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TOC

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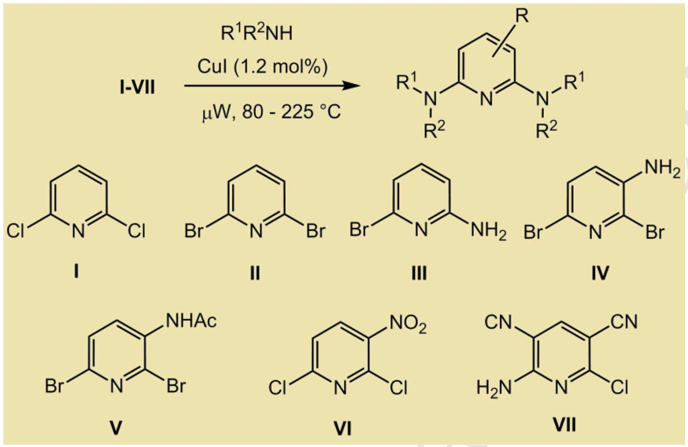

A practical synthesis of substituted 2,6-diaminopyridines *via* microwave-assisted copper-catalyzed amination of halopyridines

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Abstract

A microwave assisted copper-catalyzed amination protocol is reported utilizing a series of 2,6-dihalo- and 2-amino-6-halo pyridine precursors. Using this procedure, selective substitution of one or two halogens by aryl or alkylamines was achieved within 2-6 h with temperatures between 80-225^{o}C affording 2,6-diaminopyridines in good to excellent isolated yields. The reaction allows easy variation between educts and different N-substitutions. The target compounds are valuable precursors for the synthesis of *bis*-phosphorylated 2,6-diaminopyridines which are used as PNP pincer ligands in transition metal complexes.

Keywords: Aminations, 2,6-diaminopyridines, nucleophilic aromatic substitutions, heterocycles, microwave assisted reactions, copper catalyzed

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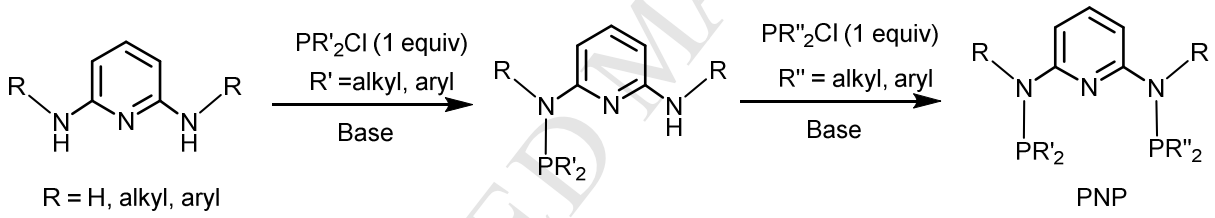
1. Introduction

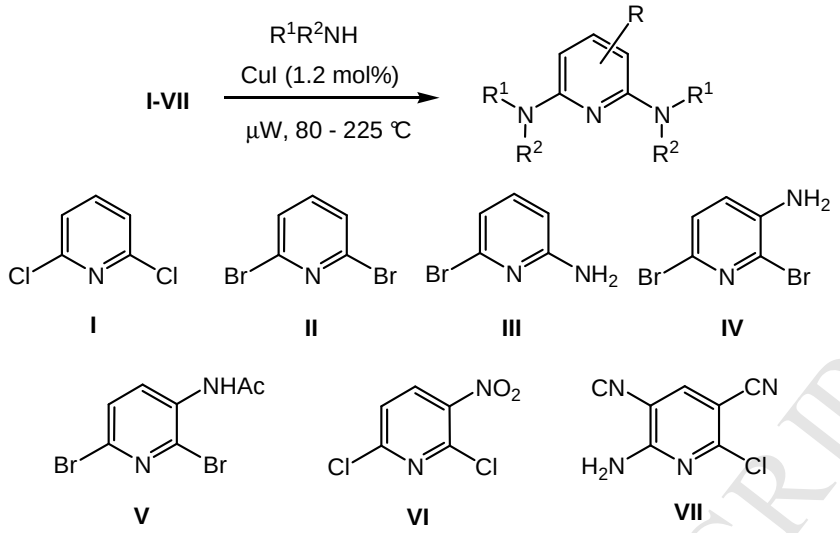
The 2,6-diaminopyridine molecule is a useful scaffold for the design of tridentate ligands in coordination and organometallic chemistry, agrochemicals, dyes, and pharmacologically potent building blocks.[1,2,3,4,5,6] The most frequently applied methods are nucleophilic substitutions often catalysed by copper, copper salts or proline[7,8,9] and Buchwald-Hartwig aminations.[10,11,12,13,14] Recently, Kempe *et al.* developed an Ir-catalyzed protocol for both symmetrically and non-symmetrically N,N'-dialkylated 2,6-diaminopyridines from 2,6-diaminopyridine and alcohols.[15] All methods basically yield the 2,6-diaminopyridines and it depends on the specific target which one performs better.

In recent years we have been focusing on the chemistry of transition metal complexes bearing PNP pincer ligands based on the 2,6-diaminopyridine scaffold.[16] In these PNP ligands the central pyridine ring contains -NRPR'$_2$ (R' = H, alkyl, R = alkyl, aryl) substituents in the two ortho positions. This methodology was first developed for the synthesis of N,N'-bis(diphenylphosphino)-2,6-diaminopyridine (PNP-Ph).[17] In these ligands the aromatic pyridine ring and the phosphine moieties are connected via NH, N-alkyl, or N-aryl linkers (Scheme 1). Accordingly, the development of a simple general method for the selective formation of N,N'-disubstituted 2,6-diamino pyridines is of great importance for the design of new PNP ligands. It has to be noted that most substituted 2,6-diaminopyridines are commercially not available.



Scheme 1

Here we describe a simple microwave assisted copper catalyzed amination protocol utilizing various 2,6-dihalo- and 2-amino-6-halo pyridine precursors **I**-**VII** as shown in Scheme 2. This simple procedure permits the selective substitution of one or two halogens by primary and secondary aryl and alkylamines in a relatively short time to afford a series of 2-amino- and/or 2,6-diaminopyridines in high isolated yields. This methodology constitutes a practical alternative to other methods.

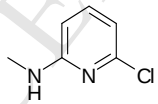
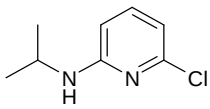
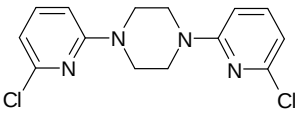
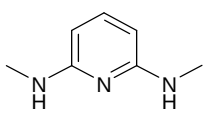


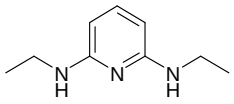
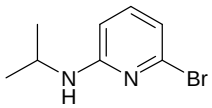
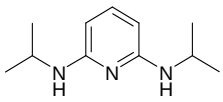
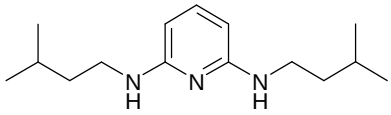
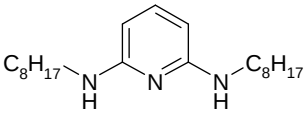
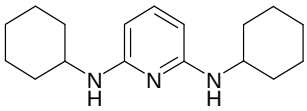
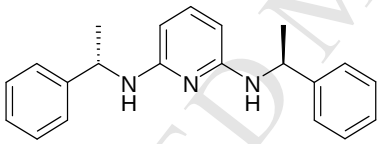
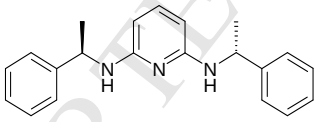
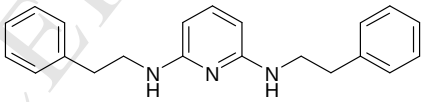
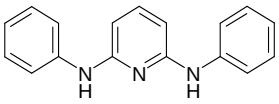
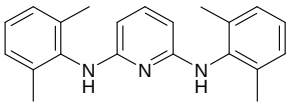
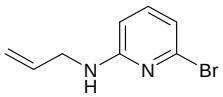
Scheme 2

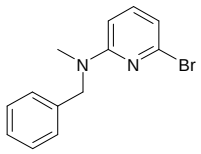
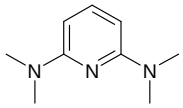
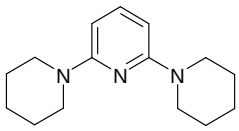
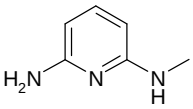
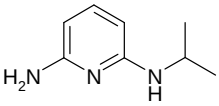
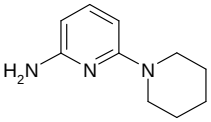
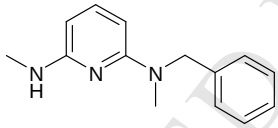
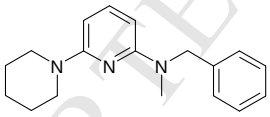
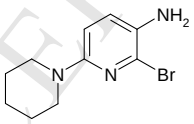
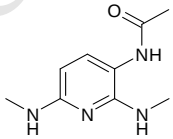
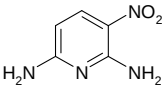
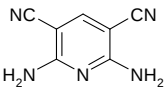
Results and discussion

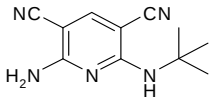
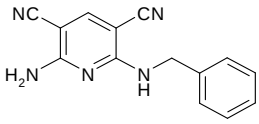
Treatment of compounds **I-VII** (4.2 mmol) with various primary and secondary amines in the presence of catalytic amounts of CuI (1.2 mol%) and traces of water (100μL) afforded selectively mono or disubstituted aminopyridines depending on the reaction conditions (Table 1). The addition of small amounts of water was necessary in order to achieve the required temperature under microwave conditions. None of these reactions required any additional organic solvents.

Table 1. Synthesis of N-substituted and N,N' disubstituted amino pyridines

Entry	Reactant	Product	t [h]	T [℃]	Yield [%]
1	**I**		2	180	94
2	**I**		4	180	82
3	**I**		4	180	78
4	**II**		2	180	93

5	**II**		2	180	90
6	**II**		3	150	83
7	**II**		5	180	63
8	**II**		4	200	75
9	**II**		4	200	73
10	**II**		5	200	61
11	**II**		4	210	85
12	**II**		4	210	84
13	**II**		3	210	88
14	**II**		6	225	43
15	**II**		6	225	19
16	**II**		3	160	82

17	**II**		30	140	92
18	**II**		4	180	78
19	**II**		4	190	78
20	**III**		5	160	83
21	**III**		8	150	62
22	**III**		5	150	95
23	**17**		5	160	83
24	**17**		5	150	96
25	**IV**		4	160	78
26	**V**		4	165	75
27	**VI**		3	135	93
28	**VII**		1.5	130	97

29	**VII**		1	80	69
30	**VII**		1	80	72

In general, the reactions of amines with 2,6-dichoropyridine (**I**) led to the exclusive formation of mono substituted products **1**-**3** in good to excellent isolated yields. It has to be noted, that even at higher temperatures the formation of disubstituted products was not observed. In the case of piperazine, both amine sites reacted with **I** and no mono substituted piperazine derivative was formed (entry 3). With 2,6-dibromopyridine (**II**), on the other hand, depending on the reaction temperature both mono and the desired disubstituted products were obtained in high yields (entries 4,5, 7 - 19) and showed a good substrate scope. Alkyl, aryl and benzylamines reacted readily to form compounds **4**-**15**. The use of chiral amines *R*- and *S*-1-phenylethane amine, allowed the preparation of chiral 2,6-diaminpyridnes (entries 11 and 12). By lowering the temperature also mono substituted aminopyridines could be obtained. This has been exemplarily shown for isopropylamine. Compound **6** could be obtained selectively (entry 6) which is an interesting building block for mixed diaminopyridines. In the case of anilines (entries 14 and 15) the reaction required a small amount of $Pd(PPh_3)_4$ as co-catalyst (0.2 mol%) and the yields were rather low. In this particular case, other established methods achieve much high yields.[18,19,20] Surprisingly, under the standard reaction conditions allyl amine and N,N-methylbenzylamine reacted only to yield the mono substituted compounds **16** and **17**. With benzylamine no identifiable products could be isolated. At higher reaction temperatures decomposition to intractable materials took place. The formation of compounds **18** and **19** demonstrates that also with secondary amines and **II** directly 2,6-diaminopyridines can be obtained. Precursors **III** and **17** were utilized as entries into mixed 2,6-diaminopyridines (entries 20-24). Finally we tested mono and dichloro and bromopyridines bearing both activating and deactivating groups (**IV**-**VII**) as synthetic entry into mixed 2,6-diaminopyridines (entries 25-30). Deactivating groups from **VI** and **VII** led to faster and better conversion under milder conditions. Moreover, the amination in the case of chlorides was faster and proceeded at much lower temperatures as compared to the bromide precursors (entries 27-30). Also the amination of **VI** and **VII** with aqueous ammonia to yield **27** and **28** worked very well with 93 and 97% isolated yields (entries 27 and 28). Compounds **25**-**30** are particularly interesting since the functional groups may allow cleavage or conversion into other functionalities. It has to be mentioned that all functionalized systems were less air sensitive than the diamines lacking additional substituents in the pyridine ring.

3. Conclusion

A microwave assisted copper-catalyzed amination protocol is reported utilizing a series of 2,6-dihalo- and 2-amino-6-halo pyridine precursors. With the exception of NH_3, methyl- and ethylamine, where

aqueous solutions were used, the reaction is basically solvent free and only traces of water were added to achieve the required temperatures under microwave conditions. This protocol generally afforded the corresponding products in good yields with easy purification steps. Using this procedure, selective substitution of one or two halogens by aryl- or alkylamines was achieved within 2-6 h at temperatures between 80-225^{o}C affording 2,6-diaminopyridines in good to excellent isolated yields. The target compounds are valuable precursors for the synthesis of *bis*-phosphorylated 2,6-diaminopyridines which are used as PNP pincer ligands in transition metal complexes.

4. Experimental section

4.1. General notes

Unless otherwise noted, chemicals were purchased from commercial suppliers and were used without further purification. Precursors **III**, **IV**, **V** and **VII** where synthesized according to the literature.[21,22,23] Microwave reactions were performed on a CEM Explorer PLS microwave unit. Column chromatography was performed on silica gel 60 from Merck. For thin layer chromatography (TLC) aluminum backed silica gel was used. Melting points were determined using a Kofler-type Leica Galen III micro hot stage microscope and are uncorrected. All samples were analyzed by LC-IT-TOF-MS in the positive ion detection mode with the recording of MS and MS/MS spectra. Room temperature ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on Bruker DXP 200 and AVANCE-250 spectrometers and were referenced internally to residual protio-solvent, and solvent resonances, respectively, and are reported relative to tetramethylsilane (δ = 0 ppm).

4.2. Typical experimental procedure for the synthesis of N-alkyl and N-aryl 2,6-diamino pyridines

Compounds **I-VII** (4.22 mmol), catalytic amounts of CuI (10 mg, 0.052 mmol) and water (100 μL) were treated with 6 equivs. of the respective amine and sealed in a 5 mL microwave vial. $Pd(PPh_3)_4$ (10 mg, 0.008 mmol) was added in the case of anilines. After the reaction was completed (see Table 1), 2 equivs of solid K_2CO_3 were added. The resulting product was obtained after filtration and washing with water as an analytically pure crystalline solid. Otherwise all volatiles were then evaporated and purified by flash column chromatography (**A**) or bulb-to-bulb distillation (**B**). In the case of methylamine and ethylamine the corresponding aqueous solution was used without extra water addition.

*4.2.1. (6-Chloropyridine-2-yl)-methyl-amine (**1**).* Prepared according to general procedure **A** with 3 equivs of methylamine. Product was obtained as white crystals. Mp: 59-60 ℃. ^{1}H NMR (DMSO-d_6) δ: 7.36 (dd, J = 8.3 Hz, J = 7.3 Hz, 1H, Py), 6.88 (bq, 1H, NH), 6.48 (d, J = 7.3, 1H, Py), 6.38 (d, J = 8.3 Hz, 1H, Py), 2.72 (d, 3H, CH_3). ^{13}C{^{1}H} NMR (DMSO-d_6) δ: 159.6 (Py), 148.5 (q, Py), 139.3 (Py), 109.6 (Py), 105.9 (Py), 27.7 (CH_3). HRMS (ESI): $[M+H]^+$, found 143.0374. $C_6H_7N_2Cl$ requires 143.0371.

*4.2.2. (6-Chloropyridine-2-yl)-isopropyl-amine (**2**).* Prepared according to general procedure **A** with 3 equivs of isopropylamine. Product was obtained as yellow oil. ^{1}H NMR (DMSO-d_6) δ: 7.36 (t, J = 7.8 Hz, 1H, Py), 6.70 (br, 1H, NH), 6.38 (d, J = 7.2 Hz, 1H, Py), 6.33 (d, J = 8.0 Hz, 1H, Py), 3.9 (sept, 1H, CH), 1.10 (d, J = 6.5 Hz, 6H, CH_3). ^{13}C{^{1}H} NMR (DMSO-d_6) δ: 159.6 (q, Py), 148.5 (q, Py), 139.3

(Py), 109.6 (Py), 105.9 (Py), 27.8 (CH_3). HRMS (ESI): $[M+H]^+$, found 171.0680. $C_8H_{11}N_2Cl$ requires 171.0684.

*4.2.3. 1,4-Bis-(6-chloropyridine-2-yl)-piperazine (**3**).* Prepared according to general procedure. The product precipitated as colorless crystals from the reaction mixture. Mp: 139-140 ℃. ^{1}H NMR (DMSO-d_6) δ: 7.6 (t, J = 7.8 Hz, 2H, Py), 6.8 (d, J = 8.5 Hz, 2H, Py), 6.68 (d, J = 7.3 Hz, 2H, Py), 3.60 (s, 8H, CH_2). $^{13}C\{^1H\}$ NMR (DMSO-d_6) δ: 158.6 (Py), 148.1 (q, Py), 140.6 (Py), 111.6 (Py), 105.4 (Py), 43.8 (CH_2). HRMS (ESI): $[M+H]^+$, found 309.0680. $C_{14}H_{14}N_4Cl_2$ requires 309.0668.[24]

*4.2.4. N,N'-Dimethyl-2,6-diaminopyridine (**4**).* Prepared according to general procedure **B**. Product was obtained as beige crystals. Mp: 60-63 ℃. ^{1}H NMR (DMSO-d_6) δ: 7.02 (t, J = 7.9 Hz, 1H, Py), 5.78 (br, J = 3.4 Hz, 2H, NH), 5.52 (d, J = 7.9 Hz, 2H, Py), 2.64 (d, J = 4.9 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (DMSO-d_6) δ: 159.1 (Py), 138.1 (Py), 93.8 (Py), 28.5 (CH_3). HRMS (ESI): $[M+H]^+$, found 138.1036. $C_7H_11N_3$ requires138.1026.[18]

*4.2.5. N,N'-Diethyl-2,6-diaminopyridine (**5**).* Prepared according to general procedure **B**. Product was obtained as yellow oil. ^{1}H NMR (DMSO-d_6) δ: 6.97 (t, J = 8.0 Hz, 1H, Py), 5.73 (t, J = 4.8 Hz, 2H, NH), 5.51 (d, J = 7.7 Hz, 2H, Py), 3.12 (m, 4H, CH_2), 1.06 (t, J = 7.1 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (DMSO-d_6) δ: 158.5 (Py), 138.0 (Py), 94.2 (Py), 35.9 (CH_2), 15.4 (CH_3). HRMS (ESI): $[M+H]^+$, found 166.1351. $C_9H_{15}N_3$ requires 166.1339.[25]

*4.2.6. (6-Bromopyridin-2-yl)-isopropyl-amine (**6**).* Prepared according to general procedure **A** with 3 equivs of methylamine. Product was obtained as yellow oil. ^{1}H NMR (DMSO-d_6) δ: 7.22 (t, J = 7.8 Hz, 1H, Py), 6.6 (s, 1H, NH), 6.6 (d, J = 7.3 Hz, 1H, Py), 6.4 (d, J = 8.0 Hz, 1H, Py), 3.9 (m, 1H, CH), 1.12 (d, J = 6.5 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (DMSO-d_6) δ: 158.4 (Py), 139.5 (Py), 139.0 (Py), 139.2 (Py), 113.3 (Py), 106.7 (Py), 41.8 (CH), 22.3 (CH_3). HRMS (ESI): $[M+H]^+$, found 215.0187. C $_8H_{11}N_3Br$ requires 215.0178.[26]

*4.2.7. N,N'-Diisopropyl-2,6-diaminopyridine (**7**).* Prepared according to general procedure **B**. Product was obtained as yellow oil. ^{1}H NMR ($CDCl_3$) δ: 7.19 (t, J = 8.0 Hz 1H, Py), 5.64 (d, J = 7.9 Hz, 2H, Py), 4.09 (s, br, 2H, NH), 3.73 (m, 2H, CH), 1.16 (d, J = 6.5 Hz, 12H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 157.6 (Py), 138.9 (Py), 94.4 (Py), 43.0 (CH), 23.1 (CH_3). HRMS (ESI): $[M+H]^+$, found 194.1650. $C_{11}H_{19}N_3$ requires 194.1652.

*4.2.8. N,N'-Bis-(3-methylbutyl)-2,6-diaminopyridine (**8**).* Prepared according to general procedure **A**. Product was obtained as yellow oil. ^{1}H NMR (DMSO-d_6) δ: 6.97 (t, J = 7.8 Hz, 1H, Py), 5.77 (t, J = 5.5 Hz, 2H, NH), 5.56 (d, J = 7.9 Hz, 2H, Py), 3.16 (q, 4H, CH_2), 1.63 (m, 2H, CH), 1.38 (q, 4H, CH_2), 0.87 (d, J = 6.6 Hz, 12H, CH_3). $^{13}C\{^1H\}$ NMR (DMSO-d_6) δ: 158.1 (Py), 137.3 (Py), 93.7 (Py), 38.9 (CH_2), 38.5 (CH_2), 25.4 (CH), 22.5 (CH_3). HRMS (ESI): $[M+H]^+$, found 250.2278. $C_{15}H_{27}N_3$ requires 250.2278.

*4.2.9. N,N'-Dioctyl-2,6-diaminopyridine (**9**).* Prepared according to general procedure **A**. Product was obtained as yellow oil. ^{1}H NMR (DMSO-d_6) δ: 6.95 (t, J= 7.9 Hz, 1H, Py), 5.80 (t, J = 5.2 Hz, 2H, NH), 5.52 (d, J = 7.7 Hz, 2H, Py), 3.12 (q, 4H, CH_2), 1.45 (quint, 4H, CH_2), 1.24 (m, 20H, CH_2), 0.85 (t, J = 6.3 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (DMSO-d_6) δ: 158.1 (Py), 137.3 (Py), 93.7 (Py), 40.8 (CH_2), 31.3

(CH_2), 29.4 (CH), 28.9 (CH), 28.8 (CH), 26.7 (CH), 22.1 (CH), 13.9 (CH_3). HRMS (ESI): $[M+H]^+$, found 334.3221. $C_{21}H_{39}N_3$ requires 334.3217.

*4.2.10. N,N'-Dicyclohexyl-2,6-diaminopyridine (**10**).* Prepared according to general procedure **A**. Product was obtained as yellow oil. ^{1}H NMR ($CDCl_3$) δ: 7.20 (t, J = 8.1 Hz, 1H, Py), 5.66 (d, J = 8.0 Hz, 2H, Py), 4.16 (d, J = 8.2 Hz, 2H, NH), 3.42 (quint, 2H, CH), 2.05 (m, 4H, CH_2), 1.76 (m, 6H, CH_2), 1.24 (m, 10H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ: 157.7 (Py), 139.1 (ArH), 94.3 (Py), 50.4 (CH), 33.6 (CH_2), 26.0 (CH_2), 25.1 (CH_2). HRMS (ESI): $[M+H]^+$, found 274.2274. $C_{17}H_{27}N_3$ requires 274.2278.

*4.2.11. N,N'-Bis-(S-1-phenylethyl)-2,6-diaminopyridine (**11**).* Prepared according to general procedure **A** with 4.2 equivs of amine. Product was obtained as colorless oil. ^{1}H NMR (DMSO-d_6) δ: 7.38-7.12 (m, 10H, Ph), 6.92 (t, J = 7.3 Hz, 1H, Py), 6.33 (d, J = 7.9 Hz, 2H, NH), 5.56 (d, J = 7.9 Hz, 2H, Ph), 4.87 (quint, 2H, CH), 1.27 (d, J = 6.8 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (DMSO-d_6) δ: 157.0 (Py), 146.9 (Ph), 137.3 (Py), 128.0 (Ph), 126.0 (Ph), 126.0 (Ph), 94.8 (Py), 49.6 (CH), 23.6 (CH_3). HRMS (ESI): $[M+H]^+$, found 318.1956. $C_{21}H_{23}N_3$ requires 318.1965.

*4.2.12. N,N'-Bis-((R)-1-phenylethyl)-2,6-diaminopyridine (**12**).* Prepared according to general procedure **A** with 4.2 equivs of amine. Product was obtained as colorless oil. ^{1}H NMR (DMSO-d_6) δ: 7.38-7.13 (m, 10H, Ph), 6.91 (t, J = 7.3 Hz, 1H, Py), 6.33 (d, J = 7.9 Hz, 2H, NH), 5.57 (d, J = 7.9 Hz, 2H, Py), 4.83 (m, 2H, CH), 1.27 (d, J = 6.8 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (DMSO-d_6) δ: 157.0 (Py), 146.9 (q, Ph), 137.3 (Py), 128.0 (Ph), 126.0 (Ph), 126.0 (Ph), 94.8 (Py), 49.6 (CH), 23.6 (CH_3). HRMS (ESI): $[M+H]^+$, found 318.1956. $C_{21}H_{23}N_3$ requires 318.1965.

*4.2.13. N,N'-Diphenethylpyridine-2,6-diamine (**13**).* Prepared according to general procedure **A** with 4.2 equivs of amine. Product was obtained as white solid. Mp: 90-91 ℃. ^{1}H NMR (DMSO-d_6) δ: 7.22 (m, 10H, ArH), 7.03 (t, J = 8.0 Hz, 1H, ArH), 6.06 (t, J = 5.0 Hz, 2H, NH), 5.62 (d, J = 7.8 Hz, 2H, ArH), 3.38 (q, 4H, CH_2), 2.82 (t, J= 7.3 Hz, 4H, CH_2). $^{13}C\{^1H\}$ NMR (DMSO-d_6) δ: 157.9 (Py), 140.1 (Ph), 137.6 (Py), 128.6 (Ph), 128.2 (Ph), 125.8 (Ph), 94.3 (Py), 42.8 (CH_2), 35.7 (CH_2). HRMS (ESI): $[M+H]^+$, found 318.1957. $C_{21}H_{23}N_3$ requires 318.1965.

*4.2.14. N,N'-Diphenyl-pyridine-2,6-diamine (**14**).* Prepared according to general procedure **A** with $Pd(PPh_3)_4$ (10 mg). Product was obtained as fawn crystals. Mp: 102-103 ℃. ^{1}H NMR (DMSO-d_6) δ: 8.78 (s, 2H, NH), 7.59 (d, 4H, Ph), 7.36 (t, J = 8.2 Hz, 1H, Py), 7.22 (m, 4H, Ph), 6.87 (t, 2H, Ph), 6.22 (d, 2H, Py). $^{13}C\{^1H\}$ NMR (DMSO-d_6) δ: 154.4 (Py), 141.7 (Ph), 138.4 (Py), 128.4 (Ph), 120.2 (Ph), 118.6 (Ph), 99.7 (Py). HRMS (ESI): $[M+H]^+$, found 262.1327. $C_{17}H_{15}N_3$ requires 262.1339.[19,20]

*4.2.15. N,N'-Bis-(2,6-dimethylphenyl)-pyridine-2,6-diamine (**15**).* Prepared according to general procedure **A** with $Pd(PPh_3)_4$ (10 mg). Product was obtained as fawn crystals. crystals. Mp: 183-185 ℃. ^{1}H NMR (DMSO-d_6) δ: 7.44 (s, 2H, NH), 7.08-7.03 (m, 7H, Ph, Py), 5.35 (d, J = 7.9 Hz, 2H, Py), 2.15 (s, 12H, CH_3). $^{13}C\{^1H\}$ NMR (DMSO-d_6) δ: 157.0 (Py), 138.5 (Py), 137.9 (Ph), 136.0 (Ph), 127.9 (Ph), 125.4 (Ph), 94.3 (Py), 18.3 (CH_3). HRMS (ESI): $[M+H]^+$, found 318.1955. $C_{21}H_{23}N_3$ requires 318.1965.[20]

*4.2.16. Allyl-(6-bromopyridine-2-yl)-amine (**16**).* Prepared according to general procedure **A**. Product was obtained as beige crystals. Mp: < 30 ℃. ^{1}H NMR (DMSO-d_6) δ: 7.27 (t, J= 7.45 Hz, 1H, Py), 7.10 (t, br, 1H, NH), 6.62 (d, J = 7.2 Hz, 1H, Py), 6.42 (d, J= 7.8 Hz, 1H, Py), 5.97-5.78 (m, 1H, C*H*=CH_2), 5.23-5.03 (m, 2H, CH=CH_2), 3.85-3.79 (m, 2H, CH_2). ^{13}C{^{1}H} NMR (DMSO-d_6) δ: 158.9 (Py), 139.4 (Py), 139.4 (Py), 135.4 (*C*H=CH_2), 115.2 (CH=CH_2), 43.0 (CH_2). HRMS (ESI): $[M+H]^+$, found 213.0012. $C_8H_9N_2Br$ requires 213.0022.[27]

*4.2.17. Benzyl-(6-bromopyridine-2-yl)-methyl-amine (**17**).* Prepared according to general procedure with 2.2 equivs. of amine. Product was obtained as beige crystals. Mp: 62.5-63.5 ℃. ^{1}H NMR (DMSO-d_6) δ: 7.27 (m, 6H, ArH), 6.74 (d, J = 7.4 Hz, 1H, ArH), 6.61 (d, J = 8.5 Hz, 1H, ArH), 4.71 (s, 2H, CH_2), 3.00 (s, 3H, CH_3). ^{13}C{^{1}H} NMR (DMSO-d_6) δ: 158.4 (Py), 140.1 (Py), 139.2 (Py), 138.1 (Ph), 128.5 (Ph), 127.0 (Ph), 126.9 (Ph), 114.2 (Py), 104.5 (Py), 52.6 (CH_2), 36.0 (CH_2). HRMS (ESI): $[M+H]^+$, found 277.0330. $C_{13}H_{13}N_2Br$ requires 277.0335.[28]

*4.2.18. N,N,N',N'-Tetramethylpyridine-2,6-diamine (**18**).* Prepared according to general procedure **B**. Product was obtained as colorless crystals. Mp: 32-33 ℃. ^{1}H NMR (DMSO-d_6) δ: 7.23 (t, J = 8.0 Hz, 1H, Py), 5.83 (d, J = 8.2 Hz, 2H, Py), 2.94 (s, 12H, CH_3). ^{13}C{^{1}H} NMR (DMSO-d_6) δ: 157.9 (Py), 138.4 (Py), 92.9 (Py), 37.3 (CH_3). HRMS (ESI): $[M+H]^+$, found 138.1035. $C_7H_{11}N_3$ requires 138.1026.[29]

*4.2.19. 2,6-Di-piperidine-1-yl-pyridine (**19**).* Prepared according to general procedure **A**. Product was obtained as colorless oil. ^{1}H NMR (DMSO-d_6) δ: 7.22 (t, J = 8.2 Hz, 1H, Py), 5.95 (d, J = 8.2 Hz, 2H, Py), 3.40 (s, 8H, CH_2), 1.52 (s, 12H; CH_2). ^{13}C{^{1}H} NMR (DMSO-d_6) δ: 157.8 (Py), 138.7 (Py), 94.7 (Py), 45.5 (CH_2), 25.0 (CH_2), 24.4 (CH_2). HRMS (ESI): $[M+H]^+$, found 246.1958. $C_{15}H_{23}N_3$ requires 246.1965.[30]

*4.2.20. N-Methyl-2,6-diaminopyridine (**20**).* Prepared according to general procedure **A**. Product was obtained as colorless crystals. Mp: 92-93 ℃. ^{1}H NMR (DMSO-d_6) δ: 7.02 (t, J = 7.7 Hz, 1H, Py), 5.79 (pd, 1H), 5.57 (t, J = 8.4 2H), 5.33 (s, 2H), 2.65 (d, J = 4.8 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (DMSO-d_6) δ: 158.9 (Py), 158.6 (Py), 137.9 (Py), 94.6 (Py), 93.8 (Py), 28.1 (CH_3). HRMS (ESI): $[M+H]^+$, found 124.0875. $C_6H_9N_3$ requires 124.0869.

*4.2.21. N-Isopropylpyridine-2,6-diamine (**21**).* Prepared according to general procedure **A**. Product was obtained as yellow oil. ^{1}H NMR (DMSO-d_6) δ: 6.98 (t, J = 7.7 Hz, 1H, Py), 5.58-5.54 (m, 3H, Py, NH), 5.27 (s, 2H, NH_2), 3.83 (m, 1H, CH), 1.07 (d, J = 6.3 Hz, 6H, CH_3). ^{13}C{^{1}H} NMR (DMSO-d_6) δ: 158.6 (Py), 157.6 (Py), 137.8 (Py), 94.9 (Py), 94.3 (Py), 41.3 (CH), 22.8 (CH_3). HRMS (ESI): $[M+H]^+$, found 152.1183. $C_8H_{13}N_3$ requires 152.1182.

*4.2.22. N-(piperidin-1-yl)-pyridine-2,6-diamine (**22**).* Prepared according to general procedure **A**. Product was obtained as colorless oil. ^{1}H NMR (DMSO-d_6) δ: 7.11 (t, J = 7.9 Hz, 1H, Py), 5.84 (d, J = 8.2 Hz, 1H, Py), 5.70 (d, J = 7.9 Hz, 1H, Py), 5.42 (s, 2H, NH_2), 3.39-3.34 (m, 4H, CH_2), 1.51 (s, 6H, CH_2). ^{13}C{^{1}H} NMR (DMSO-d_6) δ: 158.4 (Py), 158.2 (Py), 138.4 (Py), 96.0 (Py), 93.9 (Py), 45.4 (CH_2), 25.0 (CH_2), 24.4 (CH_2). HRMS (ESI): $[M+H]^+$, found 178.1338. $C_{10}H_{15}N_3$ requires 178.1339.

*4.2.23. N-Benzyl-N,N'-dimethyl-pyridine-2,6-diamine (**23**).* Prepared according to general procedure **A**. Product was obtained as yellow oil. ^{1}H NMR (DMSO-d_6) δ: 7.28-7.10 (m, 6H, Ph, Py), 5.99 (q, 1H, NH), 5.70 (t, J = 7.4 Hz, 2H, Py), 4.73 (s, 2H, CH_2), 2.91 (s, 3H, CH_3), 2.69 (d, J = 4.9 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (DMSO-d_6) δ: 158.3 (Py), 157.5 (Py), 139.7 (Ph), 138.1 (Py), 128.2 (Ph), 127.1 (Ph), 126.5 (Ph), 94.5 (Py), 92.0 (Py), 51.9 (CH_2), 35.6 (CH_3), 27.9 (CH_3). HRMS (ESI): $[M+H]^+$, found 228.1485. $C_{14}H_{17}N_3$ requires 228.1495.

*4.2.24. Benzyl-methyl-(6-piperidine-1-yl-pyridin-2-yl)-amine (**24**).* Prepared according to general procedure **A**. Product was obtained as yellow oil. ^{1}H NMR (DMSO-d_6) δ: 7.31-7.18 (m, 6H, Ph, Py), 5.97 (d, J = 7.3 Hz, 2H, Py), 5.83 (d, J = 7.3 Hz, 2H, Py), 4.70 (s, 2H, CH_2), 3.42-3.39 (m, 4H, CH_2), 2.93 (s, 3H, CH_3), 1.50 (s, 6H, CH_2). ^{13}C{^{1}H} NMR (DMSO-d_6) δ: 158.3 (Py), 157.5 (Py), 139.7 (Ph), 138.1 (Py), 128.2 (Ph), 127.1 (Ph), 126.5 (Ph), 94.5 (Py), 92.0 (Py), 51.9 (CH_2), 35.6 (CH_3), 27.9 (CH_3). HRMS (ESI): $[M+H]^+$, found 282.1954. $C_{18}H_{23}N_3$ requires 282.1965.

*4.2.25. 2-Bromo-N'6'-(piperidine-1-yl)-pyridine-3,6-diamine (**25**).* Prepared according to general procedure **A**. Product was obtained as colorless oil. ^{1}H NMR (DMSO-d_6) δ: 5.84 (d, J = 8.2 Hz, 1H, Py), 5.70 (d, J = 7.9 Hz, 1H, Py), 5.42 (s, 2H, NH_2), 3.39-3.34 (m, 4H, CH_2), 1.51 (s, 6H, CH_2). ^{13}C{^{1}H} NMR (DMSO-d_6) δ: 158.4 (Py), 158.2 (Py), 138.43 (Py), 96.0 (Py), 93.9 (Py), 45.4 (CH_2), 25.0 (CH_2), 24.4 (CH_2). HRMS (ESI): $[M-H]^+$, found 254.0285. $C_{10}H_{14}BrN_3$ requires 254.0287.

*4.2.26. N-(2,6-Bis-methylaminopyridine-3-yl)-acetamide (**26**).* Prepared according to general procedure **A**. Product was obtained as pink solid. ^{1}H NMR (DMSO-d_6) δ: 7.52 (d, J = 8.2 Hz, 1H, Py), 6.41 (br, 1H, NH), 6.28 (d, J = 8.2 Hz, 1H, Py), 3.58 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 2.42 (s, 3H, CH_3). ^{13}C{^{1}H} NMR (DMSO-d_6) δ: 156.2, 147.4, 127.1, 125.1, 103.3, 82.1, 28.2, 27.6, 13.5. HRMS (ESI): $[M+H]^+$, found fragment without – H_2O 177.1133. $C_9H_{14}N_4O$ requires 194.1168.

*4.2.27. 3-Nitropyridine-2,6-diamine (**27**).* Prepared according to general procedure with an addition of DMF (2 mL). The product was diluted with water, filtrated and recrystallized and obtained as yellow solid. Mp: 227-228 ℃. ^{1}H NMR (DMSO-d_6) δ: 7.97(d, 1H, J = 9.2 Hz, Py), 7.64 (s, br, 2H, NH_2), 7.25 (s, 2H, NH_2), 5.92 (d, J = 9.2 Hz). ^{13}C{^{1}H} NMR (DMSO-d_6) δ: 162.5 (Py), 155.9 (Py), 135.3 (Py), 117.7 (Py) 101.6 (Py). HRMS (ESI): $[M+H]^+$, found 155.0562. $C_5H_6N_4O_2$ requires 155.0564.[31]

*4.2.28. 2,6-Diaminopyridine-3,5-dicarbonitrile (**28**).* Prepared according to general procedure with 3 equivs of concentrated NH_3 and *i*PrOH (7 mL). The product was filtrated and washed with *i*PrOH and Et_2O and obtained an off-white solid. Mp: > 265 ℃. ^{1}H NMR (DMSO-d_6) δ: 8.01 (s, 1H, Py), 7.19 (s, 4H, NH_2). ^{13}C{^{1}H} NMR (DMSO-d_6) δ: 160.7 (q, Py), 148.1 (Py), 116.8 (Py), 78.7 (CH_3). HRMS (ESI): $[M+H]^+$, found 160.0619. $C_7H_5N_5$ requires 160.0618.[30]

*4.2.29. 2-Amino-6-tert-butylamino-pyridine-3,5-dicarbonitrile (**29**).* Prepared according to general procedure with 3 equivs of amine and *i*PrOH (7 mL). The product was filtrated and washed with *i*PrOH and Et_2O and obtained an off-white solid. Mp: 154-155 ℃. ^{1}H NMR (DMSO-d_6) δ: 8.02 (s, 2H, NH_2), 7.31 (s, 1H, NH), 5.98 (s, 1H, Py), 1.37 (s, 6H, CH_3), 1.21 (s, 3H, CH_3). ^{13}C{^{1}H} NMR (DMSO-d_6) δ: 160.5 (Py), 158.9 (Py), 148.1 (Py), 117.4 (2CN), 80.9 (Py), 78.1 (Py), 52.9 (*C*(CH_3)$_3$), 29.0 (CH_3), 27.6 (CH_3). HRMS (ESI): $[M+Na]^+$, found 238.1064. $C_{11}H_{13}N_5$ requires 238.1063.

*4.2.30. 2-Amino-6-benzylaminopyridine-3,5-dicarbonitrile (**30**).* Prepared according to general procedure with 3 equivs of concentrated NH_3 and *i*PrOH (7 mL). The product was filtrated and washed with *i*PrOH and Et_2O and obtained as an off-white solid. Mp: 260.5-262 ℃. ^{1}H NMR (DMSO-d_6) δ: 8.00 (s, 2H, NH_2), 7.24 (m, 7H, NH, ArH), 4.50 (d, 2H, CH_2). $^{13}C\{^1H\}$ NMR (DMSO-d_6) δ: 161.1 (Ar), 159.1 (Ar), 148.1 (Py), 139.9 (Ph), 128.6 (Ph), 128.1 (Ph), 127.2 (Ph), 117.3 (CN), 117.2 (CN), 79.8 (Py), 78.6 (Py), 44.0 (CH_2). HRMS (ESI): $[M+H]^+$, found 250.1081. $C_{14}H_{11}N_5$ requires 250.1087.

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Supplementary data

^{1}H and ^{13}C{^{1}H} NMR spectra of compounds **1** - **30**. Supplementary data associated with this article can be found at http://xxxxxxxxxxxxxxxxx.

References

1 (a) Montgomary, J. A.; Secrist, J. A. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R.; Rees, C. W.; Potts, K. T., Eds.; Pergamon: Oxford, **1984**; Vol. 5, 607; (b) Katrizky, A. R.; Qiu, G.; Long, Q.-H.; He, H.-Y.; Steel, P. J. *J. Org. Chem*. **2000**, *65*, 9201.

2 Lin, R.; Lu, Y.; Wetter, S. K.; Connolly, P. J.; Turchi, I. J.; Murray, W. V.; Emanuel, S. L.; Gruninger, R. H.; Fuentes-Pesquera, A. R.; Adams, M.; Pandey, N.; Moreno-Mazza, S.; Middleton, S. A.; Jolliffe, L. K. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 2221.

3 (a) Sathyamoorthy, G.; Soong, M. L.; Ross, T. W.; Boyer, J. H. *Heteroatom. Chem*. **1993**, *4*, 603; (b) Araki, K.; Mutai, T.; Shigemitsu, Y.; Yamada, M.; Nakajima, T.; Kuroda, S.; Shimao, I. *J. Chem. Soc., Perkin Trans*. 2 **1996**, 613.

4 Kusakabe, K.-I.; Ide, N.; Daigo, Y.; Itoh, T.; Higashino, K.; Okano, Y.; Tadano, G.; Tachibana, Y.; Y. Sato, Y.; Inoue, M.; Wada, T.; Iguchi, M.; Kanazawa, T.; Ishioka, Y.; Dohi, K.; Tagashira,S.; Kido, Y.; Sakamoto, S.; Yasuo, K.; Maeda, M.; Yamamoto, T.; Higaki, M.; Endoh,T.; Ueda, K.; Shiota, T.; Murai, H.; Nakamura, Y. *ACS Med. Chem. Lett.* **2012**, *3*, 560.

5 Lechat, P.; Tesleff, S.; Bownan, W. C. *Aminopyridines and Similarly Acting Drugs*; Pergamon: Oxford, **1982**.

6 Lawrence, S. A. in Amines: Synthesis, Properties and Applications, Cambridge University, Cambridge, **2004**.

7 Bolliger, J. L.; Frech, L.; Christian, M. *Tetrahedron* **2009**, *65*, 1180.

8 Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785.

9 Eicher, T.; Hauptmann, S. The Chemistry of Heterocycles; Wiley-VCH: Weinheim, **2003**; 269.

10 (a) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901; (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc*. **1994**, *116*, 5969.

11 (a) Marcoux, J.-F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568; (b) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617; (c) Jaime-Figueroa, S.; Liu, Y.; Muchowski, J. M.; Putman, D. G. *Tetrahedron Lett.* **1998**, *39*, 1313; (d) Marion, N.; Ecarnot, E. C.; Navarro, O.; Amoroso, D.; Bell, A.; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 3816; (e) Lorimer, A. V.; O'Connor, P. D.; Brimble, M. A. *Synthesis* **2008**, 2764.

12 Koley, M.; Schnürch, M.; Mihovilovic, M. D. *Tetrahedron*, **2011**, *67*, 4169.

13 Withbroe, G. J.; Singer, R. A.; Sieser, J. E. *Org. Process Res. Dev.* **2008**, *12*, 480.

14 Basu, B.; Jha, S.; Mridha, N. K.; Bhuiyan, Md. M. H. *Tetrahedron Letters* **2002**, *43*, 7967.

15 Blank, B.; Michlik, S.; Kempe, R. *Chem. Eur. J.* **2009**, *15*, 3790.

16 (a) Benito-Garagorri, D.; Becker, E.; Wiedermann, J.; Lackner, W.; Pollak, M.; Mereiter, K.; Kisala, J.; Kirchner, K. *Organometallics* **2006**, *25*, 1900. (b) Glatz, M.; Bichler, B.; Mastalir, M.; Stöger, B.; Mereiter, K.; Weil, M.; Pittenauer, E.; Allmaier, G.; Veiros, L. F.; Kirchner, K. *Dalton Trans.* **2015***, 44*, 281. (c) Glatz, M.; Holzhacker, C.; Bichler, B.; Mastalir, M.; Stöger, B.; Mereiter, K.; Weil, M., Veiros, L. F.; Mösch-Zanetti, N. C.; Kirchner, K. *Eur. J. Inorg. Chem.* **2015***,* submitted for publication.

17 (a) Schirmer, W.; Flörke, U.; Haupt, H.-J. *Z. Anorg. Allg. Chem.* **1987**, *545*, 83. (b) Schirmer, W.; Flörke, U.; Haupt, H.-J. *Z. Anorg. Allg. Chem.* **1989**, *574*, 239.

18 (a) Okamoto, I.; Terashima, M.; Masu, H.; Nabeta, M.; Ono, K.; Morita, N.; Katagiri, K.; Azumaya, I.; Tamura, O. *Tetrahedron* **2011**, *67*, 8536. (b) Cotton, A. F.; Chao, H.; Murillo, C. A.; Wang, Q. *Dalton Trans.*, **2006**, 5416.

19 (a) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240. (b) Cotton, F. A.; Daniels, L. M.; Lei, P.; Murillo, C. A.; Wang, X. *Inorg. Chem.* **2001**, *40*, 2778.

20 Rad'kov, V.; Dorcet, V.; Carpentier, J.-F.; Trifonov, A.; Kirillov, E. *Organometallics* **2013**, *32*, 1517.

21 (a) Hammond, P. R.; Fletcher, A. N.; Bliss, D. E.; Henry, R. A.; Atkins, R. L.; Moore, D. W. *App. Phys.* **1976**, *9*, 67. (b) Bolliger, J. L.; Frech, Christian M. *Tetrahedron* **2009**, *65*, 1180.

22 Madjumar, K. C.; Mondal, S. *Tetrahedron Lett.* **2007**, *48*, 6951.

23 Graffner-Nordberg, M.; Kolmodin, K.; Åqvist, J.; Queener, S. F; Hallberg , A. *J. Med. Chem.* **2001**, *44*, 2391.

24 Louërat, F.; Gros, P. C.; Fort, Y. *Synlett* **2006**, 1379.

25 Gallego, D.; Inoue, S.; Blom, B.; Driess, M. *Organometallics* **2014**, *33*, 6885.

26 Faust, A.; Wolff, O.; Waldvogel, S. R. *Synthesis* **2009**, 155.

27 Fa, S.-X.; Wang, L.-X.; Wang, D.-X.; Zhao, L.; Wang, M.-X. *J. Org. Chem.* **2014**, *79*, 3559.

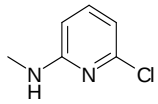
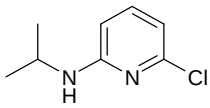
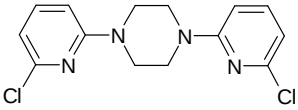
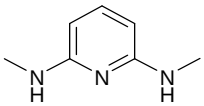
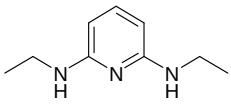
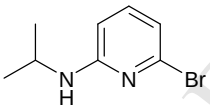
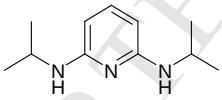
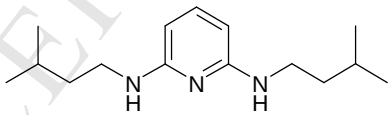
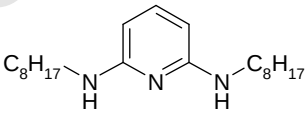
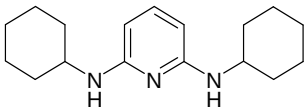
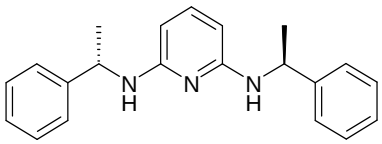
28 Bolliger, J. L.; Oberholzer, M.; Frech, C. M. *Adv. Synth. Catal.* **2011**, *353*, 945.

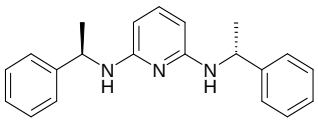
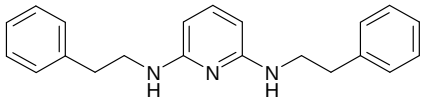
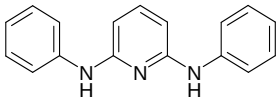
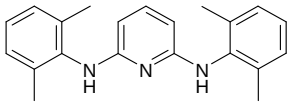
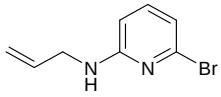
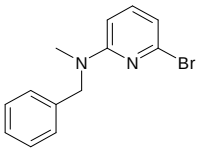
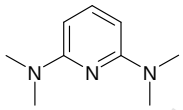
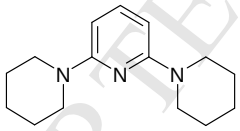
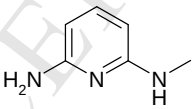
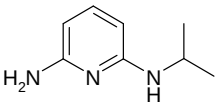
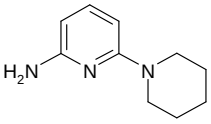
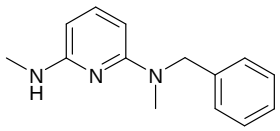
29 Samadi, D. S.; Chioua, M.; do Carmo Carreiras, M.; Marco-Contelles, J. *Synth. Commun.* **2011**, *41*, 2859.

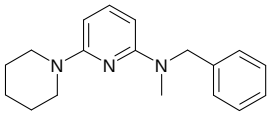
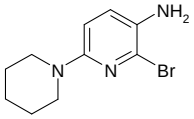
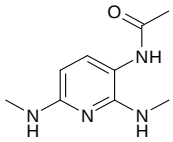
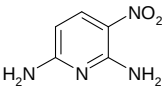
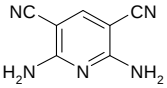
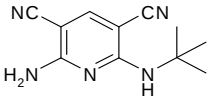
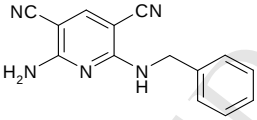
30 Prabhu, R. N.; Ramesh, R. Tetrahedron Lett. **2013**, 54, 1120.

31 Hollins, R. A.; Merwin, L. H.; Nissan, R. A.; Wilson, W. S.; Gilardi, R. *J. Heterocyclic Chem.* **1996**, *33*, 895.

Table 1. Synthesis of N-substituted and N,N' disubstituted amino pyridines

Entry	Reactant	Product	t [h]	T [℃]	Yield [%]
1	**I**		2	180	94
2	**I**		4	180	82
3	**I**		4	180	78
4	**II**		2	180	93
5	**II**		2	180	90
6	**II**		3	150	83
7	**II**		5	180	63
8	**II**		4	200	75
9	**II**		4	200	73
10	**II**		5	200	61
11	**II**		4	210	85

12	**II**		4	210	84
13	**II**		3	210	88
14	**II**		6	225	43
15	**II**		6	225	19
16	**II**		3	160	82
17	**II**		30	140	92
18	**II**		4	180	78
19	**II**		4	190	78
20	**III**		5	160	83
21	**III**		8	150	62
22	**III**		5	150	95
23	**17**		5	160	83

24	**17**		5	150	96
25	**IV**		4	160	78
26	**V**		4	165	75
27	**VI**		3	135	93
28	**VII**		1.5	130	97
29	**VII**		1	80	69
30	**VII**		1	80	72

A practical synthesis of substituted 2,6-diaminopyridines *via* microwave-assisted copper-catalyzed amination of halopyridines

Matthias Mastalir, Egon E. Rosenberg, Karl Kirchner*

Supporting Information