A Suzuki–Miyaura Approach to a Series of Forensically Relevant Pyridines

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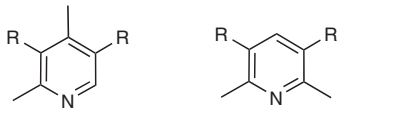
Abstract: A convenient and general method for the preparation of sixteen 3,5-diarylsubstituted 2,4- and 2,6-dimethylpyridines of high forensic importance is described. The Suzuki cross-coupling reaction between a range of ring-substituted phenylboronic acids and 3,5-dibromo-2,4-dimethylpyridine and 3,5-dibromo-2,6-dimethylpyridine was used as a key step.

Key words: cross-coupling reactions, heterocycles, chemoselectivity, amphetamine analogues, route-specific by-products

The pyridine ring is a common structural motif in a large number of naturally occurring products, having simple or very complex structures, like coenzymes and alkaloids.[1] It can also be found in compounds used in pharmacy and agriculture.[2] A range of substituted phenyl-, benzyl-, methylpyridines are also well known in the field of forensic chemistry. Several isomeric pyridines, among them 2,4-dimethyl-3,5-diphenylpyridine (**1a**) and 2,6-dimethyl-3,5-diphenylpyridine (**2a**), have been isolated as by-products from the crude amphetamine synthesized by the Leuckart method[3] (Figure 1). Further studies in this area indicated that isomeric pyridines were encountered exclusively in amphetamine that originated from the Leuckart synthesis.[4]



1a R = Ph
1b R = 4-$CH_3OC_6H_4$
2a R = Ph
2b R = 4-$CH_3OC_6H_4$

Figure 1 Forensically relevant pyridines **1a**, **1b**, **2a**, and **2b**.

The identification of these pyridines, along with certain diazines such as 4-benzylpyrimidine and 4-methyl-5-phenylpyrimidine,[3c,5] is excellent proof that confiscated amphetamine was produced according to the Leuckart protocol.

We have been involved in a study of the chemistry of 4-methoxyamphetamine (PMA) because of its recent appearance in the illicit market in the USA,[6] Australia,[5b] Japan,[7] and Europe,[8] and we have found that this dangerous synthetic drug might be readily produced from 4-methoxyphenylacetone using formamide or ammonium formate as the aminating/reducing agents.[9] We also identified and synthesized several important by-products connected with the aforementioned process.[10] Recently, we described the synthesis and identification of two members of the pyridine family, namely 2,4-dimethyl-3,5-bis(4-methoxyphenyl)pyridine (**1b**) and 2,6-dimethyl-3,5-bis(4-methoxyphenyl)pyridine (**2b**) in the crude PMA.[10b] In order to obtain a suitable reference material for our purposes, we prepared unsymmetrical pyridine **1b** according to the procedure published for its desmethyl analogue **1a**. We also proposed a three-step procedure for the preparation of symmetrical pyridine **2a**, starting from known 2,6-dimethyl-3,5-diphenylpyron-4-one.[11] Unfortunately, any attempts to prepare the methoxyphenyl analogue of the pyrone necessary for the synthesis of **2b** were unsuccessful. We therefore developed an alternative synthetic approach, which involved the Suzuki–Miyaura cross-coupling reaction between 3,5-dibromo-2,6-dimethylpyridine (**3**) and 4-methoxyboronic acid as a key step.[10b]

Continuing our interest in the chemistry of new synthetic amphetamine analogues, also known as 'designer drugs', we have turned our attention to the synthesis of a series of isomeric 2,4- and 2,6-dimethylpyridines **1** and **2** bearing phenyl rings substituted at the 3- and 5-positions of the pyridine moiety. Stimulated by the ready availability of a variety of arylboronic acids with the ring substitution pattern matching those observed in the most popular amphetamine-type drugs,[12] we employed the Suzuki–Miyaura cross-coupling protocol[13] to create the desired 3,5-diarylpyridine systems. We used 3,5-dibromo substituted 2,4- and 2,6-dimethylpyridines **3** and **4** in the palladium-catalyzed cross-coupling reaction with boronic acid components (Scheme 1, Route A).

It seemed possible that the target pyridines could be alternatively derived from the corresponding 2- and 4-chloro-substituted 3,5-diaryldimethylpyridines **5** and **6** by a classical hydrogenolysis over palladium; we had previously used this transformation in the preparation of compounds **1a**, **1b**, and **2a**.[10b] In the presented synthetic approach we planned to use the regioselective cross-coupling reaction[14] between two molecules of arylboronic acids with one molecule of trihalodimethylpyridines **7** and **8** as a key step (Scheme 1, Route B).

The palladium-catalyzed Suzuki–Miyaura cross-coupling reaction offers an attractive methodology for the introduction of aryl, alkenyl, and alkyl substituents into the electrophilic aromatic ring (ArX, where X = Cl, Br, I, OTf).[14]

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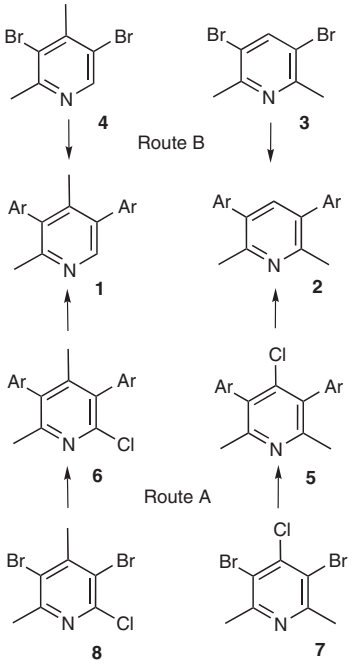
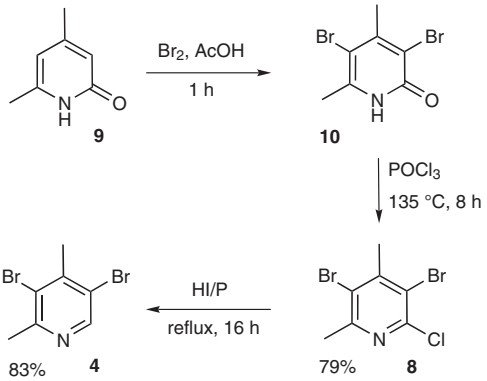
When more than one reaction center is present in the electrophilic partner (e.g. polyhalogenated homo- or heteroaromatic ring), then carefully chosen reaction conditions might allow the differentiation between two or more reactive centers, and consequently, the regio- or chemoselective introduction of the aryl, alkenyl, or alkyl group. A number of successful regio- and chemoselective Suzuki–Miyaura couplings of variously polyhalogeno-substituted azines including pyridines,[15] pyrimidines,[16] quinolines,[17] pyrazolopyrimidines,[18] and five-membered-ring heterocycles[19] with arylboronic acids have been reported in the literature.



Scheme 1 Two approaches to the target pyridines **1** and **2** synthesized in this work.

Due to a notable difference in the reactivity of C_{aryl}–Cl and C_{aryl}–Br(or I) bonds, the oxidative palladium insertion into the C_{aryl}–Br and C_{aryl}–I bond in polyhalogenated electrophiles takes place preferentially, leading to polyaryl chlorides.[20] Although such differences in reactivity manifest less intensely when comparing the C_{aryl}–Br with the C_{aryl}–I bond, the Suzuki coupling approach could also be used in the transformation of 2-bromo-5-iodopyridine into 5-arylated 2-brompyridine[21] and in the sequential diarylation of 2-bromo-3-iodopyridine.[22] Because of the electronegative character of the nitrogen atom, different positions in azines are not equally susceptible to oxidative palladium addition.[23] The pyridine ring with the same halogen atoms in equivalent positions treated with an equimolar amount of arylboronic acid usually gives a mixture of mono- and diarylated products, along with the starting material.[24] On the other hand, carefully chosen conditions may allow the formation of monosubstituted products in moderate yields.[25] The regioselectivity may be different when bulky substituents[26] or electron-donating or -withdrawing groups are present in the aryl dihalides. Other properties of the substituents such as their ability to chelate palladium(0) species, can be used to control the desired ratio of the possible regioisomers.[27]

The preparation of 3,5-dibromo-2-chloro-4,6-dimethylpyridine (**8**) was based on the analogous procedure for the synthesis of trihalopyridine **7** (Scheme 2).[10b] The chemoselective diarylation of trihalopyridines **7** and **8** was then explored. Considering the observable differences in the reactivity of the C_{aryl}–Cl and the C_{aryl}–Br bonds, it seemed possible to find appropriate cross-coupling conditions affording preferentially 3,5-diaryl-substituted chlorodimetylpyridines **5** and **6**.

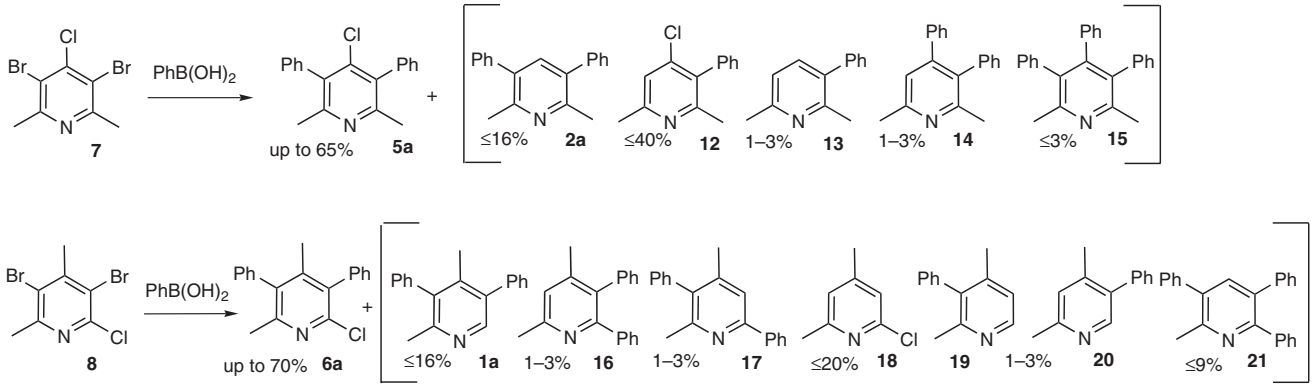


Scheme 2 Preparation of polyhalogenated pyridines **8** and **4**.

The coupling of **7** and **8** under three different conditions was explored in order to develop a suitable procedure for the future synthesis of a series of pyridines **5** and **6**. In each case we used $Pd(PPh_3)_4$ as the catalyst and two equivalents of phenylboronic acid as the reacting partner for the heteroaryl halides. The solvent system benzene–water–ethanol and the weak base sodium bicarbonate (Method A) represent common Suzuki cross-coupling conditions.[13] In Method B we used toluene–water–ethanol as a solvent system and sodium carbonate as a slightly stronger base. We also used DME as the solvent in Method C.

In this case, the addition of water (up to 30%) was necessary to improve the solubility of the base (K_2CO_3). All reactions were performed according to the conditions described for Methods A, B, and C employing 0.67 mmol of halopyridines **7** and **8** (Scheme 3). GC-MS analysis was used for monitoring the progress of the reaction together, to estimate the yield of the target product, and the distribution of major by-products (Table 1).

The starting material was fully consumed after 24 hours using Method A or C and after eight hours in the case of Method B. Neither symmetrical **7** nor unsymmetrical pyridine **8** reacted chemoselectively by Method C. In the case of trihalopyridine **8**, only traces of **6a** could be detected by GC-MS. The attempted arylation of **7** using the same method gave 4-chloro-2,6-dimethyl-3-phenylpyridine (**12**) as the main product in 34% yield. Methods A and B gave more promising results.



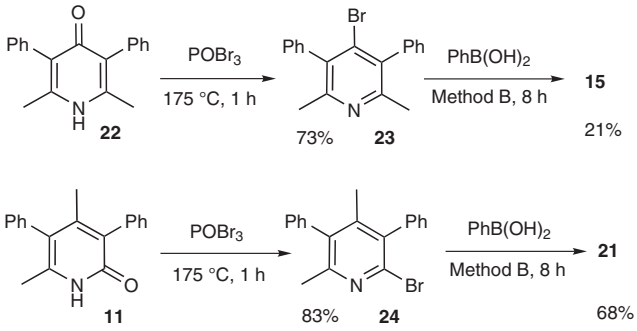
Scheme 3 Attempted regioselective synthesis of **5a** and **6a**. The yields of the target products **5a** and **6a** (for Method B) and major by-products (in brackets) were determined by GC-MS analysis and were not isolated as pure substances.

Table 1 The Cross-Coupling Reaction of Aryl Halides **7**, **8**, **3**, **4**, and **29** with Phenylboronic Acid[a]

Entry	Precursor	Product	Yield (%)[b]		
			Method A	Method B	Method C
1	**7**	**5a**	90	65[c]	29[d]
2	**8**	**6a**	69	70[e]	<1
3	**3**	**2a**	>93	>93	46[e]
4	**4**	**1a**	>93	>93	10[f]
5	**29**	**5a**	87[g,h]	60[g,i]	–

[a] Conditions: all methods: 1.0 equiv of aryl halide, 2.0 equiv of phenylboronic acid, 4% mol $Pd(PPh_3)_4$; Method A: $NaHCO_3$ (4.0 equiv), benzene–H_2O–EtOH, 80 °C, 24 h; Method B: Na_2CO_3 (4.0 equiv), toluene–H_2O–EtOH, 105 °C, 8 h; Method C: K_2CO_3 (4.0 equiv), DME–H_2O, 75 °C, 24 h.
[b] Yield determined by GC-MS analysis.[28,]
[c] For distribution of the main by-products obtained in Method B, see Scheme 3.
[d] The main product was **12**, yield: ca. 34%.
[e] The main product was **13**, yield: ca. 56%.
[f] The main products were isomeric monophenylpyridines **19** and **20**.
[g] Phenylboronic acid (1.0 equiv) was used.
[h] Products **15** and **2a** were present in ca. 6% and ca. 4% yields, respectively.
[i] Products **15** and **2a** were present in ca. 6% and 33% yields, respectively.

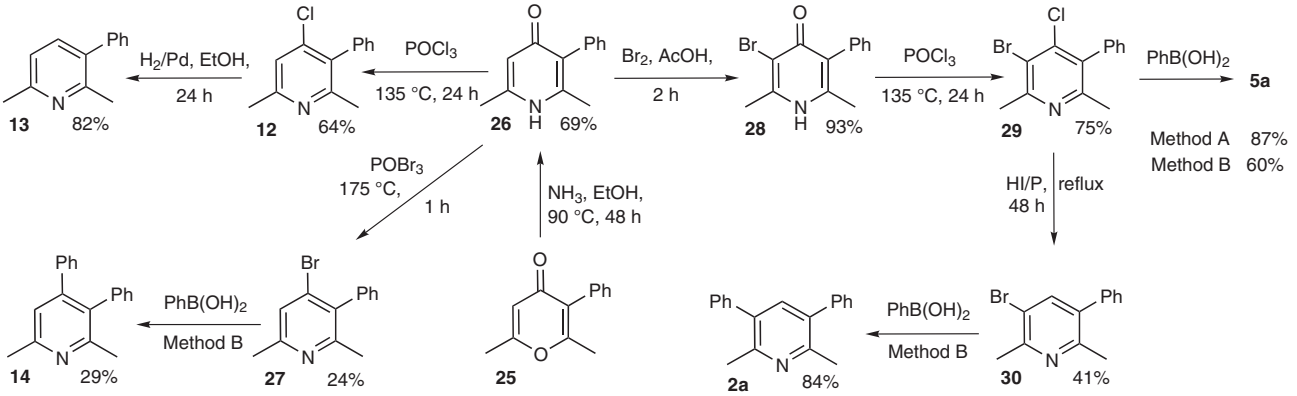
The treatment of **7** with phenylboronic acid according to Method B afforded diphenylated pyridine **5a** in 65% yield. As expected, the use of milder conditions (Method A) resulted in better selectivity and a higher yield of **5a**, which reached 90%. The cross-coupling of trihalopyridine **8** with phenylboronic acid seemed to be independent of the reaction conditions and both Methods A and B afforded diphenylated chloropyridine **6a** in approximately 70% yield. The products **5a** and **6a** showed identical GC-MS properties to those previously reported.[10b] Although the expected pyridines **5a** and **6a** were obtained in moderate to good yields, we noticed that the reaction mixtures were rich in a variety of by-products resulting from competitive reductive elimination, monophenylation, and non-chemoselective coupling at C–Cl (Scheme 3). The structures of these by-products were confirmed by their independent synthesis (compounds **12–15**, **21**) or deduced from their GC-MS data (compounds **16–20**). The formation of compounds **14–17** and **21** illustrates the fact that full chemoselectivity was not achieved and that phenylation also took place at the reaction sites bearing the chlorine atoms. In spite of the fact that exactly two equivalents of boronic acids were used, triphenylation of **7** and **8** also occurred leading to by-products **15** and **21**. We initially assumed that the appearance of triphenylpyridines resulted from the subsequent arylation of diphenylpyridines **5a** and **6a**. However, attempted independent cross-coupling of **5a** and **6a** with phenylboronic acid did not afford the expected compounds **15** and **21**. On the other hand, bromopyridines **23** and **24**, which were obtained by the treatment of pyridones **22** and **11** with $POBr_3$, were found to react with phenylboronic acid (Method B) to give the desired compounds **15** and **21** in moderate yields (Scheme 4). Such results indicate that, at least in this case, not steric but rather electronic factors govern the reaction outcome.



Scheme 4 Preparation of triphenylpyridines **15** and **21**.

The side-products **12–14** that accompanied the target pyridines **5a** and **6a** were synthesized according to Scheme 5. Thus, the known pyrone[29] **25** was aminated to afford pyridone **26**, which was subsequently used as the starting material in three different sets of reactions.

Initially, the intermediate 4-chloro-2,6-dimethyl-3-phenylpyridine (**12**), easily obtained by the treatment of **26**

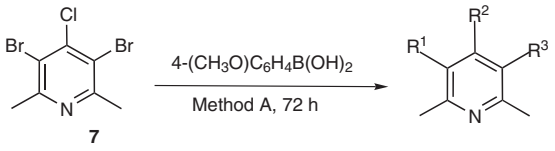


Scheme 5 Reaction sequences leading to the by-products **12**–**14** and pyridines **5a** and **2a**.

with $POCl_3$, was dechlorinated in the usual manner (H_2, Pd) to give 2,6-dimethyl-3-phenylpyridine (**13**) in 36% overall yield. Alternatively, compound **27** was obtained in low yield (24%) by the treatment of **26** with $POBr_3$ at 165 °C. The product slowly decomposed at room temperature, which is typical for C(4)–Br substituted pyridines.[30] Despite its instability, bromopyridine **27** could be employed for the cross-coupling reaction with phenylboronic acid (1.5 equiv) to give diphenylpyridine **14** in low yield (29%). Treatment of pyridone **26** with bromine in acetic acid afforded bromopyridone **28**, which after chlorination, gave bromochloropyridine **29**. The conversion of **29** to the corresponding bromopyridine **30** followed by the Suzuki cross-coupling with phenylboronic acid yielded pyridine **2a**. The Suzuki cross-coupling reaction of chlorobromopyridine **29** with one equivalent of phenylboronic acid was explored under two sets of conditions (Method A and B). Phenylation occurred in a regioselective manner and chloropyridine **5a** was obtained in 87% (Method A) and 60% (Method B) yields, respectively (Table 1, entry 5). The formation of triphenylpyridine **15** was again observed, which suggested that the presence of only one bromine atom sufficiently activated the neighboring C(4)–Cl bond.

Despite rather moderate success in the chemoselective phenylation of **7** and **8**, an additional attempt was made to obtain 4-chloro-2,6-dimethyl-3,5-bis(4-methoxyphenyl)pyridine (**5b**; Scheme 6). Even though a small excess of 4-methoxyboronic acid (2.2 equiv) was used in Method A and the cross-coupling partners were allowed to react for 72 hours, the target compound **5b** was isolated in only moderate yield (51%), accompanied by 4-chloro-2,6-dimethyl-3-(4-methoxyphenyl)pyridine (**33**) (isolated yield 17%), 3-bromo-4-chloro-2,6-dimethyl-5-(4-methoxyphenyl)pyridine (**34**) (isolated yield 11%).

In order to suppress the possible side-reaction and, therefore, improve the yield and selectivity, dibromopyridines **3** and **4** and were considered as suitable partners for arylboronic acids (Route A, Scheme 1). Dibromopyridine **4** was prepared in good yield (83%) according to the procedure used for the preparation of **3**[10b] (Scheme 2). The attempted phenylation of **3** and **4** confirmed our expectations. The synthesis of the corresponding diphenylated pyridines **1a** and **2a** proceeded in excellent yield and only a small amount of monophenylated product **13** and **19/20** could be detected by GC-MS (Table 1, entries 3 and 4). Method A worked even better giving slightly lower levels of impurities. The scope and limitations of Method A were further demonstrated by performing reactions of **3** and **4** with a variety of arylboronic acids (Table 2).



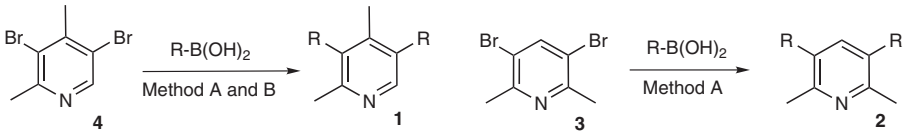
5b $R^1 = R^3 = 4\text{-}(CH_3O)C_6H_4$, R^2=Cl 51%
33 R^1 = H, R^2 = Cl, $R^3 = 4\text{-}(CH_3O)C_6H_4$ 17%
34 R^1 = Br, R^2 = Cl, $R^3 = 4\text{-}(CH_3O)C_6H_4$ 11%

Scheme 6 Attempted regioselective synthesis of 4-chloro-bis(4-methoxyphenyl)-2,6-dimethylpyridine (**5b**).

The arylation of dibromopyridine **3** gave the desired products in moderate (41–71%, compounds **2e**–**h**) to very good (81–95%, compounds **2a**–**d**) yield. In each case total conversion of the starting material was observed after 24 hours. Probably, the protodeboronation and the self-coupling reaction of 4-methylthio-, 2,5-dimethoxy-, 3,4,5-trimethoxy-, and 3,4-methylenedioxy-substituted phenylboronic acids may account for a lower yield of products **2e**–**h**.

Surprisingly, the cross-coupling reactions of dibromopyridine **4** with arylboronic acids were less straightforward than we expected. Generally, slightly lower yields were observed for compounds **1a**–**c**, **1e**, **1g**, and **1h**, in comparison with their symmetrical counterparts. Moreover, when arylboronic acids bearing the *ortho*-substituted phenyl ring were employed the starting material along with two isomeric monosubstituted products and only a small amount of the desired dicoupled pyridines **1d** and **1f** were obtained even after 48 hours.

Table 2 Results of the Suzuki Reaction of 3,5-Dibromo 2,4- and 2,6-Dimethylpyridines with Various Arylboronic Acids



Entry	Substrate	R[a]	Product	Method	Yield (%)[b]
1	**4**	Ph	**1a**	A	78
2	**4**	4-$CH_3OC_6H_4$	**1b**	A	85
3	**4**	3-$CH_3OC_6H_4$	**1c**	A	72
4	**4**	2-$CH_3OC_6H_4$	**1d**	B[c]	67
5	**4**	4-$CH_3SC_6H_4$	**1e**	A	40
6	**4**	2,5-$(CH_3O)_2C_6H_3$	**1f**	B[c]	74
7	**4**	3,4,5-$(CH_3O)_3C_6H_2$	**1g**	A	40
8	**4**	3,4-$(OCO)C_6H_3$	**1h**	A	68
9	**3**	Ph	**2a**	A	89
10	**3**	4-$CH_3OC_6H_4$	**2b**	A	95
11	**3**	3-$CH_3OC_6H_4$	**2c**	A	91
12	**3**	2-$CH_3OC_6H_4$	**2d**	A	81
13	**3**	4-$CH_3SC_6H_4$	**2e**	A	52
14	**3**	2,5-$(CH_3O)_2C_6H_3$	**2f**	A	41
15	**3**	3,4,5-$(CH_3O)_3C_6H_2$	**2g**	A	65
16	**3**	3,4-$(OCO)C_6H_3$	**2h**	A	71

[a] Arylboronic acid (2.2 equiv).
[b] Yields of isolated product based on **3** or **4**.
[c] Arylboronic acid (3 equiv).

The problem of low reactivity was easily solved when Method B was used instead of Method A. The corresponding 2-methoxyphenyl- and 2,5-dimethoxyphenyl-substituted pyridines **1d** and **1f** were isolated in acceptable yields of 67% and 74%, respectively (Table 2, entry 4 and 6). The yields of the reactions along with recorded analytical data for synthesized compounds are collected in Tables 2– 4. The analytical data of compounds **1a**, **1b**, **2a**, and **2b** matched those reported previously.[3,10b]

In summary, it was again demonstrated that the Suzuki–Miyaura cross-coupling reaction was a powerful tool for heterocycle synthesis by the preparation of 16 forensically relevant pyridines using 3,5-dibromosubstituted 2,4- and 2,6-dimethylpyridines and appropriate arylboronic acids. The identification of these compounds in the corresponding amphetamine analogues produced by the Leuckart method is currently underway.

The following compounds were prepared according to published procedures: 3,5-dibromo-2,6-dimethylpyridine (**3**),[10b] 3,5-dibromo-4-chloro-2,6-dimethylpyridine (**7**),[10b] 4-chloro-2,6-dimethyl-3,5-diphenylpyridine (**5a**),[10b] 2-chloro-4,6-dimethyl-3,5-diphenylpyridine (**6a**),[10b] 4,6-dimethyl-3,5-diphenylpyridin-2(1*H*)-one (**11**),[31] 4,6-dimethylpyridin-2(1*H*)-one (**9**),[32] 2,6-dimethyl-3,5-diphenylpyridin-4(1*H*)-one (**22**),[10b] 2,6-dimethyl-3-phenyl-4*H*-pyran-4-one (**25**),[29] 3,5-dibromo-4,6-dimethylpyridin-2(1*H*)-one (**10**).[33] Remaining substrates together with reagents and solvents were commercially available and were used without additional purification. The Suzuki cross-coupling reactions were carried out under an argon atmosphere. TLC was performed on Merck Kieselgel 60 F-254 plates. Chromatographic purification of compounds was carried out on silica gel MN Kieselgel 60 (100–200 mesh). Melting points were recorded on an Electrothermal, Model IA 9200 and are uncorrected. IR spectra were recorded on a Bruker FTIR 113v spectrometer at 2 cm^{-1} resolution working in the reflection mode; liquid samples were analyzed as films, all others neat. NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 200 MHz for ^1H NMR and 50 MHz for ^{13}C NMR, respectively. LRMS were collected on a Hewlett-Packard HP 5973 mass detector coupled with a HP 6890 Plus gas chromatograph. The column 30 m × 0.25 mm, ID with 0.25 μm film thickness was operated at a flow rate of 0.7 mL/min (helium gas) and the oven temperature was ramped between 90–300 °C at a rate of 12 °C/min. HRMS were recorded on Micromass LCT (ESI-TOF) instrument and AMD-604 double-focusing mass spectrometer.

3,5-Dibromo-2-chloro-4,6-dimethylpyridine (8)

A mixture of 3,5-dibromo-4,6-dimethylpyridin-2(1*H*)-one (**10**; 3.15 g, 11.17 mmol) and $POCl_3$ (13.7 g, 89.5 mmol) was heated in an oil

bath (135 °C) in a thick-walled Mini Flask (Supelco) closed with a solid screw cap with a Teflon/silicone septum.

After heating for 8 h, the excess $POCl_3$ was evaporated under vacuum, and the yellow oily residue was treated with ice-water (ca. 30 mL). The resulting mixture was allowed to stand for 1 h and was extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were washed with a solution of $NaHCO_3$ to adjust the pH to 7. The organic phase was dried over $MgSO_4$ and concentrated. The crude product was purified by recrystallization (MeOH–EtOAc, 1:4) to give **8** as a white solid; yield: 2.64 g (8.83 mmol, 79%); mp 99–111 °C.

IR: 2915, 1542, 1433, 1377, 1256, 1051, 719, 642 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.63 [s, 3 H, C-4(CH_3)], 2.67 [s, 3 H, C-6(CH_3)].

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.4, 25.6, 119.7, 122.5, 148.7, 150.0, 156.1.

MS (EI, 70 eV): *m*/*z* (%) = 303 (M^+, $^{81}Br/^{81}Br/^{37}Cl$, 13), 301 (M^+, $^{79}Br/^{81}Br/^{37}Cl$, $^{81}Br/^{81}Br/^{35}Cl$, 72), 299 (M^+, $^{79}Br/^{79}Br/^{37}Cl$, $^{81}Br/^{79}Br/^{35}Cl$, 100), 297 (M^+, $^{79}Br/^{79}Br/^{35}Cl$, 48), 220 (15), 182 (19).

HRMS: *m*/*z* calcd for $C_7H_6{}^{81}Br^{79}Br^{35}ClN$: 298.8535; found: 298.8531.

3,5-Dibromo-2,4-dimethylpyridine (4)

A mixture of pyridine **8** (1.44 g, 4.95 mmol), a 57% solution of aq HI (27 mL), and red phosphorus (2.1 g, 67.72 mmol) was refluxed for 16 h. The progress of the reaction was monitored by GC-MS. The red phosphorus was filtered off and the resulting clear solution was poured carefully into a sat. aq solution of $NaHCO_3$ (350 mL). The solution was extracted with CH_2Cl_2 (3 × 30 mL) and the com-

Table 3 Data for Compounds **1** and **2**

Compound	Mp (°C)	IR (cm^{-1})	MS *m*/*z* (%)	HRMS[a]	
				Calcd	Found
1c	thick oil	2957, 1604, 1457, 1229, 1047, 1027, 780, 702	319 (M^+, 100), 318 (33), 304 (11), 288 (14), 276 (4), 274 (5)	$C_{21}H_{21}NaNO_2$ 342.1470	342.1481
1d	92–95 (EtOH)	2958, 1599, 1461, 1237, 1182, 1050, 1024, 752	319 (M^+, 100), 318 (6), 304 (13), 288 (15), 274 (7), 272 (8)	$C_{21}H_{21}NaNO_2$ 342.1470	342.1487
1e	87–89 (EtOH)	2985, 1492, 1445, 1320, 1250, 1092, 817, 754	351 (M^+, 100), 350 (15), 336 (13), 303 (8), 288 (9), 175 (10)	$C_{21}H_{21}NaNS_2$ 374.1013	374.1027
1f	136–138 (EtOH)	2948, 1499, 1279, 1224, 1050, 874, 804, 726	379 (M^+, 100), 364 (15), 349 (9), 334 (22), 189 (8), 174 (5)	$C_{23}H_{25}NaNO_4$ 402.1681	402.1698
1g	133–135 (EtOH)	2936, 1581, 1456, 1408, 1319, 1235, 1123, 1055	439 (M^+, 100), 424 (37), 396 (2), 366 (4), 219 (8), 212 (4)	$C_{25}H_{29}NaNO_6$ 462.1892	462.1904
1h	110–112 (EtOH–benzene)	2894, 1487, 1332, 1100, 1037, 934, 811, 753	347 (M^+, 100), 346 (29), 316 (6), 288 (3), 189 (4), 173 (6)	$C_{21}H_{17}NaNO_4$ 370.1055	370.1071
2c	84.5–85.5	2957, 1603, 1489, 1285, 1233, 1157, 1047, 781	319 (M^+, 100), 318 (29), 304 (16), 288 (25), 274 (5), 260 (6)	$C_{21}H_{21}NaNO_2$ 342.1470	342.1487
2d	thick oil[b]	2929, 1585, 1495, 1433, 1276, 1241, 1052, 751	319 (M^+, 100), 318 (14), 304 (18), 288 (25), 274 (9), 258 (7)	$C_{21}H_{21}NaNO_2$ 342.1470	342.1480
2e	82–84 (EtOH–benzene)	2919, 1603, 1495, 1434, 1392, 1092, 1021, 820	351 (M^+, 100), 350 (7), 336 (9), 303 (7), 289 (8), 257 (5)	$C_{21}H_{21}NaNS_2$ 374.1013	374.1029
2f	thick oil[c]	2933, 1585, 1459, 1224, 1180, 1048, 860, 803	379 (M^+, 100), 364 (13), 366 (3), 334 (19), 318 (3), 189 (4)	$C_{23}H_{25}NaNO_4$ 402.1681	402.1694
2g	141.5–142.5 (EtOH)	2937, 1582, 1458, 1237, 1125, 832, 751, 686	439 (M^+, 100), 424 (31), 366 (3), 350 (5), 334 (2) 219 (6)	$C_{25}H_{29}NaNO_6$ 462.1892	462.1901
2h	105–106 (EtOH)	2894, 1498, 1451, 1234, 1103, 934, 879, 811	347 (M^+, 100), 346 (5), 316 (2), 288 (3), 189 (2), 173 (2)	$C_{21}H_{17}NaNO_4$ 370.1055	370.1068

[a] HRMS data were recorded for $[M + Na]^+$.
[b] Mp 177–180 °C, hydrochloride salt.
[c] Mp 209–211 °C, hydrochloride salt.

bined extracts were dried over $MgSO_4$. After evaporation of the solvent the pink oil was purified by column chromatography (hexane–EtOAc, 9:1) to give compound **4** as a colorless oil; yield: 1.09 g (4.11 mmol, 83%); oil at r.t. (Lit.[34] 29–30 °C).

MS (EI, 70 eV): *m/z* (%) = 367 (M^+, $^{81}Br/^{81}Br$, 48), 265(M^+, $^{79}Br/^{81}Br$, 100), 263 (M^+, $^{79}Br/^{79}Br$, 51), 186 (13), 184 (14), 104 (20).

Cross-Coupling Reaction under Suzuki Conditions; General Procedure

Method A

A vigorously magnetically stirred mixture of aryl halide **7** or **8** (0.67 mmol), phenylboronic acid (1.34 mmol), $Pd(PPh_3)_4$ (4% mol), and $NaHCO_3$ (5.36 mmol) in benzene–H_2O–EtOH (0.77:0.17:0.06, 15 mL) was heated at 80 °C (oil bath) under an argon atmosphere for 24 h. The progress of the reaction was monitored by removing a sample (20–40 μL) of the organic layer, which was diluted with EtOAc (1 mL) and analyzed by GC-MS. When the reaction was complete the mixture was cooled and partitioned between EtOAc (40 mL) and brine (20 mL). The aqueous layer was separated and additionally extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (2 × 5 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (hexane–EtOAc, cyclohexane–EtOAc, or cyclohexane–$CHCl_3$).

Method B

The procedure described in method A was applied; however, toluene was used instead of benzene and Na_2CO_3 (4 equiv) was used in place of $NaHCO_3$. The reaction mixtures were stirred at 105 °C for 8 h. GC-MS analysis and product separation was performed as described in Method A.

Method C

The procedure described in method A was applied; however, K_2CO_3 was used in place of $NaHCO_3$ and DME–H_2O (4:1, 15 mL) was used as the solvent system. The reaction mixture was stirred for 24 h at 75 °C. The progress of the reaction was monitored by removing a sample (20–40 μL), which was cooled and the solvent evaporated under a stream of nitrogen (40 °C), the residue was treated with H_2O (1 mL), and extracted with EtOAc (1 mL). The layers were separated and the organic extract (1 μL) was injected into the GC-MS system.

Table 4 NMR Data for Compounds **1** and **2**

Compound	^1H NMR ($CDCl_3$), δ	^{13}C NMR ($CDCl_3$), δ
1c	1.96 [s, 3 H, C-4(CH_3)], 2.32 [s, 3 H, C-2(CH_3)], 3.84 (s, 6 H, 2 × OCH_3), 6.74–6.81 (m, 2 H), 6.87–6.95 (m, 4 H), 7.32–7.43 (m, 2 H), 8.35 (s, 1 H, C-6)	18.2, 23.8, 55.4, 55.5, 112.8, 113.0, 114.8, 115.5, 121.5, 122.2, 129.6, 130.1, 135.6, 137.0, 140.1, 140.8, 143.0, 148.0, 155.1, 159.7, 160.1
1d	1.81 [s, 3 H, C-4(CH_3)], 2.28 [s, 3 H, C-2(CH_3)], 3.77 (s, 6 H, 2 × OCH_3), 6.95–7.07 (m, 4 H), 7.33–7.42 (m, 2 H), 7.30–7.39 (m, 2 H), 8.29 (s, 1 H, C-6)	17.4, 23.3, 55.4, 110.7, 112.0, 120.5, 120.8, 127.6, 127.8, 129.0, 129.1, 130.7, 131.4, 132.1, 133.0, 145.1, 148.2, 155.3, 157.0
1e	1.94 [s, 3 H, C-4(CH_3)], 2.30 [s, 3 H, C-2CH_3)], 2.53, 2.55 (2 s, 6 H, 2 × SCH_3), 7.10–7.14 (m, 2 H), 7.23–7.37 (m, 6 H), 8.32 (s, 1 H, C-6)	15.8, 15.9, 18.4, 24.0, 126.5, 126.9, 129.7, 130.2, 135.2, 135.4, 136.0, 136.6, 137.9, 138.1, 143.2, 148.2, 155.4
1f	1.85 [s, 3 H, C-4(CH_3)], 2.32 [s, 3 H, C-2(CH_3)], 3.72, 3.80 (2 s, 12 H, OCH_3), 6.67–6.95 (m, 6 H), 8.31 (s, 1 H, C-6)	17.5, 23.0, 55.8, 56.0, 111.8, 112.0, 113.3, 113.6, 116.6, 117.2, 128.1, 128.4, 132.2, 133.1, 145.7, 147.5, 151.2, 153.4, 153.7, 155.1
1g	20.02 [s, 3 H, C-4(CH_3)], 2.36 [s, 3 H, C-2(CH_3)], 3.87, 3.88 [2 s, 12 H, C-3′(OCH_3), C-3‴(OCH_3), C-5″(OCH_3), C-5‴(OCH_3)], 3.91, 3.93 (2 s, 6 H, C-4′, C-4″), 6.41, 6.53 (2 s, 4 H), 8.36 (s, 1 H, C-6)	18.2, 23.8, 56.4, 61.1, 61.2, 106.0, 106.9, 134.2, 134.9, 137.2, 137.4, 137.6, 143.2, 148.0, 153.3, 153.8, 155.3
1h	1.99 [s, 3 H, C-4(CH_3)], 2.35 [s, 3 H, C-2(CH_3)], 6.02, 6.03 (2 s, 4 H, OCH_2O), 6.62, 6.77 (2 dd, *J* = 8, 1.5 Hz, 2 H, C-6′, C-6″), 6.66, 6.79 (2 d, *J* = 1.5 Hz, 2 H, C-2′, C-2 ″), 6.89, 6.91 (2 d, *J* = 8 Hz, 2 H, C-5′, C-5″), 8.31 (s, 1 H, C-2)	18.2, 23.3, 101.2, 101.2, 108.4, 108.8, 109.3, 109.96, 122.1, 123.0, 131.9, 132.3, 135.5, 136.9, 144.4, 146.9, 147.1, 147.6, 148.1, 154.8
2c	2.57 (s, 6 H, 2 × CH_3), 3.84 (s, 6 H, 2 × OCH_3), 6.87–6.96 (m, 6 H), 7.31–7.39 (m, 2 H), 7.45 (s, 1 H, C-4)	22.9, 55.3, 112.8, 114.9, 121.6, 129.4, 134.2, 138.5, 141.0, 153.7, 159.5
2d	2.53 (s, 6 H, 2 × CH_3), 3.85 (s, 6 H, 2 × OCH_3), 6.95–7.05 (m, 4 H), 7.15–7.21 (m, 2 H), 7.31–7.40 (m, 2 H, Ph, C-4)	23.0, 55.3, 113.8, 130.2, 132.2, 134.0, 138.7, 153.53, 158.9
2e	2.52, 2.55 (2 s, 12 H, 2 × CH_3, 2 × SCH_3), 7.24–7.34 (m, 8 H), 7.37 (s, 1 H, C-4)	15.7, 22.9, 126.3, 129.5, 133.9, 136.2, 137.9, 138.54, 153.7
2f	2.48 (s, 6 H, 2 × CH_3), 3.74, 3.78 (2 s, 12 H, 4 × OCH_3), 6.77 (br s, 2 H), 6.89, 6.90 (br s, 4 H), 7.42 (s, 1 H, C-4)	25.0, 55.8, 56.0, 111.3, 112.0, 113.9, 117.0, 118.6, 120.8, 150.9, 153.5, 154.5
2g	2.57 (s, 6 H, 2 × CH_3), 3.88 [s, 12 H, C-3′(OCH_3), C-3″(OCH_3), C-5′(OCH_3), C-5″(OCH_3)], 3.91 [s, 6 H, C-4′(OCH_3), C-4″(OCH_3)], 6.55 (s, 4 H), 7.44 (s, 1 H, C-4)	23.0, 56.2, 61.0, 106.3, 134.4, 135.2, 138.2, 153.1, 153.7
2h	2.56 (s, 6 H, 2 × CH_3), 6.01 (s, 4 H, OCH_2O), 6.78 (dd, *J* = 8, 1.5 Hz, 2 H, C-6′), 6.81 (d, *J* = 1.5 Hz, 2 H, C-2′), 6.87 (d, *J* = 8 Hz, 2 H, C-5′), 7.37 (s, 1 H, C-4)	25.0, 101.2, 108.4, 109.6, 122.6, 134.4, 139.2, 147.1, 147.7, 153.4

For the synthesis of pyridines **14**, **15**, **21**, and pyridine **2a** from 3-bromo-5-phenyl-2,6-dimethylpyridine (**30**), 1.5 equivalents phenylboronic acid were used. The synthesis of **1a–c**, **1e**, **1g**, **1h**, and **2a–h** from dibromopyridines **3** and **4** employed 2.2 equivalents boronic acid. Compound **4** was reacted with 3.0 equivalents 2-methoxyphenyl- and 2,5-dimethoxyphenylboronic acid.

4-Bromo-2,6-dimethyl-3,5-diphenylpyridine (23)
A mixture of pyridone **22** (0.98 g, 3.56 mmol) and $POBr_3$ (4.13 g, 14.39 mmol) was heated at 175 °C for 1 h. To the cooled mixture, ice-water (ca. 30 mL) were added cautiously and the resulting solution was neutralized with solid $NaHCO_3$. The aq solution was extracted with CH_2Cl_2 (2 × 15 mL) and the combined extracts were dried over $MgSO_4$. After evaporation of the solvent, the brown solid residue was purified by column chromatography ($CHCl_3$–EtOAc, 1→10:1) to give bromopyridine **23** as a beige solid; yield: 0.89 g (2.66 mmol, 73%); mp 155–158 °C.

IR: 3053, 1600, 1525, 1403, 1304, 1028, 757, 699 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.35 (s, 6 H, 2 × CH_3), 7.19–7.25 (m, 4 H), 7.40–7.52 (m, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.3, 127.8, 128.6, 129.2, 135.6, 139.6, 155.7.

MS (EI, 70 eV): *m*/*z* (%) = 339 (M^+, ^{81}Br, 97), 337 (M^+, ^{79}Br, 100), 258 (24), 215 (63), 202 (43), 115 (33).

HRMS: *m*/*z* calcd for $C_{19}H_{16}{}^{79}BrN$: 337.0466; found: 337.0471.

2-Bromo-4,6-dimethyl-3,5-diphenylpyridine (24)
In analogy to the procedure described for **23**, the title compound was prepared from pyridone **11** (1.33 g, 4.84 mmol) followed by column chromatography (cyclohexane–$CHCl_3$, 1:1→1) to give a white solid; yield: 1.35 g (3.99 mmol, 83%); mp 246–248 °C.

IR: 3055, 1601, 1492, 1408, 1382, 866, 761, 703 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.76 [s, 3 H, C-4(CH_3)], 2.29 [s, 3 H, C-6(CH_3)], 7.15–7.25 (m, 4 H), 7.39–7.52 (m, 6 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.5, 23.4, 127.6, 127.9, 128.6, 128.8, 128.9, 129.3, 136.6, 136.7, 138.2, 139.0, 141.3, 146.7, 156.2.

MS (EI, 70 eV): *m*/*z* (%) = 339 (M^+, ^{81}Br, 96), 337 (M^+, ^{79}Br, 100), 258 (76), 243 (46), 231 (44), 215 (34).

HRMS: *m*/*z* calcd for $C_{19}H_{16}{}^{79}BrN$: 337.0466; found: 337.0469.

2,6-Dimethyl-3,4,5-triphenylpyridine (15)
According to Method B pyridine **15** was obtained from bromopyridine **23** after column chromatography (hexane–EtOAc, 20:1→6:1); yield: 21%; mp 112–115 °C.

IR: 3057, 2922, 1602, 1549, 1493, 1072, 758, 698 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.42 (s, 6 H, 2 × CH_3), 6.67–7.40 (m, 15 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.6, 115.5, 119.8, 126.1, 126.5, 126.8, 127.8, 129.6, 130.0, 130.2, 133.7, 138.0.

MS (EI, 70 eV): *m*/*z* (%) = 335 (M^+, 100), 334 (49), 320 (10), 278 (4), 215 (8), 178 (6).

HRMS: *m*/*z* calcd for $C_{25}H_{20}N$: 335.1676; found: 335.1674.

2,4-Dimethyl-3,5,6-triphenylpyridine (21)
According to Method B pyridine **21** was obtained from bromopyridine **24** after column chromatography (hexane–EtOAc, 10:1→3:1); yield: 68%; mp 123–125 °C (lit.[35] 125–126 °C).

MS (EI, 70 eV): *m*/*z* (%) = 335 (M^+, 40), 334 (100), 318 (8), 278 (3), 215 (4), 159 (4).

2,6-Dimethyl-3-phenylpyridin-4(1*H*)-one (26)
A mixture of 2,6-dimethyl-3-phenyl-4*H*-pyran-4-one (**25**; 3.65 g, 18.25 mmol), a 25% solution of aq NH_3 (35 mL), and EtOH (40 mL) was heated in a sealed glass tube at 90 °C for 48 h. After cooling, the reaction mixture was concentrated to dryness. The brown solid was recrystallized from MeOH–EtOAc to give **26** as a beige solid; yield: 2.5 g (12.56 mmol, 69%); mp 267–269 °C.

IR: 2998, 1645, 1612, 1485, 1362, 1233, 757, 700 cm^{-1}.

^1H NMR (200 MHz, CD_3OD): δ = 2.11 [s, 3 H, C-2(CH_3)], 2.31 [s, 3 H, C-6(CH_3)], 6.26 (br s, 1 H, C=CH), 7.17–7.43 (m, 5 H).

^{13}C NMR (50 MHz, CD_3OD): δ = 18.1, 18.8, 115.7, 128.4, 129.4, 131.6, 136.5, 146.4, 149.1, 180.1.

MS (EI, 70 eV): *m*/*z* (%) = 199 (M^+, 95), 198 (100), 170 (4), 128 (7), 115 (11), 89 (9).

HRMS: *m*/*z* calcd for $C_{13}H_{13}NaNO$ [M + Na]: 222.0895; found: 222.0923.

4-Chloro-2,6-dimethyl-3-phenylpyridine (12)
In analogy to the procedure described for **8**, the title compound **12** was prepared from pyridone **26** (730 mg, 3.67 mmol). Purification by column chromatography (cyclohexane–EtOAc, 1→3:1) gave **12** as a white solid; yield: 511 mg (2.35 mmol, 64%); mp 47–49 °C.

IR: 3060, 1604, 1579, 1444, 1276, 1099, 764, 700 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.31 [s, 3 H, C-2(CH_3)], 2.55 [s, 3 H, C-6(CH_3)], 7.14 (s, 1 H, C-5), 7.17–7.22 (m, 2 H), 7.39–7.50 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.1, 24.2, 121.5, 128.0, 128.7, 129.5, 132.9, 137.0, 143.7, 157.5, 157.8.

MS (EI, 70 eV): *m*/*z* (%) = 219 (M^+, ^{37}Cl, 32), 217 (M^+, ^{35}Cl, 100), 216 (98), 181 (18), 136 (34), 115 (35).

HRMS: *m*/*z* calcd for $C_{13}H_{13}{}^{35}ClN$ [M + H]: 218.0736; found: 218.0749.

2,6-Dimethyl-3-phenylpyridine (13)
A magnetically stirred mixture of chloropyridine **12** (0.237 mg, 1.09 mmol) and KOH (200 mg. 3.57 mmol) in anhyd EtOH (60 mL) was hydrogenated over 10% Pd/C (190 mg). After 24 h the catalyst was filtered off and the resulting solution was concentrated to dryness. Purification by column chromatography (cyclohexane–EtOAc, 20:1→5:1) afforded **13** as a white solid; yield: 163 mg (0.88 mmol, 82%); mp 34–36 °C (lit.[36] 185 °C/96 mmHg).

IR: 3058, 1591, 1463, 1448, 1262, 1009, 828, 764 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.48 [s, 3 H, C-2(CH_3)], 2.57 [s, 3 H, C-6(CH_3)], 7.03 (d, 1 H, C-5), 7.28–7.45 (m, 6 H, Ph, C-4).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.4, 24.3, 120.7, 127.4, 128.5, 129.2, 134.1, 140.2, 155.0, 156.6.

MS (EI, 70 eV): *m*/*z* (%) = 183 (M^+, 94), 182 (100), 181 (16), 167 (9), 141 (5), 115 (6).

HRMS: *m*/*z* calcd for $C_{13}H_{13}N$: 183.1048; found: 183.1044.

4-Bromo-2,6-dimethyl-3-phenylpyridine (27)
In analogy to the procedure described for **23**, the title compound was prepared from pyridone **26** (1.22 g, 6.13 mmol). Purification by column chromatography (hexane–$CHCl_3$, 1:1→1) gave **27** as a brown solid; yield: 385 mg (1.47 mmol, 24%); mp 61–63 °C.

IR: 3057, 1603, 1573, 1443, 1380, 1273, 807, 763 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.31 [s, 3 H, C-2(CH_3)], 2.54 [s, 3 H, C-6(CH_3)], 7.16–7.20 (m, 2 H), 7.34 (s, 1 H, C-5), 7.39–7.46 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.9, 24.4, 124.7, 127.9, 128.5, 129.2, 134.7, 134.8, 157.3, 157.3.

MS (EI, 70 eV): *m*/*z* (%) = 263 (M^+, ^{81}Br, 97), 261 (M^+, ^{79}Br, 100), 181 (30), 167 (21), 139 (28), 115 (32).

HRMS: *m*/*z* calcd for $C_{13}H_{13}{}^{79}BrN$ [M + H]: 262.0228; found: 262.0237.

2,6-Dimethyl-3,4-diphenylpyridine (14)

According to Method A, pyridine **14** was obtained from bromopyridine **27** after column chromatography (hexane–EtOAc, 20:1→5:1); yield: 29%; mp 103–106 °C (lit.[37] 106–107 °C).

MS (EI, 70 eV): *m*/*z* (%) = 259 (M^+, 100), 258 (64), 244 (28), 215 (12), 202 (17), 115 (6).

3-Bromo-2,6-dimethyl-5-phenylpyridin-4(1*H*)-one (28)

To a stirred solution of pyridone **26** (4.52 g, 22.71 mmol) in glacial AcOH (50 mL) a mixture of Br_2 (1.5 mL) in glacial AcOH (6 mL) was added dropwise. The resulting clear solution was stirred for 2 h and then concentrated under reduced pressure to half of its initial volume. The solution was poured onto H_2O (750 mL) and the light brown precipitate was filtered off and washed with a copious amounts of H_2O. The brown precipitate was dried under vacuum (40 °C) to give pyridone **28** in the next step without further purification; yield: 5.87 g (21.12 mmol, 93%); mp > 290 °C (dec.).

IR: 3264, 3049–2860, 1610, 1290, 1043, 783, 744, 649 cm^{-1}.

^{1}H NMR (200 MHz, CD_3OD): δ = 2.13 [s, 3 H, C-6(CH_3)], 2.54 [s, 3 H, C-2(CH_3)], 7.19–7.45 (m, 5 H).

^{13}C NMR (50 MHz, CD_3OD): δ = 17.9, 20.7, 128.6, 129.4, 131.6; due to the low solubility of **28** the signals of quaternary carbons were too weak to be observed.

MS (EI, 70 eV): *m*/*z* (%) = 279 (M^+, ^{81}Br, 96), 277 (M^+, ^{79}Br, 100), 197 (19), 168 (7), 128 (23), 115 (16).

HRMS: *m*/*z* calcd for $C_{13}H_{12}{}^{79}BrNO$ [M]: 277.0102; found: 277.0106.

3-Bromo-4-chloro-2,6-dimethyl-5-phenylpyridine (29)

In analogy to the procedure described for **8**, the title compound was prepared from pyridone **28** (2.18 g, 7.84 mmol). Purification by column chromatography (cyclohexane–EtOAc, 20:1→4:1) gave **29** as a white solid; yield: 1.74 g (5.87 mmol, 75%); mp 66–68 °C.

IR: 3058, 1555, 1435, 1283, 1024, 981, 771, 704 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.25 [s, 3 H, C-6(CH_3)], 2.74 [s, 3 H, C-2(CH_3)], 7.15–7.20 (m, 2 H), 7.41–7.48 (m, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.67, 26.38, 119.24, 128.14, 128.72, 129.05, 134.73, 137.26, 155.40, 157.19.

MS (EI, 70 eV): *m*/*z* (%) = 299 (M^+, ^{81}Br/^{37}Cl, 23), 297 (M^+, ^{81}Br/^{35}Cl, ^{79}Br/^{37}Cl, 100), 295 (M^+, ^{79}Br/^{35}Cl, 81), 294 (55), 180 (18), 139 (60).

HRMS: *m*/*z* calcd for $C_{13}H_{12}{}^{79}Br^{35}ClN$ [M + H]: 295.9839; found: 295.9845.

3-Bromo-2,6-dimethyl-5-phenylpyridine (30)

In analogy to the procedure described for **4**, the title compound was prepared from pyridine **29** (1.15 g, 3.88 mmol). Purification by column chromatography (hexane–EtOAc, 5:1) gave **30** as a colorless oil; yield: 418 mg (1.59 mmol, 41%). Upon storage in a refrigerator, the oil solidified to give a white, waxy solid; mp 27–30 °C.

Compound **30**, when treated with phenylboronic acid according to Method A, gave pyridine **2a** in 84% yield.

IR: 3058, 1578, 1428, 1383, 1225, 907, 768, 700 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.43 [s, 3 H, C-6(CH_3)], 2.67 [s, 3 H, C-2(CH_3)], 7.26–7.44 (m, 5 H), 7.65 (s, 1 H, C-4).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.0, 24.7, 118.4, 127.9, 128.7, 129.1, 136.3, 138.7, 140.7, 154.1, 155.2.

MS (EI, 70 eV): *m*/*z* (%) = 263 (M^+, ^{81}Br, 97), 261 (M^+, ^{79}Br, 100), 181 (33), 167 (14), 139 (24), 115 (20).

HRMS: *m*/*z* calcd for $C_{13}H_{13}{}^{79}BrN$ [M + H]: 262.0228; found: 262.0239.

4-Chloro-3,5-bis(4-methoxyphenyl)-2,6-dimethylpyridine (5b)

Halopyridine **7** (200 mg, 0.67 mmol) was treated with 4-methoxyphenylboronic acid (199 mg, 2.2 equiv, 1.47 mmol) according to Method A (48 h). Column chromatography (cyclohexane–EtOAc, 1:1) gave a white crystalline mass (195 mg) which consisted of three major compounds (according to GC-MS): 4-chloro-3,5-bis(4-methoxyphenyl)-2,6-dimethylpyridine (**5b**) (the main constituent), 4-chloro-3-(4-methoxyphenyl)-2,6-dimethylpyridine (**33**), and 3-bromo-4-chloro-5-(4-methoxyphenyl)-2,6-dimethylpyridine (**34**). The product was recrystallized from EtOAc to give 120 mg of pure **5b** as a white solid; yield: 51% (0.34 mmol); mp 151–153 °C.

IR: 2956, 1611, 1513, 1408, 1288, 1247, 1035, 828 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.34 (s, 6 H, 2 × CH_3), 3.68 (s, 6 H, 2 × OCH_3), 6.99, 7.16 (8 H, AA′XX′).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.0, 55.3, 113.8, 130.2, 132.2, 134.0, 138.7, 153.5, 158.9.

MS (EI, 70 eV): *m*/*z* (%) = 355 (M^+, ^{37}Cl, 35), 353 (M^+, ^{35}Cl, 100), 352 (17), 338 (7), 310 (5), 176 (7).

HRMS: *m*/*z* calcd for $C_{21}H_{20}{}^{35}ClNaNO_2$ [M + Na]: 376.1080; found: 376.1095.

34

The mother liquor was concentrated and submitted to column chromatography (cyclohexane–EtOAc, 10:1→1:1) to give pure pyridine **34** as white crystals (concentration of the first fraction); yield: 11% (24 mg); mp 121–123 °C.

IR: 2929, 1610, 1438, 1410, 1289, 1248, 981, 829 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.26 [s, 3 H, C-6(CH_3)], 2.73 [s, 3 H, C-2(CH_3)], 3.87 (s, 3 H, OCH_3), 6.99, 7.10 (4 H, AA′XX′).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.7, 26.3, 55.3, 114.1, 119.2, 129.8, 130.3, 155.8, 156.9, 159.3.

MS (EI, 70 eV): *m*/*z* (%) = 329 (M^+, ^{81}Br/^{37}Cl, 27), 327 (M^+, ^{81}Br/^{35}Cl , ^{79}Br/^{37}Cl, 100), 325 (M^+, ^{79}Br/^{35}Cl, 77), 312 (14), 284 (15), 282 (13).

HRMS: *m*/*z* calcd for $C_{14}H_{13}{}^{81}Br^{35}ClNO$: 326.9848; found 326.9844.

33

Concentration of the second fraction gave pyridine **33** as a white solid; yield: 17% (28 mg); mp 43–45 °C.

IR: 2982, 1611, 1543, 1454, 1246, 1177, 1038, 829 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.32 [s, 3 H, C-2(CH_3)], 2.54 [s, 3 H, C-6(CH_3)], 3.86 (s, 3 H, OCH_3), 6.98, 7.12 (4 H, AA′XX′), 7.15 (s, 1 H, C-5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.0, 55.2, 107.0, 113.9, 121.4, 129.0, 130.6, 132.5, 144.0, 157.1, 158.0, 159.1.

MS (EI, 70 eV): *m*/*z* (%) = 249 (M^+, ^{37}Cl, 35), 247 (M^+, ^{35}Cl, 100), 246 (35), 232 (33), 216 (15), 204 (36).

HRMS: *m*/*z* calcd for $C_{14}H_{14}{}^{35}ClNO$: 247.0763; found: 247.0768.

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