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

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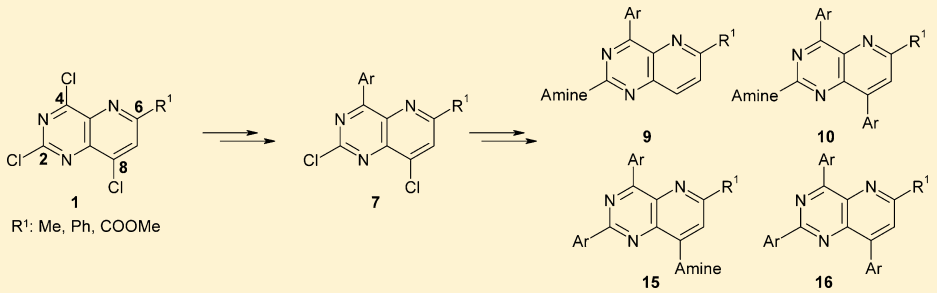
Supporting Information



ABSTRACT: We report herein an efficient route for the synthesis of 2,4,8-trichloropyrido[3,2-*d*]pyrimidines **1** with R^1 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_NAr 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_NAr, 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.[1,2] 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_NAr and metal-catalyzed cross-coupling reactions (Scheme 1).[3] 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.[4,5] Then regiocontrolled diversification of the resulting scaffold **1** is described through S_NAr[6] and metal-catalyzed cross-coupling reactions,[7] 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**[8] were heated at 140 °C in ^{i}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)

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Scheme 1. Regioselective Transformations of 1

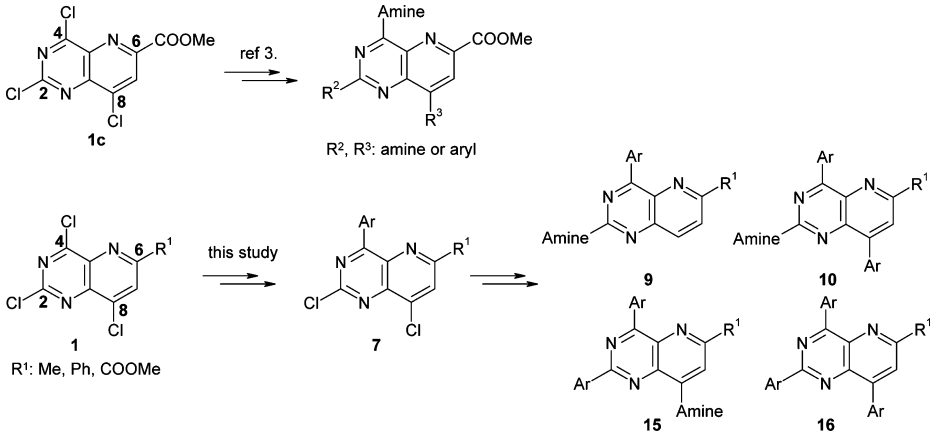
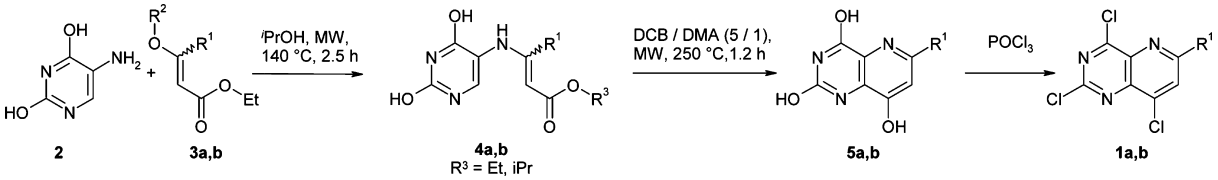


Table 1. Synthesis of 1



entry	SM	R^1	R^2	products (% yield)	
1	**3a**	Me	Et	**5a** (84)	**1a**[a] (78)
2	**3b**	Ph	Me	**5b** (86)	**1b**[b] (85)

[a]Chlorination conditions: $POCl_3$, $PhNEt_2$, reflux, 16 h. [b]Chlorination conditions: $POCl_3$, 200 °C under microwave irradiations, 1.5 h.

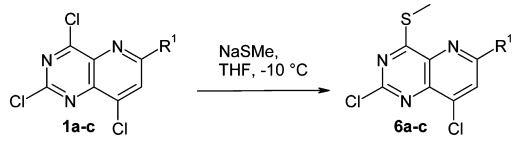
in a 5/1 ratio, a solvent mixture which ensured the solubilization of the starting material and guaranteed complete conversion. Following these conditions, derivatives **5a** and **5b** were isolated in 84% and 86% yields, respectively (Table 1, step 2, entries 1 and 2).

Two protocols were used for the last step, chlorination of derivatives **5**. A solution of **5a** with *N*,*N*-diethylaniline in an excess of $POCl_3$ 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 $POCl_3$ 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.[9]

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.[5] Suzuki−Miyaura cross-coupling reaction, using various reaction conditions, yielded either partial conversion or multiple product mixtures.[10] Coupling conditions described to be selective on 2,4-dichloropyrido[3,2-*d*]pyrimidine, using $Pd(PPh_3)_4$ as catalyst and K_2CO_3 as base, in toluene at 100 °C, did neither improve the regioselectivity nor the conversion.[11] Alternative cross-coupling reactions on derivative **1c** such as Stille cross-coupling reactions were not successful either.[10]

At this point, Liebeskind−Srogl cross-coupling reaction was investigated as an option.[12] As previously reported, S_NAr reactions on **1c** is highly regioselective at C-4.[3,5] 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.[13]

Table 2. S_NAr with Sodium Methylthiolate on 1 at C-4



entry	SM	R^1	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 $Pd(PPh_3)_4$ as catalyst and copper(I) thiophene-2-carboxylate (CuTC) as cofactor.[14] 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.[15]

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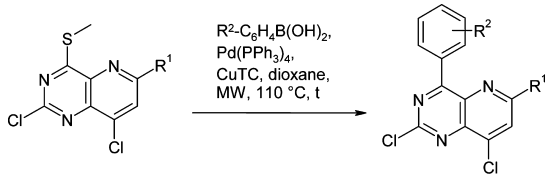
Table 3. Liebeskind–Srogl Cross-Coupling Reactions on 6 at C-4



6a-c 7a-e

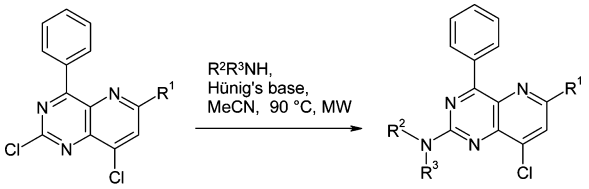
entry	SM	R^1	R^2	time (h)	product	yield (%)
1	**6a**	Me	H	0.5	**7a**	81
2	**6b**	Ph	H	1.5	**7b**	78
3	**6c**	COOMe	H	1	**7c**	79
4	**6c**	COOMe	4-MeO	1.5	**7d**	82
5	**6c**	COOMe	4-CF_3	0.5	**7e**	77

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_NAr 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.[9] 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_NAr with Diverse Amines on 7a–c at C-2



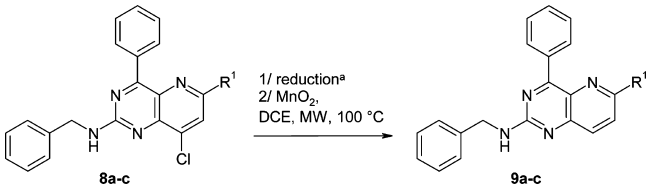
7a-c 8a-e

entry	SM	R^1	$R^2R^3NH_2$	product	yield (%)
1	**7a**	Me	$BnNH_2$	**8a**	71
2	**7b**	Ph	$BnNH_2$	**8b**	69
3	**7c**	COOMe	$BnNH_2$	**8c**	83
4	**7c**	COOMe	$BuNH_2$	**8d**	81
5	**7c**	COOMe	Et_2NH	**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_2 was added to rearomatize the pyridopyrimidine ring. The ^1H NMR spectra of dehalogenated products **9a–c** consisted of a pair of doublets corresponding to H-7 and H-8, with a J^3 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



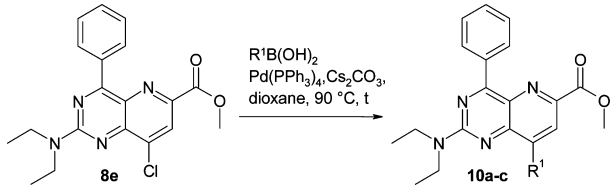
8a-c 9a-c

entry	R^1	product	yield (%)
1	Me	**9a**	75
2	Ph	**9b**	71
3	COOMe	**9c**	73

[a]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).[16]

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 $Pd(PPh_3)_4$ 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



8e 10a-c

entry	$R^1B(OH)_2$	time (h)	product	yield (%)
1	$PhB(OH)_2$	7	**10a**	80
2	4-MeO-$C_6H_4B(OH)_2$	4	**10b**	86
3	4-CF_3- $C_6H_4B(OH)_2$	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,[3] 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^1 = 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

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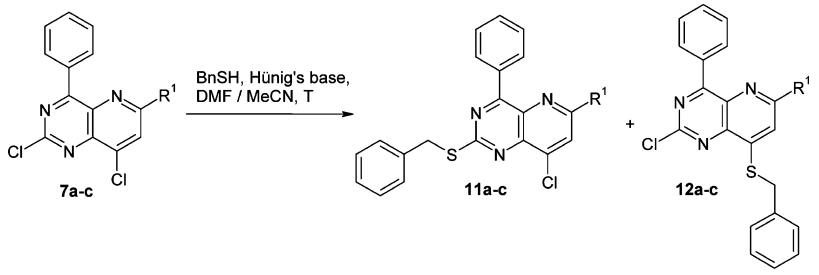
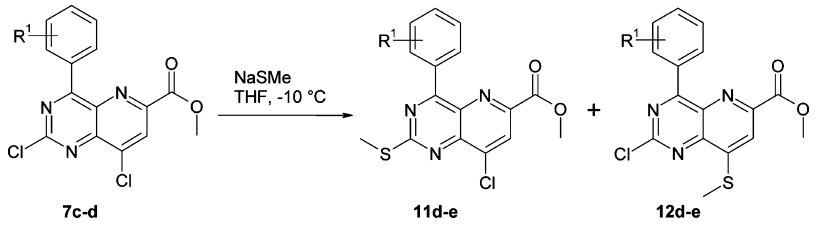
Table 7. S_NAr with Benzylthiol on 7a−c



entry	SM	R^1	T (°C)	product	UHPLC ratio[a]	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

[a]The ratios were determined on the reaction mixtures by UHPLC−MS to evaluate most accurately the regioisosomer ratio. All regioisomers were isolated and fully characterized.

Table 8. S_NAr with Sodium Methylthiolate on 7c−d



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

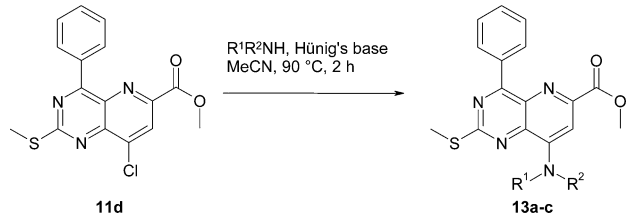
C-6. Regioisomers **11a−c** and **12a−c** were isolated in 60−73% and 12−20% yields, respectively.

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 ^1H and ^{13}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.[17] It is slightly influenced by the nature of R^1, possibly explaining the higher regioselectivity obtained with R^1 = COOMe compared with R^1 = 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 an amine at C-4.[18] 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^1R^2N	product	yield (%)
1	BnNH	**13a**	73
2	BuNH	**13b**	83
3	Et_2N	**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

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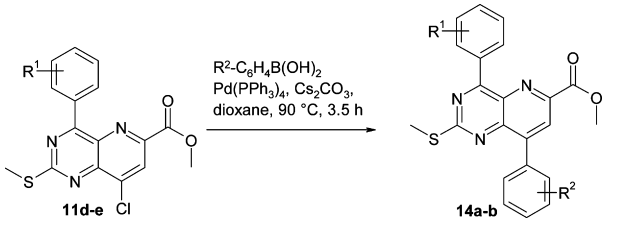
Table 10. Suzuki–Miyaura Cross-Coupling Reaction on 11d and 11e at C-8

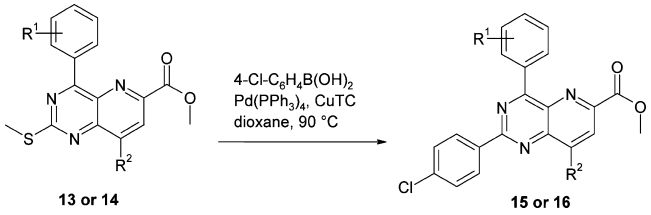


entry	SM	R^1	R^2	product	yield (%)
1	**11d**	H	4-MeO	**14a**	75
2	**11e**	4-MeO	H	**14b**	82

(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 $Pd(PPh_3)_4$ 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^1	R^2	product	yield (%)
1	**13a**	H	BnNH	**15a**	71
2	**13c**	H	Et_2N	**15b**	76
3	**14a**	H	4-MeO-C_6H_4	**16a**	80
3	**14b**	4-MeO	Ph	**16b**	69

These combinations of S_NAr 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_NAr 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_NAr, 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. ^1H NMR spectra were recorded at 300 or 400 MHz, and ^{13}C NMR spectra were recorded at 75.47 or 100.63 MHz, as indicated next to each NMR analysis. ^1H and ^{13}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 were performed on a C8 column (50 × 4.6 mm 3.5 μm) with a gradient from 95% H_2O (0.1% TFA)/5% MeCN (0.1% TFA) to 5% H_2O (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_2O.

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 ^{i}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_{max} 3195, 1684, 1633, 1552, 1417 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ_H 2.29 (s, 3H), 6.15 (s, 1H), 10.48 (s, 1H), 11.70 (s, 1H), 11.99 (br s, 1H); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_C 18.7, 113.3, 116.1, 119.8, 131.7, 148.2, 148.9, 159.8; HPLC t_R = 0.41 min; ES-MS *m/z* 194.0 $(M + H)^+$. Anal. Calcd for $C_8H_7N_3O_3$: 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_{max} 3010, 2843, 1681, 1479 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ_H 7.48–7.88 (m, 6H), 10.66 (s, 1H), 11.55 (br s, 1H), 11.85 (br s, 1H), ^{13}C NMR (75.47 MHz, DMSO-d_6) δ_C 126.8, 127.0, 128.6, 129.4, 141.8, 143.0, 149.2, 169.3; HPLC t_R = 1.51 min; ES-MS *m/z* 254 $(M - H)^-$. Anal. Calcd for $C_{13}H_9N_3O_3 \cdot 0.08H_2O$: 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 $POCl_3$ (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 $POCl_3$ 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%

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yield): mp >219 °C dec; IR ν_{max} 1545, 1454, 1388, 1145, 795 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 2.83 (s, 3H), 7.85 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_C 25.5, 130.6, 137.2, 142.7, 145.2, 155.3, 162.7, 165.5; HPLC t_R = 3.55 min; ES-MS m/z 248.0 $(M + H)^+$. Anal. Calcd for $C_8H_4Cl_3N_3$: 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 $POCl_3$ (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 ν_{max} 3012, 2843, 1681, 1479, 1420 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.56−7.58 (m, 3H), 8.19−8.22 (m, 2H), 8.43 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_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_R = 5.13 min; ES-MS m/z 310.00 $(M + H)^+$. Anal. Calcd for $C_{13}H_6Cl_3N_3{\cdot}0.05H_2O$: 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 ν_{max} 1534, 1382, 1152, 799 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 2.67 (s, 3H), 2.75 (s, 3H), 7.72 (s, 1H), ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_C 13.2, 25.1, 129.7, 138.1, 141.1, 142.1, 156.4, 160.1, 178.1; HPLC t_R = 4.20 min; ES-MS m/z 260.00 $(M + H)^+$. Anal. Calcd for $C_9H_7Cl_2N_3S$: 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 ν_{max} 1510, 1447, 1172, 803, 679 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 2.72 (s, 3H), 7.55−7.59 (m, 3H), 8.16−8.19 (m, 2H), 8.33 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_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_R = 5.40 min; ES-MS m/z 322.0 $(M + H)^+$. Anal. Calcd for $C_{14}H_9Cl_2N_3S$: 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 ν_{max} 1720, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 2.71 (s, 3H), 4.06 (s, 3H), 8.56 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_C 13.6, 54.0, 129.6, 138.4, 144.1, 144.3, 147.9, 159.5, 164.1, 180.7; HPLC t_R = 4.10 min; ES-MS m/z 303.93 $(M + H)^+$. Anal. Calcd for $C_{10}H_7Cl_2N_3O_2S$: 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 $Pd(PPh_3)_4$ (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 $NaHCO_3$ saturated solution (10 mL) and brine (10 mL), and dried over Na_2SO_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 ν_{max} 1524, 1329, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 2.78 (s, 3H), 7.55−7.60 (m, 3H), 7.79 (s, 1H), 8.42−8.45 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_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_R = 4.75 min; ES-MS m/z 290.00 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{14}H_9Cl_2N_3$ $[M + 1]^+$ 290.0246, found 290.0266. Anal. Calcd for $C_{14}H_9Cl_2N_3{\cdot}0.28H_2O$: 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 ν_{max} 2361, 2341, 1461, 774, 686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.54−7.62 (m, 6H), 8.13 (br s, 2H), 8.41 (s, 1H), 8.50 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_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_R = 5.56 min; ES-MS m/z 352.0 $(M + H)^+$. Anal. Calcd for $C_{19}H_{11}Cl_2N_3$: 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 ν_{max} 1712, 1524, 1246 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 4.08 (s, 3H), 7.57−7.65 (m, 3H), 8.59−8.62 (m, 2H), 8.64 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_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_R = 4.75 min; ES-MS m/z 333.94 $(M + H)^+$. Anal. Calcd for $C_{15}H_9Cl_2N_3O_2$: 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 ν_{max} 1723, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ_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}C NMR (75.47 MHz, $CDCl_3$) δ_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_R = 4.87 min; ES-MS m/z 363.93 $(M + H)^+$. Anal. Calcd for $C_{16}H_{11}Cl_2N_3O_3$: 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 ν_{max} 1731, 1320 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 4.09 (s, 3H), 7.86 (d, J = 8 Hz, 2H), 8.67 (s, 1H), 8.73 (d, J = 8 Hz, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_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_R = 5.31 min; ES-MS m/z 401.94 $(M + H)^+$. Anal. Calcd for $C_{16}H_8Cl_2F_3N_3O_2$: 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 ν_{max} 1556, 1450, 1355 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_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}C NMR (75.47 MHz, $CDCl_3$) δ_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_R = 5.82 min, ES-MS m/z 361.10 $(M + H)^+$. Anal. Calcd for $C_{21}H_{17}ClN_4$: 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 ν_{max} 1556, 1450, 1355 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_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}C NMR (75.47 MHz, $CDCl_3$) δ_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_R = 6.01 min; ES-MS m/z 423.230 $(M + H)^+$. Anal. Calcd for $C_{26}H_{19}ClN_4$: 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 ν_{max} 3374, 1706, 1551 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_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}C NMR (75.47 MHz, $CDCl_3$) δ_C 46.5, 53.5,

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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 $(M + H)^+$. Anal. Calcd for $C_{22}H_{17}ClN_4O_2$: 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 ν_{max} 3382, 1704, 1556 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_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); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_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 $(M + H)^+$. Anal. Calcd for $C_{19}H_{19}ClN_4O_2$: 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 ν_{max} 1717, 1520, 1335 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_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); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_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 $(M + H)^+$. Anal. Calcd for $C_{19}H_{19}ClN_4O_2$: 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).[16] 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_2 (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 ν_{max} 3253, 1591, 1352, 685 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6), δ_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), ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_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 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{21}H_{18}N_4$ $[M + 1]^+$ 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 ν_{max} 3255, 1592, 1537, 1454, 693 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ_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); ^{13}C NMR (75.47 MHz, DMSO-d_6), δ_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 $(M + H)^+$. Anal. Calcd for $C_{26}H_{20}N_4$: 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 ν_{max} 1715, 1591, 1291; ^1H NMR (300 MHz, DMSO-d_6) δ_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); ^{13}C NMR (75.47 MHz, DMSO-d_6) δ_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 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{22}H_{18}N_4O_2$ $[M+1]^+$ 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 $Pd(PPh_3)_4$ (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_2SO_4. 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 ν_{max} 1555, 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_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); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_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 $(M + H)^+$. Anal. Calcd for $C_{25}H_{24}N_4O_2$: 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 ν_{max} 1721, 1557, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_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); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_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 $(M + H)^+$. Anal. Calcd for $C_{26}H_{26}N_4O_3$: 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 ν_{max} 1711, 1558, 1321 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_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); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_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 $(M + H)^+$. Anal. Calcd for $C_{26}H_{23}F_3N_4O_2$: C, 64.99; H, 4.82; N, 11.66. Found: C, 64.65; H, 4.82; N, 11.45.

General Procedure for S_NAr 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 ν_{max} 1529, 1455, 1147, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_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); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_C 25.2, 35.9, 127.2, 128.0, 128.4, 128.6, 129.3, 131.0, 132.0, 135.5, 137.1, 138.0, 141.9, 144.4, 158.2, 166.0, 168.0; HPLC t_R = 5.90 min; ES-MS m/z 378.10 $(M + H)^+$. Anal. Calcd for $C_{21}H_{16}ClN_3S$: 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; ^1H NMR (300 MHz, $CDCl_3$) δ_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); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_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 $(M + H)^+$. Anal. Calcd for $C_{26}H_{18}ClN_3S$: C, 70.98; H, 4.12; N, 9.55. Found: C, 70.91; H, 4.16; N, 9.51.

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*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 ν_{max} 1724, 1531, 1314, 1244, 1108; ^{1}H NMR (300 MHz, DMSO-d_6) δ_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}C NMR (75.47 MHz, DMSO-d_6) δ_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_R = 5.91 min; ES-MS m/z 422.20 (M + H)$^+$. Anal. Calcd for $C_{22}H_{16}ClN_3O_2S$: 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 ν_{max} 1521, 1448, 1332, 1153, 689, 639 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_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}C NMR (75.47 MHz, $CDCl_3$) δ_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_R = 5.62 min; ES-MS m/z 378.10 (M + H)$^+$. Anal. Calcd for $C_{21}H_{16}ClN_3S$: 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 ν_{max} 1524, 1455, 684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_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}C NMR (75.47 MHz, DMSO-d_6), δ_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_R = 6.20 min; ES-MS m/z 440.1 (M + H)$^+$. Anal. Calcd for $C_{26}H_{18}ClN_3S$: 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 ν_{max} 1719, 1430, 1244, 1139; ^{1}H NMR (300 MHz, DMSO-d_6) δ_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}C NMR (75.47 MHz, DMSO-d_6) δ_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_R = 5.87 min; ES-MS m/z 422.1 (M + H)$^+$. Anal. Calcd for $C_{22}H_{16}ClN_3O_2S$: 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 S_NAr 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 ν_{max} 1721, 1531, 1251 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.78 (s, 3H), 4.05 (s, 3H), 7.56−7.58 (m, 3H), 8.52−8.55 (m, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ_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_R = 5.16 min; ES-MS m/z 345.99 (M + H)$^+$. Anal. Calcd for $C_{16}H_{12}ClN_3O_2S$: 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 ν_{max} 2821, 1722, 1525 cm^{-1}; 1H NMR (300 MHz, DMSO-d_6), δH 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}C NMR (75.47 MHz, DMSO-d_6), δ_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_R = 5.15 min; ES-MS m/z 376.0 (M + H)$^+$; HRMS (ESI) m/z calcd for $C_{17}H_{14}ClN_3O_3S$ [M + 1]$^+$ 376.0517, found 376.0523. Anal. Calcd for $C_{17}H_{14}ClN_3O_3S{\cdot}0.26H_2O$: 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 ν_{max} 1720, 1528, 1266, 1112 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_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}C NMR (75.47 MHz, $CDCl_3$) δ_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_R = 0.42 min; ES-MS m/z 417.30 (M + H)$^+$. Anal. Calcd for $C_{23}H_{20}N_4O_2S$: 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 ν_{max} 1527, 1253, 1017 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ_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}C NMR (75.47 MHz, DMSO-d_6) δ_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_R = 5.81 min; ES-MS m/z 383.3 (M + H)$^+$. Anal. Calcd for $C_{20}H_{22}N_4O_2S$: 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 ν_{max} 1736, 1530, 1236 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ_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}C NMR (75.47 MHz, DMSO-d_6) δ_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_R = 4.64 min; ES-MS m/z 383.3 (M + H)$^+$. Anal. Calcd for $C_{20}H_{22}N_4O_2S$: 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 $Pd(PPh_3)_4$ (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 Na_2SO_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 ν_{max} 2924, 2845, 1745, 1529, 1256, 1112 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_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}C NMR (400 MHz, $CDCl_3$) δ_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_R = 5.99 min; ES-MS m/z 418 (M + H)$^+$. Anal. Calcd for $C_{23}H_{19}N_3O_3S$: 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 ν_{max} 1118, 1242, 1439, 1527, 1714, 2361 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_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}C NMR (75.47 MHz, $CDCl_3$) δ_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_R = 5.77 min; ES-MS m/z 418.30 (M + H)$^+$. Anal. Calcd for $C_{23}H_{19}N_3O_3S$: 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**

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(0.14 mmol), copper(I) thiophene-2-carboxylate (40.0 mg, 0.21 mmol), and $Pd(PPh_3)_4$ (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, $NaHCO_3$ 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_2SO_4, 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 ν_{max} 3388, 3051, 1719, 1531, 1241 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_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); ^{13}C NMR (400 MHz, $CDCl_3$) δ_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, 136.4, 136.9, 137.1, 139.8, 148.6, 150.5, 158.0, 166.1, 166.1; HPLC t_R = 6.68 min; ES-MS m/z 481 $(M + H)^+$. Anal. Calcd for $C_{28}H_{21}ClN_4O_2$: 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 ν_{max} 2953, 2925, 1746, 1536, 1117 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_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); ^{13}C NMR (400 MHz, $CDCl_3$) δ_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_R = 6.02 min; ES-MS m/z 447 $(M + H)^+$. Anal. Calcd for $C_{25}H_{23}ClN_4O_2$: 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 ν_{max} 3060, 2955, 1726, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_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) ; ^{13}C NMR (400 MHz, $CDCl_3$) δ_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_R = 6.97 min; ES-MS m/z 482.0 $(M + H)^+$. Anal. Calcd for $C_{28}H_{20}ClN_3O_3$: 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 ν_{max} 2949, 2921, 1716, 1536, 1252, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_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) ; ^{13}C NMR (400 MHz, $CDCl_3$) δ_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_R = 7.06 min; ES-MS m/z 482.2 $(M + H)^+$. Anal. Calcd for $C_{28}H_{20}ClN_3O_3$: C, 69.78; H, 4.18; N, 8.72. Found: C, 69.85; H, 4.28; N, 8.61.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}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.

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(10) Suzuki cross-coupling reaction was attempted to introduce selectively a phenyl group at the C-4 position to derivative **1c**. Multiple combinations of solvents (DME/H_2O/TBAB, dioxane/MeOH, or pure dioxane), bases (K_2CO_3 or Cs_2CO_3), and catalysts ($Pd(PPh_3)_4$ or $Pd(OAc)_2$ with 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride as ligand) were tried. Unfortunately, all combinations yielded a mixture of byproducts, such as chlorine hydrolysis or multiple-coupling product, in addition to **7c** (if present). For derivatives **1a** and **1b**, the use of $Pd(PPh_3)_4$ as catalyst and K_2CO_3 as base in toluene at 100 °C yielded only 21 and 27% conversion, respectively. These same reaction conditions applied to **1c** yielded a mixture of mono- and multiple cross-coupling products (unpublished results). Stille cross-coupling reaction was used for **1c** arylation. With $Pd(OAc)_2$ as catalyst and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride as ligand, only traces of **7c** were formed, contaminated with several byproducts, such as multiple cross-coupling products and diverse chlorine hydrolysis products (unpublished results).

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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 PM5. 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
7a	0.124	0.06	0.024	0.149
7b	0.125	0.072	0.019	0.15
7c	0.135	0.101	0.002	0.15

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