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Selective palladium-catalyzed aminations on dichloropyridines

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Abstract—Palladium-catalyzed amination proved to be a valuable strategy for the selective introduction of aromatic and heteroaromatic amines, including aminopyridines and aminodiazines, on dichloropyridines. The use of mild amination conditions resulted in maximum selectivity and excellent base sensitive functional group tolerance. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The modification of the pyridine nucleus is a versatile research area, which still attracts a considerable amount of interest in modern organic chemistry. Due to its presence in numerous natural products and biologically active substances,[1] the pyridine moiety is still regarded as one of the most interesting heteroaromatic ring systems. Notwithstanding the fact that a multitude of different reactions on pyridine and its derivatives are known, as illustrated by the marvellous work of Katritzky[2] and Quéguiner,[3] there is still a need for new approaches towards pyridine functionalization. Independently discovered by Buchwald and Hartwig, the Pd-catalyzed amination reaction has established itself as one of the most versatile and powerful synthetic strategies currently available.[4,5] The amination protocol has successfully been applied in the synthesis of numerous arylamino-substituted arenes and more recently, starts to find its way in heterocyclic chemistry as exemplified by the synthesis of N^6-aryl 2′-deoxyadenosine analogues by Lakshman,[6] and of the potent H_1-antihistaminic norastemizole by Senanayake.[7] As in the case of other Pd-catalyzed cross-coupling reactions such as the Suzuki-[8] and Stille-reaction,[9] the Pd-catalyzed amination protocol was first elaborated on iodo- and bromo(hetero)arenes.[10] However, better understanding of the reaction mechanism as a result of detailed study, resulted in the development of reaction conditions which turned out to be suitable for unactivated chloro(hetero)arene substrates. Especially, the development and use of new and more electron rich ligands like 1,3-bis(diphenylphosphino)propane (DPPP) and 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)-1,1′-biphenyl (DCHPDMAB) turned out to be a factor of utmost importance.[11] A number of halogenated pyridine derivatives have been successfully used in Pd-catalyzed amination reactions including 2-chloropyridine, 3-chloropyridine and 4-chloropyridine, as well as their brominated analogues.[11–13] To the best of our knowledge, no dihalogenated pyridine derivative (with the exception of 2,6-dibromopyridine[13]) was used in amination chemistry. We were surprised by the absence of such a study and consequently we decided to probe the applicability of an amination strategy in the selective functionalization of pyridines. While this work was in progress, Desmarets reported the Ni(0)-catalyzed synthesis of substituted chloroaminopyridines starting from dichloropyridines.[14] However, minor selectivity was obtained and fairly high catalyst loadings were necessary. Moreover the use of relatively toxic nickel has to be regarded as an additional drawback of this method.[15]

2. Results and discussion

Very recently, our laboratory[16] reported very mild amination conditions for the preparation of substituted 4-amino-3(2*H*)-pyridazinones using a large excess of K_2CO_3 or Cs_2CO_3 as the base instead of NaO*t*Bu or KO*t*Bu. Although it has been reported that the latter two give the fastest reactions, their high basisity often causes problems, especially when base-sensitive substrates are employed.[4d,10a,17] Therefore we decided to investigate the use of our mild conditions for the selective Pd-catalyzed aminations of dichloropyridines. As a starting point we studied the cross-coupling of different dichloropyridines i.e. 2,3-dichloropyridine (**1a**), 2,5-dichloropyridine (**1b**) and 2,6-dichloropyridine (**1c**) with 2-aminopyridine (**2a**), 3-aminopyridine (**2b**) and 4-aminopyridine (**2c**).

As can be seen from Table 1, the reactions proceeded smoothly, affording the reaction products in good yield. Noteworthy is the fact that in every reaction the mono substituted product was formed exclusively and regioselectively. Di-aminated products could not be detected, even after prolonged reaction times in the presence of an

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Keywords: aminations; palladium; pyridines; heteroaromatic amines; regioselectivity.

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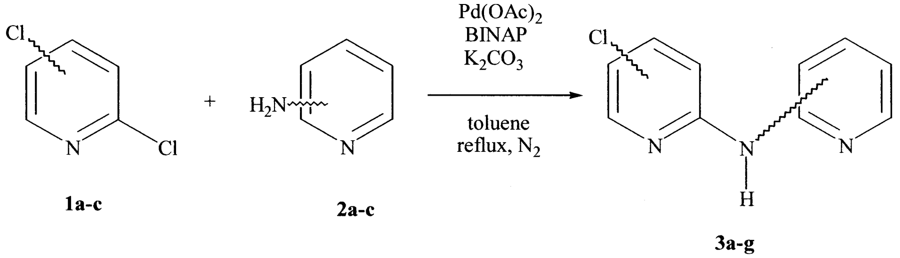
Table 1. Synthesis of substituted chloropyridines (**3**) using mild amination conditions



Entry	Dichloropyridine (**1**)	Aminopyridine (**2**)	Time (h)	Yield[a] (%)	Reaction product (**3**)[b]
1	**1a**	**2a**	18	93	**3a**
2	**1a**	**2b**	18	71	**3b**
3	**1a**	**2c**	18	80	**3c**
4	**1c**	**2a**	24	56	**3d**
5	**1b**	**2b**	24	48[c]	**3e**
6	**1c**	**2c**	24	64	**3f**
7	**1c**	**2b**	24	62	**3g**

[a] Yields reported are those of analytical pure compounds.

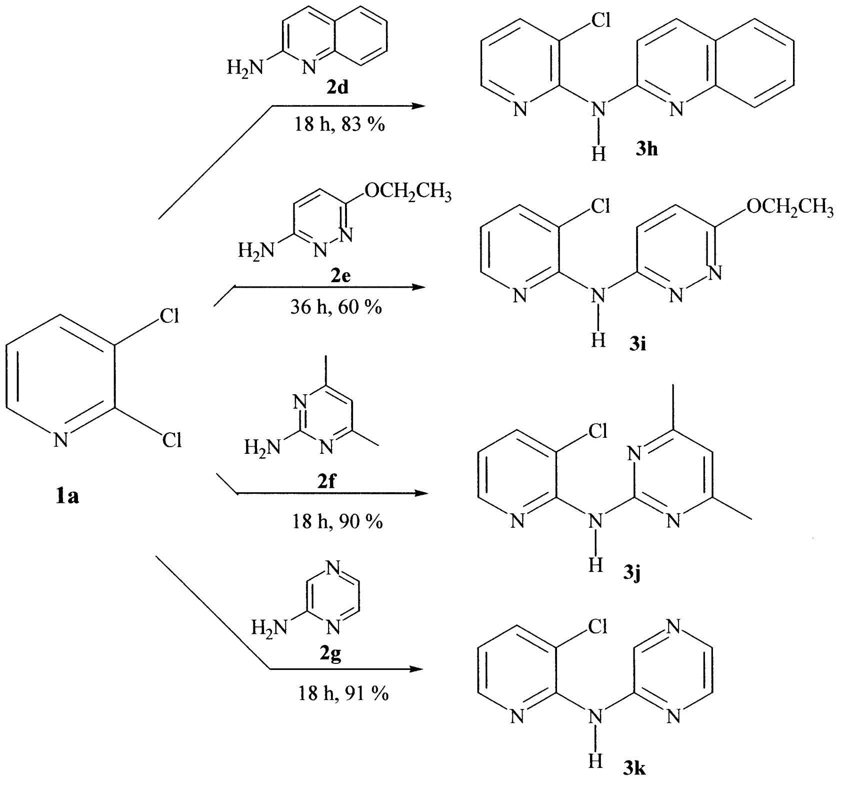
[b] General reaction conditions: 2 mol% $Pd(OAc)_2$, 2 mol% BINAP, 1.2 equiv. amine, 20 equiv. K_2CO_3.

[c] In this case 6 mol% of $Pd(OAc)_2$ and BINAP were used.

excess of amine.[18] As reported before, the use of a large amount of K_2CO_3 was found to be crucial to get the reaction to completion.[19]

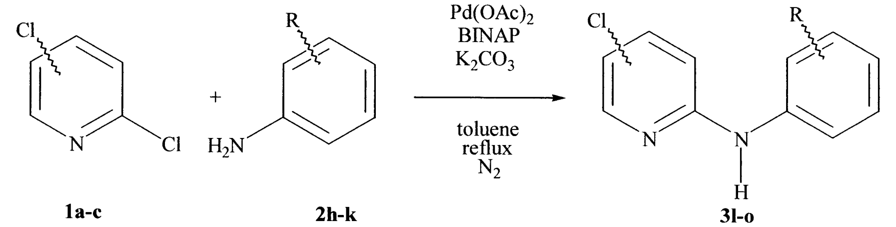
Encouraged by these promising results we examined, as a second part of this work, the possibility of introducing other amines on the pyridine skeleton. Surprisingly, a thorough literature search revealed that little work has been done on amination reactions with heteroaromatic amines. To the best of our knowledge only the three isomeric aminopyridines (**2a–c**) had been used so far.[13,20] Therefore, we felt it was worthwhile to investigate the use of other heteroaromatic amines in more detail because such an approach would allow access to potentially interesting new heterocycles. Reaction of 2,3-dichloropyridine (**1a**) with 2-aminoquinoline (**2d**), 3-amino-6-ethoxypyridazine[21] (**2e**), 2-amino-4,6-dimethylpyrimidine (**2f**) and aminopyrazine (**2g**) under our mild conditions, afforded the expected reaction products in good yield.

As illustrated in Scheme 1, heterocyclic amines turned out to be valuable coupling partners. As before, in every



Scheme 1. Amination of 2,3-dichloropyridine (**1a**) with different heteroaromatic amines.

Table 2. Introduction of substituted aniline derivatives onto dichloropyridines



Entry	Dichloropyridine (**1**)	Substituted aniline (**2**)	Substituent R	Time (h)	Yield[a] (%)	Reaction product (**3**)[b]
1	**1a**	**2h**	4–NO_2–	18	80	**3l**
2	**1a**	**2i**	4-CH_3O–	18	93	**3m**
3	**1c**	**2j**	2-CN–	40	41	**3n**
4	**1b**	**2k**	4-COOEt	18	64	**3o**

[a] Yields reported are those of analytical pure compounds.

[b] General reaction conditions: 2 mol% $Pd(OAc)_2$, 2 mol% BINAP, 1.2 equiv. amine, 20 equiv. K_2CO_3.

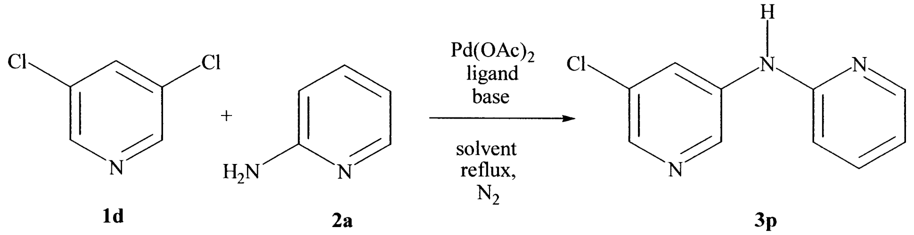
case, the amination proceeded regioselectively in the 2-position.

To further investigate the scope of this amination approach towards pyridine modification we turned our attention to substituted aniline derivatives as amine sources. To demonstrate the general suitability of our method, we chose four different anilines i.e. *p*-nitroaniline (**2h**), *p*-anisidine (**2i**), 2-aminobenzonitrile (**2j**) and benzocaine (**2k**) as test substrates. The former two are interesting because of their extreme electronic properties while the latter two incorporate base sensitive functional groups. Table 2 summarizes the results obtained.

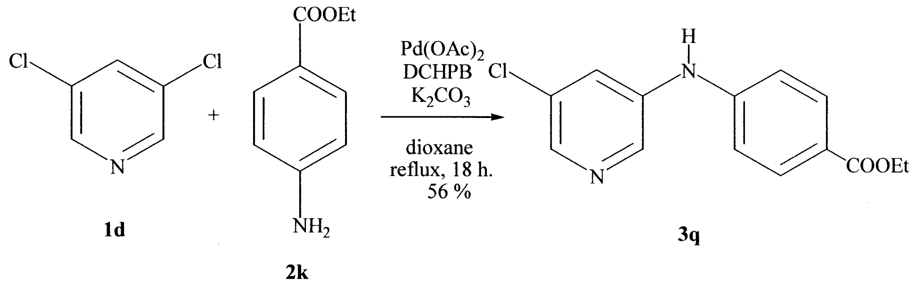
As can be seen from Table 2, both electron rich and electron poor anilines are easily introduced (entries 1, 2). Also the presence of base sensitive functional groups is well tolerated (entries 3, 4). The successful coupling of 2,3-dichloropyridine (**1a**) with the strongly deactivated *p*-nitroaniline (**2h**) is an indication of the intervention of Pd in this reaction. Indeed, formation of (3-chloro-2-pyridyl)(4-nitrophenyl)amine (**3l**) via a nucleophilic substitution reaction seems very unlikely. In control experiments we tried to prepare (3-chloro-2-pyridyl)(4-methoxyphenyl)amine (**3m**) and (2-pyridyl)(3-chloro-2-pyridyl)amine (**3a**) in the absence of $Pd(OAc)_2$. Both reactions failed and it can therefore be concluded that reaction via nucleophilic aromatic substitution can be ruled out.

To complete our study on Pd-catalyzed amination on dichloropyridines, we tried to use 3,5-dichloropyridine (**1d**) as a starting material. However, we anticipated that we might run into trouble due to the unfavourable positions of the chlorine atoms. Indeed, after reacting 3,5-dichloropyridine (**1d**) with 2-aminopyridine (**2a**) using the conditions described above, no amination product could be detected. Since the 3 and 5 positions are the most deactivated, we thought that using a more electron rich ligand might solve the problem. So we tried DPPP, DCHPDMAB and tricyclohexylphosphine (TCHP) instead of BINAP. Disappointedly, we learnt that none of these ligands were really suitable even with higher loadings of catalyst. Gratifyingly, we found that the use of the electron rich ligand 2-(dicyclohexylphosphino)biphenyl (DCHPB)

Table 3. Optimisation of the amination of 3,5-dichloropyridine



Entry	Pd-source	Ligand	Base	Solvent	Reaction time (h)	Yield (**3p**) (%)
1	$Pd(OAc)_2$ 2 mol%	BINAP 2 mol%	K_2CO_3 (20 equiv.)	Toluene	24	0
2	$Pd(OAc)_2$ 4 mol%	DCHPDMAB 4 mol%	K_2CO_3 (20 equiv.)	Toluene	24	0
3	$Pd(OAc)_2$ 2 mol%	TCHP 4 mol%	K_2CO_3 (20 equiv.)	Toluene	24	0
4	$Pd(OAc)_2$ 4 mol%	DPPP 4 mol%	K_2CO_3 (20 equiv.)	Toluene	24	0
5	$Pd(OAc)_2$ 4 mol%	DCHPB 8 mol%	K_2CO_3 (20 equiv.)	Toluene	36	15
6	$Pd(OAc)_2$ 4 mol%	DCHPB 8 mol%	*t*-BuONa (1.5 equiv.)	Toluene	36	0
7	$Pd(OAc)_2$ 4 mol%	DCHPB 8 mol%	Cs_2CO_3 (20 equiv.)	Toluene	36	0
8	$Pd(OAc)_2$ 4 mol%	DCHPB 8 mol%	K_2CO_3 (20 equiv.)	Dioxane	36	40
9	$Pd(OAc)_2$ 4 mol%	DCHPB 8 mol%	Cs_2CO_3 (20 equiv.)	Dioxane	36	0
10	$Pd(OAc)_2$ 4 mol%	DCHPB 8 mol%	*t*-BuONa (1.5 equiv.)	Dioxane	36	0
11	$Pd(OAc)_2$ 4 mol%	DCHPB 8 mol%	*t*-BuOK (1.5 equiv.)	Dioxane	36	0



Scheme 2. Reaction of 3,5-dichloropyridine (**1d**) with benzocaine (**2k**).

resulted in the formation of a small amount (15%) of the desired compound. Stimulated by this observation we decided to optimise other parameters in search of better reaction conditions (Table 3).

As can be seen from the table the use of dioxane as the solvent instead of toluene had a significant effect on the yield (entry 8). Also important to note is the fact that neither NaO*t*Bu nor Cs_2CO_3 were effective (entries 6, 7, 9 and 10) even when DCHPB is used as the ligand. Since we noted that the cation of the base might be important (compare entries 5 with 7 and 8 with 9) we also tried KO*t*Bu (entry 11). However the reaction was not successful.

To probe the applicability of these optimised reaction conditions, we also tried to introduce an arylamino substituent on 3,5-dichloropyridine (**1d**). Reaction with benzocaine (**2k**) afforded (5-chloro-3-pyridyl)(4-ethoxycarbonylphenyl)-amine (**3q**) in moderate yield as shown in Scheme 2.

The observations presented in this work regarding the selectivity of Pd-catalyzed aminations on dichloropyridines can be nicely explained considering the following theoretical model. As illustrated above, whenever a chlorine atom is present in the 2-position, it is preferentially substituted regardless of the position of the other chlorine atom. This difference in reactivity of the 2-position in comparison to the 3- and 5-positions in pyridines is analogous to observations made in classic heterocyclic chemistry.[22] This similarity can be understood if one considers the oxidative addition (the first step in Pd-catalyzed cross-coupling reactions) as a nucleophilic aromatic substitution.[23] This also explains the fact that substitution of a chlorine atom in the 3-position requires more electron rich ligands which results in an increased nucleophilicity of the Pd-catalyst thereby enhancing the possibility of oxidative addition. The exclusive formation of mono-aminated products in Pd-catalyzed aminations on 2,6-dichloropyridine (**1c**) is most probably the result of the more electron rich nature of the intermediate mono aminated chloropyridine (arising from the electron donating nature of the introduced amino substituent) which prevents a second oxidative addition.

3. Conclusions

In conclusion, we have shown that selective palladium-catalyzed amination reactions can serve as a valuable protocol in the functionalization of pyridines. Mild conditions in combination with low catalyst loading allows the selective amination of dichloropyridines. This approach might give access to useful intermediates for the synthesis of natural products and hitherto unknown pharmaceuticals.

4. Experimental

All reagents were purchased from commercial sources (Acros, Aldrich, Lancaster) and were used as such. Dioxane was distilled from sodium benzophenone before use. Column chromatography was carried out using Kieselgel 60 (Merck), 0.040–0.063 mm. Thin layer chromatography was performed on pre-coated ALUGRAM® SIL G/UV_{254} Kieselgel 60 0.25 mm TLC-plates. NMR spectra were recorded on a Varian Unity 400 MHz spectrometer in $CDCl_3$ as the solvent unless otherwise stated. In every case TMS was used as the internal standard. Chemical shifts are given in ppm and *J* values in Hz. Multiplicity is indicated using the following abbreviations: d for a doublet, t for a triplet, m for a multiplet etc. In those cases where standard ^1H and ^{13}C measurements were insufficient, additional 2D-measurements (i.e. HETCOR, LR-HETCOR, COSY) were performed for complete structure elucidation. IR spectra were recorded on a Bruker Vector 22 spectrometer. For mass spectrometric analysis, samples were dissolved in CH_3OH containing 0.1% formic acid and diluted to a concentration of approx. 10^{-5} mol/L. 1 μL injections were directed to the mass spectrometer at a flow rate of 5 μL/min CH_3OH (0.1% Formic acid), using the CapLC HLPC system (Waters, Millford). Product ion spectra and exact mass measurements were performed on a quadrupole/orthogonal-acceleration time-of-flight (Q/oaTOF) tandem mass spectrometer (qTof 2, Micromass, Manchester, UK) equipped with a standard electrospray ionisation (ESI) interface. Cone voltage (35 V) and capillary voltage (3.3 kV) were optimised on one compound and used for the series of experiments. Fragmentation was induced by low energy collisional activation using an Ar gas using a collision energy of 30 eV. Melting points were determined on a Büchi B-545 apparatus and are uncorrected.

4.1. Typical procedure for the Pd-catalyzed aminations on 2,3-dichloropyridine, 2,5-dichloropyridine and 2,6-dichloropyridine.

A round bottom flask was flushed with nitrogen and charged with $Pd(OAc)_2$ (13.5 mg, 0.06 mmol, 2%), (±)-BINAP (37.5 mg, 0.06 mmol, 2%) and toluene (10 mL). The mixture was stirred under nitrogen for 10 min. In another round bottom flask dichloropyridine (0.441 g, 3 mmol), amine (3.6 mmol, 1.2 equiv.) and K_2CO_3 (8.28 g, 60 mmol) were weighed. Then, the $Pd(OAc)_2$/BINAP solution was added, and the flask was rinsed with an additional 17 mL toluene. The resulting mixture was subsequently refluxed in an oil bath under N_2 with vigorous stirring until the starting dichloropyridine had disappeared as judged by TLC and DCI-MS. After cooling down, the solid material was filtered off and washed with 100 mL CH_2Cl_2. The solvent was evaporated and the resulting crude product was purified by flash column chromatography using the specified eluent.

4.1.1. (2-Pyridyl)(3-chloro-2-pyridyl)amine (3a). eluent: CH_2Cl_2/MeOH (96/4); yield: 0.573 g (93%); white solid; mp 48.8°C; ν_{max}(KBr): 3417, 1589, 1525, 1437, 766, 740 cm^{-1}; δ_H: 6.76 (dd, 1H, J=7.9, 4.8 Hz, H-5′), 6.90 (ddd, 1H, J=7.3, 4.9, 0.9 Hz, H-5), 7.59 (dd, 1H, J=7.9, 1.4 Hz, H-4′), 7.66 (ddd, 1H, J=8.6, 7.3, 1.8 Hz, H-4), 7.82 (br, 1H, N–H), 8.16 (dd, 1H, J=4.8, 1.4 Hz, H-6′), 8.26 (ddd, 1H, J=4.9, 1.8, 0.9 Hz, H-6), 8.44 (dd, 1H, J=8.6, 0.9 Hz, H-3); δ_C: 112.6 (C-3), 116.4 (C-5′), 117.0 (C-3′), 117.9 (C-5), 137.1 (C-4′), 138.0 (C-4), 145.7 (C-6′), 148.1 (C-6), 150.3 (C-2′), 153.1 (C-2); LRMS (ES): 170, 112, 96, 78, 51; HRMS (ESI) for $C_{10}H_9ClN_3$ $[M+H]^+$ found: 206.0473, calcd: 206.0485; $C_{10}H_8ClN_3$ calcd: C, 58.41; H, 3.92; N, 20.43, found: C, 58.49; H, 3.87; N, 20.44.

4.1.2. (3-Pyridyl)(3-chloro-2-pyridyl)amine (3b). eluent: CH_2Cl_2/MeOH (96/4); yield: 0.440 g (71%); white solid; mp 91.6°C; ν_{max}(KBr): 3257, 3108, 3063, 1605, 1526, 1434 cm^{-1}; δ_H: 6.76 (dd, 1H, J=7.7, 5.0 Hz, H-5′), 7.05 (br, 1H, N–H), 7.25 (dd, 1H, J=8.4, 4.6 Hz, H-5), 7.58 (dd, 1H, J=7.7, 1.6 Hz, H-4′), 8.12 (dd, 1H, J=5.0, 1.6 Hz, H-6′), 8.24 (ddd, 1H, J=8.4, 2.6, 1.5 Hz, H-6), 8.26 (dd, 1H, J=4.6, 1.5 Hz, H-4), 8.71 (d, 1H, J=2.6 Hz, H-2); δ_C:116.2 (C-5′), 116.5 (C-3′), 123.5 (C-5), 126.7 (C-4), 136.7 (C-3′), 137.1 (C-4′), 141.8 (C-2), 143.8 (C-6), 145.9 (C-6′), 151.0 (C-2′); LRMS (ES): 189, 179, 170, 130, 112, 94, 78, 68; HRMS (ESI) for $C_{10}H_9N_3Cl$ $[M+H]^+$ found: 206.0473, calcd: 206.0485; $C_{10}H_8N_3Cl$ calcd: C, 58.41; H, 3.92; N, 20.43, found: C, 58.46; H, 3.98; N, 20.31.

4.1.3. (4-Pyridyl)(3-chloro-2-pyridyl)amine (3c). eluent: CH_2Cl_2/MeOH (9/1); yield: 0.483 g (80%); white solid; mp 156.3°C; ν_{max}(KBr): 3252, 3162, 1603, 1514, 1424, 1335, 1211 cm^{-1}; δ_H: 6.82 (dd, 1H, J=7.7, 4.9 Hz, H-5′), 7.20 (br, 1H, N–H), 7.61–7.63 (m, 3H, H-3, H-4′), 8.20 (dd, 1H, J=4.9, 1.6 Hz, H-6′), 8.44 (d, 2H, J=6.0 Hz, H-2); δ_C: 112.9 (C-3), 117.1 (C-5′), 117.2 (C-3′), 137.3 (C-4′), 145.9 (C-6′), 146.8 (C-4), 150.3 (C-2′), 150.6 (C-2); LRMS (ES): 179, 170, 143, 116, 112, 79; HRMS (ESI) for $C_{10}H_9N_3Cl$ $[M+H]^+$ found: 206.0474, calcd: 206.0485; $C_{10}H_8N_3Cl$ calcd: C, 58.41; H, 3.92; N, 20.43, found: C, 58.50; H, 3.98; N, 20.30.

4.1.4. (2-Pyridyl)(6-chloro-2-pyridyl)amine (3d). eluent: CH_2Cl_2/MeOH (96/4); yield: 0.338 g (56%); white solid; mp 71.2°C; ν_{max}(KBr): 3258, 3166, 1591, 1529, 1463, 1437, 1159, 765 cm^{-1}; δ_H: 6.82 (dd, 1H, J=6.7, 1.4 Hz, H-5′), 6.84 (ddd, 1H, J=7.3, 4.2, 0.9 Hz, H-5), 7.42 (dd, 1H, J=8.4, 0.9 Hz, H-3), 7.52 (m, 2H, H-3′, H-4′), 7.61 (ddd, 1H, J=8.4, 7.3, 2.0 Hz, H-4), 7.91 (br, 1H, N–H), 8.23 (dd, 1H, J=4.2, 2.0 Hz, H-6); δ_C: 109.7 (C-3′), 112.2 (C-3), 115.9 (C-5′), 117.1 (C-5), 138.1 (C-4), 140.2 (C-4′), 147.9 (C-6), 149.2 (C-6′), 153.6 (C-2), 154.0 (C-2′); LRMS (ES): 170, 143, 112, 96, 78; HRMS (ESI) for $C_{10}H_9N_3Cl$ $[M+H]^+$ found: 206.0476, calcd: 206.0485; $C_{10}H_8N_3Cl$ calcd: C, 58.41; H, 3.92; N, 20.43, found: C, 58.26; H, 4.06; N, 20.53.

4.1.5. (3-Pyridyl)(5-chloro-2-pyridyl)amine (3e). eluent: CH_2Cl_2/MeOH (9/1); yield: 0.300 g (48%); white solid; mp 165.1°C; ν_{max}(KBr): 3297, 3186, 1644, 1580, 1485, 1423 cm^{-1}; δ_H: 6.72 (br, 1H, N–H), 6.73 (d, 1H, J= 8.8 Hz, H-3′), 7.26 (dd, 1H, J=8.2, 4.0 Hz, H-5), 7.48 (dd, 1H, J=8.8, 2.6 Hz, H-4′), 7.96 (dd, 1H, J=8.2, 1.2 Hz, H-4), 8.18 (d, 1H, J=2.6 Hz, H-6′) 8.28 (dd, 1H, J=4.0, 1.2 Hz, H-6), 8.58 (s, 1H, H-2); δ_C: 110.3 (C-3′), 123.0 (C-5′), 123.8 (C-5), 126.6 (C-4), 137.2 (C-3), 137.8 (C-4′), 141.8 (C-2), 143.9 (C-6), 146.8 (C-6′), 153.7 (C-2′); LRMS (ES): 189, 179, 170, 166, 144, 130, 112, 94, 78, 68; HRMS (ESI) for $C_{10}H_9N_3Cl$ $[M+H]^+$ found: 206.483, calcd: 206.485; $C_{10}H_8N_3Cl$ calcd: C, 58.41; H, 3.92; N, 20.43, found: C, 58.55; H, 3.87; N, 20.21.

4.1.6. (4-Pyridyl)(6-chloro-2-pyridyl)amine (3f). eluent: CH_2Cl_2/MeOH (9/1); yield: 0.399 g (64%); white solid; mp 180.5°C; ν_{max}(KBr): 3294, 3177, 1638, 1584, 1459, 1354, 1163, 780 cm^{-1}; δ_H (acetone-d_6): 6.92 (m, 2H, H-3′, H-5′), 7.67 (m, 3H, H-4′, H-3), 8.39 (d, 2H, J= 5.6 Hz, H-2), 9.02 (br, 1H, N–H); δ_C (acetone-d_6): 110.2 (C-3), 112.3 (C-3′), 115.3 (C-5′), 140.5 (C-4′), 147.6 (C-6′), 148.7 (C-4), 150.3 (C-2), 155.2 (C-2′); LRMS (ES): 179, 170, 143, 114, 112, 79; HRMS (ESI) for $C_{10}H_9N_3Cl$ $[M+H]^+$ found: 206.469, calcd: 206.0485; $C_{10}H_8N_3Cl$ calcd: C, 58.41; H, 3.92; N, 20.43, found: C, 58.25; H, 3.80; N, 20.60.

4.1.7. (3-Pyridyl)(6-chloro-2-pyridyl)amine (3g). eluent: CH_2Cl_2/MeOH (9/1); yield: 0.385 g (62%); white solid; mp 142.1°C; ν_{max}(KBr): 3294, 3179, 1639, 1530, 1481, 1429, 1346, 780, 698 cm^{-1}; δ_H: 6.68 (d, 1H, J=8.0 Hz, H-3′), 6.80 (d, 1H, J=7.6 Hz, H-5′), 6.94 (br, 1H, N–H), 7.28 (dd, 1H, J=8.4, 4.7 Hz, H-5), 7.45 (dd, 1H, J=8.0, 7.6 Hz, H-4′), 7.98 (ddd, 1H, J=8.4, 2.5, 1.1 Hz, H-4), 8.29 (dd, 1H, J=4.7, 1.1 Hz, H-6), 8.57 (d, 1H, J=2.5 Hz, H-2); δ_C: 107.0 (C-3′), 115.3 (C-5′), 123.9 (C-5), 127.1 (C-4), 136.9 (C-3), 140.2 (C-4′), 142.1 (C-2), 144.2 (C-6), 149.9 (C-6′), 155.4 (C-2′); LRMS (ES): 189, 170, 166, 143, 116, 112, 79; HRMS (ESI) for $C_{10}H_9N_3Cl$ $[M+H]^+$ found: 206.468, calcd: 206.0485; $C_{10}H_8N_3Cl$ calcd: C, 58.41; H, 3.92; N, 20.43, found: C, 58.72; H, 3.61; N, 20.28.

4.1.8. (2-Quinolyl)(3-chloro-2-pyridyl)amine (3h). eluent: CH_2Cl_2/MeOH (96/4); yield: 0.64 g (83%); white solid; mp 119.5°C; ν_{max}(KBr): 3400, 1592, 1502, 1430, 1331, 1028, 793 cm^{-1}; δ_H: 6.79 (dd, 1H, J=7.8, 4.9 Hz, H-5′), 7.36 (t, 1H, J=7.5, 7.5 Hz, H-6), 7.61 (dd, 1H, J=7.8, 1.1 Hz, H-4′), 7.62 (dd, 1H, J=8.0, 7.5 Hz, H-7), 7.72 (d, 1H, J=7.5 Hz, H-5), 7.83 (d, 1H, J=8.0 Hz, H-8), 8.05 (br, 1H, N–H), 8.09 (d, 1H, J=8.9 Hz, H-4), 8.18 (dd, 1H, J=4.9, 1.1 Hz, H-6′), 8.63 (d, 1H, J=8.9 Hz, H-3); δ_C: 114.1 (C-3), 116.9 (C-5′), 117.3 (C-3′), 124.3 (C-6), 125.8 (C-4a), 127.2 (C-8), 127.6 (C-5), 129.9 (C-7), 137.4 (C-4′), 137.9 (C-4), 145.7 (C-6′), 147.4 (C-8a), 150.3 (C-2′), 152.5 (C-2); LRMS (ES): 220, 146, 128; HRMS (ESI) for $C_{14}H_{10}ClN_3$ $[M+H]^+$ found: 256.0618, calcd: 256.0642; $C_{14}H_9ClN_3$ calcd: C, 65.76; H, 3.94; N, 16.43, found: C, 65.58; H, 3.89; N, 16.66.

4.1.9. (3-(6-Ethoxypyridazinyl))(3-chloro-2-pyridyl)amine (3i). eluent: Heptane/EtOAc (2.5/1); yield: 0.41 g (60%); white solid; mp 129.2°C; ν_{max}(KBr): 3404, 3061, 2979, 1595, 1519, 1436, 1403, 1294, 1031, 572 cm^{-1}; δ_H: 1.41 (t, 3H, *J*=7.1 Hz, $-CH_3$), 4.51 (q, 2H, *J*=7.1 Hz, $-CH_2-$), 6.79 (dd, 1H, *J*=7.6, 4.7 Hz, H-5′), 6.96 (d, 1H, *J*=9.7 Hz, H-5), 7.62 (dd, 1H, *J*=7.6, 1.6 Hz, H-4′), 7.88 (br, 1H, N–H), 8.10 (dd, 1H, *J*=4.7, 1.6 Hz, H-6′), 8.57 (d, 1H, *J*=9.7 Hz, H-4); δ_C: 14,75 ($-CH_3$), 63.09 ($-CH_2-$), 116.7 (C-5′), 117.0 (C-3′), 118.9 (C-5), 122.6 (C-4), 137.4 (C-4′), 145.6 (C-6′), 150.2 (C-2′), 152.6 (C-3), 162.2 (C-6); LRMS (ES): 224, 178, 166, 153, 143, 131, 127, 112, 100, 92, 80; HRMS (ESI) for $C_{11}H_{12}ClN_4O$ $[M+H]^+$ found: 251.0690, calcd: 251.0700; $C_{11}H_{11}ClN_4O$ calcd: C, 52.70; H, 4.42; N, 22.35, found: C, 52.65; H, 4.31; N, 22.51.

4.1.10. (2-(4,6-Dimethylpyrimidyl))(3-chloro-2-pyridyl)amine (3j). eluent: CH_2Cl_2/MeOH (9/1); yield: 0.637 g (90%); light yellow solid; mp 173.2°C; ν_{max}(KBr): 3186, 3025, 1606, 1424, 1339, 794 cm^{-1}; δ_H: 2.41 (s, 6H, $-CH_3$), 6.62 (s, 1H, H-5), 6.89 (dd, 1H, *J*=7.6, 4.7 Hz, H-5′), 7.63 (dd, 1H, *J*=7.6, 1.2 Hz, H-4′), 7.68 (br, 1H, N–H), 8.30 (dd, 1H, *J*=4.7, 1.2 Hz, H-6′); δ_C: 24,20 ($-CH_3$), 114.1 (C-5), 118.6 (C-5′), 120.1 (C-3′), 137.6 (C-4′), 146.6 (C-6′), 149.4 (C-2′), 158.9 (C-2), 168.2 (C-4, C-6); LRMS (ES): 199, 153, 107, 82; HRMS (ESI) for $C_{11}H_{12}ClN_4$ $[M+H]^+$ found: 235.0738, calcd: 235.0750; $C_{11}H_{11}ClN_4$ calcd: C, 56.30; H, 4.72; N, 23.87, found: C, 56.42; H, 4.78; N, 23.99.

4.1.11. (2-Pyrazyl)(3-chloro-2-pyridyl)amine (3k). eluent: CH_2Cl_2/MeOH (96/4); yield: 0.583 g (91%); white solid; mp 76.3°C; ν_{max}(KBr): 3401, 1596, 1534, 1421, 1033, 1006 cm^{-1}; δ_H: 6.86 (dd, 1H, *J*=7.8, 4.9 Hz, H-5′), 7.64 (dd, 1H, *J*=7.8, 1.6 Hz, H-4′), 7.72 (br, 1H, N–H), 8.21 (m, 3H, H-5, H-6, H-6′), 9.81 (d, 1H, *J*=1.2 Hz, H-3); δ_C: 117.0 (C-3′), 117.3 (C-5′), 136.2 (C-3), 137.4 (C-4′), 138.2 (C-5), 142.1 (C-6), 145.9 (C-6′), 149.4 (C-2), 149.7 (C-2′); LRMS (ES): 171, 153, 139, 118, 112, 79, 69, 52; HRMS (ESI) for $C_9H_8ClN_4$ $[M+H]^+$ found: 207.0435, calcd: 206.0437; $C_9H_7ClN_4$ calcd: C, 52.31; H, 3.41; N, 27.11, found: C, 52.25; H, 3.28; N, 27.06.

4.1.12. (3-Chloro-2-pyridyl)(4-nitrophenyl)amine (3l). eluent: CH_2Cl_2; yield: 0.593 g (80%); yellow solid; mp 145.2°C; ν_{max}(KBr): 3400, 1582, 1499, 1424, 1330, 1108, 840, 747 cm^{-1}; δ_H: 6.87 (dd, 1H, *J*=7.8, 4.7 Hz, H-5′), 7.38 (br, 1H, N–H), 7.65 (dd, 1H, *J*=7.8, 1.6 Hz, H-4′), 7.84 (d, 2H, *J*=9.1 Hz, H-2), 8.20 (d, 2H, *J*=9.1 Hz, H-3), 8.21 (dd, 1H, *J*=4.7, 1.6 Hz, H-6′); δ_C: 117.3 (C-3′), 117.5 (C-5′), 118.0 (C-4), 125.4 (C-3), 137.4 (C-4′), 142.0 (C-4), 145.9 (C-6′), 146.0 (C-1), 150.0 (C-2′); LRMS (ES): 203, 191, 169; HRMS (ESI) for $C_{11}H_9ClN_3O_2$ $[M+H]^+$ found: 250.0375, calcd: 250.0383; $C_{11}H_8ClN_3O_2$ calcd: C, 52.92; H, 3.23; N, 16.83, found: C, 52.75; H, 3.33; N, 16.95.

4.1.13. (3-Chloro-2-pyridyl)(4-methoxyphenyl)amine (3m). eluent: CH_2Cl_2; yield: 0.656 g (93%); yellow oil; ν_{max}(KBr): 3419, 3004, 2833, 1601, 1507, 1244, 1031, 823, 744 cm^{-1}; δ_H: 3.80 (s, 3H, $-OCH_3$), 6.64 (dd, 1H, *J*=7.8, 4.7 Hz, H-5′), 6.81 (br, 1H, N–H), 6.90 (d, 2H, *J*=8.9 Hz, H-3), 7.48 (d, 2H, *J*=8.9 Hz, H-2), 7.53 (dd, 1H, *J*=7.8, 1.6 Hz, H-4′), 8.07 (dd, 1H, *J*=4.7 Hz, 1.6, H-6′); δ_C: 55.7 ($-OCH_3$), 114.5 (C-3), 114.7 (C-5′), 115.8 (C-3′), 122.9 (C-2), 132.9 (C-1), 136.7 (C-4′), 146.1 (C-6′), 152.1 (C-2′), 156.1 (C-4); LRMS (ES): 203, 191, 185, 157, 123, 108; HRMS (ESI) for $C_{12}H_{12}ClN_2O$ $[M+H]^+$ found: 235.0617, calcd: 235.0638; $C_{12}H_{11}ClN_2O$ calcd: C, 61.41; H, 4.72; N, 11.94, found: C, 61.32; H, 4.69; N, 12.06.

4.1.14. (6-Chloro-2-pyridyl)(2-cyanophenyl)amine (3n). eluent: Heptane/EtOAc (2.5/1); yield: 0.27 g (40%); white solid; mp 154.8°C; ν_{max}(KBr): 3334, 2227, 1616, 1590, 1448, 1159, 942, 773, 741 cm^{-1}; δ_H: 6.77 (d, 1H, *J*=8.2 Hz, H-3′), 6.90 (d, 1H, *J*=7.6 Hz, H-5′) 6.99 (br, 1H, N–H), 7.05 (ddd, 1H, *J*=8.9, 7.5, 0.9 Hz, H-4), 7.55 (m, 3H, H-4′, H-5, H-6), 8.24 (d, 1H, *J*=7.5 Hz, H-3); δ_C: 101.6 (C-2), 108.9 (C-3′), 116.6 (C-5′), 117.1 (CN), 119.3 (C-3), 122.3 (C-4), 132.9 (C-6), 134.2 (C-5), 140.3 (C-4′), 143.0 (C-6′), 149.8 (C-2′), 154.0 (C-1); LRMS (ES): 194, 167, 140, 130, 112, 94, 76, 66; HRMS (ESI) for $C_{12}H_9ClN_3$ $[M+H]^+$ found: 230.0486, calcd: 230.0485; $C_{12}H_8ClN_3$ calcd: C, 62.76; H, 3.51; N, 18.30, found: C, 62.60; H, 3.36; N, 18.45.

4.1.15. (5-Chloro-2-pyridyl)(4-ethoxycarbonylphenyl)amine (3o). eluent: Heptane/EtOAc (2.5/1); yield: 0.532 g (64%); white solid; mp 171.8°C; ν_{max}(KBr): 3324, 3215, 1680, 1473, 1366, 1174, 1020, 825, 767 cm^{-1}; δ_H: 1.39 (tr, 3H, *J*=7.1 Hz, $-CH_3$), 4.35 (q, 2H, *J*=7.1 Hz, $-OCH_2-$), 6.81 (br, 1H, N–H), 6.82 (d, 1H, *J*=8.8 Hz, H-3′), 7.40 (d, 2H, *J*=8.6 Hz, H-2), 7.51 (dd, 1H, *J*=8.8, 2.6 Hz, H-4′), 7.99 (d, 2H, *J*=8.6 Hz, H-3), 8.20 (d, 1H, *J*=2.6 Hz, H-6′); δ_C: 14.5 ($-CH_3$) 60.8 ($-OCH_2-$), 111.0 (C-3′), 117.7 (C-2), 123.4 (C-5′), 124.1 (C-4), 131.3 (C-3), 137.7 (C-4′), 144.7 (C-1), 147.0 (C-6′), 153.1 (C-2′), 166.4 (C=O); LRMS (ES): 249, 231, 203, 169, 93; HRMS (ESI) for $C_{14}H_{14}ClN_2O_2$ $[M+H]^+$ found: 277.0763, calcd: 277.0744; $C_{14}H_{13}ClN_2O_2$ calcd: C, 60.77; H, 4.74; N, 10.12, found: C, 60.89; H, 4.59; N, 10.29.

4.2. Typical procedure for Pd-catalyzed aminations on 3,5-dichloropyridine.

A round bottom flask was flushed with nitrogen and charged with $Pd(OAc)_2$ (27.5 mg, 0.12 mmol, 4%), DCHPB (84 mg, 0.24 mmol, 8%) and dry dioxane (10 mL). The mixture was stirred under nitrogen for 10 minutes. In an other round bottom flask dichloropyridine (0.441 g, 3 mmol), amine (3.6 mmol, 1.2 equiv.) and K_2CO_3 (8.28 g, 60 mmol) were weighed. Then, the $Pd(OAc)_2$/DCHPB solution was added, and the flask was rinsed with an additional 17 mL dioxane. The resulting mixture was subsequently heated to reflux under N_2 with vigorous stirring until the starting dichloropyridine had disappeared as judged by TLC and DCI-MS. After cooling down, the solid material was filtered off and washed with 100 mL CH_2Cl_2. The solvent was evaporated and the resulting crude product was purified by flash column chromatography using the specified eluent.

4.2.1. (2-Pyridyl)(5-chloro-3-pyridyl)amine (3p). eluent: EtOAc; yield: 0.248 g (40%); white solid; mp 191.3°C;

ν_{max}(KBr): 3295, 3185, 2918, 1641, 1574, 1484, 1446, 1425, 1346, 1109, 774 cm^{-1}; δ_H (DMSO-d$_6$): 6.71 (ddd, 1H, J=7.3, 5.1, 0.9 Hz, H-5), 6.87 (dd, 1H, J=8.4, 0.9 Hz, H-3), 7.62 (ddd, 1H, J=8.4, 7.3, 2.0 Hz, H-4), 8.08 (d, 1H, J=2.2 Hz, H-2′), 8.41 (dd, 1H, J=5.1, 2.0 Hz, H-6), 8.54 (t, 1H, J=2.2, 2.2 Hz, H-4′), 8.61 (d, 1H, J=2.2 Hz, H-6′), 9.50 (br, 1H, N–H); δ_C (DMSO-d$_6$): 112.2 (C-3), 116.3 (C-5), 123.3 (C-4′), 131.2 (C-5′), 138.4 (C-4), 138.6 (C-6′), 139.3 (C-2′), 140.0 (C-3′), 147.8 (C-6), 155.6 (C-2); LRMS (ES): 170, 143, 116, 78; HRMS (ESI) for $C_{10}H_9N_3Cl$ $[M+H]^+$ found: 206.490, calcd: 206.0485; $C_{10}H_8N_3Cl$ calcd: C, 58.41; H, 3.92; N, 20.43, found: C, 58.26; H, 3.78; N, 20.55.

4.2.2. (5-Chloro-3-pyridyl)(4-ethoxycarbonylphenyl)-amine (3q). eluent: Heptane/EtOAc (1/1); yield: 0.462 g (56%); white solid; mp 166.2°C; ν_{max}(KBr): 3325, 1678, 1603, 1576, 1338, 1292, 1181, 1100, 831, 773 cm^{-1}; δ_H: 1.38 (tr, 3H, J=7.1 Hz, $-CH_3$), 4.36 (q, 2H, J=7.1 Hz, $-OCH_2-$), 6.36 (br, 1H, N–H), 7.06 (d, 2H, J=8.8 Hz, H-2), 7.51 (t, 1H, J=2.2, 2.2 Hz, H-4′), 7.98 (d, 2H, J=8.8 Hz, H-3), 8.19 (d, 1H, J=2.2 Hz, H-2′), 8.32 (d, 1H, J=2.2 Hz, H-6′); δ_C: 14.5 ($-CH_3$) 60.9 ($-OCH_2-$), 116.4 (C-2), 124.0 (C-4), 124.8 (C-4′), 131.8 (C-3), 132.4 (C-5′), 139.2 (C-6′), 142.0 (C-2′), 145.9 (C-1), 166.3 (C=O), (C-3′ was not observed); LRMS (ES): 249, 231, 214, 203, 169, 127; HRMS (ESI) for $C_{14}H_{14}ClN_2O_2$ $[M+H]^+$ found: 277.0753, calcd: 277.0744; $C_{14}H_{13}ClN_2O_2$ calcd: C, 60.77; H, 4.74; N, 10.12, found: C, 60.66; H, 4.56; N, 9.94.

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