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Route selection in the synthesis of C-4 and C-6 substituted thienopyrimidines

Steffen Bugge [a], Svein Jacob Kaspersen [a], Eirik Sundby [b], Bård Helge Hoff [a,*]

[a] Department of Chemistry, Norwegian University of Science and Technology, Høgskoleringen 5, NO-7491 Trondheim, Norway
[b] Sør-Trondelag University College, E.C. Dahls Gate 2, NO-7004 Trondheim, Norway

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ABSTRACT

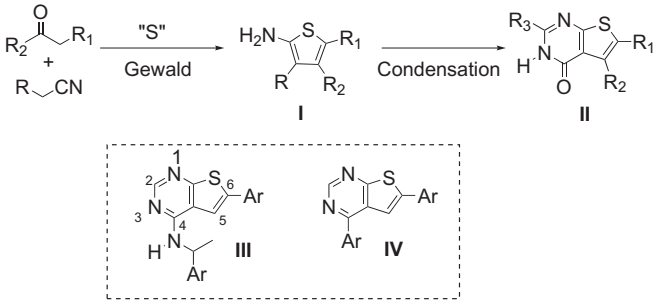
Three different routes have been investigated for the preparation of 6-aryl-*N*-(1-arylethyl)thienopyrimidin-4-amines. First the possibilities of selective Suzuki reactions on 6-bromo-4-chlorothienopyrimidine were investigated. The preference for mono arylation at C-6 could be increased, in the case of $Pd(PPh_3)_4$ catalysis, by reducing the water content of the reaction, or by using less electron rich Pd-ligands. The highest selectivity was obtained with $Pd(OAc)_2$ or $Pd_2(dba)_3$, while reactions with the more electron rich $Pd(PPh_3)_4$ and especially XPhos gave a lower mono- to dicoupled product ratio. Secondly, two alternative strategies avoiding this selectivity issue were tested. Suzuki reaction on C-6 of 6-bromothienopyrimidin-4(3*H*)-one (three examples) proceeded in 70–89% yield using $Pd(PPh_3)_4$ in dioxane/water. Similar conditions on 4-amino-6-bromo-thienopyrimidine (eight examples) gave 67–95% yield. The reaction could be performed with boronic acids containing nonprotected phenolic groups in the *ortho*, *meta* and *para* positions. By prolonging the reaction time, coupling with sterically crowded arylboronic acids was also efficient. Diarylation of 6-bromo-4-chlorothienopyrimidine gave the corresponding 4,6-diarylated derivatives in 71–80% yield depending on the nature of the arylboronic acid.

1. Introduction

Thienopyrimidines have become an interesting structural element in development of pharmaceutical compounds.[1,2] Among others, these heterocycles have been used as part of kinase inhibitors to regulate dysfunctional cell signalling in cancer cells,[3–9] as calcium receptor antagonists,[10] transglutaminase inhibitors,[11,12] as peptidase IV inhibitors[13] and against hepatitis C virus infections.[14]

A useful starting point for thienopyrimidine synthesis is the Gewald reaction,[15–18] in which an activated nitrile reacts with a carbonyl compound in the presence of a sulfur source to give substituted 2-aminothiophenes (**I**), Scheme 1. The 2-aminothiophenes (**I**) can be used to make a range of different products.[11,17,19–21] Starting with cyanoacetate esters or malonitrile, the formed 2-aminothiophenes can be condensed to give thienopyrimidines (**II**),[22,23] which we herein have used in the synthesis of a series of heterocycles like **III** and **IV**.

The preferred chemical route depends on a number of factors, most importantly being the overall cost and the space-time yield. However, in drug discovery and lead optimisation phases, the possibility of making a high number of derivatives using robust chemistry from a common precursor will reduce work effort and speed up development.



Scheme 1. Gewald reaction to give substituted 2-aminothiophenes (**I**) and condensation to give thienopyrimidines (**II**), and the target products **III** and **IV**.

The Suzuki–Miyaura reaction is very efficient for the construction of sp^2–sp^2 carbon–carbon bonds, and is ideal for creating chemical diversity due to the large array of commercially available arylboronic acids.[24,25]

A number of publications describe Suzuki cross-couplings involving thiophenes and pyrimidines, while less is published in the case of thienopyrimidines.[26,27] Regioselectivity issues in Suzuki coupling have previously been studied for chloropyrimidine,[28,29] various five-membered heterocycles,[30] pyridopyrimidines,[31] imidazopyridines,[32] and brominated thiophenes.[33]

Based on our interest in kinase inhibitors,[34] we were in need of various 6-aryl-*N*-(1-arylethyl)thienopyrimidin-4-amines **III** and

* Corresponding author. Tel.: +47 73593973; fax: +47 73544256; e-mail address: bard.helge.hoff@chem.ntnu.no (B.H. Hoff).

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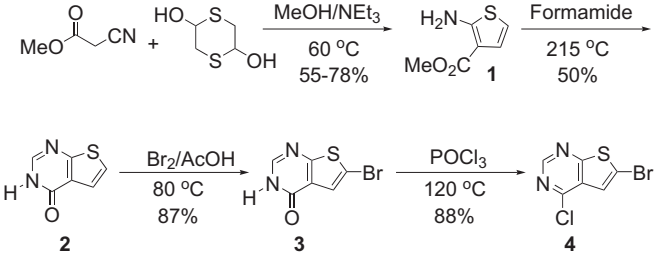
4,6-diaryl thienopyrimidines **IV**. Our aim was to prepare a series of these compounds as efficiently as possible from a late common intermediate using the Suzuki reaction as a key step.

2. Result and discussion

2.1. Starting materials

We envisioned 6-bromothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**3**) and 6-bromo-4-chlorothieno[2,3-*d*]pyrimidine (**4**) as possible late stage intermediates for making a range of 4-amino-6-aryls and 4,6-diaryl derivatives, Scheme 2.



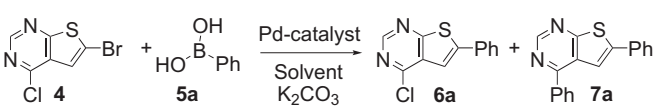
Scheme 2. Synthesis of the thienopyrimidine building blocks.

These were synthesised starting with a Gewald reaction using methyl cyanoacetate and 1,4-dithiane-2,5-diol giving the amino-ester **1**. The reaction was run thermally on a 15–100 g scale, or on a 6 g scale using microwave irradiation in sealed tubes. This gave a 55–78% yield depending on the conditions. The microwave method gave similar yields to the thermal process, but a shortening of reaction time from 3 h to minutes was achieved. The thiophene derivative **1** was then reacted with formamide at high temperature to yield thieno[2,3-*d*]pyrimidin-4(3*H*)-one (**2**). Aromatic bromination in acetic acid yielded **3** and chlorination at C-4 gave the derivative **4**. All these reactions were performed on a 15–30 g scale.

Compounds **2**–**4** were difficult to purify by chromatography due to limited solubility and by crystallisation due to co-precipitation of inorganic material. To have control of the mass balance in the Suzuki coupling steps compound **3** and **4** were purified by silica-gel filtration in gram scale. However, the following reactions were also successfully performed on semi pure materials.

2.2. Selective Suzuki coupling

We first attempted a selective Suzuki coupling on **4** at C-6 using phenylboronic acid (**5a**), Scheme 3. The building block **4** contains two reactive sites. Whereas bromo substituted positions usually reacts faster, the low electron density at C-4 in the pyrimidine unit complicates a selective reaction.[35]



Scheme 3. Attempted selective Suzuki coupling on **4**.

Employing the classical $Pd(PPh_3)_4$ system, the effect of reaction temperature and dioxane/water ratio on the degree of conversion and product distribution was investigated (Table 1).

With water/dioxane (50/50, v/v) as the solvent system, the reaction proceeded slowly at lower temperatures (Table 1, entries 1–3). However, at 110 °C full conversion was obtained in 6 h. Unfortunately, the reaction proceeded with poor selectivity (Table 1, entries 4–5), and traces of **3** was also observed due to hydrolysis of the starting material.

Table 1
Conversion and product distribution upon variation of reaction temperature and solvent composition in the reaction of **4** with **5a** using K_2CO_3 as base and $Pd(PPh_3)_4$ as Pd-source

Entry	$PhB(OH)_2$ (Eq)	Water (vol.%)	Temp (°C)	Rx time (h)	Conv. (%)[a]	**6a** (%)	**7a** (%)	Ratio **6a**/**7a**
1	1.2	50	22	6	0	0	0	—
2	1.2	50	40	24	65	52	13	4
3	1.2	50	60	24	92	61	31	2
4	1.2	50	110	6	>99	43	57	1
5	1.2	25	110	7	>99	49	51	1
6	1.0	2	110	5	92	82	10	8
7	1.0	0	110	5	86	79	7	11
8	1.0	0	110	24	95	85	10	8

[a] Conversion was measured by ^1H NMR spectroscopy.

To improve the ratio of mono- to diarylated product, and to supress hydrolysis of **4**, the water content and the amount of arylboronic acid was reduced (Table 1, entries 6–8). By using a low water content or pure dioxane a higher selectivity ratio was the result. A drawback however, was a decreased rate of reaction.

The rate of Suzuki-type couplings are amongst other thing dependent on the electronic properties of the catalyst. It was therefore investigated whether variation of the ligand affected the product ratio using $Pd(OAc)_2$, $Pd_2(dba)_3$ and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos). The less electron donating $Pd(OAc)_2$ and $Pd_2(dba)_3$ both gave a high ratio of **6a**/**7a** (Table 2, entries 1–5). However, complete conversion could not be obtained in 24 h. Use of the more electron rich XPhos resulted in a low ratio of **6a**/**7a** supporting the idea that electronic effects are important for selectivity.

Table 2
Conversion and product distribution using $Pd(OAc)_2$, $Pd_2(dba)_3$ and $Pd(OAc)_2$/XPhos in Suzuki coupling

Entry	$PhB(OH)_2$ (Eq)	Catalyst	Water (vol.%)	Rx time (h)	Conv. (%)[a]	**6a** (%)	**7a** (%)	Ratio **6**/**7**
1	1.0	$Pd(OAc)_2$	2	5	24	24	>1	>24
2	1.2	$Pd(OAc)_2$	50	5	75	71	4	17
3	1.2	$Pd_2(dba)_3$	50	5	81	77	4	20
4	1.2	$Pd_2(dba)_3$	0	24	77	74	4	20
5	1.5	$Pd_2(dba)_3$	0	24	80	77	3	25
6	1.5	$Pd(OAc)_2$ / XPhos	0	5	72	45	27	2

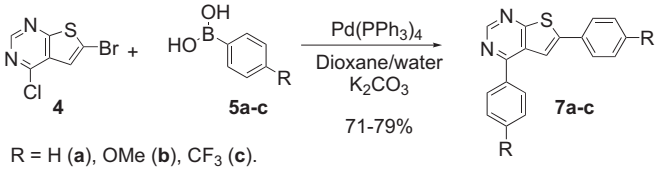
[a] Conversion was measured by ^1H NMR spectroscopy.

As opposed to reactions using $Pd(PPh_3)_4$, the ratio of mono- to diarylated products in Suzuki couplings using $Pd(OAc)_2$ and $Pd_2(dba)_3$ was not affected by the amount of water used.

A challenge with the reactions in pure dioxane was a low rate of reaction, leading to incomplete conversion. *N*,*N*-Dimethylformamide (DMF) has previously been used as a highly polar solvent in similar reactions,[32,36] and Suzuki coupling on **4** in DMF using $Pd_2(dba)_3$ gave an excellent 90/1 ratio of **6a** and the disubstituted derivatives **7a** (data not shown). However, the product could not be isolated in more than 18% yield. Degradation reactions seem to take place. This was also observed by Delia et al.[28]

In conclusion, a 25/1 ratio of mono- to dicoupled product could be obtained by changing the palladium ligand. However, the mediocre conversion complicates purification, which led to a low yield.

Diaryl coupling has been found challenging for some dihaloheterocycles.[29,37] Therefore, this transformation was tested with **4** in the synthesis of **7a**–**c**, Scheme 4.



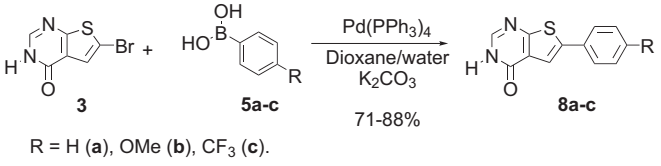
Scheme 4. Diaryl coupling on 6-bromo-4-chlorothieno[2,3-*d*]pyrimidine (**4**).

Reaction of **4** with the arylboronic acids **5a** and **b** (2.5 equiv) was run for 1 h, giving 71% and 79% yield, respectively. In the synthesis of **7c**, 3 equiv of 4-(trifluoromethyl)phenylboronic acid (**5c**) and a longer reaction time were required resulting in a 74% isolated yield. The diaryl thienopyrimidines **7a**–**c**, were purified by silica gel column chromatography, and the major loss in yield were related to fractions contaminated with the biaryls formed by dimerisation of the arylboronic acids. A slow addition protocol might increase the yield, however this was not attempted.

2.3. Suzuki coupling at C-6 of 6-bromothieno[2,3-*d*]pyrimidin-4(3*H*)-one

Given the challenges with obtaining a selective Suzuki coupling on **4**, alternative strategies were sought.

Starting with 6-bromothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**3**), coupling was undertaken using $Pd(PPh_3)_4$ and potassium carbonate in dioxane/water, Scheme 5. A possible challenge could be hydrolysis of the bromo function. However, testing showed compound **3** to be stable for 20 h at 110 °C, as no degradation was seen by ^1H NMR spectroscopy. The reactions were performed on a 150 mg scale using 1.2–1.5 equiv of the arylboronic acids **5a**–**c**. The reaction times, conversions, isolated yields and purity of the materials obtained are summarised in Table 3.



Scheme 5. Pd-catalysed arylation of 6-bromothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**3**).

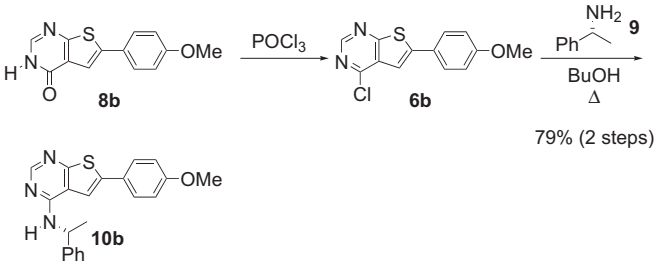
Table 3
Pd-catalysed arylation of **3** using $Pd(PPh_3)_4$ in dioxane/water

R	Eq.[a]	Rx time (h)	Conv.[b] (%)	Yield (%)	Purity (%)[c]	Prod.
H (**a**)	1.2	5	>99	87	97	**8a**
OMe (**b**)	1.2	5	>99	88	98	**8b**
CF_3 (**c**)	1.5	20	>99	71	98	**8c**

[a] Mole equivalents of arylboronic acid.
[b] Conversion was measured by ^1H NMR spectroscopy.
[c] Purity by HPLC (area %), C-18.

The Suzuki couplings to give **8a** and **8b** were complete in 5 h, giving 87–88% yield. In the synthesis of **8c** the isolated yield increased when using more 4-(trifluoromethyl)phenylboronic acid (**5c**) and extending the reaction time. The formation of biaryl products from dimerisation of the arylboronic acids was also seen in this transformation. The products **8a**–**c** are slightly soluble in base, and a pH adjustment was needed in the work up. Following extraction, the compounds **8a**–**b** were isolated by crystallisation, whereas **8c** had to be purified by silica gel column chromatography.

To verify the usefulness of the route to the 4-substituted thienopyrimidines **10**, chlorination of **8b** was performed with $POCl_3$ followed by thermal amination giving the 4-aminothienopyrimidine **10b**, Scheme 6. The overall yield of **10b** from **8b** was 79%.

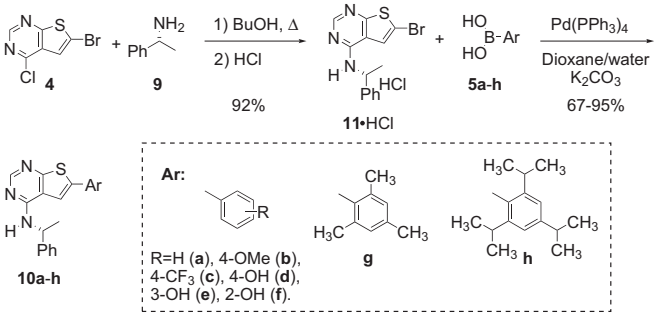


Scheme 6. Synthesis of **10b** from **8b**.

In this synthetic setting, the strategy is beneficial if a compound library containing structural diversity at C-4 of the thienopyrimidine unit is targeted. However, challenges are likely to be encountered in the chlorination step for sensitive groups incorporated at C-6.

2.4. Suzuki coupling on 6-bromo-4-amino substituted thienopyrimidine

An alternative strategy, especially useful if variation at C-6 of the thienopyrimidine is the main goal, is shown in Scheme 7. This route relies on a nucleophilic aromatic substitution at C-4 of compound **4** followed by a Suzuki coupling to give **10**. Thermal coupling of the amine **9** was completely selective and gave **11** in 90% isolated yield. The HCl-salt of **11** could be used directly in the preceding coupling with addition of one extra equivalent of base.



Scheme 7. Conversion of **11**·HCl to give **10a**–**h**.

Suzuki coupling on **11**·HCl was investigated with the more reactive $Pd(PPh_3)_4$ in dioxane/water using various arylboronic acids. Table 4 shows the reaction times, conversions, the isolated yields and the purity of the materials **10a**–**h**. For most of the couplings on **11**·HCl, high conversions and isolated yields could be achieved after 2–3 h reaction time. The products were mainly precipitated and purified as their HCl-salts. However, **10g** and **10h**, also required purification by silica gel column chromatography before crystallisation.

Table 4
Suzuki couplings on **11**·HCl using various arylboronic acids

Entry	Arylboronic acid	Rx time (h)	Conv. (%)[a]	Yield (%)	Purity (%)[b]	Prod.
1	4-H (**5a**)	2	>99	95	99	**10a**
2	4-OMe (**5b**)	2	>99	93	99	**10b**
3	4-CF_3 (**5c**)	3	>99	68	99	**10c**
4	4-OH (**5d**)	2.5	>99	80	99	**10d**
5	3-OH (**5e**)	2.5	>99	91	99	**10e**
6	2-OH (**5f**)	3	>99	92	97	**10f**
7	2,4,6-Me (**5g**)	3	>99	74	99	**10g**
8	2,4,6-*i*-Pr (**5h**)	22	>99	67	99	**10h**

[a] Conversion was measured by ^1H NMR spectroscopy.
[b] Purity by HPLC (area %), C-18.

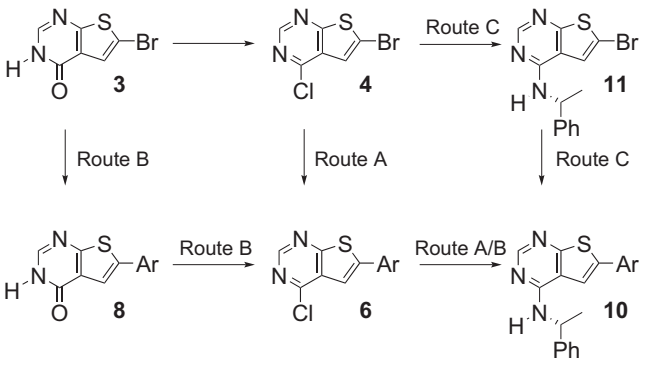
The effect of the electronic properties of the arylboronic acids was tested (Table 4, entries 1–3). This confirmed the common trend that coupling with arylboronic acids containing electron donating substituents give higher isolated yields compared to electron poor arylboronic acids (entry 3). Also, coupling employing the unprotected phenolic boronic acids **5d** and **5e** (Table 4, entries 4–6), gave good yields and rates of reaction. Thus, protection/deprotection chemistry is not needed, which make this route attractive compared to that described in Section 2.3.

Suzuki reaction of sterically crowded arylboronic acids have for some aryl halides, proceeded in a low yields.[38] Coupling of **11**·HCl with **5g** and **5h**, (Table 4, entries 7–8) gave 67–74% isolated yield. The effect of steric crowding was evident in reaction with 2,4,6-tri-*iso*propylphenyl boronic acid (**5h**), which required a 22 h reaction time.

An advantage of this route is the high conversions obtained, giving easier product separation and higher yields. The good functional group tolerance in the coupling step also avoids the need for protection/deprotection steps. Moreover, in this setting, introduction of the amine function at an earlier stage allows for more options in terms of purification.

3. Conclusion

Three different routes have been investigated and used for the synthesis of thienopyrimidines **10**, starting from the intermediates **3** and **4**, Scheme 8.



Scheme 8. Summary of the various routes.

A selective Suzuki coupling with **4** (route A) to give 6-arylated product is a challenging task. The reaction conditions have been varied to improve the selectivity. A ratio of 25 favouring **6a** over **7a** was achieved, however, incomplete conversion and challenges in purification led to a low isolated yield. Although being the ideal route (route A), it is not practical. Nevertheless, using **4** in a double Suzuki coupling proved valuable in synthesising the diaryl compounds **7a**–**c**.

An alternative strategy (route B), based on C-6 arylation on **3**, gave the compounds **8a**–**c** in 70–89% yield, which could be converted into the target **10**. This strategy is beneficial if a compound library containing structural diversity at C-4 of the pyrimidine unit is to be made. However, functional groups introduced in the aromatic moiety at C-6 must be stable in the following steps, which limits the usefulness of the method.

Route C also circumvents the selectivity issue experienced with **4**, and relies on amination to give **11** followed by a Suzuki reaction. This strategy resulted in high overall yield, and has the best functional group tolerance. When a compound library containing structural diversity at C-6 is to be made, this order of steps is most beneficial.

Biological testing of these compounds will be communicated in due course.

4. Experimental

4.1. Chemicals

1,4-Dithiane-2,5-diol, methyl cyanoacetate, formamide, Br_2, $POCl_3$, (*R*)-1-phenylethanamine (**9**), K_2CO_3, $Pd(PPh_3)_4$, $Pd(OAc)_2$, $Pd_2(dba)_3$, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) and the arylboronic acids **5a**–**e** and **5g** and **5h**, were from Sigma Aldrich. (2-Hydroxyphenyl)boronic acid (**5f**) was from Alfa Aesar. Silica gel column chromatography was performed using silica gel 60A from Sigma, pore size 40–63 μm.

4.2. Analyses

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 MHz and 100 MHz, respectively. ^{19}F NMR spectroscopy was performed on a Bruker Avance 600 operating at 564 MHz. The ^{19}F NMR shift values are relative to hexafluorobenzene. Coupling constants are in hertz. HPLC (Agilent 110-Series) with a G1379A degasser, G1311A Quatpump, G1313A ALS autosampler and a G1315D Agilent detector (230 nm) was used to determine the purity of the synthesised compounds. Conditions: a Poroshell C18 (100×3.0 mm) column, flow rate 1.0 mL/min, method A; linear gradient from H_2O+1% TFA/acetonitrile (95/5) to 0/100 over 35 min, method B: linear gradient from H_2O+1% TFA/acetonitrile (98/2) to 5/95 over 35 min. The software used with the HPLC was Agilent ChemStation. Accurate mass determination was performed with ESI or EI (70 eV) using a Finnigan MAT 95 XL. FTIR spectra were recorded on a Thermo Nicolet Avatar 330 infrared spectrophotometer. All melting points are uncorrected and measured by a Büchi melting point instrument. Optical rotation was measured with a PerkinElmer Instruments Model 341 Polarimeter. For all compounds isolated as their HCl salts, the NMR spectroscopic properties given are for the corresponding free amine, whereas the other spectroscopic and chemical properties reported are for the HCl-salt.

4.3. Synthesis

*4.3.1. Methyl 2-aminothiophene-3-carboxylate (**1**).*[18] The synthesis was carried out as described by Hallas and Towns.[18] 1,4-Dithiane-2,5-diol (15.0 g, 99.0 mmol) was mixed with MeOH (30 mL), and methyl cyanoacetate (16.3 g, 164 mmol) was added while stirring. Then NEt_3 (5.98 g, 59.1 mmol) was added dropwise over 10 min at 0 °C. The reaction temperature was slowly increased to 60 °C over 1 h, and kept stirring for 1 h. After cooling to rt, the mixture was filtered and the liquid fraction was concentrated and allowed to crystallise at −18 °C for 18 h. The solid formed was isolated, washed with *n*-heptane (3×50 mL) and dried to yield 20.1 g (128 mmol, 78%) of **1** as a yellowish solid, mp. 72–73 °C, (lit.[15] 77–78 °C); R_f ($CHCl_3$)=0.33; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.24 (s br, 2H, NH_2), 6.81 (d, *J*=5.8, 1H), 6.27 (d, *J*=5.8, 1H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.8, 164.0, 124.9, 106.5, 103.7, 50.5; IR (neat, cm^{-1}): 3421, 3319, 1655, 1316, 1273, 676; HRMS (EI, 70 eV, *m*/*z*): 157.0201 (calcd $C_6H_7NO_2S$, 157.0198, M^+). The ^1H NMR spectrum from $CDCl_3$ corresponded with that reported by Huang et al.[39]

*4.3.2. Thieno[2,3-d]pyrimidin-4(3H)-one (**2**).*[22,35] The synthesis was carried out according to the procedure of Jang et al.[35] Methyl 2-aminothiophene-3-carboxylate (**1**) (26.0 g, 165 mmol) was mixed with formamide (285 mL) and heated at 215 °C for 5 h. The reaction mixture was then cooled to rt and water (500 mL) was added,

followed by extraction with EtOAc (4×500 mL). The combined organic fractions were dried over Na_2SO_4, and concentrated. Upon storage at −18 °C a solid material precipitated, which was washed with cold EtOAc (4×100 mL). This gave 12.7 g (83.0 mmol, 50%) of **2** as a yellowish solid, mp. 245 °C (dec), (lit.[22] 245 °C, dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.45 (s br, 1H), 8.12 (s, 1H), 7.57 (d, J=5.8, 1H), 7.39 (d, J=5.8, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.2, 157.5, 145.6, 124.6, 123.8, 121.6; IR (neat, cm^{-1}): 2879, 1647, 1577, 800, 701, 635; HRMS (EI, 70 eV, m/z): 152.0045 (calcd $C_6H_4N_2OS$, 152.0044, M^+). The NMR spectroscopic data corresponds with that reported previously.[22]

*4.3.3. 6-Bromothieno[2,3-d]pyrimidin-4(3H)-one (**3**).*[40,41] Thieno[2,3-*d*]pyrimidin-4(3*H*)-one (**2**) (25.1 g, 165 mmol) was mixed with concd acetic acid (425 mL), and bromine (17.0 mL, 52.8 g, 330 mmol) was added slowly before the mixture was heated at 80 °C for 3 h. The reaction mixture was then cooled to rt and filtered to remove insoluble components. The liquid fraction was diluted with ice and neutralised using a saturated aq $NaHCO_3$ solution. The precipitated material was isolated by filtration and washed with water (6×100 mL). Drying gave 33.1 g (143 mmol, 87%) of **3** as a light brown solid, mp. 283–290 °C (dec), (lit.[40] 301–304 °C). A fraction of this material was purified before it was used in Suzuki coupling. The dry material was applied to the top of a packed silica gel plug and eluted with CH_2Cl_2, mp. 298–301 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.63 (s br, 1H), 8.14 (s, 1H), 7.55 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.0, 156.0, 146.5, 125.6, 124.6, 110.3; IR (neat, cm^{-1}): 3074, 1663, 1649, 1504, 755; HRMS (EI, 70 eV, m/z): 229.9146 (calcd $C_6H_3Br^{79}N_2OS$, 229.9144, M^+). The ^{1}H NMR spectrum corresponds with Ref. 41. ^{13}C NMR spectroscopy data has not previously been reported.

*4.3.4. 6-Bromo-4-chlorothieno[2,3-d]pyrimidine (**4**).*[41] Compound **3** (32.7 g, 142 mmol) was mixed with $POCl_3$ (100 mL) and heated at 120 °C for 3 h. Then the mixture was quenched into 5 M aq NaOH (1 L) and ice. The pH was adjusted to 7 using a saturated aq $NaHCO_3$ solution. The formed precipitate was isolated by filtration and washed with water (3×200 mL). Drying gave 31.0 g (124 mmol, 88%) of **4** as a brown solid, mp. 112–118 °C. A fraction of this material was further purified: the dry material was applied to the top of a packed silica gel plug and eluted with CH_2Cl_2, mp. 114–118 °C; R_f (CH_2Cl_2/MeOH, 98/2)=0.67; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.95 (s, 1H), 7.89 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.9, 153.2, 152.5, 130.2, 122.9, 118.5; IR (neat, cm^{-1}): 3082, 1508, 1411, 959, 832, 816, 760; HRMS (EI, 70 eV, m/z): 247.8813 (calcd $C_6H_2Br^{79}Cl^{35}N_2S$, 247.8811, M^+). The ^{1}H NMR spectrum corresponds with Ref. 41. ^{13}C NMR spectroscopic data and a reference melting point have not been identified.

*4.3.5. 4-Chloro-6-phenylthieno[2,3-d]pyrimidine (**6a**) from **4**.*[42] Compound **4** (201 mg, 0.806 mmol) was mixed with phenylboronic acid (**5a**) (147 mg, 1.21 mmol), finely powdered K_2CO_3 (337 mg, 2.44 mmol), $Pd_2(dba)_3$ (37 mg, 0.040 mmol) and 1,4-dioxane (4 mL). The reaction was then stirred at 130 °C for 5 h. The solvent was removed and the residue was suspended in water (50 mL) and extracted with diethyl ether (3×50 mL). After drying and concentration, the crude product was purified by silica gel column chromatography (*n*-pentane/acetone, 19/1). This gave 68 mg (0.276 mmol, 34%) of **6a** as a pale white solid, mp. 142–143 °C, (lit.[42] 143–145 °C, petroleum ether/EtOAc); R_f (*n*-pentane/acetone, 19/1)=0.28; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.93 (s, 1H), 8.01 (s, 1H), 7.96–7.92 (m, 2H), 7.57–7.47 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 167.6, 153.3, 152.8, 145.3, 131.8, 130.8, 130.1, 129.4 (2C), 126.8 (2C), 115.0; IR (neat, cm^{-1}): 3067 (w), 1418, 1234, 949, 823, 755; HRMS (EI, 70 eV, m/z): 246.0015 (calcd $C_{12}H_7Cl^{35}N_2S$, 246.0013, M^+). ^{1}H and ^{13}C NMR spectroscopic data have previously not been reported.

*4.3.6. 4-Chloro-6-(4-methoxyphenyl)thieno[2,3-d]pyrimidine (**6b**).* Compound **8b** (112 mg, 0.44 mmol) was mixed with neat $POCl_3$ (5 mL) and heated at 120 °C for 3 h. Then the mixture was quenched into 5 M aq NaOH and ice. The pH was adjusted to 7 using a saturated aq $NaHCO_3$ solution. The formed precipitate was isolated by filtration and washed with water (3×20 mL) and *n*-pentane (2×20 mL). This gave 106 mg (0.38 mmol, 88%) of **6b** as a brownish solid, mp. 157–160 °C; HPLC purity (method B): 98%, t_R=30.5 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.87 (s, 1H), 7.83 (s, 1H), 7.87–7.85 (m, 2H), 7.08–7.06 (m, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 167.8, 161.2, 153.2, 152.9, 145.9, 131.4, 128.8, 124.8, 115.3, 113.6, 55.9; IR (neat, cm^{-1}): 2836, 1605, 1488, 1229, 1024, 810, 759; HRMS (EI, 70 eV, m/z): 276.0119 (calcd $C_{13}H_9ClN_2OS$, 276.0119, M^+).

*4.3.7. 4,6-Diphenylthieno[2,3-d]pyrimidine (**7a**).* Compound **4** (202 mg, 0.811 mmol) was mixed with phenylboronic acid (**5a**) (249 mg, 2.04 mmol, 2.5 equiv), finely powdered K_2CO_3 (341 mg, 2.47 mmol), $Pd(PPh_3)_4$ (47 mg, 0.040 mmol), 1,4-dioxane (2 mL) and water (2 mL). The reaction was then stirred at 110 °C for 3 h. The solvent was removed and the residue was dissolved in EtOAc (25 mL) and washed with water (3×15 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated onto silica gel. The obtained material was purified by silica gel column chromatography (*n*-pentane/EtOAc, 3/1). This gave 185 mg (0.643 mmol, 79%) of **7a** as a yellowish solid, mp. 115–117 °C; R_f (*n*-pentane/EtOAc, 3/1)=0.35; HPLC purity (method A): 97%, t_R=40.0 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.14 (s, 1H), 8.11–8.06 (m, 2H), 8.07 (s, 1H), 7.95–7.90 (m, 2H), 7.67–7.61 (m, 3H), 7.56–7.44 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.7, 159.4, 153.1, 143.7, 136.9, 132.4, 130.6, 129.7, 129.33 (2C), 129.30 (2C), 129.0 (2C), 128.9, 126.8 (2C), 116.3; IR (neat, cm^{-1}): 1484, 1351, 748, 701, 686; HRMS (EI, 70 eV, m/z): 288.0714 (calcd $C_{18}H_{12}N_2S$, 288.0716, M^+).

*4.3.8. 4,6-Bis(4-methoxyphenyl)thieno[2,3-d]pyrimidine (**7b**).* Compound **7b** was made as described in Section 4.3.7 starting with (4-methoxyphenyl)boronic acid (**5b**) (305 mg, 2.01 mmol, 2.5 equiv). This gave 199 mg (0.570 mmol, 71%) of **7b** as a yellowish solid, mp. 147–150 °C; R_f (diethyl ether/*n*-pentane, 3/1)=0.29; HPLC purity (method A): 98%, t_R=39.5 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.04 (s, 1H), 8.11–8.07 (m, 2H), 7.95 (s, 1H), 7.89–7.83 (m, 2H), 7.20–7.15 (m, 2H), 7.11–7.05 (m, 2H), 3.89 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.4, 161.2, 160.4, 158.4, 152.7, 143.3, 131.0 (2C), 129.4, 128.6, 128.2 (2C), 125.0, 114.8, 114.7 (2C), 114.4 (2C), 55.4 (2C); IR (neat, cm^{-1}): 2924, 2853, 1490, 1245, 1175, 1017, 820, 779; HRMS (EI, 70 eV, m/z): 348.0926 (calcd $C_{20}H_{16}N_2O_2S$, 348.0927, M^+).

*4.3.9. 4,6-Bis(4-(trifluoromethyl)phenyl)thieno-[2,3-d]pyrimidine (**7c**).* Compound **7c** was made as described in Section 4.3.7 but starting from compound **4** (131 mg, 0.525 mmol) and (4-(trifluoromethyl)phenyl)boronic acid (**5c**) (300 mg, 1.58 mmol, 3.0 equiv), and reacting for 21.5 h. The crude material was purified by silica gel column chromatography (EtOAc/*n*-pentane, 3/1). This gave 164 mg (0.386 mmol, 74%) of **7c** as a yellowish solid, mp. 173–175 °C; R_f (EtOAc/*n*-pentane, 3/1)=0.34; HPLC purity (method B): 98%, t_R=38.2 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.21 (s, 1H), 8.27–8.25 (m, 3H), 8.16–8.13 (m, 2H), 7.98–7.96 (m, 2H), 7.86–7.84 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.6, 158.9, 154.0, 142.7, 141.0, 136.6, 130.9 (q, J=32.7) 130.7 (2C), 130.6 (2C), 130.0 (q, J=29.5) 129.4, 128.0 (2C) 126.5 (q, J=3.9), 126.2 (q, J=3.9), 124.5 (q, J=271.9), 124.4 (q, J=272.6), 118.7; ^{19}F NMR (564 MHz, DMSO-d_6) δ: −63.9 (s), −63.7 (s); IR (neat, cm^{-1}): 2922, 1324, 1108, 1063, 830,

758; HRMS (EI, 70 eV, *m/z*): 423.0387, (calcd $C_{20}H_{10}F_6N_2S$, 423.0387, M^+).

*4.3.10. 6-Phenylthieno[2,3-d]pyrimidin-4(3H)-one (**8a**).*[43] Compound **3** (175 mg, 0.757 mmol) was mixed with phenylboronic acid (**5a**) (111 mg, 0.910 mmol, 1.2 equiv), finely powdered K_2CO_3 (230 mg, 1.67 mmol), $Pd(PPh_3)_4$ (44 mg, 0.04 mmol), 1,4-dioxane (2 mL) and water (2 mL). The reaction was then stirred at 110 °C for 5 h. The solvent was removed and the crude product was suspended in saturated aq NH_4Cl solution (30 mL), and extracted with EtOAc (4×50 mL). The combined organic fractions were dried over Na_2SO_4 and concentrated. Purification by crystallisation from EtOAc (10 mL), using *n*-pentane (30 mL) as the anti-solvent gave 151 mg (0.661 mmol, 87%) of **8a** as a brownish solid, mp. 262–265 °C, (lit.[43] 263–265 °C); HPLC purity (method A): 99%, t_R=14.0 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.54 (s br, 1H), 8.14 (s, 1H), 7.80 (s, 1H), 7.79–7.73 (m, 2H), 7.50–7.42 (m, 2H), 7.41–7.34 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.4, 157.2, 146.0, 139.6, 132.7, 129.3 (2C), 128.6, 126.1, 125.8 (2C), 117.3; IR (neat, cm^{-1}): 3060, 1658, 1638, 752, 689; HRMS (EI, 70 eV, *m/z*): 228.0353 (calcd $C_{12}H_8N_2OS$, 228.0352, M^+). ^{1}H and ^{13}C NMR spectroscopic data have not previously been reported.

*4.3.11. 6-(4-Methoxyphenyl)thieno[2,3-d]pyrimidin-4(3H)-one (**8b**).* Compound **8b** was prepared as described in Section 4.3.10 starting with compound **3** (174 mg, 0.754 mmol) and (4-methoxyphenyl)boronic acid (**5b**) (137 mg, 0.902 mmol, 1.2 equiv). This gave 172 mg (0.666 mmol, 88%) of **8b** as a brownish solid, mp. 296–299 °C; HPLC purity (method B): 98%, t_R=29.5 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.51 (s, 1H), 8.11 (s, 1H), 7.65 (s, 1H), 7.70–7.68 (m, 2H), 7.02–6.99 (m, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.4, 160.2, 157.8, 146.0, 140.4, 127.7 (2C), 126.6, 125.8, 116.2, 115.1 (2C), 55.8; IR (neat, cm^{-1}): 2838, 1646, 1249, 1173, 826, 774; HRMS (EI, 70 eV, *m/z*): 258.0458 (calcd $C_{13}H_{10}N_2O_2S$, 258.0457, M^+).

*4.3.12. 6-(4-(Trifluoromethyl)phenyl)thieno[2,3-d]pyrimidin-4(3H)-one (**8c**).* The reaction and extractive work-up was performed as described in Section 4.3.10, starting with compound **3** (156 mg, 0.675 mmol) and (4-(trifluoromethyl)phenyl)boronic acid (**5c**) (192 mg, 1.01 mmol, 1.5 equiv), and reacting for 20 h. The crude product was purified by silica gel column chromatography (EtOAc) giving 139 mg (0.476 mmol, 71%) of **8c** as a white solid, mp. 280–283 °C; R_f (EtOAc)=0.41; HPLC purity (method B): 97%, t_R=24.6 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.62 (s, 1H), 8.18 (s, 1H), 7.99–7.97 (m, 3H), 7.79–7.77 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.7, 157.6, 147.0, 137.9, 137.1, 128.9 (q, *J*=32.0), 126.9 (2C), 126.6–126.5 (m, 2C), 124.5 (q, *J*=272.0), 120.0 (2C); ^{19}F NMR (564 MHz, DMSO-d_6) δ: −63.5 (s); IR (neat, cm^{-1}): 2852, 1663, 1320, 1124, 1109, 1067, 832, 775, 569; HRMS (EI, 70 eV, *m/z*): 296.0226 (calcd $C_{13}H_7F_3N_2OS$, 296.0226, M^+).

*4.3.13. (R)-6-Bromo-N-(1-phenylethyl)thieno[2,3-d]pyrimidin-4-amine (**11**).* Compound **4** (700 mg, 2.81 mmol) was mixed with (*R*)-1-phenylethanamine (**9**) (1.07 mL, 1.02 g, 8.42 mmol) and 1-butanol (12 mL), and agitated at 145 °C for 15 h. Then the mixture was cooled to rt, diluted with diethyl ether (150 mL) and washed with water (3×50 mL) and saturated aq NaCl solution (20 mL). After drying over Na_2SO_4 and concentration in vacuum the crude oil was dried under reduced pressure for 48 h. The crude product was purified by precipitation from diethyl ether (100 mL)/HCl in diethyl ether (1 mL) at −18 °C for 24 h. The product was isolated by filtration and washed with diethyl ether (3×30 mL). Drying gave 957 mg (2.58 mmol, 92%) of **11a**·HCl as a white solid, mp. 210–214 °C; $[\alpha]_D^{20}$ −184.3 (*c* 0.95, DMSO); HPLC purity (method A): 99%, t_R=33.2 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.27 (s, 1H), 8.23 (d, *J*=7.8, 1H), 7.99 (s, 1H), 7.42–7.37 (m, 2H), 7.34–7.28 (m, 2H), 7.24–7.19 (m, 1H), 5.51–5.42 (m, 1H), 1.53 (d, *J*=7.0, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.5, 154.8, 154.1, 144.4, 128.3 (2C), 126.7, 126.0 (2C), 122.8, 116.8, 109.6, 49.1, 22.4; IR (neat, cm^{-1}): 1602, 1583, 1474, 1364, 765, 698; HRMS (EI, 70 eV, *m/z*): 332.9929 (calcd $C_{14}H_{12}Br^{79}N_3S$, 332.9930, M^+).

*4.3.14. (R)-6-Phenyl-N-(1-phenylethyl)thieno[2,3-d]pyrimidin-4-amine (**10a**).* Compound **11**·HCl (201 mg, 0.543 mmol) was mixed with phenylboronic acid (**5a**) (104 mg, 0.850 mmol), finely powdered K_2CO_3 (301 mg, 2.18 mmol), $Pd(PPh_3)_4$ (32 mg, 0.028 mmol), 1,4-dioxane (2 mL) and water (2 mL). The reaction was then stirred at 110 °C for 2 h under an N_2 atmosphere. The solvent was removed and the product was dissolved in EtOAc (25 mL) and washed with water (3×20 mL) and saturated aq NaCl solution (15 mL). The organic phase was dried over Na_2SO_4, filtered, added HCl in diethyl ether (0.5 mL) and cooled to −18 °C for 29 h. The resulting mixture was filtered and the solid material was washed with diethyl ether (3×15 mL). Drying gave 189 mg (0.514 mmol, 95%) of **10a**·HCl as a white solid, mp. 223–228 °C (dec); $[\alpha]_D^{20}$ −293.6 (*c* 1.02, DMSO); HPLC purity (method A): 99%, t_R=21.1 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.29 (s, 1H), 8.24 (d, *J*=7.9, 1H), 8.21 (s, 1H), 7.72–7.68 (m, 2H), 7.54–7.48 (m, 2H), 7.46–7.37 (m, 3H), 7.36–7.30 (m, 2H), 7.25–7.20 (m, 1H), 5.56–5.47 (m, 1H), 1.57 (d, *J*=7.0, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.1, 155.8, 153.9, 144.6, 138.1, 133.2, 129.4 (2C), 128.6, 128.3 (2C), 126.7, 126.1 (2C), 125.6 (2C), 117.4, 115.6, 49.1, 22.5; IR (neat, cm^{-1}): 1609, 1484, 753, 700, 689; HRMS (ESI, *m/z*): 332.1216 (calcd $C_{20}H_{18}N_3S$, 332.1216, M+H^+).

*4.3.15. (R)-6-(4-Methoxyphenyl)-N-(1-phenylethyl)thieno[2,3-d]pyrimidin-4-amine (**10b**).* Compound **10b** was made as described in Section 4.3.14 starting with (4-methoxyphenyl)boronic acid (**5b**) (126 mg, 0.827 mmol). This gave 201 mg (0.506 mmol, 93%) of **10b**·HCl as a white solid, mp. 245 °C (dec); $[\alpha]_D^{20}$ −313.2 (*c* 1.14, DMSO); HPLC purity (method A): 99%, t_R=20.8 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.26 (s, 1H), 8.17 (d, *J*=7.9, 1H), 8.04 (s, 1H), 7.65–7.60 (m, 2H), 7.45–7.41 (m, 2H), 7.35–7.29 (m, 2H), 7.24–7.19 (m, 1H), 7.09–7.05 (m, 2H), 5.55–5.46 (m, 1H), 3.82 (s, 3H), 1.56 (d, *J*=7.0, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.7, 159.6, 155.6, 153.5, 144.7, 138.2, 128.3 (2C), 127.0 (2C), 126.7, 126.1 (2C), 125.8, 117.6, 114.8 (2C), 113.9, 55.3, 49.0, 22.5; IR (neat, cm^{-1}): 1606, 1493, 1255, 828, 766, 700; HRMS (ESI, *m/z*): 362.1323 (calcd $C_{21}H_{20}N_3OS$, 362.1322, M+H^+).

*4.3.16. (R)-6-(4-Methoxyphenyl)-N-(1-phenylethyl)thieno[2,3-d]pyrimidin-4-amine (**10b**) from **6b**.* Compound **6b** (148 mg, 0.535 mmol) was mixed with (*R*)-1-phenylethanamine (**9**) (205 mg, 1.69 mmol), and 1-butanol (2 mL) and agitated at 145 °C for 24 h. The mixture was cooled to rt, diluted with EtOAc (50 mL) and washed with water (3×25 mL) and saturated aq NaCl solution (15 mL). After drying over Na_2SO_4 and concentration in vacuum, the crude oil was purified by silica gel column chromatography (Et_2O/MeOH, 19/1). This gave 172 mg (0.476 mmol, 89%), mp. 179–182 °C; $[\alpha]_D^{20}$ −303.0 (*c* 1.12, DMSO); R_f (Et_2O/MeOH, 19/1)=0.42; HPLC purity (method A): 98%, t_R=20.8 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.26 (s, 1H), 8.17 (d, *J*=7.9, 1H), 8.04 (s, 1H), 7.65–7.60 (m, 2H), 7.45–7.41 (m, 2H), 7.35–7.29 (m, 2H), 7.24–7.19 (m, 1H), 7.09–7.05 (m, 2H), 5.54–5.47 (m, 1H), 3.82 (s, 3H), 1.56 (d, *J*=7.0, 3H).

*4.3.17. (R)-N-(1-Phenylethyl)-6-(4-(trifluoromethyl)phenyl)thieno[2,3-d]pyrimidin-4-amine (**10c**).* Compound **11**·HCl (201 mg, 0.542 mmol) was mixed with (4-(trifluoromethyl)phenyl)boronic acid (**5c**) (158 mg, 0.833 mmol), finely powdered K_2CO_3 (298 mg, 2.16 mmol), $Pd(PPh_3)_4$ (30 mg, 0.026 mmol), 1,4-dioxane (2 mL) and water (2 mL). The reaction was then stirred at 110 °C for 3 h under an N_2 atmosphere. The solvent was removed and the product

was dissolved in CH_2Cl_2 (30 mL) and washed with water (3×20 mL), and saturated aq NaCl solution (20 mL). The organic phase was dried over Na_2SO_4, and filtered. To the CH_2Cl_2 phase was added HCl in diethyl ether (3 mL) and the mixture was kept at −18 °C for 18 h. The precipitated product was isolated by filtration and washed with diethyl ether (3×15 mL). Drying gave 160 mg (0.366 mmol, 68%) of **10c**·HCl as a white solid, mp. 280 °C (dec); $[\alpha]_D^{20}$ −281.4 (*c* 1.05, DMSO); HPLC purity (method A): 99%, t_R=26.7 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.44 (d, *J*=7.8, 1H), 8.39 (s, 1H), 8.32 (s, 1H), 7.88–7.80 (m, 4H), 7.47–7.42 (m, 2H), 7.35–7.29 (m, 2H), 7.24–7.19 (m, 1H), 5.56–5.47 (m, 1H), 1.58 (d, *J*=7.1, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.3, 156.0, 154.2, 144.4, 137.1–137.0 (m), 136.1, 128.3 (q, *J*=32.1), 128.3 (2C), 127.1 (q, *J*=282.8), 126.8, 126.3 (q, *J*=3.7, 2C), 126.10 (2C), 126.09 (2C), 117.9, 117.4, 49.2, 22.4; ^{19}F NMR (564 MHz, DMSO-d_6) δ: −60.6 (s); IR (neat, cm^{-1}): 2495, 1601, 1318, 1114, 1068, 697; HRMS (ESI, *m*/*z*): 400.1082 (calcd $C_{21}H_{17}F_3N_3S$, 400.1090, M+H$^+$).

*4.3.18. (R)-4-(4-(1-Phenylethylamino)thieno[2,3-d]pyrimidin-6-yl) phenol (**10d**).* Compound **10d** was made as described in Section 4.3.14 starting with (4-hydroxyphenyl)boronic acid (**5d**) (112 mg, 0.812 mmol). The reaction time was 2.5 h. This gave 165 mg (0.430 mmol, 80%) of **10d**·HCl as a white solid, mp. 185–187 °C; $[\alpha]_D^{20}$ −304.1 (*c* 0.98, DMSO); HPLC purity (method A): 99%, t_R=16.8 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.84 (s, 1H), 8.24 (s, 1H), 8.13 (d, *J*=7.9, 1H), 7.97 (s, 1H), 7.54–7.49 (m, 2H), 7.45–7.40 (m, 2H), 7.35–7.29 (m, 2H), 7.24–7.19 (m, 1H), 6.91–6.86 (m, 2H), 5.55–5.46 (m, 1H), 1.56 (d, *J*=7.0, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.5, 158.0, 155.5, 153.4, 144.7, 138.8, 128.3 (2C), 127.1 (2C), 126.7, 126.1 (2C), 124.3, 117.6, 116.1 (2C), 113.2, 49.0, 22.5; IR (neat, cm^{-1}): 3057 (br), 2978 (br), 1606, 1492, 832, 765, 698; HRMS (ESI, *m*/*z*): 348.1164 (calcd $C_{20}H_{18}N_3OS$, 348.1165, M+H$^+$).

*4.3.19. (R)-3-(4-(1-Phenylethylamino)thieno-[2,3-d]pyrimidin-6-yl) phenol (**10e**).* Compound **10e** was made as described in Section 4.3.14 starting with (3-hydroxyphenyl)boronic acid (**5e**) (113 mg, 0.817 mmol), and reacting for 2.5 h. This gave 188 mg (0.488 mmol, 91%) of **10e**·HCl as a white solid, mp. 175–178 °C; $[\alpha]_D^{20}$ −303.7 (*c* 0.99, DMSO); HPLC purity (method A): 99%, t_R=17.6 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.73 (s, 1H), 8.28 (s, 1H), 8.23 (d, *J*=7.9, 1H), 8.14 (s, 1H), 7.46–7.41 (m, 2H), 7.36–7.27 (m, 3H), 7.25–7.19 (m, 1H), 7.15–7.11 (m, 1H), 7.10–7.07 (m, 1H), 5.56–5.47 (m, 1H), 1.57 (d, *J*=7.0, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.0, 158.0, 155.8, 153.9, 144.6, 138.3, 134.4, 130.4, 128.3 (2C), 126.7, 126.1 (2C), 117.4, 116.5, 115.7, 115.4, 112.3, 49.0, 22.5; IR (neat, cm^{-1}): 3059 (br), 2929 (br), 1600, 1583, 764, 698; HRMS (ESI, *m*/*z*): 348.1164 (calcd $C_{20}H_{18}N_3OS$, 348.1165, M+H$^+$).

*4.3.20. (R)-2-(4-(1-Phenylethylamino)thieno[2,3-d]pyrimidin-6-yl) phenol (**10f**).* The reaction was performed as described in Section 4.3.14 starting with (2-hydroxyphenyl)boronic acid (**5f**) (113 mg, 0.819 mmol), and reacting for 3 h. Work-up was done by extraction using diethyl ether (75 mL) followed by washing with water (3×15 mL), and a saturated aq NaCl solution (20 mL). The organic phase was dried over Na_2SO_4, and filtered. To the diethyl ether phase was added HCl in diethyl ether (1 mL) and the mixture was kept at −18 °C for 12 h. The precipitated product was isolated by filtration and washed with cold diethyl ether (3×15 mL). Drying gave 191 mg (0.497 mmol, 92%) of **10f**·HCl as a white solid, mp. 201–203 °C; $[\alpha]_D^{20}$ −308.1 (*c* 0.75, DMSO); HPLC purity (method A): 97%, t_R=17.7 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.42 (s, 1H), 8.62 (s, 1H), 8.24 (s, 1H), 8.22 (d, *J*=8.0, 1H), 7.69–7.65 (n, 1H), 7.45–7.41 (m, 2H), 7.35–7.29 (m, 2H), 7.24–7.18 (m, 2H), 7.03–6.99 (m, 1H), 6.97–6.91 (m, 1H), 5.57–5.48 (m, 1H), 1.57 (d, *J*=7.1, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.4, 155.5, 153.9, 153.4, 144.8, 134.9, 129.3, 128.3 (2C), 127.8, 126.6, 126.1 (2C), 120.1, 119.6, 116.5, 116.3, 116.2, 48.9, 22.5; IR (neat, cm^{-1}): 3068 (br), 2978 (br), 1603, 1453, 1104, 751, 700; HRMS (EI, 70 eV, *m*/*z*): 347.1087 (calcd $C_{20}H_{17}N_3OS$, 347.1087, M$^+$).

*4.3.21. (R)-6-Mesityl-N-(1-phenylethyl)thieno[2,3-d]pyrimidin-4-amine (**10g**).* The reaction and extractive work-up were performed as described in Section 4.3.14 starting with mesitylboronic acid (**5 g**) (136 mg, 0.827 mmol). The reaction time was 3 h. The crude product was absorbed onto silica and purified by silica gel column chromatography (*n*-pentane/EtOAc, 3/1). The purified product was dissolved in diethyl ether (50 mL), and HCl in diethyl ether (1 mL) was added. The solution was then cooled to −18 °C for 93 h, and the resulting solid material was isolated by filtration, and washed with diethyl ether (3×15 mL). Drying gave 164 mg (0.401 mmol, 74%) of **10g**·HCl as a pale white solid, mp. 217–221 °C; $[\alpha]_D^{20}$ −171.3 (*c* 1.03, DMSO); R_f (*n*-pentane/EtOAc, 3/1)=0.36. HPLC purity (method A): 99%, t_R=43.1 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.31 (s, 1H), 8.12 (d, *J*=7.9, 1H), 7.51 (s, 1H), 7.45–7.41 (m, 2H), 7.35–7.29 (m, 2H), 7.24–7.19 (m, 1H), 7.00 (s, 2H), 5.56–5.47 (m, 1H), 2.29 (s, 3H), 2.13 (s, 6H), 1.55 (d, *J*=7.0, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.1, 155.7, 153.4, 144.6, 138.0 (2C), 137.1, 136.4, 129.8, 128.3 (2C), 128.2 (2C), 126.7, 126.1 (2C), 118.9, 116.7, 49.0, 22.4, 20.7, 20.3 (2C); IR (neat, cm^{-1}): 1606, 1495, 850, 762, 699; HRMS (EI, 70 eV, *m*/*z*): 373.1607 (calcd $C_{23}H_{23}N_3S$, 373.1607, M$^+$).

*4.3.22. (R)-N-(1-Phenylethyl)-6-(2,4,6-tri-isopropylphenyl)thieno [2,3-d]pyrimidin-4-amine (**10h**).* The reaction was performed as described in Section 4.3.14 starting with (2,4,6-triisopropylphenyl) boronic acid (**5h**) (203 mg, 0.818 mmol). The reaction time was 22 h. Work-up was done by extraction using diethyl ether (20 mL), followed by washing with water (3×15 mL), and a saturated aq NaCl solution (20 mL). The concentrated crude product was absorbed onto silica and purified by flash chromatography (*n*-pentane/EtOAc, 1/1). Then the free amine was precipitated as it HCl salt by dissolving in diethyl ether (2 mL) followed by slow addition of *n*-pentane (30 mL) and HCl in diethyl ether (2 mL). The material isolated after 23 h at −18 °C, was washed with *n*-pentane (3×15 mL). Drying gave 228 mg (0.364 mmol, 67%) of **10h**·HCl as a pale white solid, mp. 215–219 °C; $[\alpha]_D^{20}$ −127.2 (*c* 1.08, DMSO); R_f (*n*-pentane/EtOAc, 1/1)=0.90; HPLC purity (method A): 99%, t_R=52.3 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.32 (s, 1H), 8.13 (d, *J*=7.9, 1H), 7.54 (s, 1H), 7.45–7.41 (m, 2H), 7.35–7.30 (m, 2H), 7.24–7.19 (m, 1H), 7.13 (s, 2H), 5.58–5.48 (m, 1H), 2.93 (sept, *J*=6.8, 1H), 2.83–2.70 (m, 2H), 1.56 (d, *J*=7.1, 3H), 1.24 (d, *J*=6.8, 6H), 1.15–1.09 (m, 12H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.0, 155.7, 153.5, 149.6, 148.17, 148.16, 144.6, 136.2, 128.3 (2C), 127.3, 126.7, 126.2 (2C), 120.6 (2C), 119.4, 116.5, 49.1, 33.7, 30.2 (2C), 24.5 (2C), 24.0, 23.94, 23.86 (2C), 22.4; IR (neat, cm^{-1}): 2959, 2867, 1605, 1363, 877, 761, 698; HRMS (EI, 70 eV, *m*/*z*): 457.2543 (calcd $C_{29}H_{35}N_3S$, 457.2546, M$^+$).

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