JOC The Journal of Organic Chemistry

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# Regioselective Synthesis of 2,8-Disubstituted 4-Aminopyrido[3,2-*d*]pyrimidine-6-carboxylic Acid Methyl Ester Compounds

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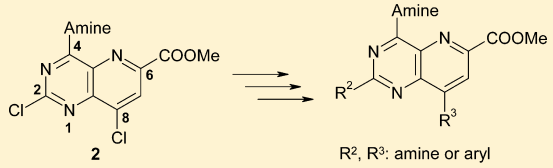
Supporting Information

**ABSTRACT:** We report herein the synthesis of 4-amino-2,8-dichloropyrido[3,2-*d*]pyrimidine derivatives **2** and their regioselective diversification through $S_NAr$ and metal-catalyzed cross-coupling reactions. While amination of **2** took place selectively at C-2, the regioselectivity of thiol or thiolate addition depended on the reaction conditions. Selective C-8 addition was obtained in DMF with Hünig's base and C-2 addition in $^i$PrOH. These C-2 or C-8 regioselective thiolations provided an opportunistic way to selectively activate either of the two positions toward the metal-catalyzed cross-coupling reaction. The chloride could be efficiently substituted by Suzuki−Miyaura reaction and the sulfanyl group by Liebeskind−Srogl cross-coupling reaction, demonstrating the orthogonality of both reactive centers. The development of regioselective conditions for these different transformations yielded the synthesis of 4-amino-2,6,8-trisubstituted pyrido[3,2-*d*]pyrimidine derivatives, with various substituents.




## INTRODUCTION

Pyridopyrimidines are an important class of heterocycles that display a range of significant biological properties, including functioning as anticancer, antiviral, and anti-inflammatory agents. With the aim to produce biased libraries, we were particularly interested in the 4-aminopyrido[3,2-*d*]pyrimidine heterocycle, a motif found in bioactive compounds such as phosphoinositide 3-kinase ($PI_3K$), tyrosine kinase and protein kinases inhibitors,[1,2] chemokine antagonists,[3] and hepatitis C virus (HCV) replication inhibitors.[4] To be able to modulate their biopharmaceutical profile and druglike properties, our goal was to develop a flexible and efficient route to introduce additional specificity handles on the main core. Starting from the reported synthesis of 2,4,8-trichloropyrido[3,2-*d*]-pyrimidine-6-carboxylic acid methyl ester **1**,[5] a first amination at C-4 would leave chloride at C-2 and C-8 and ester at C-6 as additional reactive centers for further diversity. To be of general utility, regioselective transformation of each reactive center must be achievable. We report herein the synthesis of 4-amino-2,8-dichloropyrido[3,2-*d*]pyrimidine derivatives **2** and their regioselective diversification, using two classes of reaction, $S_NAr$ and metal-catalyzed cross-coupling reactions.

## RESULTS AND DISCUSSION

Diverse amines were selected for the preparation of a series of **2**, including primary and secondary amines and anilines. When a stoichiometric amount of the amine was added to **1** in the presence of Hünig's base, the corresponding regioselective substitution products **2a**−**f** were isolated in high yields (Table 1). Addition of anilines, substituted with neutral, electron-donating, or electron-withdrawing groups, indicated the high reactivity of the C-4−Cl bond toward $S_NAr$ (Table 1, entries 4−6). C-4 regioselectivity of this first addition was unambiguously confirmed by X-ray crystal structure analysis on further substituted analogues **5c** and **6c**. The regioselectivity of the first amination is in line with the reported C-4 addition to 2,4-dichloropyrido[3,2-*d*]pyrimidine and additional internal investigations.[6]

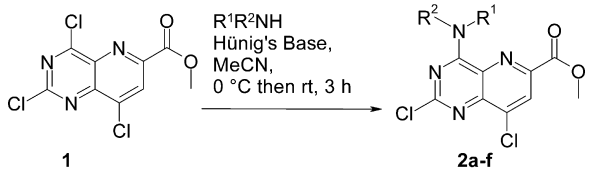
To study the reactivity of the two remaining chloride at C-2 and C-8, various $S_NAr$ and metal-catalyzed cross-coupling reactions were investigated on compounds **2b** and **2c**. Amination was first explored, with three different amines, butylamine and benzylamine as primary amines and diethylamine as secondary amine. Reaction of a solution of **2b** or **2c** in a mixture of MeCN and DMF with 5 equiv of amine at 90 °C led after 1 h to derivatives **3a**−**d** in good yields (Table 2, entries 1−4). Excess amine did not give multiple additions but allowed complete conversion into a single regioisomer **3a**−**d**. As C-2 showed good reactivity toward amination, reaction with aniline was tried. A complete conversion could be achieved only in dioxane as solvent. After 48 h at reflux, derivative **3e** was isolated in 72% yield (Table 2, entry 5).[7]

The regioselective amination on **2** was further probed by chloride reduction of compound **3c** and **3e** yielding **4a** and **4b**, respectively (Scheme 1). The $^1$H NMR spectrum of

**Received:** September 6, 2011
**Published:** November 28, 2011

   dx.doi.org/10.1021/jo201834d | *J. Org. Chem.* 2012, 77, 243−252

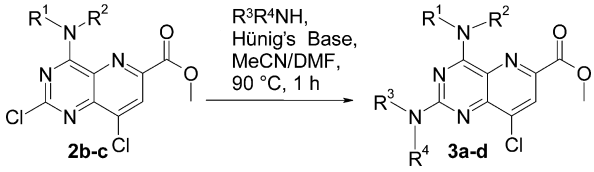
**Table 1. $S_NAr$ with Diverse Amines on 1 at C-4**




1 2a-f

| entry | amine | product | yield (%) |
|---|---|---|---|
| 1 | $^c$Hex-$NH_2$ | **2a** | 77 |
| 2 | $Me_2NH$ | **2b** | 80 |
| 3 | $Et_2NH$ | **2c** | 73 |
| 4 | $PhNH_2$ | **2d** | 82 |
| 5 | *p*-OMe-$PhNH_2$ | **2e** | 80 |
| 6 | *p*-$CF_3$-$PhNH_2$ | **2f** | 78 |

**Table 2. $S_NAr$ with Diverse Amines on 2b−c at C-2**

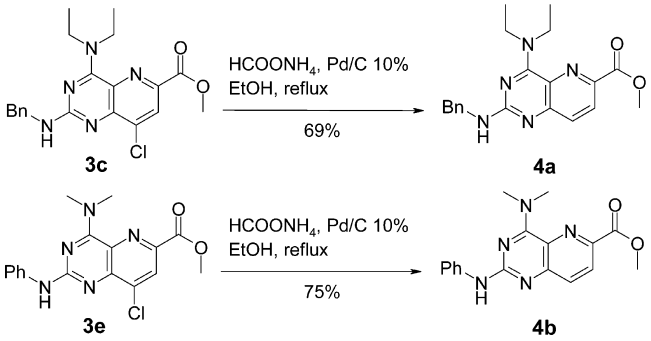



2b-c 3a-d

| entry | **2**, $R^1R^2N$ | $R^3R^4NH$ | product | yield (%) |
|---|---|---|---|---|
| 1 | **2b**, $Me_2N$ | $BuNH_2$ | **3a** | 77 |
| 2 | **2b**, $Me_2N$ | $BnNH_2$ | **3b** | 79 |
| 3 | **2c**, $Et_2N$ | $BnNH_2$ | **3c** | 82 |
| 4 | **2b**, $Me_2N$ | $Et_2NH$ | **3d** | 81 |
| 5[a] | **2b**, $Me_2N$ | $PhNH_2$ | **3e** | 72 |

[a]Reaction was performed in dioxane at reflux.

**Scheme 1. Reduction of C-8 Chloride on 3c and 3e**

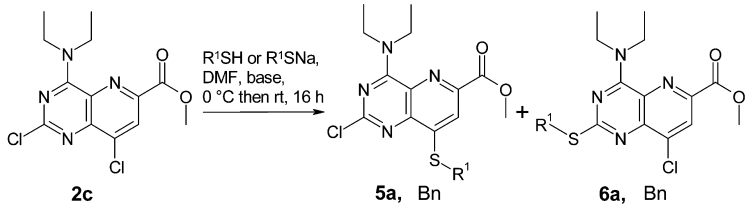



3c 4a 3e 4b

dehalogenated products **4a** and **4b** consisted of a pair of doublets at $\delta$ 7.88 and 8.23 ppm and at $\delta$ 7.80 and 8.17 ppm, respectively, corresponding to H-7 and H-8, with a $J^3$ coupling constant of 8.7 Hz. These results conclusively proved that **3c** and **3e** are substituted with benzylamine or aniline at C-2, leaving a chloride substituent at position 8. In conclusion, **2** amination is highly C-2 regioselective and independent of the nature of the amine.

$S_NAr$ reactions on 2,8-dichloro-4-diethylaminopyrido[3,2-*d*]pyrimidine **2c** were further studied with thiols as nucleophiles. Benzylthiol or *p*-thiocresol in the presence of Hünig's base or sodium methyl thiolate were added in DMF. Reactions were performed between 0 °C and room temper-

**Table 3. $S_NAr$ with Diverse Thiols or Sodium Methyl Thiolate on 2c**




2c

| entry | $R^1SH$ or $R^1SNa$[b] | base | products | UHPLC ratio[a] | yield (%) |
|---|---|---|---|---|---|
| 1 | BnSH | Hünig's base | **5a/6a** | 73/25 | 65/17 |
| 2 | *p*-$CH_3$-PhSH | Hünig's base | **5b/6b** | 68/32 | 62/28 |
| 3 | MeSNa | | **5c/6c** | 97/3 | 77/0 |

[a]Ratio measured on reaction mixtures. [b]1 equiv of thiol or sodium methyl thiolate was used.


dx.doi.org/10.1021/jo201834d | *J. Org. Chem.* 2012, 77, 243−252

**Scheme 2. Addition of BnSH on 6b at C-8**

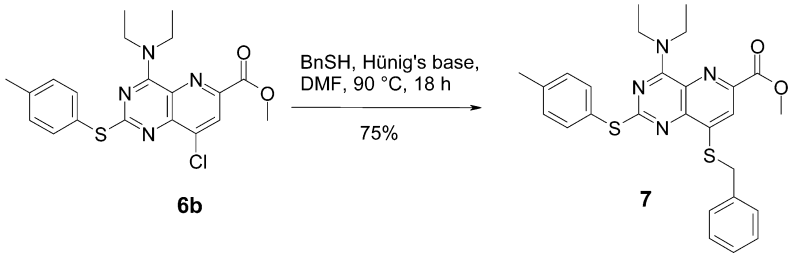
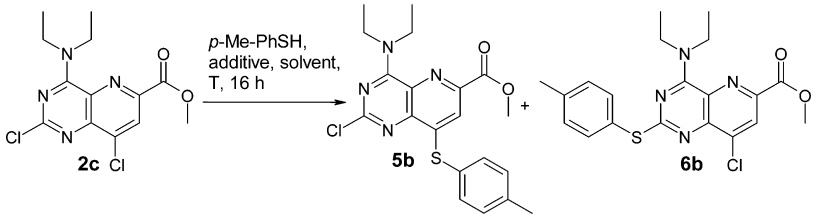



**Table 4. Influence of Basic or Acidic Media, Nature of the Solvent, and Temperature on Regioisomers Formation**




| entry | $T$ (°C) | solvent | $p$-Me-PhSH (equiv) | additive | C-8 (**5b**)/C-2 (**6b**) |
|---|---|---|---|---|---|
| 1 | 0 | DMF | 1 | Hünig's base (3 equiv) | 9/1[8] |
| 2 | 0 | DMF | 1 | | no reaction |
| 3 | 90 | DMF | 1 | | 0/1 (25% conversion) |
| 4 | 0 | DMF | 1 | HCl[a] (1 equiv) | 0/1 |
| 5 | 90 | $^{i}$PrOH | 5 | Hünig's base (3 equiv) | 0/1 |
| 6 | 90 | $^{i}$PrOH | 5 | | 0/1 |
| 7 | rt | $^{i}$PrOH | 5 | | 0/1 (20% conversion) |
| 8 | 90 | DMF/$^{i}$PrOH | 5 | Hünig's base (3 equiv) | 9/1 |
| 9 | 90 | DMF/$^{i}$PrOH | 5 | | 0/1 |

[a]With a 4 M solution of HCl in dioxane.

ature to avoid double addition, as observed at higher temperature. After 2 h at 0 °C, the reaction mixture was allowed to warm to room temperature. Under these conditions and different from the above amination, two regioisomers were formed with benzylthiol and *p*-thiocresol as nucleophiles in ratios of 73/25 and 68/32, respectively (Table 3, entries 1 and 2). With sodium methylthiolate as nucleophile, the reaction was more selective leading to the formation of only traces of the second regioisomer (3%, Table 3, entry 3). These regioisomeric ratios were accurately determined on the reaction mixtures by UHPLC-MS (Table 3). All of the regioisomers were isolated with overall yields ranging from 77 to 90% and fully characterized.

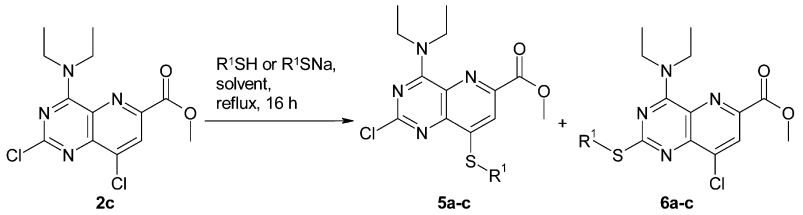
The regioselectivity of the thiol addition was assigned on the basis of the results of NOESY experiments performed on derivatives **5a**/**6a**, **5b**/**6b**, and **5c**/**6c**. NOESY correlation between the benzylic protons of the thioether and H-7 for derivative **5a** and between the methyl of the thioether and H-7 for derivative **5c** were observed, confirming that the thiol addition takes place predominately at position 8. The structures of **5c** and **6c** were confirmed from X-ray crystal structure analysis. In addition, the X-ray crystal structures confirmed the first amination at C-4. No relevant information on **5b** or **6b** structures could be obtained from NOESY experiments. In order to attribute the substitution pattern of **6b**, the remaining chloride was substituted with a nucleophile selected for its reactivity and its potential to present NOESY correlations. Benzylthiol was chosen for this purpose, and reaction with **6b** in DMF in the presence of Hünig's base afforded derivative **7** in 75% yield (Scheme 2). The NOESY correlation observed between the benzylic protons and H-7 confirmed that the benzylthiol group was at the C-8 position and consequently that *p*-thiocresol was at the C-2 position. The full characterization of **6a** and **5b** indicated that they were regioisomers of **5a** and **6b**, showing, respectively, the same mass but different retention time in UHPLC-MS and different $^{1}$H and $^{13}$C NMR chemical shifts. For this reason, their identities were deduced from the assignment of **5a** and **6b** structures.

Reaction conditions for the addition of thiol to **2c** were further explored with *p*-thiocresol in order to optimize the regioselectivity and to find out which parameters were influencing this regioselectivity, such as the nature of the solvent, the presence of a base or an acid, and the temperature of the reaction (Table 4). As before, the regioisomeric ratios were determined on the reaction mixture by UHPLC-MS.

In DMF at 0 °C and in the presence of Hünig's base, *p*-thiocresol added to **2c** predominately at C-8 (Table 4, entry 1). We could expect that the presence of the base ensures the deprotonation of the *p*-thiocresol, affording the thiolate as reactive species and the neutralization of the HCl liberated during the reaction. Under such conditions, C-8 appears to be the most reactive center. In the absence of base, no reaction was observed at rt (Table 4, entry 2). In this reaction, *p*-thiocresol is probably not nucleophilic enough to react with **2c**. At 90 °C, 25% of **6b** was formed, leaving 75% of starting material (Table 4, entry 3). The liberated HCl may influence the regioselectivity and favor C-2 addition. Indeed, the presence of 1 equiv of HCl yielded selectively C-2 addition, with complete conversion at 0 °C to rt (Table 4, entry 4). This observed inversion of regioselectivity can be explained via the


dx.doi.org/10.1021/jo201834d | J. Org. Chem. 2012, 77, 243−252

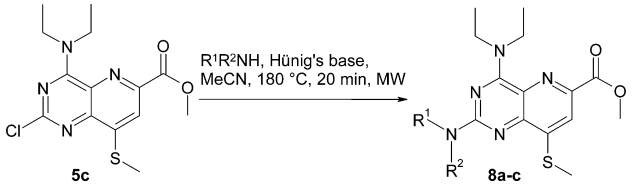
**Table 5. $S_NAr$ of Diverse Thiols and Thiolates on 2c**




| entry | $R^1SH$ or $R^1SNa$ | solvent | products | UHPLC ratio | yield (%) |
|---|---|---|---|---|---|
| 1 | BnSH[a] | $^i$PrOH | **5a/6a** | 0/100 | −/6 |
| 2 | *p*-$CH_3$-PhSH[a] | $^i$PrOH | **5b/6b** | 0/100 | −/83 |
| 3 | MeSNa[b] | MeOH | **5c/6c** | 3/97 | −/73 |

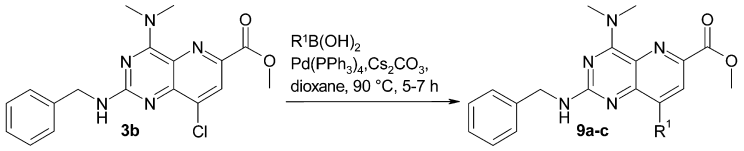
[a]5 equiv of thiol was used. [b]1 equiv of sodium methyl thiolate was used.

**Table 6. $S_NAr$ with Amines on 5c at C-2**




| entry | amine | product | yield (%) |
|---|---|---|---|
| 1 | $BnNH_2$ | **8a** | 74 |
| 2 | $BuNH_2$ | **8b** | 71 |
| 3 | $Et_2NH$ | **8c** | 72 |

**Table 7. Suzuki−Miyaura Cross-Coupling Reactions on 3b at C-8**




| entry | $R^1B(OH)_2$ | product | yield (%) |
|---|---|---|---|
| 1 | $PhB(OH)_2$ | **9a** | 82 |
| 2 | *p*-OMe-$PhB(OH)_2$ | **9b** | 82 |
| 3 | *p*-$CF_3$-$PhB(OH)_2$ | **9c** | 78 |

protonation of derivative **2c**. On the basis of calculated p$K_a$ values, N-1 is the most basic center.[9] Protonation at this site does not significantly affect the partial charges at C-2 and C-8, respectively.[10] In contrast, the LUMO density is the highest at C-8 for the neutral and at C-2 for the protonated form. This indicates that the reaction is not charge but orbital controlled.

These same reactions were performed in a protic solvent such as $^i$PrOH. As **2c** was not soluble in this solvent, the reaction mixture was heated at refluxing temperature to ensure the dissolution of the starting material. In addition, an excess of *p*-thiocresol was used for a complete conversion, without influencing the observed regioselectivity and multiple addition. Addition of a base did not influence the regioselectivity and yielded the formation of the C-2 adduct as unique regioisomer (Table 4, entries 5 and 6). At rt, the same regioselectivity was observed, with only 20% of conversion probably due to limited solubility of **2c** in $^i$PrOH (Table 4, entry 7). The opportunity of hydrogen bonding in $^i$PrOH could direct C-2 addition, even under basic conditions.[10] Interestingly, in a $^i$PrOH/DMF mixture the regioselectivity was directly influenced by the base, yielding mainly C-8 addition in the presence of Hünig's base and C-2 addition without any base (Table 4, entries 8 and 9). In the presence of Hünig's base, DMF could interfere with hydrogen bonding between **2c** and $^i$PrOH, yielding fast addition of deprotonated form of *p*-thiocresol to C-8. In the absence of Hünig's base, activation of **2c** through hydrogen bonding with $^i$PrOH is required to ensure *p*-thiocresol addition, yielding C-2 regioselectivity.[10]

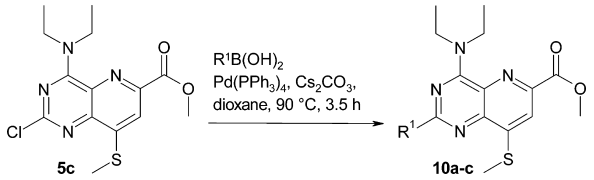
With the aim to study the C-2 or C-8 addition reversibility under the different reaction conditions, *p*-thiocresol was added into a solution of **2c** in $^i$PrOH, and the mixture was heated to 90 °C until 50% conversion into **6b**. Then, DMF and Hünig's base were added. After few hours at rt, a 50:50 mixture of both regioisomers was obtained, demonstrating that the formation of each regioisomer was irreversible. Regioisomers **5b** and **6b** were stable in both reaction conditions, in DMF with Hünig's base at 0 °C and rt or in $^i$PrOH at 90 °C.

At this point, we could conclude that C-2 addition of thiol or thiolate to derivative **2** was favored under acidic conditions and/or protic solvents, while C-8 addition was majoritarly observed in polar aprotic solvent in the presence of a tertiary amine such as Hünig's base.

Conditions favoring C-2 thiolation were used with the same three thiols as previously described, namely: benzylthiol, *p*-

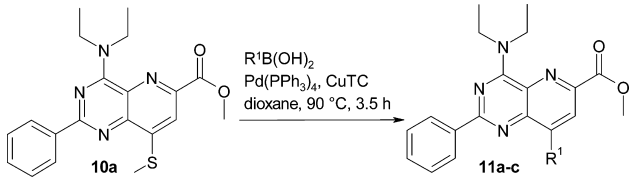

dx.doi.org/10.1021/jo201834d | J. Org. Chem. 2012, 77, 243−252

**Table 8. Suzuki–Miyaura Cross-Coupling Reaction on 5c at C-2**




| entry | $R^1B(OH)_2$ | product | yield (%) |
|---|---|---|---|
| 1 | $PhB(OH)_2$ | **10a** | 88 |
| 2 | *p*-OMe-$PhB(OH)_2$ | **10b** | 79 |
| 3 | *p*-$CF_3$-$PhB(OH)_2$ | **10c** | 84 |

**Table 9. Liebeskind–Srogl Cross-Coupling Reactions on 10a at C-8**




| entry | $R^1B(OH)_2$ | product | yield (%) |
|---|---|---|---|
| 1 | $PhB(OH)_2$ | **11a** | 84 |
| 2 | *p*-OMe-$PhB(OH)_2$ | **11b** | 88 |
| 3 | *p*-$CF_3$-$PhB(OH)_2$ | **11c** | 87 |

[a]2 equiv of boronic acid for completion.

thiocresol, and sodium methyl thiolate (Table 5). Only partial conversion could be achieved with benzylthiol, even at refluxing temperature, affording **6a** in very low yield (Table 5, entry 1). *p*-Thiocresol was more reactive under such conditions, and compound **6b** was isolated in 83% yield (Table 5, entry 2). When sodium methyl thiolate was used, MeOH was selected as solvent to avoid possible transesterification observed in $^i$PrOH, and compound **6c** was isolated in 73% yield (Table 5, entry 3).

We took advantage of the optimized access to both regioisomers **5c** and **6c** in order to further explore the synthesis of diverse 2,8-disubstituted 4-aminopyrido[3,2-*d*]-pyrimidine analogues. Chloride reactivity toward $S_NAr$ and cross-coupling reactions, such as Suzuki–Miyaura reaction, and transformation of methylsulfanyl group via Liebeskind–Srogl cross-coupling reactions were investigated. We first studied the reaction of derivative **5c** with amines. Addition of primary or secondary amines at 180 °C in MeCN under microwave irradiations yielded 2,4-diamino-8-methylsulfanylpyrido[3,2-*d*]-pyrimidines **8** in 71–74% yields (Table 6).

Further transformation of the C-8-SMe bond on derivative **8**, via Liebeskind-Srogl cross-coupling reactions, would give access to the same products as Suzuki–Miyaura cross-coupling reaction on derivative **3** (Table 7 below), which is synthetically shorter (being two vs three steps from **1**). For this reason, we focused on this second approach, starting from derivative **3b** (Table 7). Suzuki–Miyaura cross-coupling reactions of **3b** were performed under classical conditions using $Pd(PPh_3)_4$ as catalyst and $Cs_2CO_3$ as base in dioxane. Diverse boronic acids with electron-donating or electron-withdrawing groups were selected. Reaction mixtures were heated at 90 °C, affording after 5–7 h derivatives **9a** to **9c** in good yields (Table 7, entries 1–3).

Second, derivative **5c** was diversified via two successive metal-catalyzed cross-coupling reactions. Selective mono-cross-coupling reaction on its precursor **2c** was tedious. A mixture of mono- and bis-coupling products was obtained. Taking advantage of the differentiation of both reactive centers at C-2 and C-8, and their known orthogonal reactivity,[11] derivative **5c** was first submitted to Suzuki–Miyaura cross-coupling reactions (Table 8). The same reaction conditions as described previously were selected, affording derivatives **10a–c** in 79 to 88% yields (Table 8, entries 1–3). Under such conditions, the methylsulfanyl group remained unchanged. Parallel to our work, Guillaumet et al. published similar approach to differentiate C-4 and C-2 chloride on the 2,4-dichloropyrido-[3,2-*d*]pyrimidine.[12]

A different aryl group was further introduced at C-8 on derivative **10a** via Liebeskind–Srogl cross-coupling reaction. Compounds **11** were obtained using a stoichiometric amount of boronic acid derivatives, with $Pd(PPh_3)_4$ as catalyst and copper(I) thiophene-2-carboxylate (CuTC) as cofactor (Table 9). After 3.5 h in dioxane at 90 °C, compounds **11** were isolated in good yields (Table 9). With the poorly reactive *p*-trifluoromethylphenylboronic acid, the reaction had to be repeated twice to get a complete conversion. These two successive cross-coupling reactions, i.e., the first Suzuki–Miyaura followed by the Liebeskind–Srogl cross-coupling, allowed the introduction of two different aryl groups at positions C-2 and C-8, yielding novel and diverse compounds **11** in good yields and selectivity.

## ■ CONCLUSIONS

We have reported the synthesis of 4-amino-2,8-dichloropyrido-[3,2-*d*]pyrimidines derivatives **2** and their controlled regioselective diversification through different set of $S_NAr$ and metal-catalyzed cross-coupling reactions. While amination took place selectively at C-2 of **2**, the regioselectivity of thiol or thiolate addition depended on the nature of the solvent (protic or polar aprotic solvents) and the pH of the reaction mixture. Addition at C-8 took place in DMF with Hünig's base and at C-2 in


dx.doi.org/10.1021/jo201834d | J. Org. Chem. 2012, 77, 243–252

$^{i}$PrOH. These C-2 or C-8 regioselective thiolations provided an opportunistic way of differentiating the two positions toward metal-catalyzed cross-coupling reaction. 2-Chloro-4-amino-8-(methylthio)pyrido[3,2-*d*]pyrimidine derivative **5c** was further diversified either through amination or through two successive metal-catalyzed cross-coupling reactions. In this second alternative, a first aryl group was introduced selectively at C-2 through Suzuki−Miyaura reaction, demonstrating the orthogonality of both reactive centers (C−Cl vs C−SMe). A second aryl group was introduced through Liebeskind−Srogl cross-coupling reaction at the C−SMe bond. With the development of highly regioselective conditions for the synthesis of 2,6,8-trisubstituted 4-aminopyrido[3,2-*d*]pyrimidine derivatives, we were able to prepare a wide variety of analogues. This strategy is currently being applied to structurally related polysubstituted heterocyclic derivatives and will be reported in the future.

## EXPERIMENTAL SECTION

**General Procedures.** The commercially available starting materials were used without further purification. $^{1}$H 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. $^{1}$H and $^{13}$C chemical shifts ($\delta$) were internally referenced to the residual solvent peak. Mass spectra were acquired by electrospray ionization. Melting points were reported without correction. 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.

**General Procedure for $S_NAr$ with Amines on Derivative 1 at C-4.** To a solution of 2,4,8-trichloropyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **1** (50 mg, 0.17 mmol) in MeCN (0.25 mL) was added an amine (0.17 mmol) dissolved in MeCN (0.25 mL) in the presence of Hünig's base (90 $\mu$L; 0.51 mmol) at 0 °C. The reaction mixture was allowed to warm to rt and was stirred for 3 h. MeCN was removed under reduced pressure. The resulting solid was triturated in MeOH, filtered, and dried under vacuum to afford compounds **2a** to **2f**.

**2,8-Dichloro-4-cyclohexylaminopyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (2a):** yield = 77%; dark pink solid; mp 205−206 °C dec; IR $\nu_{max}$ 3548, 1725, 1231 cm$^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.16−1.33 (m, 1H), 1.33−1.57 (m, 3H), 1.65−1.77 (m, 1H), 1.77−1.92 (m, 3H), 2.05−2.15 (m, 2H), 4.04 (s, 3H), 4.20 (br m, 1H), 7.56 (d, $J$ = 8 Hz, 1H), 8.42 (s, 1H); $^{13}$C NMR (75.47 MHz, $CDCl_3$) $\delta$ 25.2, 25.8, 32.8, 50.8, 53.7, 129.0, 131.4, 143.0, 145.1, 145.2, 160.3, 161.9, 164.2; HPLC $t_R$ = 4.77 min; ES-MS $m/z$ 355.27 (M + H)$^+$. Anal. Calcd for $C_{15}H_{16}Cl_2N_4O_2$: C, 50.72; H, 4.54; N, 15.77. Found: C, 50.38; H, 4.21; N, 15.39.

**2,8-Dichloro-4-dimethylaminopyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (2b):** yield = 80%; pink solid; mp 216−217 °C dec; IR $\nu_{max}$ 1716, 1208 cm$^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.45 (s, 3H), 4.01 (s, 6H), 8.40 (s, 1H); $^{13}$C NMR (75.47 MHz, $CDCl_3$) $\delta$ 42.3, 43.3, 53.5, 128.0, 133.3, 142.5, 143.2, 147.9, 160.1, 160.7, 164.3; HPLC $t_R$ = 3.81 min; ES-MS $m/z$ 301.00 (M + H)$^+$. Anal. Calcd for $C_{11}H_{10}Cl_2N_4O_2$: C, 43.87; H, 3.35; N, 18.61. Found: C, 43.71; H, 3.34; N, 18.93.

**2,8-Dichloro-4-diethylaminopyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (2c):** yield = 73%; dark orange solid; mp 128−129 °C; IR $\nu_{max}$ 2932, 1742, 1254 cm$^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.33 (t, $J$ = 7 Hz, 3H), 1.44 (t, $J$ = 7 Hz, 3H), 3.89 (q, $J$ = 7 Hz, 2H), 3.99 (s, 3H), 4.01 (s, 3H), 4.34 (q, $J$ = 7 Hz, 2H), 8.38 (s, 1H); $^{13}$C NMR (75.47 MHz, $CDCl_3$) $\delta$ 12.1, 14.2, 47.2, 47.4, 53.4, 127.9, 132.8, 142.3, 143.3, 148.0, 159.6, 160.4, 164.4; HPLC $t_R$ = 4.83 min; ES-MS $m/z$ 328.99 (M + H)$^+$. Anal. Calcd for $C_{13}H_{14}Cl_2N_4O_2$: C, 47.43; H, 4.29; N, 17.02. Found: C, 47.18; H, 4.29; N, 16.89.

**2,8-Dichloro-4-phenylaminopyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (2d):** yield = 82%; dark orange solid; mp 223−224 °C dec; IR $\nu_{max}$ 3338, 1731, 1574 cm$^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.07 (s, 3H), 7.24 (t, $J$ = 8 Hz, 1H), 7.45 (t, $J$ = 8 Hz, 2H), 7.90 (d, $J$ = 8 Hz, 2H), 8.49 (s, 1H), 9.45 (br s, 1H); $^{13}$C NMR (75.47 MHz, $CDCl_3$) $\delta$ 53.8, 121.6, 126.0, 129.3, 129.6, 131.3, 137.0, 143.7, 145.3, 145.8, 158.5, 161.4, 163.9; HPLC $t_R$ = 4.48 min; ES-MS $m/z$ 349.19 (M + H)$^+$. Anal. Calcd for $C_{15}H_{10}Cl_2N_4O_2$: C, 51.60; H, 2.89; N, 16.05; Cl, 20.31. Found: C, 51.24; H, 2.76; N, 15.82; Cl, 19.95.

**2,8-Dichloro-4-(4-methoxyphenylamino)pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (2e):** yield = 80%; yellow solid; mp 231−232 °C dec; IR $\nu_{max}$ 3333, 1729, 1574, 1248 cm$^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.85 (s, 3H), 4.07 (s, 3H), 6.96−6.99 (m, 2H), 7.78−7.81 (m, 2H), 8.48 (s, 1H), 9.36 (br s, 1H); $^{13}$C NMR (75.47 MHz, $CDCl_3$) $\delta$ 53.8, 55.9, 114.7, 123.3, 129.2, 130.1, 131.4, 143.5, 145.3, 145.6, 157.8, 158.2, 161.6, 164.0; HPLC $t_R$ = 4.42 min; ES-MS $m/z$ 379.22 (M + H)$^+$. Anal. Calcd for $C_{16}H_{12}Cl_2N_4O_3$: C, 50.68; H, 3.19; N, 14.77. Found: C, 51.03; H, 3.52; N, 14.48.

**2,8-Dichloro-4-(4-trifluoromethylphenylamino)pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (2f):** yield = 78%; dark orange solid; mp 192−193 °C dec; IR $\nu_{max}$ 1723, 1572, 1316, 1106 cm$^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.09 (s, 3H), 7.72 (d, $J$ = 8.5 Hz, 2H), 8.08 (d, $J$ = 8.5 Hz, 2H), 8.53 (s, 1H), 9.61 (br s, 1H); $^{13}$C NMR (75.47 MHz, $CDCl_3$) $\delta$ 53.9, 121.3, 124.2 (q, $J$ = 267.2 Hz), 126.9 (q, $J$ = 3.7 Hz), 127.5 (q, $J$ = 32 Hz), 129.5, 131.1, 140.1, 144.1, 145.4, 146.2, 158.6, 161.1, 163.8; HPLC $t_R$ = 5.23 min; ES-MS $m/z$ 417.20 (M + H)$^+$. Anal. Calcd for $C_{16}H_9Cl_2F_3N_4O_2$: C, 46.07; H, 2.17; N, 13.43. Found: C, 45.72; H, 2.47; N, 13.34.

**4-(4-Methoxyphenylamino)pyrido[3,2-*d*]pyrimidine-6-carboxylic Acid Methyl Ester (2g).** To a solution of **2e** (500 mg, 1.32 mmol) in a 1:1 mixture of methanol and dichloromethane (50 mL) was added 10% Pd/C (50 mg), and the reaction mixture was put under 1.5 bar of hydrogen for 6 h at rt. The catalyst was removed by filtration, and the filtrate was concentrated. The crude product was purified by column chromatography using 10−12% ethyl acetate in petroleum ether as eluent to afford compound **2g** as pale yellow solid (0.292 mg, 73% yield): mp 131−132 °C; IR $\nu_{max}$ 3464, 1726, 1604, 1541, 1280, 1031 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.86 (s, 3H), 4.09 (s, 3H), 6.99−7.01 (dd, $J$ = 6.8, 2.2 Hz, 2H), 7.79−7.81 (dd, $J$ = 6.8, 2.2 Hz, 2H), 8.36−8.38 (d, $J$ = 8.7 Hz, 1H), 8.45−8.47 (d, $J$ = 8.7 Hz, 1H), 8.77 (s, 1H), 9.39 (br s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 53.1, 55.5, 114.3, 123.3, 128.2, 130.4, 131.5, 136.8, 145.7, 145.8, 156.9, 157.7, 157.8, 164.5; HPLC $t_R$ = 2.75 min; ES-MS $m/z$ 311.2 (M + H)$^+$. Anal. Calcd for $C_{16}H_{14}N_4O_3$: C, 61.93; H, 4.55; N, 18.05. Found: C, 61.98; H, 4.59; N, 18.01.

**General Procedure for $S_NAr$ with Amines on Derivative 2 at C-2.** To a solution of derivative **2** (0.32 mmol) in a mixture of MeCN (2.0 mL) and DMF (2.0 mL) was added an amine (1.6 mmol) inthe presence of Hünig's base (0.17 mL, 0.96 mmol). The reaction mixture was stirred at 90 °C for 1 h. Solvents were removed under vacuum. The resulting solid was triturated in MeOH, filtered, and dried under vacuum to afford derivatives **3a**−**d**.

**2-Butylamino-8-chloro-4-dimethylaminopyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (3a):** yield = 77%; yellow solid; mp 112−113 °C; IR $\nu_{max}$ 3400, 1697, 1537 cm$^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.96 (t, $J$ = 7.4 Hz, 3H), 1.43 (m, 2H), 1.57−1.72 (br m, 2H), 2.99−4.20 (br m, 8H), 3.96 (s, 3H), 5.30 (br s, 1H), 8.23 (s, 1H); $^{13}$C NMR (75.47 MHz, $CDCl_3$) $\delta$ 14.2, 20.5, 32.3, 41.8, 42.2, 53.0, 127.6, 137.3, 149.2, 160.3, 160.8, 165.3; HPLC $t_R$ = 3.08 min; ES-MS $m/z$ 338.38 (M + H)$^+$. Anal. Calcd for $C_{15}H_{20}ClN_5O_2$: C, 53.33; H, 5.97; N, 20.73. Found: C, 53.64 H, 5.59; N, 20.51.

**2-Benzylamino-8-chloro-4-dimethylaminopyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (3b):** yield = 79%; yellow solid; mp 157−158 °C; IR $\nu_{max}$ 3381, 1699, 1534 cm$^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$+ 0.7% TFA)[13] $\delta$ 3.45 (s, 3H), 4.01 (s, 3H), 4.07 (s, 3H), 4.72 (d, $J$ = 6.0 Hz, 2H), 7.25−7.38 (m, 5H), 8.38 (s, 1H), 9.02 (br t, $J$ = 6.0 Hz, 1H); $^{13}$C NMR (75.47 MHz, $CDCl_3$+ 0.7%


dx.doi.org/10.1021/jo201834d | J. Org. Chem. 2012, 77, 243−252

TFA) $\delta$ 43.2, 43.7, 45.8, 53.6, 127.5, 127.9, 128.9, 129.3, 129.5, 133.0, 136.7, 137.4, 142.2, 151.9, 158.2, 163.3; HPLC $t_R$ = 3.05 min; ES-MS $m/z$ 372.04 $(M + H)^+$. Anal. Calcd for $C_{18}H_{18}ClN_5O_2$: C, 58.15; H, 4.88; N, 18.83. Found: C, 57.70; H, 5.05; N, 18.90.

**2-Benzylamino-8-chloro-4-diethylaminopyrido[3,2-*d*]-pyrimidine-6-carboxylic acid methyl ester (3c):** yield = 82%; light yellow solid; mp 100.7−101.9 °C; IR $\nu_{max}$ 1707, 1561, 1535, 1338 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$ + 0.7% TFA)[13] $\delta$ 1.20 (t, $J$ = 7.0 Hz, 3H), 1.46 (t, $J$ = 6.8 Hz, 3H), 3.77 (q, $J$ = 7.0, 2H), 3.99 (s, 3H), 4.36 (q, $J$ = 6.8 Hz, 2H), 4.70 (d, $J$ = 5.9 Hz, 2H), 7.22−7.35 (m, 5H), 8.38 (s, 1H), 9.35 (br t, $J$ = 5.9 Hz, 1 H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$ + 0.7% TFA) $\delta$ 11.5, 13.7, 45.5, 47.9, 48.0, 53.2, 127.0, 127.6, 128.8, 128.9, 129.2, 133.0, 137.0, 137.5, 142.1, 152.2, 157.1, 163.2, HPLC $t_R$ = 3.90 min; ES-MS $m/z$ 400.40 $(M + H)^+$. Anal. Calcd for $C_{20}H_{22}ClN_5O_2$: C, 60.07; H, 5.55; N, 17.51; Cl, 8.87. Found: C, 59.73; H, 5.39; N, 17.19; Cl, 8.68.

**2-Diethylamino-8-chloro-4-dimethylaminopyrido[3,2-*d*]-pyrimidine-6-carboxylic acid methyl ester (3d):** yield = 81%; yellow solid; mp 119−120 °C; IR $\nu_{max}$ 1711, 1537 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.24 (br s, 6H), 3.35−3.95 (br m, 10H), 3.95 (s, 3H), 8.20 (s, 1H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$) $\delta$ 13.62, 41.93, 42.50, 52.93, 127.33, 130.96, 136.58, 138.75, 149.39, 158.67, 160.54, 165.47; HPLC $t_R$ = 3.07 min; ES-MS $m/z$ 338.39 $(M + H)^+$; Anal. Calcd for $C_{15}H_{20}ClN_5O_2$: C, 53.33; H, 5.97; N, 20.73. Found: C, 53.25; H, 5.93; N, 20.47.

**Methyl 2-Anilino-8-chloro-4-(dimethylamino)pyrido[3,2-*d*]-pyrimidine-6-carboxylate (3e).** To a solution of 2,8-dichloro-4-dimethylaminopyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **2b** (95 mg; 0.32 mmol) in dioxane (4 mL) was added aniline (36 mg; 0.38 mmol). The reaction mixture was stirred at reflux for 2 days. The resulting precipitate was filtered, triturated in MeOH, filtered, and dried under vacuum to afford compound **3e** as a pale yellow solid (85.9 mg, 75% yield): mp 204−205 °C dec; IR $\nu_{max}$ 3370, 1707, 1519, 1261 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$ + 0.7% TFA)[13] $\delta$ 3.50 (s, 3H), 4.02 (s, 3H), 4.11 (s, 3H), 7.15−7.24 (m, 1H), 7.33−7.42 (m, 2H), 7.56−7.62 (m, 2H), 8.39 (s, 1H), 11.24 (br s, 1H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$+ 0.7% TFA) $\delta$ 43.5, 43.8, 53.5, 122.6, 126.1, 129.1, 129.5, 129.6, 133.5, 136.2, 137.8, 142.3, 150.3, 158.4, 163.3; HPLC $t_R$ = 3.56 min; ES-MS $m/z$ 358 $(M + H)^+$. Anal. Calcd for $C_{17}H_{16}ClN_5O_2$: C, 57.07; H, 4.51; N, 19.57. Found: C, 57.11; H, 4.53; N, 19.36.

**General Procedure for Chloride Reduction of Derivative 3.** A mixture of 2,4-diamino-8-chloropyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **3** (0.24 mmol), ammonium formate (4.87 mmol), and 10% Pd/C (25.5 mg, 0.024 mmol) in EtOH (20 mL) was stirred at reflux for 45 min. The reaction mixture was concentrated in vacuo. The residue was taken up in 5% MeOH in DCM and filtered through a short plug of Celite, which was further washed with the same solvents mixture. The solvents were evaporated, and the resulting solid was dissolved in DCM (25 mL),washed with saturated solution of $NaHCO_3$ (20 mL) and brine (20 mL), and dried on anhydrous $MgSO_4$. After evaporation of the solvents, the resulting solid was triturated in MeOH, filtered, and dried under vacuum to afford derivatives **4a** and **4b**.

**2-Benzylamino-4-diethylaminopyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (4a):** yield = 69%; yellow solid; mp 138.5−139.5 °C; IR $\nu_{max}$ 2940, 1714, 1536, 1337, 1290 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$ + 0.7% TFA)[13] $\delta$ 1.14 (t, $J$ = 7.1 Hz, 3H), 1.39 (t, $J$ = 7.0 Hz, 3H), 3.70 (q, $J$= 7.1 Hz, 2H), 3.93 (s, 3H), 4.34 (q, $J$ = 7.0 Hz, 2H), 4.63 (d, $J$ = 5.8 Hz, 2H), 7.15−7.31 (m, 5H), 7.88 (d, $J$ = 8.7 Hz, 1H), 8.23 (d, $J$ = 8.7 Hz, 1H), 8.99 (br t, $J$ = 5.3 Hz, 1H), 13.13 (br s, 1H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$ + 0.7% TFA) $\delta$ 11.6, 13.8, 45.3, 47.5, 47.6, 53.0, 126.1, 127.0, 127.6, 128.0, 128.8, 129.3, 137.3, 139.5, 142.7, 152.1, 157.5, 164.1; HPLC $t_R$ = 3.90 min; ES-MS $m/z$ 366.30 $(M + H)^+$. Anal. Calcd for $C_{20}H_{23}N_5O_2$: C, 65.74; H, 6.34; N, 19.16. Found: C, 65.36; H, 6.41; N, 18.89.

**4-Dimethylamino-2-phenylaminopyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (4b):** yield = 75%; light yellow solid; mp 159.2−160.3 °C; IR $\nu_{max}$ 2944, 1706, 1523, 1441, 1258 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.18−4.21 (br m, 6H), 3.98 (s, 3H), 6.99−7.09 (m, 1H), 7.17 (br s, 1H), 7.28−7.39 (m, 2H), 7.65−7.75 (m, 2H), 7.80 (d, $J$ = 8.7 Hz, 1H), 8.17 (d, $J$ = 8.7 Hz, 1H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$ + 0.7% TFA)[13] $\delta$ 42.9, 43.3, 53.1, 122.1, 125.4, 126.5, 128.4, 128.9, 129.3, 136.6, 140.0, 142.6, 150.2, 158.7, 164.0; HPLC $t_R$ = 3.02 min; ES-MS $m/z$ 324.38 $(M + H)^+$. Anal. Calcd for $C_{17}H_{17}N_5O_2$·0.1 $H_2O$: C, 62.80; H, 5.33; N, 21.54. Found: C, 62.82; H, 5.71; N, 21.23.

**General Procedure for $S_NAr$ Reaction of Thiol to Derivative 2c in DMF.** To a solution of 2,8-dichloro-4-diethylaminopyrido[3,2-*d*]pyrimidine **2c** (151 mg, 0.46 mmol) in DMF (4.0 mL) was added a thiol (0.46 mmol) in the presence of Hünig's base (0.24 mL, 1.38 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and allowed warm to rt for 14 h. The solvents were evaporated. The resulting mixture was dissolved in a mixture 1:1 mixture of MeCN and DMSO (1.5 mL) and was purified by preparative HPLC to isolate both regioisomers **5a−b** and **6a−b**.

**2-Chloro-4-diethylamino-8-benzylsulfanylpyrido[3,2-*d*]-pyrimidine-6-carboxylic acid methyl ester (5a):** yield = 65%; off-white solid; mp 101.4−102.4 °C; IR $\nu_{max}$ 1504, 1346, 1248, 1128 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.23−1.26 (m, 3H), 1.33−1.37 (m, 3H), 3.73−3.75 (m, 2H), 3.91 (s, 3H), 4.31−4.33 (m, 2H), 4.42 (s, 2H), 7.29−7.39 (m, 3H), 7.50−7.52 (m, 2H), 8.13 (s, 1H), $^{13}C$ NMR (75.47 MHz, DMSO-$d_6$) $\delta$ 11.6, 13.9, 33.9, 45.9, 46.3, 52.9, 120.7, 127.6, 128.7, 129.0, 129.4, 135.6, 142.6, 146.5, 148.8, 156.8, 158.9, 164.3; HPLC $t_R$ = 6.17 min; ES-MS $m/z$ 417.3 $(M + H)^+$. Anal. Calcd for $C_{20}H_{21}ClN_4O_2S$: C, 57.62; H, 5.08; N, 13.44; Cl, 8.50. Found: C, 57.42; H, 5.17; N, 13.34; Cl, 8.46.

**2-Benzylsulfanyl-4-diethylamino-8-chloropyrido[3,2-*d*]-pyrimidine-6-carboxylic acid methyl ester (6a):** yield = 17%; off-white solid; mp 118.3−119.3 °C; IR $\nu_{max}$ 1713, 1440, 1352 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.16−1.27 (br m, 3H), 1.30−1.42 (br m, 3H), 3.67−3.81 (br m, 2H), 3.92 (s, 3H), 4.21−4.33 (br m, 2H), 4.48 (s, 2H), 7.23−7.34 (m, 3H), 7.48−7.51 (m, 2H), 8.36 (s, 1H); $^{13}C$ NMR (75.47 MHz, DMSO-$d_6$) $\delta$ 11.6, 13.9, 34.6, 45.7, 46.3, 52.8, 126.9, 127.1, 128.4, 128.8, 131.6, 138.3, 139.7, 141.2, 145.7, 156.9, 163.6, 169.4; HPLC $t_R$ = 6.13 min; ES-MS $m/z$ 417.3 $(M + H)^+$. Anal. Calcd for $C_{20}H_{21}ClN_4O_2S$: C, 57.62; H, 5.08; N, 13.44; Cl, 8.50. Found: C, 57.85; H, 5.09; N, 13.43; Cl, 8.48.

**2-Chloro-4-diethylamino-8-*p*-tolylsulfanylpyrido[3,2-*d*]-pyrimidine-6-carboxylic acid methyl ester (5b):** yield = 62%; light yellow solid; mp 195.2−196.2 °C; IR $\nu_{max}$ 2940, 2356, 1716, 1347, 1129 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.23−1.27 (m, 3H), 1.31−1.37 (m, 3H), 2.43 (s, 3H), 3.65−3.90 (m, 2H), 3.80 (s, 3H), 4.30−4.33 (m, 2H), 7.35 (s, 1H), 7.44 (d, $J$ = 7.9 Hz, 2H), 7.54 (d, $J$ = 8.2 Hz, 2H); $^{13}C$ NMR (75.47 MHz, DMSO-$d_6$) $\delta$ 11.6, 13.8, 20.9, 45.9, 46.3, 52.8, 120.4, 124.2, 126.7, 131.3, 135.6, 140.6, 141.1, 142.7, 145.5, 150.6, 158.8, 164.2; HPLC $t_R$ = 6.06 min; ES-MS $m/z$ 417.1 $(M + H)^+$. Anal. Calcd for $C_{20}H_{21}ClN_4O_2S$: C, 57.62; H, 5.08; N, 13.44; Cl, 8.50. Found: C, 57.62; H, 4.85; N, 13.70; Cl, 8.10.

**2-Chloro-4-diethylamino-8-methylsulfanylpyrido[3,2-*d*]-pyrimidine-6-carboxylic Acid Methyl Ester (5c).** To a solution of 2,8-dichloro-4-diethylaminopyrido[3,2-*d*]pyrimidine **2c** (151 mg, 0.46 mmol) in DMF (4.0 mL) was added sodium methyl thiolate (0.46 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and was allowed to warm to rt for 14 h. The solvents were evaporated. The resulting mixture was dissolved in a 1:1 mixture of MeCN and DMSO (1.5 mL) and was purified by preparative HPLC, affording **5c** as a light yellow solid (120.7 mg, 77% yield). The other regioisomer, **6c** (3% of the crude mixture), could not be isolated: mp 153−154 °C; IR $\nu_{max}$ 1716, 1251 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.30 (br m, 3H), 1.41 (br m, 3H), 2.53 (s, 3H), 3.81 (br m, 2H), 3.97 (s, 3H), 4.36 (br m, 2H), 7.97 (s, 1H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$) $\delta$ 12.25, 14.25, 14.40, 46.82, 47.16, 53.21, 120.07, 129.96, 143.17, 147.86, 151.03, 158.52, 159.80, 165.63; HPLC $t_R$ = 5.05 min; ES-MS $m/z$ 341.32 $(M + H)^+$. Anal. Calcd for $C_{14}H_{17}ClN_4O_2S$: C, 49.34; H, 5.03; N, 16.44. Found: C, 49.07; H, 5.03; N, 16.29.

**2-*p*-Tolylsulfanyl-4-diethylamino-8-chloropyrido[3,2-*d*]-pyrimidine-6-carboxylic Acid Methyl Ester (6b).** To a solution of 2,8-dichloro-4-diethylaminepyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **2c** (60 mg, 0.18 mmol) in $^i$PrOH (5.4 mL) was added


dx.doi.org/10.1021/jo201834d | J. Org. Chem. 2012, 77, 243−252

*p*-thiocresol (112 mg, 0.9 mmol). After 16 h at reflux, solvents were removed under vacuo. The resulted residue was dissolved in a 1:1 mixture of MeCN and DMSO (1.5 mL) and was purified by preparative HPLC, affording derivative **6b** as a beige solid (62.2 mg, 83% yield): mp 137.8−138.8 °C; IR $\nu_{max}$ 1713, 1532, 1504, 1435, 1345, 1245, 1129 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 0.82 (br m, 3H), 1.29 (br m, 3H), 2.37 (s, 3H), 3.36 (br m, 2H), 3.90 (s, 3H), 4.17−4.19 (br m, 4H), 7.29 (d, $J$ = 7.7 Hz, 2H), 7.52 (d, $J$ = 7.8 Hz, 2H), 8.31 (s, 1H); $^{13}C$ NMR (75.47 MHz, DMSO-$d_6$) $\delta$ 11.4, 13.7, 20.8, 45.7, 46.1, 52.8, 126.1, 127.0, 129.5, 131.6, 135.4, 138.9, 139.8, 141.2, 146.1, 156.8, 163.6, 170.2, HPLC $t_R$ = 5.69 min; ES-MS $m/z$ 417.1 $(M + H)^+$. Anal. Calcd for $C_{20}H_{21}ClN_4O_2S$: C, 57.62; H, 5.08; N, 13.44; Cl, 8.50. Found: C, 57.21; H, 4.99; N, 13.08; Cl, 8.12.

**2-Methylsulfanyl-4-diethylamino-8-chloropyrido[3,2-*d*]-pyrimidine-6-carboxylic Acid Methyl Ester (6c).** To a solution of 2,8-dichloro-4-diethylaminopyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **2c** (60 mg, 0.18 mmol) in MeOH (5.4 mL) was added sodium methyl thiolate (12.6 mg, 0.18 mmol). After 16 h at reflux, solvent was removed under vacuo. The resulting residue was dissolved in a 1:1 mixture of MeCN and DMSO (1.5 mL) and was purified by preparative HPLC, affording derivative **6c** as an orange solid (45 mg, 73% yield): mp 122.5−123.5 °C; IR $\nu_{max}$ 2359, 1737, 1435, 1244, 1130 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.25−1.41 (br m, 6H), 2.61 (s, 3H), 3.84 (br m, 2H), 3.91 (s, 3H), 4.33 (br m, 2H), 8.33 (s, 1H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$) $\delta$ 11.9, 14.0, 14.6, 46.3, 46.8, 52.8, 127.3, 132.0, 140.8, 140.9, 146.6, 157.3, 164.5, 171.5, HPLC $t_R$ = 4.31 min; ES-MS $m/z$ 341.1 $(M + H)^+$. Anal. Calcd for $C_{14}H_{17}ClN_4O_2S$: C, 49.34; H, 5.03; N, 16.44. Found: C, 49.39; H, 5.07; N, 16.39.

**8-Benzylsulfanyl-4-diethylamino-2-*p*-tolylsulfanylpyrido-[3,2-*d*]pyrimidine-6-carboxylic Acid Methyl Ester (7).** To a solution of **6b** (200 mg, 0.48 mmol) in DMF (5 mL) was added benzylthiol (89 mg, 0.72 mmol) in the presence of Hünig's base (0.25 mL, 1.44 mmol). The reaction mixture was stirred at 90 °C for 18 h. The solvent was removed under vacuum. The crude product was purified by flash column chromatography using 2−3% ethyl acetate in petroleum ether as eluent to afford derivative **7** as pale yellow solid (180 mg, 75% yield): mp 131−132 °C; IR $\nu_{max}$ 1715, 1502, 1435, 1345, 1243, 1128 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$), 0.88−0.92 (br m, 3H), 1.35 (br m, 3H), 2.36 (s, 3H), 3.41 (br m, 2H), 3.94 (s, 3H), 4.21 (s, 2H), 4.27 (br m, 2H), 7.18−7.20 (d, $J$ = 7.8 Hz, 2H), 7.27−7.30 (m, 1H), 7.33−7.36 (m, 2H), 7.45−7.48 (d, $J$ = 8.5 Hz, 2H), 7.53−7.55(d, $J$ = 8.0 Hz, 2H), 8.04 (s, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$), 11.7, 14.0, 21.2, 35.5, 46.0, 46.3, 52.6, 120.4, 127.3, 127.5, 128.6, 129.0, 129.1, 129.3, 135.4, 135.8, 138.7, 141.1, 146.8, 148.07, 157.5, 165.4, 169.7; HPLC $t_R$ = 7.05 min; ES-MS $m/z$ 505.0 $(M + H)^+$. Anal. Calcd for $C_{27}H_{28}N_4O_2S_2$: C, 64.26; H, 5.59; N, 11.10. Found: C, 64.31; H, 5.63; N, 11.07.

**General Procedure for $S_NAr$ with Amines on Derivative 5c at C-2.** To a solution of 2-chloro-4-diethylamino-8-methylsulfanylpyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **5c** (100 mg, 0.29 mmol) in MeCN (4 mL) was added an amine (1.47 mmol) in the presence of Hünig's base (0.16 mL, 0.9 mmol). The reaction was heated at 180 °C under MW irradiations for 20 min. Solvent was removed under vacuum, and the resulting solid was triturated in MeOH, filtered, and dried under vacuum to afford derivatives **8a** to **8c**.

**2-Benzylamino-4-diethylamino-8-methylsulfanylpyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (8a):** yield = 74%; yellow solid; mp 121−122 °C; IR $\nu_{max}$ 3548, 1725, 1231 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.04−1.48 (br m, 6H), 2.50 (s, 3H), 3.50−3.88 (br m, 2H), 3.95 (s, 3H), 4.00−4.51 (br m, 2H), 4.56−4.78 (m, 2H), 5.50 (br s, 1H), 7.18−7.49 (m, 5H), 7.86 (s, 1H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$) $\delta$ 14.0, 14.2, 46.1, 46.3, 52.8, 119.7, 127.4, 127.9, 128.3, 128.8, 129.1, 138.4, 140.1, 148,9, 159.4, 159.7, 166.4; HPLC $t_R$ = 3.90 min; ES-MS $m/z$ 412.52 $(M + H)^+$. Anal. Calcd for $C_{21}H_{25}N_5O_2S$: C, 61.29; H, 6.12; N, 17.02. Found: C, 61.17; H, 6.12; N, 16.95.

**2-Butylamino-4-diethylamino-8-methylsulfanylpyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (8b):** yield = 71%; yellow oil; IR $\nu_{max}$ 1712, 1530 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.93 (t, $J$ = 7 Hz, 3H), 1.33−1.40 (m, 6H), 1.41−1.45 (m, 2H), 1.58−1.62 (m, 2H), 2.49 (s, 3H), 3.45 (d, $J$ = 6 Hz, 2H), 3.60−3.86 (br m, 2H), 3.93 (s, 3H), 4.04−4.40 (br m, 2H), 5.29 (br s, 1H), 7.84 (s, 1H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$) $\delta$ 12.2, 13.2, 13.7, 13.8, 20.2, 26.8, 32.0, 41.3, 45.8, 52.3, 119.2, 127.0, 127.6, 137.6, 145.3, 148.7,159.2, 166.0; HPLC $t_R$ = 3.91 min; ES-MS $m/z$ 378.07$(M + H)^+$. Anal. Calcd for $C_{18}H_{27}N_5O_2S$: C, 57.27; H, 7.21; N, 18.55. Found: C, 57.33; H, 7.23; N, 18.51.

**2,4-Diethylamino-8-methylsulfanylpyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (8c):** yield =72%; yellow solid; mp 127−128 °C; IR $\nu_{max}$ 1706, 1527 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.22−1.26 (m, 6H), 1.31−1.36 (m, 6H), 2.49 (s, 3H), 3.69−3.70 (m, 4H), 3.95 (s, 3H), 4.03−4.28 (br m, 4H), 7.93 (s, 1H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$) $\delta$ 13.7, 14.1, 42.4, 46.2, 52.7, 119.5, 127.0, 137.5, 146.4, 149.1, 158.0, 159.3, 166.6; HPLC $t_R$ = 3.97 min; ES-MS $m/z$ 378.10 $(M + H)^+$. Anal. Calcd for $C_{18}H_{27}N_5O_2S$: C, 57.27; H, 7.21; N, 18.55. Found: C, 56.94; H, 7.01; N, 18.21.

**General Procedure for Suzuki-Myaura Cross-Coupling Reactions on Derivative 3b at C-8.** To a suspension of 2-benzylamino-8-chloro-4-dimethylaminopyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **3b** (112 mg, 0.30 mmol) and a boronic acid (1.50 mmol) in dioxane (2.0 mL) were added $Cs_2CO_3$ (293 mg, 0.90 mmol) and $Pd(PPh_3)_4$ (17.3 mg, 0.015 mmol) under inert atmosphere. The reaction mixture was heated at 90 °C for 5−7 h. After complete conversion, water was added (10 mL), and the desired product was extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried on anhydrous $Na_2SO_3$, and filtered on Celite. After evaporation of the solvents, the crude products were dissolved in a 1:1 mixture of MeCN and DMSO (1.5 mL) and were purified by preparative HPLC, affording derivatives **9**.

**2-Benzylamino-4-dimethylamino-8-phenylpyrido[3,2-*d*]-pyrimidine-6-carboxylic acid methyl ester (9a):** yield = 82%; yellow solid; mp 118−119 °C; IR $\nu_{max}$ 2922, 1713, 1533, 1243 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.40−3.90 (br s, 6H), 3.98 (s, 3H), 4.62 (br s, 2H), 5.39 (br s, 1H), 7.24−7.39 (m, 8H), 7.75−7.78 (m, 2H), 8.20 (s, 1H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$) $\delta$ 30.1, 42.0, 46.0, 52.9, 127.1, 127.2, 127.4, 128.0, 128.2, 128.6, 128.8, 130.6, 137.4, 140.2, 143.6, 159.5, 161.6, 166.2; HPLC $t_R$ = 3.73 min; ES-MS $m/z$ 414.05 $(M + H)^+$. Anal. Calcd for $C_{24}H_{23}N_5O_2$: C, 69.72; H, 5.61; N, 16.94. Found: C, 69.29; H, 6.02; N, 16.63.

**2-Benzylamino-4-dimethylamino-8-(4-methoxyphenyl)-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (9b):** yield = 82%; yellow solid; mp 151−152 °C; IR $\nu_{max}$ 3392, 1698, 1532, 1247 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.40−3.75 (br m, 6H), 3.80 (s, 3H), 3.92 (s, 3H), 4.57 (d, $J$ = 6 Hz, 2H), 5.38 (br s, 1H), 6.88 (d, $J$ = 8 Hz, 2H), 7.26−7.28 (m, 5H), 7.70−7.73 (m, 2H), 8.13 (s, 1H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$) $\delta$ 29.7, 41.7, 45.6, 52.5, 55.3, 113.3, 126.1, 127.0, 127.6, 128.1, 128.4, 129.1, 129.3, 131.5, 135.9, 138.0, 139.9, 159.2, 159.7, 161.3, 165.9; HPLC $t_R$ = 3.42 min; ES-MS $m/z$ 444.19 $(M + H)^+$. Anal. Calcd for $C_{25}H_{25}N_5O_3$: C, 67.71; H, 5.68; N, 15.79. Found: C, 67.41; H, 5.94; N, 15.59.

**2-Benzylamino-4-dimethylamino-8-(4-trifluoro-methylphenyl)pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (9c):** yield = 78%; yellow solid; mp 176−177 °C; IR $\nu_{max}$ 3411, 1700, 1522, 1251 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.34−3.74 (br m, 6H), 3.99 (s, 3H), 4.59 (br s, 2H), 5.44 (br s, 1H), 7.28−7.32 (m, 5H), 7.65−7.72 (m, 2H), 7.82−7.85 (m, 2H), 8.18 (s, 1H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$) $\delta$ 29.7, 41.9, 45.7, 52.6, 124.3 (q, $J$ = 272.0 Hz), 124.9 (q, $J$ = 4.1 Hz), 127.2, 127.5, 127.6, 128.6, 130.6, 130.7 (q, $J$ = 34.8 Hz), 138.0, 139.7, 140.2, 140.6, 148.2, 156.7, 159.3, 165.7, 169.1; HPLC $t_R$ = 4.23 min; ES-MS $m/z$ 482.16 $(M + H)^+$. Anal. Calcd for $C_{25}H_{22}F_3N_5O_2$: C, 62.37; H, 4.61; N, 14.55. Found: C, 61.98; H, 5.01; N, 14.82.

**General Procedure for Suzuki−Myaura cross-Coupling Reactions on Derivative 5c at C-2.** A solution of 2-chloro-4-diethylamino-8-methylsulfanylpyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **5c** (82 mg, 0.24 mmol), boronic acid (1.20 mmol), $Cs_2CO_3$ (238 mg, 0.72 mmol), and $Pd(PPh_3)_4$ (14 mg, 0.012 mmol) in dioxane (2.0 mL) was heated at 90 °C for 3.5 h under inert atmosphere. After complete conversion, water was added (10 mL),


dx.doi.org/10.1021/jo201834d | *J. Org. Chem.* 2012, 77, 243−252

and the desired product was extracted with DCM (3 × 10 mL). Combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, and filtered on Celite. After evaporation of the solvents, the resulting solid was triturated in MeOH, filtered, and dried under vacuum to afford derivatives **10a** to **10c**.

**2-Phenyl-4-diethylamino-8-methylsulfanylpyrido[3,2-*d*]-pyrimidine-6-carboxylic acid methyl ester (10a):** yield = 88%; yellow solid; mp 167−168 °C; IR $\nu_{max}$ 1718, 1519 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.44 (t, $J$ = 7 Hz, 6H), 2.58 (s, 3H), 3.85−4.15 (br m, 2H), 4.00 (s, 3H), 4.25−4.55 (br m, 2H), 7.46−7.48 (m, 3H), 8.01 (s, 1H), 8.56−8.59 (m, 2H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$) $\delta$ 12.5, 14.3, 14.7, 46.7, 53.1, 119.7, 128.6, 129.1, 130.1, 131.0, 138.7, 142.4, 147.3, 151.8, 159.2, 160.8, 166.1; HPLC $t_R$ = 5.77 min; ES-MS $m/z$ 383.40 $(M + H)^+$. Anal. Calcd for $C_{20}H_{22}N_4O_2S$: C, 62.81; H, 5.80; N, 14.65. Found: C, 62.47; H, 5.88; N, 14.74.

**2-(4-Methoxyphenyl)-4-diethylamino-8-methyl-sulfanylpyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (10b):** yield = 79%; yellow solid; mp 147−148 °C; IR $\nu_{max}$ 1733, 1519, 1240 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.43 (t, $J$ = 7 Hz, 6H), 2.56 (s, 3H), 3.75−4.10 (br m, 2H), 3.88 (s, 3H), 3.99 (s, 3H), 4.10−4.55 (br m, 2H), 6.98 (d, $J$ = 9 Hz, 2H), 7.98 (s, 1H), 8.52 (d, $J$ = 9 Hz, 2H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$) $\delta$ 12.3, 13.9, 14.1, 46.2, 52.6, 55.3, 113.5, 119.1, 129.4, 130.4, 131.0, 141.6, 146.9, 150.8, 158.7, 160.1, 161.8, 165.7; HPLC $t_R$ = 5.40 min; ES-MS $m/z$ 413.40 $(M + H)^+$. Anal. Calcd for $C_{21}H_{24}N_4O_3S$: C, 61.15; H, 5.86; N, 13.58. Found: C, 61.13; H, 5.54; N, 13.44.

**2-(4-Trifluoromethylphenyl)-4-diethylamino-8-methylsulfanylpyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (10c):** yield = 84%; yellow solid; mp 148−149 °C; IR $\nu_{max}$ 1721, 1521, 1321 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.25−1.85 (br m, 6H), 2.58 (s, 3H), 3.75−4.15 (br m, 2H), 4.01 (s, 3H), 4.20−4.65 (br m, 2H), 7.72 (d, $J$ = 8 Hz, 2H), 8.02 (s, 1H), 8.67 (d, $J$ = 8 Hz, 2H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$) $\delta$ 12.1, 14.1, 14.2, 46.6, 46.7, 52.9, 119.5, 124.6 (q, $J$ = 272.5 Hz), 125.3 (q, $J$ = 3.4 Hz), 129.1, 130.0, 132.1 (q, $J$ = 31.2 Hz), 141.8, 142.7, 146.9, 151.8, 159.0, 159.1, 165.8; HPLC $t_R$ = 6.54 min; ES-MS $m/z$ 451.41 $(M + H)^+$. Anal. Calcd for $C_{21}H_{21}F_3N_4O_2S$: C, 55.99; H, 4.70; N, 12.44. Found: C, 55.61; H, 4.53; N, 12.24.

**General Procedure for Liebeskind−Srogl Cross-Coupling Reaction on Derivative 10a at C-8.** To a mixture of 2-phenyl-4-diethylamino-8-methylsulfanylpyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester **10a** (54 mg, 0.14 mmol), a boronic acid (0.14 mmol), copper(I) thiophene-2-carboxylate (27 mg, 0.14 mmol), and $Pd(PPh_3)_4$ (8 mg, 0.007 mmol) was added dioxane (3.0 mL) under inert atmosphere. The reaction was stirred at 90 °C and monitored by LCMS. After 3.5 h, a saturated solution of $NaHCO_3$ (10 mL) was added, and the desired product was extracted with DCM (3 × 10 mL). Combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, and filtered on Celite. After evaporation of the solvents, the resulting solid was triturated in MeOH, filtered and dried under vacuum to afford derivatives **11a** to **11c**.

**4-Diethylamino-2,8-diphenylpyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (11a:).** yield = 84%; yellow solid; mp 147−147 °C; IR $\nu_{max}$ 2921, 1737, 1524, 1231 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.25−1.65 (br m, 6H), 3.75−4.20 (br m, 2H), 4..02 (s, 2H), 4.20−4.55 (br m, 2H), 7.43−7.45 (m, 3H), 7.49−7.58 (m, 3H), 7.91−7.94 (m, 2H), 8.38 (s, 1H), 8.45−8.49 (m, 2H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$) $\delta$ 10.9, 13.0, 46.7, 52.6, 126.6, 128.1, 128.2, 128.7, 128.9, 130.6, 130.7, 136.3, 136.6, 139.2, 142.5, 146.7, 150.2, 151.4, 159.2, 160.8; HPLC $t_R$ = 5.09 min; ES-MS $m/z$ 428.99 $(M + H)^+$. Anal. Calcd for $C_{25}H_{24}N_4O_2$: C, 72.80; H, 5.86; N, 13.58. Found: C, 72.58; H, 5.46; N, 13.83.

**2-Phenyl-4-diethylamino-8-(4-methoxyphenyl)pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (11b):** yield = 88%; yellow solid; mp 165−166 °C; IR $\nu_{max}$ 1715, 1511, 1242 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.30−1.65 (br m, 6H), 3.80−4.20 (br m, 2H), 3.93 (s, 3H), 4.02 (s, 3H), 4.20−4.60 (br m, 2H), 7.10 (d, $J$ = 8 Hz, 2H), 7.47 (m, 3H), 7.92 (d, $J$ = 8 Hz, 2H), 8.36 (s, 1H), 8.47−8.49 (m, 2H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$) $\delta$ 13.7, 14.3, 46.6, 52.7, 55.4, 113.6, 125.9, 128.2, 128.8, 129.0, 130.4, 132.2, 133.0, 138.7, 142.4, 146.3, 147.1, 159.3, 160.2, 160.7, 165.7; HPLC $t_R$ = 4.93 min; ES-MS $m/z$ 443.09 $(M + H)^+$. Anal. Calcd for $C_{26}H_{26}N_4O_3$: C, 70.57; H, 5.92; N, 12.66. Found: C, 70.38; H, 6.05; N, 12.48.

**2-Phenyl-4-diethylamino-8-(4-trifluoromethylphenyl)-pyrido[3,2-*d*]pyrimidine-6-carboxylic acid methyl ester (11c):** yield = 87%; yellow solid; mp 193−194 °C; IR $\nu_{max}$ 1712, 1521, 1320 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.35−1.65 (br m, 6H), 3.85−4.20 (br m, 2H), 4.03 (s, 3H), 4.25−4.65 (br s, 2H), 7.45−7.47 (m, 3H), 7.80 (d, $J$ = 8 Hz, 2H), 7.98 (d, $J$ = 8 Hz, 2H), 8.37 (s, 1H), 8.44−8.46 (m, 2H); $^{13}C$ NMR (75.47 MHz, $CDCl_3$) $\delta$ 12.1, 14.4, 46.7, 52.8, 124.2 (q, $J$ = 272.2 Hz), 125.0 (q, $J$ = 3.6 Hz), 126.6, 128.5, 128.9, 130.6 (q, $J$ = 32.6 Hz), 130.8, 131.2, 133.2, 138.6, 140.5, 142.5, 145.3, 147.2, 159.2, 161.4, 165.5; HPLC $t_R$ = 6.23 min; ES-MS $m/z$ 481.16 $(M + H)^+$.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

$^1H$ and $^{13}C$ NMR spectra of the synthesized compounds and ORTEP representation of **5c** and **6c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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## ■ 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 this manuscript.

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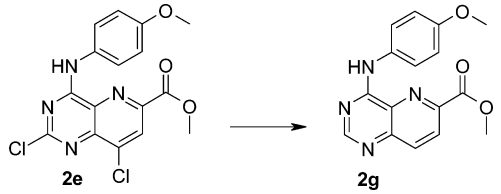
(6) (a) Tikad, A.; Routier, S.; Akssira, M.; Guillaumet, G. *Org. Biomol. Chem.* **2009**, *7*, 5113−5118. (b) C-4 regioselective addition of amines, including anilines, was further confirmed by chloride reduction of compound **2e.** The $^{1}$H NMR spectrum of dehalogenated products **2g** consisted of a pair of doublets at $\delta$ 8.37 and 8.46 ppm, corresponding to H-7 and H-8, with an $J^{3}$ coupling constant of 8.7 Hz. This result proved that **2e** is substituted with a chloride at C-8. Additional NMR experiments on **2g** did not give us the confirmation that aniline is at position 4, but regioselective C-4 addition was proven for secondary amine addition such as diethyl amine (confirmed by X-ray analysis of **5c** and **6c**). This result was also in line with the reported regioselective C-4 amination of 2,4-dichloropyrido[3,2-*d*]pyrimidine.[6a]

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(8) This reaction was performed in the presence of an internal standard, confirming the complete conversion of **2c** into **5b** and **6b** and the reported UHPLC regioisomer's ratio (unpublished results).

(9) p$K_a$ values were calculated with the Marvin method from Chemaxon, ACD/PhysChem Suite (version 12.01), from Advanced Chemistry Development, Inc., Toronto, ON, Canada, and with semiempirical calculations. All three methods indicated N-1 as the most basic center.

(10) Semiempirical calculations of the neutral or N-1 protonated form of **2c**; minimization, followed by conformational search (60° steps) around 5 rotatable bonds (i.e. 7776 points each) using MM3. All local minima (94 and 106, resp.) extracted and minimized with PM5. All calculations done with Scigress Explorer 7.7 (Fujitsu Ltd).

| **2c** | **C-2 Partial Charge** | **C-2 LUMO Density** | **C-8 Partial Charge** | **C-8 LUMO Density** |
|---|---|---|---|---|
| Neutral form | 0.20 | 0.104 | -0.011 | 0.167 |
| N-1 Protonated form | 0.19 | 0.177 | -0.067 | 0.103 |

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(13) Addition of 0.7% of TFA to NMR samples prepared in $CDCl_3$ yielded $^{1}$H and $^{13}$C NMR spectra with higher resolution (see the Supporting Information).