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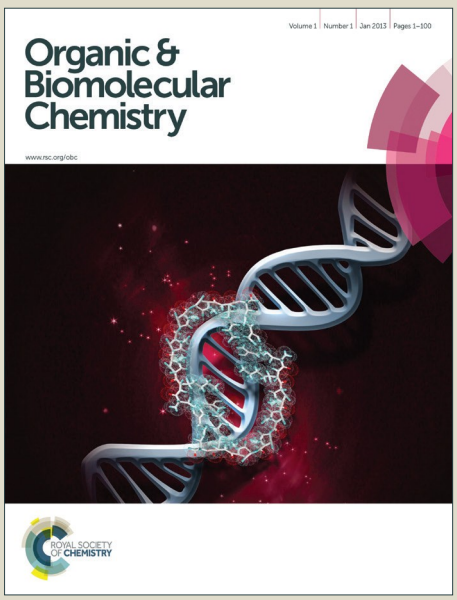

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Synthesis of Tetraarylpyridines by Chemo-Selective Suzuki-Miyaura Reactions of 3,5-Dibromo-2,6-dichloropyridine

Sebastian Reimann[a,b], Silvio Parpart[a], Peter Ehlers[a,b], Muhammad Sharif[b,c], Anke Spannenberg[b], Peter Langer*[a,b]

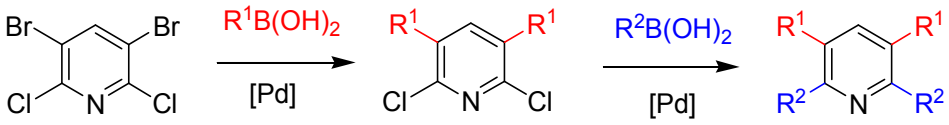
[a] Universität Rostock, Institut für Chemie, A.-Einstein-Str. 3a, 18059 Rostock, Germany
E-Mail: peter.langer@uni-rostock.de

[b] Leibniz-Institut für Katalyse e.V. an der Universität Rostock, A.-Einstein-Str. 29a, 18059 Rostock, Germany

[c] Department of Chemistry, COMSATS Institute of Information Technology 22060, Abbottabad, Pakistan

Abstract: Chemoselective Suzuki-Miyaura reactions on 3,5-dibromo-2,6-dichloropyridine were studied. The optimized reaction conditions allow for the facile access of 3-aryl- and 3,5-diarylpyridines in good yields. Suzuki-Miyaura reactions of the selectively synthesized 2,6-dichloro-3,5-diarylpyridines gave the corresponding 2,3,5,6-tetraarylpyridines, containing two different aryl moieties.

Keywords: cross-coupling, chemo-selectivity, palladium, pyridines, Suzuki-Miyaura reaction



Introduction

Pyridines represent one of the most widely studied class of heterocycles to date. Pyridine and its derivatives can be found in many natural products and are of great importance in pharmaceutical and agrochemical research.[1] Pyridines are found in nearly all branches of synthetic chemistry, such as catalysis, supramolecular chemistry and coordination chemistry as well as material science.[2] Thus, new and efficient synthetic methodologies are required for the synthesis of functionalized pyridines. In this context, palladium catalyzed cross coupling reactions offer a convenient and versatile method for the introduction of various functionalities to the pyridine core, starting from easy accessible halogenated pyridines. Today, Suzuki-Miyaura reactions are by far the most prominent variant of palladium catalyzed cross-coupling reactions.[3] This fact is attributed to the broad and easy accessibility of boronic acids, their low toxicity and high stability against air and moisture. Moreover, boronic acids allow mild reaction conditions and a facile separation of inorganic by-products with low toxicity.

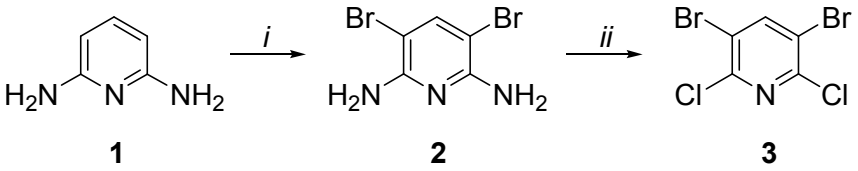
In particular, site- and chemo-selective cross-coupling reactions found increasing attention in recent years, as they allow the iterative introduction of various functionalities.[4] Site selective cross-coupling reactions of pyridines can be mainly controlled by electronic effects induced by the withdrawing nature of the nitrogen atom and/or by steric or chelating effects of functional groups. In contrast, chemo-selective cross-coupling reactions take usually advantage from different rates of the oxidative addition of Pd(0) to the C-X bond. In this regard many research groups, including ours, studied selective functionalizations of *N*-heterocycles by cross-coupling reactions.[5] Recently, the group of Schmitt and, independently, our own group reported the first selective pentafold arylation of pyridine derivatives by cross-coupling methods.[6] The synthetic strategy and the type of pyridine substrate employed by both groups were completely different.

Palladium catalyzed cross-coupling reactions of tetrahalogenated pyridines, containing both chlorine and bromine leaving groups at the same time, have, to the best of our knowledge, not been previously reported. The first attack of Pd catalyzed cross coupling reactions of polyhalogenated substrates usually occurs at the sterically least hindered and at the electronically most deficient position. The employment of polyhalogenated pyridines containing different types of halogen atoms, which in fact possess different leaving group abilities, allows to introduce an additional parameter to control the regioselectivity of the reactions. Herein, we report our results regarding chemo-selective Suzuki-Miyaura reactions of 3,5-dibromo-2,6-dichloropyridine. Palladium catalyzed cross-coupling reactions of this type of substrate have not been reported to date. Classic reactions are also very rare. The employment of 3,5-dibromo-2,6-

dichloropyridine as a substrate allows to change the regioselectivity of cross-coupling reactions as compared to 2,3,5,6-tetrachloropyridine and pentachloropyridine.[6b]

Results and Discussion

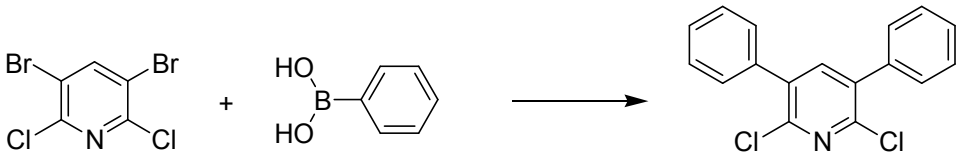
3,5-Dibromo-2,6-dichloropyridine **3** was synthesized according to a modified literature procedure in two steps.[7] Commercially available 2,6-diaminopyridine (**1**) was converted into 2,6-diamino-3,5-dibromopyridine (**2)** using bromine in glacial acetic acid. The following diazotization of **2** in the presence of $NaNO_2$ and hydrochloric acid yielded **3** (Scheme 1). This structurally simple molecule has, to the best of our knowledge, never been employed as a substrate in Pd catalyzed cross-coupling reactions before.



1 **2** **3**

Scheme 1. Synthesis of **3**; *i*, **1**, Br_2, AcOH, 20 h, 20 °C; *ii*, **2**, $NaNO_2$, HCl, 20 h, 20 °C (38% isolated yield after two steps).

Subsequently, a general catalytic system for the twofold chemo-selective Suzuki-Miyaura reaction of 3,5-dibromo-2,6-dichloropyridine **3** with phenylboronic acid was developed (Scheme 2; Table 1). During our optimization, the employment of either XPhos or SPhos proved to be unsatisfactory in terms of yields, due to the favored formation of 2,3,5,6-tetraphenylpyridine. Likewise, the reaction proceeded sluggishly in the presence of $Pd(OAc)_2$ using the ligand-free protocol of Liu et al. in aqueous DMF at room temperature.[8] In contrast, the employment of $P(Cy)_3$ and *n*$BuPAd_2$ (Ad = adamantyl)[5] improved the yield to 70 % and 80 %, respectively. The best yield was obtained when 5 mol% of $PdCl_2(PPh_3)_2$ was used as the catalyst. Lower amounts of catalyst or boronic acid did not afford higher yields.



3 **4a**

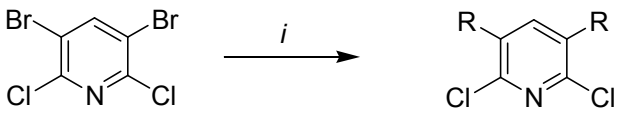
Scheme 2. Optimization - Synthesis of 2,6-dichloro-3,5-diphenylpyridine

Table 1. Optimization – Synthesis of 2,6-dichloro-3,5-diphenylpyridine.

	$PhB(OH)_2$ (equiv.)	solvent	T (°C)	Pd source [mol%]	Ligand [mol%]	Yield[a] (%)
1	2.4	toluene	100	$Pd(PPh_3)_4$ [5]	-	46
2	2.4	toluene	100	$PdCl_2(PPh_3)_2$ [5]	-	82 (74)[b]
3	2.1	toluene	100	$PdCl_2(CH_3CN)_2$ [2.5]	XPhos [5]	38
4	2.1	toluene	100	$PdCl_2(CH_3CN)_2$ [2.5]	SPhos [5]	15
5	2.1	toluene	100	$PdCl_2(CH_3CN)_2$ [2.5]	$P(Cy)_3$ [5]	80
6	2.1	toluene	100	$PdCl_2(CH_3CN)_2$ [2.5]	*n*BuPAd$_2$ [5]	70
7	2.4	DMF/H_2O	rt	$Pd(OAc)_2$ [2]	-	6
8	2.4	toluene	100	$PdCl_2(PPh_3)_2$ [3]	-	73
9	2.4	toluene	100	$PdCl_2(PPh_3)_2$ [1]	-	53
10	2.2	toluene	100	$PdCl_2(PPh_3)_2$ [5]	-	65
11	2.6	toluene	100	$PdCl_2(PPh_3)_2$ [5]	-	79

[a] GC yield using hexadecane as internal standard; [b] isolated yield

Using our optimized conditions, the reaction of **3** with electron donating, electron withdrawing and sterically demanding boronic acids afforded the corresponding 2,6-dichloro-3,5-diarylpyridines **4a-f** in 58-74% yield and with very good chemo-selectivity.



3 **4a-f**

Scheme 3. Synthesis of compounds **4a-f**: *i*, **3** (1.0 equiv.), R-B(OH)$_2$ (2.4 equiv.), $PdCl_2(PPh_3)_2$ (5 mol%), K_3PO_4 (3.0 equiv.), toluene, 100 °C, 20 h.

Table 2. Synthesis of 2,6-dichloro-3,5-diarylpyridines **4a-f**.

4	R	Yields of **4** (%)[a]
a	C_6H_5	74
b	4-*t*BuC_6H_4	58
c	4-(MeO)C_6H_4	60
d	4-(CF_3)C_6H_4	68
e	3-(MeO)C_6H_4	69
f	2-(MeO)C_6H_4	50

[a] isolated yields

The structure of compound **4a** was independently confirmed by X-ray crystal structure analysis, which unambiguously proved the constitution of the molecule (Figure 1). The phenyl groups in position 3 and 5 are twisted out of plane from the central pyridine moiety.

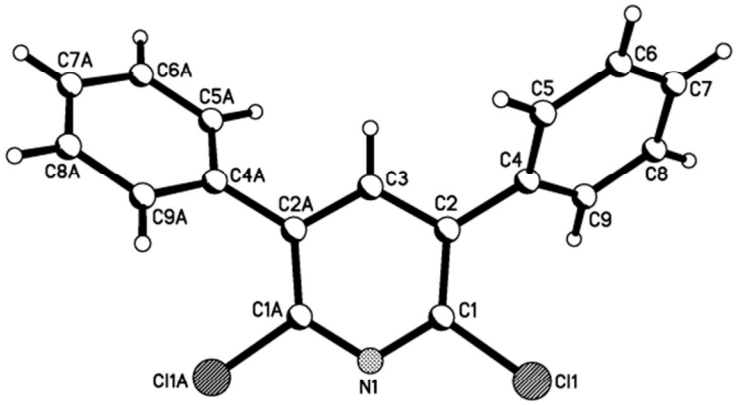
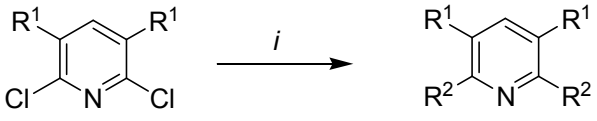


Figure 1. Molecular structure **4a**. Displacement ellipsoids are drawn at the 30% propability level.

Subsequently, 2,6-dichloro-3,5-diarylpyridines **4a** and **4d** were used for the synthesis of corresponding tetraarylpyridines, containing two different aryl moieties. The same conditions, which already gave excellent results for the synthesis of 3,5-dichloro-2,6-diarylpyridines **4a-f**, were successfully employed to prepare the desired products.[7] The reactions of **4a,f** with various boronic acids, possessing electron donating or electron withdrawing substituents, afforded the desired tetraarylpyridines **5a-d** in good yields.



4a,f **5a-d**

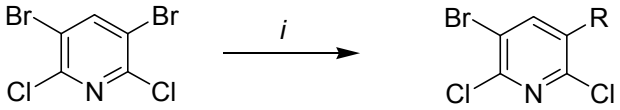
Scheme 4. Synthesis of compounds **5a-d**: *i*, **4a,f** (1.0 equiv.), R^2-$B(OH)_2$ (4.0 equiv.) $Pd(dba)_2$ (2.5 mol%), *n*$BuPAd_2$ (5.0 mol%), K_3PO_4 (4.0 equiv.), toluene, 100 °C, 20 h.

Table 3. Synthesis of 2,3,5,6-tetraarylpyridines **5** starting from **4**.

5	R^1	R^2	Yields of **5** (%)[a]
a	C_6H_5	4-(MeO)C_6H_4	79
b	C_6H_5	4-(CF_3)C_6H_4	74
c	4-(CF_3)C_6H_4	C_6H_5	75
d	4-(CF_3)C_6H_4	4-(MeO)C_6H_4	58

[a] isolated yields

The mono-substitution of 3,5-dibromo-2,6-dichloropyridine was next studied. The best yields were obtained using 1.2 equivalents of boronic acid, 5 mol% $Pd(PPh_3)_4$ as catalyst and 3.0 equivalents of K_3PO_4 as base in toluene. The reaction of **3** with different boronic acids afforded the corresponding mono-arylated pyridines **6a-f** in 49-64% yield and with good chemo-selectivity. In case of compounds **6b** and **6f**, possessing electron donating groups, the formation of 2,5-dichloro-3,5-diarylpyridines was observed.



3 **6a-f**

Scheme 5. Synthesis of compounds **6a-f**: *i*, **3** (1.0 equiv.), R-$B(OH)_2$ (1.2 equiv.), $Pd(PPh_3)_4$ (5.0 mol%), K_3PO_4 (3.0 equiv.), toluene, 100 °C, 20 h.

Table 4. Synthesis of 3,5-dibromo-2-chloro-6-arylpyridines **6a-f**.

6	R	Yields of **6** (%)[a]
a	C_6H_5	57
b	4-MeC_6H_4	49
c	4-*t*BuC_6H_4	52

d	4-PhC_6H_4	64
e	4-(CF_3)C_6H_4	57
f	3-(MeO)C_6H_4	56

[a] isolated yields

The structure of compound **6b** was independently confirmed by X-ray crystal structure analysis (Figure 2). Likewise to compound **4a**, the aryl ring is twisted out of plane from the pyridine.

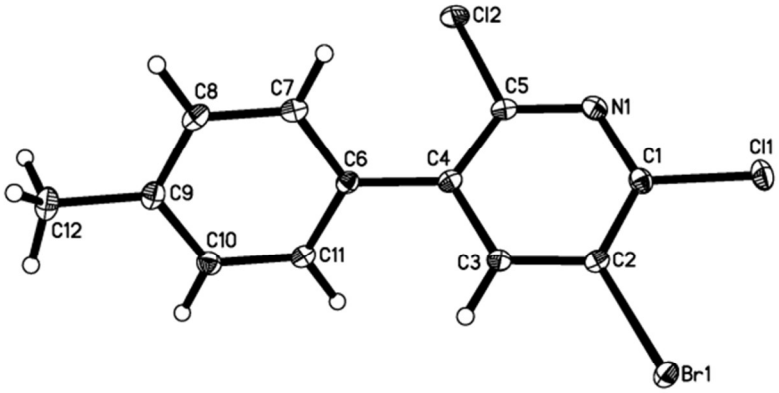
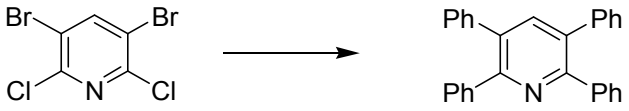


Figure 2. Molecular Structure of **6b**. Displacement ellipsoids are drawn at the 30%probability level.

Finally, we studied the tetrafold arylation of pyridine **3**. The optimization showed that SPhos and *n*BuPAd_2 gave excellent yields of tetraarylpyridine **7a**. (Scheme 6, Table 5). The tetrafold coupling could be performed in excellent yield when the amount of palladium catalyst was reduced to 1.25 mol%.



3 **7a**

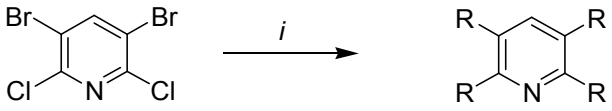
Scheme 6. Optimization – Synthesis of **7a**.

Table 5. Optimization – Synthesis 2,3,5,6-tetraphenylpyridine **7a**.

	$PhB(OH)_2$ (equiv.)	Pd source [mol%]	Ligand [mol%]	Yield (%)[a]
1	7	$PdCl_2(PPh_3)_2$ [2.5]	-	80
2	7	$Pd(PPh_3)_4$ [2.5]	-	90
3	7	$PdCl_2(CH_3CN)_2$ [2.5]	$P(Cy)_3$ [5]	92
4	7	$PdCl_2(CH_3CN)_2$ [2.5]	*n*$BuPAd_2$ [5]	95
5	7	$PdCl_2(CH_3CN)_2$ [2.5]	SPhos [5]	96
6	7	$PdCl_2(CH_3CN)_2$ [1.25]	SPhos [5]	96

[a] Isolated yields

Using optimized conditions, tetraarylpyridines **7a-e** were obtained in excellent yields. Lower yields were initially observed for products **7f** and **7g** when sterically hindered boronic acids were used. However, in these cases, the yields could be significantly improved when the catalyst amount was increased to 4.0 mol%.



3 **7**

Scheme 7. Synthesis of compounds **7a-f**: *i*, **3** (1.0 equiv.), R-B(OH)$_2$ (7.0 equiv.), $PdCl_2(CH_3CN)_2$ (1.25 mol%), SPhos (5.0 mol%), K_3PO_4 (7.5 equiv.), toluene, 100°C, 19 h.

Table 6. Synthesis of 2,3,5,6-tetraarylpyridines **7** starting from **3**.

7	R	Yield [%][a]
a	C_6H_5	96
b	4-MeC_6H_4	91
c	4-*t*BuC_6H_4	97
d	4-(CF_3)C_6H_4	97
e	2-FC_6H_4	99
f	2-(MeO)C_6H_4	86[b]
g	2,3,4-$(MeO)_3C_6H_2$	48[b]

[a] Isolated yields; [b] using 4.0 mol% $PdCl_2(CH_3CN)_2$ and 8.0 mol% SPhos

Conclusion

In conclusion, Suzuki-Miyaura reactions of 3,5-dibromo-2,6-dichloropyridine allowed for the chemo-selective synthesis of 3-bromo-2,6-dichloro-5-aryl-pyridines and 2,6-dichloro-3,5-diaryl-pyridines in good to excellent yields. Palladium catalyzed coupling reactions of this substrate have, to the best of our knowledge, not been previously reported. Classic reactions of this substrate are also very rare. The employment of 3,5-dibromo-2,6-dichloropyridine as the substrate substrate allows, by employment of two different leaving groups, a complete change of the regioselectivity as compared to reactions of 2,3,5,6-tetrachloropyridine and pentachloropyridine.[6b] The order of coupling reactions could be changed by the use of the new substrate which contains both chlorine and bromine leaving groups. The 2,6-dichloro-3,5-diarylpyridines proved to be excellent starting materials for further functionalizations, as

shown by additional Suzuki-Miyaura reactions which led to tetraarylpyridines containing two different aryl moieties. Finally, tetrafold Suzuki reactions of 2,6-dichloro-3,5-dibromopyridine were also developed affording functionalized 2,3,5,6-tetraarylpyridines in excellent yields.

Experimental

General. All reactions were carried out in oven-dried pressure tubes under argon atmosphere. Solvents for reactions were dried and distilled by standard methods or purchased in extra dry quality. Solvents for liquid chromatography and extraction were always distilled prior to use (heptane, ethyl acetate, dichloromethane). All chemicals, if not otherwise stated, including, ligands, boronic acids and bases, were purchased from commercial sources and used without further purification. *^{1}H-NMR Spectroscopy:* Bruker AV 300 (300 MHz) and Bruker AV 400 (400 MHz). All NMR spectra presented in this work were recorded in $CDCl_3$ solution. All chemical shifts are given in ppm. All coupling constants are indicated as *J*. References: TMS or residual $CHCl_3$ were taken as internal standard. Peak characterization: s = singlet, brs = broad singlet, d = doublet, brd = broad doublet, t = triplet, dd = doublet of doublet, q = quartet, m = multiplet. *^{13}C-NMR Spectroscopy:* Bruker AV 300 (75 MHz) and Bruker AV 400 (100 MHz). All NMR spectra presented in this work were recorded in $CDCl_3$ solution. All chemical shifts are given in ppm. All coupling constants are indicated as *J*. References: TMS or residual $CHCl_3$ were taken as internal standard. Peak characterization: d = doublet, t = triplet, q = quartet. DEPT method was used for determining the presence of primary, secondary, tertiary and quaternary carbon atoms. *^{19}F-NMR Spectroscopy:* Bruker AV 300 (282 MHz). *Mass Spectrometry (MS):* Finnigan MAT 95 XP (electron ionization EI, 70 eV); 6890 N/5973 (Agilent), 6210 Time-of-Flight LC/MS (Agilent). *Gas Chromatography MS (GCMS):* Agilent HP-5890 with an Agilent HP-5973 Mass Selective Detector (EI) and HP-5 capillary column using helium carrier gas. Only the measurements with an average deviation from the theoretical mass of ± 2 mDa were accounted as correct. *High resolution MS (HRMS (ESI)):* Agilent 1969A TOF. Only the measurements with an average deviation from the theoretical mass of ± 2 mDa were accounted as correct. *Infrared Spectroscopy (IR):* Nicolet 550 FT-IR spectrometer with ATR sampling technique for solids as well as liquids. Signal characterization: w = weak, m = medium, s = strong. *X-ray Crystallography:* Data were collected on a Bruker Kappa APEX II Duo diffractometer. The structure was solved by direct methods and refined by full-matrix least-squares procedures on F2 with the SHELXTL software package (Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112.). XP (Bruker AXS) was used for graphical representation. CCDC 986651-986652 contain the supplementary crystallographic data for this paper. These data can be

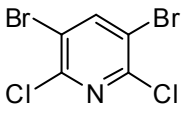
obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. *Elemental Analysis (EA):* C/H/N/S - Microanalysator TruSpec CHNS (Leco). *Melting point determination (mp):* Micro-Hot-Stage Galen^{TM} III Cambridge Instruments. The melting points have not been corrected. *Thin layer chromatography (TLC):* Merck Silica 60 F254 on aluminum tin foil from Macherey-Nagel. Detection with UV light at 254 nm and/or 366 nm without dipping reagent. *Column Chromatography:* Separation on Fluka silica gel 60 (0.063-0.200 mm, 70-320 mesh). Eluents were distilled before use.

General Procedure for the synthesis of starting material 3.

To a stirred solution of HOAc (200 mL/0.1 mol of **1**; 100%) and 2,6-diaminopyridine **1** (10.9 g, 0.1 mol) was added bromine (11.4 mL, 0.22 mol) at 10 °C. The temperature was allowed to warm to 20 °C and the reaction mixture was stirred for additional 20 h. Na_2SO_3 was added to the solution (20 mL, 0.1 M) and subsequently Na_2CO_3 (0.1 M) until a neutral ph-value was reached. The latter was extracted with EtOAc (8 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. 2,6-Diamino-3,5-dibromopyridine **2** was obtained as a brownish solid and used for the second step without further purification.

To a stirred solution of HCl and 2,6-diamino-3,5-dibromopyridine **2** (15 g, 0.056 mol) was added $NaNO_2$ (9.3 g, 0.14 mol) at room temperature. The solution was stirred for 20 h. Subsequently, water was added (300 mL) and the latter was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. 2,6-Dichloro-3,5-dibromopyridine **3** was obtained as colorless solid (6.5 g, 38% over two steps) after purification by flash chromatography (*n*-hexane/EtOAc).

3,5-Dibromo-2,6-dichloropyridine (3).



Compound **38** was isolated as a colorless solid; mp = 87-88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 118.9 (C-Br), 146.5 (CH), 148.5 (C-Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3081 (w), 3028 (w), 1516 (m), 1371 (s), 1324 (m), 1297 (m), 1222 (w), 1165 (s), 1053 (m), 1037 (s), 921 (m), 845 (w), 712 (m), 667 (m), 622 (w), 588 (m), 496 (m), 462 (m). GC-MS (EI, 70 eV): m/z (%): 305 (M^+, 100), 303 (39), 272 (10), 270 (15), 268 (7), 228 (7), 226 (14), 224 (9), 191 (7), 189 (6), 164 (4), 153 (6), 147 (10), 145 (16), 112 (5), 110 (14), 86 (5), 84 (16), 75 (26), 74 (9), 49 (11). HRMS (EI, 70 eV): calcd. for $C_5HBr_2Cl_2N$ (M^+): 302.78473, found 302.784924 and calcd. for

$C_5HBr^{81}BrCl_2N$ (M^+): 304.78268, found 304.782710 and calcd. for $C_5H^{81}Br_2Cl_2N$ (M^+): 306.78064, found 306.780338 and calcd. for $C_5H^{81}Br_2Cl^{37}ClN$ (M^+): 308.77769, found 308.777837. Anal. calcd. for $C_5HBr_2Cl_2N$ (305.78): C, 19.64; H, 0.33; N, 4.659. Found: C, 19.80; H, 0.3439; N, 4.658.

General procedure for the synthesis of 2,6-dichloro-3,5-diaryl-substituted pyridines 4a-f

An oven-dried and argon-flushed pressure tube was charged with 3,5-dibromo-2,6-dichloropyridine **3** (0.33 mmol), $PdCl_2(PPh_3)_2$ (5.0 mol%), boronic acid (0.8 mmol) and K_3PO_4 (0.98 mmol), followed by anhydrous toluene (4.0 mL). The tube was sealed with a Teflon valve and the reaction mixture was stirred at 100 °C for 20 h. The cooled reaction mixture was diluted with water and extracted with DCM. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography.

2,6-Dichloro-3,5-diphenylpyridine (4a)

Starting with 3,5-dibromo-2,6-dichloropyridine **3** (100 mg, 0.327 mmol), $PdCl_2(PPh_3)_2$ (11.5 mg, 5.0 mol%), phenylboronic acid (95.7 mg, 0.785 mmol), K_3PO_4 (208 mg, 0.981 mmol) and toluene (4.0 mL), **4a** was isolated as a colorless oil (73 mg, 74%); mp = 128-129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41-7.49 (m, 10H, CH), 7.67 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 128.5 (CH), 128.6 (CH), 129.2 (CH), 135.8 (C), 136.0 (C), 142.7 (CH), 146.8 (C-Cl). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3057 (w), 2921 (w), 2027 (w), 1959 (w), 1577 (m), 1530 (w), 1445 (m), 1384 (s), 1223 (w), 1120 (m), 1029 (m), 1006 (w), 870 (w), 765 (m), 700 (s), 671 (m), 650 (w), 598 (w), 523 (w), 464 (w), 377 (w). GC-MS (EI, 70 eV): m/z (%): 303 (M^+, 20), 299 (100), 264 (3), 229 (11), 228 (18), 227 (23), 203 (4), 202 (16), 201 (9), 176 (2), 150 (3), 132 (2), 126 (2), 114 (8), 101 (7), 100 (6), 88 (4), 77 (4), 75 (3), 51 (4). HRMS (EI, 70 eV): calcd. for $C_{17}H_{11}Cl_2N$ (M^+): 299.02631, found 299.02605 and calcd. for $C_{17}H_{11}Cl^{37}ClN$ (M^+): 301.02336, found 301.02348 and calcd. for $C_{17}H_{11}{}^{37}Cl_2N$ (M^+): 303.02041, found 303.02057.

General procedure for the synthesis of 2,3,5,6-tetraaryl-substituted pyridines 5a-d

An oven-dried and argon-flushed pressure tube was charged with the appropriate 2,6-dichloro-3,5-diaryl-substituted pyridines **4** (0.3 mmol), $Pd(dba)_2$ (2.5 mol%), *n*BuPAd$_2$ (5.0 mol%),

boronic acid (1.2 mmol) and K_3PO_4 (1.2 mmol) followed by anhydrous toluene (5.0 mL). The tube was sealed with a Teflon valve and the reaction mixture was stirred at 100 °C for 20 h. The cooled reaction mixture was diluted with water and extracted with DCM. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography.

2,6-Bis(4-methoxyphenyl)-3,5-diphenylpyridine (5a)

Starting with 2,6-dichloro-3,5-diphenylpyridine 5**a** (128 mg, 0.29 mmol), $Pd(dba)_2$ (4.2 mg, 2.5 mol%), *n*BuPAd$_2$ (5.2 mg, 5.0 mol%), 4-methoxyphenylboronic acid (175 mg, 1.15 mmol), K_3PO_4 (245 mg, 1.15 mmol) and toluene (5.0 mL), **5a** was isolated as a colorless solid (102 mg, 79%); mp = 204-206 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.66 (s, 6H, MeO), 6.65-6.69 (m, 4H, CH), 7.14-7.20 (m, 10H, CH), 7.34-7.38 (m, 4H, CH), 7.60 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.2 (MeO), 113.1 (CH), 127.0 (CH), 128.3 (CH), 129.4 (CH), 131.4 (CH), 132.5 (C), 133.3 (C), 140.1 (C), 141.2 (CH), 154.6 (C), 159.3 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3054 (w), 3030 (w), 2951 (w), 2929 (w), 2834 (w), 1604 (s), 1577 (m), 1506 (s), 1446 (s), 1421 (s), 1386 (m), 1299 (m), 1246 (s), 1172 (s), 1108 (w), 1074 (w), 1030 (m), 1005 (w), 911 (w), 878 (w), 837 (s), 792 (m), 769 (s), 756 (m), 733 (w), 699 (s), 641 (m), 619 (w), 559 (m), 538 (m), 524 (w), 417 (w). GC-MS (EI, 70 eV): m/z (%): 444 (M^+, 21), 443 (72), 442 (100), 400 (3), 399 (9), 398 (9), 355 (9), 341 (3), 328 (2), 292 (2), 281 (2), 207 (3), 184 (5), 183 (6), 177 (9), 170 (4), 169 (5). HRMS (ESI, 70 eV): calcd. for $C_{31}H_{26}NO_2$ ($[M+H]^+$): 444.19581, found 444.19624. Anal. calcd. for $C_{31}H_{25}NO_2$ (443.54): C, 83.95; H,5.68; N, 3.16. Found: C, 84.08; H, 5.728; N, 2.953.

General procedure for the synthesis of 3-bromo-2,6-dichloro-5-aryl-substituted pyridines 6a-f

An oven-dried and argon-flushed pressure tube was charged with 3,5-dibromo-2,6-dichloropyridine **3** (0.33 mmol), $Pd(PPh_3)_4$ (5.0 mol%), boronic acid (0.4 mmol) and K_3PO_4 (0.98 mmol), followed by anhydrous toluene (4.0 mL). The tube was sealed with a Teflon valve and the reaction mixture was stirred at 100 °C for 20 h. The cooled reaction mixture was diluted with water and extracted with DCM. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography.

3-Bromo-2,6-dichloro-5-phenylpyridine (6a)

Starting with 3,5-dibromo-2,6-dichloropyridine **3** (100 mg, 0.327 mmol), $Pd(PPh_3)_4$ (18.9 mg, 5.0 mol%), phenylboronic acid (47.8 mg, 0.392 mmol), K_3PO_4 (208 mg, 0.981 mmol) and toluene (4.0 mL), **6a** was isolated as a colorless oil (56 mg, 57%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39-7.48 (m, 5H, CH), 7.90 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 118.6 (C-Br), 128.6 (CH), 129.0 (CH), 129.1 (CH), 135.1 (C), 137.0 (C), 144.6 (CH), 147.0 (C), 148.2 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3054 (w), 2923 (w), 1809 (w), 1603 (w), 1562 (w), 1513 (m), 1446 (m), 1387 (s), 1336 (m), 1221 (m), 1171 (m), 1115 (m), 1076 (w), 1037 (w), 1013 (m), 908 (m), 859 (m), 764 (s), 734 (w), 695 (s), 578 (s), 543 (m), 459 (w), 403 (w). GC-MS (EI, 70 eV): m/z (%): 303 (M^+, 100), 301 (66), 268 (3), 266 (2), 189 (13), 188 (6), 187 (38), 186 (5), 152 (13), 151 (14), 136 (3), 126 (6), 125 (6), 112 (2), 111 (2), 100 (3), 99 (4), 77 (3), 75 (5), 74 (4), 63 (4), 62 (3), 51 (4). HRMS (EI, 70 eV): calcd. for $C_{11}H_6BrCl_2N$ (M^+): 300.90552, found 300.90537 and calcd. for $C_{11}H_6{}^{81}BrCl_2N$ (M^+): 302.90347, found 300.90302 and calcd. for $C_{11}H_6{}^{81}BrCl^{37}ClN$ (M^+): 304.90052, found 304.90072. Anal. calcd. for $C_{11}H_6BrCl_2N$ (302.98): C, 43.61; H, 2.00; N, 4.62. Found: C, 44.01; H, 1.715; N, 4.499.

General procedure for the synthesis of 2,3,5,6-tetraaryl-substituted pyridines 7a-f

An oven-dried and argon-flushed pressure tube was charged with 3,5-dibromo-2,6-dichloropyridine **3** (0.25 mmol), $PdCl_2(MeCN)_2$, SPhos, boronic acid (1.75 mmol) and K_3PO_4 (1.88 mmol), followed by anhydrous toluene (4.0 mL). The tube was sealed with a Teflon valve and the reaction mixture was stirred at 100 °C for 20 h. The cooled reaction mixture was diluted with water and extracted with DCM. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography.

2,3,5,6-Tetraphenylpyridine (7a)

Starting with 3,5-dibromo-2,6-dichloropyridine **3** (75.7 mg, 0.25 mmol), $PdCl_2(MeCN)_2$ (0.8 mg, 1.25 mol%), SPhos (5.1 mg, 5.0 mol%), phenylboronic acid (213 mg, 1.75 mmol), K_3PO_4 (398 mg, 1.88 mmol) and toluene (4.0 mL), **7a** was isolated as a colorless solid (92 mg, 96%); mp = 244-246 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22-7.30 (m, 16H, CH), 7.47-7.51 (m, 4H, CH), 7.77 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 127.5 (CH), 128.0 (CH), 128.1 (CH), 128.6 (CH), 129.8 (CH), 130.4 (CH), 134.6 (C), 139.8 (C), 139.9 (C), 141.5 (CH), 155.5 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3080 (w), 3054 (w), 3023 (w), 2927 (w), 2857 (w), 1444 (m), 1416 (s), 1386 (m), 1179 (w), 1072 (w), 1017 (w), 908 (m), 854 (w), 779 (m), 757 (s), 732 (m), 690 (s), 537 (m), 528 (m), 499 (m), 409 (w), 390 (w). GC-MS (EI, 70 eV): m/z (%): 384 (M^+, 16), 383 (66), 382 (100), 306 (3), 305 (3), 304 (10), 303 (7), 302 (6), 276 (8), 190 (7), 189 (5), 188 (3), 183 (13), 77

(4). HRMS (ESI, 70 eV): calcd. for $C_{29}H_{22}N$ ($[M+H]^+$): 384.17468, found 384.17447. Anal. calcd. for $C_{29}H_{21}N$ (383.48): C, 90.83; H, 5.52; N, 3.65. Found: C, 90.50; H, 5.329; N, 3.431.

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