Suzuki–Miyaura and Negishi Approaches to a Series of Forensically Relevant Pyridines and Pyrimidines

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Abstract: A library of 5-aryl-4-methylpyrimidines, phenyl ring-substituted derivatives of 4-benzylpyrimidines, 2,6-benzylpyridines, and 2,6-dibenzyl-4-methylpyridines were prepared. The synthesis of 5-aryl-4-methylpyrimidines was accomplished by Suzuki–Miyaura cross-coupling reaction between arylboronic acids and 5-bromo-4-methylpyrimidine. The 4-benzylpyrimidines and 2,6-benzylpyridines were synthesized by treatment of 4-bromopyrimidine and 2,6-dibromopyridine derivatives with ring-substituted benzylzinc reagents.

Key words: cross-coupling reaction, amphetamine analogues, Leuckart synthesis, drugs, heterocycles

Polysubstituted pyridine and pyrimidine ring systems are important motifs in compounds often encountered in pharmaceutical industry and agriculture.[1] In forensic chemistry, phenyl-, methyl-, and benzylpyridines and the corresponding benzyl- and methylphenylpyrimidines are well known as synthetic by-products in illegally synthesized amphetamine and its ring-substituted analogues.[2,3]

Because these compounds were identified exclusively in amphetamines synthesized by the Leuckart method,[4] they had been considered as the so-called 'route-specific' markers. Therefore, the identification of these compounds in the reaction mixtures or in seized 'street' material (in the form of tablets, capsules, powders) clearly points out that the drugs were produced according to the Leuckart protocol.

The formation of 4-benzyl- and 5-aryl-4-methylpyrimidines was proposed to proceed through the condensation of two molecules of formamide with one molecule of arylacetone. The condensation of two molecules of arylacetone and one of formamide leads to different methyl-, phenyl-, and benzylpyridines.[3c,5] The substitution pattern of the heterocycles depends on the arrangement of the aforementioned components, which take part in the condensation processes.[6]

As a part of our research program designed to identify new 'route-specific' markers of amphetamine analogues prepared by the Leuckart method,[3c,6,7] it was decided to obtain four families of heterocycles, namely 5-aryl-4-methylpyrimidines **1a–m**, 4-benzylpyrimidines **2a–i**, 2,6-dibenzylpyridines **3a–i**, and 2,6-dibenzyl-4-methylpyridines **4a–i** (Figure 1).

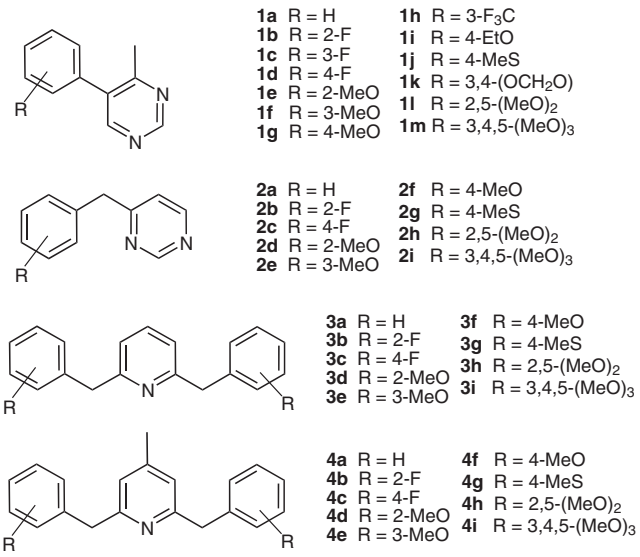

Figure 1 Forensically relevant pyrimidines **1a–m**, **2a–i** and pyridines **3a–i**, **4a–i**

In this paper, we demonstrate that aryl substituted pyrimidines **1a–m** are readily available by the Suzuki–Miyaura cross-coupling reaction between appropriately halogenated pyrimidine and arylboronic acids. Benzylpyrimidines **2a–i** and dibenzylpyridines **3a–i** and **4a–i**, were prepared by the reaction of benzylzinc reagents with bromo-substituted pyridines and pyrimidines.

5-Aryl-4-methylpyrimidines

The traditional synthesis of substituted pyrimidines involves condensation of two components bearing the desired substituents at appropriate positions.[8] According to this strategy, 5-phenyl-4-methylpyrimidine (**1a**), its 4-methoxy- (**1g**), and 4-methylthio- (**1j**) substituted derivatives were previously prepared by treatment of the corresponding arylacetones with tris-formamidomethane in the presence of formamide.[9] In our case, where the access to a larger library of pyrimidines was necessary, this methodology was not promising. The major drawback of this approach was the necessity for the preparation of a range of arylacetones with highly variable phenyl substituents.

We expected that the Suzuki–Miyaura cross-coupling reaction between appropriately halogenated pyrimidine ring and commercially available arylboronic acids would be an

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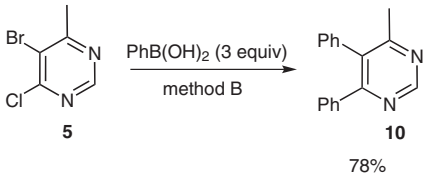
effective way to the desired pyrimidines **1a**–**m**. Recently, this methodology has been used by us to create a library of 2,6-dimethyl- and 3,4-dimethyl-3,5-diarylpyridines.[10]

Our experiments were started with 5-bromo-4-chloro-6-methylpyrimidine (**5**), assuming that a regioselective monoarylation of **5** at the C-5 position would deliver 5-aryl-4-chloro-6-methylpyrimidines,[11] which could be then easily transformed into 5-aryl-4-methylpyrimidines by simple dehalogenation on H_2/Pd/C.

There are several examples of the regioselective arylation of di- and trihalopyrimidines in the literature.[11] Delia et al.[12] have found that the reactivity of 2,4,6-trichloro- and 2,4,6-triiodopyrimidine was in the order: C-4 > C-6 > C-2. Parry et al.[13] reported that the treatment of 2,4-dichloropyrimidine with 2-chloropyridylboronic acid led mainly to 4-monosubstituted product. A similar order of reactivity was observed by Ceide et al.,[14] who reported that the reaction of 2,4-dichloropyrimidine with phenylboronic acid under microwave conditions took place at C-4 position predominantly. The same team investigated a stepwise arylation of 2,4,5-trichloro- and 2,4-dichloro-5-bromopyrimidine by a microwave-mediated Suzuki cross-coupling reaction. The order of reactivity for trichloropyrimidine was C-4 > C-5 > C-2. In the case of 2,4-dichloro-5-bromopyrimidine, the first phenyl ring was introduced predominantly at C-5 position by using Pd(dppb)Cl_2 as a catalyst, indicating a reversed reactivity. This experiment was repeated using 5-bromo-4-chloro-6-methylpyrimidine (**5**), which is easily accessible in three steps starting from commercially available 4-hydroxy-2-mercapto-6-methylpyrimidine.[15] The products of the reaction were identified on the basis of their mass spectra,[16] taking into account the molecular ions and characteristic mass isotopic pattern of halogens. The results of the experiment are summarized in Table 1.

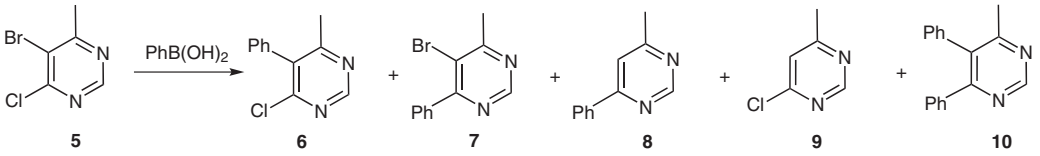
When the reaction of **5** with $PhB(OH)_2$ was carried out under common Suzuki reaction conditions (method A), surprisingly 5-bromo-4-methyl-6-phenylpyrimidine (**7**) was observed as the sole product (GC-MS yield ca. 76%). When the reaction was repeated on a larger scale, **7** was isolated in 62% yield. Similar regioselectivity was achieved when Cs_2CO_3 instead of Na_2CO_3 was used as a base (method F), although the overall conversion of the substrate and the yield of **7** were lower. The catalytic systems based on Buchwald ligand S-Phos[18] (method E) and $PdCl_2$ (ligandless Method D) led mainly to the diarylated pyrimidine **10**. The identity of **10** was confirmed by its independent synthesis, according to Scheme 1.



Scheme 1 Synthesis of diphenylpyridine **10**

The most promising results were obtained in the case of methods B and C. When the reaction was carried out with Pd$(OAc)_2$/P(*o*-tolyl)$_3$ in a combination with 3 equivalents of K_3PO_4 in toluene–H_2O–EtOH (10:2:1) solvent system, the selectivity towards chlorophenylpyrimidine **6** was improved to ca. 33%. However, the conversion of the substrate was moderate (ca. 62%) and the reaction mixture

Table 1 Attempted Regioselective Phenylation of Pyrimidine **5**

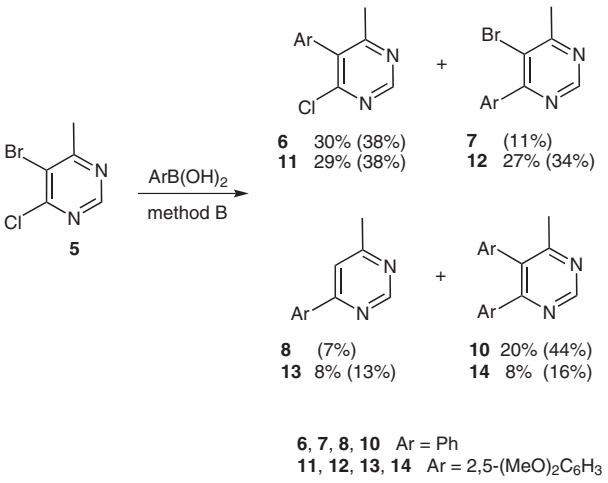


Method[a]	Conv. (%)	Yield (%)[b]				
		6	**7**	**8**[c]	**9**[c]	**10**
A	77	traces	76 (62)	traces	traces	traces
B	>98	56	4	3	1	34
C	62	33	7	4	10	6
D	53	4	3	8	traces	38
E	74	4	3	traces	traces	67
F	50	1	48	traces	traces	1

[a] Conditions: Method A: $PhB(OH)_2$ (1.1 equiv), Pd$[PPh_3]_4$ (6 mol%), Na_2CO_3 (3 equiv), toluene–H_2O–EtOH (10:2:1), 80 °C, 16 h; method B: $PhB(OH)_2$ (1.1 equiv), $PdCl_2$(dppf)CH_2Cl_2 (6 mol%), K_3PO_4 (3 equiv), 1,4-dioxane, 90 °C, 16 h; method C: $PhB(OH)_2$ (1.1 equiv), Pd$(OAc)_2$ (5 mol%), P(*o*-Tol)$_3$ (10 mol%), K_3PO_4 (3 equiv), toluene–H_2O–EtOH (10:2:1), 80 °C, 16 h; method D: $PhB(OH)_2$ (1.1 equiv), $PdCl_2$ (10 mol%), K_3PO_4 (3 equiv), toluene–EtOH (8:2), 80 °C, 24 h; method E: $PhB(OH)_2$ (1.1 equiv), Pd$(OAc)_2$ (3 mol%), S-Phos (6 mol%), K_3PO_4 (3 equiv), toluene, 90 °C, 8 h; method F: $PhB(OH)_2$ (1.1 equiv), Pd$[PPh_3]_4$ (5 mol%),Cs_2CO_3 (3 equiv), toluene–H_2O–EtOH (10:2:1), 80 °C, 48 h.
[b] GC-MS yield, isolated yield given in parentheses.
[c] Compound **8** and **9** were identified based on their mass spectra published in mass spectral library.[17]

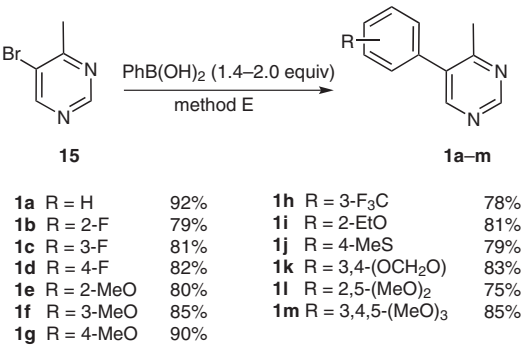
contained substantial amounts of other cross-coupling products. Better result were observed when the reaction was performed with $PdCl_2(dppf)CH_2Cl_2$ complex in 1,4-dioxane (method B). As shown in Table 1, the conversion was excellent and the GC-MS yield of the desired pyrimidine **6** was 56%.

With these promising results in our hands, the reaction of compound **5** as a substrate was explored with 1.2 equivalents of phenylboronic acid under method B, on the scale 10-fold larger than in a preliminary test. Unfortunately, the desired product **6** was isolated only in 30% yield, together with disubstituted pyrimidine **10** (yield 20%), accompanied by 5-bromo-6-methyl-4-phenylpyrimidine (**7**) and 4-methyl-6-phenylpyrimidine (**8**) in GC-MS yield of 11% and 7%, respectively (Scheme 2). A similar outcome of the reaction was observed when 2,5-dimethoxyphenylboronic acid was used instead of its phenyl derivative. In this case, the main product isolated from the reaction mixture was 4-chloro-5-(2,5-dimethoxyphenyl)-6-methylpyrimidine (**11**) (29%). Repeated separations by column chromatography led to the isolation of 5-bromo-4-(2,5-dimethoxyphenyl)-6-methylpyrimidine (**12**), 4-(2,5-dimethoxyphenyl)-6-methylpyrimidine (**13**), and 4,5-bis(2,5-dimethoxyphenyl)-6-methylpyrimidine (**14**) with 27%, 8% and 8% yield, respectively.



Scheme 2 Attempted regioselective arylation of **5** using phenylboronic and 2,5-dimethoxyphenylboronic acid; the GC-MS yields of products in crude reaction mixtures are given in parentheses

Considering the above results and the observed difficulties in selective monoarylation of bromochloropyrimidine **5**, we decided to simplify our approach. In order to suppress possible side-reactions, 5-bromo-4-methylpyrimidine (**15**) was chosen as a substrate for cross-coupling reactions (Scheme 3). The initial tests using methods A, B, C, E, and F gave in each case a full conversion of the starting material and 4-methyl-5-phenylpyrimidine as the sole product, accompanied only by a small amount of biphenyl. The GC-MS monitoring indicated that in each case a full conversion of the substrate was achieved after four hours. When methods D and E were employed, pyrimidine **15** was consumed in less than one hour. Therefore, we decided that method E will be suitable to perform a series of reactions between **15** and a wide range of arylboronic acids. Arylboronic acids with a ring substitution pattern matching those present in the most popular amphetamine-type drugs were chosen for the coupling reaction.[19] The cross-coupling leading to phenyl- (**1a**), 2-, 3-, 4-methoxyphenyl- (**1e**–**g**), 2-ethoxyphenyl- (**1i**) 4-methylthiophenyl- (**1j**) and 3,4-methylenedioxyphenyl- (**1k**) substituted pyrimidines proceeded smoothly with good (78–85%) to excellent (>85%) yield.



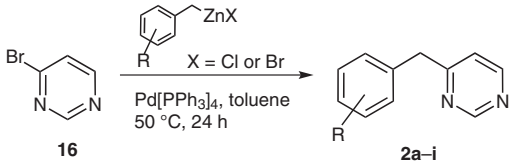
Scheme 3 Synthesis of 5-aryl-4-methylpyrimidines **1a**–**m**

Initially, when 1.4 equivalents of 2-, 3-, 4-fluorophenyl-, 2,5-dimethoxyphenyl-, and 3,4,5-trimethoxyphenyl-substituted boronic acids were used, slightly lower yields were obtained for compounds **1b**–**d**, **1l**, **1m** (45–55%). Presumably, a self-condensation and protodeboronation reactions, typical for electron-rich and electron-deficient boronic acids, account for the observed drop of the yield. Indeed, the GC-MS screening of crude reaction mixtures revealed the presence of protodeboronation products (1,3-dimethoxy- and 1,2,3-trimethoxybenzene) and the corresponding ring substituted diaryls. The problem was solved when the amount of arylboronic acid was increased from 1.4 to 2 equivalents. This slight modification led us to isolate fluorinated and polymethoxylated pyrimidines in 75–85% yields.

4-Benzylpyrimidines

After initial experiments, it was realized that the low-yield preparation of 4-benzylpyrimidine (**2a**) from phenylacetonitrile anion and 4,6-dichloropyrimidine with subsequent dehalogenation of 4-benzyl-6-chloropyrimidine on Pd/C, had already been described.[20] The same authors prepared 4-benzyl-6-chloropyrimidine by treatment of 4,6-dichloropyrimidine with benzyl(tributylphosphonium) ylide. In a simpler approach, 4-benzylpyrimidine (**2a**), its 4-methoxy **2f**, and 4-methylthio **2g** derivatives were prepared (also in low yield), by benzylation of pyrimidine with the corresponding benzylmagnesium reagents, with subsequent oxidation of intermediary 4-benzyl-3,4-dihydropyrimidines.[9b]

It was envisioned that the alternative approach based on the Negishi cross-coupling between 4-bromopyrimidine **16** and benzylzinc reagents (Scheme 4) might be more ef-



2a	R = H	81%	**2f**	R = 4-MeO	77%
2b	R = 2-F	39%	**2g**	R = 4-MeS	36%
2c	R = 4-F	74%	**2h**	R = 2,5-$(MeO)_2$	75%
2d	R = 2-MeO	72%	**2i**	R = 3,4,5-$(MeO)_3$	29%
2e	R = 3-MeO	80%			

Scheme 4 Synthesis of 4-benzylpyrimidines **2a–i**

fective, allowing the construction of a larger library of derivatives.

4-Bromopyrimidine, the preparation of which was described recently in a patent literature,[20] was subjected to a series of cross-coupling reactions with an array of commercially available benzylzinc reagents [Scheme 4, R = H, 2-MeO, 3-MeO, 4-MeO, 4-F, 2,5-$(MeO)_2$] to give benzylpyrimidines in good yields (72–81%). The reactions leading to 4-MeS-, 3,4,5-$(MeO)_3$- and 2-F-substituted benzylpyrimidines **2b**, **2g**, and **2i** were carried out with the corresponding benzylzinc reagents prepared according to the improved method proposed by Knochel et al.[22]

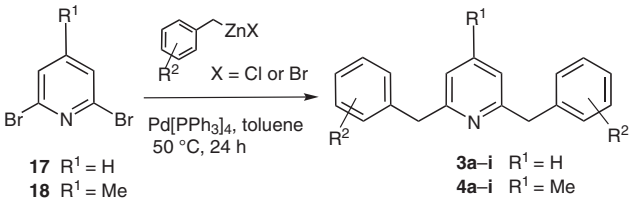
2,6-Dibenzylpyridines

Dibenzylpyridine **3a** and its 4-methylated isomer **4a** represent a novel class of impurities identified in amphetamine synthesized by the Leuckart method.[23] In order to extend our investigation to other amphetamine analogues, an access to a library of ring-substituted 2,6-dibenzyl **3a–i** and 2,6-dibenzyl-4-methylpyridines **4a–i** was needed.

Minato et al.[24] have shown that the monomethylation of 2,6-dichloro- and 2,6-dibromopyridine could be achieved under Pd(0)- and Ni(0)-catalyzed cross-coupling reaction with benzylzinc bromide. The formation of considerable amount of dibenzylated pyridine **4a** was observed (up to 15%), even when 1.1 equivalents of benzylzinc reagent was employed. By applying this general method to 2,6-dibromopyridine (**17**) and by increasing the amount of benzylzinc bromide (up to 3.6 equiv) dibenzylpyrimidine **3a** was obtained in 83% yield. Under identical conditions, starting from 2,6-dibromo-4-methylpyridine (**18**), dibenzylated product **4a** was obtained in 89% yield (Scheme 5). GC-MS screening revealed that full conversion of substrates **17** and **18** was achieved within 16 hours at 50 °C, and only traces of monobenzylated products, namely 2-bromo-6-benzyl- and 2-bromo-6-benzyl-4-methylpyridine could be detected.

Considering the above results, cross-coupling reactions were carried out employing different ring-substituted benzylzinc reagents (Scheme 5). High yields of the reactions (72–85%) were obtained for fluoro- **3b**,**c**, **4b**,**c**, and monomethoxy **3d–f**, **4d–f** substituted products (Scheme 5).

However, the introduction of 4-methylthio-, 2,5-dimethoxy-, and 3,4,5-trimethoxybenzyl substituents re-



3a	R^2 = H	83%	**3f**	R^2 = 4-MeO	80%
3b	R^2 = 2-F	72%	**3g**	R^2 = 4-MeS	39%
3c	R^2 = 4-F	85%	**3h**	R^2 = 2,5-$(MeO)_2$	50%
3d	R^2 = 2-MeO	81%	**3i**	R^2 = 3,4,5-$(MeO)_3$	32%
3e	R^2 = 3-MeO	79%			

4a	R^2 = H	89%	**4f**	R^2 = 4-MeO	80%
4b	R^2 = 2-F	75%	**4g**	R^2 = 4-MeS	30%
4c	R^2 = 4-F	79%	**4h**	R^2 = 2,5-$(MeO)_2$	45%
4d	R^2 = 2-MeO	72%	**4i**	R^2 = 3,4,5-$(MeO)_3$	29%
4e	R^2 = 3-MeO	78%			

Scheme 5 Synthesis of 2,6-dibenzylpyridines **3a–i** and **4a–i**

sulted in lower yields. In the latter case, the GC-MS analysis of the crude reaction mixture indicated the presence of a significant amount of 2,5-dimethoxyphenyl- and 3,4,5-trimethoxyphenyl-substituted 1,2-diarylethanes. These compounds arose from a competitive self-condensation reaction of benzylzinc reagents that influenced the overall yield of products **3h–i** and **4h–i**.

In a recently published study, Knochel et al.[22] described some benzylation reactions performed with a catalytic system based on the Buchwald ligand S-Phos. The same catalyst applied in our study furnished dibenzylpyrimidine **3a** and **4a** in less than three hours, although the yield of the product did not improve noticeably.

In conclusion, we have developed an efficient method for the synthesis of a series of phenyl ring-substituted 5-aryl-4-methylpyrimidines **1a–m** and benzylpyrimidines **2a–i**, which are important in the field of forensic chemistry. The third group of compounds, ring-substituted 2,6-dibenzylpyridines **3a–i** and their 4-methyl derivatives **4a–i**, was synthesized on the basis of the described procedure. The arylation and benzylation of appropriately halogenated heterocycles were effectively performed using Suzuki–Miyaura cross-coupling or Negishi reactions.

Melting points are uncorrected (Electrothermal, Model IA 9200). IR spectra were recorded on a Bruker Vertex spectrometer equipped with IR Hyperion 2000 microscope, from 400–4000 cm^{-1} and working in the reflection mode. The spectral data consisted of 16 scans with 2 cm^{-1} resolution. 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. Chemical shifts are reported in ppm and coupling constants (*J*) are given in hertz (Hz). The low-resolution mass spectra were collected on a Hewlett-Packard HP 5973 mass detector coupled with 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 0.6 mL/min (helium gas) and the oven temperature was ramped between 80–310 °C at a rate of 12 °C/min. HRMS data were recorded on Micromass LCT (ESI-TOF) instrument.

The following compounds were prepared according to published procedures: 5-bromo-4-chloro-6-methylpyrimidine (**5**),[15b] 5-bromo-4-methylpyrimidine (**15**),[15b] 2,6-dibromo-4-methylpyridine (**18**),[25] and 4-bromopyrimidine (**16**).[21] 2-Fluorobenzylzinc chloride, 4-methylthiobenzyl bromide, and 3,4,5-trimethoxybenzyl chloride[22] were prepared according to the literature. Other substrates together with reagents and solvents were purchased from commercial manufacturers and were used without additional purification. The Suzuki cross-coupling reactions and Negishi reaction were carried out under N_2 or argon atmosphere. TLC was performed on the Merck Kieselgel 60 F-254 plates. Chromatographic purification of compounds was carried out on silica gel MN Kieselgel 60 (100–200 mesh).

Cross-Coupling Reaction under Suzuki Conditions; Regioselective Phenylation of Pyrimidine 5; General Procedures (Table 1)
Trial reactions were carried out on microscale.

Method A
A vigorously magnetically stirred mixture of aryl halide **5** (0.12 mmol), phenylboronic acid (17 mg, 0.14 mmol), $Pd(PPh_3)_4$ (8.1 mg, 6 mol%), and $NaHCO_3$ (35 mg, 0.42 mmol) in a solvent system consisting of toluene (2 mL), H_2O (0.4 mL), and EtOH (0.2 mL) was heated at 80 °C (oil bath) under N_2 atmosphere for 16 h. After cooling, a sample (20–40 μL) of the organic layer taken from the reaction mixture was diluted with EtOAc (1 mL) and was directly analyzed by GC-MS.

Method B
A vigorously magnetically stirred mixture of aryl halide **5** (0.12 mmol), phenylboronic acid (17 mg, 0.14 mmol), $PdCl_2(dppf)CH_2Cl_2$ (4.9 mg, 5 mol%), and K_3PO_4 (89 mg, 0.42 mmol) in 1,4-dioxane (2.5 mL) was heated at 90 °C (oil bath) under N_2 atmosphere for 16 h. After cooling, a sample (20–40 μl) taken from the reaction mixture was diluted with H_2O (4 mL) and extracted with EtOAc (1 mL). The organic layer was separated and analyzed directly by GC-MS.

Product Separation (10-Fold Scale): After cooling, the solvent was evaporated under vacuum and the residue was treated with H_2O (25 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The products were separated by column chromatography.

Method C
A vigorously magnetically stirred mixture of aryl halide **5** (0.12 mmol), phenylboronic acid (17 mg, 0.14 mmol), Pd(OAc) (1.5 mg, 5 mol%), P(*o*-tolyl)$_3$ (3.6 mg, 10 mol%), and K_3PO_4 (89 mg, 0.42 mmol) in a solvent system consisting of toluene (2 mL), H_2O (0.4 mL), and EtOH (0.2 mL) was heated at 80 °C (oil bath) under N_2 atmosphere for 16 h. For GC-MS analysis, see method A.

Method D
A vigorously magnetically stirred mixture of aryl halide **5** (0.12 mmol), phenylboronic acid (17 mg, 0.14 mmol), $PdCl_2$ (2.1 mg, 10 mol%), and K_3PO_4 (89 mg, 0.42 mmol) in a solvent system consisting of toluene (1.6 mL) and EtOH (0.4 mL) was heated at 80 °C (oil bath) under N_2 atmosphere for 24 h. A sample (20–40 μL) of reaction mixture was added to H_2O (4 mL) and extracted with EtOAc (1 mL). The organic layer was separated and analyzed directly by GC-MS.

Method E
A vigorously magnetically stirred mixture of aryl halide **5** (0.12 mmol), phenylboronic acid (17 mg, 0.14 mmol), Pd(OAc) (0.8 mg, 3 mol%) and S-Phos (3.0 mg, 6 mol%), and K_3PO_4 (89 mg, 0.42 mmol) in toluene (2.5 mL) was heated at 90 °C (oil bath) under N_2 atmosphere for 8 h. GC-MS analysis was performed as described for method A.

Method F
Analogous to method A, with the exception that Cs_2CO_3 was used instead of Na_2CO_3 and the reaction was continued for 48 h. GC-MS analysis was performed as described for method A.

4-Methyl-5,6-diphenylpyrimidine (10)
5-Bromo-4-chloro-6-methylpyrimidine (**5**; 100 mg, 0.48 mmol) was reacted with phenylboronic acid (175 mg, 1.45 mmol) according to method B. Column chromatography (hexane–EtOAc, 5:2) gave **10** as a white solid; yield: 93 mg (78%); mp 131–133 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, CH_3), 7.09–7.40 (m, 10 H, H_{Ph}), 9.14 (s, 1 H, H_{pyrim}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.7, 127.9, 128.0, 128.8, 129.0, 129.9, 130.0, 132.8, 136.6, 138.2, 157.1, 163.6, 166.2.

MS (EI, 70 eV): *m*/*z* (%) = 245 (100), 246 (26), 204 (8), 117 (7), 115 (7), 176 (6), 217 (4), 151 (4).

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{14}N_2$ + Na: 269.0960; found: 269.0966.

5-Bromo-4-methyl-6-phenylpyrimidine (7)
Pyrimidine **5** (100 mg, 0.48 mmol) was reacted with phenylboronic acid (64 mg, 0.52 mmol) according to method B. Column chromatography (hexane–EtOAc, 10:1) gave **7** as a pale yellow solid; yield: 75 mg (62%); mp 66–68 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.76 (s, 3 H, CH_3), 7.45–7.52 (m, 2 H, H_{Ph}), 7.69–7.74 (m, 3 H, H_{Ph}), 9.00 (s, 1 H, H_{pyrim}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.1, 120.5, 128.3, 129.4, 130.0, 137.9, 156.1, 165.2, 167.8.

MS (EI, 70 eV): *m*/*z* (%) = 169 (100), 248 (24), 250 (23), 128 (20), 115 (15), 101 (12), 142 (11), 182 (7).

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_9BrN_2$ + Na: 270.9847; found: 270.9844.

4-Chloro-6-methyl-5-phenylpyrimidine (6)
Pyrimidine **5** (250 mg, 1.2 mmol) was reacted with phenylboronic acid (624 mg, 5.2 mmol) according to method B. Column chromatography (hexane–EtOAc, 5:1) gave 275 mg of white solid containing a mixture of products, including 4-chloro-6-methyl-5-phenylpyrimidine (**6**) and 4-methyl-5,6-diphenylpyrimidine (**10**) as the main constituents. Repeated column chromatography (cyclohexane–EtOAc, 10:1 → 5:1) (first fraction) afforded 74 mg (30%) as a pale yellow solid; mp 46–48 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.36 (s, 3 H, CH_3), 7.21–7.26 (m, 2 H, H_{Ph}), 7.45–7.51 (m, 3 H, H_{Ph}), 8.85 (s, 1 H, H_{pyrim}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.7, 128.3, 128.9, 129.0, 129.1, 134.6, 156.1, 156.9, 167.6.

MS (EI, 70 eV): *m*/*z* (%) = 204 (100), 141 (52), 115 (31), 203 (30), 206 (29), 140 (20), 136 (18), 169 (12).

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_9ClN_2$ + Na: 227.0352; found: 227.0350.

The second fraction gave 60 mg (20%) of 4-methyl-5,6-diphenylpyrimidine (**10**). Pyrimidine **8** was not isolated in purity suitable to perform its NMR characterization.

Reaction of 5 with 2,5-Dimethoxyphenylboronic Acid; 4-Chloro-5-(2,5-dimethoxyphenyl)-6-methylpyrimidine (11) and Products 12–14
Pyrimidine **5** (250 mg, 1.2 mmol) was treated with 2,5-dimethoxyphenylboronic acid (936 mg, 5.2 mmol) according to method B.

Column chromatography (cyclohexane–EtOAc, 20:1 → 10:1) gave in the first fraction 93 mg (yield 29%) of **11** as a white solid; mp 104–106 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, CH_3), 3.73 and 3.80 (2 s, each 3 H, 2 × OCH_3), 6.69–6.71 (m, 1 H, H_{aryl}), 6.96–6.98 (m, 2 H, H_{aryl}), 8.84 (s, 1 H, H_{pyrim}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.3, 56.0, 56.3, 112.5, 115.1, 116.2, 124.2, 130.9, 150.7, 153.8, 156.9, 160.8, 168.3.

MS (EI, 70 eV): *m*/*z* (%) = 264 (100), 208 (54), 266 (32), 214 (26), 249 (24), 210 (17), 188 (14), 199 (10).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{13}ClN_2O_2$ + Na: 287.0563; found: 287.0570.

5-Bromo-4-(2,5-dimethoxyphenyl)-6-methylpyrimidine (12)

The concentration of second fraction gave 101 mg (27%) of **12**; mp 100–102 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.73 (s, 3 H, CH_3), 3.76 and 3.79 (2 s, each 3 H, 2 × OCH_3), 6.82–6.83 (m, 1 H, H_{aryl}), 6.94–6.98 (m, 2 H, H_{aryl}), 9.00 (s, 1 H, H_{pyrim}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.7, 56.0, 56.3, 112.6, 115.0, 116.4, 123.0, 128.2, 150.7, 153.7, 156.0, 164.7, 166.8.

MS (EI, 70 eV): *m*/*z* (%) = 229 (100), 214 (79), 308 (68), 310 (67), 199 (45), 201 (43), 186 (23), 169 (18).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{13}BrN_2O_2$ + Na: 331.0058; found: 331.0054.

After repeated column chromatography (hexane–$CHCl_3$, 3:1 → 1:1), the third fraction furnished two additional compounds **13** and **14**.

4-(2,5-Dimethoxyphenyl)-6-methylpyrimidine (13)

Yield: 22 mg (8%); pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.60 (s, 3 H, CH_3), 3.84 and 3.86 (2 s, each 3 H, 2 × OCH_3), 6.97–6.99 (m, 2 H, H_{aryl}), 7.55–6.56 (m, 1 H, H_{aryl}), 7.82 (d, *J* = 0.4 Hz, 1 H, H-5$_{pyrim}$), 9.14 (d, *J* = 0.4 Hz, 1 H, H-2$_{pyrim}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.6, 56.1, 56.4, 113.3, 115.4, 117.8, 121.5, 126.9, 152.3, 154.1, 158.5, 162.4, 166.6.

MS (EI, 70 eV): *m*/*z* (%) = 230 (100) 229 (95), 201 (56), 95 (49), 215 (32), 199 (31), 174 (22), 159 (19).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{14}N_2O_2$ + Na: 253.0953; found: 253.0954.

4,5-Bis(2,5-dimethoxyphenyl)-6-methylpyrimidine (14)

Yield: 35 mg (8%); white solid; mp 86–88 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, CH_3), 3.49, 3.60, 3.66, 3.67 (4 s, each 3 H, 4 × OCH_3), 6.49–5.65 (m, 2 H, H_{aryl}), 6.74–7.79 (m, 4 H, H_{aryl}), 9.12 (s, 1 H, H_{pyrim}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.0, 55.6, 55.7, 55.8, 55.9, 111.1, 111.8, 114.4, 115.4, 115.7, 116.4, 125.8, 128.6, 131.1, 150.5, 150.8, 153.1, 153.2, 156.9, 163.7, 166.3.

MS (EI, 70 eV): *m*/*z* (%) = 366 (100), 335 (95), 229 (31), 231 (30), 305 (27), 351 (26), 336 (23), 349 (11).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{22}N_2O_4$ + Na: 389.1477; found: 389.1480.

5-Aryl-4-methylpyrimidines 1a–m; General Procedure

According to method E, a mixture of 5-bromo-4-methylpyrimidine (**15**; 200 mg, 1.15 mmol), the corresponding arylboronic acid (1.61 mmol, 1.4 equiv), $Pd(OAc)_2$ (5.5 mg, 3 mol%), S-Phos (29 mg, 6 mol%), 3 equiv of K_3PO_4 (730 mg, 3.45 mmol, 3 equiv) in toluene (12 mL) was vigorously stirred and heated in an oil bath (90 °C) for 8 h. After cooling to r.t., the toluene layer was washed with brine (2 × 5 mL), dried ($MgSO_4$), evaporated under reduced pressure, and the residue was purified by column chromatography using cyclohexane–EtOAc (10:1 → 5:1) and hexane–$CHCl_3$ (3:1 → 1:1) solvent systems. In the case of product **1b**–**d** and **1l**,**m**, 2 equiv of the corresponding arylboronic acid were used.

5-Phenyl-4-methylpyrimidine (1a)

Yield: 182 mg (92%); pale yellow solid; mp 75–76 °C (Lit.[7b] mp 75–75.5 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, CH_3), 7.28–7.35 (m, 2 H, H_{Ph}), 7.55–6.56 (m, 1 H, H_{Ph}), 7.43–7.54 (m, 2 H, H_{Ph}), 8.54 (s, 1 H, H-6$_{pyrim}$), 9.08 (s, 1 H, H-2$_{pyrim}$).

^{13}C NMR and MS were consistent with the literature data.[9b]

5-(2-Fluorophenyl)-4-methylpyrimidine (1b)

Yield: 172 mg (79%); yellow solid; mp 30–32 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.46 (d, *J* = 1.4 Hz, 3 H, CH_3), 7.17–7.33 (m, 3 H, H_{aryl}), 7.41–7.52 (m, 1 H, H_{aryl}), 8.54 (s, 1 H, H-6$_{pyrim}$), 9.12 (s, 1 H, H-2$_{pyrim}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.6 (d, *J* = 3.2 Hz), 116.0 (d, ^2J = 21.4 Hz), 123.4 (d, ^2J = 15.9 Hz), 124.6 (d, *J* = 3.9 Hz), 129.3, 130.8 (d, ^3J = 7.9 Hz), 131.1 (d, ^4J = 2.7 Hz), 156.8, 157.8, 159.6 (d, ^1J = 247 Hz), 165.6.

MS (EI, 70 eV): *m*/*z* (%) = 188 (100), 120 (81), 133 (28), 187 (22) 169 (15), 94 (6), 107 (5), 146 (5).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_9FN_2$ + Na: 211.0647; found: 211.0650.

5-(3-Fluorophenyl)-4-methylpyrimidine (1c)

Yield: 176 mg (81%); pale yellow solid; mp 58–60 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.53 (s, 3 H, CH_3), 7.03–7.21 (m, 3 H, H_{aryl}), 7.42–7.53 (m, 1 H, H_{aryl}), 8.54 (s, 1 H, H-6$_{pyrim}$), 9.10 (s, 1 H, H-2$_{pyrim}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.8, 115.4 (d, ^2J = 21 Hz), 116.1 (d, ^2J = 22 Hz), 124.8 (d, ^4J = 2.8 Hz), 130.5 (d, ^3J = 8.3 Hz), 133.8, 137.9 (d, ^3J = 8.1 Hz), 156.2, 157.5, 162.7 (d, ^1J = 248 Hz), 164.4.

MS (EI, 70 eV): *m*/*z* (%) = 188 (100), 120 (61), 187 (49), 133 (34), 94 (6), 160 (5), 107 (5), 146 (4).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_9FN_2$ + Na: 211.0647; found: 211.0644.

5-(4-Fluorophenyl)-4-methylpyrimidine (1d)

Yield: 178 mg (82%); beige solid; mp 61–62 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.51 (s, 3 H, CH_3), 7.14–7.35 (m, 4 H, H_{aryl}), 8.52 (s, 1 H, H-6$_{pyrim}$), 9.08 (s, 1 H, H-2$_{pyrim}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.9, 115.9 (d, ^2J = 21 Hz), 130.8 (d, ^3J = 8.1 Hz), 131.7 (d, ^4J = 3.5 Hz), 134.0, 156.3, 157.3, 162.8 (d, ^1J = 248 Hz), 164.5.

MS (EI, 70 eV): *m*/*z* (%) = 188 (100), 120 (53), 187 (44), 133 (22), 107 (5), 146 (5), 160 (4), 168 (4).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_9FN_2$ + Na: 211.0647; found: 211.0650.

5-(2-Methoxyphenyl)-4-methylpyrimidine (1e)

Yield: 185 mg (80%); pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, CH_3), 3.79 (s, 3 H, OCH_3), 6.99–7.18 (m, 3 H, H_{Ph}), 7.39–7.48 (m, 1 H, H_{Ph}), 8.48 (s, 1 H, H-6$_{pyrim}$), 9.07 (s, 1 H, H-2$_{pyrim}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.6, 55.3, 110.9, 120.8, 124.7, 130.2, 130.7, 131.9, 156.6, 156.8, 157.1, 165.8.

MS (EI, 70 eV): *m*/*z* (%) = 200 (100), 131 (18), 144 (16), 169 (9), 89 (9), 185 (6), 103 (5), 115 (4).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{12}N_2O$ + Na: 223.0847; found: 223.0848.

5-(3-Methoxyphenyl)-4-methylpyrimidine (1f)
Yield: 196 mg (85%); white solid; mp 68–69 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.53 (s, 3 H, CH_3), 3.86 (s, 3 H, OCH_3), 6.84–7.01 (m, 3 H, H_{aryl}), 7.36–7.44 (m, 1 H, H_{aryl}), 8.54 (s, 1 H, H-6_{pyrim}), 9.08 (s, 1 H, H-2_{pyrim}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.9, 55.3, 113.6, 114.9, 121.4, 129.9, 134.7, 137.1, 156.2, 157.2, 159.7, 164.4.

MS (EI, 70 eV): *m*/*z* (%) = 200 (100), 199 (17), 169 (15), 102 (10), 132 (7), 142 (6), 185 (6), 157 (5).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{12}N_2O$ + Na: 223.0847; found: 223.0851.

5-(4-Methoxyphenyl)-4-methylpyrimidine (1g)
Yield: 208 mg (90%); pale yellow solid; mp 56–58 °C (Lit.[7b] mp 56–58 °C).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, CH_3), 3.87 (s, 3 H, OCH_3), 6.99, 7.03, 7.24, 7.28 (AA′XX′ system, 4 H, H_{aryl}), 8.51 (s, 1 H, H-6_{pyrim}), 9.04 (s, 1 H, H-2_{pyrim}).

^{13}C NMR and MS data were consistent with the literature data.[9b]

4-Methyl-5-[3-(trifluoromethyl)phenyl]pyrimidine (1h)
Yield: 214 mg (78%); pale yellow solid; mp 54–57 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.64 (s, 3 H, CH_3), 7.01–7.23 (m, 3 H, H_{aryl}), 7.40–7.54 (m, 1 H, H_{aryl}), 8.55 (s, 1 H, H-6_{pyrim}), 9.13 (s, 1 H, H-2_{pyrim}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.0, 125.4–126.0 (m), 126.7, 129.6, 131.2, 132.5, 133.8, 136.8, 156.5, 157.9, 164.6.

MS (EI, 70 eV): *m*/*z* (%) = 238 (100), 176 (62), 237 (59), 169 (18), 115 (9), 219 (8), 151 (5), 176 (4).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_9F_3N_2$ + Na: 261.0616; found: 261.0619.

5-(2-Ethoxyphenyl)-4-methylpyrimidine (1i)
Yield: 200 mg (81%); beige solid; mp 72–74 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7 Hz, 3 H, CH_2CH_3), 2.40 (s, 3 H, CH_3 at C-4_{pyrim}), 4.04 (q, *J* = 6.9 Hz, 2 H, CH_2CH_3), 6.96–7.18 (m, 3 H, H_{aryl}), 7.36–7.45 (m, 1 H, H_{aryl}), 8.48 (s, 1 H, H-6_{pyrim}), 9.06 (s, 1 H, H-2_{pyrim}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.8, 22.8, 63.9, 111.9, 120.8, 125.0, 130.3, 130.9, 132.2, 156.1, 157.0, 157.2, 165.9.

MS (EI, 70 eV): *m*/*z* (%) = 214 (100), 186 (62), 118 (61), 171 (33), 185 (30), 131 (23), 89 (9), 199 (7).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{14}N_2O$ + Na: 237.1004; found: 237.1007.

4-Methyl-5-[4-(methylthio)phenyl]pyrimidine (1j)
Yield: 197 mg (79%); yellow solid; mp 62–64 °C (Lit.[7b] oil).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.52 and 2.54 (2 s, each 3 H, OCH_3 and SCH_3), 7.23, 7.28, 7.34, 7.38 (AA′XX′ system, 4 H, H_{aryl}), 8.52 (s, 1 H, H-6_{pyrim}), 9.07 (s, 1 H, H-2_{pyrim}).

^{13}C NMR and MS data were consistent with the literature data.[9b]

4-Methyl-5-(3,4-methylenedioxyphenyl)pyrimidine (1k)
Yield: 205 mg (83%); beige solid; mp 138–140 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, CH_3), 6.05 (s, 2 H, CH_2), 6.75–6.94 (m, 3 H, H_{aryl}), 8.50 (s, 1 H, H-6_{pyrim}), 9.05 (s, 1 H, H-2_{pyrim}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.9, 101.4, 108.7, 109.4, 122.7, 129.4, 134.6, 147.8, 148.0, 156.3, 157.0, 164.5.

MS (EI, 70 eV): *m*/*z* (%) = 214 (100), 213 (38), 155 (15), 146 (9), 102 (7), 145 (7), 183 (5), 88 (4).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{10}N_2O_2$ + Na: 237.0640; found: 237.0647.

5-(2,5-Dimethoxyphenyl)-4-methylpyrimidine (1l)
Yield: 199 mg (75%); pale yellow solid; mp 59–61 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, CH_3), 3.73 and 3.81 (2 s, each 3 H, 2 × OCH_3), 6.72–6.74 (m, 1 H, H_{aryl}), 6.93–6.95 (m, 2 H, H_{aryl}), 8.48 (s, 1 H, H-6_{pyrim}), 9.01 (s, 1 H, H-2_{pyrim}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.6, 55.8, 55.9, 111.9, 114.4, 116.7, 125.5, 131.7, 150.8, 153.5, 156.7, 157.2, 165.8.

MS (EI, 70 eV): *m*/*z* (%) = 230 (100), 174 (87), 215 (8), 119 (6), 188 (5), 200 (4), 147 (4), 159 (3).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{14}N_2O_2$ + Na: 253.0953; found: 253.0955.

4-Methyl-5-(3,4,5-trimethoxyphenyl)pyrimidine (1m)
Yield: 255 mg (85%); beige solid; mp 124–126 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.55 (s, 3 H, CH_3), 3.89 (s, 6 H, 2 × OCH_3 at C-3 and C-5), 3.92 (s, 3 H, OCH_3 at C-4), 6.51 (s, 2 H, H_{aryl}), 8.55 (s, 1 H, H-6_{pyrim}), 9.07 (s, 1 H, H-2_{pyrim}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.9, 56.3, 61.0, 106.2, 131.3, 135.0, 138.1, 153.4, 156.2, 157.1, 164.4.

MS (EI, 70 eV): *m*/*z* (%) = 260 (100), 245 (55), 131 (16), 217 (9), 187 (8), 161 (5), 202 (5), 144 (4).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{16}N_2O_3$ + Na: 283.1059; found: 283.1062.

4-Benzylpyrimidines 2a–i; General Procedure
The preparation of 4-methyl-, 2-fluoro-, and 3,4,5-trimethoxybenzylzinc halides and further benzylation reactions were carried out in flame-dried glassware under argon atmosphere. The benzylzinc reagents (as a solution in THF) were transferred with gas-tight syringe (Agilent Technologies). To a magnetically stirred mixture of 4-bromopyrimidine (**16**; approx. 150 mg, 0.94 mmol) and $Pd[PPh_3]_4$ (5 mol%) in anhyd THF (10 mL) was added the corresponding benzylzinc reagent in THF (3.5 mL of 0.5 M solution, 1.80 equiv) over 5 min. The reaction mixture was stirred and heated at 50 °C for 24 h. After cooling, the reaction was quenched with sat. aq NH_4Cl (2 mL) and the solvent was evaporated under reduced pressure. The residue was taken up with H_2O (25 mL), extracted with CH_2Cl_2 (2 × 10 mL), and the combined extracts were dried ($MgSO_4$). After concentration, the brown residue was purified by column chromatography using cyclohexane–EtOAc (20:1 → 5:1) or hexane–$CHCl_3$ (3:1 → 1:2) solvent systems.

4-Benzylpyrimidine (2a)
Yield: 130 mg (81%); yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.11 (s, 2 H, CH_2), 7.10 (dd, *J* = 5.0, 1.5 Hz, 1 H, H-5_{pyrim}), 7.21–7.31 (m, 5 H, H_{Ph}), 8.59 (d, *J* = 5 Hz, 1 H, H-6_{pyrim}), 9.14 (d, *J* = 1.5 Hz, 1 H, H-2_{pyrim}).

^{13}C NMR and MS data were consistent with the literature data.[7b]

4-(2-Fluorobenzyl)pyrimidine (2b)
Yield: 69 mg (39%); yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.15 (s, 2 H, CH_2), 7.03–7.34 (m, 5 H, H_{aryl} and H-5_{pyrim}), 8.60 (d, *J* = 5.4 Hz, 1 H, H-6_{pyrim}), 9.14 (br s, 1 H, H-2_{pyrim}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 37.5 (d, ^3J = 2.35 Hz), 115.8 (d, ^2J = 21.3 Hz), 120.5 (d, ^4J = 1.5 Hz), 124.3, 124.7 (d, ^3J = 3.2 Hz), 129.2 (d, ^2J = 8.7 Hz), 131.7 (^3J = 3.9 Hz), 157.3, 158.7, 158.9, 166.0 (d, ^1J = 238.2 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 169 (100), 133 (12), 109 (10), 160 (9), 83 (8), 161 (6), 107 (5), 187 (5).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_9FN_2$ + Na: 211.0647; found: 211.0649.

4-(4-Fluorobenzyl)pyrimidine (2c)
Yield: 131 mg (74%); pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.09 (s, 2 H, CH_2), 6.98–7.12 (m, 3 H, H_{aryl} and H-5_{pyrim}), 7.19–7.27 (m, 2 H, H_{aryl}), 8.60 (d, *J* = 5.2 Hz, 1 H, H-6_{pyrim}), 9.14 (d, *J* = 0.8 Hz, 1 H, H-2_{pyrim}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 43.5, 115.9 (d, ^2J = 21.4 Hz), 120.7, 130.9 (^3J = 7.9 Hz), 133.2 (^4J = 2.6 Hz), 157.3, 159.0, 162.1 (^1J = 246.5 Hz), 169.3.

MS (EI, 70 eV): *m*/*z* (%) = 187 (100), 188 (36), 109 (22), 133 (17), 160 (9), 83 (8), 161 (6), 107 (5).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_9FN_2$ + Na: 211.0647; found: 211.0652.

4-(2-Methoxybenzyl)pyrimidine (2d)
Yield: 135 mg (72%); pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, OCH_3), 4.12 (s, 2 H, CH_2), 6.87–6.98 (m, 2 H, H_{aryl}), 7.10 (dd, *J* = 5.0, 1.5 Hz, 1 H, H-5_{pyrim}), 7.20–7.32 (m, 2 H, H_{aryl}), 8.54 (d, *J* = 5 Hz, 1 H, H-6_{pyrim}), 9.11 (d, *J* = 1.5 Hz, 1 H, H-2_{pyrim}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 38.9, 55.5, 110.8, 120.5, 121.0, 125.9, 128.7, 131.3, 156.8, 157.6, 158.7, 169.8.

MS (EI, 70 eV): *m*/*z* (%) = 169 (100), 91 (9), 115 (8), 142 (8), 115 (7), 185 (6), 155 (5), 93 (4).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{12}N_2O$ + Na: 223.0847; found: 223.0845.

4-(3-Methoxybenzyl)pyrimidine (2e)
Yield: 151 mg (80%); pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, OCH_3), 4.09 (s, 2 H, CH_2), 6.79–6.86 (m, 3 H, H_{aryl}), 7.12 (dd, *J* = 5.0, 1.0 Hz, 1 H, H-5_{pyrim}), 7.21–7.29 (m, 1 H, H_{aryl}), 8.59 (d, *J* = 5 Hz, 1 H, H-6_{pyrim}), 9.14 (br s, 1 H, H-2_{pyrim}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 44.4, 55.4, 112.5, 115.2, 119.4, 120.8, 121.8, 130.1, 157.2, 158.9, 160.1, 169.5.

MS (EI, 70 eV): *m*/*z* (%) = 199 (100), 200 (47), 185 (11), 184 (10), 157 (9), 169 (7), 156 (7), 130 (5).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{12}N_2O$ + Na: 223.0847; found: 223.0847.

4-(4-Methoxybenzyl)pyrimidine (2f)
Yield: 145 mg (77%); waxy pale yellow solid; mp ~30–35 °C (Lit.[9b] oil).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.79 (s, 3 H, OCH_3), 4.05 (s, 2 H, CH_2), 6.84, 6.88, and 7.14, 7.18 (AA′XX′ system, 4 H, H_{aryl}), 7.09 (dd, *J* = 5.0, 1.5 Hz, 1 H, H-5_{pyrim}), 8.57 (d, *J* = 5 Hz, 1 H, H-6_{pyrim}), 9.12 (d, *J* = 1.5 Hz, 1 H, H-2_{pyrim}).

^{13}C NMR and MS were consistent with the literature data.[7b]

4-(4-Methylthiobenzylo)pyrimidine (2g)
Yield: 73 mg (36%); yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.46 (s, 3 H, SCH_3), 4.11 (s, 2 H, CH_2), 7.05–7.20 (AA′XX′ system, 4 H, H_{aryl}), 7.09 (dd, *J* = 4.9, 0.9 Hz, 1 H, H-5_{pyrim}), 8.55 (d, *J* = 4.8 Hz, 1 H, H-6_{pyrim}), 9.11 (br s, 1 H, H-2_{pyrim}).

^{13}C NMR and MS were consistent with the literature data.[7b]

4-(2,5-Dimethoxybenzyl)pyrimidine (2h)
Yield: 163 mg (75%); yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.76 and 3.74 (2 s, each 3 H, OCH_3), 4.10 (s, 2 H, CH_2), 6.79–6.82 (m, 3 H, H_{aryl}), 7.90 (dd, *J* = 5.2, 1.0 Hz, 1 H, H-5_{pyrim}), 8.55 (d, *J* = 5.4 Hz, 1 H, H-6_{pyrim}), 9.12 (d, *J* = 1.1 Hz, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 39.0, 55.9, 56.1, 111.8, 112.8, 117.4, 120.6, 126.9, 151.8, 153.8, 156.9, 158.7, 169.6.

MS (EI, 70 eV): *m*/*z* (%) = 199 (100), 200 (22), 184 (18), 230 (15), 155 (9), 172 (8), 118 (7), 215 (5).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{14}N_2O_2$ + Na: 253.0953; found: 253.0953.

4-(3,4,5-Trimethoxybenzyl)pyrimidine (2i)
Yield: 71 mg (29%); pale brown oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.83 (s, 3 H, OCH_3 at C-4), 3.84 (s, 6 H, 2 OCH_3 at C-3 and C-5), 4.06 (s, 2 H, CH_2), 6.50 (s, 2 H, H_{aryl}), 7.17 (dd, *J* = 5.2, 1.4 Hz, 1 H, H-5_{pyrim}), 8.62 (d, *J* = 5.0 Hz, 1 H, H-6_{pyrim}), 9.15 (d, *J* = 1.2 Hz, 1 H, H-2_{pyrim}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 44.5, 56.2, 60.9, 106.2, 120.6, 132.9, 136.9, 153.5, 157.1, 158.7, 169.3.

MS (EI, 70 eV): *m*/*z* (%) = 260 (100), 245 (79), 131 (14), 159 (12), 172 (10), 185 (8), 213 (7), 181 (5).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{16}N_2O_3$ + Na: 283.1059; found: 283.1060.

2,6-Dibenzylpyridines 3a–i and 2,6-Dibenzyl-4-methylpyridines 4a–i; General Procedure
To a magnetically stirred mixture of 2,6-dibromopyridine (**17**; 150 mg, 0.63 mmol) or 2,6-dibromo-4-methylpyridine (**18**; 157 mg, 0.63 mmol) and $Pd[PPh_3]_4$ (8 mol%) in anhyd THF (6 mL) was added the corresponding benzylzinc reagent in THF (7 mL of 0.5 M solution, 3.6 equiv) over 5 min. The reaction mixture was stirred and heated at 50 °C for 24 h. After cooling, the reaction was quenched with sat. aq NH_4Cl (3 mL) and the solvent was evaporated under reduced pressure. The residue was taken up with H_2O (25 ml), extracted with CH_2Cl_2 (2 × 15 mL), and the combined extracts were dried ($MgSO_4$). After concentration, the brown residue was purified by column chromatography using cyclohexane–EtOAc (10:1 → 5:1) or hexane–$CHCl_3$ (4:1 → 1:1) solvent systems.

The synthesis of **3a** and **4a** was repeated using catalytic system based on $Pd(OAc)_2$ (6%) and S-Phos (10%). Under this condition full conversion of substrates was observed in less then 3 h.

2,6-Dibenzylpyridine (3a)
Yield: 136 mg (83%); colorless oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.16 (s, 4 H, 2 × CH_2), 6.87 (d, *J* = 7.7 Hz, 2 H, H-3_{py} and H-5_{py}), 7.16–7.30 (m, 10 H, H_{Ph}), 7.43 (t, *J* = 7.7 Hz, 1 H, H-4_{py}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 44.9, 120.7, 126.5, 128.7, 129.4, 137.1, 139.8, 160.7.

MS (EI, 70 eV): *m*/*z* (%) = 258 (100), 259 (46), 180 (19), 167 (11), 166 (10), 91 (7), 153 (4), 115 (4).

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{19}H_{17}N$ + Na: 282.1259; found: 282.1260.

2,6-Bis(2-fluorobenzyl)pyridine (3b)
Yield: 135 mg (72%); pale yellow solid; mp 50–53 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.18 (s, 4 H, 2 CH_2), 6.90 (d, *J* = 7.8 Hz, 2 H, H-3$_{py}$ and H-5$_{py}$), 6.99–7.25 (m, 8 H, H$_{aryl}$), 7.45 (t, *J* = 7.7 Hz, 1 H, H-4$_{py}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 37.6 (d, ^3J = 2.5 Hz), 115.5 (d, ^2J = 22.1 Hz), 120.6, 124.3 (d, ^4J = 4.0 Hz), 126.6 (d, ^2J = 16.0 Hz), 128.3 (d, ^3J = 8.8 Hz), 131.6 (d, ^3J = 4.8 Hz), 137.3, 159.4, 161.2 (d, ^1J = 244.5 Hz).

MS (EI, 70 eV): *m/z* (%) = 276 (100), 198 (30), 186 (10), 109(9), 295 (8), 294 (7), 187 (6), 133 (6).

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{19}H_{15}F_2N$ + Na: 318.1070; found: 318.1075.

2,6-Bis(4-Fluorobenzyl)pyridine (3c)
Yield: 159 mg (85%); pale brown solid; mp 60–63 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.11 (s, 4 H, 2 × CH_2), 6.88 (d, *J* = 7.6 Hz, 2 H, H-3$_{py}$ and H-5$_{py}$), 6.93–7.02 (m, 4 H, H$_{aryl}$), 7.17–7.25 (m, 4 H, H$_{aryl}$), 7.46 (t, *J* = 7.6 Hz, 1 H, H-4$_{py}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 43.9, 115.4 (d, ^2J = 21.6 Hz), 120.7, 130.7 (d, ^3J = 7.5 Hz), 135.4 (d, ^4J = 3.2 Hz), 137.3, 160.5, 161.8 (d, ^1J = 244.2 Hz).

MS (EI, 70 eV): *m/z* (%) = 294 (100), 295 (61), 198 (45), 109 (15), 186 (13), 187 (10), 133 (6), 83 (6).

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{19}H_{15}F_2N$ + Na: 318.1070; found: 318.1073.

2,6-Bis(2-methoxybenzyl)pyridine (3d)
Yield: 164 mg (81%); pale yellow solid; mp 69–71 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.79 (s, 6 H, 2 × OCH_3), 4.18 (s, 4 H, 2 × CH_2), 6.78–6.92 (m, 6 H, H$_{aryl}$ overlapped with H-3$_{py}$ and H-5$_{py}$), 7.14–7.25 (m, 4 H, H$_{aryl}$), 7.37 (t, *J* = 7.8 Hz, 1 H, H-4$_{py}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 38.8, 55.6, 110.6, 120.1, 120.7, 127.8, 128.3, 131.0, 136.8, 157.7, 160.4.

MS (EI, 70 eV): *m/z* (%) = 288 (100), 265 (11), 319 (10), 167 (10), 213 (9), 91 (8), 272 (6), 318 (5).

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{21}NO_2$ + Na: 342.1470; found: 342.1475.

2,6-Bis(3-methoxybenzyl)pyridine (3e)
Yield: 160 mg (78%); beige solid; mp 52–53 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.75 (s, 6 H, 2 × OCH_3), 4.13 (s, 4 H, 2 × CH_2), 6.73–6.87 (m, 6 H, H$_{aryl}$), 6.89 (d, *J* = 7.7 Hz, 2 H, H-3$_{py}$ and H-5$_{py}$), 7.17–7.21 (m, 2 H, H$_{aryl}$), 7.43 (t, *J* = 7.7 Hz, 1 H, H-4$_{py}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 44.7, 55.1, 111.8, 114.8, 120.6, 121.5, 129.4, 137.0, 141.2, 159.7, 160.3.

MS (EI, 70 eV): *m/z* (%) = 318 (100), 319 (72), 288 (11), 167 (6), 260 (60, 210(5), 121 (5), 303 (4).

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{21}NO_2$ + Na: 342.1470; found: 342.1473.

2,6-Bis(4-methoxybenzyl)pyridine (3f)
Yield: 162 mg (80%); colorless solid; mp 94–95 °C.

^{1}H NMR (200 MHz, $CDCl_3$): 3.78 (s, 6 H, 2 × OCH_3), 4.10 (s, 4 H, 2 × CH_2), 6.82, 6.86, 7.16, 7.21 (10 H, AA′XX′ system overlapped with H-3$_{py}$ and H-5$_{py}$), 7.42 (t, *J* = 7.4 Hz, 1 H, H- 4$_{py}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 44.0, 55.4, 114.1, 120.4, 130.3, 131.9, 137.1, 158.3, 161.0.

MS (EI, 70 eV): *m/z* (%) = 319 (100), 318 (89), 304 (65), 210 (23), 121 (22), 167 (15), 196 (13), 198 (11).

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{21}NO_2$ + Na: 342.1470; found: 342.1475.

2,6-Bis(4-methylthiobenzyl)pyridine (3g)
Yield: 87 mg (39%); pale yellow solid; mp 112–113 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.46 (s, 6 H, 2 × SCH_3), 4.10 (s, 4 H, 2 × CH_2), 6.87 (d, *J* = 7.8 Hz, 2 H, H-3$_{py}$ and H-5$_{py}$), 7.19 (br s, 8 H, H$_{aryl}$), 7.43 (t, *J* = 7.8 Hz, 1 H, H-4$_{py}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.3, 44.3, 120.6, 127.2, 129.9, 136.2, 136.8, 137.2, 160.6.

MS (EI, 70 eV): *m/z* (%) = 351 (100), 350 (36), 335 (23), 303 (18), 137 (11), 167 (9), 179 (7), 226 (6).

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{21}H_{21}NS_2$ + Na: 374.1013; found: 374.1014.

2,6-Bis(2,5-dimethoxybenzyl)pyridine (3h)
Yield: 120 mg (50%); yellow oil (GC-MS purity approx. 90%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.71 and 3.76 (2 s, each 6 H, OCH_3), 4.15 (s, 4 H, 2 × CH_2), 6.69–6.86 (m, 8 H, H$_{aryl}$ overlapped with H-3$_{py}$ and H-5$_{py}$), 7.39 (t, *J* = 7.8 Hz, 1 H, H-4$_{py}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.8, 55.8, 56.3, 111.8, 112.1, 117.1, 120.3, 129.5, 136.9, 151.9, 153.7, 160.2.

MS (EI, 70 eV): *m/z* (%) = 348 (100), 379 (15), 318 (15), 243 (10), 230 (6), 154 (5), 363 (4), 290 (4).

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{23}H_{25}NO_4$ + Na: 402.1681; found: 402.1686.

2,6-Bis(3,4,5-trimethoxybenzyl)pyridine (3i)
Yield: 89 mg (32%); pale brown solid (GC-MS purity approx. 91%); mp 98–101 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.80 (s, 12 H, 4 × OCH_3 at C-3 and C-5), 3.82 (s, 6 H, 2 × OCH_3 at C-4), 4.10 (s, 4 H, 2 × CH_2), 6.50 (s, 4 H, H$_{aryl}$), 6.95 (d, *J* = 7.6 Hz, 2 H, H-3$_{py}$ and H-5$_{py}$), 7.51 (t, *J* = 7.6 Hz, 1 H, H-4$_{py}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 45.2, 56.2, 61.0, 106.3, 120.7, 135.4, 136.7, 137.3, 153.4, 160.5.

MS (EI, 70 eV): *m/z* (%) = 439 (100), 424 (45), 438 (19), 395 (10), 313 (8), 181 (7), 212 (7), 256 (5).

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{25}H_{29}NO_6$ + Na: 462.1893; found: 462.1897.

2,6-Dibenzyl-4-methylpyridine (4a)
Yield: 151 mg (89%); pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.08 (s, 3 H, CH_3), 4.05 (s, 4 H, 2 × CH_2), 6.62 (s, 2 H, H-3$_{py}$ and H-5$_{py}$), 7.10–7.23 (m, 10 H, H$_{Ph}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.2, 44.7, 121.7, 126.4, 128.7, 129.4, 140.0, 148.9, 160.4.

MS (EI, 70 eV): *m/z* (%) = 272 (100), 272 (36), 258 (11), 194 (9), 180 (8), 167 (8), 91 (6), 115 (5).

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{19}N$ + Na: 296.1415; found: 296.1410.

2,6-Bis(2-fluorobenzyl)pyridine (4b)
Yield: 145 mg (75%); yellow solid; mp 44–47 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, CH_3), 4.14 (s, 4 H, 2 × CH_2), 6.72 (s, 2 H, H-3$_{py}$ and H-5$_{py}$), 7.00–7.23 (m, 8 H, H$_{aryl}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.2, 37.4 (d, ^3J = 3.2 Hz), 115.5 (d, ^2J = 22.0 Hz), 121.6 (d, J = 1.6 Hz), 124.2 (d, ^4J = 2.8 Hz), 126.8 (d, ^2J = 15.8 Hz), 128.3 (d, ^3J = 7.9 Hz), 131.6 (d, ^3J = 4.7 Hz), 148.4, 159.2, 161.2 (d, ^1J = 243.8 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 289 (100), 308 (22), 309 (15), 212 (12), 294 (10), 198 (10), 109 (6), 185 (6).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{17}F_2N$ + Na: 332.1227; found: 332.1227.

2,6-Bis(4-fluorobenzyl)-4-methylpyridine (4c)
Yield: 152 mg (79%); pale yellow solid; mp 71–73 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.19 (s, 3 H, CH_3), 4.07 (s, 4 H, 2 × CH_2), 6.70 (s, 2 H, H-3$_{py}$ and H-5$_{py}$), 6.92–7.24 (m, 8 H, H$_{aryl}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.1, 43.8, 115.4, (d, ^2J = 21.7 Hz), 121.7, 130.7 (d, ^3J = 7.6 Hz), 135.5 (d, ^4J = 3.3 Hz), 148.4, 160.3, 161.7 (d, ^1J = 243.8 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 308 (100), 309 (38), 212 (22), 294 (20), 109 (17), 198 (11), 185 (7), 133 (5).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{17}F_2N$ + Na: 332.1227; found: 332.1222.

2,6-Bis(2-methoxybenzyl)-4-methylpyridine (4d)
Yield: 150 mg (72%); pale yellow solid; mp 57–59 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.13 (s, 3 H, CH_3), 3.80 (s, 6 H, 2 × OCH_3), 4.14 (s, 4 H, 2 × CH_2), 6.63 (s, 2 H, H-3$_{py}$ and H-5$_{py}$), 6.85–6.92 (m, 4 H, H$_{aryl}$), 7.13–7.22 (m, 4 H, H$_{aryl}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.2, 38.5, 55.6, 110.6, 120.7, 121.2, 127.7, 128.5, 131.0, 147.7, 157.6, 160.1.

MS (EI, 70 eV): *m*/*z* (%) = 302 (100), 303 (19), 270 (12), 91 (10), 332 (8), 286 (7), 121 (7), 181 (6).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{23}NO_2$ + Na: 356.1627; found: 356.1628.

2,6-Bis(3-methoxybenzyl)-4-methylpyridine (4e)
Yield: 162 mg (78%); yellow solid; mp 45–47 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, CH_3), 3.76 (s, 6 H, 2 × OCH_3), 4.09 (s, 4 H, 2 × CH_2), 6.72 (s, 2 H, H-3$_{py}$ and H-5$_{py}$), 6.74–6.87 (m, 6 H, H$_{aryl}$), 7.17–7.21 (m, 2 H, H$_{aryl}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.0, 44.5, 55.1, 111.7, 114.8, 121.5, 121.6, 129.4, 141.3, 148.0, 159.7, 160.0.

MS (EI, 70 eV): *m*/*z* (%) = 332 (100), 333 (51), 302 (9), 318 (8), 274 (6), 168 (5), 121 (5), 183 (4).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{23}NO_2$ + Na: 356.1627; found: 356.1630.

2,6-Bis(4-methoxybenzyl)-4-methylpyridine (4f)
Yield: 165 mg (80%); pale beige solid; mp 96–98 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.15 (s, 3 H, CH_3), 3.78 (s, 6 H, 2 × OCH_3), 4.06 (s, 4 H, 2 × CH_2), 6.67 (s, 2 H, H-3$_{py}$ and H-5$_{py}$), 6.82, 6.86, 7.16, 7.21 (AA′XX′, 8 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.2, 43.8, 55.4, 114.1, 121.5, 130.3, 132.1, 148.1, 158.3, 160.8.

MS (EI, 70 eV): *m*/*z* (%) = 332 (100), 333 (88), 318 (79), 224 (19), 121 (18), 210 (8), 181 (7), 274 (7).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{23}NO_2$ + Na: 356.1627; found: 356.1625.

2,6-Bis(4-methylthiobenzyl)-4-methylpyridine (4g)
Yield: 68 mg (30%); beige solid; mp 97–99 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, CH_3) 2.47 (s, 6 H, 2 × SCH_3), 4.06 (s, 4 H, 2 × CH_2), 6.67 (s, 2 H, H-3$_{py}$ and H-5$_{py}$), 7.19 (br s, 8 H, H$_{aryl}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.3, 21.1, 44.1, 121.7, 127.2, 129.9, 136.1, 136.9, 148.3, 160.3.

MS (EI, 70 eV): *m*/*z* (%) = 365 (100), 364 (65), 350 (23), 137 (10), 240 (8), 194 (8), 121 (6), 302 (5).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{23}NS_2$ + Na: 388.1170; found: 388.1177.

2,6-Bis(2,5-dimethoxybenzyl)-4-methylpyridine (4h)
Yield: 110 mg (45%); pale brown oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.14 (s, 3 H, CH_3), 3.71 and 3.76 (2 s, each 6 H, OCH_3), 4.11 (s, 4 H, 2 × CH_2), 6.66 (s, 2 H, H-3$_{py}$ and H-5$_{py}$), 6.76–6.90 (m, 6 H, H$_{aryl}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.2, 38.5, 55.8, 56.3, 111.8, 112.0, 117.0, 121.4, 129.7, 130.3, 148.0, 151.7, 153.7, 160.0.

MS (EI, 70 eV): *m*/*z* (%) = 362 (100), 332 (11), 393 (7), 257 (5), 181 (7), 121 (5), 211 (4), 304 (4).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{27}NO_4$ + Na: 416.1838; found: 416.1840.

2,6-Bis(3,4,5-trimethoxybenzyl)-4-methylpyridine (4i)
Yield: 82 mg (29%); pale yellow solid; mp 122–124 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.23 (s, 3 H, CH_3), 3.81 (s, 12 H, 4 × OCH_3 at C-3 and C-5), 3.82 (s, 6 H, 2 × OCH_3 at C-4), 4.05 (s, 4 H, 2 × CH_2), 6.50 (s, 4 H, H$_{aryl}$), 6.77 (s, 2 H, H-3$_{py}$ and H-5$_{py}$).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.3, 45.0, 56.3, 61.0, 106.3, 121.8, 135.5, 136.6, 148.4, 153.4, 160.3.

MS (EI, 70 eV): *m*/*z* (%) = 453 (100), 439 (71), 454 (31), 422 (8), 392 (6), 407 (6), 181 (5), 219 (5).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{31}NO_6$ + Na: 476.2049; found: 476.2051.

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