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Efficient microwave-assisted synthesis of highly functionalized pyrimidine derivatives

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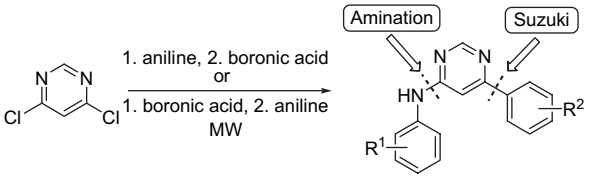
Abstract—A generally applicable one-pot procedure for the rapid, easy, and diverse asymmetric functionalization of pyrimidines was developed that requires minimum efforts for the purification of the final products. 4-Amino-6-aryl-substituted pyrimidines are prepared in good yields by combined microwave-assisted amination and Suzuki–Miyaura cross-coupling reactions. The acid-mediated amination reaction affords the products as easily separable salts in 30–40 min reaction time.

1. Introduction

The multiple diverse functionalization of heterocycles is of great importance in the synthesis of pharmacologically active compounds.[1] The formation of carbon–carbon, carbon—oxygen, and carbon–nitrogen bonds represent the most desirable and useful, but also the most challenging conversions in this respect. (Hetero)aryl–(hetero)aryl carbon–carbon bonds are well represented in drugs and can be synthesized conveniently by metal-catalyzed Suzuki–Miyaura, Stille, Kumada-Corriu, Negishi, or Hiyama cross-coupling reactions.[2] Correspondingly, efficient copper- and palladium-catalyzed carbon–nitrogen and carbon–oxygen bond forming processes, such as the Buchwald–Hartwig reaction, have been developed for the functionalization of aryl halides in the last decade.[2–5] A wide variety of catalytic processes for the functionalization of aromatic ring systems is therefore available. The application of metal-catalyzed reactions to the modification of heteroaromatic rings, however, is reported to a lesser extent.[3,4,6–8]

As part of our efforts in the synthesis of new effective protein kinase inhibitors, we focused on the preparation of pyrimidine derivatives.[9] The symmetrically disubstituted 4,6-dichloropyrimidine was derivatized by both an amino functionality and a (hetero)aryl moiety (Scheme 1).



Scheme 1. Difunctionalization of 4,6-dichloropyrimidine.

For the formation of the pyrimidine–(hetero)aryl C–C bond we used the Suzuki–Miyaura cross-coupling,[10] since a large number of diverse substituted boronic acids and esters are commercially available; additionally, they are stable even under demanding reaction conditions and they are of low toxicity. For the amination reaction, we explored several reaction conditions, ranging from nucleophilic substitution[11] to palladium- or copper-catalyzed reactions (see below). Taking advantage of the technique of microwave-assisted organic synthesis (MAOS),[12] we developed a generally applicable methodology for the rapid, easy, and diverse asymmetric functionalization of pyrimidines. Minimum efforts for the purification of the final products are required, which are available in a short reaction time, and without the requirement for special reaction conditions, such as inert gas or degassed solvents.

2. Result and discussion

The commercially available and symmetrically substituted 4,6-dichloropyrimidine was used as starting material for the preparation of new difunctionalized pyrimidines. In the first reaction step, one of the chlorine atoms is substituted either by an amine or by an (hetero)aryl moiety, yielding

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a monosubstituted chloropyrimidine derivative. This intermediate can subsequently be subjected to either Suzuki–Miyaura cross-coupling or amination, giving the final asymmetrically disubstituted products. We initially established separate protocols for amination and Suzuki–Miyaura-coupling reactions using 4,6-dichloropyrimidine. Subsequently, we performed three different sets of experiments. We first carried out the amination reaction, isolated the intermediate and did the Suzuki–Miyaura cross-coupling as the second step. In the next set of experiments we performed the cross-coupling reaction and subjected the isolated intermediates afterwards to amination. Finally, we simplified the methodology and carried out the cross-coupling and the amination reaction in a one-pot synthesis without isolation of the intermediates.

2.1. Acid- and base-mediated aminations

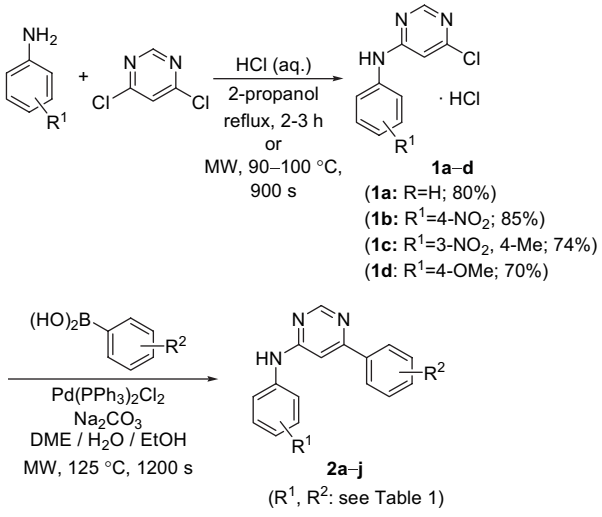
The amination of pyrimidine derivatives can be achieved via acid- or base-mediated nucleophilic substitution.[13–16] We therefore explored several reaction conditions in a model reaction between 4,6-dichloropyrimidine and aniline. These included acid- (aqueous hydrochloric acid) and base-mediated (Hunig's base (DIPEA), sodium hydride, sodium carbonate, caesium carbonate, potassium phosphate, sodium *tert*-butoxide), as well as copper- (copper(I) iodide, copper(I) iodide/*N*,*N*′-dimethylethylenediamine, copper(I) iodide/2,2,6,6-tetramethylhepta-3,5-dione, and copper(I) triflate)[17] and palladium-catalyzed[3,8,16,18] ($Pd(dppf)Cl_2$) reaction conditions at 100, 180 or 240 °C for 900 s in a microwave synthesizer. A number of different solvents, such as DMF, dioxane, methanol, ethanol, 2-propanol, and NMP or DME, were used. All base-mediated reactions showed product formation only at elevated temperatures with yields below 50%. The notable exception included the use of Hunig's base in NMP at 240 °C, yielding 60–70% of the amination product. Addition of any Cu-catalyst (20 mol %, sodium carbonate and DMF), and the $Pd(dppf)Cl_2$-catalyzed reaction (5 mol %, sodium *tert*-butoxide and dioxane) gave increased yields of up to 60–70%. However, all of the above conditions worked only at elevated temperatures with the drawback of considerable formation of the symmetrically disubstituted amination product as by-product, as well as the requirement for a subsequent work-up and isolation procedure. In marked contrast, the microwave-mediated amination worked very well with aqueous hydrochloric acid in 2-propanol[14] at moderate temperatures (100 °C), yielding the desired phenyl-(6-phenyl-pyrimidin-4-yl)-amine (**1a**) in more than 80% yield, even when only catalytic amounts of hydrochloric acid were used. The mono-amination product was formed almost exclusively, and only traces of the symmetrically disubstituted product were detected by LC–MS analysis. The product was isolated as the HCl-salt by filtration. Protonation of one of the nitrogen atoms of the dichloropyrimidine results in activation of the heteroaromatic system toward nucleophilic attack. The small amount of non-protonated amine in the equilibrium of mainly protonated amine and non-protonated species is a sufficient nucleophile, and the equilibrium is shifted toward the non-protonated amine as the reaction proceeds. Other strong acids, such as sulfuric acid or *p*-toluenesulfonic acid, worked similarly well. As an additional advantage, concentrated sulfuric acid does not contain water, which prevents formation of the hydroxy-substituted pyrimidine by-product in slow amination reactions by nucleophilic displacement of chlorine with water. In this respect, the use of 2-propanol as a solvent was beneficial over sterically less hindered methanol or ethanol, as only traces of isopropoxy-substituted by-products were observed.

2.2. Suzuki–Miyaura cross-coupling reactions

The Suzuki–Miyaura reaction of 4,6-dichloropyrimidine[7,15,19] was not optimized. Yields of 50–63% were obtained with a system containing $Pd(PPh_3)_2Cl_2$, sodium carbonate, and DME/ethanol/water under microwave irradiation at 125 °C for 1200 s.

2.3. Amination/Suzuki–Miyaura sequence

To explore the best sequence of the amination and the Suzuki–Miyaura reaction, we started with the amination reaction first (Scheme 2 and Table 1). A set of four different mono-aminated pyrimidines **1a–d** was synthesized in good yields (70–85%) using the previously established protocol for the acid-mediated reaction of 4,6-dichloropyrimidine. The amination reactions were carried out by heating to reflux for 2–3 h to allow the synthesis of larger quantities of **1a–d**. However, microwave irradiation (90–100 °C, 900 s) was equally successful in shorter reaction time. The products **1a–d** were isolated as HCl-salts by filtration. In the following step, the microwave-assisted Suzuki–Miyaura cross-coupling of **1a–d** with various substituted benzeneboronic acids gave access to products **2a–j** in good yields (60–99%; Table 1). Electron-withdrawing as well as electron-donating groups in the boronic acid coupling partner were well tolerated, even in the sterically problematic *ortho*-position.



Scheme 2. Amination of 4,6-dichloropyrimidine with aromatic amines and subsequent Suzuki–Miyaura cross-coupling.

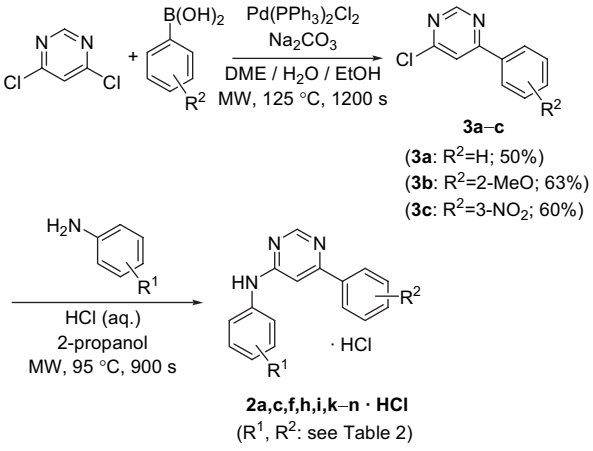
In the next experiment, we switched the order of the reaction sequence (Scheme 3 and Table 2). We initially synthesized three phenyl-substituted chloropyrimidines **3a–c** by Suzuki–Miyaura reaction of 4,6-dichloropyrimidine with the corresponding boronic acids under microwave-assisted conditions. Unfortunately, the coupling gave only moderate yields (50–63%). The subsequent amination step under acid-mediated microwave-assisted conditions usually gave the

Table 1. 4,6-Disubstituted pyrimidines **2a–j** produced via Scheme 2[a]

Entry	R^1	R^2	Isolated yield of 2nd step (%)	Overall yield (%)
1	H	H	87 (**2a**)	70
2	H	2-Me	99 (**2b**)	79
3	H	2-OMe	81 (**2c**)	65
4	H	2-COMe	81 (**2d**)	65
5	H	3-CH_2OH	85 (**2e**)	68
6	H	3-NO_2	93 (**2f**)	74
7	H	4-OMe	86 (**2g**)	69
8	4-OMe	H	79 (**2h**)	55
9	4-NO_2	H	60 (**2i**)	51
10	3-NO_2-4-Me	H	79 (**2j**)	58

[a] Typical procedure. First step: 10 mmol aromatic amine, 13 mmol 4,6-dichloropyrimidine, 15 mL 2-propanol, 1.5 mL concd HCl, reflux, 2.5 h; or 1 mmol aromatic amine, 1.3 mmol 4,6-dichloropyrimidine, 2 mL 2-propanol, 200–300 μL concd HCl, MW, 90–100 °C, 900 s. Second step: 1 mmol **1**, 1.25 mmol boronic acid, 3.5 equiv Na_2CO_3, 2 mol % $Pd(PPh_3)_2Cl_2$, 6 mL DME, 0.8 mL EtOH, 1.2 mL H_2O, MW, 125 °C, 1200 s.

final products **2a–j** as HCl-salts after filtration in moderate to good yields (55–96%). The amination reaction with electron-poor monosubstituted pyrimidines proceeds in slightly better yields than with electron-rich ones (Table 2, entries 3–5, 7, and 8).



Scheme 3. Suzuki–Miyaura cross-coupling of 4,6-dichloropyrimidine and subsequent amination with aromatic amines.

Table 2. 4,6-Disubstituted pyrimidines **2a–j** produced via Scheme 3[a]

Entry	R^1	R^2	Isolated yield for 2nd step (%)	Overall yield (%)
1	H	H	83 (**2a**·HCl)	42
2	2-Me	H	55 (**2k**)[b]	27
3	4-OMe	H	79 (**2h**·HCl)	40
4	4-NO_2	H	90 (**2i**·HCl)	45
5	4-COOMe	H	96 (**2l**·HCl)	48
6	H	2-OMe	66 (**2c**·HCl)	42
7	4-Br	2-OMe	86 (**2m**·HCl)	54
8	3-Br	3-NO_2	89 (**2n**·HCl)	53
9	H	3-NO_2	78 (**2f**·HCl)	47

[a] Typical procedure. First step: 8 mmol boronic acid, 9.6 mmol 4,6-dichloropyrimidine, 3 equiv Na_2CO_3, 2 mol % $Pd(PPh_3)_2Cl_2$, 15 mL DME, 2 mL EtOH, 3 mL H_2O, MW, 125 °C, 1200 s. Second step: 1 mmol **3**, 1.05 mmol aniline, 2 mL 2-propanol, 0.2 mL concd HCl, MW, 95 °C, 900 s.

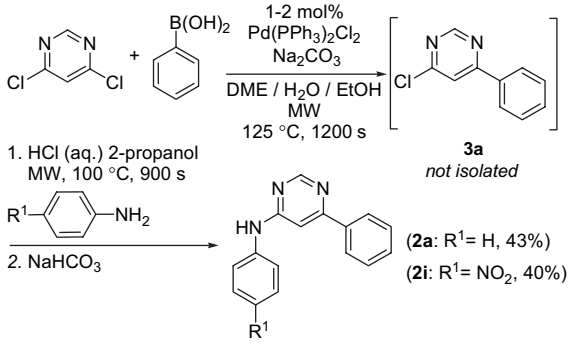
[b] Isolated as the free base by basic work-up and flash column chromatography.

The Suzuki/amination reaction sequence (Scheme 3) is preferable for aromatic amines that are more valuable or contain other reactive functionalities (such as a halogen, see Table 2, entries 7 and 8). The formation of undesirable side products in the Suzuki–Miyaura cross-coupling can thus be avoided by this sequence.

The principal flexibility of this methodology, which enabled the two reaction sequences to be performed in both directions, allowed the introduction of substituents on the aniline side or on the aryl side, which could subsequently be functionalized, for example, by metal-catalyzed cross-coupling reactions of the bromoaniline side-chain (Table 2, entries 7 and 8), or by subsequent reactions of the hydroxymethylene side-chain (Table 2, entry 5). This is an important requirement for the further modification of pyrimidine-based scaffolds as protein kinase inhibitors.

2.4. One-pot procedure

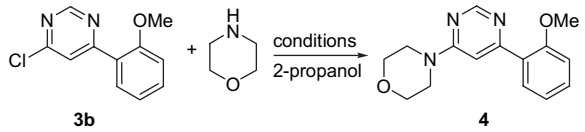
To demonstrate that the methodology can be simplified, we now conducted the sequence of Suzuki–Miyaura and subsequent amination reaction as a one-pot procedure. For that purpose, we used a simple model system consisting of benzeneboronic acid and aniline as well as *p*-nitroaniline as reactants. The reaction mixture was acidified and heated with the aromatic amine after an initial Suzuki–Miyaura cross-coupling (Scheme 4). The reaction sequence got completed in only 35 min under microwave irradiation. The products **2a** and **2i** were isolated in moderate yields after flash column chromatography (43% and 40%, respectively), which is comparable to the overall yields of the stepwise procedure (Table 2, entries 1 and 4).



Scheme 4. One-pot reaction of 4,6-dichloropyrimidine with benzene boronic acid and aromatic amines.

2.5. Amination with aliphatic amines

In order to extend the scope of the methodology, we performed the amination of the Suzuki–Miyaura product with aliphatic amines as the coupling partner (Scheme 5). The use of an excess of hydrochloric acid gave only traces of the desired amination product using **3b** and morpholine (Table 3, entry 1). This is in distinct contrast to the previously described reactions with aniline derivatives. Under the applied reaction conditions the aliphatic amine group is most likely quantitatively protonated due to its higher basicity, in contrast to an aromatic amino group. A nucleophilic substitution on the monosubstituted chloropyrimidine is therefore not possible.



Scheme 5. Amination with morpholine.

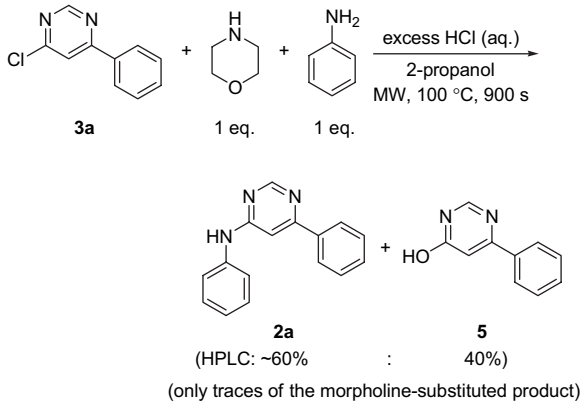
Table 3. Results of the synthesis of **4** produced via Scheme 5[a]

Entry	Acid/base	*T* [°C]	HPLC-yield of **4** (%)
1	3 equiv HCl	100	<2
2	~0.5 equiv HCl	100	50 (50% recov. SM)
3	—	115	80 (65% isolated yield)
4	2 equiv DIPEA	115	80

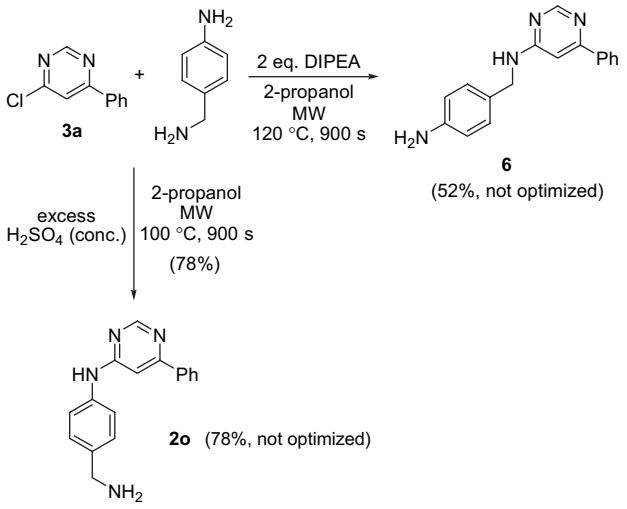
[a] Typical procedure: 1 mmol **3b**, 1.2 mmol morpholine, 3 mL 2-propanol, MW, 900 s.

The reaction results, however, in the formation of product **4** in low yields, when substoichiometrical amounts of hydrochloric acid are present (Table 3, entry 2), which is consistent with this explanation. The reaction was equally effective under relatively mild conditions, i.e., heating the mixture of starting materials without acid in the microwave synthesizer (Table 3, entry 3), or with additional Hunig's base (Table 3, entry 4). The aromatic amines react very slowly, if at all, under these basic conditions.

In a competition experiment of **3a** with aniline and morpholine under acidic conditions (Scheme 6), an estimated yield of 60% of the reaction product of **3a** with aniline was observed by HPLC analysis. Only traces of the morpholine-substituted product were detected by HPLC–MS analysis. The remaining 40% could be attributed to the by-product 6-phenyl-pyrimidin-4-ol (**5**) that is formed by nucleophilic attack of water at the chloropyrimidine. This difference in reactivity between the aromatic and the aliphatic amino groups was further exploited for the synthesis of different regioisomers by using 4-aminomethyl-phenylamine as a coupling partner that contains both an aliphatic and aromatic amino group (Scheme 7). The more nucleophilic benzylic amino group reacts with the pyrimidine under basic conditions (52% HPLC-yield of **6**), while the aromatic amino group added to the pyrimidine core under acidic conditions (78% HPLC-yield of **2o**).



Scheme 6. Competitive acid-mediated amination of 4-chloro-6-phenyl-pyrimidine (**3a**) with morpholine and aniline.



Scheme 7. Amination of 4-chloro-6-phenyl-pyrimidine (**3a**) with 4-aminomethyl-phenylamine.

3. Conclusion

We presented an efficient, flexible, and easy to perform two-step procedure for the synthesis of 4-amino-6-aryl-pyrimidines by the combined amination and Suzuki–Miyaura cross-coupling of 4,6-dichloropyrimidine. Either the Suzuki–Miyaura or the amination reaction was performed as the first step in the synthetic sequence. Using microwave-assisted organic synthesis, all reactions were completed in a short time. We could further demonstrate that the process is feasible as a one-pot procedure, thus simplifying the work-up procedure. The amination with aromatic amines under acidic conditions was straightforward and the products of this reaction were isolated by filtration of the HCl-salts. Aliphatic amines did not react under the applied acidic conditions, but a switch in reactivity from an aromatic to an aliphatic amino group was achieved by applying basic conditions. Extensive investigations to use this methodology for the general synthesis of highly functionalized amino-(hetero)aryl-heterocycles are currently underway in our laboratory.

4. Experimental

4.1. General

All reagents and solvents were used as purchased. The microwave-assisted reactions were carried out in a Personal Chemistry Emrys Optimizer instrument in sealed vials. Flash column chromatography was carried out on Merck silica gel 60 (0.040–0.063 mm), using cyclohexane (*c*Hex) and ethyl acetate (EtOAc) as eluents. The melting points are uncorrected and represent values obtained on recrystallized or chromatographically purified material. ^{1}H (200 MHz) and ^{13}C (66 MHz) NMR spectra were measured in $CDCl_3$ or DMSO-d_6 on a Varian Gemini 200 instrument. The chemical shifts δ are given in parts per million relative to $CHCl_3$ (δ (^{1}H)=7.26; δ (^{13}C)=77.0) in $CDCl_3$, and to DMSO-d_6 (δ (^{1}H)=2.49; δ (^{13}C)=39.7). HPLC–MS analyses were performed with a Waters 2795 Separation Module equipped with a Waters 2996 PDA detector and a Micromass ZQ

2000 mass detector (electrospray ionization with +ve/–ve switching). Standard LC–MS conditions are: Waters XTerra MS 5 μm C18, 3.0×50 mm at 35 °C; flow 0.8 mL/min, gradient 98% 1 mM aqueous ammonium acetate/2% acetonitrile to 100% acetonitrile over 7 min. HPLC purity is given as the mean value of the area under the peak curve at three different wavelengths (215, 254, and 310 nm). Elemental analyses were performed at the Leibniz-Institute for Organic Catalysis, Rostock, Germany, and at Mikroanalytisches Labor Pascher, Remagen–Bandorf, Germany. The purity of new compounds was assessed by ^{1}H NMR spectroscopy and HPLC or microanalysis.

4.2. General procedures

4.2.1. General method 1 (GM1): amination reaction. The aromatic amine (1.00 mmol) and the 4-chloropyrimidine derivative (0.95–1.30 mmol) were dissolved in 2 mL of 2-propanol. Concd HCl (37%, 200–300 μL) was added under stirring, and the mixture was heated in the microwave synthesizer at 95–100 °C for 900 s. The mixture was stored at 4 °C overnight. The precipitated product was filtered off, washed with a small amount of ice-cold 2-propanol, and dried in vacuum.

4.2.2. General method 2 (GM2): Suzuki–Miyaura cross-coupling reaction. The 4-chloropyrimidine derivative (1.00 mmol), the boronic acid (1.25 mmol), sodium carbonate (2.00–3.50 mmol), and $Pd(PPh_3)_2Cl_2$ (2 mol %) were suspended in a mixture of 6.0 mL of DME, 0.8 mL of EtOH, and 1.2 mL of water. The mixture was heated in the microwave synthesizer at 125 °C for 1200 s. Water was added, and the mixture was extracted three times with EtOAc. Satd aqueous NH_4Cl was added to the aqueous layer (pH=∼7), and the mixture was extracted two more times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by flash column chromatography (*c*Hex/EtOAc mixtures) to afford the product.

4.2.3. General method 3 (GM3): one-pot Suzuki–Miyaura/amination reaction. The boronic acid (1.0 mmol), 4,6-dichloropyrimidine (1.1–1.2 mmol), sodium carbonate (3.0 mmol), and $Pd(PPh_3)_2Cl_2$ (1–2 mol %) were suspended in a mixture of 2.5–3.0 mL of DME, 0.4 mL of EtOH, and 0.5 mL of water. The mixture was heated in the microwave synthesizer at 125 °C for 1200 s. 2-Propanol (1 mL) and the aromatic amine (1.1–1.3 mmol) were added, and the mixture was acidified with concd HCl (37%). The mixture was heated in the microwave synthesizer at 100 °C for 900 s. Satd aqueous $NaHCO_3$ was added, and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by flash column chromatography (*c*Hex/EtOAc mixtures).

4.3. Synthesis of monosubstituted pyrimidines

4.3.1. (6-Chloro-pyrimidin-4-yl)-phenyl-amine hydrochloride (1a). Aniline (1.00 g, 10.7 mmol) and 4,6-dichloropyrimidine (2.07 g, 13.9 mmol, 1.3 equiv) were dissolved in 15 mL of 2-propanol. Concd HCl (37%, 1.5 mL) was added under stirring, and the mixture was heated under reflux for 2.5 h. The mixture was stored at 4 °C overnight. The off-white precipitate was filtered off, washed with a small amount of cold 2-propanol, and dried in vacuum, to give **1a** (2.07 g, 80%). Off-white solid; ^{1}H NMR (200 MHz, DMSO-d_6) δ 6.92 (1H, s), 7.06 (1H, t, J=7.3 Hz), 7.28–7.39 (2H, m), 7.65 (2H, d, J=8.9 Hz), 8.46 (1H, s), 10.22 (1H, br s); ESIMS m/z=206/208 (MH^+).

4.3.2. (6-Chloro-pyrimidin-4-yl)-(4-nitro-phenyl)-amine hydrochloride (1b). 4-Nitroaniline (1.00 g, 7.2 mmol) and 4,6-dichloropyrimidine (1.40 g, 9.4 mmol, 1.3 equiv) were dissolved in 15 mL of 2-propanol. Concd HCl (37%, 1.5 mL) was added under stirring, and the mixture was heated under reflux for 2.5 h. The mixture was stored at 4 °C overnight. The yellow precipitate was filtered off, washed with a small amount of cold 2-propanol, and dried in vacuum, to give **1b** (1.75 g, 85%). Yellow solid; ^{1}H NMR (200 MHz, DMSO-d_6) δ 6.98 (1H, s), 7.94 (2H, d, J=9.5 Hz), 8.24 (2H, d, J=9.5 Hz), 8.64 (1H, s), 10.54 (1H, br s); ESIMS m/z=251/253 (MH^+).

4.3.3. (6-Chloro-pyrimidin-4-yl)-(4-methyl-3-nitro-phenyl)-amine hydrochloride (1c). 4-Methyl-3-nitro-aniline (500 mg, 3.29 mmol) and 4,6-dichloropyrimidine (637 mg, 4.27 mmol, 1.3 equiv) were dissolved in 15 mL of 2-propanol. Concd HCl (37%, 1 mL) was added under stirring, and the mixture was heated under reflux for 2.5 h. The mixture was stored at 4 °C overnight. The yellow-brown precipitate was filtered off, washed with a small amount of cold 2-propanol, and dried in vacuum, to give **1c** (730 mg, 74%). Pale brown solid; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.46 (3H, s), 6.93 (1H, s), 7.45 (1H, d, J=8.3 Hz), 7.83 (1H, dd, J=8.3 Hz, J=2.2 Hz), 8.48 (1H, d, J=2.2 Hz), 8.55 (1H, s), 10.49 (1H, br s); ESIMS m/z=265/267 (MH^+).

4.3.4. (6-Chloro-pyrimidin-4-yl)-(4-methoxy-phenyl)-amine hydrochloride (1d). 4-Methoxyaniline (1.00 g, 8.1 mmol) and 4,6-dichloropyrimidine (1.57 g, 10.6 mmol, 1.3 equiv) were dissolved in 15 mL of 2-propanol. Concd HCl (37%, 1.5 mL) was added under stirring, and the mixture was heated under reflux for 2.5 h. The mixture was stored at 4 °C overnight. The slightly greenish precipitate was filtered off, washed with a small amount of cold 2-propanol, and dried in vacuum, to give **1d** (1.55 g, 70%). Pale green solid; ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.74 (3H, s), 6.74 (1H, s), 6.94 (2H, d, J=8.7 Hz), 7.48 (2H, d, J=8.7 Hz), 8.39 (1H, s), 9.93 (1H, br s); ESIMS m/z=236/238 (MH^+).

4.3.5. 4-Chloro-6-phenyl-pyrimidine (3a). Benzeneboronic acid (1.00 g, 8.2 mmol), 4,6-dichloropyrimidine (1.47 g, 9.8 mmol, 1.2 equiv), sodium carbonate (2.61 g, 24.6 mmol, 3.0 equiv), and $Pd(PPh_3)_2Cl_2$ (115 mg, 2 mol %) were suspended in a mixture of 15 mL of DME, 2 mL of EtOH, and 3 mL of water. The mixture was heated in the microwave synthesizer at 125 °C for 1200 s. Water was added, and the mixture was extracted three times with EtOAc. Satd aqueous NH_4Cl was added to the aqueous layer (pH=∼7), and the mixture was extracted two more times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by flash column chromatography (*c*Hex/EtOAc 20:1) to afford **3a** (0.78 g, 50%).

Colorless solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.47–7.57 (3H, m), 7.74 (1H, s), 8.03–8.10 (2H, m), 9.03 (1H, s); ESIMS m/z=191/193 (MH^+).

4.3.6. 4-Chloro-6-(2-methoxy-phenyl)-pyrimidine (3b). 2-Methoxybenzeneboronic acid (1.20 g, 7.9 mmol), 4,6-dichloropyrimidine (1.41 g, 9.5 mmol, 1.2 equiv), sodium carbonate (2.51 g, 23.7 mmol, 3.0 equiv), and $Pd(PPh_3)_2Cl_2$ (100 mg, 2 mol %) were suspended in a mixture of 15 mL of DME, 2 mL of EtOH, and 3 mL of water. The mixture was heated in the microwave synthesizer at 125 °C for 1500 s. Water was added, and the mixture was extracted three times with EtOAc. Satd aqueous NH_4Cl was added to the aqueous layer (pH=~7), and the mixture was extracted two more times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by flash column chromatography (*c*Hex/EtOAc 15:1–10:1) to afford **3b** (1.10 g, 63%). Colorless solid; ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.91 (3H, s), 7.12 (1H, m), 7.23 (1H, d, J=8.4 Hz), 7.55 (1H, m), 7.98 (1H, d, J=7.9 Hz), 8.12 (1H, s), 9.09 (1H, s); ESIMS m/z= 221/223 (MH^+).

4.3.7. 4-Chloro-6-(3-nitro-phenyl)-pyrimidine (3c). 3-Nitrobenzeneboronic acid (1.00 g, 6.0 mmol), 4,6-dichloropyrimidine (1.07 g, 7.2 mmol, 1.2 equiv), sodium carbonate (1.91 g, 18.0 mmol, 3.0 equiv), and $Pd(PPh_3)_2Cl_2$ (80 mg, 2 mol %) were suspended in a mixture of 15 mL of DME, 2 mL of EtOH, and 3 mL of water. The mixture was heated in the microwave synthesizer at 125 °C for 1200 s. Water was added, and the mixture was extracted three times with EtOAc. Satd aqueous NH_4Cl was added to the aqueous layer (pH=~7), and the mixture was extracted two more times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by flash column chromatography (*c*Hex/EtOAc 10:1–3:1) to afford **3c** (0.85 g, 60%). Pale yellow solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74 (1H, t, J=8.1 Hz), 7.85 (1H, d, J=1.5 Hz), 8.36–8.48 (2H, m), 8.95 (1H, t, J=2.3 Hz), 9.11 (1H, d, J=1.5 Hz); ESIMS m/z=236/238 (MH^+).

4.4. Synthesis of disubstituted pyrimidines

4.4.1. Phenyl-(6-phenyl-pyrimidin-4-yl)-amine (2a) and phenyl-(6-phenyl-pyrimidin-4-yl)-amine hydrochloride (2a·HCl). Method 1: following GM1, **3a** (100 mg, 0.525 mmol) and aniline (50 μL, 0.551 mmol, 1.05 equiv) were reacted in 1 mL of 2-propanol and 150 μL of concd HCl (37%) at 95 °C in the microwave synthesizer. Cooling and filtration afforded **2a**·HCl (125 mg, 83%). Yellow solid; mp 258–259 °C (EtOH/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.18 (1H, t, J=7.2 Hz), 7.34 (1H, s), 7.37–7.48 (2H, m), 7.59–7.66 (3H, m), 7.71 (2H, d, J=7.6 Hz), 7.91–7.98 (2H, m), 8.87 (1H, s), 10.96 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 103.2, 121.7, 125.1, 127.2, 129.0, 129.3, 130.8, 132.1, 137.4, 153.4, 153.6, 161.5; ESIMS m/z=248 (MH^+); elemental analysis calcd for $C_{16}H_{14}ClN_3$: C, 67.72; H, 4.97; N, 14.81. Found: C, 66.94; H, 5.18; N, 14.50.

Method 2: following GM2, **1a** (100 mg, 0.413 mmol), benzeneboronic acid (63 mg, 0.516 mmol, 1.25 equiv), sodium carbonate (153 mg, 1.450 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (6 mg, 2 mol %) were reacted in a mixture of 3.0 mL of DME, 0.4 mL of EtOH, and 0.6 mL of water in the microwave synthesizer. Flash column chromatography (*c*Hex/EtOAc 4:1) afforded **2a** (90 mg, 87%). Colorless solid; mp 185–186 °C (EtOAc/*c*Hex); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.03 (1H, t, J=7.3 Hz), 7.24 (1H, d, J=1.4 Hz), 7.35 (2H, t, J=7.3 Hz), 7.49–7.57 (3H, m), 7.72 (2H, d, J=7.3 Hz), 7.98–8.07 (2H, m), 8.72 (1H, d, J=1.4 Hz), 9.68 (1H, s); ^{13}C NMR (66 MHz, $CDCl_3$) δ 99.9, 122.3, 124.8, 126.9, 128.7, 129.5, 130.3, 137.4, 138.3, 158.8, 161.6, 163.7; HPLC purity 98%; ESIMS m/z=248 (MH^+), 246 ($M-H^-$).

Method 3: following GM3, benzeneboronic acid (120 mg, 0.98 mmol), 4,6-dichloropyrimidine (161 mg, 1.10 mmol, 1.1 equiv), sodium carbonate (313 mg, 3.00 mmol, 3.0 equiv), and $Pd(PPh_3)_2Cl_2$ (7 mg, 1 mol %) were reacted in a mixture of 2.5 mL of DME, 0.4 mL of EtOH, and 0.5 mL of water in the microwave synthesizer. 2-Propanol (1.0 mL) and aniline (116 μL, 1.30 mmol) were added, the mixture was acidified with concd HCl (37%), and again reacted in the microwave synthesizer. Flash column chromatography (*c*Hex/EtOAc 4:1) afforded **2a** (104 mg, 43%).

4.4.2. Phenyl-(6-*o*-tolyl-pyrimidin-4-yl)-amine (2b). Following GM2, **1a** (100 mg, 0.413 mmol), 2-methylbenzeneboronic acid (70 mg, 0.516 mmol, 1.25 equiv), sodium carbonate (153 mg, 1.450 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (6 mg, 2 mol %) were reacted in 3.0 mL DME, 0.4 mL EtOH, and 0.6 mL water. After neutralization with $NaHCO_3$, extraction of the organic layer with EtOAc, drying over Na_2SO_4, and evaporation, flash column chromatography (*c*Hex/EtOAc 5:1) afforded **2b** (107 mg, 99%). Colorless solid; mp 111–112 °C (MeCN/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.38 (3H, s), 6.86 (1H, s), 7.03 (1H, t, J=7.3 Hz), 7.25–7.46 (6H, m), 7.71 (2H, d, J=8.3 Hz), 8.69 (1H, s), 9.65 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 20.0, 106.1, 119.8, 122.4, 125.9, 128.7, 128.8, 129.0, 130.7, 135.4, 138.3, 139.6, 157.5, 160.3, 164.5; HPLC purity 98%; ESIMS m/z=262 (MH^+), 260 ($M-H^-$).

4.4.3. [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-phenyl-amine (2c) and [6-(2-methoxy-phenyl)-pyrimidin-4-yl]-phenyl-amine hydrochloride (2c·HCl). Method 1: following GM1, **3b** (70 mg, 0.32 mmol) and aniline (29 μL, 0.32 mmol) were reacted in 1 mL of 2-propanol and 150 μL of concd HCl (37%) at 95 °C. Compound **2c**·HCl was isolated after filtration (66 mg, 66%). Yellow solid; mp 193–194 °C (2-propanol/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.90 (3H, s), 7.12–7.36 (4H, m), 7.44 (2H, t, J=8.0 Hz), 7.55–7.75 (4H, m), 8.90 (1H, s), 11.25 (1H, br s); ^{13}C (66 MHz, DMSO-d_6) δ 55.9, 106.2, 112.3, 119.9, 120.9, 121.8, 125.1, 129.0, 130.2, 133.3, 137.4, 153.3, 154.6, 156.9, 161.2; ESIMS m/z= 278 (MH^+); elemental analysis calcd for $C_{17}H_{16}ClN_3O\cdot H_2O$: C, 61.54; H, 5.47; N, 12.66. Found: C, 61.62; H, 5.41; N, 12.55.

Method 2: following GM2, **1a** (100 mg, 0.413 mmol), 2-methoxybenzeneboronic acid (78 mg, 0.516 mmol, 1.25 equiv), sodium carbonate (153 mg, 1.450 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (6 mg, 2 mol %) were reacted in a mixture of

3.0 mL of DME, 0.4 mL of EtOH, and 0.6 mL of water. Flash column chromatography (*c*Hex/EtOAc 2:1) afforded **2c** (93 mg, 81%). Colorless solid; mp 139–140 °C (EtOAc/*c*Hex), ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.89 (3H, s), 6.96–7.21 (3H, m), 7.28–7.51 (4H, m), 7.72 (2H, d, J=8.0 Hz), 7.96 (1H, d, J=8.1 Hz), 8.70 (1H, s), 9.63 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 55.6, 106.9, 112.0, 119.7, 120.5, 122.2, 125.8, 128.7, 130.1, 131.1, 139.9, 157.4, 157.7, 159.4, 160.3; HPLC purity 97%; ESIMS m/z=278 (MH^+), 276 ($M-H^-$).

4.4.4. 1-[2-(6-Phenylamino-pyrimidin-4-yl)-phenyl]-ethanone (2d). Following GM2, **1a** (100 mg, 0.413 mmol), 2-acetylbenzeneboronic acid (85 mg, 0.516 mmol, 1.25 equiv), sodium carbonate (153 mg, 1.450 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (6 mg, 2 mol %) were reacted in a mixture of 3.0 mL of DME, 0.4 mL of EtOH, and 0.6 mL of water. Flash column chromatography (*c*Hex/EtOAc 2:1) afforded **2d** (96 mg, 81%). Colorless solid; mp 129–130 °C (EtOAc/*c*Hex); ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.33 (3H, s), 6.99–7.10 (2H, m), 7.35 (2H, t, J=8.0 Hz), 7.54–7.75 (6H, m), 8.61 (1H, s), 9.78 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 30.3, 104.5, 120.0, 122.6, 127.3, 128.8, 129.5, 130.4, 136.6, 139.5, 141.4, 157.5, 160.7, 162.6, 202.7; HPLC purity 99%; ESIMS m/z=290 (MH^+), 288 ($M-H^-$).

4.4.5. [3-(6-Phenylamino-pyrimidin-4-yl)-phenyl]-methanol (2e). Following GM2, **1a** (100 mg, 0.413 mmol), 3-hydroxymethylbenzeneboronic acid (78 mg, 0.516 mmol, 1.25 equiv), sodium carbonate (153 mg, 1.450 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (6 mg, 2 mol %) were reacted in a mixture of 3.0 mL of DME, 0.4 mL of EtOH, and 0.6 mL of water. Flash column chromatography (*c*Hex/EtOAc 1:1–1:3) afforded **2e** (97 mg, 85%). Colorless solid; mp 161–162 °C (EtOAc/*c*Hex); ^{1}H NMR (200 MHz, DMSO-d_6) δ 4.60 (2H, d, J=6.0 Hz), 5.34 (1H, t, J=6.0 Hz), 7.03 (1H, t, J=7.2 Hz), 7.24–7.54 (5H, m), 7.73 (2H, d, J=8.0 Hz), 7.90 (1H, d, J=6.6 Hz), 8.03 (1H, s), 8.72 (1H, s), 9.69 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 62.7, 101.9, 119.7, 122.3, 124.3, 124.7, 128.3, 128.6, 128.8, 136.7, 139.8, 143.2, 158.2, 161.0, 161.2; HPLC purity 97%; ESIMS m/z=278 (MH^+), 276 ($M-H^-$).

4.4.6. [6-(3-Nitro-phenyl)-pyrimidin-4-yl]-phenyl-amine (2f) and [6-(3-nitro-phenyl)-pyrimidin-4-yl]-phenyl-amine hydrochloride (2f·HCl). Method 1: following GM1, **3c** (150 mg, 0.637 mmol) and aniline (61 μL, 0.669 mmol, 1.05 equiv) were reacted in 1.5 mL of 2-propanol and 150 μL of concd HCl (37%) at 95 °C. Filtration gave **2f**·HCl (164 mg, 78%). Yellow solid; mp 276–277 °C (EtOH/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.13 (1H, t, J=7.8 Hz), 7.33–7.45 (3H, m), 7.72 (2H, d, J=8.0 Hz), 7.87 (1H, t, J=8.0 Hz), 8.35–8.45 (2H, m), 8.79 (1H, t, J=1.8 Hz), 8.86 (1H, s), 10.52 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 103.5, 120.8, 121.6, 123.9, 125.5, 129.0, 130.8, 133.1, 136.1, 138.5, 148.3, 155.7, 156.6, 161.2; ESIMS m/z=293 (MH^+); elemental analysis calcd for $C_{16}H_{13}ClN_4O_2$: C, 58.46; H, 3.99; N, 17.04. Found: C, 58.78; H, 4.02; N, 16.80.

Method 2: following GM2, **1a** (100 mg, 0.413 mmol), 3-nitrobenzeneboronic acid (86 mg, 0.516 mmol, 1.25 equiv), sodium carbonate (153 mg, 1.450 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (6 mg, 2 mol %) were reacted in a mixture of 3.0 mL of DME, 0.4 mL of EtOH, and 0.6 mL of water. Flash column chromatography (*c*Hex/EtOAc 4:1) afforded **2f** (112 mg, 93%). Yellow solid; mp 156–157 °C (EtOAc/*c*Hex); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.05 (1H, t, J=7.3 Hz), 7.29–7.42 (3H, m), 7.72 (2H, d, J=8.8 Hz), 7.83 (1H, t, J=8.0 Hz), 8.25–8.48 (2H, m), 8.75 (1H, s), 8.80 (1H, s), 9.79 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 102.7, 119.9, 120.9, 122.6, 124.7, 128.8, 130.5, 132.4, 138.4, 139.5, 148.2, 158.4, 158.5, 161.0; HPLC purity 95%; ESIMS m/z=293 (MH^+), 291 ($M-H^-$).

4.4.7. [6-(4-Methoxy-phenyl)-pyrimidin-4-yl]-phenyl-amine (2g). Following GM2, **1a** (100 mg, 0.413 mmol), 4-methoxybenzeneboronic acid (78 mg, 0.516 mmol, 1.25 equiv), sodium carbonate (153 mg, 1.450 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (6 mg, 2 mol %) were reacted in a mixture of 3.0 mL of DME, 0.4 mL of EtOH, and 0.6 mL of water. Flash column chromatography (*c*Hex/EtOAc 4:1–3:1) afforded **2g** (99 mg, 86%). Colorless solid; mp 170–171 °C (EtOAc/*c*Hex); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.82 (3H, s), 6.96–7.12 (3H, m), 7.17 (1H, s), 7.34 (2H, t, J=8.1 Hz), 7.71 (2H, d, J=8.1 Hz), 7.99 (2H, d, J=8.8 Hz), 8.65 (1H, s), 9.63 (1H, br s); ^{13}C NMR (66 MHz, $CDCl_3$) δ 55.4, 98.5, 114.1, 122.4, 124.9, 128.4, 129.6, 129.7, 138.2, 158.7, 161.5, 161.6, 163.3; HPLC purity 99%; ESIMS m/z=278 (MH^+), 276 ($M-H^-$).

4.4.8. (4-Methoxy-phenyl)-(6-phenyl-pyrimidin-4-yl)-amine (2h) and (4-methoxy-phenyl)-(6-phenyl-pyrimidin-4-yl)-amine hydrochloride (2h·HCl). Method 1: following GM1, **3a** (100 mg, 0.525 mmol) and *p*-anisidine (68 mg, 0.551 mmol, 1.05 equiv) were reacted in 1 mL of 2-propanol and 150 μL of concd HCl (37%) at 95 °C. Filtration and drying gave **2h**·HCl (130 mg, 79%). Yellow solid; mp 261–262 °C (EtOH/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.78 (3H, s), 7.01 (2H, d, J=9.0 Hz), 7.40 (1H, s), 7.57–7.69 (5H, m), 7.88–7.96 (2H, m), 8.85 (1H, s), 11.62 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 55.3, 102.7, 114.2, 123.6, 127.2, 129.3, 130.0, 130.5, 132.1, 152.7, 153.3, 156.8, 161.2; ESIMS m/z=278 (MH^+); elemental analysis calcd for $C_{17}H_{16}ClN_3O$: C, 65.07; H, 5.14; N, 13.39; found: C, 64.87; H, 5.23; N, 13.20.

Method 2: following GM2, **1d** (100 mg, 0.368 mmol), benzeneboronic acid (56 mg, 0.460 mmol, 1.25 equiv), sodium carbonate (136 mg, 1.290 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (5 mg, 2 mol %) were reacted in a mixture of 3.0 mL of DME, 0.4 mL of EtOH, and 0.6 mL of water. Flash column chromatography (*c*Hex/EtOAc 4:1) afforded **2h** (81 mg, 79%). Colorless solid; mp 152–153 °C (EtOH); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.74 (3H, s), 6.94 (2H, d, J=8.8 Hz), 7.12 (1H, s), 7.46–7.61 (5H, m), 7.95–8.04 (2H, m), 8.64 (1H, s), 9.50 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 55.1, 101.1, 114.0, 122.0, 126.3, 128.8, 130.2, 132.5, 137.0, 155.0, 158.3, 160.9, 161.1; HPLC purity 96%; ESIMS m/z=278 (MH^+), 276 ($M-H^-$).

4.4.9. (4-Nitro-phenyl)-(6-phenyl-pyrimidin-4-yl)-amine (2i) and (4-nitro-phenyl)-(6-phenyl-pyrimidin-4-yl)-amine hydrochloride (2i·HCl). Method 1: following GM1, **3a** (100 mg, 0.525 mmol) and 4-nitroaniline (76 mg,

0.551 mmol, 1.05 equiv) were reacted in 1 mL of 2-propanol and 150 μL of concd HCl (37%) at 95 °C. Filtration and drying afforded **2i**·HCl (155 mg, 90%). Yellow solid; mp 251–252 °C (2-propanol/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.57–7.65 (4H, m), 7.97–8.12 (4H, m), 8.28 (2H, d, J=9.0 Hz), 8.97 (1H, s), 11.39 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 104.2, 119.5, 125.0, 126.9, 129.2, 131.4, 133.9, 141.7, 145.5, 156.2, 158.6, 161.0; ESIMS m/z=293 (MH^+); elemental analysis calcd for $C_{16}H_{13}ClN_4O_2$: C, 58.46; H, 3.99; N, 17.04. Found: C, 59.14; H, 4.06; N, 16.80.

Method 2: following GM2, **1b** (100 mg, 0.346 mmol), benzeneboronic acid (53 mg, 0.433 mmol, 1.25 equiv), sodium carbonate (128 mg, 1.210 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (5 mg, 2 mol %) were reacted in a mixture of 3.0 mL of DME, 0.4 mL of EtOH, and 0.6 mL of water at 125 °C for 2400 s. Flash column chromatography (*c*Hex/EtOAc 3:1) afforded **2i** (61 mg, 60%). Yellow solid; mp 218–219 °C (MeCN/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.39 (1H, s), 7.51–7.60 (3H, m), 7.98–8.12 (4H, m), 8.26 (2H, d, J=9.5 Hz), 8.88 (1H, s), 10.44 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 103.5, 118.4, 125.0, 126.5, 128.9, 130.6, 136.3, 140.8, 146.4, 158.0, 160.3, 161.9; HPLC purity 97%; ESIMS m/z=293 (MH^+), 291 ($M-H^-$).

Method 3: following GM3, benzeneboronic acid (100 mg, 0.82 mmol), 4,6-dichloropyrimidine (147 mg, 0.98 mmol, 1.2 equiv), sodium carbonate (304 mg, 2.46 mmol, 3.0 equiv), and $Pd(PPh_3)_2Cl_2$ (12 mg, 2 mol %) were reacted in a mixture of 3.0 mL of DME, 0.4 mL of EtOH, and 0.5 mL of water. 1 mL of 2-Propanol, and 4-nitroaniline (125 mg, 0.90 mmol, 1.1 equiv) were added, the mixture was acidified with concd HCl (37%), and again reacted in the microwave synthesizer. After neutralization with $NaHCO_3$, extraction of the organic layer with EtOAc, drying over Na_2SO_4 and evaporation, flash column chromatography (*c*Hex/EtOAc 3:1) afforded **2i** (96 mg, 40%).

4.4.10. (4-Methyl-3-nitro-phenyl)-(6-phenyl-pyrimidin-4-yl)-amine (2j). Following GM2, **1c** (100 mg, 0.332 mmol), benzeneboronic acid (51 mg, 0.415 mmol, 1.25 equiv), sodium carbonate (123 mg, 1.16 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (5 mg, 2 mol %) were reacted in a mixture of 3.0 mL of DME, 0.4 mL of EtOH, and 0.6 mL of water. Flash column chromatography (*c*Hex/EtOAc 4:1) afforded **2j** (80 mg, 79%). Yellow solid; mp 191–192 °C (EtOAc/*c*Hex); ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.47 (3H, s), 7.25 (1H, s), 7.45 (1H, d, J=8.4 Hz), 7.49–7.58 (3H, m), 7.86 (1H, dd, J=2.2 Hz, J=8.4 Hz), 8.00–8.08 (2H, m), 8.59 (1H, d, J=2.2 Hz), 8.79 (1H, s), 10.06 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 19.0, 102.5, 114.3, 123.9, 125.7, 126.4, 128.9, 130.4, 133.0, 136.6, 138.9, 148.6, 158.1, 160.6, 161.4; HPLC purity 95%; ESIMS m/z=307 (MH^+), 305 ($M-H^-$).

4.4.11. (6-Phenyl-pyrimidin-4-yl)-*o*-tolyl-amine (2k). Following GM1, **3a** (100 mg, 0.525 mmol) and *o*-toluidine (59 μL, 0.551 mmol, 1.05 equiv) were reacted in 1 mL of 2-propanol and 150 μL of concd HCl (37%) at 95 °C. Satd aqueous $NaHCO_3$ was added, and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by flash column chromatography (*c*Hex/EtOAc 3:1) to afford **2k** (75 mg, 55%). Colorless solid; mp 126–127 °C (EtOAc/*c*Hex); ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.24 (3H, s), 7.05–7.32 (4H, m), 7.45–7.55 (4H, m), 7.92–8.01 (2H, m), 8.58 (1H, s), 9.03 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 17.9, 100.2, 125.1, 125.2, 126.2, 126.3, 128.8, 130.2, 130.5, 130.6, 132.4, 136.9, 158.3, 161.3, 162.0; HPLC purity 99%; ESIMS m/z=262 (MH^+), 260 ($M-H^-$).

4.4.12. 4-(6-Phenyl-pyrimidin-4-ylamino)-benzoic acid methyl ester hydrochloride (2l·HCl). Following GM1, **3a** (73 mg, 0.383 mmol) and methyl 4-aminobenzoate (61 mg, 0.402 mmol, 1.05 equiv) were reacted in 800 μL of 2-propanol and 120 μL of concd HCl (37%) at 95 °C. Filtration and drying gave **2l**·HCl (125 mg, 96%). Slightly yellow solid; mp 270–272 °C (EtOH/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.84 (3H, s), 7.56–7.67 (4H, m), 7.91–8.04 (6H, m), 8.96 (1H, s), 11.50 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 51.9, 103.5, 119.4, 123.6, 126.8, 129.1, 130.3, 131.3, 134.2, 143.5, 156.4, 158.5, 161.0, 165.7; ESIMS m/z=306 (MH^+), 304 ($M-H^-$); elemental analysis calcd for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.29. Found: C, 63.65; H, 4.70; N, 12.00.

4.4.13. (4-Bromo-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine hydrochloride (2m·HCl). Following GM1, **3b** (200 mg, 0.906 mmol) and 4-bromoaniline (156 mg, 0.906 mmol) were reacted in 2 mL of 2-propanol and 200 μL of concd HCl (37%) at 95 °C. Filtration and drying afforded **2m**·HCl (305 mg, 86%). Colorless solid; mp 248–249 °C (2-propanol/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.90 (3H, s), 7.17 (1H, t, J=7.2 Hz), 7.28 (1H, d, J=7.9 Hz), 7.44 (1H, s), 7.56–7.77 (6H, m), 8.93 (1H, s), 11.56 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 56.0, 106.8, 112.4, 116.8, 119.7, 120.9, 123.4, 130.2, 131.8, 133.4, 137.0, 152.1, 153.3, 157.0, 161.1; ESIMS m/z=356/358 (MH^+), 354/356 ($M-H^-$); elemental analysis calcd for $C_{17}H_{15}BrClN_3O$: C, 52.00; H, 3.85; N, 10.70. Found: C, 51.84; H, 3.65; N, 10.60.

4.4.14. (3-Bromo-phenyl)-[6-(3-nitro-phenyl)-pyrimidin-4-yl]-amine hydrochloride (2n·HCl). Following GM1, **3c** (150 mg, 0.637 mmol) and 3-bromoaniline (73 μL, 0.669 mmol, 1.05 equiv) were reacted in 1.5 mL of 2-propanol and 150 μL of concd HCl (37%) at 95 °C. Filtration and drying afforded **2n**·HCl (230 mg, 89%). Yellow solid; mp 272–273 °C (2-propanol/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.23–7.39 (2H, m), 7.52 (1H, s), 7.67 (1H, td, J=7.5 Hz, J=1.9 Hz), 7.88 (1H, t, J=8.0 Hz), 8.18 (1H, t, J=1.9 Hz), 8.37–8.45 (2H, m), 8.80 (1H, t, J=1.8 Hz), 8.90 (1H, s), 10.74 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 103.9, 118.9, 121.4, 121.6, 122.3, 125.4, 125.7, 130.7, 132.9, 136.5, 140.6, 148.2, 156.6, 157.1, 160.9, 161.0; ESIMS m/z=371/373 (MH^+), 369/371 ($M-H^-$); elemental analysis calcd for $C_{16}H_{12}BrClN_4O_2$: C, 47.14; H, 2.97; N, 13.74. Found: C, 47.29; H, 2.89; N, 13.90.

4.4.15. (4-Aminomethyl-phenyl)-(6-phenyl-pyrimidin-4-yl)-amine (2o). Following GM1, **3a** (84 mg, 0.441 mmol) and 4-aminobenzylamine (50 μL, 0.441 mmol) were reacted

in 2 mL of 2-propanol and 120 μL of concd H_2SO_4 (98%) at 100 °C for 900 s. The sulfate salt of **2o** was isolated after filtration. Satd aqueous $NaHCO_3$ solution was added (pH=8–9) to the solid, and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent afforded **2o** (95 mg, 78%). Slightly yellow solid; mp 153–155 °C (EtOAc); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.68 (2H, s), 7.21 (1H, s), 7.29 (2H, d, J=8.9 Hz), 7.47–7.57 (3H, m), 7.62 (2H, d, J=8.9 Hz), 7.96–8.05 (2H, m), 8.68 (1H, s), 9.64 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 45.1, 101.6, 119.8, 126.3, 127.5, 128.8, 130.2, 136.9, 137.8, 138.2, 158.3, 161.0, 161.0; HPLC purity 94%; ESIMS m/z=277 (MH^+), 275 ($M-H^-$).

4.4.16. 4-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-morpholine hydrochloride (4). A suspension of **3b** (75 mg, 0.34 mmol) and morpholine (36 μL, 0.41 mmol, 1.2 equiv) in 1.0 mL of 2-propanol was heated in the microwave synthesizer at 115 °C for 900 s. Concd HCl (37%, 300 μL) was added. After storage at 4 °C overnight, the colorless precipitate was filtered, washed with cold 2-propanol, and dried to afford **4** (68 mg, 65%). Colorless solid; mp 231–232 °C (2-propanol/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.69–3.78 (4H, m), 3.86 (3H, s), 3.87–3.96 (4H, m), 7.16 (1H, t, J=7.8 Hz), 7.26 (1H, d, J=8.1 Hz), 7.34 (1H, s), 7.56–7.68 (2H, m), 8.83 (1H, s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 45.1, 55.9, 65.6, 102.6, 112.0, 119.5, 120.8, 130.7, 133.4, 151.2, 151.5, 156.7, 160.8; HPLC purity 98%; ESIMS m/z=272 (MH^+).

4.4.17. (4-Amino-benzyl)-(6-phenyl-pyrimidin-4-yl)-amine (6). Compound **3a** (50 mg, 0.262 mmol) and 4-aminobenzylamine (33 μL, 0.288 mmol, 1.1 equiv) were suspended in 1.5 mL of 2-propanol, treated with DIPEA (63 μL, 0.524 mmol, 2.0 equiv) and reacted at 120 °C for 900 s in the microwave synthesizer. The solvent was evaporated and the crude product purified by flash column chromatography (*c*Hex/EtOAc 1:1) to afford **6** (41 mg, 52%). Colorless solid; mp 156–157 °C (MeCN/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 4.37 (2H, d, J=5.9 Hz), 4.97 (2H, s), 6.52 (2H, d, J=8.1 Hz), 6.95 (1H, s), 7.02 (2H, d, J=8.1 Hz), 7.43–7.54 (3H, m), 7.75 (1H, t, J=5.9 Hz), 7.91–8.03 (2H, m), 8.49 (1H, s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 43.4, 100.7, 113.7, 125.9, 126.2, 128.3, 128.6, 129.9, 137.2, 147.6, 158.3, 159.8, 162.8; HPLC purity 99%; ESIMS m/z=277 (MH^+), 275 ($M-H^-$).

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