

# Access and Regioselective Transformations of 6-Substituted 4-Aryl-2,8-dichloropyrido[3,2-*d*]pyrimidine Compounds

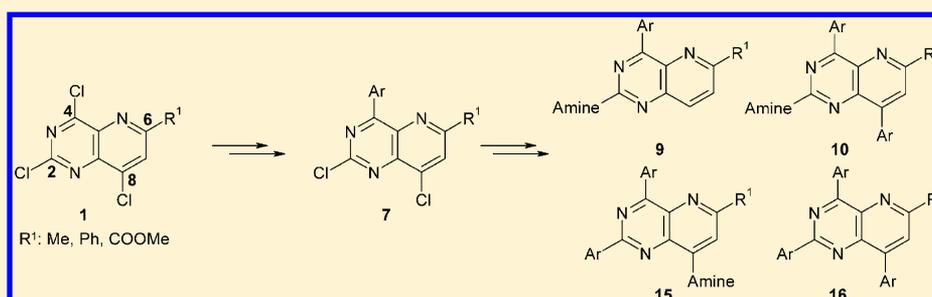
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## Supporting Information



**ABSTRACT:** We report herein an efficient route for the synthesis of 2,4,8-trichloropyrido[3,2-*d*]pyrimidines **1** with R<sup>1</sup> substituents at C-6. The potential of such scaffolds was demonstrated by the possibility to displace regioselectively each aromatic chloride to introduce diversity. Sequential sulfur nucleophilic addition followed by Liebeskind–Srogl cross-coupling reaction yielded unprecedented aryl introduction at C-4 on a trichloropyrido[3,2-*d*]pyrimidine derivative. The reactivity difference of the remaining two chlorides toward S<sub>N</sub>Ar reactions was investigated. Amination yielded high C-2 regioselectivity, while thiolation was influenced by C-6 substituents, resulting in medium to high C-2 versus C-8 regioselectivity. The last chloride was efficiently displaced by S<sub>N</sub>Ar, Suzuki–Miyaura cross-coupling reaction, or reduction. C-2 arylation as a final step was also possible by Liebeskind–Srogl cross-coupling reaction on the previously introduced C-2 thioether. A concise and highly divergent synthetic use of **1** was developed, thereby providing an efficient approach to explore the structure–activity relationship of pyrido[3,2-*d*]pyrimidine derivatives such as **9**, **10**, **15**, and **16**.

## INTRODUCTION

Given the vastness of the chemical space, the challenge for medicinal chemists is to identify cores that are more likely to lead to drug candidates.<sup>1,2</sup> In our continued effort to design lead-like arrays of compounds to be included in our corporate screening collection, we were particularly interested in the accessibility of heterocyclic scaffolds bearing several reactive sites, which could be functionalized regioselectively for straightforward synthesis of analogues. In this context, we have recently reported the synthesis of 4-amino-2,8-dichloropyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester derivative **1c** and its regioselective diversification through S<sub>N</sub>Ar and metal-catalyzed cross-coupling reactions (Scheme 1).<sup>3</sup> We report herein an extension of our studies on pyrido[3,2-*d*]pyrimidines with a general synthesis of 2,4,8-trichloropyrido[3,2-*d*]pyrimidines **1** having methyl, phenyl, and ester groups at C-6 and the successive and selective displacement of the different chlorides. The synthesis of such a scaffold **1**, with different groups at C-6, provided an interesting challenge. Only two examples were reported.<sup>4,5</sup> Then regiocontrolled diversification of the resulting scaffold **1** is described through S<sub>N</sub>Ar<sup>6</sup> and metal-catalyzed

cross-coupling reactions,<sup>7</sup> starting with a C-4 arylation, and leading to a set of novel and diverse C–N- and C–C-substituted pyrido[3,2-*d*]pyrimidines **9**, **10**, **15**, and **16** (Scheme 1).

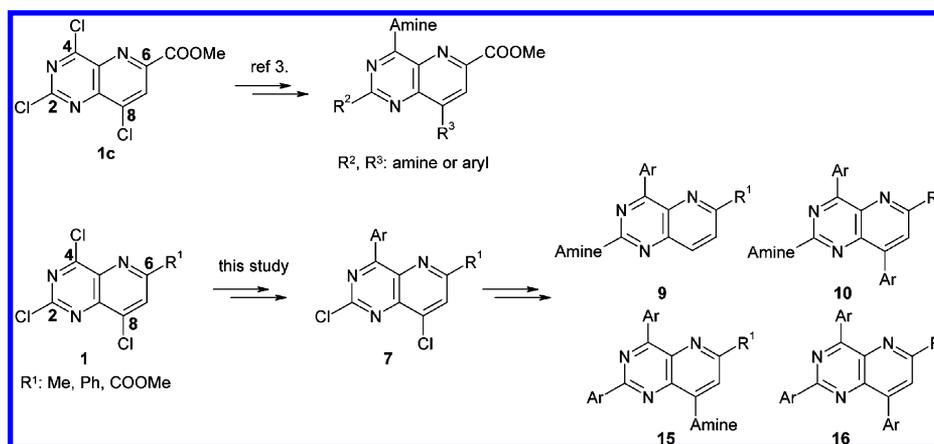
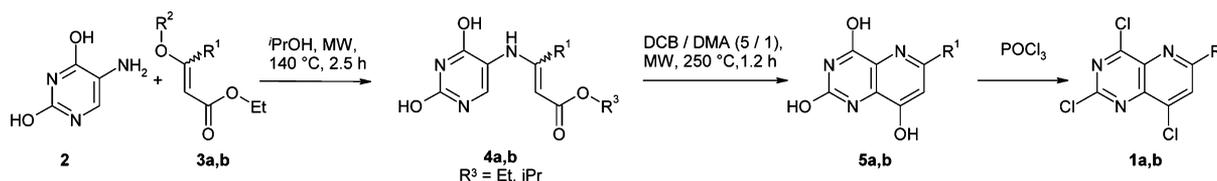
## RESULTS AND DISCUSSION

We first developed a general protocol for the synthesis of **1**, substituted at C-6 with a methyl or an aryl group, starting from aminouracil **2** and 3-substituted 3-alkoxyacrylic acid alkyl esters **3** (Table 1).

Aminouracil **2** and 3-substituted 3-alkoxyacrylic acid alkyl esters **3**<sup>8</sup> were heated at 140 °C in *t*-PrOH under microwave irradiation, yielding enamines **4a,b** as a mixture of ethyl and isopropyl esters having *E* and *Z* isomers. This mixture was used without any purification in the next step. In the second step, cyclization of enamines **4** into 6-substituted 2,4,8-trihydroxy-pyrido[3,2-*d*]pyrimidines **5** was performed at 250 °C under microwave irradiation. The reaction was performed in a mixture of dimethylacetamide (DMA) and 1,2-dichlorobenzene (DCB)

Received: January 25, 2012

Published: April 13, 2012

Scheme 1. Regioselective Transformations of **1**Table 1. Synthesis of **1**

entry	SM	R <sup>1</sup>	R <sup>2</sup>	products (% yield)
1	3a	Me	Et	5a (84) 1a <sup>a</sup> (78)
2	3b	Ph	Me	5b (86) 1b <sup>b</sup> (85)

<sup>a</sup>Chlorination conditions: POCl<sub>3</sub>, PhNEt<sub>2</sub>, reflux, 16 h. <sup>b</sup>Chlorination conditions: POCl<sub>3</sub>, 200 °C under microwave irradiations, 1.5 h.

in a 5/1 ratio, a solvent mixture which ensured the solubilization of the starting material and guaranteed complete conversion. Following these conditions, derivatives **5a** and **5b** were isolated in 84% and 86% yields, respectively (Table 1, step 2, entries 1 and 2).

Two protocols were used for the last step, chlorination of derivatives **5**. A solution of **5a** with *N,N*-diethylaniline in an excess of POCl<sub>3</sub> was heated at reflux to lead after 16 h to derivative **1a** in 78% yield (Table 1, step 3, entry 1). We found that **5b** was efficiently transformed into 6-substituted 2,4,8-trichloropyrido[3,2-*d*]pyrimidine **1b** in neat POCl<sub>3</sub> heated for 1.5 h at 200 °C under microwave irradiation. Derivative **1b** was obtained in 85% yield (Table 1, step 3, entry 2). An efficient access to 6-substituted 2,4,8-trichloropyrido[3,2-*d*]pyrimidines **1a,b** was developed in three steps with 30–52% overall yield. The use of microwave irradiation allowed us to shorten the reaction time from overnight to 1.5 to 2.5 h.<sup>9</sup>

Selective displacement of the different chlorides in compounds **1** was then investigated. We focus this study on the regioselective metal-catalyzed cross-coupling reaction of **1** at C-4 (Scheme 1). For this, in addition to derivatives **1a,b**, derivative **1c** was also used and prepared according to the literature.<sup>5</sup> Suzuki–Miyaura cross-coupling reaction, using various reaction conditions, yielded either partial conversion or multiple product mixtures.<sup>10</sup> Coupling conditions described to be selective on 2,4-dichloropyrido[3,2-*d*]pyrimidine, using Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst and K<sub>2</sub>CO<sub>3</sub> as base, in toluene at 100 °C, did neither improve the regioselectivity nor the conversion.<sup>11</sup> Alternative cross-coupling reactions on derivative **1c** such as Stille cross-coupling reactions were not successful either.<sup>10</sup>

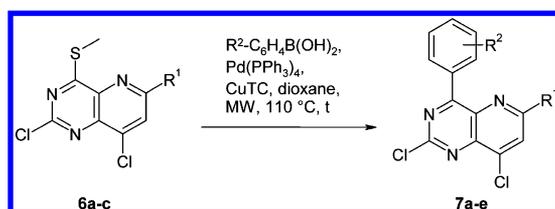
At this point, Liebeskind–Srogl cross-coupling reaction was investigated as an option.<sup>12</sup> As previously reported, S<sub>N</sub>Ar

reactions on **1c** is highly regioselective at C-4.<sup>3,5</sup> Taking advantage of it, sulfur nucleophilic addition was performed regioselectively at C-4 to lead to **6**. Sodium methylthiolate was added to a solution of derivative **1** in THF at –10 °C. At this temperature, derivatives **6a–c** were obtained in good yields (Table 2, entries 1–3). At higher temperatures, multiple methylsulfanyl addition products were formed.<sup>13</sup>

Table 2. S<sub>N</sub>Ar with Sodium Methylthiolate on **1** at C-4

entry	SM	R <sup>1</sup>	product	yield (%)
1	1a	Me	6a	84
2	1b	Ph	6b	85
3	1c	COOMe	6c	84

Arylation of derivatives **6a–c** was then achieved via Liebeskind–Srogl cross-coupling reactions with boronic acid derivatives having different electronic properties such as unsubstituted or substituted aryl with electron-donating or -withdrawing groups (Table 3). The reactions were performed in dioxane at 100 °C under microwave irradiation with Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst and copper(I) thiophene-2-carboxylate (CuTC) as cofactor.<sup>14</sup> 4-Aryl-2,8-dichloropyrido[3,2-*d*]pyrimidine derivatives **7a–e** were isolated in 77–82% yields (Table 3). No side reaction took place at the two remaining C–Cl bonds, which is in agreement with the orthogonality of the Liebeskind–Srogl methylsulfanyl cross-coupling protocol versus the Suzuki–Miyaura reaction.<sup>15</sup>

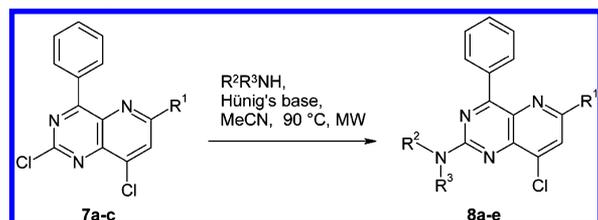
**Table 3. Liebeskind–Srogl Cross-Coupling Reactions on 6 at C-4**

entry	SM	R <sup>1</sup>	R <sup>2</sup>	time (h)	product	yield (%)
1	6a	Me	H	0.5	7a	81
2	6b	Ph	H	1.5	7b	78
3	6c	COOMe	H	1	7c	79
4	6c	COOMe	4-MeO	1.5	7d	82
5	6c	COOMe	4-CF <sub>3</sub>	0.5	7e	77

In addition, the nature of C-6 substituent of derivatives **6** (Table 3, entries 1–3) and the electronic properties of the boronic acid derivatives (Table 3, entries 3–5) had no impact on the reaction time or on the isolated yield. This two-step process, methylsulfanyl aromatic substitution followed by Liebeskind–Srogl cross-coupling reaction, yielded the selective introduction of C–C bond at position 4.

The reactivity difference between the two remaining chlorides at positions 2 and 8 of derivatives **7** was then studied. S<sub>N</sub>Ar and metal-catalyzed cross-coupling reactions were investigated.

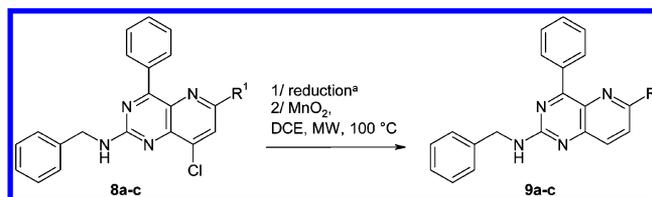
Amination of **7** was achieved with the addition of an amine at 90 °C in MeCN under microwave irradiation.<sup>9</sup> Reaction of derivatives **7a–c** with benzylamine yielded derivatives **8a–c** in yield ranging from 69 to 83% (Table 4, entries 1–3). Similar

**Table 4. S<sub>N</sub>Ar with Diverse Amines on 7a–c at C-2**

entry	SM	R <sup>1</sup>	R <sup>2</sup> R <sup>3</sup> NH <sub>2</sub>	product	yield (%)
1	7a	Me	BnNH <sub>2</sub>	8a	71
2	7b	Ph	BnNH <sub>2</sub>	8b	69
3	7c	COOMe	BnNH <sub>2</sub>	8c	83
4	7c	COOMe	BuNH <sub>2</sub>	8d	81
5	7c	COOMe	Et <sub>2</sub> NH	8e	85

yields were obtained with addition to **7c** of primary amine and secondary amines, such as butylamine and diethylamine, affording derivatives **8d** and **8e** in 81 and 85% yield, respectively (Table 4, entries 4 and 5). Selective C-2 addition was always obtained even in the presence of an excess of amine.

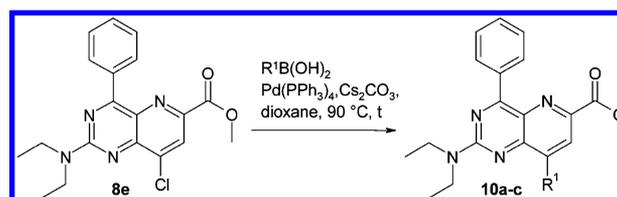
Dehalogenation of the remaining chloride of **8a–c** afforded compounds **9a–c** in 70–75% yield (Table 5, entries 1–3). As partial reduction of the pyrido[3,2-*d*]pyrimidines core occurred during this reaction, MnO<sub>2</sub> was added to rearomatize the pyridopyrimidine ring. The <sup>1</sup>H NMR spectra of dehalogenated products **9a–c** consisted of a pair of doublets corresponding to H-7 and H-8, with a *J*<sup>3</sup> coupling constant of 8.9 Hz. These results conclusively proved that benzylamine added regioselectively to **7** at C-2, leaving a chloride substituent at position 8.

**Table 5. Reduction of C-8 Chloride on 8a–c**

entry	R <sup>1</sup>	product	yield (%)
1	Me	9a	75
2	Ph	9b	71
3	COOMe	9c	73

<sup>a</sup>Dehalogenation using continuous-flow hydrogenation reactor: 10% Pd/C cartridge at 70 °C with a flow of 4 mL/min at 5–7 bar (“Full Hydrogen” mode).<sup>16</sup>

This first succession of transformations proceeded well to provide 2,4,6-trisubstituted pyrido[3,2-*d*]pyrimidine derivatives **9**. Alternatively, reactivity of the chloride at C-8 on derivatives **8** was evaluated toward metal-catalyzed cross-coupling reactions. Suzuki–Miyaura cross-coupling reaction, with Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst and cesium carbonate as base, afforded **10a–c** in 76–86% yields (Table 6, entries 1–3). It was possible to use

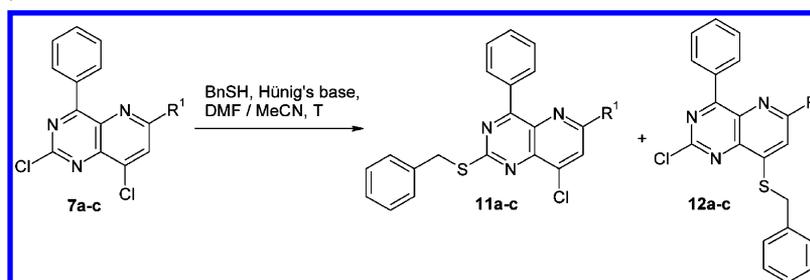
**Table 6. Suzuki–Miyaura Cross-Coupling Reaction on 8e at C-8**

entry	R <sup>1</sup> B(OH) <sub>2</sub>	time (h)	product	yield (%)
1	PhB(OH) <sub>2</sub>	7	10a	80
2	4-MeO-C <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	4	10b	86
3	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> B(OH) <sub>2</sub>	3.5	10c	82

boronic acid derivatives with electron-donating and electron-withdrawing group substitution.

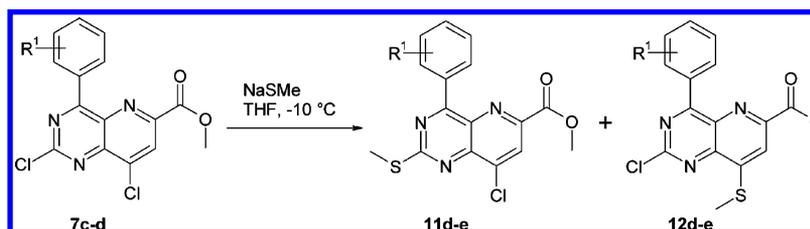
Thus, we have described C-2 amination of derivatives **7** and C-8 reactivity of the resulting 4-aryl-2-aminopyrido[3,2-*d*]pyrimidines **8** toward reduction and Suzuki–Miyaura cross-coupling reactions. C-2-regioselective arylation of **7** is next reported.

As already observed for compound **1** or 4-amino-2,8-dichloropyrido[3,2-*d*]pyrimidine derivatives,<sup>3</sup> direct arylation of derivative **7** via metal-catalyzed cross-coupling reactions yielded either partial conversion or multiple site reactions. As previously described, the two remaining chlorides needed to be first differentiated by selective thiolation of one of them. The regioselectivity of the thiolation was studied with benzylthiol and sodium methylthiolate. Benzylthiol in the presence of Hünig's base was added to a solution of derivatives **7a–c** in a mixture of MeCN and DMF. Contrary to the regioselective amination, two regioisomers were formed, derivatives **11** and **12**, with the benzylsulfanyl substituent at C-2 or C-8 positions, respectively (Table 7, entries 1–3). While thiolation of **7a** and **7b** took place at 90 °C under microwave irradiation (Table 7, entries 1 and 2), this reaction surprisingly occurred at room temperature with derivative **7c** (R<sup>1</sup> = COOMe, Table 7, entry 3). The higher reactivity of **7c** compared to **7a** and **7b** may be explained by the presence of an electron-withdrawing group at

Table 7.  $S_NAr$  with Benzylthiol on 7a–c

entry	SM	R <sup>1</sup>	T (°C)	product	UHPLC ratio <sup>a</sup>	yield (%)
1	7a	Me	90	11a/12a	74/26	60/20
2	7b	Ph	90	11b/12b	72/28	60/18
3	7c	COOMe	rt	11c/12c	83/17	73/12

<sup>a</sup>The ratios were determined on the reaction mixtures by UHPLC–MS to evaluate most accurately the regioisomer ratio. All regioisomers were isolated and fully characterized.

Table 8.  $S_NAr$  with Sodium Methylthiolate on 7c–d

entry	SM	R <sup>1</sup>	product	UPLC ratio	yield (%)
1	7c	H	11d/12d	92/8	60/0
2	7d	4-OMe	11e/12e	92/8	57/0

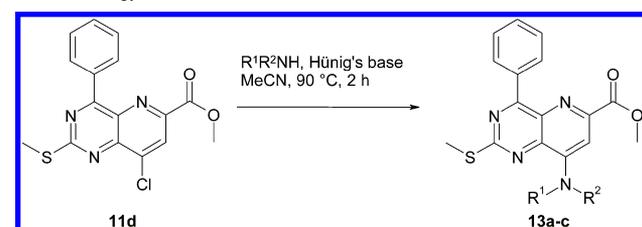
C-6. Regioisomers 11a–c and 12a–c were isolated in 60–73% and 12–20% yields, respectively.

Attribution of the substitution pattern of derivatives 12a–c was based on the results of NOESY experiments. For these derivatives, NOESY correlation between the benzylic protons of the thioether and H-7 were observed, confirming that the minor regioisomers resulted from thiol addition at position 8. No relevant information on major regioisomers 11a–c could be obtained from NOESY experiments, but they show the same mass but a different retention time in UHPLC–MS and different <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts than 12a–c. The identity of 11a–c was deduced from the assignment of 12a–c structure, respectively, confirming that thiolation of 7a–c took place predominantly at C-2. Partial charge distribution between C-2 and C-8 of 7 may drive the observed regioselectivity at C-2.<sup>17</sup> It is slightly influenced by the nature of R<sup>1</sup>, possibly explaining the higher regioselectivity obtained with R<sup>1</sup> = COOMe compared with R<sup>1</sup> = Me or Ph (Table 7, entry 3 versus 1 and 2). Interestingly, a pyrido[3,2-d]pyrimidine derivative with an aryl substituent at C-4 activates more the C-2 position for nucleophilic attack compared with an electron-donating group, such as an amine at C-4.<sup>18</sup> In addition, the preferred C-2 regioselectivity is not influenced by the nature of the nucleophile, such as an amine, a thiol, or a thiolate.

Thiolation was further investigated with sodium methylthiolate on derivatives 7c and 7d, having phenyl and 4-OMe-phenyl groups at C-4, respectively. This reaction was performed at –10 °C in THF to avoid double thiolation observed at higher temperature. Under these conditions, conversion did not exceed 75%, but a good regioselectivity for 11d–e was obtained with an 11d–e/12d–e ratio of 92/8. Derivatives 11d–e were

obtained in 57 and 60% yield, respectively (Table 8, entries 1 and 2). Such a transformation offered a convenient way to differentiate the two remaining reactive centers at C-2 and C-8, leading to key scaffolds 11. Derivative 11d was selected for further diversification.

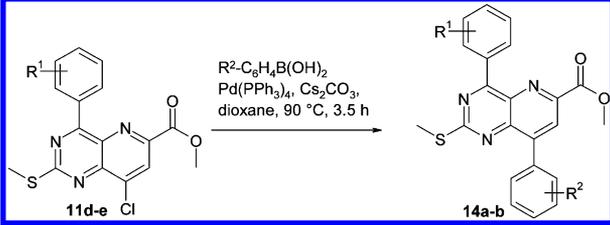
The remaining chloride of derivative 11d was readily substituted with diverse primary and secondary amines in MeCN. After 2 h at 90 °C, derivatives 13a–c were isolated in 73–84% yields (Table 9, entries 1–3). The position and nature

Table 9.  $S_NAr$  with Diverse Amines on 11d at C-8

entry	R <sup>1</sup> R <sup>2</sup> N	product	yield (%)
1	BnNH	13a	73
2	BuNH	13b	83
3	Et <sub>2</sub> N	13c	84

of each substituent of derivatives 13 corroborate with X-ray crystallographic analysis of derivative 13b. This result also confirms the reactivity order of the three chlorides of derivatives 1.

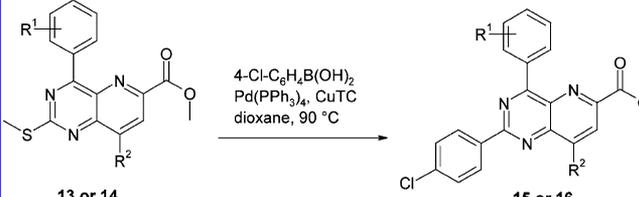
Alternatively, derivatives 11d and 11e were transformed by Suzuki–Miyaura reaction into 14a and 14b in 75–82% yield, respectively (Table 10). When previously described conditions

**Table 10. Suzuki–Miyaura Cross-Coupling Reaction on 11d and 11e at C-8**


entry	SM	R <sup>1</sup>	R <sup>2</sup>	product	yield (%)
1	11d	H	4-MeO	14a	75
2	11e	4-MeO	H	14b	82

(Table 6) were used, the methylsulfanyl group remained unchanged, demonstrating for this transformation the orthogonality of both reactive centers at C-2 and C-8.

Then, compounds 13a–c and 14a,b could be used as obvious intermediates for Liebeskind–Srogl reaction for the introduction of an additional C–C bond at C-2. A stoichiometric amount of boronic acid derivatives was used, with Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst and copper(I) thiophene-2-carboxylate (CuTC) as cofactor. After 3.5 h in dioxane at 90 °C, compounds 15 and 16 were isolated in 69–80% yields (Table 11).

**Table 11. Liebeskind–Srogl Cross-Coupling Reaction on 13 or 14 at C-2**


entry	SM	R <sup>1</sup>	R <sup>2</sup>	product	yield (%)
1	13a	H	BnNH	15a	71
2	13c	H	Et <sub>2</sub> N	15b	76
3	14a	H	4-MeO-C <sub>6</sub> H <sub>4</sub>	16a	80
3	14b	4-MeO	Ph	16b	69

These combinations of S<sub>N</sub>Ar and cross-coupling reactions allowed the successive and regioselective introduction of a wide diversity of groups at C-4, C-2, and C-8, yielding novel and diverse compounds 15 and 16 in good yields.

## CONCLUSIONS

Following an efficient synthetic route for compounds 1 with various groups at C-6, we have reported the potential of trichloropyrido[3,2-*d*]pyrimidine scaffolds and their regioselective chloride displacement. Selective C-4 arylation was achieved via the tandem sulfur nucleophilic addition followed by Liebeskind–Srogl cross-coupling reaction. The reactivity difference of the remaining two chlorides toward S<sub>N</sub>Ar reactions was investigated, with the preferred C-2 addition of amine, thiol, or thiolate derivatives. The last chloride at C-8 was efficiently displaced by S<sub>N</sub>Ar, Suzuki–Miyaura cross-coupling reaction, or reduction. The observed reactivity order was not influenced by the nature of the C-6 substituent. C-2 arylation as a final step was also possible by Liebeskind–Srogl cross-coupling reaction on the previously introduced C-2 thioether. With the development of a robust route for the synthesis of scaffold 1

and regioselective conditions for the displacement of the three chlorides, we were able to prepare a wide variety of analogues, as shown with representative examples in this paper, such as compounds 9, 10, 15, and 16. This versatile strategy has been applied for the production of a large array of compounds that are currently under biological evaluation, in particular as lipid, tyrosine, and protein kinase inhibitors.

## EXPERIMENTAL SECTION

**General Procedures.** The commercially available starting materials were used without further purification. Melting points were reported without correction. IR analyses were performed by attenuated total reflectance (ATR) FT-IR spectroscopy. <sup>1</sup>H NMR spectra were recorded at 300 or 400 MHz, and <sup>13</sup>C NMR spectra were recorded at 75.47 or 100.63 MHz, as indicated next to each NMR analysis. <sup>1</sup>H and <sup>13</sup>C chemical shifts (δ) were internally referenced to the residual solvent peak. Mass spectra and high-resolution mass spectra were acquired by electrospray ionization. The HPLC analysis was performed on a C8 column (50 × 4.6 mm 3.5 μm) with a gradient from 95% H<sub>2</sub>O (0.1% TFA)/5% MeCN (0.1% TFA) to 5% H<sub>2</sub>O (0.1% TFA)/95% MeCN (0.1% TFA) over 8 min with a flow of 2 mL/min. The preparative HPLC purifications were performed with a mass-directed autopurification system. All HPLC purifications were performed with a gradient of MeCN/H<sub>2</sub>O.

The microwave chemistry was performed on a single-mode microwave reactor Emrys Optimiser from Personal Chemistry or a single-mode microwave reactor Initiator 60 from Biotage in sealed reaction vessels.

Unless otherwise mentioned, all reactions described in this paper were monitored by LC–MS and stopped when all of the starting material was converted into the product(s) or when no further conversion was observed.

**General Procedure for Synthesis of Enamine 4 and Trihydroxypyrido[3,2-*d*]pyrimidines 5.** A mixture of 5-aminouracil 2 (1.0 g; 7.87 mmol) and derivative 3 (8.65 mmol) in <sup>i</sup>PrOH (5.0 mL) was heated at 140 °C for 2.5 h under microwave irradiation. The resulting yellow precipitate was filtered off, washed twice with MeOH and once with diethyl ether, and dried under suction affording enamines 4. A mixture of ethyl and isopropyl esters (products from trans-esterification) was obtained. Compounds 4a,b were used without further purification in the next step. A suspension of derivative 4 (4.18 mmol) in a mixture of DMA (1.0 mL) and 1,2-dichlorobenzene (5.0 mL) was heated at 250 °C for 1.2 h under microwave irradiation. A solid precipitated out. It was filtered, washed twice with MeOH and once with diethyl ether, and dried under suction, affording derivatives 5.

**6-Methyl-1,5-dihydropyrido[3,2-*d*]pyrimidine-2,4,8-trione (5a):** yield = 84%; pale brown solid; mp >300 °C dec; IR ν<sub>max</sub> 3195, 1684, 1633, 1552, 1417 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ<sub>H</sub> 2.29 (s, 3H), 6.15 (s, 1H), 10.48 (s, 1H), 11.70 (s, 1H), 11.99 (br s, 1H); <sup>13</sup>C NMR (75.47 MHz, DMSO-*d*<sub>6</sub>) δ<sub>C</sub> 18.7, 113.3, 116.1, 119.8, 131.7, 148.2, 148.9, 159.8; HPLC t<sub>R</sub> = 0.41 min; ES-MS *m/z* 194.0 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>8</sub>H<sub>7</sub>N<sub>3</sub>O<sub>3</sub>: C, 49.75; H, 3.65; N, 21.75. Found: C, 49.66; H, 3.49; N, 21.96.

**6-Phenyl-1,5-dihydropyrido[3,2-*d*]pyrimidine-2,4,8-trione (5b):** yield = 86%; beige solid; mp >300 °C dec; IR ν<sub>max</sub> 3010, 2843, 1681, 1479 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ<sub>H</sub> 7.48–7.88 (m, 6H), 10.66 (s, 1H), 11.55 (br s, 1H), 11.85 (br s, 1H); <sup>13</sup>C NMR (75.47 MHz, DMSO-*d*<sub>6</sub>) δ<sub>C</sub> 126.8, 127.0, 128.6, 129.4, 141.8, 143.0, 149.2, 169.3; HPLC t<sub>R</sub> = 1.51 min; ES-MS *m/z* 254 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>13</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>·0.08H<sub>2</sub>O: C, 60.83; H, 3.60; N, 16.37. Found: C, 60.44; H, 3.48; N, 16.47.

**2,4,8-Trichloro-6-methylpyrido[3,2-*d*]pyrimidine (1a).** A suspension of derivative 5a (600 mg, 3.11 mmol) in a mixture of POCl<sub>3</sub> (15.0 mL) and *N,N*-diethylaniline (0.6 mL) was stirred at reflux for 16 h. The mixture was then cooled down to room temperature and POCl<sub>3</sub> was removed under vacuum at 40 °C. The reaction mixture was then cooled down to 0 °C and ice was added. A solid precipitated out. It was filtered, washed twice with MeOH and once with diethyl ether, and dried under suction, affording 1a as a beige solid (600 mg, 78%

yield): mp >219 °C dec; IR  $\nu_{\max}$  1545, 1454, 1388, 1145, 795  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  2.83 (s, 3H), 7.85 (s, 1H);  $^{13}\text{C NMR}$  (75.47 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  25.5, 130.6, 137.2, 142.7, 145.2, 155.3, 162.7, 165.5; HPLC  $t_{\text{R}}$  = 3.55 min; ES-MS  $m/z$  248.0 ( $\text{M} + \text{H}$ ) $^+$ . Anal. Calcd for  $\text{C}_8\text{H}_4\text{Cl}_3\text{N}_3$ : C, 38.67; H, 1.62; N, 16.91; Cl, 42.8. Found: C, 38.29; H, 1.70; N, 16.62; Cl, 42.52.

**2,4,8-Trichloro-6-phenylpyrido[3,2-d]pyrimidine (1b).** A suspension of derivative **5b** (793 mg, 3.11 mmol) in  $\text{POCl}_3$  (15 mL) was heated at 200 °C under microwave irradiation for 1.5 h. The reaction mixture was then cooled to 0 °C, and ice was added. A solid precipitated out. It was filtered, washed twice with MeOH and once with diethyl ether, and dried under suction, affording **1b** as a brown solid (816 mg, 85% yield): mp >300 °C dec; IR  $\nu_{\max}$  3012, 2843, 1681, 1479, 1420  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.56–7.58 (m, 3H), 8.19–8.22 (m, 2H), 8.43 (s, 1H);  $^{13}\text{C NMR}$  (75.47 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  126.6, 127.2, 128.7, 130.9, 135.6, 137.0, 142.8, 144.8, 154.8, 158.8, 165.7; HPLC  $t_{\text{R}}$  = 5.13 min; ES-MS  $m/z$  310.00 ( $\text{M} + \text{H}$ ) $^+$ . Anal. Calcd for  $\text{C}_{13}\text{H}_6\text{Cl}_3\text{N}_3 \cdot 0.05\text{H}_2\text{O}$ : C, 50.13; H, 1.97; N, 13.49; Cl, 34.15. Found: C, 49.74; H, 2.07; N, 13.85; Cl, 34.12.

**General Procedure for Synthesis of Derivatives 6.** To a suspension of derivative **1** (0.32 mmol) in THF (2 mL) was added sodium methylthiolate (22.4 mg, 0.32 mmol) at –10 °C. The reaction was stirred at –10 °C for 3 h. A solid precipitated out. It was filtered, washed twice with MeOH and once with diethyl ether, and dried under suction, affording derivatives **6**.

**2,8-Dichloro-4-methylsulfanyl-6-methylpyrido[3,2-d]pyrimidine (6a):** yield = 84%; off-white solid; mp 145.5–146.5 °C; IR  $\nu_{\max}$  1534, 1382, 1152, 799  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  2.67 (s, 3H), 2.75 (s, 3H), 7.72 (s, 1H);  $^{13}\text{C NMR}$  (75.47 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  13.2, 25.1, 129.7, 138.1, 141.1, 142.1, 156.4, 160.1, 178.1; HPLC  $t_{\text{R}}$  = 4.20 min; ES-MS  $m/z$  260.00 ( $\text{M} + \text{H}$ ) $^+$ . Anal. Calcd for  $\text{C}_9\text{H}_7\text{Cl}_2\text{N}_3\text{S}$ : C, 41.55; H, 2.71; N, 16.15; Cl, 27.26. Found: C, 41.67; H, 2.82; N, 16.11; Cl, 27.10.

**2,8-Dichloro-4-methylsulfanyl-6-phenylpyrido[3,2-d]pyrimidine (6b):** yield = 85%; pale yellow solid; mp 186.6–187.6 °C; IR  $\nu_{\max}$  1510, 1447, 1172, 803, 679  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  2.72 (s, 3H), 7.55–7.59 (m, 3H), 8.16–8.19 (m, 2H), 8.33 (s, 1H);  $^{13}\text{C NMR}$  (75.47 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  13.2, 126.2, 127.6, 129.2, 130.9, 136.5, 138.4, 141.5, 142.9, 156.7, 157.1, 179.0; HPLC  $t_{\text{R}}$  = 5.40 min; ES-MS  $m/z$  322.0 ( $\text{M} + \text{H}$ ) $^+$ . Anal. Calcd for  $\text{C}_{14}\text{H}_9\text{Cl}_2\text{N}_3\text{S}$ : C, 52.19; H, 2.82; N, 13.04. Found: C, 52.10; H, 2.85; N, 13.02.

**2,8-Dichloro-4-methylsulfanylpyrido[3,2-d]pyrimidine-6-carboxylic Acid Methyl Ester (6c):** yield = 84%; gray solid; mp 229–230 °C; IR  $\nu_{\max}$  1720, 1248  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  2.71 (s, 3H), 4.06 (s, 3H), 8.56 (s, 1H);  $^{13}\text{C NMR}$  (75.47 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  13.6, 54.0, 129.6, 138.4, 144.1, 144.3, 147.9, 159.5, 164.1, 180.7; HPLC  $t_{\text{R}}$  = 4.10 min; ES-MS  $m/z$  303.93 ( $\text{M} + \text{H}$ ) $^+$ . Anal. Calcd for  $\text{C}_{10}\text{H}_7\text{Cl}_2\text{N}_3\text{O}_2\text{S}$ : C, 39.49; H, 2.32; N, 13.82. Found: C, 39.19; H, 2.37; N, 13.71.

**General Procedure for Synthesis of Derivatives 7.** To a solution of derivative **6** (0.78 mmol) in dioxane (4 mL) were added a boronic acid derivative (1.55 mmol), copper(I) thiophene-2-carboxylate (295.6 mg, 1.55 mmol), and  $\text{Pd}(\text{PPh}_3)_4$  (46.2 mg, 0.04 mmol) under inert atmosphere. The reaction was heated under microwave irradiation at 110 °C for 0.5–1.5 h. After filtration through Celite, the residue was diluted with DCM (15 mL), washed with  $\text{NaHCO}_3$  saturated solution (10 mL) and brine (10 mL), and dried over  $\text{Na}_2\text{SO}_4$ . After solvents were removed under vacuum at 40 °C, the solid obtained was suspended in MeOH, filtered, washed twice with MeOH and once with diethyl ether, and dried under suction to afford derivatives **7a–e**.

**2,8-Dichloro-4-phenyl-6-methylpyrido[3,2-d]pyrimidine (7a):** yield = 81%; pale yellow solid; mp 158.5–159.5 °C; IR  $\nu_{\max}$  1524, 1329, 1150  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  2.78 (s, 3H), 7.55–7.60 (m, 3H), 7.79 (s, 1H), 8.42–8.45 (m, 2H);  $^{13}\text{C NMR}$  (75.47 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  25.5, 128.3, 129.1, 131.8, 132.3, 134.7, 137.8, 142.5, 145.9, 157.3, 160.8, 169.1; HPLC  $t_{\text{R}}$  = 4.75 min; ES-MS  $m/z$  290.00 ( $\text{M} + \text{H}$ ) $^+$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{14}\text{H}_9\text{Cl}_2\text{N}_3$  [ $\text{M} + 1$ ] $^+$  290.0246, found 290.0266. Anal. Calcd for  $\text{C}_{14}\text{H}_9\text{Cl}_2\text{N}_3 \cdot 0.28\text{H}_2\text{O}$ : C,

56.96; H, 3.26; N, 14.23; Cl, 24.02. Found: C, 56.58; H, 3.11; N, 14.23; Cl, 24.09.

**2,8-Dichloro-4,6-diphenylpyrido[3,2-d]pyrimidine (7b):** yield = 78%; off-white solid; mp 158 °C dec; IR  $\nu_{\max}$  2361, 2341, 1461, 774, 686  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  7.54–7.62 (m, 6H), 8.13 (br s, 2H), 8.41 (s, 1H), 8.50 (m, 2H);  $^{13}\text{C NMR}$  (75.47 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  125.7, 127.7, 128.3, 129.3, 131.0, 131.8, 132.4, 134.8, 136.8, 138.1, 143.4, 146.2, 157.6, 158.0, 169.8; HPLC  $t_{\text{R}}$  = 5.56 min; ES-MS  $m/z$  352.0 ( $\text{M} + \text{H}$ ) $^+$ . Anal. Calcd for  $\text{C}_{19}\text{H}_{11}\text{Cl}_2\text{N}_3$ : C, 64.79; H, 3.15; N, 11.93; Cl, 20.13. Found: C, 64.34; H, 3.15; N, 11.85; Cl, 19.92.

**2,8-Dichloro-4-phenylpyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (7c):** yield = 79%; brown solid; mp 230–231 °C; IR  $\nu_{\max}$  1712, 1524, 1246  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  4.08 (s, 3H), 7.57–7.65 (m, 3H), 8.59–8.62 (m, 2H), 8.64 (s, 1H);  $^{13}\text{C NMR}$  (75.47 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  53.8, 128.5, 128.7, 132.8, 132.9, 134.2, 137.8, 144.6, 147.8, 148.5, 160.2, 164.0, 170.6; HPLC  $t_{\text{R}}$  = 4.75 min; ES-MS  $m/z$  333.94 ( $\text{M} + \text{H}$ ) $^+$ . Anal. Calcd for  $\text{C}_{15}\text{H}_9\text{Cl}_2\text{N}_3\text{O}_2$ : C, 53.92; H, 2.71; N, 12.57. Found: C, 53.65; H, 2.93; N, 12.23.

**2,8-Dichloro-4-(4-methoxyphenyl)pyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (7d):** yield = 82%; brown solid; mp 247–248 °C; IR  $\nu_{\max}$  1723, 1251  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  3.94 (s, 3H), 4.09 (s, 3H), 7.09 (d,  $J$  = 9 Hz, 2H), 8.60 (s, 1H), 8.79 (d,  $J$  = 9 Hz, 2H);  $^{13}\text{C NMR}$  (75.47 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  54.0, 56.0, 114.6, 127.1, 128.5, 135.4, 138.0, 144.6, 148.0, 148.1, 160.4, 164.1, 164.3, 169.4; HPLC  $t_{\text{R}}$  = 4.87 min; ES-MS  $m/z$  363.93 ( $\text{M} + \text{H}$ ) $^+$ . Anal. Calcd for  $\text{C}_{16}\text{H}_{11}\text{Cl}_2\text{N}_3\text{O}_3$ : C, 52.77; H, 3.04; N, 11.54. Found: C, 52.38; H, 3.16; N, 11.19.

**2,8-Dichloro-4-(4-trifluoromethylphenyl)pyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (7e):** yield = 77%; beige solid; mp 183–184 °C; IR  $\nu_{\max}$  1731, 1320  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  4.09 (s, 3H), 7.86 (d,  $J$  = 8 Hz, 2H), 8.67 (s, 1H), 8.73 (d,  $J$  = 8 Hz, 2H);  $^{13}\text{C NMR}$  (75.47 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  53.9, 124.0 (q,  $J$  = 278.9 Hz), 125.5 (q,  $J$  = 3.6 Hz), 128.8, 133.0, 133.9 (q,  $J$  = 31.2 Hz), 137.3, 137.6, 145.0, 148.0, 148.9, 160.2, 163.8, 169.2; HPLC  $t_{\text{R}}$  = 5.31 min; ES-MS  $m/z$  401.94 ( $\text{M} + \text{H}$ ) $^+$ . Anal. Calcd for  $\text{C}_{16}\text{H}_8\text{Cl}_2\text{F}_3\text{N}_3\text{O}_2$ : C, 47.79; H, 2.00; N, 10.45. Found: C, 47.94; H, 2.24; N, 10.13.

**General procedure for Synthesis of Derivatives 8.** To a solution of derivative **7** (0.21 mmol) in MeCN (1 mL) was added the amine (0.42 mmol) in the presence of Hünig's base (0.075 mL; 0.42 mmol). The reaction mixture was heated at 90 °C for 20 min to 1 h under microwave irradiation. After solvents were removed under vacuum at 40 °C, the resulting solid was suspended in MeOH, filtered, washed twice with MeOH and once with diethyl ether, and dried under suction to afford derivatives **8a** to **8e**.

**2-Benzylamino-4-phenyl-6-methyl-8-chloropyrido[3,2-d]pyrimidine (8a):** yield = 71%; off-white solid; mp 127.2–128.2 °C; IR  $\nu_{\max}$  1556, 1450, 1355  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  2.63 (s, 3H), 4.82 (d,  $J$  = 5.70 Hz, 2H), 5.86 (br s, 1H), 7.28–7.37 (m, 3H), 7.46–7.52 (m, 5H), 7.56 (s, 1H), 8.28 (br s, 2H);  $^{13}\text{C NMR}$  (75.47 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  24.8, 46.0, 127.4, 127.9, 128.0, 128.1, 128.6, 130.6, 131.6, 131.7, 134.2, 135.4, 136.2, 139.0, 154.0, 158.6, 167.8; HPLC  $t_{\text{R}}$  = 5.82 min, ES-MS  $m/z$  361.10 ( $\text{M} + \text{H}$ ) $^+$ . Anal. Calcd for  $\text{C}_{21}\text{H}_{17}\text{ClN}_4$ : C, 69.90; H, 4.75; N, 15.53; Cl, 9.82. Found: C, 69.83; H, 4.78; N, 15.47; Cl, 9.77.

**2-Benzylamino-4-phenyl-6-phenyl-8-chloropyrido[3,2-d]pyrimidine (8b):** yield = 69%; off-white solid; mp 126.2–127.2 °C; IR  $\nu_{\max}$  1556, 1450, 1355  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  4.87 (d,  $J$  = 5.1 Hz, 2H), 5.94 (br s, 1H), 7.29–7.39 (m, 3H), 7.47–7.49 (m, 5H), 7.52–7.61 (m, 3H), 8.04–8.06 (m, 2H), 8.20 (s, 1H), 8.34 (br s, 2H);  $^{13}\text{C NMR}$  (75.47 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  46.1, 124.7, 126.9, 127.4, 127.9, 128.2, 128.6, 129.0, 129.5, 130.0, 130.6, 131.7, 131.8, 134.3, 136.3, 137.9, 138.9, 151.9, 160.4, 166.1, HPLC  $t_{\text{R}}$  = 6.01 min; ES-MS  $m/z$  423.230 ( $\text{M} + \text{H}$ ) $^+$ . Anal. Calcd for  $\text{C}_{26}\text{H}_{19}\text{ClN}_4$ : C, 73.84; H, 4.53; N, 13.25; Cl, 8.38. Found: C, 73.43; H, 4.56; N, 12.96; Cl, 8.32.

**2-Benzylamino-4-phenyl-8-chloro-pyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (8c):** yield = 83%; yellow solid; mp 200–201 °C; IR  $\nu_{\max}$  3374, 1706, 1551  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  3.99 (s, 3H), 4.85 (br s, 2H), 6.10 (br s, 1H), 7.84–7.53 (m, 8H), 8.38–8.41 (m, 3H);  $^{13}\text{C NMR}$  (75.47 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  46.5, 53.5,

128.0, 128.2, 128.6, 128.7, 129.1, 131.7, 132.1, 132.5, 135.7, 138.7, 141.6, 142.5, 148.4, 159.9, 165.1, 169.6; HPLC  $t_R$  = 5.34 min; ES-MS  $m/z$  405.03 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>22</sub>H<sub>17</sub>ClN<sub>4</sub>O<sub>2</sub>: C, 65.27; H, 4.23; N, 13.84. Found: C, 65.29; H, 4.27; N, 13.46.

**2-Butylamino-4-phenyl-8-chloropyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (8d)**: yield = 81%; yellow solid; mp 183–184 °C; IR  $\nu_{\max}$  3382, 1704, 1556 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_H$  0.99 (t,  $J$  = 7 Hz, 3H), 1.48 (q,  $J$  = 7 Hz, 2H), 1.69–1.71 (m, 2H), 3.66–3.68 (m, 2H), 4.00 (s, 3H), 5.80 (br s, 1H), 7.55 (br m, 3H), 8.41–8.62 (m, 3H); <sup>13</sup>C NMR (75.47 MHz, CDCl<sub>3</sub>)  $\delta_C$  14.0, 20.3, 31.5, 41.8, 53.2, 128.0, 128.3, 129.6, 131.4, 132.0, 135.6, 141.2, 141.9, 148.2, 159.9, 164.9, 169.2; HPLC  $t_R$  = 5.60 min; ES-MS  $m/z$  370.93 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>19</sub>H<sub>19</sub>ClN<sub>4</sub>O<sub>2</sub>: C, 61.54; H, 5.16; N, 15.11; Cl, 9.56. Found: C, 61.57; H, 5.00; N, 14.72; Cl, 9.58.

**2-Diethylamino-4-phenyl-8-chloropyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (8e)**: yield = 85%; yellow solid; mp 123–124 °C; IR  $\nu_{\max}$  1717, 1520, 1335 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_H$  1.33 (br s, 6H), 3.88 (q,  $J$  = 7 Hz, 4H), 4.00 (s, 3H), 7.53–7.56 (m, 3H), 8.38 (s, 1H), 8.50–8.52 (m, 2H); <sup>13</sup>C NMR (75.47 MHz, CDCl<sub>3</sub>)  $\delta_C$  12.9, 14.0, 43.1, 53.3, 127.8, 128.5, 131.4, 132.2, 134.7, 136.5, 141.0, 141.3, 148.9, 158.8, 165.3, 168.2; HPLC  $t_R$  = 6.10 min; ES-MS  $m/z$  371.07 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>19</sub>H<sub>19</sub>ClN<sub>4</sub>O<sub>2</sub>: C, 61.54; H, 5.16; N, 15.11. Found: C, 61.25; H, 5.18; N, 14.76.

**General Procedure for Synthesis of Derivatives 9.** A solution of derivative 8 (0.25 mmol) in a mixture of MeOH and EtOAc (11 mL) was passed through a continuous-flow hydrogenation reactor equipped with a 10% Pd/C cartridge at 70 °C with a flow of 0.4 mL/min at 5–7 bar ("Full Hydrogen" mode).<sup>16</sup> Partial reduction of the heterocycle was observed together with the desired product 9. After evaporation of the solvents, the residue was dissolved in dichloroethane (3 mL), and MnO<sub>2</sub> (5.0 mmol) was added. The reaction mixture was heated under microwave irradiation at 100 °C for 15 min. After filtration through Celite and evaporation of the solvent under vacuum at 40 °C, the residue was dissolved in a minimum mixture of MeCN/DMSO and purified by a mass-directed autopurification system to afford derivatives 9a–c.

**2-Benzylamino-4-phenyl-6-methylpyrido[3,2-d]pyrimidine (9a)**: yield = 75%; pale yellow solid; mp 115.2–116.4 °C; IR  $\nu_{\max}$  3253, 1591, 1352, 685 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta_H$  2.56 (s, 3H), 4.64 (d,  $J$  = 6.2 Hz, 2H), 7.19–7.24 (m, 1H), 7.28–7.34 (m, 2H), 7.39–7.42 (m, 2H), 7.52–7.56 (m, 3H), 7.57 (d,  $J$  = 8.9 Hz, 1H), 7.82 (d,  $J$  = 8.9 Hz, 1H), 8.10 (br s, 1H), 8.19–8.22 (m, 2H); <sup>13</sup>C NMR (75.47 MHz, DMSO-*d*<sub>6</sub>)  $\delta_C$  24.4, 44.2, 126.5, 127.2, 127.6, 128.2, 128.9, 130.0, 131.0, 133.6, 133.8, 136.4, 140.2, 152.6, 154.0, 158.6; HPLC  $t_R$  = 4.37 min, ES-MS  $m/z$  327.09 (M + H)<sup>+</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>21</sub>H<sub>18</sub>N<sub>4</sub> [M + 1]<sup>+</sup> 327.1609, found 327.1605.

**2-Benzylamino-4,6-diphenylpyrido[3,2-d]pyrimidine (9b)**: yield = 71%; pale yellow solid; mp 119.0–120.0 °C; IR  $\nu_{\max}$  3255, 1592, 1537, 1454, 693 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta_H$  4.69 (d,  $J$  = 6.1 Hz, 2H), 7.23–7.25 (m, 1H), 7.30–7.35 (m, 2H), 7.42–7.52 (m, 5H), 7.59–7.61 (m, 3H), 7.99 (d,  $J$  = 8.9 Hz, 1H), 8.12–8.15 (m, 2H), 8.27–8.30 (m, 3H), 8.33 (d,  $J$  = 8.9 Hz, 1H); <sup>13</sup>C NMR (75.47 MHz, DMSO-*d*<sub>6</sub>)  $\delta_C$  44.2, 125.3, 126.6, 127.3, 127.6, 127.8, 128.2, 128.9, 129.2, 130.2, 130.3, 131.1, 134.4, 134.6, 138.1, 138.2, 142.9, 149.7, 151.3, 160.1; HPLC  $t_R$  = 4.62 min, ES-MS  $m/z$  389.20 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>26</sub>H<sub>20</sub>N<sub>4</sub>: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.25; H, 5.22; N, 14.38.

**2-Benzylamino-4-phenylpyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (9c)**: yield = 73%; pale yellow solid; mp 151.4–152.4 °C; IR  $\nu_{\max}$  1715, 1591, 1291; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>)  $\delta_H$  3.89 (s, 3H), 4.69 (d,  $J$  = 6.1 Hz, 2H), 7.21–7.44 (m, 5H), 7.56–7.61 (m, 3H), 8.00 (d,  $J$  = 8.9 Hz, 1H), 8.23 (d,  $J$  = 8.9 Hz, 1H), 8.30–8.32 (m, 2H), 8.67 (t,  $J$  = 6.0 Hz, 1H); <sup>13</sup>C NMR (75.47 MHz, DMSO-*d*<sub>6</sub>)  $\delta_C$  44.5, 52.5, 126.7, 127.2, 127.3, 127.8, 127.9, 128.3, 130.7, 131.2, 132.8, 134.4, 139.5, 142.0, 159.5, 164.6; HPLC  $t_R$  = 4.75 min, ES-MS  $m/z$  371.0 (M + H)<sup>+</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>22</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub> [M+1]<sup>+</sup> 371.1508, found 371.1499.

**General Procedure for Synthesis of Derivatives 10.** A solution of boronic acid derivative (0.25 mmol), 8e (89.0 mg, 0.24 mmol), cesium carbonate (237.8 mg, 0.73 mmol), and Pd(PPh<sub>3</sub>)<sub>4</sub> (11.6 mg,

0.01 mmol) in dioxane (2 mL) was heated at 90 °C under inert atmosphere. After 3.5–7 h, the reaction mixture was cooled to rt and filtered through Celite. The filtrate was evaporated under reduced pressure. The residue was diluted with DCM (15 mL), washed with water (10 mL), brine (10 mL), and dried over Na<sub>2</sub>SO<sub>4</sub>. After evaporation of the solvents under vacuum at 40 °C, the resulting solid was suspended in MeOH, filtered, washed twice with MeOH and once with diethyl ether, and dried under suction to afford derivatives 10a–10c.

**2-Diethylamino-4,8-diphenylpyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (10a)**: yield = 80%; yellow solid; mp 133–134 °C; IR  $\nu_{\max}$  1555, 1240 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_H$  1.24–1.29 (m, 6H), 3.76 (br m, 4H), 4.01 (s, 3H), 7.45–7.52 (m, 3H), 7.56–7.58 (m, 3H), 7.90–7.93 (m, 2H), 8.36 (s, 1H), 8.52–8.55 (m, 2H); <sup>13</sup>C NMR (75.47 MHz, CDCl<sub>3</sub>)  $\delta_C$  13.4, 14.2, 42.9, 53.2, 127.2, 128.2, 128.4, 128.9, 130.7, 131.1, 132.3, 134.8, 136.8, 137.1, 142.0, 145.0, 149.9, 158.5, 166.3, 168.2; HPLC  $t_R$  = 5.16 min; ES-MS  $m/z$  345.99 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>25</sub>H<sub>24</sub>N<sub>4</sub>O<sub>2</sub>: C, 72.80; H, 5.86; N, 13.58. Found: C, 72.40; H, 5.82; N, 13.35.

**2-Diethylamino-4-phenyl-8-(4-methoxyphenyl)pyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (10b)**: yield = 86%; yellow solid; mp 129–130 °C; IR  $\nu_{\max}$  1721, 1557, 1248 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_H$  1.28 (t,  $J$  = 7 Hz, 6H), 3.79 (br m, 4H), 3.91 (s, 3H), 4.01 (s, 3H), 7.03 (d,  $J$  = 9 Hz, 2H), 7.54–7.56 (m, 3H), 7.93 (d,  $J$  = 9 Hz, 2H), 8.34 (s, 1H), 8.51–8.54 (m, 2H); <sup>13</sup>C NMR (75.47 MHz, CDCl<sub>3</sub>)  $\delta_C$  13.7, 13.9, 42.9, 53.2, 55.7, 113.8, 114.5, 126.5, 128.1, 128.3, 129.2, 131.0, 132.0, 132.3, 134.8, 137.2, 142.1, 144.5, 149.5, 158.4, 160.4, 166.4, 168.2; HPLC  $t_R$  = 6.43 min; ES-MS  $m/z$  443.56 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>26</sub>H<sub>26</sub>N<sub>4</sub>O<sub>3</sub>: C, 70.57; H, 5.92; N, 12.66. Found: C, 70.52; H, 5.95; N, 12.61.

**2-Diethylamino-4-phenyl-8-(4-trifluoromethylphenyl)pyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (10c)**: yield = 82%; yellow solid; mp 165–166 °C; IR  $\nu_{\max}$  1711, 1558, 1321 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_H$  1.27 (br s, 6H), 3.77 (br m, 4H), 4.02 (s, 3H), 7.55–7.57 (m, 3H), 7.75 (d,  $J$  = 8 Hz, 2H), 8.02 (d,  $J$  = 8 Hz, 2H), 8.35 (s, 1H), 8.53–8.54 (m, 2H); <sup>13</sup>C NMR (75.47 MHz, CDCl<sub>3</sub>)  $\delta_C$  13.3, 13.8, 42.8, 53.0, 124.3 (q,  $J$  = 277.8 Hz), 124.8 (q,  $J$  = 3.6 Hz), 127.0, 128.2, 130.4 (q,  $J$  = 30.0 Hz), 130.7, 131.0, 132.0, 134.7, 136.6, 140.2, 141.6, 143.1, 148.9, 158.3, 165.8, 168.1; HPLC  $t_R$  = 6.94 min; ES-MS  $m/z$  481.36 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>26</sub>H<sub>23</sub>F<sub>3</sub>N<sub>4</sub>O<sub>2</sub>: C, 64.99; H, 4.82; N, 11.66. Found: C, 64.65; H, 4.82; N, 11.45.

**General Procedure for S<sub>N</sub>Ar with Benzylthiol on Derivatives 7a–c.** To a solution of derivative 7 (0.21 mmol) in MeCN (1.0 mL) and DMF (1.0 mL) was added benzylthiol (123.3 mL, 1.05 mmol) in the presence of Hünig's base (0.11 mL; 0.62 mmol). The reaction mixture was heated at 90 °C for 1 h under microwave irradiation. As two regioisomers were formed during the reaction, the reaction mixture was purified by mass-directed autopurification system. Derivatives 11a–c and 12a–c were isolated.

**2-Benzylsulfanyl-4-phenyl-6-methyl-8-chloropyrido[3,2-d]pyrimidine (11a)**: yield = 60%; pale yellow solid; mp 121.5–122.5 °C; IR  $\nu_{\max}$  1529, 1455, 1147, 690 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_H$  2.67 (s, 3H), 4.57 (s, 2H), 7.21–7.31 (m, 3H), 7.48–7.50 (m, 3H), 7.55–7.58 (m, 2H), 7.65 (s, 1H), 8.30–8.33 (m, 2H); <sup>13</sup>C NMR (75.47 MHz, CDCl<sub>3</sub>)  $\delta_C$  25.2, 35.9, 127.2, 128.4, 128.4, 128.6, 129.3, 131.0, 132.0, 135.5, 137.1, 138.0, 141.9, 144.0, 158.2, 166.0, 168.0; HPLC  $t_R$  = 5.90 min; ES-MS  $m/z$  378.10 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>21</sub>H<sub>16</sub>ClN<sub>3</sub>S: C, 66.75; H, 4.26; N, 11.05; Cl, 9.38. Found: C, 66.73; H, 4.26; N, 11.05; Cl, 9.36.

**2-Benzylsulfanyl-4,6-diphenyl-8-chloropyrido[3,2-d]pyrimidine (11b)**: yield = 60%; pale yellow solid; mp 146–147 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta_H$  4.63 (s, 2H), 7.23–27 (m, 1H), 7.27–7.36 (m, 2H), 7.54–7.56 (m, 3H), 7.59–7.65 (m, 5H), 8.23–8.31 (m, 4H), 8.85 (s, 1H); <sup>13</sup>C NMR (75.47 MHz, CDCl<sub>3</sub>)  $\delta_C$  34.9, 125.7, 127.1, 127.4, 128.0, 128.4, 129.0, 129.1, 130.5, 131.1, 131.7, 135.0, 136.7, 136.8, 137.9, 141.7, 144.1, 155.4, 166.3, 167.4; HPLC  $t_R$  = 6.47 min; ES-MS  $m/z$  440.10 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>26</sub>H<sub>18</sub>ClN<sub>3</sub>S: C, 70.98; H, 4.12; N, 9.55. Found: C, 70.91; H, 4.16; N, 9.51.

**2-Benzylsulfanyl-4-phenyl-8-chloropyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (11c):** yield = 73%; pale orange solid; mp 135.4–136.4 °C; IR  $\nu_{\max}$  1724, 1531, 1314, 1244, 1108;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta_{\text{H}}$  3.95 (s, 3H), 4.63 (s, 2H), 7.23–7.36 (m, 3H), 7.56–7.68 (m, 5H), 8.33–8.34 (m, 2H), 8.35 (s, 1H);  $^{13}\text{C}$  NMR (75.47 MHz, DMSO- $d_6$ )  $\delta_{\text{C}}$  35.0, 53.2, 127.2, 128.0, 128.1, 128.4, 129.1, 131.6, 131.9, 134.7, 136.7, 137.7, 141.8, 145.5, 146.2, 163.5, 166.9, 170.1; HPLC  $t_{\text{R}}$  = 5.91 min; ES-MS  $m/z$  422.20 (M + H) $^+$ . Anal. Calcd for  $\text{C}_{22}\text{H}_{16}\text{ClN}_3\text{O}_2\text{S}$ : C, 62.63; H, 3.82; N, 9.96; Cl, 8.40. Found: C, 62.30; H, 3.72; N, 9.84; Cl, 8.49.

**2-Chloro-4-phenyl-6-methyl-8-benzylsulfanylpyrido[3,2-d]pyrimidine (12a):** yield = 20%; pale orange solid; mp 172.3–173.3 °C; IR  $\nu_{\max}$  1521, 1448, 1332, 1153, 689, 639  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  2.70 (s, 3H), 4.29 (s, 2H), 7.34–7.35 (m, 2H), 7.37 (s, 1H), 7.38–7.40 (m, 1H), 7.46–7.51 (m, 2H), 7.52–7.56 (m, 3H), 8.42–8.46 (m, 2H);  $^{13}\text{C}$  NMR (75.47 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  25.8, 35.5, 122.3, 128.0, 128.2, 128.9, 129.0, 131.4, 132.2, 134.6, 135.2, 135.8, 144.1, 146.6, 149.6, 160.0, 168.6; HPLC  $t_{\text{R}}$  = 5.62 min; ES-MS  $m/z$  378.10 (M + H) $^+$ . Anal. Calcd for  $\text{C}_{21}\text{H}_{16}\text{ClN}_3\text{S}$ : C, 66.75; H, 4.27; N, 11.12; Cl, 9.38. Found: C, 66.95; H, 4.32; N, 10.72; Cl, 9.45.

**2-Chloro-4,6-diphenyl-8-benzylsulfanylpyrido[3,2-d]pyrimidine (12b):** yield = 18%; off-white solid; mp 180.5–181.5 °C; IR  $\nu_{\max}$  1524, 1455, 684  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  4.41 (s, 2H), 7.30–7.37 (m, 1H), 7.37–7.45 (m, 2H), 7.50–7.55 (m, 3H), 7.55–7.70 (m, 5H), 7.96 (s, 1H), 7.98–8.07 (m, 2H), 8.50–8.60 (m, 2H);  $^{13}\text{C}$  NMR (75.47 MHz, DMSO- $d_6$ )  $\delta_{\text{C}}$  33.7, 119.9, 126.1, 127.6, 127.7, 128.0, 128.1, 128.7, 129.1, 130.6, 131.5, 131.9, 134.8, 135.8, 137.4, 146.5, 149.9, 154.5, 156.6, 168.9; HPLC  $t_{\text{R}}$  = 6.20 min; ES-MS  $m/z$  440.1 (M + H) $^+$ . Anal. Calcd for  $\text{C}_{26}\text{H}_{18}\text{ClN}_3\text{S}$ : C, 70.98; H, 4.12; N, 9.55; Cl, 8.06. Found: C, 70.56; H, 4.38; N, 9.39; Cl, 7.90.

**2-Chloro-4-phenyl-8-benzylsulfanylpyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (12c):** yield = 12%; pale yellow solid; mp 150.8–151.8 °C; IR  $\nu_{\max}$  1719, 1430, 1244, 1139;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta_{\text{H}}$  4.04 (s, 3H), 4.62 (s, 2H), 7.23–7.35 (m, 3H), 7.51–7.61 (m, 5H), 8.48–8.52 (m, 2H), 8.55 (s, 1H);  $^{13}\text{C}$  NMR (75.47 MHz, DMSO- $d_6$ )  $\delta_{\text{C}}$  36.1, 53.4, 127.4, 128.0, 128.3, 128.5, 129.3, 131.8, 132.3, 134.8, 137.0, 137.5, 143.4, 145.9, 146.2, 164.3, 166.9, 167.2, 169.1, 171.6; HPLC  $t_{\text{R}}$  = 5.87 min; ES-MS  $m/z$  422.1 (M + H) $^+$ . Anal. Calcd for  $\text{C}_{22}\text{H}_{16}\text{ClN}_3\text{O}_2\text{S}$ : C, 62.63; H, 3.82; N, 9.96; Cl, 8.40. Found: C, 62.55; H, 3.83; N, 10.00; Cl, 8.39.

**General Procedure for  $\text{S}_{\text{N}}\text{Ar}$  with Sodium Methylthiolate on Derivatives 7c and 7d.** To a solution of derivative 7 (0.21 mmol) in THF (2.0 mL) was added sodium methylthiolate (14.7 mg, 0.21 mmol). The reaction mixture was stirred at –10 °C for 4 h. After removal of the solvents under vacuum, the residue was dissolved in a 1:1 mixture of DMSO and water (1 mL) and was purified by mass-directed autopurification system. Derivatives 11d and 11e were isolated.

**2-Methylsulfanyl-4-phenyl-8-chloropyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (11d):** yield = 60%; beige solid; mp 165–166 °C; IR  $\nu_{\max}$  1721, 1531, 1251  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  2.78 (s, 3H), 4.05 (s, 3H), 7.56–7.58 (m, 3H), 8.52–8.55 (m, 3H);  $^{13}\text{C}$  NMR (75.47 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  15.3, 53.8, 128.3, 128.7, 132.2, 132.7, 135.2, 137.2, 143.7, 146.2, 146.6, 164.7, 167.2, 173.0; HPLC  $t_{\text{R}}$  = 5.16 min; ES-MS  $m/z$  345.99 (M + H) $^+$ . Anal. Calcd for  $\text{C}_{16}\text{H}_{12}\text{ClN}_3\text{O}_2\text{S}$ : C, 55.57; H, 3.50; N, 12.15. Found: C, 55.15; H, 3.57; N, 11.85.

**2-Methylsulfanyl-4-(4-methoxyphenyl)-8-chloropyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (11e):** yield = 57%; yellow solid; mp 197–198 °C; IR  $\nu_{\max}$  2821, 1722, 1525  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta_{\text{H}}$  2.77 (s, 3H), 3.92 (s, 3H), 4.05 (s, 3H), 7.06–7.09 (m, 2H), 8.52 (s, 1H), 8.68–8.72 (m, 2H);  $^{13}\text{C}$  NMR (75.47 MHz, DMSO- $d_6$ )  $\delta_{\text{C}}$  14.9, 53.4, 55.5, 113.9, 127.4, 127.7, 134.5, 136.9, 143.2, 145.3, 146.2, 162.9, 164.3, 165.4, 172.4; HPLC  $t_{\text{R}}$  = 5.15 min; ES-MS  $m/z$  376.0 (M + H) $^+$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{14}\text{ClN}_3\text{O}_3\text{S}$  [M + 1] $^+$  376.0517, found 376.0523. Anal. Calcd for  $\text{C}_{17}\text{H}_{14}\text{ClN}_3\text{O}_3\text{S}$ : C, 53.66; H, 3.85; N, 11.04; Cl, 9.32. Found: C, 53.93; H, 3.75; N, 10.64; Cl, 9.59.

**General Procedure for Synthesis of Derivative 13.** To a solution of 11d (100 mg, 0.29 mmol) in MeCN (4 mL) was added the amine (1.44 mmol) in presence of Hünig's base (0.151 mL, 0.87 mmol). The reaction was heated at 90 °C for 2 h. Solvents were removed

under vacuum at 40 °C, and the solid obtained was suspended in MeOH, filtered, washed twice with MeOH and once with diethyl ether, and dried under suction. Derivative 13a was further purified by mass-directed autopurification system. Derivatives 13a–c were isolated.

**2-Methylsulfanyl-4-phenyl-8-benzylaminopyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (13a):** yield = 73%; yellow solid; mp 150.0–151.0 °C; IR  $\nu_{\max}$  1720, 1528, 1266, 1112  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  2.69 (s, 3H), 3.98 (s, 3H), 4.63 (d,  $J$  = 5.8 Hz, 2H), 6.70 (t,  $J$  = 5.6 Hz, 1H), 7.33–7.41 (m, 5H), 7.43 (s, 1H), 7.53–7.55 (m, 3H), 8.61–8.64 (m, 2H);  $^{13}\text{C}$  NMR (75.47 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  14.9, 46.8, 53.0, 102.7, 127.3, 127.9, 128.2, 129.0, 131.2, 132.2, 135.0, 135.8, 137.0, 140.2, 147.5, 149.2, 165.9, 166.2, 167.7; HPLC  $t_{\text{R}}$  = 0.42 min; ES-MS  $m/z$  417.30 (M + H) $^+$ . Anal. Calcd for  $\text{C}_{23}\text{H}_{20}\text{N}_4\text{O}_2\text{S}$ : C, 66.33; H, 4.84; N, 13.45. Found: C, 66.15; H, 4.80; N, 13.34.

**2-Methylsulfanyl-4-phenyl-8-butylaminopyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (13b):** yield = 83%; yellow-orange solid; mp 124.5–125.5 °C; IR  $\nu_{\max}$  1527, 1253, 1017  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta_{\text{H}}$  0.95 (t,  $J$  = 7.3 Hz, 3H), 1.38–1.48 (m, 2H), 1.61–1.71 (m, 2H), 2.73 (s, 3H), 3.40 (q,  $J$  = 6.8 Hz, 2H), 3.89 (s, 3H), 7.29 (s, 1H), 7.53–7.60 (m, 3H), 8.44–8.47 (m, 2H);  $^{13}\text{C}$  NMR (75.47 MHz, DMSO- $d_6$ )  $\delta_{\text{C}}$  13.8, 14.8, 20.3, 30.9, 42.5, 53.0, 102.1, 128.1, 131.1, 132.2, 135.0, 135.9, 140.2, 147.5, 149.3, 165.8, 166.4, 167.3, HPLC  $t_{\text{R}}$  = 5.81 min; ES-MS  $m/z$  383.3 (M + H) $^+$ . Anal. Calcd for  $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_2\text{S}$ : C, 62.81; H, 5.80; N, 14.65. Found: C, 62.79; H, 5.83; N, 14.62.

**2-Methylsulfanyl-4-phenyl-8-diethylaminopyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (13c):** yield = 84%; yellow solid; mp 110.5–111.0 °C; IR  $\nu_{\max}$  1736, 1530, 1236  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta_{\text{H}}$  1.28 (t,  $J$  = 6.9 Hz, 6H), 2.63 (s, 3H), 3.87 (s, 3H), 3.92 (q,  $J$  = 6.4 Hz, 4H), 7.42 (s, 1H), 7.51–7.63 (m, 3H), 8.28–8.31 (m, 2H);  $^{13}\text{C}$  NMR (75.47 MHz, DMSO- $d_6$ )  $\delta_{\text{C}}$  12.7, 13.9, 46.4, 52.6, 107.7, 127.7, 130.6, 131.6, 136.0, 137.0, 141.7, 146.4, 149.4, 164.4, 165.5, 166.3, HPLC  $t_{\text{R}}$  = 4.64 min; ES-MS  $m/z$  383.3 (M + H) $^+$ . Anal. Calcd for  $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_2\text{S}$ : C, 62.81; H, 5.80; N, 14.65. Found: C, 62.68; H, 5.47; N, 14.81.

**General Procedure for Synthesis of Derivatives 14.** A solution of boronic acid derivative (0.24 mmol), derivative 11 (0.24 mmol), cesium carbonate (234.6 mg, 0.72 mmol), and  $\text{Pd}(\text{PPh}_3)_4$  (11.5 mg, 0.01 mmol) in dioxane (2.0 mL) was heated at 90 °C for 3.5 h under inert atmosphere. DCM (15 mL) was added to the reaction mixture, and the mixture was washed with water (10 mL) and brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$  and filtered on Celite. The solvents were removed under vacuum at 40 °C. The resulting was suspended in MeOH, filtered, washed twice with MeOH and once with diethyl ether, and dried under suction to afford derivative 14 as a solid.

**2-Methylsulfanyl-4-(4-phenyl)-8-methoxyphenylpyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (14a):** yield = 75%; yellow solid; mp 168–170 °C; IR  $\nu_{\max}$  2924, 2845, 1745, 1529, 1256, 1112  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  2.65 (s, 3H), 3.93 (s, 3H), 4.05 (s, 3H), 7.09–7.06 (d,  $J$  = 6.9 Hz, 2H), 7.59–7.57 (m, 3H), 7.94–7.92 (d,  $J$  = 6.8 Hz, 2H), 8.50 (s, 1H), 8.56–8.53 (m, 2H);  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  14.8, 53.1, 55.4, 113.7, 126.5, 127.5, 128.2, 131.3, 132.0, 132.3, 135.4, 136.9, 146.2, 146.2, 146.7, 160.6, 165.3, 167.1, 170.7; HPLC  $t_{\text{R}}$  = 5.99 min; ES-MS  $m/z$  418 (M + H) $^+$ . Anal. Calcd for  $\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}_3\text{S}$ : C, 66.17; H, 4.59; N, 10.07. Found: C, 66.21; H, 4.63; N, 10.04.

**2-Methylsulfanyl-4-(4-methoxyphenyl)-8-phenylpyrido[3,2-d]pyrimidine-6-carboxylic acid methyl ester (14b):** yield = 82%; yellow solid; mp 226.0–227.0 °C; IR  $\nu_{\max}$  1118, 1242, 1439, 1527, 1714, 2361  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$  2.59 (s, 3H), 3.92 (s, 3H), 4.06 (s, 3H), 7.07 (m, 2H), 7.49–7.55 (m, 3H), 7.88–7.91 (m, 2H), 8.49 (s, 1H), 8.70 (m, 2H);  $^{13}\text{C}$  NMR (75.47 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$  14.7, 53.2, 55.5, 113.8, 127.1, 128.0, 128.1, 129.2, 130.6, 134.4, 135.4, 137.0, 145.8, 146.6, 147.0, 162.6, 165.3, 165.8, 170.8; HPLC  $t_{\text{R}}$  = 5.77 min; ES-MS  $m/z$  418.30 (M + H) $^+$ . Anal. Calcd for  $\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}_3\text{S}$ : C, 66.17; H, 4.59; N, 10.06. Found: C, 65.89; H, 4.49; N, 9.80.

**General Procedure for Synthesis of Derivatives 15 and 16.** Boronic acid derivative (0.21 mmol), derivative 13a, 13c, or 14a,b

(0.14 mmol), copper(I) thiophene-2-carboxylate (40.0 mg, 0.21 mmol), and Pd(PPh<sub>3</sub>)<sub>4</sub> (23.1 mg, 0.02 mmol) were added to dioxane (3.0 mL) under inert atmosphere. The reaction was stirred at 90 °C. After 3.5 h, NaHCO<sub>3</sub> saturated solution (10 mL) was added, and the resulting mixture was extracted with DCM (2 × 15 mL). Combined organic layers were washed with brine (15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered through Celite. After having removed solvents under vacuum at 40 °C, the resulting solid was triturated in MeOH, filtered, and dried under vacuum to afford derivatives **15** and **16**.

**8-Benzylamino-2-(4-chlorophenyl)-4-phenylpyrido[3,2-d]-pyrimidine-6-carboxylic acid methyl ester (15a)**: yield = 71%; pale yellow solid; mp 210–212 °C; IR  $\nu_{\max}$  3388, 3051, 1719, 1531, 1241 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  4.01 (s, 3H), 4.73–4.71 (d, *J* = 5.9 Hz, 2H), 7.24–7.20 (t, *J* = 7.4 Hz, 1H), 7.41–7.35 (m, 1H), 7.45–7.42 (m, 4H), 7.52–7.49 (m, 3H), 7.61–7.57 (m, 3H), 8.63–8.60 (m, 2H), 8.75–8.72 (m, 2H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  46.9, 53.0, 102.4, 127.3, 127.9, 128.2, 128.8, 129.0, 130.0, 131.1, 132.1, 135.9, 136.2, 136.9, 137.1, 139.8, 148.6, 150.5, 158.0, 166.1, 166.1; HPLC *t*<sub>R</sub> = 6.68 min; ES-MS *m/z* 481 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>28</sub>H<sub>21</sub>ClN<sub>4</sub>O<sub>2</sub>: C, 69.92; H, 4.40; N, 11.65. Found: C, 69.93; H, 4.48; N, 11.49.

**2-(4-Chlorophenyl)-8-diethylamino-4-phenylpyrido[3,2-d]-pyrimidine-6-carboxylic acid methyl ester (15b)**: yield = 76%; yellow solid; mp 183–185 °C; IR  $\nu_{\max}$  2953, 2925, 1746, 1536, 1117 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  1.49–1.45 (t, *J* = 6.9 Hz, 6H), 4.03 (s, 3H), 4.09–4.05 (m, 4H), 7.51–7.49 (d, *J* = 8.6 Hz, 2H), 7.57–7.50 (m, 4H), 8.55–8.53 (d, *J* = 8.48 Hz, 2H), 8.63–8.61 (m, 2H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  12.8, 47.2, 53.0, 107.5, 128.0, 128.7, 129.7, 130.6, 132.1, 136.5, 136.7, 137.0, 138.7, 142.0, 147.5, 151.3, 156.2, 166.5, 166.9; HPLC *t*<sub>R</sub> = 6.02 min; ES-MS *m/z* 447 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>25</sub>H<sub>23</sub>ClN<sub>4</sub>O<sub>2</sub>: C, 67.18; H, 5.19; N, 12.54. Found: C, 67.19; H, 5.21; N, 12.49.

**2-(4-Chlorophenyl)-8-(4-methoxyphenyl)-4-phenylpyrido[3,2-d]-pyrimidine-6-carboxylic acid methyl ester (16a)**: yield = 80%; yellow solid; mp 236–239 °C; IR  $\nu_{\max}$  3060, 2955, 1726, 1250 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  3.98 (s, 3H), 4.10 (s, 3H), 7.17–7.5 (d, *J* = 8.7 Hz, 2H), 7.52–7.50 (d, *J* = 8.6 Hz, 2H), 7.65–7.64 (m, 3H), 8.01–7.99 (d, *J* = 8.7 Hz, 2H), 8.58 (s, 1H), 8.65–8.62 (d, *J* = 8.6 Hz, 2H), 8.71–8.69 (m, 2H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  53.2, 55.4, 113.8, 126.2, 127.7, 128.2, 128.9, 130.4, 131.2, 132.3, 132.4, 136.0, 136.2, 137.5, 137.8, 146.8, 147.6, 148.4, 160.2, 160.8, 165.3, 167.4; HPLC *t*<sub>R</sub> = 6.97 min; ES-MS *m/z* 482.0 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>28</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>3</sub>: C, 69.78; H, 4.18; N, 8.72. Found: C, 69.82; H, 4.22; N, 8.60.

**2-(4-Chlorophenyl)-4-(4-methoxyphenyl)-8-phenylpyrido[3,2-d]-pyrimidine-6-carboxylic acid methyl ester (16b)**: yield = 69%; yellow solid; mp 217–219 °C; IR  $\nu_{\max}$  2949, 2921, 1716, 1536, 1252, cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{H}}$  3.96 (s, 3H), 4.10 (s, 3H), 7.16–7.14 (d, *J* = 7.0 Hz, 2H), 7.49–7.47 (d, *J* = 6.9 Hz, 2H), 7.64–7.58 (m, 3H), 7.98–7.95 (m, 2H), 8.57 (s, 1H), 8.61–8.58 (d, *J* = 6.8 Hz, 2H), 8.85–8.83 (d, *J* = 7.0 Hz, 2H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\text{C}}$  53.2, 55.4, 113.8, 126.8, 128.2, 128.7, 128.8, 129.3, 130.4, 130.8, 134.3, 135.5, 136.1, 137.4, 137.7, 146.7, 147.1, 148.8, 160.3, 162.5, 165.2, 166.2; HPLC *t*<sub>R</sub> = 7.06 min; ES-MS *m/z* 482.2 (M + H)<sup>+</sup>. Anal. Calcd for C<sub>28</sub>H<sub>20</sub>ClN<sub>3</sub>O<sub>3</sub>: C, 69.78; H, 4.18; N, 8.72. Found: C, 69.85; H, 4.28; N, 8.61.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

<sup>1</sup>H and <sup>13</sup>C NMR spectra of the synthesized compounds and ORTEP representation and cif file of **13b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank Prof. Lanny Liebeskind from Emory University as well as Prof. Jérôme Lacour, Prof. Alexandre Alexakis from University of Geneva, and Dr. Dominique Swinnen from Merck Serono for their advice and fruitful discussions. We acknowledge Dr. Wolfgang Sauer from Merck Serono for semiempirical calculations, Dr. Pierre-André Pittet from Merck Serono for his support in NMR experiments and interpretation, and Gordon Campbell from Merck Serono for proofreading the manuscript.

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(17) Semiempirical calculations of **7a–c**; minimization, followed by conformational search (60° steps) around five rotatable bonds (i.e., 7776 points each) using MM3. All local minima (94 and 106, respectively) extracted and minimized with PMS. All calculations done with Scigress Explorer 7.7 (Fujitsu Ltd.).

7	C-2 partial charge	C-2 LUMO density	C-8 partial charge	C-8 LUMO density
<b>7a</b>	0.124	0.06	0.024	0.149
<b>7b</b>	0.125	0.072	0.019	0.15
<b>7c</b>	0.135	0.101	0.002	0.15

(18) Comparison between (Table 7, entry 3) and (Table 3, entry 1) of ref 3.