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Palladium Cross-Coupling

Regioselective Synthesis of 2,4-Substituted Pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidines through Sequential Pd-Catalyzed Arylation and S_NAr Reactions

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Abstract: The synthesis and regioselective functionalization of rare 2,4-disubstituted-pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidine derivatives is reported. C-4 aminations were performed by chlorine nucleophilic substitution S_NAr reactions, and their efficiencies were compared with those for direct one-pot amide C–O activation with bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP) as a reagent. The latter method was used to perform palladium-catalyzed C-4 (het)arylation. Finally, two C-4 amino and aryl derivatives were prepared on a large scale and engaged in desulfurative Liebeskind–Srogl-type reactions under microwave irradiation to afford the envisioned compound library. Each step was optimized, and the results are discussed.

Introduction

The building of multi-heterocyclic derivatives and the discovery of new methods for their functionalization are solutions to obtain new compounds and pursue the exploration of chemical space. Among the nitrogen-containing heterocycles, bicyclic derivatives have been studied intensively, and many of them have been used to design bioactive molecules.

Tricyclic fused heteroaromatic derivatives have been researched less frequently, but many of them have been generated in basic chemistry studies. It now appears necessary to provide synthetic methods for their functionalization through reproducible and versatile strategies. To answer this crucial lack of knowledge, we sought to design and functionalize tricyclic pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidines with pharmacologically compatible pyrazolopyridine and pyrazolopyrimidine cores in the same fused framework. The supplementary ring fusion will provide a high bioactive potential.

Although the biological properties of pyridopyrimidines are now well described, the rare pyrazolopyridine derivatives have also shown potent diuretic (**I,** FK-453, Figure 1)[1] and antiherpetic properties (**II**, GW3733)[2] as well as p38 kinase[3] and melatonin receptor inhibitions (**III**).[4] Additionally, pyrazolo[3,4-*d*]pyrimidines have emerged as a significant motif in drug-discovery programs and have been used as antifolates (**IV**),[5] phospholipase inhibitors,[6] cyclooxygenase (COX) inhibitors (**V**),[7] and kinase inhibitors (**VI** and **VII**).[8]

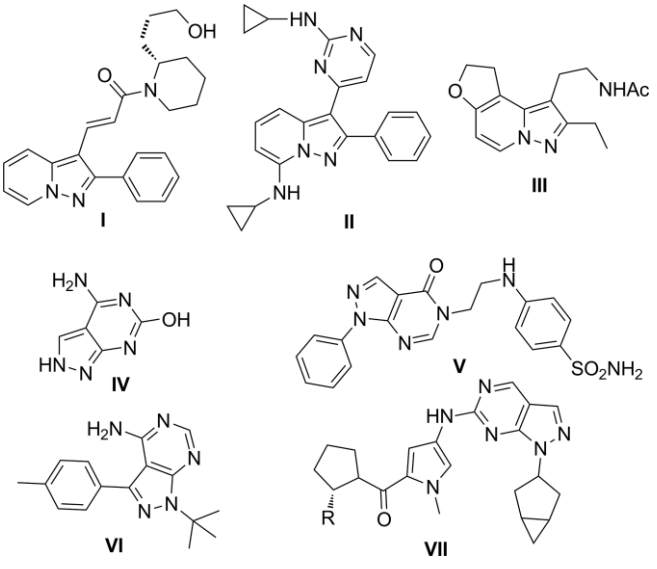

Figure 1. Some examples of bioactive pyrazolopyridines and pyrazolopyrimidines.

In our previous research, we focused on the double chlorine discrimination of **1**[9] as this strategy was applied efficiently to the pyridopyrimidine series (Scheme 1).[10] In this paper, we wish to present another pathway based on recent advances, that is, (1) S_NAr reactions, (2) direct functionalization of phenolic compounds by an in situ C–O activation strategy, and (3) our knowledge of desulfurization through Liebeskind–Srogl cross-coupling reactions. We used the 2-(methylthio)pyrimidinone **2**

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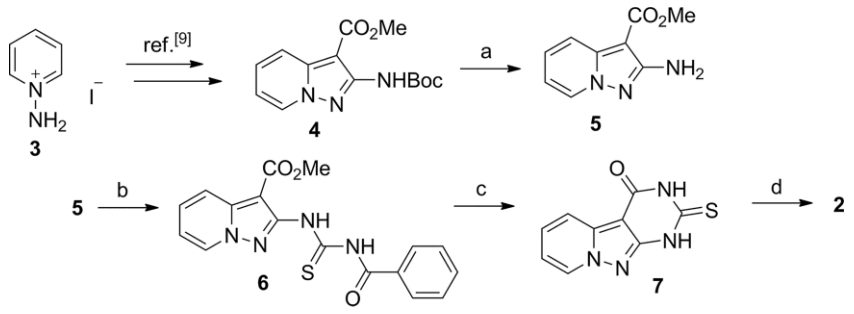


Scheme 1. Synthesis pathway to the thioether **2**. Reagents and conditions: (a) TFA/CH_2Cl_2 (1:10), 4 h, r.t.., quantitative; (b) benzoyl isothiocyanate (1.2 equiv.), $CHCl_3$, 12 h, r.t.., 75 %; (c) EtONa (1.1 equiv.), EtOH, 8 h, reflux, 97 %; (d) MeI (1.0 equiv.), NaOH (1.0 equiv.), EtOH, 2 h, r.t., 79 %.

(Figure 2), which is a good partner to achieve regiocontrolled C-2 and C-4 diversification.

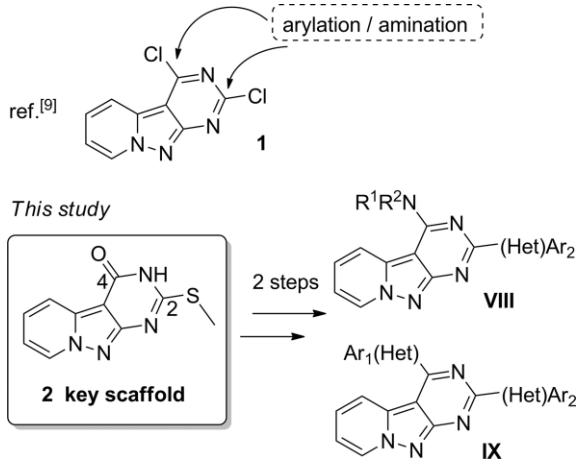


Figure 2. Regioselective transformations of **2**.

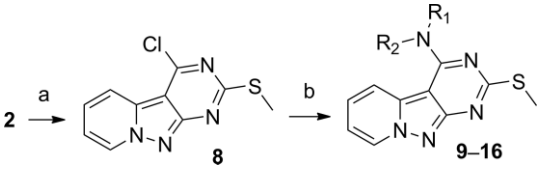
Various amines and hetaryl groups were next used to increase the molecular diversity and afford C-2 and C-4 amino/hetaryl-disubstituted pyridopyrazolopyrimidines of types **VIII** and **IX**.

Results and Discussion

To prepare the key intermediate **2**, the most suitable starting material was considered to be the previously reported *N*-Boc-pyrazolopyridineamine **4**[9] (Boc = *tert*-butyloxycarbonyl), which was obtained from the commercially available aminopyridinium iodide salt **3** (Scheme 1). The deprotection of the Boc group was achieved with trifluoroacetic acid (TFA) to afford amine **5** in quantitative yield. The synthesis of pyrimidinethione **7** was achieved through the preliminary preparation of several thioureas bearing removable groups.

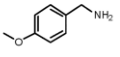
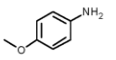
We chose 4-methoxybenzyl (PMB),[11] trimethylsilyl (TMS)[12] and benzoyl ureas to react with **5**; surprisingly, the only efficient reaction was achieved with **5** and benzoyl isothiocyanate,[13] which led to **6** in a 75 % yield after 12 h at room temperature. In EtOH under reflux, annulation occurred with a stoichiometric amount of sodium ethanoate to afford **7** in a near quantitative yield. As expected, the benzoyl group did not survive under these basic conditions. Finally, the typical treatment of **7** with iodomethane (1.0 equiv.) in basic media at room temperature afforded the target methyl thioether **2** in an excellent yield after only 2 h (Scheme 1). This methodology proved to be highly efficient and amenable to multigram-scale reactions.

To achieve the selective functionalization of the tricyclic heterocycle, we first envisioned regioselective amination through a C-4 S_NAr reaction (general procedure A, Scheme 2, Table 1). To achieve this objective, we first prepared the chloro derivative **8** with an excess of $POCl_3$ at 80 °C in 73 % yield. The



Scheme 2. Amination at C-4 through S_NAr reactions. Reagents and conditions: (a) $POCl_3$, 80 °C, 3 h, 73 %; (b) HNR^1R^2 (1.0 equiv.), Et_3N (1.05 equiv.), THF; see Table 1 for other parameters (general procedure A).

Table 1. Scope of amination from **8** under S_NAr conditions (general procedure A) or from **2** by PyBroP in situ activation (general procedure B).

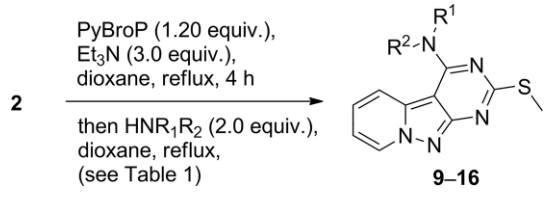
Entry	NHR_1R_2	Product	General procedure A time, temp., yield[a]	General procedure B time, yield[a]
1		**9**	3 h, r.t. 65 %	4 h 86 %
2		**10**	3 h, r.t. 90 %	4 h 92 %
3		**11**	3 h, r.t. 95 %	4 h 89 %
4		**12**	24 h, r.t. 90 %	4 h 95 %
5		**13**	24 h, 80 °C 61 %[b]	4 h 81 %
6		**14**	72 h, 80 °C 85 %	12 h 87 %
7		**15**	72 h, 80 °C 65 %[b]	12 h 82 %
8		**16**	72 h, 80 °C 74 %	12 h 88 %

[a] Isolated yield after column chromatography. [b] The starting material was recovered (11 %).

reaction of **8** with primary and secondary aliphatic amines as well as benzylamines or anilines led to derivatives **9**–**16** with yields of 61 to 95 %.

A relative variability of the S_NAr method was observed. Although reproducible results were obtained for each assay, the yields depended fully on the nature of the amine used. If the reactivity of the amine was lower (Table 1, Entries 5–8), a large increase in the time as well as the temperature was required. Consequently, degradation was favored, and the yield of the isolated product decreased significantly.

The modest results obtained for general procedure A prompted us to find an alternative. Therefore, we performed the amination of **2** in one pot through in situ activation of the C–O bond[14] by taking advantage of the tautomerizability of amide **2** (general procedure B, Scheme 3) in basic media.

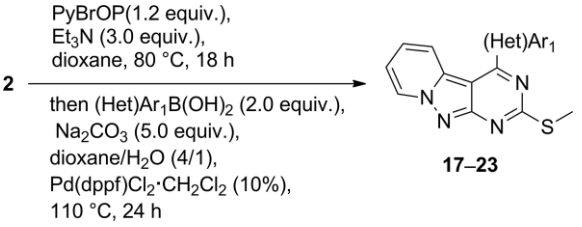


Scheme 3. One-pot amination at C-4 through a C–O PyBroP activation.

The first assay with bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP)[15] as the coupling activator showed excellent reactivity. The activated species formed in situ were detected by TLC after 4 h. To achieve the S_NAr reaction, we next added the desired amine and observed the formation of C-4 amino derivatives **9**–**16** after only a few additional hours, specifically, 4 h for alkyl- and benzylamines and 12 h for anilines. If all of the reagents were introduced with **2** at the beginning of the reaction, the S_NAr reactions were less efficient.[16] For example, the reaction of **2** in the direct presence of morpholine, Et_3N, and PyBroP led to **11** in only 60 % yield whatever the reaction time (starting material recovered).

These interesting amido activations of tricyclic heteroaromatic complex systems prompted us to explore the C-2 (het)arylation of **2** by an original PyBroP-mediated C–O activation. The one-pot sequence involved the use of PyBroP and Et_3N for 18 h to fully consume the starting material **2** (TLC monitoring), and then a solution of *p*-tolylboronic acid (2.0 equiv.), K_2CO_3 (3.0 equiv.), and $PdCl_2(PPh_3)_2$ was added in a dioxane/water mixture to launch the arylation. After an additional 24 h, the desired product **17** was formed in an encouraging 18 % yield, whereas the starting material was recovered in 50 % yield. The change of the base to Na_2CO_3 increased the yield of **17** to 51 %, and the use of 10 mol-% of catalyst led to a further increase in efficiency (88 % yield of **17**). Finally, the best system for the quantitative conversion required $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ [10 %, dppf = 1,1′-bis(diphenylphosphino)ferrocene] as the catalyst. The C-4 tolyl derivative **17** was now purified in an excellent 90 % yield (Scheme 4).

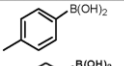
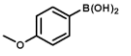
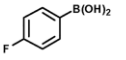
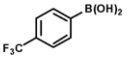
The generalization of this one-pot cross-coupling strategy (Table 2) was achieved with diverse (het)aryl boronic acids and led to **17**–**23**. The introduction of *para*- or *meta*-methoxyphenyl substituents was successfully achieved without any difficulties.



Scheme 4. One-pot (het)arylation at C-4 from **2** by a C–O amide activation.

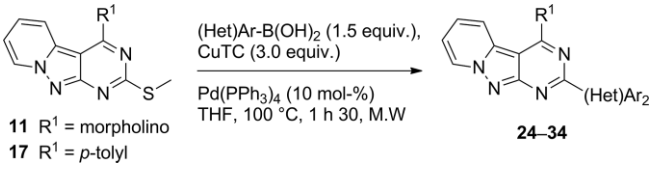
The decreased yield for an *ortho*-methoxyphenyl-substituted boronic acid (Table 2, Entry 4) indicated a sensitivity to steric effects for this assay. Reactivity was fully restored for aromatics with *para* electron-withdrawing groups such as F or CF_3 (Table 2, Entries 5 and 6), but the use of 3-pyridine strongly diminished the yield of the C–O amide hetarylation (Table 2, Entry 7).

Table 2. Scope of (het)arylation from **2** under C–O amid activation.

Entry	(Het)Ar$_1$B(OH)$_2$	Product	Yield[a]
1		**17**	90 %
2		**18**	89 %
3		**19**	83 %
4		**20**	76 %
5		**21**	95 %
6		**22**	84 %
7		**23**	35 %

[a] Isolated yield after column chromatography.

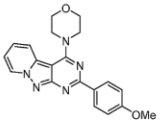
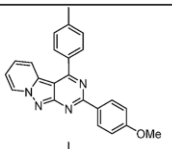
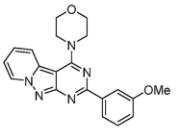
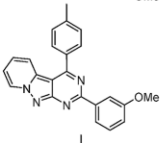
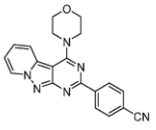
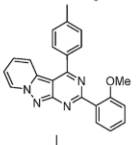
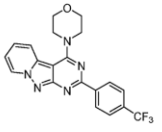
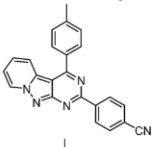
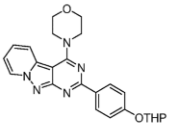
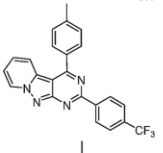
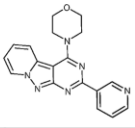
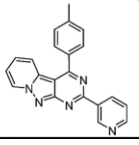
The previously obtained C-4 aminated and (het)arylated compounds **9**–**23** could then be used to achieve the regiocontrolled diversification of the pyridopyrazolopyrimidine core and furnish the target derivatives of types **VIII** and **IX**. For this, we used classical Liebeskind–Srogl cross-coupling conditions[17] with an arylboronic acid in the presence of $Pd(PPh_3)_4$ (10 mol-%) and copper(I) thiophene-2-carboxylate (CuTC) in tetrahydrofuran (THF) at 100 °C under microwave irradiation. The scope of the method was studied only with **11** and **17**, which were prepared on a gram scale (Scheme 5).



Scheme 5. Desulfurative cross-coupling reactions at C-2 to form derivatives of type **VIII** and **IX**.

From the C-4-morpholino derivative **11**, the desulfurative cross-coupling reaction was performed with phenyl boron de-

Table 3. Scope of the desulfurative cross-coupling reaction at C-2.

Entry	Starting material	Compound **VIII**	Yield[a]	Entry	Starting material	Compound **IX**	Yield[a]
1	**11**		**24**, 69 %	7	**17**		**29**, 67 %
2	**11**		**25**, 42 %	8	**17**		**30**, 42 %
3	**11**		**26**, 55 %	9	**17**		**31**, 31 %
4	**11**		**27**, 59 %	10	**17**		**32**, 65 %
5	**11**		**28**, 41 %	11	**17**		**33**, 64%
6	**11**		starting material recovered	12	**17**		**34**, 44%

[a] Isolated yield after column chromatography.

rivatives bearing *p*-OMe, *m*-OMe, *p*-OTHP (THP = tetrahydropyranyl), *p*-CN, and *p*-CF_3 groups. The assays yielded the desired derivatives **24**–**28** with yields ranging from 41 to 69 % (Table 3). With 3-pyridinyl boronic acid, the reaction failed (Table 3, Entry 6), and starting material **11** was fully recovered. From the C-4 hetarylated derivative **17**, phenyl and pyridinyl boronic acids afforded the attempted derivatives of type **IX**. The reactivity for methoxyphenyl boronic acids followed the order *para* > *meta* > *ortho* (Table 3, Entries 7–9). Whatever the electronic character of the *para* aryl group, the yields remained approximately 65 %. Fortunately, the use of 3-pyridinyl boronic acid (Table 3, Entry 12) was successful, and the final compound **34** was isolated in a satisfying yield.

Conclusions

We have developed a straightforward strategy to C-4 amino/(het)Ar and C-2 (het)Ar pyridopyrazolopyrimidines. Although a 4-Cl derivative reacted smoothly, the direct C–O activation of an amide function with PyBroP produced better results. This C-4 amination/heteroarylation was achieved in high yields. One-pot strategies reduced the number of steps, decreased the reaction time and temperature, and contributed to eco-efficiency of these processes. Afterwards, the monosubstituted 2-SMe intermediates reacted under Liebeskind–Srogl conditions. This multiple and regioselective functionalization of pyridopyrazolopyrimidines offers nice prospects in the organic chemistry and medicinal chemistry fields.

Experimental Section

General: Reactions were monitored by thin-layer chromatography (TLC) with using silica gel (60 F254) plates, and the compounds were visualized by UV irradiation. Flash column chromatography was performed with silica gel 60 (230–400.13 mesh, 0.040 0.063 mm). The melting points were measured with samples in open capillary tubes. The infrared spectra of compounds were recorded with a Thermo Scientific Nicolet iS10 instrument. The ^1H and ^{13}C NMR spectra were recorded with Bruker DPX 250 (^{13}C, 62 MHz), Bruker Avance II 250 (^{13}C, 63 MHz), Bruker Avance 400 (^{13}C, 101 MHz), or Bruker Avance III HD Nanobay 400 (^{13}C, 101 MHz) spectrometers. The chemical shifts are given in ppm from tetramethylsilane as an internal standard. The coupling constants (*J*) are reported in Hz. High-resolution mass spectra (HRMS) were recorded with a Maxis Bruker 4G instrument.

Methyl 2-Aminopyrazolo[1,5-*a*]pyridine-3-carboxylate (5): A solution of 2-*N*-Boc-amino ester **4**[9] (1.071 mmol, 0.5 g) in a mixture of CH_2Cl_2/TFA (10:1, 3 mL) was stirred at room temperature for 4 h. After the complete disappearance of the starting material, the solvent was removed in vacuo, and then a saturated (satd.) aqueous (aq.) K_2CO_3 solution (10 mL) was added slowly. The residue was extracted with EtOAc (3 × 20 mL). The volatiles were evaporated under reduced pressure, and the crude material was purified by

column chromatography (petroleum ether/EtOAc, 4:6) to give **5** as a beige solid in quantitative yield, m.p. 128–129 °C. R_f (petroleum ether/EtOAc, 4:6) = 0.5. IR [attenuated total reflection (ATR) diamond]: $\tilde{\nu}$ = 3416, 3315, 1530, 1440, 1204, 1122, 784, 715 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (dt, J = 6.8, J = 1.2 Hz, 1 H), 7.81 (d, J = 8.8 Hz, 1 H), 7.30 (ddd, J = 8.8, J = 6.8 Hz, J = 1.2 Hz, 1 H), 6.78 (td, J = 6.8, J = 1.2 Hz, 1 H), 5.25 (s, 2 H, NH_2), 3.91 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.2 (CO), 159.9 (Cq),141.9 (Cq), 128.4 (CH_{Ar}), 127.5 (CH_{Ar}), 117.3 (CH_{Ar}), 112.4 (CH_{Ar}), 87.65 (Cq), 50.9 (CH_3) ppm. HRMS (ESI): calcd. for $C_9H_{10}N_3O_2$ $[M + H]^+$ 192.0770; found 192.0768.

Methyl 2-(3-Benzoylthioureido)pyrazolo[1,5-*a*]pyridine-3-carboxylate (6): A suspension of benzoyl isothiocyanate (6.27 mmol, 0.84 mL) and amino ester **5** (5.23 mmol, 1.0 g) in $CHCl_3$ (10 mL) was stirred at room temperature overnight. The volatiles were evaporated under reduced pressure, and the residue was purified by silica gel flash chromatography (petroleum ether/EtOAc, 5:5) to afford the desired thiourea **6** as a yellow solid (1.39 g, 75 %), m.p. 180–181 °C. R_f (petroleum ether/EtOAc, 4:6) = 0.8. IR (ATR diamond): $\tilde{\nu}$ = 3056, 1694, 1524, 1448, 1321, 1208, 1029, 1106, 853, 781 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 13.84 (s, 1 H, NH), 9.30 (s, 1 H, NH), 8.60 (s, 1 H), 8.06 (d, J = 8.8 Hz, 1 H), 7.99 (d, J = 8.8 Hz, 2 H), 7.69–7.61 (m, 1 H), 7.59–7.50 (m, 2 H), 7.46 (t, J = 8.0 Hz, 1 H), 6.99 (t, J = 6.8 Hz, 1 H),4.04 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.3 (CO), 165.6 (CS), 163.9 (CO), 151.3 (Cq), 140.7 (Cq), 133.7 (Cq), 131.7 (CH_{Ar}), 129.8 (CH_{Ar}), 129.2 (2 × CH_{Ar}), 128.5 (CH_{Ar}), 127.8 (2 × CH_{Ar}), 118.5 (CH_{Ar}), 114.0 (CH_{Ar}), 93.0 (Cq), 51.7 (CH_3) ppm. HRMS (ESI): calcd. for $C_{17}H_{15}N_4O_3S$ $[M + H]^+$ 355.0859; found 355.0860.

2-Thioxo-2,3-dihydropyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidin-4(1*H*)-one (7): To a suspension of **6** (1.41 mmol, 0.5 g) in EtOH (10 mL) was added a solution of NaOEt in EtOH (1.55 mmol, 2.68 M). The reacting mixture was heated under reflux for 8 h then cooled to room temperature and neutralized to pH 7 with pure AcOH. The solvents were evaporated under reduced pressure, and the resulting precipitate was collected by filtration, washed with water (2 × 10 mL), and dried under vacuum to afford **7** as a white solid (298 g, 97 %), m.p. 387–359 °C. R_f (petroleum ether/EtOAc, 4:6) = 0.01. IR (ATR diamond): $\tilde{\nu}$ = 2994, 1639, 1583, 1429, 1295, 1130, 1062, 826, 775, 641 cm^{-1}. ^1H NMR {400 MHz, [D_6]dimethyl sulfoxide ([D_6]DMSO)}: δ = 13.29 (s, 1 H, NH), 12.03 (s, 1 H, NH), 8.90 (d, J = 6.8 Hz, 1 H), 7.94 (d, J = 8.8 Hz, 1 H), 7.69 (t, J = 8.8 Hz, 1 H), 7.28 (td, J = 6.8, J = 1.2 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 176.8 (CO), 157.2 (CO), 154.1 (Cq), 138.3 (Cq), 130.8 (CH_{Ar}), 130.1 (CH_{Ar}), 117.2 (CH_{Ar}), 116.3 (CH_{Ar}), 92.6 (Cq) ppm. HRMS (ESI) calcd. for $C_9H_7N_4OS$ $[M + H]^+$ 219.0335; found 219.0334.

2-(Methylthio)pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidin-4(3*H*)-one (2): A suspension of thioamide **7** (4.58 mmol, 1.0 g) in EtOH (80 mL) was stirred at room temperature. A solution of NaOH (4.58 mmol, 0.183 g) in water (2 mL) was added dropwise, and the resulting mixture was stirred for 15 min. Methyl iodide (4.58 mmol, 0.282 mL) was then added; after 2 h, the solvent was removed under vacuum. The residue was poured into water (30 mL), and the solution was neutralized to pH 7 with HCl (1 N). The precipitate was collected by filtration, washed with water (10 mL), and dried under reduced pressure to afford **2** as a white solid (0.840 g, 79 %), m.p. 299–300 °C. R_f (petroleum ether/EtOAc, 4:6) = 0.32. IR (ATR diamond): $\tilde{\nu}$ = 3056, 2894, 1675, 1640, 1581, 1431, 1321, 1225, 1158, 1064, 825, 775, 654 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 12.32 (s, 1 H, NH), 8.87 (d, J = 6.8 Hz, 1 H), 8.00 (d, J = 8.8 Hz, 1 H), 7.62 (t, J = 8.8 Hz, 1 H), 7.26 (t, J = 6.8 Hz, 1 H), 2.54 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 163.2 (CO), 162.0 (Cq), 160.6 (Cq), 137.6 (Cq), 130.0 (CH_{Ar}), 128.15 (CH_{Ar}), 117.9 (CH_{Ar}), 116.0 (CH_{Ar}), 94.8 (Cq), 13.5 (CH_3) ppm. HRMS (ESI): calcd. for $C_{10}H_9N_4OS$ $[M + H]^+$ 233.0492; found 233.0490.

4-Chloro-2-(methylthio)pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidine (8): $POCl_3$ (20 mL) was dissolved in a sealed tube of **2** (4.3 mmol, 1.0 g). The reaction mixture was stirred at 80 °C for 3 h, cooled to room temperature, and concentrated under reduced pressure. The residue was poured into a satd. aq. $NaHCO_3$ solution (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude solid was then purified by silica gel flash chromatography (petroleum ether/EtOAc, 6:4) to afford **8** (780 mg, 73 %) as a yellow solid, m.p. 193–194 °C. R_f (petroleum ether/EtOAc, 4:6) = 0.62. IR (ATR diamond): $\tilde{\nu}$ = 2925, 1639, 1584, 1502, 1428, 1299, 1176, 1038, 850, 785, 688 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.84 (dt, J = 6.8, J = 1.2 Hz, 1 H), 8.46–8.23 (m, 1 H), 7.73 (ddd, J = 8.8, J = 6.8 Hz, J = 1.2 Hz, 1 H), 7.43 (td, J = 6.8, J = 1.2 Hz, 1 H), 2.70 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.6 (Cq), 163.2 (Cq), 155.1 (Cq), 135.8 (Cq), 130.5 (CH_{Ar}), 128.6 (CH_{Ar}), 120.0 (CH_{Ar}), 119.1 (CH_{Ar}), 102.9 (Cq), 15.2 (CH_3) ppm. HRMS (ESI): calcd. for $C_{10}H_8ClN_4S$ $[M + H]^+$ 251.0153; found 251.0155.

General Procedure A for S_NAr Reaction: To a solution of **8** (0.39 mmol, 100 mg) in dry THF (7 mL) were successively added the corresponding amine R^1R^2NH (1.00 equiv.) and Et_3N (1.05 equiv., 41 mg). The reaction mixture was stirred at the required temperature (see Table 1) until the starting material **8** was converted completely. The solvent was evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography to give the desired mono-aminated compounds **9**–**16**.

General Procedure B (PyBroP-Mediated C–O Activation): In a microwave vial, **2** (0.43 mmol, 100 mg) and PyBroP (0.51 mmol, 240 mg) were dissolved in 1,4-dioxane (4 mL). Et_3N (1.29 mmol, 0.17 mL) was then added, and the mixture was degassed by argon bubbling for 10 min. The sealed tube was heated at 80 °C for 4 h. After cooling, the corresponding amine (2.0 equiv.) was added, and the mixture was stirred for the required time and temperature (see Table 1). After cooling, the solvents were evaporated under reduced pressure, and the crude residue was purified by silica gel column chromatography to give the desired mono-aminated compounds **9**–**16**.

2-(Methylthio)-*N*-propylpyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidin-4-amine (9): After purification by silica gel flash chromatography (petroleum ether/EtOAc, 4:6), **9** was obtained as a light brown solid from *n*-propylamine in 65 % yield by general procedure A or in 86 % yield by general procedure B, m.p.195–196 °C. R_f (petroleum ether/EtOAc, 3:7) = 0.3. IR (ATR diamond): $\tilde{\nu}$ = 3390, 2925, 1636, 1589, 1537, 1359, 1266, 1198, 1144, 992, 792 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.69 (d, J = 6.8 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 1 H), 7.49 (ddd, J = 8.8, J = 6.8 Hz, J = 1.2 Hz, 1 H), 7.12 (td, J = 6.8, J = 1.2 Hz, 1 H), 5.60 (s, 1 H, NH), 3.76–3.63 (m, 2 H), 2.64 (s, 3 H), 1.76 (q, J = 7.4 Hz, 2 H), 1.03 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.6 (Cq), 162.5 (Cq), 157.0 (Cq), 134.6 (Cq), 129.6 (CH), 126.3 (CH), 117.2 (CH), 115.2 (CH), 90.8 (Cq), 43.0 (CH_2), 23.0 (CH_2), 14.3 (CH_3), 11.6 (CH_3) ppm. HRMS (ESI): calcd. for $C_{13}H_{16}N_5S$ $[M + H]^+$ 274.1121; found 274.1124.

***N*-(4-Methoxybenzyl)-2-(methylthio)pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidin-4-amine (10):** After purification by silica gel flash chromatography (petroleum ether/EtOAc, 4:6), **10** was obtained as white solid from *p*-methoxybenzylamine in 90 % yield by general procedure A or in 92 % yield by general procedure B, m.p. 231–232 °C. R_f (petroleum ether/EtOAc, 3:7) = 0.4. IR (ATR diamond):

$\tilde{\nu}$ = 3011, 1583, 1510, 1440, 1358, 1250, 1194, 1030, 915, 816, 754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, J = 6.8 Hz, 1 H), 7.65 (d, J = 8.8 Hz, 1 H), 7.47 (ddd, J = 8.8, J = 6.8 Hz, J = 1.2 Hz, 1 H), 7.39–7.33 (m, 2 H), 7.13 (td, J = 6.8, J = 1.2 Hz, 1 H), 6.90 (d, J = 8.8 Hz, 2 H), 5.32 (NH, s, 1 H), 4.87 (d, J = 5.3 Hz, 2 H), 3.81 (s, 3 H), 2.66 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.8 (Cq), 162.9 (Cq), 159.1 (Cq), 156.5 (Cq), 134.2 (Cq), 130.1 (Cq), 129.5 (CH), 129.3 (2 × CH_{Ar}), 125.9 (CH_{Ar}), 116.8 (CH_{Ar}), 115.0 (CH_{Ar}), 114.1 (2 × CH_{Ar}), 90.5 (Cq), 55.1 (CH_3), 44.5 (CH_2), 14.1 (CH_3) ppm. HRMS (ESI): calcd. for $C_{18}H_{18}N_5OS$ $[M + H]^+$ 352.1227; found 352.1231.

4-[2-(Methylthio)pyrido(1′,2′:1,5)pyrazolo[3,4-*d*]pyrimidin-4-yl]morpholine (11): After purification by silica gel flash chromatography (petroleum ether/EtOAc, 4:6), **11** was obtained as a white solid from morpholine in 95 % yield by general procedure A or in 89 % yield by general procedure B, m.p. 214–215 °C. R_f (petroleum ether/EtOAc, 3:7) = 0.42. IR (ATR diamond): $\tilde{\nu}$ = 2859, 1627, 1525, 1429, 1367, 1266, 1202, 1108, 970, 862, 747 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.75 (dt, J = 6.8, 1.2 Hz, 1 H), 7.68 (dt, J = 8.8, J = 1.2 Hz, 1 H), 7.55 (ddd, J = 8.8, J = 6.8 Hz, J = 1.2 Hz, 1 H), 7.21 (td, J = 6.8, J = 1.2 Hz, 1 H), 3.97–3.74 (m, 8 H), 2.65 (s, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 170.9 (Cq), 164.3 (Cq), 160.0 (Cq), 134.2 (Cq), 129.6 (CH_{Ar}), 126.2 (CH_{Ar}), 118.8 (CH_{Ar}), 115.6 (CH_{Ar}), 92.3 (Cq), 66.7 (2 × CH_2), 48.3 (2 × CH_2), 14.3 (CH_3) ppm. HRMS (ESI): calcd. for $C_{14}H_{16}N_5OS$ $[M + H]^+$ 302.1070; found 302.1071.

2-(Methylthio)-4-(piperidin-1-yl)pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidine (12): After purification by silica gel flash chromatography (petroleum ether/EtOAc, 4:6), **12** was obtained as a white solid from cyclohexylamine in 90 % yield by general procedure A or in 95 % yield by general procedure B, m.p. 169–170 °C; R_f (petroleum ether/EtOAc, 3:7) = 0.57. IR (ATR diamond): $\tilde{\nu}$ = 2928, 1628, 1556, 1525, 1375, 1299, 1240, 1188, 1025, 950, 793 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, J = 6.8 Hz, 1 H), 7.72 (d, J = 8.8 Hz, 1 H), 7.51 (t, J = 8.8 Hz, 1 H), 7.17 (t, J = 6.8 Hz, 1 H), 3.83–3.68 (m, 4 H), 2.65 (s, 3 H), 1.79 (s, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.5 (Cq), 164.0 (Cq), 159.8 (Cq), 134.3 (Cq), 129.3 (CH_{Ar}), 125.6 (CH_{Ar}), 118.6 (CH_{Ar}), 115.0 (CH_{Ar}), 92.2 (Cq), 48.7 (2 × CH_2), 25.7 (2 × CH_2), 24.4 (CH_2), 14.0 (CH_3) ppm. HRMS (ESI): calcd. for $C_{15}H_{18}N_5S$ $[M + H]^+$ 300.1277; found 300.1276.

***N*-Cyclohexyl-2-(methylthio)pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidin-4-amine (13):** After purification by silica gel flash chromatography (petroleum ether/EtOAc, 4:6), **13** was obtained as a white solid from piperidine in 61 % yield by general procedure A or in 81 % yield by general procedure B, m.p. 191–192 °C. R_f (petroleum ether/EtOAc, 3:7) = 0.47. IR (ATR diamond): $\tilde{\nu}$ = 3485, 2924, 1636, 1533, 1359, 1274, 1202, 1138, 990, 791, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.66 (d, J = 6.8 Hz, 1 H), 7.73 (d, J = 8.8 Hz, 1 H), 7.47 (t, J = 8.8 Hz, 1 H), 7.09 (t, J = 6.8 Hz, 1 H), 5.10 (d, J = 7.4 Hz, 1 H), 4.39–4.27 (m, 1 H), 2.63 (s, 3 H), 2.23–2.09 (m, 2 H), 1.83–1.70 (m, 2 H), 1.73–1.62 (m, 1 H), 1.55–1.38 (m, 2 H), 1.40–1.16 (m, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.8 (Cq), 163.05 (Cq), 156.2 (Cq), 134.4 (Cq), 129.4 (CH_{Ar}), 126.0 (CH_{Ar}), 117.0 (CH_{Ar}), 115.0 (CH_{Ar}), 90.7 (Cq), 49.55 (CH), 33.25 (2 × CH_2), 25.7 (CH_2), 24.95 (2 × CH_2), 14.3 (CH_3) ppm. HRMS (ESI): calcd. for $C_{16}H_{20}N_5S$ $[M + H]^+$ 314.1434; found 314.1431.

2-(Methylthio)-*N*-phenylpyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidin-4-amine (14): After purification by silica gel flash chromatography (petroleum ether/EtOAc, 4:6), **14** was obtained as a white solid from aniline in 85 % yield by general procedure A or by 85 % yield by general procedure B, m.p.228–229 °C. R_f (petroleum ether/EtOAc, 3:7) = 0.62. IR (ATR diamond): $\tilde{\nu}$ = 3005, 1634, 1522, 1438, 1301, 1195, 1065, 951, 790, 747 cm^{-1}. ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 9.27 (NH, s, 1 H), 9.01 (dt, J = 6.8, J = 1.2 Hz, 1 H), 8.65 (d, J = 8.8 Hz, 1 H), 7.80–7.69 (m, 3 H), 7.41–7.35 (m, 3 H), 7.17 (td, J = 6.8, J = 1.2 Hz, 1 H),2.50 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $[D_6]$DMSO): δ = 170.2 (Cq), 163.0 (Cq), 155.1 (Cq), 139.1 (Cq), 134.4 (Cq), 130.0 (CH_{Ar}), 128.8 (2 × CH_{Ar}), 127.1 (CH_{Ar}), 123.7 (2 × CH_{Ar}), 124.6 (CH_{Ar}), 119.6 (CH_{Ar}), 117.2 (CH_{Ar}), 91.2 (Cq), 14.0 (CH_3) ppm. HRMS (ESI): calcd. for $C_{16}H_{14}N_5S$ $[M + H]^+$ 308.0964; found 308.0962.

***N*-(3-Chlorophenyl)-2-(methylthio)pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidin-4-amine (15):** After purification by silica gel flash chromatography (petroleum ether/EtOAc, 5:5), **15** was obtained as a white solid from 3-chloroaniline in 65 % yield by general procedure A or in a 82 % yield by general procedure B, m.p. 179–180 °C. R_f (petroleum ether/EtOAc, 3:7) = 0.22. IR (ATR diamond): $\tilde{\nu}$ = 3242, 2921, 1635, 1530, 1435, 1266, 1202, 1111, 905, 761 cm^{-1}. ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 9.87 (NH, s, 1 H), 9.06 (d, J = 6.8 Hz, 1 H), 8.87 (d, J = 8.8 Hz, 1 H), 7.96 (s, 1 H), 7.83 (ddd, J = 8.8, J = 6.8 Hz, J = 1.2 Hz, 1 H), 7.75 (d, J = 8.8 Hz, 1 H), 7.56–7.40 (m, 2 H), 7.25 (d, J = 8.8 Hz, 1 H), 2.51 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $[D_6]$DMSO): δ = 168.7 (Cq), 160.2 (Cq), 154.3 (Cq), 139.8 (Cq),134.4 (Cq), 132.7 (Cq), 130.2 (CH_{Ar}), 130.15 (CH_{Ar}), 128.0 (CH_{Ar}), 124.4 (CH_{Ar}), 123.3 (CH_{Ar}),122.1 (CH_{Ar}), 119.7 (CH_{Ar}),117.7 (CH_{Ar}), 91.2 (Cq), 13.8 (CH_3) ppm. HRMS (ESI): calcd. for $C_{16}H_{13}ClN_5S$ $[M + H]^+$ 342.0575; found 342.0572.

***N*-(4-Methoxyphenyl)-2-(methylthio)pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidin-4-amine (16):** After purification by silica gel flash chromatography (petroleum ether/EtOAc, 4:6), **16** was obtained as a white solid from *p*-anisidine in 74 % yield by general procedure A or in 88 % yield by general procedure B, m.p. 262–263 °C. R_f (petroleum ether/EtOAc, 3:7) = 0.5. IR (ATR diamond): $\tilde{\nu}$ = 2954, 1644, 1565, 1505, 1367, 1245, 1107, 1062, 828,752 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.70 (d, J = 6.8 Hz, 1 H), 7.49–7.41 (m, 2 H), 7.34 (ddd, J = 8.8, J = 6.8 Hz, J = 1.2 Hz, 1 H), 7.13 (t, J = 6.8 Hz, 1 H), 7.02 (d, J = 8.8 Hz, 1 H), 6.95–6.86 (m, 2 H), 3.83 (s, 3 H), 2.65 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.4 (Cq), 163.5 (Cq), 157.4 (Cq), 155.8 (Cq), 134.6 (Cq), 131.3 (Cq), 129.6 (CH_{Ar}), 126.3 (CH_{Ar}), 125.1 (2 × CH_{Ar}), 118.6 (CH_{Ar}), 115.8 (CH_{Ar}), 114.6 (2 × CH_{Ar}), 91.0 (Cq), 55.7 (CH_3), 14.3 (CH_3) ppm. HRMS (ESI): calcd. for $C_{17}H_{16}N_5OS$ $[M + H]^+$ 338.1070; found 338.1070.

General Procedure C for the Direct Arylation by C–OH Bond Activation: To an argon-degassed solution of **2** (0.43 mmol, 100 mg) in dioxane (4 mL) in a sealed tube were added successively PyBroP (0.51 mmol, 240 mg) and Et_3N (1.29 mmol, 0.17 mL). After 18 h at 80 °C, the reaction mixture was cooled, and a solution containing the required arylboronic acid (2.0 equiv.), Na_2CO_3 (5.0 equiv.), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (10 mol-%) in H_2O (1 mL) was added. The sealed vial was heated at 110 °C and stirred for an additional 24 h. After cooling to room temperature, the volatiles were evaporated under reduced pressure, and the crude material was diluted in CH_2Cl_2 (20 mL). The organic layer was washed with water (10 mL), dried with $MgSO_4$, filtered, and concentrated under vacuum. The crude mixture was purified by silica gel column chromatography to give the desired monoarylated compounds **17**–**23**.

2-(Methylthio)-4-(*p*-tolyl)pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidine (17): With *p*-tolylboronic acid as the coupling reagent and by general procedure C, **17** was isolated as a yellow solid in 90 % yield after purification by silica gel flash chromatography (petroleum ether/EtOAc, 6:4), m.p. 185–184 °C; R_f (petroleum ether/EtOAc, 3:7) = 0.52. IR (ATR diamond): $\tilde{\nu}$ = 2922, 1635, 1577, 1528, 1435, 1240, 1184, 1002, 799, 752, 634 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.84 (d, J = 6.8 Hz, 1 H), 7.99 (d, J = 8.8 Hz, 1 H), 7.81 (d, J = 7.7 Hz, 2 H), 7.48 (t, J = 8.8 Hz, 1 H), 7.40 (d, J = 7.7 Hz, 2 H), 7.31 (t, J = 6.8 Hz, 1 H), 2.74 (s, 3 H), 2.49 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.3 (Cq), 163.7 (Cq), 163.1 (Cq), 141.3 (Cq), 135.9 (Cq),

134.8 (Cq), 129.8 (CH_{Ar}), 129.7 (2 × CH_{Ar}), 128.8 (2 × CH_{Ar}), 126.7 (CH_{Ar}), 119.5 (CH_{Ar}), 117.8 (CH_{Ar}), 101.75 (Cq), 21.7 (CH_3), 14.6 (CH_3) ppm. HRMS (ESI): calcd. for $C_{17}H_{15}N_4S$ $[M + H]^+$ 307.1012; found 307.1016.

4-(4-Methoxyphenyl)-2-(methylthio)pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidine (18): With 4-methoxyphenylboronic acid as the coupling reagent and by general procedure C, **18** was isolated as a yellow solid in 89 % yield after purification by silica gel flash chromatography (petroleum ether/EtOAc, 5:5), m.p. 219–220 °C. R_f (petroleum ether/EtOAc, 3:7) = 0.47. IR (ATR diamond): $\tilde{\nu}$ = 2918, 1633, 1533, 1507, 1344, 1261, 1185, 1021, 841, 755, 621 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.84 (d, J = 6.8 Hz, 1 H), 8.03 (dt, J = 8.8, 1.2 Hz, 1 H), 7.93–7.86 (m, 2 H), 7.50 (ddd, J = 8.8, J = 6.8 Hz, J = 1.2 Hz, 1 H), 7.31 (td, J = 6.8, J = 1.2 Hz, 1 H), 7.18–7.07 (m, 2 H), 3.93 (s, 3 H), 2.74 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.2 (Cq), 163.2 (Cq), 162.0 (Cq), 135.9 (Cq), 130.6 (2 × CH_{Ar}), 130.0 (Cq), 129.9 (CH_{Ar}), 126.7 (CH_{Ar}), 119.4 (CH_{Ar}), 117.8 (CH_{Ar}), 114.4 (2 × CH_{Ar}), 101.6 (Cq), 55.6 (CH_3), 14.6 (CH_3) ppm. HRMS (ESI): calcd. for $C_{17}H_{15}N_4OS$ $[M + H]^+$ 323.0961; found 323.0964.

4-(3-Methoxyphenyl)-2-(methylthio)pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidine (19): With 3-methoxyphenylboronic acid as the coupling reagent and by general procedure C, **19** was isolated as a yellow solid in 83 % yield after purification by silica gel flash chromatography (petroleum ether/EtOAc, 5:5), m.p. 226–227 °C. R_f (petroleum ether/EtOAc, 3:7) = 0.6. IR (ATR diamond): $\tilde{\nu}$ = 3002, 1637, 1520, 1432, 1286, 1188, 1025, 872, 757 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.82 (d, J = 6.8 Hz, 1 H), 7.59 (dd, J = 6.8, J = 1.2 Hz, 1 H), 7.54 (td, J = 8.8, J = 1.2 Hz, 1 H),7.47–7.37 (m, 2 H), 7.33–7.24 (m, 1 H), 7.16 (t, J = 7.4 Hz, 1 H), 7.10 (d, J = 8.8 Hz, 1 H), 3.69 (s, CH_3), 2.74 (s, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.9 (Cq), 162.0 (Cq), 160.9 (Cq), 156.5 (Cq), 135.8 (Cq), 131.4 (CH_{Ar}), 130.5 (CH_{Ar}), 129.2 (CH_{Ar}), 126.4 (Cq), 126.1 (CH_{Ar}), 121.1 (CH_{Ar}), 119.3 (CH_{Ar}), 117.3 (CH_{Ar}), 110.9 (CH_{Ar}), 103.3 (Cq), 55.3 (CH_3), 14.2 (CH_3) ppm. HRMS (ESI): calcd. for $C_{17}H_{15}N_4OS$ $[M + H]^+$ 323.0961; found 323.0959.

4-(2-Methoxyphenyl)-2-(methylthio)pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidine (20): With 2-methoxyphenylboronic acid as the coupling reagent and by general procedure C, **20** was isolated as a yellow solid in 76 % yield after purification by silica gel flash chromatography (petroleum ether/EtOAc, 5:5), m.p. 208–209 °C. R_f (petroleum ether/EtOAc, 3:7) = 0.5. IR (ATR diamond): $\tilde{\nu}$ = 2920, 1633, 1526, 1434, 1264, 1183, 1038, 841, 763 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.85 (d, J = 6.8 Hz, 1 H) 7.99 (d, J = 8.8 Hz, 1 H), 7.56–7.40 (m, 4 H), 7.32 (t, J = 6.8 Hz, 1 H),7.21–7.05 (m, 1 H), 3.90 (s, 3 H), 2.74 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.3 (Cq), 163.5 (Cq),162.1 (Cq),160.2 (Cq), 138.9 (Cq),135.8 (Cq),130.0 (CH_{Ar}), 129.9 (CH_{Ar}), 126.8 (CH_{Ar}), 121.1 (CH_{Ar}), 119.5 (CH_{Ar}), 118.0 (CH_{Ar}), 117.0 (CH_{Ar}), 113.8 (CH_{Ar}), 101.7 (Cq), 55.6 (CH_3), 14.6 (CH_3) ppm. HRMS (ESI): calcd. for $C_{17}H_{15}N_4OS$ $[M + H]^+$ 323.0961; found 323.0960.

4-(4-Fluorophenyl)-2-(methylthio)pyrido[1′,2′:1,5]pyrazolo-[3,4-*d*]pyrimidine (21): With 4-fluorophenylboronic acid as the coupling reagent and by general procedure C, **21** was isolated as a yellow solid in 95 % yield after purification by silica gel flash chromatography (petroleum ether/EtOAc, 5:5), m.p. 248–249 °C. R_f (petroleum ether/EtOAc, 3:7) = 0.57. IR (ATR diamond): $\tilde{\nu}$ = 3081, 1632, 1561, 1503, 1431, 1340, 1181, 1116, 869, 758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.85 (dt, J = 6.8, J = 1.2 Hz, 1 H), 7.96–7.91 (m, 3 H), 7.52 (ddd, J = 8.8, J = 6.8 Hz, J = 1.2 Hz, 1 H), 7.37–7.28 (m, 3 H), 2.74 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.3 (Cq), 164.5 (d, $^1J_{C,F}$ = 251.4 Hz, CF), 163.15 (Cq), 162.4 (Cq), 135.7 (Cq), 133.7 (d, $^4J_{C,F}$ = 3.2 Hz, Cq), 131.0 (d, $^3J_{C,F}$ = 8.6 Hz, 2 × CH), 130.0 (CH_{Ar}), 127.0 (CH_{Ar}), 119.2 (CH_{Ar}), 118.0 (CH_{Ar}), 116.2 (d, $^2J_{C,F}$ = 21.8 Hz, 2 × CH), 101.65 (Cq), 14.6 (S-CH_3) ppm. HRMS (ESI): calcd. for $C_{16}H_{12}FN_4S$ $[M + H]^+$ 311.0761; found 311.0763.

2-(Methylthio)-4-[4-(trifluoromethyl)phenyl]pyrido[1′,2′:1,5]-pyrazolo[3,4-*d*]pyrimidine (22): With 4-trifluoromethylphenylboronic acid as the coupling reagent and by general procedure C, **22** was isolated as a yellow solid in 84 % yield after purification by silica gel flash chromatography (petroleum ether/EtOAc, 5:5), m.p. 197–199 °C. R_f (petroleum ether/EtOAc, 3:7) = 0.7. IR (ATR diamond): $\tilde{\nu}$ = 3066, 1633, 1531, 1434, 1325, 1240, 1066, 859, 757, 639 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.87 (d, J = 6.8 Hz, 1 H), 8.03 (d, J = 7.7 Hz, 2 H), 7.88 (d, J = 7.7 Hz, 3 H), 7.54 (t, J = 8.8 Hz, 1 H), 7.37 (t, J = 6.8 Hz, 1 H), 2.74 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.4 (Cq), 163.0 (Cq), 161.8 (Cq), 141.0 (Cq), 135.5 (Cq), 132.7 (q, $^2J_{C,F3}$ = 32.8 Hz, Cq), 130.0 (CH_{Ar}), 129.3 (2 × CH_{Ar}), 127.2 (CH_{Ar}), 126.0 (q, $^3J_{C,F3}$ = 3.8 Hz, 2 × CH_{Ar}), 121.1 (q, $^1J_{C,F3}$ = 279 Hz, CF_3), 119.1 (CH_{Ar}), 118.3 (CH_{Ar}), 101.6 (Cq), 14.6 (CH_3) ppm. HRMS (ESI): calcd. for $C_{17}H_{12}F_3N_4S$ $[M + H]^+$ 361.0729; found 361.0733.

2-(Methylthio)-4-(pyridin-3-yl)pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]-pyrimidine (23): With 3-pyridinylboronic acid as the coupling reagent and by general procedure C, **23** was isolated as a yellow solid in 35 % yield after purification by silica gel flash chromatography (petroleum ether/EtOAc, 1:9), m.p. 252–253 °C. R_f (petroleum ether/EtOAc, 3:7) = 0.01. IR (ATR diamond): $\tilde{\nu}$ = 3073, 1631, 1431, 1352, 1241, 1181, 1027, 836, 752 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.17 (s, 1 H), 9.00–8.80 (m, 2 H), 8.26 (dt, J = 8.8, J = 1.2 Hz, 1 H), 7.93 (d, J = 8.8 Hz, 1 H), 7.64–7.46 (m, 2 H), 7.37 (td, J = 6.8, 1.2 Hz, 1 H), 2.75 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.4 (Cq), 162.9 (Cq), 160.3 (Cq), 151.7 (CH_{Ar}), 149.4 (CH_{Ar}), 136.4 (CH_{Ar}), 135.4 (Cq), 133.5 (Cq), 130.0 (CH_{Ar}), 127.2 (CH_{Ar}), 123.9 (CH_{Ar}), 119.0 (CH_{Ar}), 118.2 (CH_{Ar}), 101.7 (Cq), 14.5 (CH_3) ppm. HRMS (ESI): calcd. for $C_{15}H_{12}N_5S$ $[M + H]^+$ 394.0808; found 394.0807.

General Procedure D for C-2 Liebeskind–Srogl Cross-Coupling Reaction: Compound **11** or **17** (70 mg, 1 equiv.), arylboronic acid (1.5 equiv.), CuTC (3 equiv.), and $Pd(PPh_3)_4$ (10 mol-%) were dissolved in anhydrous THF (5 mL) under argon in a microwave vial. The reaction was heated at 100 °C under microwave irradiation for 90 min. After cooling, the solvent was evaporated under reduced pressure, and the residue was diluted in aq. satd. $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (5 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography to afford the desired compounds **24**–**34**.

4-[2-(4-Methoxyphenyl)pyrido(1′,2′:1,5)pyrazolo[3,4-*d*]pyrimidin-4-yl]morpholine (24): From **11** with 4-methoxyphenylboronic acid as the coupling reagent and by general procedure D, **24** was isolated as a white solid in 69 % yield after purification by silica gel flash chromatography (petroleum ether/EtOAc, 4:6), m.p. 206–208 °C. R_f (petroleum ether/EtOAc, 4:6) = 0.12. IR (ATR diamond): $\tilde{\nu}$ = 3002, 1606, 1531, 1440, 1411, 1246, 1156, 1102, 1021, 943, 842, 796 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.83 (d, J = 6.8 Hz, 1 H), 8.60 (d, J = 8.0 Hz, 2 H), 7.75 (d, J = 8.8 Hz, 1 H), 7.55 (t, J = 8.8 Hz, 1 H), 7.23 (td, J = 6.8, J = 1.2 Hz, 1 H), 7.00 (d, J = 8.0 Hz, 2 H), 4.02–3.81 (m, 8 H + 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.6 (Cq), 165.0 (Cq), 161.6 (Cq), 161.1 (Cq), 134.0 (Cq), 131.2 (Cq), 130.4 (2 × CH_{Ar}), 129.6 (CH_{Ar}), 125.7 (CH_{Ar}), 119.0 (CH_{Ar}),115.7 (CH_{Ar}), 113.5 (2 × CH_{Ar}), 93.4 (Cq), 66.7 (2 × CH_2), 55.3 (CH_3), 48.4 (2 × CH_2) ppm. HRMS (ESI): calcd. for $C_{20}H_{20}N_5O_2$ $[M + H]^+$ 362.1612; found 362.1610.

4-[2-(3-Methoxyphenyl)pyrido(1′,2′:1,5)pyrazolo[3,4-*d*]pyrimidin-4-yl]morpholine (25): From **11** with 3-methoxyphenylboronic

acid as the coupling reagent and by general procedure D, **25** was isolated as a yellow solid in 42 % yield after purification by silica gel flash chromatography (petroleum ether/EtOAc, 5:5), m.p. 195–196 °C. R_f (petroleum ether/EtOAc, 4:6) = 0.15. IR (ATR diamond): $\tilde{\nu}$ = 2962, 1633, 1531, 1435, 1320, 1228, 1105, 1026, 882, 792 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.84 (d, J = 6.8 Hz, 1 H), 8.28–8.21 (m, 2 H), 7.78 (d, J = 8.8 Hz, 1 H), 7.57 (t, J = 8.8 Hz, 1 H), 7.39 (t, J = 6.8 Hz, 1 H), 7.27–7.22 (m, 1 H), 7.07–7.02 (m, 1 H), 3.96–3.91 (m, 11 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.0 (Cq), 162.6 (Cq), 161.2 (Cq), 159.8 (Cq), 140.2 (Cq), 134.1 (Cq), 129.7 (CH_{Ar}), 129.2 (CH_{Ar}), 126.0 (CH_{Ar}), 121.5 (CH_{Ar}), 119.3 (CH_{Ar}), 117.0 (CH_{Ar}), 116.1 (CH_{Ar}), 113.4 (CH_{Ar}), 93.8 (Cq), 66.9 (2 × CH_2), 55.5 (CH_3), 48.6 (2 × CH_2) ppm. HRMS (ESI): calcd. for $C_{20}H_{20}N_5O_2$ $[M + H]^+$ 362.1612; found 362.1610.

4-(4-Morpholinopyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidin-2-yl)-benzonitrile (26): From **11** with 4-cyanophenylboronic acid as the coupling reagent and by general procedure D, **26** was isolated as a yellow solid in 55 % yield after purification by silica gel flash chromatography (petroleum ether/EtOAc, 3:7), m.p. 281–282 °C. R_f (petroleum ether/EtOAc, 4:6) = 0.17. IR (ATR diamond): $\tilde{\nu}$ = 2851, 2224, 1629, 1526, 1436, 1331, 1231, 1105, 1015, 946, 860, 794, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.87 (d, J = 6.8 Hz, 1 H), 8.73 (d, J = 8.0 Hz, 2 H), 7.82 (d, J = 8.8 Hz, 1 H), 7.76 (d, J = 8.0 Hz, 2 H), 7.62 (t, J = 8.8 Hz, 1 H), 7.31 (t, J = 6.8 Hz, 1 H), 3.96 (s, 8 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.6 (Cq), 161.2 (Cq), 160.8 (Cq), 142.8 (Cq), 134.0 (Cq), 132.0 (2 × CH_{Ar}), 129.7 (CH_{Ar}), 129.1 (2 × CH_{Ar}), 126.2 (CH_{Ar}), 119.4 (CH_{Ar}), 119.0 (Cq), 116.3 (CH_{Ar}), 113.4 (Cq), 93.9 (Cq), 66.7 (2 × CH_2), 48.4 (2 × CH_2) ppm. HRMS (ESI): calcd. for $C_{20}H_{17}N_6O$ $[M + H]^+$ 357.1458; found 357.1457.

4-{2-[4-(Trifluoromethyl)phenyl]pyrido(1′,2′:1,5)pyrazolo[3,4-*d*]pyrimidin-4-yl}morpholine (27): From **11** with 4-trifluoromethylphenylboronic acid as the coupling reagent and by general procedure D, **27** was isolated as a yellow solid in 59 % yield after purification by silica gel flash chromatography (petroleum ether/EtOAc, 5:5), m.p. 236–237 °C. R_f (petroleum ether/EtOAc, 4:6) = 0.25. IR (ATR diamond): $\tilde{\nu}$ = 2951, 1632, 1529, 1436, 1313, 1156, 1098, 1064, 944, 744 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 9.12 (d, J = 6.8 Hz, 1 H), 8.68 (d, J = 8.8 Hz, 2 H), 8.03 (d, J = 8.8 Hz, 1 H), 7.88 (d, J = 8.8 Hz, 2 H), 7.78 (t, J = 8.8 Hz, 1 H), 7.50 (t, J = 6.8 Hz, 1 H), 4.01–3.79 (m, 8 H) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 163.8 (Cq), 160.4 (Cq),159.6 (Cq), 142.3 (Cq), 133.5 (Cq), 130.1 (q, $^2J_{C\text{-}F3}$ = 30.9 Hz, Cq), 129.8 (CH_{Ar}), 128.7 (2 × CH_{Ar}), 127.1 (CH_{Ar}), 125.2 (q, $^3J_{C,F3}$ = 3.8 Hz, 2 × CH_{Ar}), 124.2 (q, $^1J_{C,F3}$ = 271.8 Hz, Cq), 120.0 (CH_{Ar}), 92.8 (Cq), 117.1 (CH_{Ar}), 66.0 (2 × CH_2), 47.8 (2 × CH_2) ppm. HRMS (ESI): calcd. for $C_{20}H_{17}F_3N_5O$ $[M + H]^+$ 400.1380; found 400.1378.

4-(2-{4-[(Tetrahydro-2*H*-pyran-2-yl)oxy]phenyl}pyrido(1′,2′:1,5)-pyrazolo[3,4-*d*]pyrimidin-4-yl)morpholine (28): From **11** with 4-(tetrahydro-2*H*-pyran-2-yloxy)phenylboronic acid as the coupling reagent and by general procedure D, **28** was isolated as a white solid in 41 % yield after purification by silica gel flash chromatography (petroleum ether/EtOAc, 4:6), m.p. 152–153 °C. R_f (petroleum ether/EtOAc, 4:6) = 0.17. IR (ATR diamond): $\tilde{\nu}$ = 831, 947, 1238, 1437, 1532, 2161, 2959 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.81 (d, J = 6.8 Hz, 1 H), 8.57 (d, J = 8.0 Hz, 2 H), 7.73 (d, J = 8.8 Hz, 1 H), 7.53 (t, J = 8.8 Hz, 1 H), 7.21 (t, J = 6.8 Hz, 1 H), 7.13 (d, J = 8.0 Hz, 2 H), 5.52 (t, J = 3.3 Hz, 1 H), 3.99–3.85 (m, 9 H), 3.69–3.56 (m, 1 H), 2.11–1.96 (m, 1 H), 1.93–1.85 (m, 2 H), 1.78–1.56 (m, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.8 (Cq), 162.4 (Cq), 160.9 (Cq), 158.9 (Cq), 133.8 (Cq), 131.8 (Cq), 130.1 (2 × CH_{Ar}), 129.3 (CH_{Ar}), 125.5 (CH_{Ar}), 118.8 (CH_{Ar}), 115.7 (2 × CH_{Ar}), 115.5 (CH_{Ar}), 96.0 (CH), 93.2 (Cq), 66.5 (2 × CH_2), 61.8 (CH_2), 48.2 (2 × CH_2), 30.1 (CH_2), 25.0 (CH_2), 18.5 (CH_2) ppm. HRMS (ESI): calcd. for $C_{24}H_{26}N_5O_3$ $[M + H]^+$ 432.2030; found 432.2028.

2-(4-Methoxyphenyl)-4-(*p*-tolyl)pyrido[1′,2′:1,5]pyrazolo-[3,4-*d*]pyrimidine (29): From **17** with 4-methoxyphenylboronic acid as the coupling reagent and by general procedure D, **29** was isolated as a white solid in 67 % yield after purification by silica gel flash chromatography (petroleum ether/EtOAc, 4:6), m.p. 216–217 °C. R_f (petroleum ether/EtOAc, 4:6) = 0.5. IR (ATR diamond): $\tilde{\nu}$ = 3012, 1633, 1531, 1432, 1254, 1114, 1021, 804, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.90 (d, J = 6.8 Hz, 1 H), 8.74 (d, J = 8.8 Hz, 2 H), 8.10 (d, J = 8.8 Hz, 1 H), 7.94 (d, J = 8.8 Hz, 2 H), 7.55–7.39 (m, 3 H), 7.38–7.26 (m, 1 H), 7.03 (d, J = 8.8 Hz, 2 H), 3.90 (s, 3 H), 2.52 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.45 (Cq), 163.9 (Cq), 162.4 (Cq), 141.6 (Cq), 136.4 (Cq), 136.1 (Cq), 131.8 (Cq), 131.3 (2 × CH), 130.2 (CH), 130.2 (2 × CH), 129.5 (2 × CH), 126.6 (CH), 120.3 (CH), 118.4 (CH), 114.3 (2 × CH), 103.3 (Cq), 91.0 (Cq), 56.0 (CH_3), 22.2 (CH_3) ppm. HRMS (ESI): calcd. for $C_{23}H_{19}N_4O$ $[M + H]^+$ 367.1553; found 367.1556.

2-(3-Methoxyphenyl)-4-(*p*-tolyl)pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]-pyrimidine (30): From **17**, with 3-methoxyphenylboronic acid as the coupling reagent and by general procedure D, **30** was isolated as a yellow solid in 42 % yield after purification by silica gel flash chromatography (petroleum ether/EtOAc, 4:6), m.p. 218–219 °C. R_f (petroleum ether/EtOAc, 4:6) = 0.47. IR (ATR diamond): $\tilde{\nu}$ = 2835, 1635, 1534, 1434, 1356, 1045, 1264, 789, 722 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.94 (d, J = 6.8 Hz, 1 H), 8.55–8.31 (m, 2 H), 8.15 (d, J = 8.8 Hz, 1 H), 7.97 (d, J = 8.8 Hz, 2 H), 7.63–7.31 (m, 5 H), 7.06 (d, J = 8.8 Hz, 1 H), 3.95 (s, 3 H), 2.53 (s, 3 H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 163.9 (Cq), 163.5 (Cq), 163.3 (Cq), 159.8 (Cq), 141.1 (Cq), 139.9 (Cq), 135.6 (Cq), 135.4 (Cq), 129.6 (CH_{Ar}), 129.6 (2 × CH_{Ar}), 129.3 (CH_{Ar}), 128.9 (2 × CH_{Ar}), 126.1 (CH_{Ar}), 121.7 (CH_{Ar}), 119.8 (CH_{Ar}), 118.1 (CH_{Ar}), 117.4 (CH_{Ar}), 113.2 (CH_{Ar}), 110.1 (Cq), 55.5 (CH_3), 21.6 (CH_3) ppm. HRMS (ESI): calcd. for $C_{23}H_{19}N_4O$ $[M + H]^+$ 367.1553; found 367.1553.

2-(2-Methoxyphenyl)-4-(*p*-tolyl)pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]-pyrimidine (31): From **17** with 2-methoxyphenylboronic acid as the coupling reagent and by general procedure D, **31** was isolated as a yellow solid in 31 % yield after purification by silica gel flash chromatography (petroleum ether/EtOAc, 4:6), m.p. 175–176 °C. R_f (petroleum ether/EtOAc, 4:6) = 0.1. IR (ATR diamond): $\tilde{\nu}$ = 2833, 1633, 1556, 1508, 1428, 1242, 1129, 1020, 812, 754, 633 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.96 (d, J = 6.8 Hz, 1 H), 8.13 (d, J = 8.8 Hz, 1 H), 7.96 (dd, J = 8.8, J = 1.2 Hz, 1 H), 7.91 (d, J = 7.7 Hz, 2 H), 7.55–7.48 (m, 1 H), 7.42 (t, J = 7.2 Hz, 3 H), 7.37 (td, J = 6.8, J = 1.2 Hz, 1 H), 7.12–7.04 (m, 2 H), 3.93 (s, 3 H), 2.50 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.7 (Cq), 163.9 (Cq), 163.1 (Cq), 158.2 (Cq), 141.1 (Cq), 135.5 (Cq), 135.4 (Cq), 132.3 (CH_{Ar}), 130.8 (CH_{Ar}), 129.9 (CH_{Ar}), 129.7 (2 × CH_{Ar}), 129.5 (Cq), 129.0 (2 × CH_{Ar}), 126.2 (CH_{Ar}), 120.7 (CH_{Ar}), 119.9 (CH_{Ar}), 118.3 (CH_{Ar}), 112.4 (CH_{Ar}), 102.9 (Cq), 56.3 (CH_3), 21.7 (CH_3) ppm. HRMS (ESI): calcd. for $C_{23}H_{19}N_4O$ $[M + H]^+$ 367.1553; found 367.1553.

4-(*p*-Tolyl)-2-[4-(trifluoromethyl)phenyl]pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidine (32): From **17**, with 4-trifluoromethylphenylboronic acid as the coupling reagent and by general procedure D, **32** was isolated as a yellow solid in 65 % yield after purification by silica gel flash chromatography (petroleum ether/EtOAc, 5:5), m.p. 179–180 °C. R_f (petroleum ether/EtOAc, 4:6) = 0.75. IR (ATR diamond): $\tilde{\nu}$ = 3039, 1633, 1509, 1432, 1321, 1164, 1105, 1065, 1016, 805, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.97 (d, J = 6.8 Hz, 1 H), 8.89 (d, J = 8.0 Hz, 2 H), 8.17 (d, J = 8.8 Hz, 1 H), 7.95 (d, J = 8.0 Hz, 2 H), 7.76 (d, J = 8.0 Hz, 2 H), 7.54 (t, J = 8.8 Hz, 1 H), 7.47 (d, J = 8.0 Hz, 2 H), 7.39 (t, J = 6.8 Hz, 1 H), 2.53 (s, 3 H) ppm. ^{13}C

NMR (101 MHz, $CDCl_3$): δ = 164.3 (Cq), 163.4 (Cq), 162.2 (Cq), 141.9 (Cq), 141.5 (Cq), 140.2 (Cq), 135.5 (Cq), 132.1 (q, $^2J_{C,F3}$ = 32.0 Hz, Cq), 129.9 (CH_{Ar}), 129.8 (2 × CH_{Ar}), 129.4 (2 × CH_{Ar}), 129.0 (2 × CH_{Ar}), 126.5 (CH_{Ar}), 125.3 (q, $^3J_{C,F3}$ = 4.0 Hz, 2 × CH_{Ar}), 124.4 (q, $^1J_{C,F3}$ = 273.0 Hz, Cq), 120.1 (CH_{Ar}), 118.6 (CH_{Ar}), 103.8 (Cq), 21.7 (CH_3) ppm. HRMS (ESI): calcd. for $C_{23}H_{16}F_3N_4$ $[M + H]^+$ 405.1322; found 405.1320.

4-[4-(*p*-Tolyl)pyrido(1′,2′:1,5)pyrazolo[3,4-*d*]pyrimidin-2-yl]-benzonitrile (33): From **17** with 4-cyanophenylboronic acid as the coupling reagent and by general procedure D, **33** was isolated as a yellow solid in 64 % yield after purification by silica gel flash chromatography (petroleum ether/EtOAc, 4:6), m.p. 263–264 °C. R_f (petroleum ether/EtOAc, 4:6) = 0.55. IR (ATR diamond): $\tilde{\nu}$ = 2921, 2221, 1634, 1557, 1509, 1433, 1266, 1117, 978, 801, 752 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.97 (d, J = 6.8 Hz, 1 H), 8.89 (d, J = 8.0 Hz, 2 H), 8.19 (d, J = 8.8 Hz, 1 H), 7.95 (d, J = 8.0 Hz, 2 H), 7.80 (d, J = 8.0 Hz, 2 H), 7.57 (t, J = 8.8 Hz, 1 H), 7.48 (d, J = 8.0 Hz, 2 H), 7.42 (t, J = 6.8 Hz, 1 H), 2.54 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.3 (Cq), 163.3 (CN), 161.5 (Cq), 142.7 (Cq), 141.6 (Cq), 135.6 (Cq), 135.2 (Cq), 132.2 (2 × CH), 129.9 (CH_{Ar}), 129.8 (2 × CH_{Ar}), 129.5 (2 × CH_{Ar}), 128.9 (2 × CH_{Ar}), 126.7 (CH_{Ar}), 120.1 (CH_{Ar}), 119.1 (Cq), 118.8 (CH_{Ar}),113.7 (Cq), 103.7 (Cq), 21.7 (CH_3) ppm. HRMS (ESI): calcd. for $C_{23}H_{16}N_5$ $[M + H]^+$ 362.1400; found 362.1399.

2-(Pyridin-3-yl)-4-(*p*-tolyl)pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidine (34): From **17** with 3-pyridinylboronic acid as the coupling reagent and by general procedure D, **34** was isolated as a yellow solid in 44 % yield after purification by silica gel flash chromatography (petroleum ether/EtOAc, 4:6), m.p. 238–239 °C. R_f (petroleum ether/EtOAc, 4:6) = 0.05. IR (ATR diamond): $\tilde{\nu}$ = 2919, 1634, 1533, 1434, 1357, 1273, 1128, 1023, 834, 801, 714 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.96 (s, 1 H), 9.02 (d, J = 8.8 Hz, 1 H), 8.96 (d, J = 6.8 Hz, 1 H), 8.74 (s, 1 H), 8.18 (d, J = 8.8 Hz, 1 H), 7.97 (d, J = 8.0 Hz, 2 H), 7.56 (t, J = 8.8 Hz, 1 H), 7.52–7.42 (m, 3 H), 7.40 (t, J = 6.8 Hz, 1 H), 2.54 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.4 (Cq), 163.4 (Cq), 161.8 (Cq), 151.2 (CH_{Ar}), 150.8 (CH_{Ar}), 142.6 (Cq), 141.5 (Cq), 136.4 (Cq), 135.6 (Cq), 135.4 (CH_{Ar}), 129.9 (CH_{Ar}), 129.8 (2 × CH_{Ar}), 129.0 (2 × CH_{Ar}), 126.6 (CH_{Ar}), 123.4 (CH_{Ar}), 120.1 (CH_{Ar}), 118.6 (CH_{Ar}), 103.6 (Cq), 21.7 (CH_3) ppm. HRMS (ESI): calcd. for $C_{21}H_{16}N_5$ $[M + H]^+$ 338.1400; found 338.1400.

Supporting Information (see footnote on the first page of this article): ^1H, ^{13}C, and ^{13}C DEPT NMR spectra for all compounds.

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