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Three successive and regiocontrolled palladium cross-coupling reactions to easily synthesize novel series of 2,4,6-tris(het)aryl pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidines†

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The first access to tris(het)arylated pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidine derivatives is reported. The series were generated from 4-chloroaminopyridinium, which afforded the key intermediate bearing three leaving groups, *i.e.* a C-2 methylsulfanyl, a lactame carbonyl group in C-4 and a chlorine atom in C-6. The regioselective reactions led to the tris(het)aryl derivatives with satisfying to high yields. The three successive cross-coupling reactions occurred first in C-6 by the displacement of chlorine, next in C-4 position by a sequential Pd-catalyzed phosphonium coupling and finally in C-2 under a Pd/Cu-catalyzed desulfurative cross-coupling reaction. The optimization and scope of each reaction are discussed and the original compounds characterized.

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Introduction

Nitrogen-containing and fused heterocyclic compounds have attracted considerable attention in directed and targeted organic synthesis and many products have been used in materials and medicinal chemistry programs. With a view to increasing molecular diversity, our aim was to design rare tricyclic pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidines (PPPy), which incorporate a tricyclic system and four nitrogen atoms, two of which are vicinal. This fused tricyclic heterocycle contains a pyrazolopyridine core which has been used in diverse biologically and pharmaceutical active molecules including diuretic¹ and antihypertensive drugs,² and as p38 kinase inhibitors³ and melatonin receptor ligands.⁴ It also contains a pyrimidine natural moiety, which is known to possess a potential role in several biological processes and to have emerged as a significant motif in drug-discovery programs.⁵

In order to build such a multi-heterocyclic compound, our group recently focused on developing new functionalization protocols⁶ to explore the chemical space, an indispensable key to design future useful molecules.

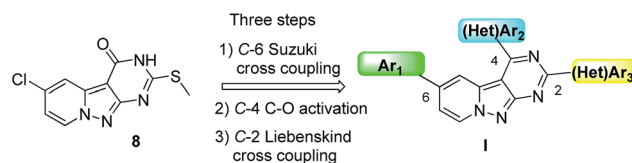


Fig. 1 Access to 2,4,6-tris(het)arylated pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidines **I** from the unique platform **8**.

In order to build C-2 and C-4 disubstituted PPPy derivatives, we developed a straightforward strategy which included successive C-4 *in situ* C–O activation and a C-2 desulfurization through Liebeskind–Srogl cross-coupling reactions.⁷ To provide a versatile platform we then sought to design a new flexible route to access 2,4,6-trisubstituted PPPy's **I** from a unique intermediate *i.e.* the 6-chloro-2-(methylthio)pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidin-4(3*H*)-one **8**.

We report herein the preparation of **8** and its regioselective functionalization by different types of palladium catalyzed reactions. After optimization of the reaction conditions, this strategy was achieved using three successive (het)arylations in the following order C-6, C-4 and then C-2 positions (Fig. 1). The scope and limits are discussed for each step.

Results and discussion

Compound **8** was obtained *via* a 7-step sequence partially based on our previous work.^{7,8} Dimethyl 5-chloropyrazolo[1,5-*a*]pyridine-2,3-dicarboxylate **2** was obtained after a [3 + 2] cycloaddition between the 1-amino-4-chloropyridinium iodide **1**

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(ref. 9 and 10) with dimethyl acetylenedicarboxylate (DMAD). A regioselective saponification furnished the hemiester **3**, which was subjected to an isocyanate generation under Curtius rearrangement. The unstable isocyanate function was quenched with *tert*-butanol to afford the Boc protected (het)aryl amine **4**. After removal of the carbamate and benzoylisothiocyanate condensation, the thiourea **6** was subjected to annelation and finally a regioselective sulfur methylation led to **8** in satisfying yields (Scheme 1). This methodology proved to be highly efficient and amenable to multigram scale to access the unique and challenging tricyclic structure in sufficient amounts to pursue the optimization of the (het)arylation process.

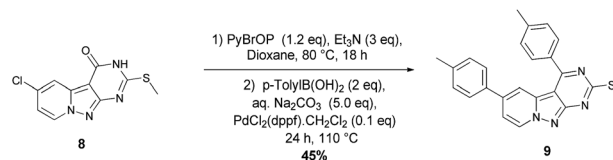
1. Suzuki–Miyaura arylation in C-6

The functionalization of the C-4 position of compound **8** was first attempted *via* a C–O direct activation involving PyBrOP¹¹ to generate the required *in situ* generated *O*-phosphonium leaving group (Scheme 2). However, this route proved to be unsuitable since only the disubstituted product **9** was isolated in 45% yield with no trace of the mono C-4-arylated molecule. This result seems to indicate that the 6-Cl atom is as reactive as the activated 4-O atom under palladium catalyzed conditions.

In an attempt to selectively substitute one of the two positions (C-6 or C-4), we began by the regioselective functionalization of the C-6 position. Using several experimental coupling Suzuki–Miyaura conditions exploited in our previous research,¹² this first test did not allow the formation of the C–C bond, as only the starting material **8** was recovered (Table 1, entry 1). The same behavior was observed using the conditions reported in Scheme 2, as if pyrimidinone exerted a negative impact on C-6 reactivity in basic and aqueous media.

To circumvent this problem, we switched the palladium source and tested the catalytic system XantPhos/Pd(OAc)₂.¹³ The reaction was carried out in dioxane under microwave irradiation at 150 °C using potassium carbonate as a base. To our delight these conditions provided the desired product **10** in 63% yield (Table 1, entry 3).

Next, the generalization of this approach was examined (Table 2). Results were found to be satisfactory as the majority of the boronic substrates employed provided the coupling products. Electron rich or deactivated aryl as well as naphthyl



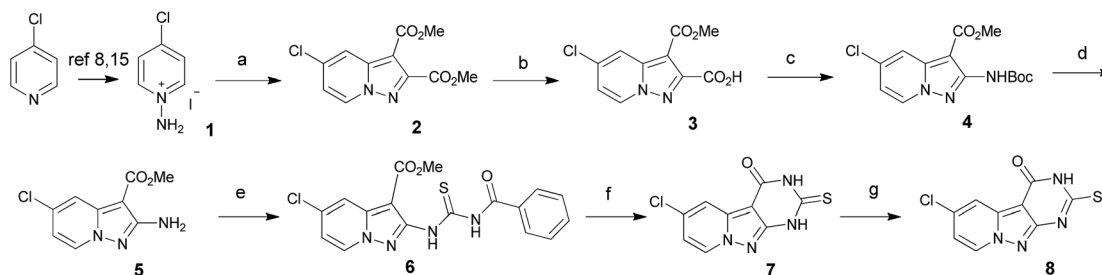
Scheme 2 Phosphonium-mediated Suzuki type cross coupling reaction from **8**.

residues were introduced with good yields ranging from 56 to 73%. In all cases a full conversion of starting material and formation of a unique product were observed. The decrease in yield was mainly due to difficulties encountered during purification steps.

2. (Het)arylations under direct C–O activation in C-4

After having regioselectively introduced the C-6 aryl group, the direct C-4 arylation *via* PyBrOP amid activation was undertaken, applying the operating conditions previously established for the synthesis of **9**.⁷ The reaction sequence involved first the activation of the C–O bond using Et₃N to favor the formation of the oxanion which was *in situ* quenched by PyBrOP (1.2 eq.) activating agent. The second step, which required the addition of boronic acid and PdCl₂(dppf)·CH₂Cl₂ as catalyst, was successfully achieved under thermal conditions. Initially, we carried out our investigations on **10**, **11** and **13** (Table 3), which carry an electro-donor aryl group in C-6. The coupling reactions were achieved with representative boronic acids. Aryl and thiophenyl groups were easily introduced (entries 1, 4, 5, 7, 8, 9). The decreases in yield of purified product are mainly due to the purification step. Some difficulties occurred with the deactivated fluorophenyl and pyridinyl groups (entries 2, 6). The reactions appear incomplete and the corresponding starting materials were recovered. All modifications of the experimental conditions were inefficient. In the pyridinyl series, the introduction of a strong electrodonor OMe group restored the reactivity (entry 3).


While all reactions were inefficient starting from **15** (entry 11), we were able to introduce the 4-cyanophenyl group on **14** (entry 10) and derivative **25** was formed with an average yield of 40% whereas 21% of starting material still remained



Scheme 1 Synthetic route for **8**: (a) DMAD (1.5 eq.), K₂CO₃ (1.4 eq.), DMF, r.t., 12 h, 86%; (b) NaOH (2N) (1.0 eq.), CH₃OH, r.t., 6 h, 81%; (c) (i) Et₃N (1.3 eq.), ClCO₂Et (1.5 eq.), THF, −10 °C, 1.5 h, (ii) NaN₃ (1.7 eq.), −10 °C, 1.5 h, (iii) *t*-butanol, 6 h, 67%; (d) TFA/CH₂Cl₂ (1/1), 4 h, r.t., quant.; (e) benzoylisothiocyanate (1.2 eq.), CHCl₃, 12 h, r.t., 84%; (f) EtONa (1.1 eq.), EtOH, 8 h, reflux, 97%; (g) MeI (1.0 eq.), NaOH (1.0 eq.), EtOH, 6 h, r.t., 80%.

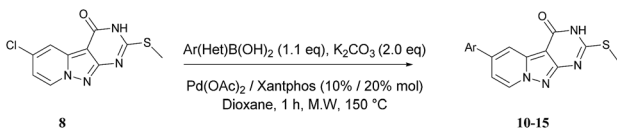


Table 1 Suzuki–Miyaura conditions for C-6 reaction of **8**

			Yield in 10 (%)
Entry	Conditions		
1	<i>p</i> -TolylB(OH) ₂ (1.2 eq.), DME/H ₂ O (2/1), Na ₂ CO ₃ (2 eq.), Pd(PPh ₃) ₄ (5% mol), 30 min, M.W, 120 °C		ND ^a
2	<i>p</i> -TolylB(OH) ₂ (1.1 eq.), 1,4-dioxane/H ₂ O (4/1), Na ₂ CO ₃ (3.0 eq.), PdCl ₂ (dppf)·CH ₂ Cl ₂ (10% mol), 1 h/M.W, 150 °C		ND ^a
3	<i>p</i> -TolylB(OH) ₂ (1.1 eq.), 1,4-dioxane, K ₂ CO ₃ (2.0 eq.), Pd(OAc) ₂ /xantphos (10%/20% mol), 1 h/M.W, 150 °C		63 ^b

^a Not detected. Starting material **8** was recovered at the end of the reaction. ^b Yield is indicated as isolated compound.

Table 2 Exemplification of Suzuki–Miyaura cross coupling in C-6 from **8**

			
Entry	Ar	Compound	Yields ^a (%)
1		10	63
2		11	73
3		12	68
4		13	70
5		14	66
6		15	56

^a Yields are indicated as isolated compounds.

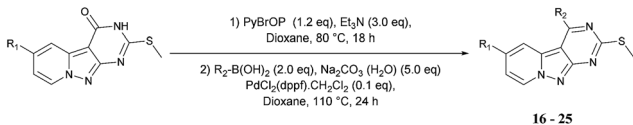
unchanged after 24 h. In order to improve the overall conversion, a longer reaction time (72 h), was used but degradation occurred.

Based on the results obtained, we can conclude that the electronic properties of the C-6 aryl moieties strongly affect the reactivity of the C-4 position. The best conversions were always obtained with the simultaneous presence of electron donor substituents (mesomeric or inductive effect) on the C-6 position as well as on the boronic acid used.

3. (Het)arylations under Liebeskind–Srogl in C-2

We next applied the third Liebeskind–Srogl¹⁴ method to the 4,6-bis(het)arylated derivatives in an attempt to furnish original

Table 3 Exemplification of amid direct arylation in C-4

				
Entry	Substrate	Boronic acids	Product	Yield ^a (%) (SM%) ^b
1	10		16	55
2			17	47 ^c (28)
3			18	64 ^c
4	11		19	78
5			20	70
6			21	36 (46)
7	13		22	63
8			23	61
9			24	52
10	14		25	40 (21), 33 ^e
11	15		—	ND ^d

^a Yields are indicated as isolated compounds. ^b SM starting material recovered. ^c Reaction time of the second step 48 h. ^d ND: Not detected. ^e Reaction time of the second step 72 h.

2,4,6-trisubstituted compounds. The reactivity of the three thiophenes **18**, **19**, and **22** was explored in the presence of boronic acids, using an (het)arylboronic acid in the presence of Pd(PPh₃)₄ and copper(i) thiophene-2-carboxylate (CuTC) in THF at 100 °C under microwave irradiation.⁷ To our great



Table 4 Exemplification of the Liebeskind–Srogl arylation in C-2

Entry	Substrate	Final compound	Yield (%) ^a
1	18		70
2	19		78
3	22		61

^a Yields are indicated as isolated compounds.

satisfaction, the first test using 4-methoxyphenyl boronic acid as coupling partner gave **26** in a good 70% yield (Table 4). By changing both starting precursors (**19** and **22**) and the coupling partners, the tri-substituted tricycles **27** and **28** were readily isolated with 78% and 61% yields respectively (Table 4). The efficiency of this last reaction in C-2 seems insensitive to the nature of the 4,6-bis(het)arylated derivatives and boronic acids used.

Conclusions

In summary, we have described in this work several synthetic pathways for the preparation of a new pyrido[1',2':1,5]pyrazolo[3,4-d]pyrimidine scaffold, and have build several libraries of C-2, C-4, C-6 (het)arylated pyrido[1',2':1,5]pyrazolo[3,4-d]pyrimidines. First, the C-6 chlorine atom was substituted using a Suzuki–Miyaura cross coupling reaction. The resulting C-6-arylated products were engaged in a direct C–O activation from an amide function with PyBroP activation followed by a palladium catalyzed reaction to produce a series of C-4,6 bis-(het)arylated compounds. We proved that electron criteria governed the reactivity and efficiency. Finally, the 2-SMe residual function reacted under Liebeskind–Srogl conditions to afford the desired tri-substituted derivatives. The efficiency of the global sequence involving three successive and

unprecedented cross coupling reactions will certainly prove useful to others in the future to develop poly functionalized heterocyclic PPPY series.

Experimental

Reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. Compounds were visualized by UV irradiation. Flash column chromatography was performed on silica gel 60 (230–400.13 mesh, 0.040 0.063 mm). Melting points (Mp [°C]) were taken on samples in open capillary tubes and are uncorrected. The infrared spectra of compounds, recorded on a Thermo Scientific Nicolet iS10, are given in cm^{−1}. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance II 250 (¹³C, 63 MHz), Bruker Avance 400 (¹³C, 101 MHz), or on a Bruker Avance III HD nanobay 400 (¹³C, 101 MHz). Chemical shifts are given in parts per million from tetramethylsilane (TMS) as internal standard. Coupling constants (*J*) are reported in hertz (Hz). High-resolution mass spectra (HRMS) were performed on a Maxis Bruker 4G.

4. Characterization data

1-Amino-4-chloro-pyridinium iodide 1:⁹ In a 50 mL round bottom flask, 4-chloropyridine hydrochloride (3.48 g, 23.2 mmol, 1.0 eq.) was placed in water (10 mL). The solution was cooled at 0–5 °C under stirring, then sodium bicarbonate (4.48 g, 46.4 mmol, 2.0 eq.) was added carefully over 10 min. After 30 min, the mixture was extracted with CH₂Cl₂ (3 × 10 mL), dried over Na₂SO₄, and filtered. The filtrate was placed in a 50 mL round bottom flask, and a solution of *O*-(mesitylene-sulfonyl)hydroxylamine (MSH)¹⁵ (5.0 g, 23.2 mmol, 1.0 eq.) in CH₂Cl₂ (10 mL) was added (after drying over Na₂SO₄). The mixture was stirred overnight at room temperature under inert atmosphere and an aqueous HI solution was added (4 mL, 45%) and stirred for 30 min. The resulting solution was kept in a refrigerator to crystallize the desired compound **1** as orange crystals (2.12 g, 35%). Mp 145–146 °C; *R*_f (petroleum ether : EtOAc, 4 : 6) = 0.1; IR (ATR diamond, cm^{−1}) ν 833, 950, 1119, 1471, 1607, 3054, 3167; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.18 (d, *J* = 7.0 Hz, 2H), 8.46 (s, 2H, NH₂), 8.76 (d, *J* = 7.0 Hz, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 128.2 (2 × CH), 139.4 (2 × CH), 145.4 (Cq); HRMS (ESI) [*M* + *H*]⁺ calcd for C₅H₇ClN₂: 129.0214, found: 129.0214.

Dimethyl 5-chloropyrazolo[1,5-*a*]pyridine-2,3-dicarboxylate 2. To a stirred solution of 1-amino-4-chloropyridin-1-ium iodide **1** (0.8 g, 3.11 mmol, 1.0 eq.) in DMF (10 mL) were added K₂CO₃ (0.6 g, 4.36 mmol, 1.4 eq.) and dimethyl acetylenedicarboxylate (0.66 g, 4.6 mmol, 1.5 eq.). The mixture was stirred at room temperature for 18 h. The solvent was evaporated under reduced pressure, the residue was purified by flash chromatography (petroleum ether : EtOAc, 5 : 5) to give **2** as yellow crystals (523 mg, 86%). Mp 120–121 °C; *R*_f (petroleum ether : EtOAc, 4 : 6) = 0.87; IR (ATR diamond, cm^{−1}) ν 724, 811, 862, 1093, 1217, 1357, 1510, 1689, 3085; ¹H NMR (400 MHz, CDCl₃) δ 3.94 (s, 3H, CH₃), 4.03 (s, 3H, CH₃), 7.02 (dd, *J* = 7.3, 2.3 Hz, 1H), 8.16 (d, *J* = 2.3 Hz, 1H), 8.43 (d, *J* = 7.3 Hz, 1H); ¹³C



NMR (101 MHz, DMSO- d_6) δ 51.8 (CH₃), 53.0 (CH₃), 102.7 (Cq), 116.7 (CH), 118.7 (CH), 129.7 (CH), 135.2 (Cq), 141.5 (Cq), 148.1 (Cq), 162.0 (CO), 162.7 (CO); HRMS (ESI) [M + H]⁺ calcd for C₁₁H₁₀ClN₂O₄: 269.0324, found: 269.0321.

5-Chloro-3-(methoxycarbonyl)pyrazolo[1,5-*a*]pyridine-2-carboxylic acid 3. To a mixture of 2 (0.5 g, 1.86 mmol, 1.0 eq.) in MeOH (60 mL) was added NaOH (2N) (2.1 mmol) in one portion. The solution was stirred at room temperature for 6 h, and then the solvent was removed. The residue was dissolved in H₂O (100 mL) and the mixture was acidified to pH 1 using a 10% aqueous HCl solution. The resulting solid was collected by filtration, washed with Et₂O (20 mL), and dried under reduced pressure to give 3 (383 mg, 81%) as a white solid. Mp 238–239 °C; *R*_f (petroleum ether : EtOAc, 2 : 8) = 0.1; IR (ATR diamond, cm^{−1}) ν 664, 764, 856, 1105, 1209, 1379, 1480, 1621, 1750, 2651, 3083; ¹H NMR (400 MHz, CDCl₃) δ 4.15 (s, 3H, CH₃), 7.17 (dd, *J* = 7.3, 2.3 Hz, 1H), 8.14 (d, *J* = 2.3 Hz, 1H), 8.64 (d, *J* = 7.3 Hz, 1H), 14.34 (s, 1H, OH); ¹³C NMR (101 MHz, DMSO- d_6) δ 52.1 (CH₃), 100.8 (Cq), 126.9 (CH), 127.8 (CH), 131.8 (CH), 135.1 (Cq), 140.8 (Cq), 150.4 (Cq), 132.3 (CO), 134.2 (CO); HRMS (ESI) [M + H]⁺ calcd for C₁₀H₈ClN₂O₄: 255.0167 [M + H]⁺, found: 255.0164.

Methyl-2-((*tert*-butoxycarbonyl)amino)-5-chloropyrazolo[1,5-*a*]pyridine-3-carboxylate 4. Starting from acid 3 (1.0 g, 3.92 mmol, 1.0 eq.), compound 4 was prepared following the procedure described in ref. 7 after purification by flash chromatography on silica gel (petroleum ether : EtOAc, 5 : 5) as a white solid (0.857 g, 67%). Mp 188–190 °C; *R*_f (petroleum ether : EtOAc, 4 : 6) = 0.8; IR (ATR diamond, cm^{−1}) ν 779, 850, 1123, 1221, 1268, 1369, 1434, 1534, 1685, 2980, 3338; ¹H NMR (400 MHz, CDCl₃) δ 1.55 (s, 9H, 3 × CH₃), 3.96 (s, 3H, CH₃), 6.86 (dd, *J* = 7.3, 2.3 Hz, 1H), 7.85 (d, *J* = 2.3 Hz, 1H), 8.44 (d, *J* = 7.3 Hz, 1H), 8.97 (s, 1H, NH); ¹³C NMR (101 MHz, CDCl₃) δ 28.6 (3 × CH₃), 51.9 (CH₃), 82.1 (Cq), 90.0 (Cq), 114.9 (CH), 117.1 (CH), 130.5 (CH), 135.9 (Cq), 140.8 (Cq), 151.1 (Cq), 154.1 (CO), 165.1 (CO); HRMS (ESI) [M + H]⁺ calcd for C₁₄H₁₇ClN₃O₄: 326.0902 [M + H]⁺, found: 326.0901.

Methyl 2-amino-5-chloropyrazolo[1,5-*a*]pyridine-3-carboxylate 5. Starting from Boc-aminoester 4 (0.5 g, 1.53 mmol, 1.0 eq.), compound 5 was prepared following the procedure described in ref. 7 as a white solid in quantitative yield. Mp 196–197 °C; *R*_f (petroleum ether : EtOAc, 4 : 6) = 0.67; IR (ATR diamond, cm^{−1}) ν 776, 864, 1009, 1112, 1280, 1437, 1620, 1678, 3104, 3422; ¹H NMR (400 MHz, CDCl₃) δ 3.92 (s, 3H, CH₃), 5.26 (s, 2H, NH₂), 6.75 (dd, *J* = 7.3, 2.3 Hz, 1H), 7.78 (d, *J* = 2.3 Hz, 1H), 8.11 (d, *J* = 7.3 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 51.0 (CH₃), 87.8 (Cq), 113.4 (CH), 116.2 (CH), 128.7 (CH), 134.3 (Cq), 141.8 (Cq), 160.3 (Cq), 164.7 (CO); HRMS (ESI) [M + H]⁺ calcd for C₉H₉ClN₃O₂: 226.0378 [M + H]⁺, found: 226.0375.

Methyl 2-(3-benzoylthioureido)-5-chloropyrazolo[1,5-*a*]pyridine-3-carboxylate 6. Starting from aminoester 5 (1.0 g, 4.43 mmol, 1.0 eq.), compound 6 was prepared following the procedure described in ref. 7 after purification by flash chromatography on silica gel (petroleum ether : EtOAc, 4 : 6) as a yellow solid (1.44 g, 84%). Mp 201–202 °C; *R*_f (petroleum ether : EtOAc, 4 : 6) = 0.90; IR (ATR diamond, cm^{−1}) ν 698, 807, 1006, 1112, 1156, 1303, 1435, 1529, 1678, 3040; ¹H NMR (400 MHz, CDCl₃) δ 4.05

(s, 3H, CH₃), 6.95 (dd, *J* = 7.3, 2.3 Hz, 1H), 7.59–7.47 (m, 2H), 7.71–7.62 (m, 1H), 7.98 (d, *J* = 7.3 Hz, 2H), 8.04 (d, *J* = 2.3 Hz, 1H), 8.49 (d, *J* = 7.3 Hz, 1H), 9.27 (s, 1H, NH), 13.85 (s, 1H, NH); ¹³C NMR (101 MHz, CDCl₃) δ 52.2 (CH₃), 93.45 (Cq), 115.7 (CH), 117.8 (CH), 128.1 (2 × CH), 129.5 (2 × CH), 130.6 (Cq), 131.9 (CH), 134.1 (Cq), 136.1 (CH), 141.2 (Cq), 152.3 (Cq), 163.9 (CO), 165.9 (CO), 176.6 (CS); HRMS (ESI) [M + H]⁺ calcd for C₁₇H₁₄ClN₄O₃S: 289.0470 [M + H]⁺, found: 389.0468.

6-Chloro-2-thioxo-2,3-dihydropyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidin-4(1*H*)-one 7. Starting from thiourea 6 (1 g, 2.57 mmol), compound 7 was obtained following the procedure described in ref. 7 as a white solid (0.63 g, 97%). Mp > 360 °C; *R*_f (petroleum ether : EtOAc, 4 : 6) = 0.10; IR (ATR diamond, cm^{−1}) ν 764, 824, 1106, 1208, 1379, 1480, 1621, 1750, 2652, 3083; ¹H NMR (400 MHz, DMSO- d_6) δ 7.36 (dd, *J* = 7.3, 2.3 Hz, 1H), 7.92 (d, *J* = 2.3 Hz, 1H), 8.95 (d, *J* = 7.3 Hz, 1H), 12.15 (s, 1H, NH), 13.36 (s, 1H, NH); ¹³C NMR (101 MHz, DMSO- d_6) δ 92.8 (Cq), 115.9 (CH), 116.9 (CH), 132.1 (CH), 135.6 (Cq), 138.6 (Cq), 154.4 (Cq), 157.0 (CO), 177.0 (CS); HRMS (ESI) [M + H]⁺ calcd for C₉H₆ClN₄O₂S: 252.9945 [M + H]⁺, found: 252.9942.

6-Chloro-2-(methylthio)pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidin-4(3*H*)-one 8. Starting from compound 7 (0.5 g, 1.97 mmol, 1.0 eq.) and following the procedure described in ref. 7, with a reaction time adjusted to 6 h, compound 8 was obtained as a white solid (0.422 g, 80%). Mp 248–249 °C; *R*_f (petroleum ether : EtOAc, 4 : 6) = 0.57; IR (ATR diamond, cm^{−1}) ν 648, 782, 861, 1121, 1252, 1432, 1522, 1635, 2820, 3033; ¹H NMR (400 MHz, DMSO- d_6) δ 2.58 (s, 3H, CH₃), 7.38 (dd, *J* = 7.3, 2.3 Hz, 1H), 8.00 (d, *J* = 2.3 Hz, 1H), 8.96 (d, *J* = 7.3 Hz, 1H), 12.37 (s, 1H, NH); ¹³C NMR (101 MHz, DMSO- d_6) δ 13.4 (CH₃), 94.8 (Cq), 116.6 (CH), 117.0 (CH), 131.6 (CH), 134.0 (Cq), 138.0 (Cq), 158.7 (Cq), 161.9 (Cq), 162.4 (CO); HRMS (ESI) [M + H]⁺ calcd for C₁₀H₈ClN₄O₂S: 267.0102 [M + H]⁺, found: 267.0100.

5. General procedure A for Suzuki–Miyaura cross coupling reaction

A solution of compound 8 (100 mg, 0.37 mmol, 1.0 eq.) in 1,4-dioxane (4 mL) was degassed by argon bubbling. Potassium carbonate (103 mg, 0.74 mmol, 2.0 eq.), boronic acid (1.1 eq.), xantphos (43 mg, 0.074 mmol, 0.2 eq.) and Pd(OAc)₂ (8.0 mg, 0.037 mmol, 0.1 eq.) were then added and the reaction mixture was heated to 150 °C for 1 h under microwave irradiation. The crude material was concentrated under reduced pressure, and the residue was diluted in CH₂Cl₂ (10 mL). The organic layers were washed with water (10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was then purified by flash chromatography on silica to provide the desired compounds 10–15.

6. General procedure B for the palladium catalyzed direct cross-coupling reactions involving a PyBroP-mediated C–O activation

A suitable compound 10–11, 13–15 and PyBroP (1.2 eq.) were dissolved in 1,4-dioxane (4 mL) and Et₃N (3.0 eq.) was then added. Under stirring, the mixture was degassed by argon bubbling for 10 min and then heated at 80 °C for 18 h. After



cooling, the required (het)arylboronic acid (2.0 eq.), Na₂CO₃ (5.0 eq.) in H₂O (1 mL) and PdCl₂(dppf)·CH₂Cl₂ (10 mol%) were added. After heating at 110 °C for 24 hours generally, volatiles were removed under reduced pressure and the crude material diluted in CH₂Cl₂ (20 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered, concentrated under reduced pressure, and purified by chromatography on silica gel to give the desired bis-arylated compounds **16–25**.

7. General procedure C for Liebeskind–Srogl cross-coupling reaction

A microwave vial with THF (4 mL) under inert atmosphere was charged with the corresponding 4,6-bis(het)aryl-2-(methylthio)-6-arylpyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidines **18**, **19** or **22**, the corresponding aryl boronic acid (1.5 eq.), CuTC (3.0 eq.), and Pd(PPh₃)₄ (10 mol%). The mixture was heated under microwave irradiation at 100 °C for 1 h 30 min. After cooling to r.t., the solvent was removed under reduced pressure, the residue was diluted in aq. satd NaHCO₃ solution (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried with MgSO₄, filtered, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel to provide the desired products **26–28**.

2-(Methylthio)-4,6-di-*p*-tolylpyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidine 9. Starting from product **8** (50 mg, 0.18 mmol, 1.0 eq.) following the procedure **B**, using *p*-tolylboronic acid (49 mg, 0.36 mmol, 2.0 eq.), compound **9** was obtained after purification by flash chromatography on silica gel (petroleum ether : EtOAc, 6 : 4) as a white solid (33 mg, 45%). Mp 222–223 °C; *R*_f (petroleum ether : EtOAc, 4 : 6) = 0.80; IR (ATR diamond, cm^{−1}) ν 796, 1005, 1163, 1244, 1452, 1578, 1641, 2919; ¹H NMR (400 MHz, CDCl₃) δ 2.42 (s, 3H, CH₃), 2.50 (s, 3H, CH₃), 2.74 (s, 3H, CH₃), 7.31 (d, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.56–7.49 (m, 1H), 7.86 (d, *J* = 7.8 Hz, 2H), 8.16 (s, 1H), 8.83 (d, *J* = 7.3 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 14.5 (S-CH₃), 21.2 (CH₃), 21.6 (CH₃), 101.9 (Cq), 115.9 (CH), 116.8 (CH), 126.7 (2 × CH), 128.8 (2 × CH), 129.5 (2 × CH), 129.5 (CH), 129.6 (Cq), 130.1 (2 × CH), 134.6 (Cq), 134.7 (Cq), 136.0 (Cq), 139.3 (Cq), 139.9 (Cq), 141.3 (Cq), 163.5 (Cq), 172.2 (Cq); HRMS (ESI) [M + H]⁺ calcd for C₂₄H₂₁N₄S: 397.1481 [M + H]⁺, found: 397.1481.

2-(Methylthio)-6-(*p*-tolyl)pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidin-4(3*H*)-one 10. Following the general procedure **A** using *p*-tolylboronic acid (57 mg, 0.41 mmol, 1.1 eq.), compound **10** was obtained after purification by flash chromatography on silica gel (petroleum ether : EtOAc, 5 : 5) as a white solid (76 mg, 63%). Mp 302–303 °C; *R*_f (petroleum ether : EtOAc, 4 : 6) = 0.62; IR (ATR diamond, cm^{−1}) ν 666, 783, 873, 1001, 1122, 1210, 1363, 1447, 1580, 1643, 2829; ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.39 (s, 3H, CH₃), 2.59 (s, 3H, CH₃), 7.36 (d, *J* = 7.8 Hz, 2H), 7.63 (dd, *J* = 7.3, 2.3 Hz, 1H), 7.87–7.70 (m, 2H), 8.14 (d, *J* = 2.3 Hz, 1H), 8.95 (d, *J* = 7.3 Hz, 1H), 12.34 (s, 1H, NH); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 13.4 (CH₃), 21.2 (S-CH₃), 94.7 (Cq), 113.5 (CH), 114.9 (CH), 127.2 (2 × CH), 130.3 (2 × CH), 130.4 (CH), 134.3 (Cq), 138.1 (Cq), 139.3 (Cq), 140.1 (Cq), 158.8 (Cq), 161.7 (Cq),

161.85 (CO); HRMS (ESI) [M + H]⁺ calcd for C₁₇H₁₅N₄O₂S: 323.0961 [M + H]⁺, found: 323.0961.

6-(4-Methoxyphenyl)-2-(methylthio)pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidin-4(3*H*)-one 11. Following the general procedure **A** using *p*-methoxyphenylboronic acid (62 mg, 0.41 mmol, 1.1 eq.), compound **11** was obtained after purification by flash chromatography on silica gel (petroleum ether : EtOAc, 5 : 5) as a white solid (92 mg, 73%). Mp 295–296 °C; *R*_f (petroleum ether : EtOAc, 4 : 6) = 0.50; IR (ATR diamond, cm^{−1}) ν 956, 1033, 1113, 1251, 1453, 1518, 1661, 2835; ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.59 (s, 3H, CH₃), 3.84 (s, 3H, CH₃), 7.18–6.99 (m, 2H), 7.61 (dd, *J* = 7.3, 2.3 Hz, 1H), 7.91–7.76 (m, 2H), 8.10 (d, *J* = 2.3 Hz, 1H), 8.92 (d, *J* = 7.3 Hz, 1H), 12.31 (s, 1H, NH); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 12.9 (S-CH₃), 55.3 (O-CH₃), 94.1 (Cq), 112.4 (CH), 114.3 (CH), 114.7 (2 × CH), 128.2 (2 × CH), 128.9 (Cq), 129.9 (CH), 137.7 (Cq), 139.4 (Cq), 158.3 (Cq), 160.1 (Cq), 161.2 (Cq), 161.3 (CO); HRMS (ESI) [M + H]⁺ calcd for C₁₇H₁₅N₄O₂S: 339.0910 [M + H]⁺, found: 339.0909.

6-(3-Methoxyphenyl)-2-(methylthio)pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidin-4(3*H*)-one 12. Following the general procedure **A** using *m*-methoxyphenylboronic acid (62 mg, 0.41 mmol, 1.1 eq.), compound **12** was obtained after purification by flash chromatography on silica gel (petroleum ether : EtOAc, 5 : 5) as a white solid (86 mg, 68%). Mp 266–267 °C; *R*_f (petroleum ether : EtOAc, 4 : 6) = 0.57; IR (ATR diamond, cm^{−1}) ν 775, 863, 1054, 1170, 1455, 1578, 1667, 2833; ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.59 (s, 3H, CH₃), 3.87 (s, 3H, CH₃), 7.06 (d, *J* = 7.8 Hz, 1H), 7.37 (s, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.64 (dd, *J* = 7.3, 2.3 Hz, 1H), 8.16 (d, *J* = 2.3 Hz, 1H), 8.97 (d, *J* = 7.3 Hz, 1H), 12.35 (s, 1H, NH); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 13.4 (S-CH₃), 55.7 (O-CH₃), 94.9 (Cq), 112.2 (CH), 114.2 (CH), 115.3 (CH), 115.4 (CH), 119.7 (CH), 130.4 (CH), 130.8 (CH), 138.0 (Cq), 138.8 (Cq), 140.1 (Cq), 158.8 (Cq), 160.3 (Cq), 161.8 (Cq), 161.9 (CO); HRMS (ESI) [M + H]⁺ calcd for C₁₇H₁₅N₄O₂S: 339.0910 [M + H]⁺, found: 339.0907.

2-(Methylthio)-6-(naphthalen-2-yl)pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidin-4(3*H*)-one 13. Following the general procedure **A** using 2-naphthylboronic acid (71 mg, 0.41 mmol, 1.1 eq.), compound **13** was obtained after purification by flash chromatography on silica gel (petroleum ether : EtOAc, 5 : 5) as a white solid (94 mg, 70%). Mp 311–312 °C; *R*_f (petroleum ether : EtOAc, 4 : 6) = 0.65; IR (ATR diamond, cm^{−1}) ν 746, 803, 960, 1181, 1475, 1582, 1644, 1739, 3044; ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.60 (s, 3H, CH₃), 7.71–7.51 (m, 2H), 7.80 (dd, *J* = 7.3, 2.3 Hz, 1H), 8.00 (dd, *J* = 9.9, 6.2 Hz, 2H), 8.10 (dd, *J* = 9.3, 4.5 Hz, 2H), 8.33 (d, *J* = 2.3 Hz, 1H), 8.49 (d, *J* = 2.0 Hz, 1H), 9.03 (d, *J* = 7.3 Hz, 1H), 12.38 (s, 1H, NH); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 13.4 (S-CH₃), 94.9 (Cq), 114.3 (CH), 115.2 (CH), 124.9 (CH), 126.8 (CH), 127.2 (CH), 127.45 (CH), 128.0 (CH), 129.05 (CH), 129.4 (CH), 130.5 (CH), 133.4 (Cq), 133.6 (Cq), 134.5 (Cq), 138.1 (Cq), 139.9 (Cq), 158.8 (Cq), 161.8 (CO), 161.9 (CO); HRMS (ESI) [M + H]⁺ calcd for C₂₀H₁₅N₄O₂S: 359.0961 [M + H]⁺, found: 359.0959.

6-(4-Fluorophenyl)-2-(methylthio)pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidin-4(3*H*)-one 14. Following the general procedure **A** using *p*-fluorophenylboronic acid (57 mg, 0.41 mmol, 1.1 eq.), compound **14** was obtained after purification by flash



chromatography on silica gel (petroleum ether : EtOAc, 5 : 5) as a white solid (80 mg, 66%). Mp 319–320 °C; R_f (petroleum ether : EtOAc, 4 : 6) = 0.62; IR (ATR diamond, cm^{-1}) ν 658, 784, 870, 1107, 1233, 1445, 1647, 2819; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 2.59 (s, 3H, CH_3), 7.37 (t, J = 8.6 Hz, 2H), 7.61 (dd, J = 7.3, 2.3 Hz, 1H), 7.99–7.88 (m, 2H), 8.13 (d, J = 2.3 Hz, 1H), 8.96 (d, J = 7.3 Hz, 1H), 12.34 (s, 1H, NH); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 13.4 (S- CH_3), 94.8 (Cq), 114.0 (CH), 115.0 (CH), 116.6 (d, $^2J_{\text{C-F}}$ = 21.6 Hz, 2 \times CH), 129.7 (d, $^3J_{\text{C-F}}$ = 8.5 Hz, 2 \times CH), 130.4 (CH), 133.8 (d, $^4J_{\text{C-F}}$ = 3.1 Hz, Cq), 138.0 (Cq), 139.1 (Cq), 158.8 (Cq), 161.8 (Cq), 161.8 (CO), 163.2 (d, $^1J_{\text{C-F}}$ = 247 Hz, CF); HRMS (ESI) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{12}\text{FN}_4\text{OS}$: 327.0710 $[\text{M} + \text{H}]^+$, found: 327.0710.

2-(Methylthio)-6-(4-(trifluoromethyl)phenyl)pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidin-4(3*H*)-one 15. Following the general procedure **A** using *p*-trifluorophenylboronic acid (78 mg, 0.41 mmol, 1.1 eq.), compound **15** was obtained after purification by flash chromatography on silica gel (petroleum ether : EtOAc, 5 : 5) as a white solid (79 mg, 56%). Mp 342–343 °C; R_f (petroleum ether : EtOAc, 4 : 6) = 0.66; IR (ATR diamond, cm^{-1}) ν 811, 1015, 1109, 1330, 1574, 1650, 2833, 3044; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 2.58 (s, 3H, CH_3), 7.67 (dd, J = 7.3, 2.3 Hz, 1H), 7.87 (d, J = 8.0 Hz, 2H), 8.08 (d, J = 8.0 Hz, 2H), 8.21 (d, J = 2.3 Hz, 1H), 9.00 (d, J = 7.3 Hz, 1H), 12.38 (s, 1H, NH); ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 12.9 (S- CH_3), 94.7 (Cq), 114.4 (CH), 114.5 (CH), 124.1 (q, $^1J_{\text{C-F}_3}$ = 272 Hz, CF_3), 126.0 (q, $^3J_{\text{C-F}_3}$ = 3.3 Hz, 2 \times CH), 127.8 (2 \times CH), 129.4 (q, $^2J_{\text{C-F}_3}$ = 32 Hz, Cq), 130.2 (CH), 137.3 (Cq), 137.8 (Cq), 140.8 (Cq), 158.3 (Cq), 161.4 (Cq), 161.5 (CO); HRMS (ESI) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{12}\text{F}_3\text{N}_4\text{OS}$: 377.0678 $[\text{M} + \text{H}]^+$, found: 377.0676.

4-(4-Methoxyphenyl)-2-(methylthio)-6-(*p*-tolyl)pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidine 16. Starting from product **10** (50 mg, 0.15 mmol, 1.0 eq.), following the general procedure **B**, using *p*-methoxyphenylboronic acid (47 mg, 0.31 mmol, 2.0 eq.), compound **16** was obtained after purification by flash chromatography on silica gel (petroleum ether : EtOAc, 6 : 4) as a yellow solid (35 mg, 55%). Mp 266–267 °C; R_f (petroleum ether : EtOAc, 4 : 6) = 0.85; IR (ATR diamond, cm^{-1}) ν 775, 846, 1023, 1118, 1444, 1577, 1653, 2976; ^1H NMR (400 MHz, CDCl_3) δ 2.43 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 3.93 (s, 3H, CH_3), 7.12 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H), 7.50 (d, J = 7.8 Hz, 2H), 7.56 (dd, J = 7.3 Hz, 1H), 7.95 (d, J = 8.5 Hz, 2H), 8.20 (s, 1H), 8.85 (d, J = 7.3 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 14.6 (S- CH_3), 21.3 (CH_3), 55.7 (CH_3), 101.9 (Cq), 114.4 (2 \times CH), 115.9 (CH), 117.1 (CH), 126.9 (2 \times CH), 129.6 (Cq), 129.8 (CH), 130.3 (2 \times CH), 130.7 (2 \times CH), 134.7 (Cq), 136.3 (Cq), 139.6 (Cq), 140.3 (Cq), 162.2 (Cq), 162.9 (Cq), 163.5 (Cq), 171.8 (Cq); HRMS (ESI) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{21}\text{N}_4\text{OS}$: 413.1431 $[\text{M} + \text{H}]^+$, found: 413.1430.

4-(4-Fluorophenyl)-2-(methylthio)-6-(*p*-tolyl)pyrido[1',2':1,5]pyrazole[3,4-*d*]pyrimidine 17. Starting from product **10** (50 mg, 0.15 mmol, 1.0 eq.), following the general procedure **B**, using *p*-fluorophenylboronic acid (43 mg, 0.31 mmol, 2.0 eq.), (reaction time of the second step 48 h), compound **17** was obtained after purification by flash chromatography on silica gel (petroleum ether : EtOAc, 6 : 4) as a yellow solid (29 mg, 47%). Mp 225–226 °C; R_f (petroleum ether : EtOAc, 4 : 6) = 0.89; IR (ATR diamond, cm^{-1}) ν 799, 870, 1121, 1450, 1559, 1636, 1732, 2921;

^1H NMR (400 MHz, CDCl_3) δ 2.45 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 7.39–7.28 (m, 4H), 7.50 (d, J = 7.8 Hz, 2H), 7.58 (dd, J = 7.3, 2.3 Hz, 1H), 8.02–7.96 (m, 2H), 8.09 (d, J = 2.3 Hz, 1H), 8.87 (d, J = 7.3 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 14.4 (CH_3), 21.2 (S- CH_3), 101.8 (Cq), 115.5 (CH), 116.0 (d, $^2J_{\text{C-F}}$ = 21.8 Hz, 2 \times CH), 117.0 (CH), 126.7 (2 \times CH), 129.7 (CH), 130.2 (2 \times CH), 130.9 (d, $^3J_{\text{C-F}}$ = 8.7 Hz, 2 \times CH), 133.7 (d, $^4J_{\text{C-F}}$ = 3.2 Hz, Cq), 134.4 (Cq), 135.8 (Cq), 139.5 (Cq), 140.2 (Cq), 162.2 (Cq), 163.4 (Cq), 164.4 (d, $^1J_{\text{C-F}}$ = 248 Hz, CF), 172.2 (Cq); HRMS (ESI) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{18}\text{FN}_4\text{S}$: 401.1231 $[\text{M} + \text{H}]^+$, found: 401.1231.

4-(6-Methoxypyridin-3-yl)-2-(methylthio)-6-(*p*-tolyl)pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidine 18. Starting from product **10** (50 mg, 0.15 mmol, 1.0 eq.), following the general procedure **B**, using 6-methoxy-3-pyridinylboronic acid (47 mg, 0.31 mmol, 2.0 eq.), with a 48 h reaction time for the second step, compound **18** was obtained after purification by flash chromatography on silica gel (petroleum ether : EtOAc, 4 : 6) as a yellow solid (30 mg, 64%). Mp 230–231 °C; R_f (petroleum ether : EtOAc, 4 : 6) = 0.82; IR (ATR diamond, cm^{-1}) ν 798, 870, 1010, 1165, 1285, 1449, 1494, 1636, 2925; ^1H NMR (400 MHz, CDCl_3) δ 2.43 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 4.07 (s, 3H, CH_3), 6.98 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 7.8 Hz, 2H), 7.59–7.49 (m, 3H), 8.12 (s, 1H), 8.19 (d, J = 8.8 Hz, 1H), 8.81 (d, J = 2.3 Hz, 1H), 8.85 (d, J = 7.3 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 14.6 (CH_3), 21.3 (S- CH_3), 54.1 (O- CH_3), 101.9 (Cq), 111.4 (CH), 115.6 (CH), 117.2 (CH), 126.9 (Cq), 126.9 (2 \times CH), 129.8 (CH), 130.2 (2 \times CH), 134.5 (Cq), 135.9 (Cq), 139.2 (CH), 139.6 (Cq), 140.5 (Cq), 147.9 (CH), 160.7 (Cq), 163.5 (Cq), 165.9 (Cq), 172.3 (Cq); HRMS (ESI) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{20}\text{N}_5\text{OS}$: 414.1383 $[\text{M} + \text{H}]^+$, found: 414.1381.

6-(4-Methoxyphenyl)-2-(methylthio)-4-(*p*-tolyl)pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidine 19. Starting from product **11** (50 mg, 0.147 mmol, 1.0 eq.), following the general procedure **B**, using *p*-tolylboronic acid (40 mg, 0.295 mmol, 2.0 eq.), compound **19** was obtained after purification by flash chromatography on silica gel (petroleum ether : EtOAc, 4 : 6) as a yellow solid (47 mg, 78%). Mp 209–210 °C; R_f (petroleum ether : EtOAc, 4 : 6) = 0.39; IR (ATR diamond, cm^{-1}) ν 724, 1020, 1117, 1247, 1452, 1604, 1638, 2951; ^1H NMR (400 MHz, CDCl_3) δ 2.50 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 7.06–6.99 (m, 2H), 7.41 (d, J = 7.8 Hz, 2H), 7.57–7.48 (m, 3H), 7.90–7.84 (m, 2H), 8.13 (d, J = 2.2 Hz, 1H), 8.82 (d, J = 7.3 Hz, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 14.4 (CH_3), 21.6 (S- CH_3), 55.4 (O- CH_3), 101.8 (Cq), 114.85 (2 \times CH), 115.3 (CH), 116.6 (CH), 128.1 (2 \times CH), 128.8 (2 \times CH), 129.5 (2 \times CH), 129.5 (CH), 129.7 (Cq), 134.7 (Cq), 136.0 (Cq), 139.6 (Cq), 141.3 (Cq), 160.5 (Cq), 163.4 (Cq), 163.5 (Cq), 172.1 (Cq); HRMS (ESI) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{21}\text{N}_4\text{OS}$: 413.1431 $[\text{M} + \text{H}]^+$, found: 413.1428.

4-[6-(4-Methoxyphenyl)-2-(methylthio)pyrido[1',2':1,5]pyrazole[3,4-*d*]pyrimidin-4-yl]benzonitrile 20. Starting from product **11** (50 mg, 0.147 mmol, 1.0 eq.), following the general procedure **B**, using 4-cyanophenylboronic acid (43 mg, 0.295 mmol, 2.0 eq.), compound **20** was obtained after purification by flash chromatography on silica gel (petroleum ether : EtOAc, 4 : 6) as a yellow solid (62 mg, 70%). Mp > 360 °C; R_f (petroleum ether : EtOAc, 4 : 6) = 0.59; IR (ATR diamond, cm^{-1}) ν 813, 1037, 1164, 1244, 1452, 1572, 1637, 2227, 3044; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 2.74 (s, 3H, CH_3), 3.89 (s, 3H, CH_3),



7.10–7.00 (m, 2H), 7.52–7.45 (m, 2H), 7.58 (dd, $J = 7.3, 2.3$ Hz, 1H), 7.97–7.89 (m, 3H), 8.13–8.05 (m, 2H), 8.86 (d, $J = 7.3$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 14.6 (S-CH₃), 55.6 (O-CH₃), 101.8 (Cq), 114.65 (Cq), 115.0 (CH), 115.2 (2 \times CH), 117.3 (CH), 118.4 (Cq), 128.2 (2 \times CH), 129.4 (Cq), 129.7 (2 \times CH), 130.0 (CH), 132.8 (2 \times CH), 135.7 (Cq), 140.5 (Cq), 142.0 (Cq), 161.0 (Cq), 161.2 (Cq), 163.5 (Cq), 172.6 (Cq); HRMS (ESI) $[\text{M} + \text{H}]^+$ calcd for C₂₄H₁₈N₅OS: 424.1227 $[\text{M} + \text{H}]^+$, found: 424.1224.

6-(4-Methoxyphenyl)-2-(methylthio)-4-(pyridin-3-yl)pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidine 21. Starting from product 11 (50 mg, 0.147 mmol, 1.0 eq.), following the general procedure B, using 3-pyridinylboronic acid (36 mg, 0.295 mmol, 2.0 eq.), compound 21 was obtained after purification by flash chromatography on silica gel (petroleum ether : EtOAc, 4 : 6) as a yellow solid (21 mg, 36%). Mp 222–223 °C; R_f (petroleum ether : EtOAc, 4 : 6) = 0.46; IR (ATR diamond, cm⁻¹) ν 793, 1118, 1163, 1250, 1454, 1522, 1643, 2161, 2926; ^1H NMR (400 MHz, CDCl₃) δ 2.75 (s, 3H, CH₃), 3.87 (s, 3H, CH₃), 7.07–6.98 (m, 2H), 7.64–7.50 (m, 4H), 7.99 (d, $J = 2.3$ Hz, 1H), 8.29 (dd, $J = 7.3, 2.3$ Hz, 1H), 8.86 (d, $J = 7.3$ Hz, 2H), 9.22 (s, 1H); ^{13}C NMR (101 MHz, CDCl₃) δ 14.6 (S-CH₃), 55.6 (O-CH₃), 102.1 (Cq), 115.0 (CH), 115.1 (2 \times CH), 117.3 (CH), 124.0 (CH), 128.3 (2 \times CH), 129.5 (Cq), 129.9 (CH), 135.9 (Cq), 133.7 (Cq), 136.6 (CH), 140.5 (Cq), 149.6 (CH), 151.9 (CH), 160.4 (Cq), 160.9 (Cq), 163.4 (Cq), 172.5 (Cq); HRMS (ESI) $[\text{M} + \text{H}]^+$ calcd for C₂₂H₁₈N₅OS: 400.1227 $[\text{M} + \text{H}]^+$, found: 400.1226.

4-(4-Methoxyphenyl)-2-(methylthio)-6-(naphthalen-2-yl)pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidine 22. Starting from product 13 (50 mg, 0.139 mmol, 1.0 eq.), following the general procedure B, using 4-methoxyphenylboronic acid (42 mg, 0.279 mmol, 2.0 eq.), compound 22 was obtained after purification by flash chromatography on silica gel (petroleum ether : EtOAc, 5 : 5) as a yellow solid (39 mg, 63%). Mp 271–272 °C; R_f (petroleum ether : EtOAc, 4 : 6) = 0.62; IR (ATR diamond, cm⁻¹) ν 763, 795, 841, 1031, 1168, 1245, 1444, 1555, 1635, 2933; ^1H NMR (400 MHz, CDCl₃) δ 2.74 (s, 3H, CH₃), 3.93 (s, 3H, CH₃), 7.14 (d, $J = 8.4$ Hz, 2H), 7.60–7.53 (m, 2H), 7.72–7.65 (m, 2H), 8.02–7.86 (m, 5H), 8.07 (s, 1H), 8.33 (s, 1H), 8.89 (d, $J = 7.0$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl₃) δ 14.5 (CH₃), 55.5 (CH₃), 101.6 (Cq), 114.2 (2 \times CH), 116.4 (CH), 117.0 (CH), 124.2 (CH), 126.4 (CH), 127.0 (CH), 127.1 (CH), 127.7 (CH), 128.4 (CH), 129.3 (CH), 129.6 (CH), 129.9 (Cq), 130.6 (2 \times CH), 133.2 (Cq), 133.4 (Cq), 134.7 (Cq), 136.0 (Cq), 139.7 (Cq), 162.0 (Cq), 163.0 (Cq), 163.5 (Cq), 172.2 (Cq); HRMS (ESI) $[\text{M} + \text{H}]^+$ calcd for C₂₇H₂₁N₄OS: 449.1430 $[\text{M} + \text{H}]^+$, found: 449.1431.

2-[2-(Methylthio)-6-(naphthalen-2-yl)pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidin-4-yl]benzonitrile 23. Starting from product 13 (50 mg, 0.139 mmol, 1.0 eq.), following the general procedure B, using 2-cyanophenylboronic acid (41 mg, 0.279 mmol, 2.0 eq.), compound 23 was obtained after purification by flash chromatography on silica gel (petroleum ether : EtOAc, 6 : 4) as a yellow solid (38 mg, 61%). Mp 258–259 °C; R_f (petroleum ether : EtOAc, 4 : 6) = 0.80; IR (ATR diamond, cm⁻¹) ν 726, 804, 908, 1124, 1165, 1276, 1445, 1558, 1637, 2228, 2925, 3061; ^1H NMR (400 MHz, CDCl₃) δ 2.75 (s, 3H, CH₃), 7.61–7.53 (m, 3H), 7.79–7.68 (m, 3H), 8.03–7.82 (m, 7H), 8.90 (d, $J = 7.0$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl₃) δ 14.5 (CH₃), 102.4 (Cq), 112.2 (Cq), 116.0 (CH), 117.4 (Cq), 117.8 (CH), 124.1 (CH), 126.6 (CH), 127.0 (CH),

127.2 (CH), 127.7 (CH), 128.4 (CH), 129.3 (CH), 129.9 (CH), 130.0 (CH), 130.6 (CH), 132.9 (CH), 133.3 (Cq), 133.7 (Cq), 134.1 (CH), 134.5 (Cq), 135.7 (Cq), 140.4 (Cq), 140.6 (Cq), 159.4 (Cq), 163.1 (Cq), 172.6 (Cq); HRMS (ESI) $[\text{M} + \text{H}]^+$ calcd for C₂₇H₁₈N₅S: 444.1277 $[\text{M} + \text{H}]^+$, found: 444.1278.

2-(Methylthio)-6-(naphthalen-2-yl)-4-(thiophen-2-yl)pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidine 24. Starting from product 13 (50 mg, 0.139 mmol, 1.0 eq.), following the general procedure B, using 2-thienylboronic acid (35 mg, 0.279 mmol, 2.0 eq.), compound 24 was obtained after purification by flash chromatography on silica gel (petroleum ether : EtOAc, 6 : 4) as a yellow solid (31 mg, 52%). Mp 240–241 °C; R_f (petroleum ether : EtOAc, 4 : 6) = 0.90; IR (ATR diamond, cm⁻¹) ν 793, 959, 1168, 1229, 1349, 1444, 1557, 1638, 2921, 3074; ^1H NMR (400 MHz, CDCl₃) δ 2.71 (s, 3H, CH₃), 7.30 (t, $J = 4.2$ Hz, 1H), 7.60–7.53 (m, 2H), 7.69 (m, 2H), 7.74 (m, 1H), 7.96–7.86 (m, 2H), 8.04–7.96 (m, 2H), 8.11 (s, 1H), 8.66 (s, 1H), 8.88 (d, $J = 7.1$ Hz, 1H); ^{13}C NMR (101 MHz, CDCl₃) δ 14.4 (CH₃), 100.9 (Cq), 116.4 (CH), 117.2 (CH), 124.2 (CH), 126.5 (CH), 127.0 (CH), 127.1 (CH), 127.7 (CH), 127.8 (CH), 128.4 (CH), 129.3 (CH), 129.5 (CH), 129.7 (CH), 130.8 (CH), 133.3 (Cq), 133.4 (Cq), 134.7 (Cq), 135.7 (Cq), 140.0 (Cq), 141.3 (Cq), 156.4 (Cq), 163.6 (Cq), 171.9 (Cq); HRMS (ESI) $[\text{M} + \text{H}]^+$ calcd for C₂₄H₁₇N₄S₂: 425.0889 $[\text{M} + \text{H}]^+$, found: 425.0890.

4-[6-(4-Fluorophenyl)-2-(methylthio)pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidin-4-yl]benzonitrile 25. Starting from product 14 (50 mg, 0.153 mmol, 1.0 eq.), following the general procedure B, using 4-cyanophenylboronic acid (45 mg, 0.3 mmol, 2.0 eq.), compound 25 was obtained by purification by flash chromatography on silica gel (petroleum ether : EtOAc, 4 : 6) as a yellow solid (25 mg, 40%). Mp 343–344 °C; R_f (petroleum ether : EtOAc, 4 : 6) = 0.43; IR (ATR diamond, cm⁻¹) ν 817, 1048, 1166, 1448, 1574, 1732, 2229, 2918, 3079; ^1H NMR (400 MHz, DMSO- d_6) δ 2.65 (s, 3H, CH₃), 7.40 (t, $J = 8.6$ Hz, 2H), 7.92–7.78 (m, 2H), 7.98–7.89 (m, 1H), 8.02 (d, $J = 2.3$ Hz, 1H), 8.20 (t, $J = 6.8$ Hz, 4H), 9.25 (d, $J = 7.3$ Hz, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 14.2 (CH₃), 102.2 (Cq), 113.9 (Cq), 116.1 (CH), 116.8 (d, $^2J_{\text{C-F}} = 21.8$ Hz, 2 \times CH), 118.5 (CH), 129.8 (d, $^3J_{\text{C-F}} = 8.5$ Hz, 2 \times CH), 130.1 (2 \times CH), 131.05 (CH), 131.05 (Cq), 133.5 (2 \times CH), 133.65 (d, $J_{\text{C-F}} = 3.1$ Hz, Cq), 135.3 (Cq), 139.1 (Cq), 141.6 (Cq), 161.5 (Cq), 163.0 (Cq), 163.3 (d, $^1J_{\text{C-F}} = 248.0$ Hz, CF), 171.1 (Cq); HRMS (ESI) $[\text{M} + \text{H}]^+$ calcd for C₂₃H₁₅FN₅S: 412.1027 $[\text{M} + \text{H}]^+$, found: 412.1024.

2-(4-Methoxyphenyl)-4-(6-methoxypyridin-3-yl)-6-*p*-tolylpyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidine 26. Starting from 18 (50 mg, 0.12 mmol, 1.0 eq.), using 4-methoxyphenylboronic acid (28 mg, 0.18 mmol, 1.5 eq.) as coupling reagent and following the general procedure C, compound 26 was isolated by purification by flash chromatography on silica gel (petroleum ether : EtOAc, 4 : 6) as white solid (40 mg, 70%). Mp 239–240 °C; R_f (petroleum ether : EtOAc, 4 : 6) = 0.50; IR (ATR diamond, cm⁻¹) ν 800, 870, 1019, 1120, 1287, 1451, 1493, 1602, 1712, 2991; ^1H NMR (400 MHz, CDCl₃) δ 2.43 (s, 3H, CH₃), 3.90 (s, 3H, CH₃), 4.09 (s, 3H, CH₃), 7.03 (d, $J = 8.5$ Hz, 3H), 7.32 (d, $J = 7.8$ Hz, 2H), 7.60–7.50 (m, 3H), 8.22 (s, 1H), 8.33 (dd, $J = 8.5, 2.3$ Hz, 1H), 8.72 (d, $J = 8.5$ Hz, 2H), 8.99–8.87 (m, 2H); ^{13}C NMR (101 MHz, CDCl₃) δ 21.2 (CH₃), 54.0 (CH₃), 55.3 (CH₃), 111.2 (CH), 113.7 (2 \times CH), 115.7 (CH), 117.2 (CH), 126.8 (2 \times CH), 127.8 (Cq),



129.6 (CH), 130.1 (2× CH), 130.6 (2× CH), 130.9 (Cq), 134.5 (Cq), 135.5 (Cq), 139.1 (CH), 139.2 (Cq), 139.3 (Cq), 139.7 (Cq), 143.2 (Cq), 147.9 (CH), 160.7 (Cq), 161.9 (Cq), 163.3 (Cq), 165.7 (Cq); HRMS (ESI) $[M + H]^+$ calcd for $C_{29}H_{24}N_5O_2$: 474.1925 $[M + H]^+$, found: 474.1921.

6-(4-Methoxyphenyl)-2-(6-methylpyridin-3-yl)-4-(p-tolyl)pyrido[1',2':1,5]pyrazolo[3,4-d]pyrimidine 27. Starting from **19** (50 mg, 0.12 mmol, 1.0 eq.), using 6-methyl-3-pyridinyl boronic acid (25 mg, 0.18 mmol, 1.5 eq.) as coupling reagent and following the general procedure C, compound **27** was isolated by purification by flash chromatography on silica gel (petroleum ether : EtOAc, 4 : 6) as yellow solid (43 mg, 78%). Mp 207–208 °C; R_f (petroleum ether : EtOAc, 4 : 6) = 0.40; IR (ATR diamond, cm^{-1}) ν 835, 1033, 1278, 1455, 1605, 1731, 2849, 2918; 1H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 7.04 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 7.7 Hz, 2H), 7.35 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 7.8 Hz, 3H), 7.99 (d, J = 7.7 Hz, 2H), 8.29 (s, 1H), 9.09–8.89 (m, 2H), 9.86 (s, 1H); ^{13}C DEPT NMR (101 MHz, $DMSO-d_6$) δ 21.6 (CH_3), 24.3 (CH_3), 55.5 (CH_3), 114.9 (2× CH), 115.1 (CH), 115.8 (CH), 117.3 (CH), 128.2 (2× CH), 129.0 (2× CH), 129.6 (2× CH), 129.7 (CH), 139.0 (CH), 149.8 (CH); HRMS (ESI) $[M + H]^+$ calcd for $C_{29}H_{24}N_5O$: 458.1975 $[M + H]^+$, found: 458.1977.

4-[4-(4-Methoxyphenyl)-6-(naphthalen-2-yl)pyrido[1',2':1,5]pyrazolo[3,4-d]pyrimidin-2-yl]benzonitrile 28. Starting from **22** (50 mg, 0.10 mmol, 1.0 eq.), using 4-cyanophenylboronic acid (24 mg, 0.16 mmol, 1.5 eq.) as coupling reagent and following the general procedure C, compound **28** was isolated by purification by flash chromatography on silica gel (petroleum ether : EtOAc, 4 : 6) as white solid (34 mg, 61%). Mp 329–330 °C; R_f (petroleum ether : EtOAc, 4 : 6) = 0.75; IR (ATR diamond, cm^{-1}) ν 802, 1026, 1119, 1254, 1510, 1605, 1685, 2224, 2918; 1H NMR (250 MHz, $DMSO-d_6$) δ 3.90 (s, 3H, CH_3), 7.29 (d, J = 8.5 Hz, 2H), 7.64–7.48 (m, 2H), 7.81 (d, J = 8.7 Hz, 1H), 8.22–7.88 (m, 8H), 8.35 (d, J = 7.2 Hz, 2H), 8.70 (d, J = 8.2 Hz, 2H), 9.28 (d, J = 7.1 Hz, 1H); HRMS (ESI) $[M + H]^+$ calcd for $C_{33}H_{22}N_5O$: 504.1819 $[M + H]^+$, found: 504.1820.

Conflicts of interest

No conflict of interest for authors.

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