESI): *m*/*z* = 239 and 241 [M + H]$^+$.

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Anal. Calcd for $C_{11}H_8Cl_2N_2$ (5 mol% pentane): C, 55.67; H, 3.57; N, 11.54. Found: C, 56.01; H, 3.16; N, 11.23.

4-Chloro-*N*-(3,4,5-trimethoxyphenyl)pyridin-2-amine (5s)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.85 (s, 9 H), 7.57 (s, 2 H), 6.63 (s, 1 H), 6.72 (d, *J* = 4.6 Hz, 1 H), 6.78 (s, 1 H), 8.07 (d, *J* = 4.6 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 56.6, 61.4, 100.3, 108.0, 115.6, 135.3, 135.8, 145.6, 149.7, 154.2, 158.0.

MS (ESI): *m*/*z* = 295 and 297 $[M + H]^+$.

Anal. Calcd for $C_{14}H_{15}ClN_2O_3$ (10 mol% pentane): C, 57.68; H, 5.41; N, 9.28. Found: C, 58.05; H, 5.05; N, 9.19.

4-Chloro-*N*-(2-methoxyphenyl)pyridin-2-amine (5t)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.89 (s, 3 H), 6.73 (dd, *J* = 1.6, 7.5 Hz, 1 H), 6.85 (d, *J* = 1.5 Hz, 1 H), 6.91 (dd, *J* = 1.8, 7.7 Hz, 1 H), 6.95–7.04 (m, 3 H), 7.95 (dd, *J* = 1.8, 7.5 Hz, 1 H), 8.11 (d, *J* = 5.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.7, 108.8, 110.5, 115.3, 119.2, 120.9, 122.6, 129.3, 144.7, 149.1, 149.2, 156.7.

MS (ESI): *m*/*z* = 235 and 237 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{11}ClN_2O$ (5 mol% pentane): C, 61.75; H, 4.91; N, 11.76. Found: C, 62.04; H, 4.60; N, 11.50.

4-Chloro-*N*-phenylpyridin-2-amine (5u)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.72 (dd, *J* = 1.6, 5.5 Hz, 1 H, H3), 6.84 (d, *J* = 1.6 Hz, 1 H, H5), 6.85 (br s, 1 H), 7.13 (t, *J* = 7.2 Hz, 1 H), 7.30 (d, *J* = 7.2 Hz, 2 H), 7.36 (dd, *J* = 7.2, 7.8 Hz, 2 H), 8.08 (d, *J* = 5.5 Hz, 1 H, H2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 107.9, 115.8, 121.7, 124.2, 129.9, 140.0, 145.6, 149.7, 157.6.

MS (ESI): *m*/*z* = 205 and 207 $[M + H]^+$.

Anal. Calcd for $C_{11}H_9ClN_2$ (7 mol% Et_2O): C, 64.62; H, 4.66; N, 13.35. Found: C, 65.01; H, 4.23; N, 12.91.

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References

(1) (a) Tasler, S.; Mueller, O.; Wieber, T.; Herz, T.; Krauss, R.; Totzke, F.; Kubbutat, M. H. G.; Schaechtele, C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1349. (b) Huang, H.; Hutta, D. A.; Hu, H.; DesJarlais, R. L.; Schubert, C.; Petrounia, I. P.; Chaikin, M. A.; Manthey, C. L.; Player, M. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2355. (c) Suzuki, T.; Igari, S.; Hirasawa, A.; Hata, M.; Ishiguro, M.; Fujieda, H.; Itoh, Y.; Hirano, T.; Nakagawa, H.; Ogura, M.; Makishima, M.; Tsujimoto, G.; Miyata, N. *J. Med. Chem.* **2008**, *51*, 7640. (d) Adams, J. L.; Faitg, T. H.; Johnsion, N. W.; Pen, X. Int. Patent Appl. WO 2009/105498, **2009**.

(2) Arrington, K. L.; Dudkin, V. Y.; Fraley, M. E.; Wang, C.; Hoffman, J. M.; Kreatsoulas, C. Int. Patent Appl. WO 2006/135604, **2006**.

(3) Asaki, T.; Sugiyama, Y.; Segawa, J. Int. Patent Appl. WO 2005/063709, **2005**.

(4) (a) Barlaam, B. C.; Foote, K. M.; Ple, P. Int. Patent Appl. WO 2009/153589, **2009**. (b) Barlaam, B.; Foote, K.; Hassall, L.; Hawkins, J.; Jones, C.; Le Griffon, A.; Morgentin, R.; Peru, A.; Plé, P. *Synth. Commun.* **2011**, in press.

(5) Regioselectivity was confirmed by NMR studies on intermediates and final compounds made by two different methods.[4]

(6) Abad, A.; Agullo, C.; Cunat, A. C.; Vilanova, C. *Synthesis* **2005**, 915.

(7) Patrice Koza developed a robust method (0.2% attrition) for the rapid purification of a wide range of compounds by preparative HPLC/MS. Koza, P.; unpublished results.

(8) (a) Challis, B. C.; Challis, J. A. In *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley: New York, **1970**, 731–857. (b) Vogel, A. I. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Furniss, B. S.; Hannaford, A. J.; Smith, P. W.; Tatchell, A. R., Eds.; Wiley: New York, **1989**, 1273–1274.

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