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A Strategy for the Triarylation of Pyrrolopyrimidines by Using Microwave-Promoted Cross-Coupling Reactions

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New pyrrolo[2,3-*d*]pyrimidines that have aryl groups at the 2-, 4-, and 6-positions were prepared by the arylation reaction of 4-chloro-7-methyl-2-(methylthio)-6-phenylpyrrolo-[2,3-*d*]pyrimidine (**6**) and the corresponding arylboronic acid under Suzuki–Miyaura conditions followed by a second arylation under Liebeskind–Srogl cross-coupling conditions. A parallel study that began with the C-2 chemoselective arylation of **6** under Liebeskind–Srogl conditions followed by a Suzuki–Miyaura coupling at C-4 was carried out, and the results of each route were compared. All of the tranformations were performed under microwave irradiation.

Introduction

The pyrrolo[2,3-*d*]pyrimidines also known as deazapurines, because of their structural similarity to natural purines, are interesting templates for drug discovery programs in medicinal chemistry[1] and have proved to be valuable scaffolds in organic chemistry.[2] Compounds that contain a pyrrolopyrimidine nucleus have a variety of biological effects including antibacterial,[3] anti-inflammatory,[4] antiparasitic,[5] and antitumor properties.[6] In addition to these pharmaceutical applications, substituted arylpyrimidine, arylpurine, and deazapurine cores with π-conjugated systems exhibit interesting photophysical properties.[7]

Diaryl-, triaryl-, and tetraarylpurines have been prepared by intramolecular pyrimidine cyclizations[8] and nucleophilic substitutions of halogenated purines.[9] Consecutive diarylations at the C-4 and C-2 positions of purines under Pd-catalyzed classical Suzuki–Miyaura conditions have been reported by Hocek et al.,[9a,9b] and the same authors selectively prepared 4,5-diarylpyrrolo[2,3-*d*]pyrimidines from 4-(phenylthio)-5-iodopyrrolo[2,3-*d*]pyrimidine.[10] Tumkevicius et al. obtained 2,4,7-triarylpyrrolo[2,3-*d*]pyrimidines from the corresponding 2,4-dichloropyrrolopyrimidines by using a combination of Suzuki–Miyaura cross-coupling reactions with arylboronic acids and *N*-arylation reactions with aryl halides.[11]

In previous reports related to the synthesis of pyrrolopyrimidines, we employed stepwise arylations at the C-4 and C-5 positions of 6-aryl-4,6-dihalopyrrolo[2,3-*d*]pyrimidines,[12] and more recently, we reported details of a one-pot synthesis of 4,6-disubstituted pyrrolopyrimidines.[13] The substitution of pyrrolopyrimidines is often difficult to control, and selectivity plays an special role when different substituents need to be introduced.[14]

In this current work, a more selective strategy was developed to obtain 2,4,6-triarylpyrrolo[2,3-*d*]pyrimidines from 4-chloro-7-methyl-2-(methylthio)-6-phenylpyrrolo[3,2-*d*]pyrimidines. The presence of different leaving groups at the C-2 and C-4 positions of the heterocycle allows for highly selective arylations under Suzuki–Miyaura and Liebeskind–Srogl conditions.

Results and Discussion

Retrosynthetic analysis suggests that 2,4,6-trisubstituted pyrrolo[2,3-*d*]pyrimidines (IUPAC numbering is used throughout the manuscript) can be synthesized by a general approach from monocyclic compounds, which involves an intramolecular cyclization and double arylations under cross-coupling conditions. Among several possibilities, we chose to prepare a versatile key intermediate for the formation of 2,4,6-triarylated pyrrolopyrimidines from commercially available 4,6-dihydroxy-2-(methylthio)pyrimidine (**1**).

4,6-Dichloro-2-(methylthio)pyrimidine (**2**) was obtained in 93% yield by applying the procedure of Raboisson et al., which involved dichlorination of 4,6-dihydroxy-2-(methylthio)pyrimidine with $POCl_3$ and *N*,*N*-diethylaniline.[15] 5-Alkynylpyrimidine **5** was then prepared by the direct and regioselective substitution of **2** using methylamine followed by iodination at the C-5 position of 4-chloro-6-(methylamino)-2-(methylthio)pyrimidine (**3**) using *N*-iodosuccin-

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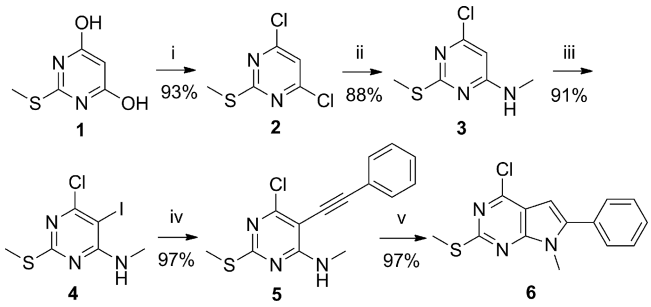
imide (NIS) and then a Sonogashira-type alkynylation by using phenylacetylene under microwave irradiation. The last step involves an intramolecular cyclization of acetylene derivative **5** to give 6-arylated deazapurine **6** under conditions that we previously established for related compounds.[13] Our synthetic route towards target **6** included a combination of these five steps with an overall yield of 70% (Scheme 1).



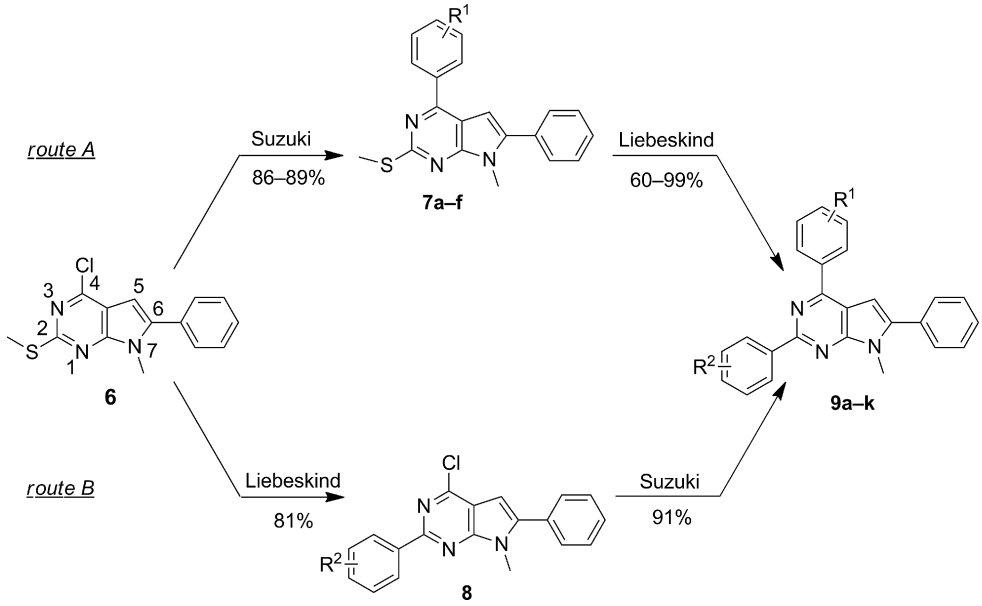
Scheme 1. Reagents and conditions: (i) $POCl_3$, *N*,*N*-diethylaniline; (ii) CH_3NH_2·HCl, NEt_3, *i*PrOH, reflux, 8 h; (iii) NIS, CH_3CN, microwave (MW), 100 °C, 15 min; (iv) $Pd(dba)_2$ (dba = dibenzylideneacetone), P(*o*-furyl)$_3$, CuI, phenylacetylene, tetrahydrofuran (THF)/NEt_3, MW, 100 °C, 30 min; (v) Cs_2CO_3, CH_3CN, MW, 100 °C, 30 min.

Considering the attraction of a concise and rapid synthetic procedure that would allow the preparation of a series of 2,4,6-trisubstituted pyrrolopyrimidines, we were primarily interested in the arylation of heterocyclic intermediate **6**. Thus, 4-chloro-7-methyl-2-(methylthio)-6-phenylpyrrolo[2,3-*d*]pyrimidine (**6**) was considered an important substructure, which would have applications beyond the current work. Retrosynthetic analysis suggests two general approaches for the preparation of 2,4,6-trisubstituted pyrrolopyrimidines from key building block **6** (Scheme 2, routes A and B).

One approach involves a Pd-catalyzed Suzuki–Miyaura cross-coupling reaction of 4-halopyrrolopyrimidines by employing arylboronic acids followed by a $Pd(PPh_3)_4$/CuTC catalyzed (TC = thiophene-2-carboxylate) C-2 arylation using arylboronic acid under Liebeskind–Srogl conditions (Scheme 2, route A). On the other hand, the sequence could be performed in reverse (Scheme 2, route B). Both arylation reactions were catalyzed by palladium to generate the C–C bonds, and a set of six substituted phenylboronic acids were selected for the arylations at the C-2 and C-4 positions (Tables 1 and 3).

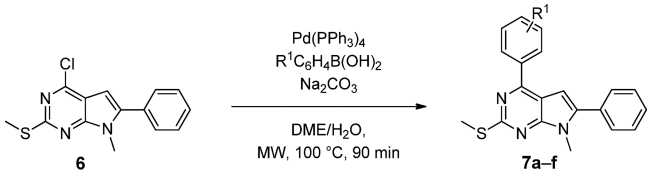
To explore this double arylation process and highlight its synthetic appeal, new compounds **7a**–**7f** were prepared by arylation at the C-4 position of pyrrolopyrimidine **6** using different arylboronic acids under Suzuki–Miyaura conditions and microwave irradiation. According to the results, neither the position (Table 1, Entries 1–3) nor the nature (Table 1, Entries 1–4, electron-donating groups, Entry 5, electron-withdrawing group) of the aryl substituent in the boronic acid affected the outcome of the reaction (Table 1, Entries 1–6). In addition, the pyridine substituent also provided product **7f** in excellent yield (Table 1, Entry 6).

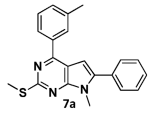
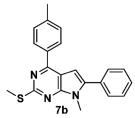
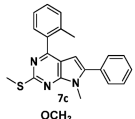
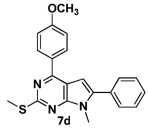
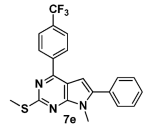
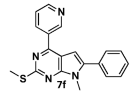
By following route A, the next step involved desulfuration of the C-2 position under Liebeskind–Srogl conditions.[16] The optimization of the Liebeskind–Srogl cross-coupling reaction conditions was performed by using diarylated intermediates **7a** and **7d** and the corresponding arylboronic acid and by modifying the catalyst and thiophilic metal cocatalyst (Table 2). The solvent and temperature were also varied (Table 2, Entry 4). The desulfurative coupling of nitrogenated aromatic thioethers **7a** and **7d** with the boronic acid proceeded in higher yields by using copper(I) 3-methylsalicylate (CuMeSal, Table 2, Entries 1 and 5) than by using copper(I) thiophene-2-carboxylate (Table 2, Entries 2–4 and 6). The replacement of a methylthio group bonded to an aromatic nucleus generally af-



Scheme 2. Approaches towards the preparation of pyrrolopyrimidine derivatives.

Table 1. Arylation under Suzuki–Miyaura reaction conditions.[a]

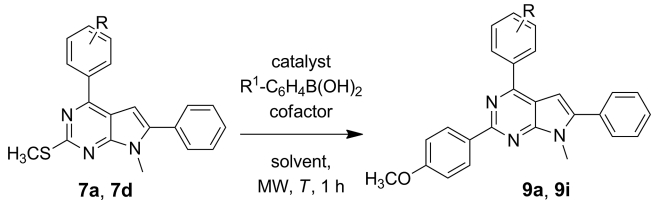


Entry	R^1	Compound	Yield[a]
1	3-CH_3		86%
2	4-CH_3		92%
3	2-CH_3		98%
4	4-CH_3O		99%
5	4-CF_3		94%
6	3-pyridyl		98%

[a] Yield of isolated and purified compound.

fords the corresponding products in low yields.[17] However in this case, the presence of the electronegative nitrogen atoms in the heteroaromatic nucleus (in the α positions to the reaction site) favor the cross-coupling reaction.[18]

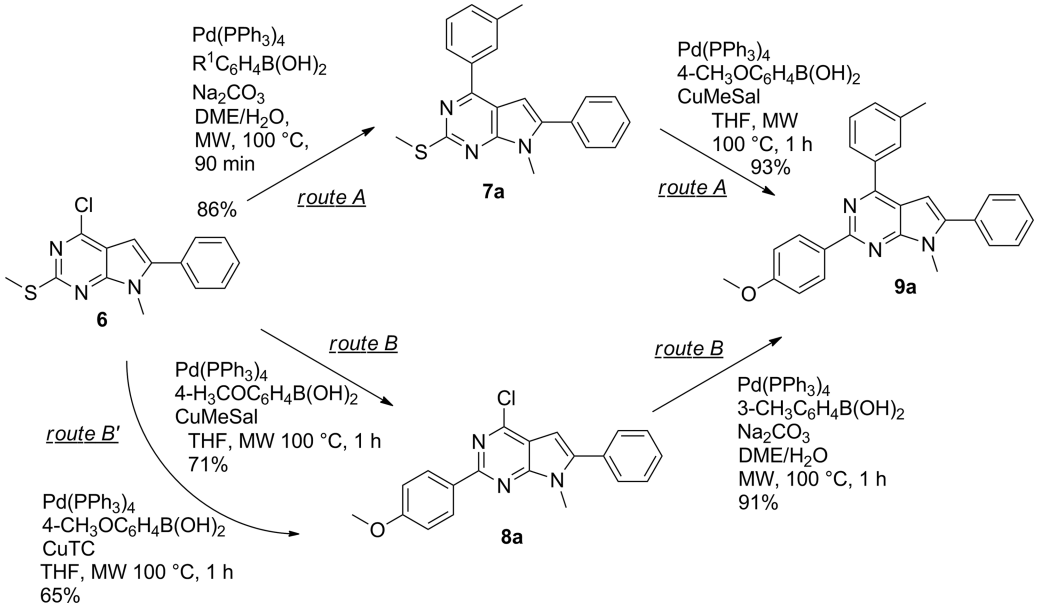
Table 2. Optimization of the Liebeskind–Srogl cross-coupling reaction.



Entry	R	Catalyst	Cocatalyst	Solvent	*T* [°C]	% Yield **7**,**9**	
1	3-CH_3 (**7a**)	$Pd(PPh_3)_4$	CuMeSal	THF	100	93[a] (**9a**)	–
2	3-CH_3 (**7a**)	$Pd(PPh_3)_4$	CuTC	THF	100	93 (**9a**)	–
3	4-CH_3O (**7d**)	$Pd(PPh_3)_4$	CuTC	THF	100	64[b] (**9i**)	36[b] (**7d**)
4	4-CH_3O (**7d**)	$Pd(PPh_3)_4$	CuTC	dioxane	130	68[b] (**9i**)	32[b] (**7d**)
5	4-CH_3O (**7d**)	$Pd(PPh_3)_4$	CuMeSal	THF	100	88[a] (**9i**)	–
6	4-CH_3O (**7d**)	$Pd_2(dba)_3$, $P(o\text{-furyl})_3$	CuTC	THF	100	49[b] (**9i**)	51[b] (**7d**)

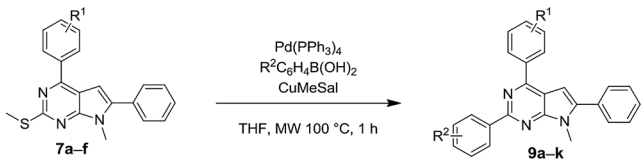
[a] Yield of isolated and purified compound. [b] Ratio determined by ^1H NMR spectroscopic analysis.

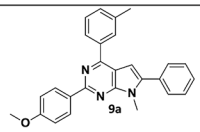
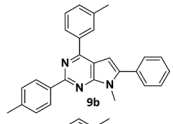
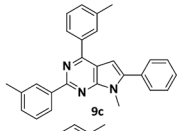
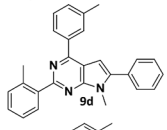
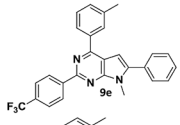
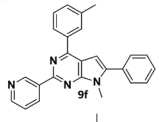
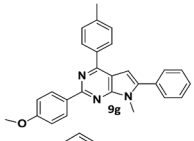
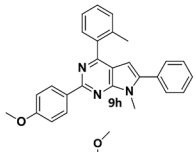
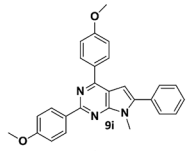
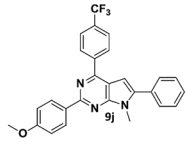
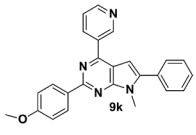
CuTC was less effective than CuMeSal as a cocatalyst and led to an incomplete reaction, which was confirmed by the presence of a mixture of triarylated derivative **9** and starting material **7** (Table 2, Entries 3, 4, and 6). Therefore, this arylation was best performed under microwave irradiation in THF at 100 °C for 1 h with $Pd(PPh_3)_4$ as the catalyst and CuMeSal as a cocatalyst. The optimized Liebeskind–Srogl conditions were then applied to methylthio-substituted deazapurines **7a**–**7f** to explore the scope of this reaction.



Scheme 3. Comparison of both routes (A and B) for the arylation at the C-2 and C-4 positions of pyrrolopyrimidines.

Table 3. Arylation under Liebeskind–Srogl reaction conditions.[a]



Entry	R^1	R^2	Compound	Yield[a]
1	3-CH_3	4-CH_3O		93%
2	–	4-CH_3		99%
3	–	3-CH_3		89%
4	–	2-CH_3		60%
5	–	4-CF_3		95%
6	–	3-pyridyl		96%
7	4-CH_3	4-CH_3O		97%
8	2-CH_3	–		95%
9	4-CH_3O	–		88%
10	4-CF_3	–		99%
11	3-pyridyl	–		86%

[a] Yield of isolated and purified compound.

According to the results, the electronic character of the substituents of the arylboronic acids did not affect the reaction (Table 3, Entries 1–4 and 7–11, electron-donating substituents, Entry 5, electron-withdrawing substituent). Nitrogenated heterocycles such as a pyridine group also led to good yields (Table 3, Entry 6). Nevertheless, the position of the aryl substituent influenced the reaction process, as evidenced by the *ortho*-methylphenyl group of compound **9d** (Table 3, Entry 4). In this case, the yield was lower as a result of the steric hindrance from the *ortho*-methyl group.

Finally, the diarylation process was performed by reversing the order of the two steps (Scheme 2, route B). Thus, the arylation of **6** under the optimized Liebeskind–Srogl conditions at 100 °C (external temperature) chemoselectively afforded deazapurine **8**, which was obtained by displacement of the methylthio group located between two nitrogen atoms of compound **6** (Scheme 3). A subsequent arylation at the 4-position under the previously optimized Suzuki conditions led to triaryl-substituted pyrrolopyrimidine **9a** (Scheme 3). Keeping in mind not only the lower yield of route B (65%) compared with that of route A (80%) but also the difficulty in isolating the product, this route was discarded. As with route A, both cocatalysts for the Liebeskind reaction were tested in route B, and a better result was obtained by using CuMeSal (Scheme 3, route B) than with CuTC (Scheme 3, route B′; overall yields of 65 vs. 59%, respectively).

In this work related to Suzuki–Miyaura and Liebeskind–Srogl couplings as well as in previous studies,[12,13] we have used microwave irradiation. The use of microwave irradiation as opposed to conventional heating significantly increases the yield and accelerates the rate of a reaction. In general, the use of microwave irradiation provides a change in the thermodynamic properties of the reagents. This is revealed by a decrease in the Gibbs free energy of activation for a chemical reaction, which results from the storage of microwave energy or the energy of vibration for a reagent or substrate and is known as an enthalpy effect.[19]

Conclusions

An efficient and robust route to prepare 2,4,6-triarylated pyrrolo[2,3-*d*]pyrimidines has been developed from key intermediate **6**. Of the two routes explored, the more efficient involved the Suzuki–Miyaura cross-coupling reaction followed by a Liebeskind reaction, which provided higher yields and had a broader substrate scope than the reverse process. The process, which began with the arylation at C-2 under Liebeskind–Srogl conditions, was less effective. The use of microwave irradiation accelerated the reaction rate to provide the arylated pyrrolopyrimidines in excellent yields.

A variety of substituents can be selectively introduced at the C-2 and C-4 positions of pyrrolopyrimidine **6**. It is notable that substituents can be introduced at these positions during the last steps of a synthesis, thereby providing an efficient approach to the construction of a compound library. In the future, this approach will also be used for the preparation of compounds related to pyrrolopyrimidines.

Experimental Section

General Methods: Microwave-assisted reactions were carried out in a Biotage Initiator microwave synthesis instrument, and the external temperature was measured with an IR sensor. The reactions were monitored by thin layer chromatography using silica gel (60 F254, Merck) plates. Compounds were visualized by UV irradiation. Column chromatography was performed with silica gel 60 (230–400 mesh, 0.040–0.063 mm). Melting points were measured by using open capillary tubes in a MFB-595010M Gallenkamp apparatus with a digital thermometer. IR spectra were obtained with an FTIR Perkin–Elmer 1600 infrared spectrophotometer. The ^{1}H and ^{13}C NMR spectroscopic data were recorded with Bruker 250 MHz (^{13}C NMR, 63 MHz), Varian Gemini-300 (^{13}C NMR, 75.5 MHz), Varian Gemini-400 (^{13}C NMR, 100 MHz), and Bruker 400 MHz (^{13}C NMR, 100 MHz) spectrometers. The ^{19}F NMR spectroscopic data were recorded with a Bruker (376 MHz, $CDCl_3$) spectrometer by using C_6F_6 as the internal standard (δ = 0 ppm). Chemical shifts are reported in parts per million relative to the central peak of the solvent as the internal standard: $CHCl_3$ [δ = 7.26 ppm (^{1}H NMR)], $CDCl_3$ [δ = 77.16 ppm (^{13}C NMR)], CHD_2OD [δ = 3.31 ppm (^{1}H NMR)], CD_3OD [δ = 49.45 ppm (^{13}C NMR)], [D_5]DMSO [δ = 2.49 (^{1}H NMR)], and [D_6]DMSO [δ = 39.51 ppm (^{13}C NMR)]. The following abbreviations are used to describe the multiplicity of the signal in the proton spectra: s (singlet), d (doublet), t (triplet), q (quadruplet), and m (multiplet). Coupling constants are reported in Hertz. High resolution mass spectra were performed on a Maxis Bruker 4G by using the ICOA platform at the University of Orléans (France) or on a LC/MSD-TOF (2006, Agilent technologies) at the "Center of mass spectrometry" at the University of Barcelona (Spain). All reagents were of high quality or purified before use. Organic solvents were of analytical grade or purified by standard procedures.

General Procedure A (Amination): To a solution of the dichloropyrimidine (1.0 mmol) in 2-propanol (1.0 mL) were added triethylamine (1.2 mmol) and the amine (1.2 mmol). The reaction was stirred and heated at the reflux temperature of 2-propanol (or of the amine if it is lower) until there was complete consumption of the starting material as determined by TLC analysis. After cooling, the solvent was removed in vacuo. Water (15 mL) was added, and the mixture was then extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with NH_4Cl (10 mL). Evaporation of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography.

General Procedure B (Pyrimidine Iodination): A solution of the *N*-methylpyrimidine-4-amine (1.0 mmol) and NIS (3.0 mmol) in acetonitrile (2 mL) was transferred into a special microwave tube, and the mixture was irradiated in a microwave oven at 100 °C for 15 min. The progress of the reaction was monitored by TLC analysis. After cooling, the solvent was removed. Dichloromethane (20 mL) was added, and the organic layer was washed with $Na_2S_2O_3$ (aqueous saturated solution, 2 × 16 mL) and NaOH (10%, 2 × 16 mL). Evaporation of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography or recrystallization.

General Procedure C (Sonogashira Coupling): A mixture of the 5-iodopyrimidine (1.0 mmol), the alkyne (2.0 mmol), $Pd(dba)_2$ (0.03 mmol), tri(2-furyl)phosphine (0.06 mmol), and CuI (0.04 mmol) in dry THF (1 mL) and dry triethylamine (3.5 mL) was transferred into a special microwave tube and irradiated in a microwave oven at 100 °C for 30 min. The progress of the reaction was monitored by TLC analysis. After cooling, the mixture was diluted with NH_4Cl (aqueous saturated solution, 15 mL), and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried with $MgSO_4$ and filtered through Celite®. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography.

General Procedure D (Cyclization): A solution of the alkyne (1.0 mmol) and cesium carbonate (1.0 mmol) in acetonitrile (4.5 mL) was transferred into a special microwave tube, and the mixture was irradiated in a microwave oven at 100 °C for the required time. The progress of the reaction was monitored by TLC analysis. After cooling, the solvent was removed in vacuo. Water (20 mL) was added to the mixture, and the crude reaction mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic phases were washed with Na_2CO_3 (aqueous saturated solution, 15 mL) and brine (15 mL). Evaporation of the solvent under reduced pressure gave the crude product, which was directly purified by silica gel column chromatography.

General Procedure E (Suzuki–Miyaura Coupling at C-4): Under argon, a mixture of the 4-chloropyrrolo[2,3-*d*]pyrimidine (1.0 mmol), the boronic acid (1.05 mmol), sodium carbonate (2.0 mmol), and tetrakis(triphenylphosphine)palladium (0.02 mmol) in a degassed solvent mixture of 1,2-dimethoxyethane (DME, 3.8 mL) and H_2O (0.6 mL) was transferred into a special microwave tube and irradiated in a microwave oven at 100 °C for 60–90 min. The progress of the reaction was monitored by TLC analysis. After cooling, the mixture was diluted with a mixture of brine and water (1:1, 20 mL), and the aqueous solution was extracted with ethyl acetate (3 × 20 mL). The evaporation of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography.

General Procedure F (Liebeskind–Srogl Coupling at C-2): Under argon, a mixture of 4,6-diaryl-2-(methylthio)pyrrolo[2,3-*d*]pyrimidine (1.0 mmol), the boronic acid (1.5 mmol), CuMeSal (3.0 mmol), and tetrakis(triphenylphosphine)palladium (0.1 mmol) in degassed THF (8.0 mL) was transferred into a special microwave tube and irradiated in a microwave oven at 100 °C for 60 min. The progress of the reaction was monitored by TLC analysis. After cooling, the mixture was diluted with dichloromethane (20 mL), and the resulting mixture was washed with a saturated solution of Na_2CO_3 until the aqueous washings were completely colorless. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by silica gel column chromatography.

4,6-Dichloro-2-(methylthio)pyrimidine (2): 2-(Methylthio)pyrimidin-4,6-diol (2.00 g, 12.6 mmol) and *N*,*N*-diethylaniline (3.65 mL) were added slowly to phosphorus oxychloride (23.3 mL), which was cooled on ice. The mixture was slowly warmed to reflux, heated at this temperature for 2.5 h, and then evaporated. The resulting mixture was added to crushed ice and then extracted with ethyl acetate (3×). The combined organic layers were washed with water (3×) and brine (1×) and then concentrated. The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 9:1) to afford **2** (2.30 g, 11.8 mmol, 93% yield) as colorless crystals; m.p. 42–43 °C (pentane). IR [attenuated total reflectance (ATR) diamond]: $\tilde{\nu}$ = 2956, 2928, 2855, 1539, 1532, 1509, 1469, 1358, 1272, 1215, 1099, 843, 825, 80 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.57 (s, 3 H, SCH_3), 6.89 (s, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_3), 115.6 (CH), 161.2 (2 Cq), 174.1 (Cq) ppm. HRMS (ESI): calcd. for $C_5H_5Cl_2N_2S$ [M + H]$^+$ 194.9545; found 194.9539.

6-Chloro-*N*-methyl-2-(methylthio)pyrimidin-4-amine (3): The reaction was carried out by following general procedure A and starting

from 4,6-dichloro-2-(methylthio)pyrimidine (**2**, 2.30 g, 11.8 mmol) and $MeNH_2$·HCl (955 mg, 14.1 mmol). The reaction was stirred and heated at the reflux temperature of 2-propanol. The crude product was purified by silica gel column chromatography (dichloromethane/ethyl acetate, 6:4) to afford **3** (1.97 g, 10.4 mmol, 88% yield) as an off-white solid; m.p. 129–131 °C (ethyl acetate). IR (ATR diamond): $\tilde{\nu}$ = 3261, 3138, 2928, 1564, 1493, 1423, 1360, 1273, 1224, 1117, 965, 806, 677 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.48 (s, 3 H, SCH_3), 2.93 (s, 3 H, NCH_3), 5.40 (s, 1 H, NH), 6.03 (s, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (CH_3), 28.4 (CH_3), 96.4 (CH), 159.4 (Cq), 163.6 (Cq), 172.1 (Cq) ppm. HRMS (ESI): calcd. for $C_6H_9ClN_3S$ $[M + H]^+$ 190.0200; found 190.0197.

6-Chloro-5-iodo-*N*-methyl-2-(methylthio)pyrimidin-4-amine (4): The reaction was carried out by following general procedure B and starting from pyrimidine **3** (1.90 g, 10.0 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 5:5) to afford **4** (2.89 g, 9.17 mmol, 91% yield) as a white solid; m.p. 142–144 °C (ethyl acetate). IR (ATR diamond): $\tilde{\nu}$ = 3397, 3378, 2919, 1564, 1526, 1483, 1410, 1375, 1321, 1254, 1221, 1135, 1096, 992, 931, 825, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.51 (s, 3 H, SCH_3), 3.05 (s, J = 4.9 Hz, 3 H, NCH_3), 5.55 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (CH_3), 29.4 (CH_3), 72.9 (Cq), 161.6 (Cq), 162.0 (Cq), 171.7 (Cq) ppm. HRMS (ESI): calcd. for $C_6H_8ClIN_3S$ $[M + H]^+$ 315.9167; found 315.9162.

6-Chloro-*N*-methyl-2-(methylthio)-5-(phenylethynyl)pyrimidin-4-amine (5): The reaction was carried out by following general procedure C amd starting from iodinated pyrimidine **4** (2.22 g, 7.04 mmol) and phenylacetylene (1.54 mL, 14.1 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 6:4) to afford **5** (1.97 mg, 6.80 mmol, 97% yield) as a yellow solid; m.p. 131–133 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 3342, 2932, 1553, 1488, 1366, 1220, 1082, 938, 853, 811, 751, 687 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.55 (s, 3 H, SCH_3), 3.11 (d, J = 5.0 Hz, 3 H, NCH_3), 5.67 (s, 1 H, NH), 7.34–7.41 (m, 3 H, H-Ar), 7.50–7.57 (m, 2 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4 (CH_3), 28.4 (CH_3), 80.2 (Cq), 96.1 (Cq), 101.4 (Cq), 122.4 (Cq), 128.6 (2 CH), 129.1 (CH), 131.6 (2 CH), 158.7 (Cq), 162.1 (Cq), 170.8 (Cq) ppm. HRMS (ESI): calcd. for $C_{14}H_{13}ClN_3S$ $[M + H]^+$ 290.0513; found 290.0510.

4-Chloro-7-methyl-2-(methylthio)-6-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (6): The reaction was carried out by following general procedure D and starting from alkyne **5** (1.87 g, 6.45 mmol). Microwave irradiation was applied for 30 min. The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 5:5) to afford **6** (1.81 mg, 6.25 mmol, 97% yield) as an off-white solid; m.p. 94–96 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 2930, 1587, 1531, 1486, 1375, 1236, 1179, 1127, 960, 866, 748, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.66 (s, 3 H, SCH_3), 3.79 (s, 3 H, NCH_3), 6.53 (s, 1 H, 5-H), 7.46–7.54 (m, 5 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (SCH_3), 30.4 (NCH_3), 98.9 (CH), 114.2 (Cq), 129.0 (2 CH), 129.1 (CH), 129.2 (2 CH), 131.1 (Cq), 141.8 (Cq), 150.6 (Cq), 151.4 (Cq), 152.7 (Cq) ppm. HRMS (ESI): calcd. for $C_{14}H_{13}ClN_3S$ $[M + H]^+$ 290.0513; found 290.0511.

7-Methyl-2-(methylthio)-6-phenyl-4-(*m*-tolyl)-7*H*-pyrrolo[2,3-*d*]-pyrimidine (7a): The reaction was carried out by following general procedure E and starting from the 4-chloropyrrolopyrimidine **6** (300 mg, 1.04 mmol) and 3-tolylboronic acid (147.8 mg, 1.09 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 7:3) to afford **7a** (308 mg, 0.890 mmol, 86% yield) as a yellow solid; m.p. 152–155 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 2924, 1557, 1485, 1358, 1333, 1261, 1147, 962, 744, 700 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.47 (s, 3 H, CH_3), 2.74 (s, 3 H, SCH_3), 3.84 (s, 3 H, NCH_3), 6.78 (s, 1 H, 5-H), 7.31 (d, J = 7.5 Hz, 1 H, H-Ar), 7.41 (t, J = 7.7 Hz, 1 H, H-Ar), 7.44–7.59 (m, 5 H, H-Ar), 7.96 (d, J = 7.8 Hz, 1 H, H-Ar), 7.99 (s, 1 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (CH_3), 21.7 (CH_3), 30.1 (CH_3), 100.2 (CH), 112.8 (Cq), 126.2 (CH), 128.6 (CH), 128.8 (CH), 128.9 (2 CH), 129.2 (2 CH), 129.6 (CH), 130.9 (CH), 131.8 (Cq), 138.2 (Cq), 138.5 (Cq), 141.5 (Cq), 154.7 (Cq), 157.1 (Cq), 164.0 (Cq) ppm. HRMS (ESI): calcd. for $C_{21}H_{20}N_3S$ $[M + H]^+$ 346.1372; found 346.1370.

7-Methyl-2-(methylthio)-6-phenyl-4-(*p*-tolyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (7b): The reaction was carried out by following general procedure E and starting from 4-chloropyrrolopyrimidine **6** (50.0 mg, 0.173 mmol) and 4-tolylboronic acid (24.6 mg, 0.181 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 5:5) to afford **7b** (55.0 mg, 0.159 mmol, 92% yield) as a pale yellow solid; m.p. 106–108 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 2924, 1553, 1487, 1362, 1334, 1262, 1179, 1147, 954, 835, 750, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 2.74 (s, 3 H, SCH_3), 3.83 (s, 3 H, NCH_3), 6.78 (s, 1 H, 5-H), 7.33 (d, J = 7.9 Hz, 2 H, H-Ar), 7.42–7.52 (m, 3 H, H-Ar), 7.53–7.58 (m, 2 H, H-Ar), 8.10 (d, J = 7.9 Hz, 2 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (CH_3), 21.6 (CH_3), 30.1 (CH_3), 100.1 (CH), 112.6 (Cq), 128.7 (CH), 128.8 (2 CH), 128.9 (2 CH), 129.1 (2 CH), 129.5 (2 CH), 131.7 (Cq), 135.5 (Cq), 140.3 (Cq), 141.4 (Cq), 154.7 (Cq), 156.7 (Cq), 163.9 (Cq) ppm. HRMS (ESI): calcd. for $C_{21}H_{20}N_3S$ $[M + H]^+$ 346.1372; found 346.1371.

7-Methyl-2-(methylthio)-6-phenyl-4-(*o*-tolyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (7c): The reaction was carried out by following general procedure E and starting from 4-chloropyrrolopyrimidine **6** (50.0 mg, 0.173 mmol) and 2-tolylboronic acid (24.6 mg, 0.181 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 2:8) to afford **7c** (58.6 mg, 0.170 mmol, 98% yield) as a dark yellow solid; m.p. 74–76 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 2922, 2359, 1557, 1489, 1357, 1332, 1254, 1184, 1142, 958, 750, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, CH_3), 2.70 (s, 3 H, SCH_3), 3.85 (s, 3 H, NCH_3), 6.39 (s, 1 H, 5-H), 7.28–7.37 (m, 3 H, H-Ar), 7.42–7.55 (m, 6 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (CH_3), 20.5 (CH_3), 30.1 (CH_3), 100.1 (CH), 114.6 (Cq), 125.7 (CH), 128.8 (CH), 128.9 (2 CH), 129.1 (2 CH), 129.2 (CH), 130.0 (CH), 131.2 (CH), 131.7 (Cq), 136.9 (Cq), 137.3 (Cq), 141.4 (Cq), 154.2 (Cq), 159.5 (Cq), 163.8 (Cq) ppm. HRMS (ESI): calcd. for $C_{21}H_{20}N_3S$ $[M + H]^+$ 346.1372; found 346.1372.

4-(4-Methoxyphenyl)-7-methyl-2-(methylthio)-6-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (7d): The reaction was carried out by following general procedure E and starting from 4-chloropyrrolopyrimidine **6** (50.0 mg, 0.173 mmol) and (4-methoxyphenyl)boronic acid (27.5 mg, 0.181 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 2:8) to afford **7d** (62.0 mg, 0.172 mmol, 99% yield) as a yellow solid; m.p. 55–57 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 2924, 1553, 1509, 1488, 1336, 1250, 1171, 1029, 956, 838, 748, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.73 (s, 3 H, SCH_3), 3.82 (s, 3 H, OCH_3), 3.88 (s, 3 H, NCH_3), 6.77 (s, 1 H, 5-H), 7.04 (d, J = 8.3 Hz, 2 H, H-Ar), 7.42–7.58 (m, 5 H, H-Ar), 8.18 (d, J = 8.3 Hz, 2 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (CH_3), 30.1

(CH_3), 55.5 (CH_3), 100.1 (CH), 112.2 (Cq), 114.1 (2 CH), 128.7 (CH), 128.8 (2 CH), 129.1 (2 CH), 130.5 (2 CH), 130.8 (Cq), 131.7 (Cq), 141.2 (Cq), 154.7 (Cq), 156.3 (Cq), 161.3 (Cq), 163.8 (Cq) ppm. HRMS (ESI): calcd. for $C_{21}H_{20}N_3OS$ $[M + H]^+$ 362.1322; found 362.1319.

7-Methyl-2-(methylthio)-6-phenyl-4-[4-(trifluoromethyl)phenyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (7e): The reaction was carried out by following general procedure E and starting from the 4-chloropyrrolopyrimidine **6** (50.0 mg, 0.173 mmol) and [4-(trifluoromethyl)-phenyl]boronic acid (34.4 mg, 0.181 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 6:4) to afford **7e** (64.7 mg, 0.162 mmol, 94% yield) as a light green solid; m.p. 131–133 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 2923, 1557, 1489, 1358, 1331, 1254, 1184, 1142, 958, 758, 750, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.73 (s, 3 H, SCH_3), 3.84 (s, 3 H, NCH_3), 6.74 (s, 1 H, 5-H), 7.46–7.58 (m, 5 H, H-Ar), 7.77 (d, J = 8.1 Hz, 2 H, H-Ar), 8.27 (d, J = 8.1 Hz, 2 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (CH_3), 30.1 (CH_3), 99.5 (CH), 113.0 (Cq), 124.2 (q, J = 272 Hz, Cq), 125.7 (q, J = 4 Hz, 2 CH), 128.9 (2 CH), 129.0 (CH), 129.1 (2 CH), 129.3 (2 CH), 131.4 (Cq), 131.5 (Cq), 131.7 (q, J = 32 Hz, Cq), 141.6 (Cq), 142.4 (Cq), 154.9 (Cq), 164.1 (Cq) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.66 (CF_3) ppm. HRMS (ESI): calcd. for $C_{21}H_{17}F_3N_3S$ $[M + H]^+$ 400.1090; found 400.1088.

7-Methyl-2-(methylthio)-6-phenyl-4-(pyridin-3-yl)-7*H*-pyrrol[2,3-*d*]pyrimidine (7f): The reaction was carried out by following general procedure E and starting from 4-chloropyrrolopyrimidine **6** (50.0 mg, 0.173 mmol) and (3-pyridinyl)boronic acid (22.3 mg, 0.181 mmol). The crude product was purified by silica gel column chromatography (dichloromethane/ethyl acetate, 6:4) to afford **7f** (54.5 mg, 0.169 mmol, 98% yield) as a yellow solid; m.p. 137–139 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 2997, 1542, 1487, 1359, 1323, 1268, 1193, 1154, 1024, 956, 744, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.73 (s, 3 H, SCH_3), 3.85 (s, 3 H, NCH_3), 6.77 (s, 1 H, 5-H), 7.44–7.57 (m, 6 H, H-Ar), 8.48 (d, J = 7.8 Hz, 1 H, H-Ar), 8.72 (s, 1 H, H-Ar), 9.41 (s, 1 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (CH_3), 30.2 (CH_3), 99.4 (CH), 112.9 (Cq), 123.4 (CH), 129.0 (2 CH), 129.1 (CH), 129.2 (2 CH), 131.4 (Cq), 134.1 (Cq), 136.2 (CH), 142.4 (Cq), 150.1 (CH), 150.9 (CH), 153.8 (Cq), 154.8 (Cq), 164.3 (Cq) ppm. HRMS (ESI): calcd. for $C_{19}H_{17}N_4S$ $[M + H]^+$ 333.1168; found 333.1167.

4-Chloro-2-(4-methoxyphenyl)-7-methyl-6-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (8a): The reaction was carried out by following general procedure F and starting from the 4-chloropyrrolopyrimidine **6** (50.0 mg, 0.173 mmol) and (4-methoxyphenyl)boronic acid (39.3 mg, 0.259 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 2:8) to afford **8** (48.9 mg, 0.140 mmol, 81% yield) as a beige solid; m.p. 125–126 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 2925, 1588, 1530, 1463, 1394, 1244, 1168, 1129, 1022, 954, 761, 743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 3 H, OCH_3), 3.89 (s, 3 H, NCH_3), 6.59 (s, 1 H, 5-H), 7.00 (d, J = 8.4 Hz, 2 H, H-Ar), 7.45–7.58 (m, 5 H, H-Ar), 8.50 (d, J = 8.4 Hz, 2 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.4 (NCH_3), 55.5 (OCH_3), 98.9 (CH), 113.9 (2 CH), 115.5 (Cq), 129.0 (2 CH), 129.1 (CH), 129.2 (2 CH), 129.8 (2 CH), 130.5 (Cq), 131.3 (Cq), 142.9 (Cq), 151.5 (Cq), 153.8 (Cq), 157.6 (Cq), 161.5 (Cq) ppm. HRMS (ESI): calcd. for $C_{20}H_{17}ClN_3O$ $[M + H]^+$ 350.1055; found 350.1052.

2-(4-Methoxyphenyl)-7-methyl-6-phenyl-4-(*m*-tolyl)-7*H*-pyrrolo-[2,3-*d*]pyrimidine (9a): The reaction was carried out by following general procedure F and starting from the 4-arylpyrrolopyrimidine **7a** (50 mg, 0.15 mmol) and (4-methoxyphenyl)boronic acid (33.0 mg, 0.22 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 5:5) to afford **9a** (54.7 mg, 0.14 mmol, 93% yield) as a pale yellow solid; m.p. 138–140 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 3053, 2915, 1550, 1512, 1487, 1374, 1299, 1243, 1166, 1031, 748, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.51 (s, 3 H, CH_3), 3.91 (s, 3 H, OCH_3), 3.95 (s, 3 H, NCH_3), 6.86 (s, 1 H, 5-H), 7.05 (d, J = 8.2 Hz, 2 H, H-Ar), 7.33 (d, J = 7.0 Hz, 1 H, H-Ar), 7.44–7.61 (m, 6 H, H-Ar), 8.16–8.04 (m, 2 H, H-Ar), 8.67 (d, J = 8.2 Hz, 2 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8 (CH_3), 30.1 (CH_3), 55.5 (CH_3), 100.2 (CH), 113.8 (2 CH), 114.0 (Cq), 126.3 (CH), 128.6 (CH), 128.8 (CH), 128.9 (2 CH), 129.2 (2 CH), 129.7 (2 CH), 129.8 (CH), 130.7 (CH), 132.0 (Cq), 132.2 (Cq), 138.5 (Cq), 139.1 (Cq), 142.6 (Cq), 154.8 (Cq), 156.7 (Cq), 157.6 (Cq), 161.1 (Cq) ppm. HRMS (ESI): calcd. for $C_{27}H_{24}N_3O$ $[M + H]^+$ 406.1914; found 406.1910.

7-Methyl-6-phenyl-4-(*m*-tolyl)-2-(*p*-tolyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (9b): The reaction was carried out by following general procedure F and starting from 4-arylpyrrolopyrimidine **7a** (50.0 mg, 0.145 mmol) and 4-tolylboronic acid (29.5 mg, 0.217 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 7:3) to afford **9b** (56.1 mg, 0.144 mmol, 99% yield) as a yellow solid; m.p. 153–154 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 3052, 2916, 2855, 1552, 1488, 1374, 1304, 1262, 1168, 834, 766, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.48 (s, 3 H, CH_3), 2.54 (s, 3 H, CH_3), 3.96 (s, 3 H, NCH_3), 6.88 (s, 1 H, 5-H), 7.35 (d, J = 7.6 Hz, 3 H, H-Ar), 7.45–7.55 (m, 4 H, H-Ar), 7.58–7.63 (m, 2 H, H-Ar), 8.09–8.18 (m, 2 H, H-Ar), 8.64 (d, J = 7.8 Hz, 2 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (CH_3), 21.8 (CH_3), 30.0 (CH_3), 100.2 (CH), 114.2 (Cq), 126.3 (CH), 128.1 (2 CH), 128.6 (CH), 128.8 (CH), 128.9 (2 CH), 129.1 (2 CH), 129.2 (2 CH), 129.6 (CH), 130.7 (CH), 131.9 (Cq), 136.7 (Cq), 138.4 (Cq), 139.0 (Cq), 139.5 (Cq), 142.8 (Cq), 154.7 (Cq), 156.6 (Cq), 157.7 (Cq) ppm. HRMS (ESI): calcd. for $C_{27}H_{24}N_3$ $[M + H]^+$ 390.1965; found 390.1963.

7-Methyl-6-phenyl-2,4-di-*m*-tolyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (9c): The reaction was carried out by following general procedure F and starting from 4-arylpyrrolopyrimidine **7a** (50.0 mg, 0.145 mmol) and 3-tolylboronic acid (29.5 mg, 0.217 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 7:3) to afford **9c** (50.3 mg, 0.129 mmol, 89% yield) as a pale yellow solid; m.p. 154–156 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 3047, 2917, 1552, 1488, 1394, 1373, 1261, 920, 861, 768, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.52 (s, 6 H, 2 CH_3), 3.98 (s, 3 H, NCH_3), 6.88 (s, 1 H, 5-H), 7.28 (d, J = 7.7 Hz, 1 H, H-Ar), 7.34 (d, J = 7.6 Hz, 1 H, H-Ar), 7.40–7.55 (m, 5 H, H-Ar), 7.58–7.63 (m, 2 H, H-Ar), 8.06–8.16 (m, 2 H, H-Ar), 8.49–8.56 (m, 2 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8 (2 CH_3), 30.1 (CH_3), 100.2 (CH), 114.4 (Cq), 125.4 (CH), 126.3 (CH), 128.4 (CH), 128.6 (CH), 128.7 (CH), 128.8 (CH), 128.9 (2 CH), 129.2 (2 CH), 129.7 (CH), 130.4 (CH), 130.8 (CH), 131.9 (Cq), 138.0 (Cq), 138.5 (Cq), 139.0 (Cq), 139.3 (Cq), 143.0 (Cq), 154.7 (Cq), 156.8 (Cq), 157.8 (Cq) ppm. HRMS (ESI): calcd. for $C_{27}H_{24}N_3$ $[M + H]^+$ 390.1964; found 390.1966.

7-Methyl-6-phenyl-4-(*m*-tolyl)-2-(*o*-tolyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (9d): The reaction was carried out by following general procedure F and starting from 4-arylpyrrolopyrimidine **7a** (50.0 mg, 0.145 mmol) and 2-tolylboronic acid (29.5 mg, 0.217 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 7:3) to afford **9d** (34.0 mg, 8.73×10^{-2} mmol, 60% yield) as a white solid; m.p. 114–116 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 3056, 2918, 1549, 1488, 1396,

1375, 1260, 745, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.49 (s, 3 H, CH_3), 2.74 (s, 3 H, CH_3), 3.94 (s, 3 H, NCH_3), 6.91 (s, 1 H, 5-H), 7.30–7.38 (m, 4 H, H-Ar), 7.42–7.56 (m, 4 H, H-Ar), 7.59–7.65 (m, 2 H, H-Ar), 8.02–8.12 (m, 3 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8 (2 CH_3), 30.2 (CH_3), 100.0 (CH), 113.7 (Cq), 126.0 (CH), 126.3 (CH), 128.7 (CH), 128.9 (2 CH), 129.3 (3 CH), 129.7 (2 CH), 130.7 (CH), 130.9 (CH), 131.3 (CH), 131.9 (Cq), 137.4 (Cq), 138.5 (Cq), 138.9 (Cq), 139.8 (Cq), 143.0 (Cq), 154.4 (Cq), 156.6 (Cq), 160.3 (Cq) ppm. HRMS (ESI): calcd. for $C_{27}H_{24}N_3$ [M + H]$^+$ 390.1965; found 390.1963.

7-Methyl-6-phenyl-4-(*m*-tolyl)-2-[4-(trifluoromethyl)phenyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (9e): The reaction was carried out by following general procedure F and starting from 4-arylpyrrolopyrimidine **7a** (50.0 mg, 0.145 mmol) and [4-(trifluoromethyl)phenyl]-boronic acid (41.2 mg, 0.217 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 7:3) to afford **9e** (61.1 mg, 0.138 mmol, 95% yield) as a white solid; m.p. 137–139 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 2917, 1551, 1318, 1165, 1119, 1063, 858, 769, 747, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.53 (s, 3 H, CH_3), 3.95 (s, 3 H, NCH_3), 6.89 (s, 1 H, 5-H), 7.32–7.39 (m, 1 H, H-Ar), 7.45–7.62 (m, 6 H, H-Ar), 7.77 (d, J = 8.0 Hz, 2 H, H-Ar), 8.06–8.15 (m, 2 H, H-Ar), 8.83 (d, J = 7.9 Hz, 2 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8 (CH_3), 30.1 (CH_3), 100.3 (CH), 114.9 (Cq), 124.6 (q, J = 272 Hz, Cq), 125.4 (q, J = 4 Hz, 2 CH), 126.3 (CH), 128.4 (2 CH), 128.7 (CH), 129.0 (3 CH), 129.2 (2 CH), 129.6 (CH), 130.9 (CH), 131.1 (q, J = 32 Hz, Cq), 131.7 (Cq), 138.6 (Cq), 138.7 (Cq), 142.7 (Cq), 143.6 (Cq), 154.5 (Cq), 156.0 (Cq), 156.7 (Cq) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.39 (CF_3) ppm. HRMS (ESI): calcd. for $C_{27}H_{21}F_3N_3$ [M + H]$^+$ 444.1682; found 444.1680.

7-Methyl-6-phenyl-2-(pyridin-3-yl)-4-(*m*-tolyl)-7*H*-pyrrolo[2,3-*d*]-pyrimidine (9f): The reaction was carried out by following general procedure F and starting from 4-arylpyrrolopyrimidine **7a** (50.0 mg, 0.145 mmol) and (3-pyridinyl)boronic acid (26.7 mg, 0.217 mmol). The crude product was purified by silica gel column chromatography (dichloromethane/ethyl acetate, 85:15) to afford **9f** (52.3 mg, 0.139 mmol, 96% yield) as a pale yellow solid; m.p. 136–138 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 3053, 2918, 1538, 1487, 1373, 1290, 909, 777, 749, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, CH_3), 3.93 (s, 3 H, NCH_3), 6.87 (s, 1 H, 5-H), 7.32–7.36 (m, 1 H, H-Ar), 7.42–7.55 (m, 5 H, H-Ar), 7.56–7.60 (m, 2 H, H-Ar), 8.04–8.14 (m, 2 H, H-Ar), 8.95 (d, J = 6.6 Hz, 1 H, H-Ar) ppm. Two proton signals from the pyridine unit were missing. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8 (CH_3), 30.1 (CH_3), 100.3 (CH), 114.8 (Cq), 126.2 (CH), 128.7 (CH), 128.9 (2 CH), 129.0 (CH), 129.2 (2 CH), 129.6 (CH), 130.0 (CH), 130.9 (CH), 131.6 (Cq), 132.1 (Cq), 132.2 (Cq), 135.1 (CH), 138.5 (Cq), 138.7 (Cq), 143.5 (Cq), 149.7 (CH), 154.4 (Cq), 155.6 (CH), 156.7 (Cq) ppm. HRMS (ESI): calcd. for $C_{25}H_{21}N_4$ [M + H]$^+$ 377.1761; found 377.1760.

2-(4-Methoxyphenyl)-7-methyl-6-phenyl-4-(*p*-tolyl)-7*H*-pyrrolo-[2,3-*d*]pyrimidine (9g): The reaction was carried out by following general procedure F and starting from 4-arylpyrrolopyrimidine **7b** (50 mg, 0.145 mmol) and (4-methoxyphenyl)boronic acid (33.0 mg, 0.217 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 5:5) to afford **9g** (56.9 mg, 0.140 mmol, 97% yield) as a yellow solid; m.p. 169–171 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 3048, 2917, 1552, 1509, 1464, 1375, 1299, 1244, 1161, 1035, 840, 749, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.48 (s, 3 H, CH_3), 3.91 (s, 3 H, OCH_3), 3.94 (s, 3 H, NCH_3), 6.86 (s, 1 H, 5-H), 7.05 (d, J = 8.5 Hz, 2 H, H-Ar), 7.38 (d, J = 7.7 Hz, 2 H, H-Ar), 7.42–7.54 (m, 3 H, H-Ar), 7.59 (d, J = 7.2 Hz, 2 H, H-Ar), 8.24 (d, J = 7.8 Hz, 2 H, H-Ar), 8.68 (d, J = 8.5 Hz, 2 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (CH_3), 30.1 (CH_3), 55.5 (CH_3), 100.2 (CH), 113.7 (Cq), 113.8 (2 CH), 128.7 (CH), 128.8 (2 CH), 129.0 (2 CH), 129.1 (2 CH), 129.5 (2 CH), 129.6 (2 CH), 132.0 (Cq), 132.2 (Cq), 136.3 (Cq), 140.0 (Cq), 142.5 (Cq), 154.8 (Cq), 156.4 (Cq), 157.5 (Cq), 161.1 (Cq) ppm. HRMS (ESI): calcd. for $C_{27}H_{24}N_3O$ [M + H]$^+$ 406.1914; found 406.1910.

2-(4-Methoxyphenyl)-7-methyl-6-phenyl-4-(*o*-tolyl)-7*H*-pyrrolo-[2,3-*d*]pyrimidine (9h): The reaction was carried out by following general procedure F and starting from 4-arylpyrrolopyrimidine **7c** (50 mg, 0.145 mmol) and (4-methoxyphenyl)boronic acid (33.0 mg, 0.217 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 2:8) to afford **9h** (55.8 mg, 0.138 mmol, 95% yield) as a white solid; m.p. 128–130 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 3057, 2929, 1560, 1376, 1300, 1246, 1160, 1031, 842, 759, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.55 (s, 3 H, CH_3), 3.90 (s, 3 H, OCH_3), 3.97 (s, 3 H, NCH_3), 6.51 (s, 1 H, 5-H), 7.03 (d, J = 8.6 Hz, 2 H, H-Ar), 7.32–7.37 (m, 1 H, H-Ar), 7.37–7.42 (m, 2 H, H-Ar), 7.43–7.52 (m, 3 H, H-Ar), 7.56 (d, J = 7.3 Hz, 2 H, H-Ar), 7.67 (d, J = 7.3 Hz, 1 H, H-Ar), 8.62 (d, J = 8.6 Hz, 2 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 (CH_3), 30.0 (CH_3), 55.5 (CH_3), 100.1 (CH), 113.8 (2 CH), 115.7 (Cq), 125.7 (CH), 128.7 (CH), 128.8 (2 CH), 129.0 (CH), 129.1 (2 CH), 129.7 (2 CH), 130.1 (CH), 131.3 (CH), 131.9 (Cq), 132.2 (Cq), 137.1 (Cq), 138.0 (Cq), 142.4 (Cq), 154.3 (Cq), 157.3 (Cq), 159.1 (Cq), 161.1 (Cq) ppm. HRMS (ESI): calcd. for $C_{27}H_{24}N_3O$ [M + H]$^+$ 406.1914; found 406.1913.

2,4-Bis(4-methoxyphenyl)-7-methyl-6-phenyl-7*H*-pyrrolo[2,3-*d*]-pyrimidine (9i): The reaction was carried out by following general procedure F and starting from the 4-arylpyrrolopyrimidine **7d** (50.0 mg, 0.138 mmol) and (4-methoxyphenyl)boronic acid (31.5 mg, 0.207 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 2:8) to afford **9i** (51.2 mg, 0.121 mmol, 88% yield) as a yellow solid; m.p. 155–156 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 2918, 1605, 1510, 1459, 1372, 1248, 1158, 1026, 837, 750, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 6 H, OCH_3), 3.94 (s, 3 H, NCH_3), 6.85 (s, 1 H, 5-H), 7.04 (d, J = 7.9 Hz, 2 H, H-Ar), 7.09 (d, J = 7.9 Hz, 2 H, H-Ar), 7.44–7.55 (m, 3 H, H-Ar), 7.56–7.63 (m, 2 H, H-Ar), 8.31 (d, J = 7.9 Hz, 2 H, H-Ar), 8.66 (d, J = 7.9 Hz, 2 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.1 (CH_3), 55.5 (CH_3), 55.6 (CH_3), 100.2 (CH), 113.3 (Cq), 113.8 (2 CH), 114.2 (2 CH), 128.7 (CH), 128.9 (2 CH), 129.2 (2 CH), 129.6 (2 CH), 130.5 (2 CH), 131.8 (Cq), 132.0 (Cq), 132.2 (Cq), 142.4 (Cq), 154.8 (Cq), 156.0 (Cq), 157.4 (Cq), 161.1 (Cq), 161.2 (Cq) ppm. HRMS (ESI): calcd. for $C_{27}H_{24}N_3O_2$ [M + H]$^+$ 422.1863; found 422.1864.

2-(4-Methoxyphenyl)-7-methyl-6-phenyl-4-[4-(trifluoromethyl)phenyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (9j): The reaction was carried out by following general procedure F and starting from 4-arylpyrrolopyrimidine **7e** (50 mg, 0.125 mmol) and (4-methoxyphenyl)boronic acid (28.5 mg, 0.188 mmol). The crude product was purified by silica gel column chromatography (petroleum ether/dichloromethane, 7:3) to afford **9j** (57.1 mg, 0.124 mmol, 99% yield) as a light green solid; m.p. 150–152 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 2936, 1565, 1378, 1320, 1247, 1166, 1107, 1030, 843, 755, 695 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 3 H, OCH_3), 3.95 (m, 3 H, NCH_3), 6.81 (s, 1 H, 5-H), 7.05 (d, J = 8.5 Hz, 2 H, H-Ar), 7.45–7.56 (m, 3 H, H-Ar), 7.56–7.63 (m, 2 H, H-Ar), 7.82 (d, J = 8.0 Hz, 2 H, H-Ar), 8.40 (d, J = 8.0 Hz, 2 H, H-Ar), 8.65 (d, J = 8.5 Hz, 2 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.1 (CH_3),

55.5 (CH_3), 99.6 (CH), 113.9 (2 CH), 114.1 (Cq), 124.6 (q, J = 271 Hz, Cq), 125.7 (q, J = 4 Hz, 2 CH), 129.0 (2 CH), 129.1 (CH), 129.2 (2 CH), 129.3 (2 CH), 129.7 (2 CH), 131.5 (q, J = 32 Hz, Cq), 131.7 (Cq), 131.8 (Cq), 142.5 (Cq), 143.5 (Cq), 154.6 (Cq), 155.0 (Cq), 157.6 (Cq), 161.3 (Cq) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.61 (CF_3) ppm. HRMS (ESI): calcd. for $C_{27}H_{21}F_3N_3O$ $[M + H]^+$ 460.1631; found 460.1629.

2-(4-Methoxyphenyl)-7-methyl-6-phenyl-4-(pyridin-3-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidine (9k): The reaction was carried out by following general procedure F and starting from the 4-arylpyrrolopyrimidine **7f** (50 mg, 0.155 mmol) and (4-methoxyphenyl)boronic acid (28.5 mg, 0.233 mmol). The crude product was purified by silica gel column chromatography (dichloromethane/ethyl acetate, 6:4) to afford **9k** 52.6 mg, 0.134 mmol, 86% yield) as a yellow solid; m.p. 166–167 °C (pentane). IR (ATR diamond): $\tilde{\nu}$ = 3048, 2926, 1583, 1557, 1488, 1374, 1302, 1239, 1163, 1024, 853, 752, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 3 H, OCH_3), 3.93 (s, 3 H, NCH_3), 6.83 (s, 1 H, 5-H), 7.03 (d, J = 8.3 Hz, 2 H, H-Ar), 7.44–7.55 (m, 4 H, H-Ar), 7.58 (d, J = 7.4 Hz, 2 H, H-Ar), 8.62 (m, 3 H, H-Ar), 8.84 (s, 1 H, H-Ar), 9.58 (s, 1 H, H-Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.1 (CH_3), 55.5 (CH_3), 99.4 (CH), 113.9 (2 CH), 114.0 (Cq), 124.1 (CH), 128.8 (Cq), 128.9 (2 CH), 129.0 (CH), 129.1 (2 CH), 129.6 (2 CH), 131.6 (Cq), 131.7 (Cq), 136.1 (CH), 143.4 (Cq), 150.0 (CH), 150.5 (CH), 153.4 (Cq), 154.8 (Cq), 157.6 (Cq), 161.2 (Cq) ppm. HRMS (ESI): calcd. for $C_{25}H_{21}N_4O$ $[M + H]^+$ 393.1710; found 393.1709.

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