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A Regioselective Approach to Trisubstituted 2 (or 6)-Arylaminopyrimidine-5-carbaldehydes and Their Application in the Synthesis of Structurally and Electronically Unique G∧C Base Precursors

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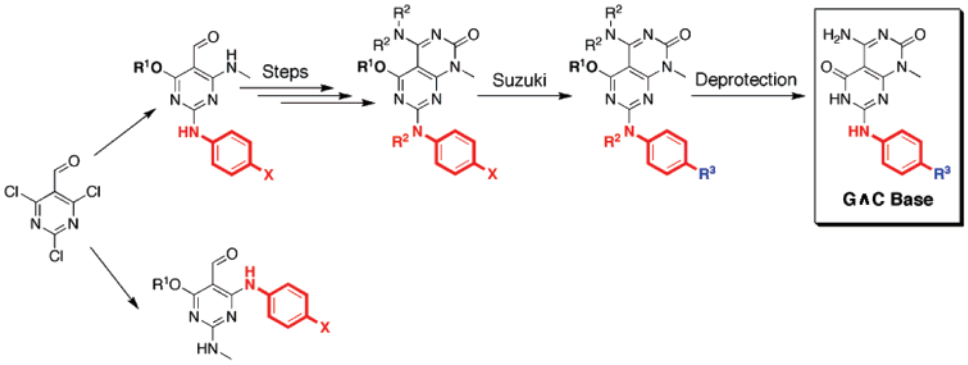
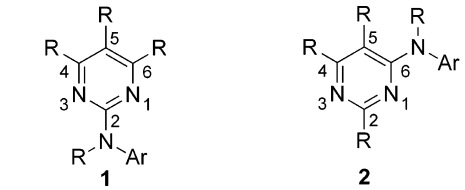


An efficient regioselective synthesis of trisubstituted 2(or 6)-arylaminopyrimidine-5-carbaldehydes has been developed via an S_NAr reaction of 2,4,6-trichloropyrimidine-5-carbaldehyde with aniline, methylamine, and alkoxide nucleophiles using a combination of phase-transfer catalysis and more traditional S_NAr reaction conditions. We demonstrate that in a few synthetic steps, highly functionalized fused-bicyclic pyrimidine substrates can be accessed from the trisubstituted 2-arylaminopyrimidine-5-carbaldehydes. Furthermore, these fused-bicyclic compounds are readily derivatized using the Suzuki cross-coupling reaction to generate electronically and structurally unique G∧C base precursors.

Introduction

Substituted pyrimidines such as those displaying an arylamine at position 2 or 6 as illustrated in Scheme 1 are an interesting class of heterocycles that are widely distributed in natural products and synthetic analogues thereof.[1] They display a range of significant biological properties and, as a result, have many important applications in the area of therapeutics. For example, certain 2-arylaminopyrimidines have been designed to serve as reverse transcriptase inhibitors for HIV[2] as well as angiogenesis inhibitors for the treatment of cancer.[3] Many 6-arylaminopyrimidines have equally important roles given their potential for

SCHEME 1. General 2- and 6-Arylaminopyrimidines



1 2-arylaminopyrimidine

2 6-arylaminopyrimidine

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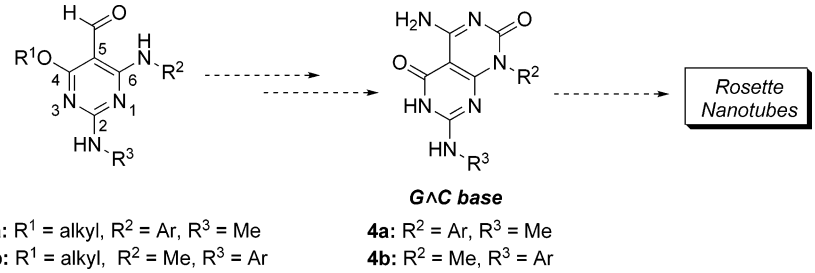
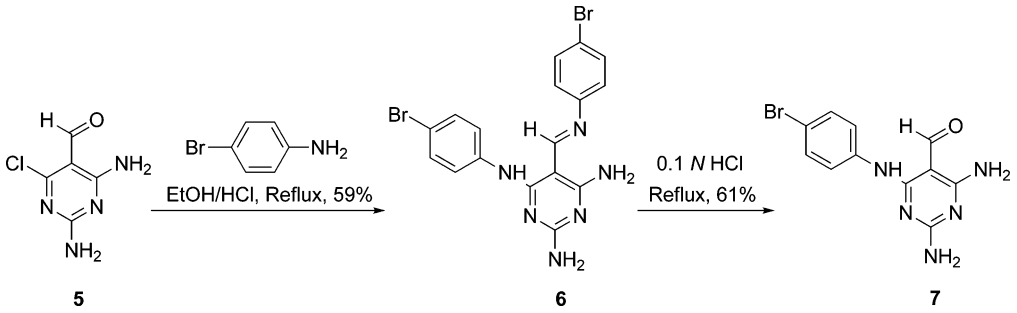
SCHEME 2. Synthetic Approach to G∧C Bases 4a/4b



SCHEME 3. Imine Formation and Hydrolysis



preventing carcinomatous disorders[4] and their ability to activate caspases and induce apoptosis,[5] to name a few.

During the course of our investigations on the self-assembly[6] of G∧C bases into rosette nanotubes (RNTs),[7] we aspired to have a flexible, reproducible, and scalable synthetic approach to 6-arylaminopyrimidine **3a** and 2-arylaminopyrimidine **3b**, in order to prepare G∧C bases of the general form **4a** and **4b**, respectively (Scheme 2). These tetrasubstitued heterocyclic molecules **3a/3b** were to contain an arylamine such as aniline, 4-iodoanilin, or 4-bromoaniline at position 6 (or 2), an alkyl ether at position 4, as well as methylamine at position 2 (or 6). Furthermore, a formyl group at position 5 was to serve as a building block for further elaboration of the pyrimidine core to generate **4a/4b**.

Although methodologies for the synthesis of substituted pyrimidines have been developed, many involve the construction

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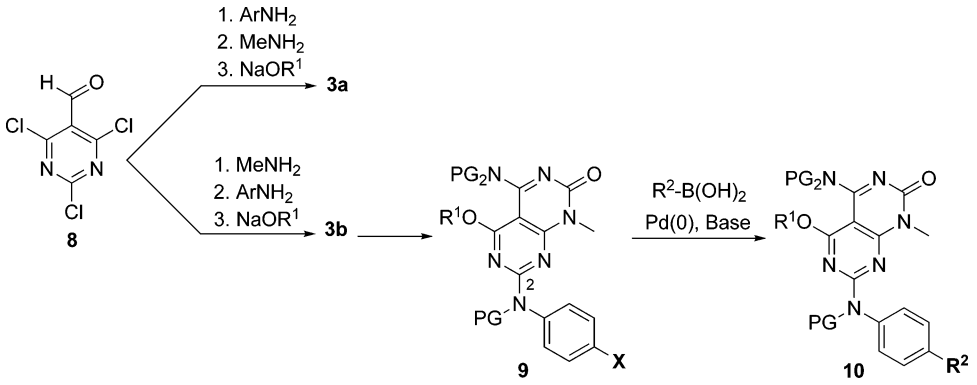
SCHEME 4. Synthetic Approach to G∧C Base Precursor 10

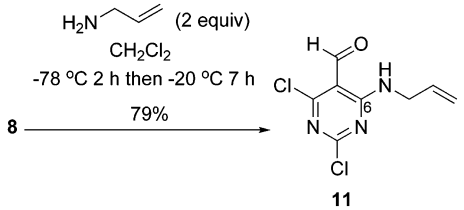


of the heterocyclic ring using building blocks already displaying the required substituents.[8] Alternatively, a potentially more concise and flexible synthetic approach is the direct introduction of functional groups into the pyrimidine ring via displacement of halides and other leaving groups. Unfortunately, this approach can lead to moderate or low yields of the desired product, especially when using aniline nucleophiles, since high temperatures, excess nucleophile (which can lead to disubstitution and other side reactions), and extended reaction lengths are often necessary.[9] In addition to the aforementioned obstacles, the presence of a 5-formyl group on the pyrimidine ring (i.e., **3a**/**3b**), which can serve as a handle for functionalization, constitutes a further challenge. O'Brien and co-workers reported, for example, that treatment of pyrimidine **5** with 2 equiv of 4-bromoaniline led to the formation of imine **6**, which required an additional hydrolysis step under refluxing conditions in order to generate the desired aldehyde **7** (Scheme 3).[10] The overall yield for the two steps was 36%. Clearly, a methodology that would provide rapid entry into substituted pyrimidines containing a 2(or 6)-arylamine group without troublesome side reactions would be of great value.

Herein, we demonstrate that through the judicious choice of reaction conditions, highly functionalized trisubstituted arylaminopyrimidine-5-carbaldehydes **3a** and **3b** can be obtained in an efficient and scalable manner from 2,4,6-trichloropyrimidine-5-carbaldehyde (**8**) via direct, sequential introduction of nucleophilic reagents. Moreover, we describe the assembly of tricyclic compound **9** from pyrimidine **3b** and the subsequent implementation of a Pd cross-coupling reaction as a flexible strategy to generate structurally and electronically unique G∧C base precursors **10** (Scheme 4).

Results and Discussion

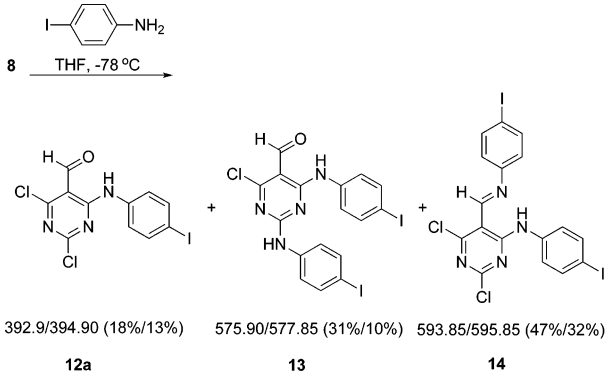
Synthesis of the 2-Methylamino-4-chloro-6-arylaminopyrimidine Regioisomer (3a). We have shown from our previous work[7b] that pyrimidine **11** shown in eq 1 can be readily accessed via an S_NAr reaction of 2,4,6-trichloropyrimidine-5-carbaldehyde (**8**)[11] in the presence of allylamine. The exclusive formation of



(1)

the 6-substituted compound **11** under the conditions described is attributed to the directing influence of the aldehyde through either the formation of a hydrogen bond with the allylamine nucleophile or the formation of a transient intermediate aminol that delivers the amine selectively to position 6. It is important, however, to monitor the reaction temperature and length closely since side products such as the disubstituted product can often form.

By using the same approach described in eq 1, the synthesis of 6-arylaminopyrimidine **3a** (Ar = 4-iodoaniline) was commenced by treating 2,4,6-trichloropyrimidine-5-carbaldehyde (**8**) with 2.0 equiv of 4-iodoaniline in THF at −78 °C as illustrated in eq 2. A complex mixture of products formed that, surprisingly, were not easily separated and characterized due to their poor solubility in hexane, acetone, chloroform, CH_2Cl_2, and DMSO. The EI and CI mass spectra of the mixture, however, revealed the peaks 392.9/394.90 (18%/13%), 575.90/577.85 (31%/10%), 593.85/595.85 (47%/32%), which were tentatively assigned to compounds **12a**, **13**, and **14**, respectively (eq 2).



(2)

On the basis of the notion that imine **14** was present in the mixture, the crude material was refluxed in a 0.1 N solution of HCl[10] to hydrolyze the imine to the monosubstituted pyrimidine **12a**. Unfortunately, the CI and EI mass spectra obtained after the hydrolysis reaction were not very encouraging. The $[M]^+$ peak corresponding to imine **14** still remained and the $[M]^+$ peak for the desired compound **12a** (or its expected fragmentation pattern) was no longer evident. The S_NAr reaction was subsequently repeated by treating 2,4,6-trichloropyrimidine-5-carbaldehyde (**8**) with 1.0 equiv of 4-iodoaniline and 1.0 equiv

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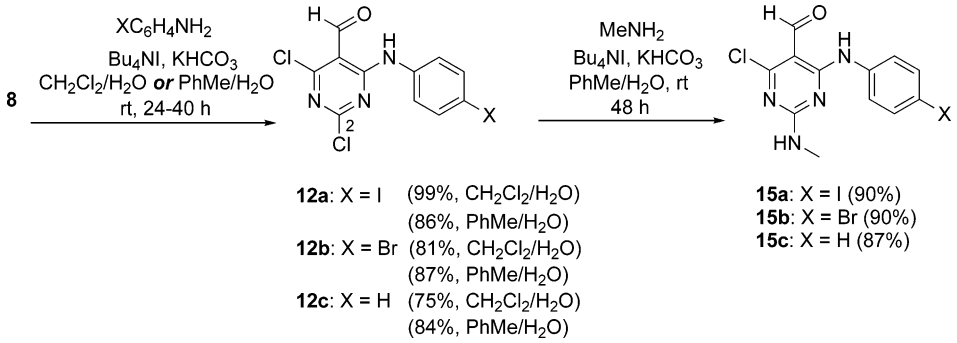
SCHEME 5. Synthesis of 15a−c under PTC Conditions



of Et_3N in THF at −78 °C in an attempt to minimize the disubstituted product **13**. This reaction was also unsuccessful as a mixture of products were obtained. It was therefore apparent that alternative conditions for this reaction were necessary in order to avoid the synthesis of imine **14** during the course of generating **12a**. In particular, it was important to neutralize the aniline hydrohalide byproduct of the reaction since this was required for imine formation.

The S_NAr reaction was thus explored under phase transfer catalysis (PTC) conditions. PTC in general has proven to be a powerful tool in organic synthesis, having the advantage of mild reaction conditions, being operationally simple and adaptable to larger scale production and offering environmental and cost benefits.[12] Although phase transfer catalyst have been widely implemented in nucleophilic displacement reactions involving aliphatic substrates, their use in S_NAr reactions have been explored to a lesser extent.[13]

We envisioned the S_NAr reaction of 2,4,6-trichloropyrimidine-5-carbaldehyde (**8**) with 4-iodoaniline to occur in a biphasic system (organic solvent/H_2O) containing a weak base (i.e., $KHCO_3$) and a phase transfer catalyst such as tetrabutylammonium iodide (TBAI).[14] Under these conditions it was feasible that the bicarbonate anion present as the TBA salt (i.e., $Bu_4N^+HCO_3^-$) would neutralize the aniline hydrohalide byproduct of the S_NAr reaction, possibly at the interface between the two solvent phases, to produce $Bu_4N^+Cl^-$ and H_2CO_3, the later of which would dissociate into H_2O and CO_2. The $Bu_4N^+HCO_3^-$ could then be regenerated from $Bu_4N^+Cl^-$, thereby permitting the neutralization reaction to be repeated. The formation of imine **14** would therefore be prevented due to the absence of acid, and the presence of water in the medium. This reaction also offered the advantage of requiring only 1.0 equiv of amine nucleophile (unlike eq 2), which would minimize the possibility of forming the disubstituted product **13**.

Gratifyingly, in practice, treatment of 2,4,6-trichloropyrimidine-5-carbaldehyde (**8**) with 4-iodoaniline (1.0 equiv) in the presence of TBAI (0.05 equiv) and $KHCO_3$ (1.2 equiv) in a 2:1 mixture of CH_2Cl_2/H_2O for 24 h at rt generated pyrimidine **12a** in nearly quantitative yield (Scheme 5). The structure of **12a** was successfully verified by single-crystal X-ray diffraction analysis. High yields of **12b** and **12c** were also obtained with 4-bromoaniline (81%) and aniline (75%) nucleophiles, respectively. This reaction was readily adapted to larger scales, as exemplified by the synthesis of **12c**, which was conducted on a 45 g (212 mmol) scale. Substituting CH_2Cl_2 with toluene, which is a more environmentally acceptable solvent for larger scale preparation, had little impact on the yields as **12a**, **12b**, and **12c** were obtained in 86%, 87%, and 84% yield, respectively, after 24 h at rt.

The second aromatic substitution reaction at position 2 of pyrimidine **12a−c** was subsequently effected in high yields in the presence of methylamine (3.0 equiv), TBAI (0.05 equiv), and $KHCO_3$ (1.2 equiv) in a 1:1 solution of toluene/H_2O at rt for 48 h (Scheme 5).[15] The products of the reaction, **15a−c**, precipitated out of solution and were simply collected via filtration. Although the reactions did proceed with only 1.0 equiv of methylamine, a significant quantity of starting material remained after 48 h (i.e., 67% yield for **15a** with 19% recovered starting material **12a**), which is a direct result of the decreased electrophilicity of the pyrimidine core relative to compound **8**.

Synthesis of the 2-Arylamino-4-chloro-6-methylaminopyrimidine-5-carbaldehyde Regioisomer (3b). Having established a simple and efficient methodology for the synthesis of 2-methylamino-6-arylaminopyrimidine derivatives **15a−c**, it was envisioned that by simply reversing the order of the two nucleophilic substitution reactions the other regiosiomer **3b** could be obtained. Indeed, 2,4-dichloro-6-(methylamino)pyrimidine-5-carbaldehyde (**16**) was readily prepared from compound **8** in 92% yield in the presence of methylamine (1.0 equiv) under our standard PTC conditions (TBAI (0.05 equiv), $KHCO_3$ (1.2 equiv), toluene/H_2O (1:1)) as illustrated in Scheme 6. A brief comparison study was also performed whereby 2,4,6-

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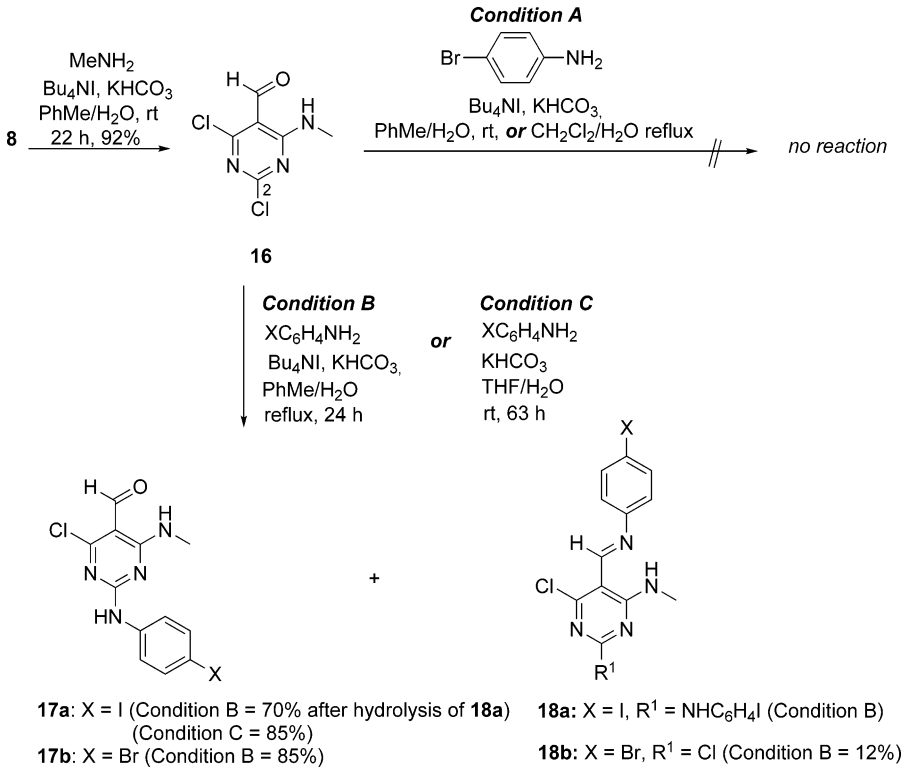
(15) Position 2 of 6-substituted-2,4-dichloropyrimidine-5-carbaldehyde is the most reactive site for the S_NAr reaction since a negative charge can be delocalized on the two nitrogen atoms in the ring. Position 4, alternatively, is less reactive since there is little directing effect from the aldehyde group as it is already hydrogen bonded to the amine hydrogen at position 6.

SCHEME 6. Synthesis of 17a/17b Using PTC Conditions



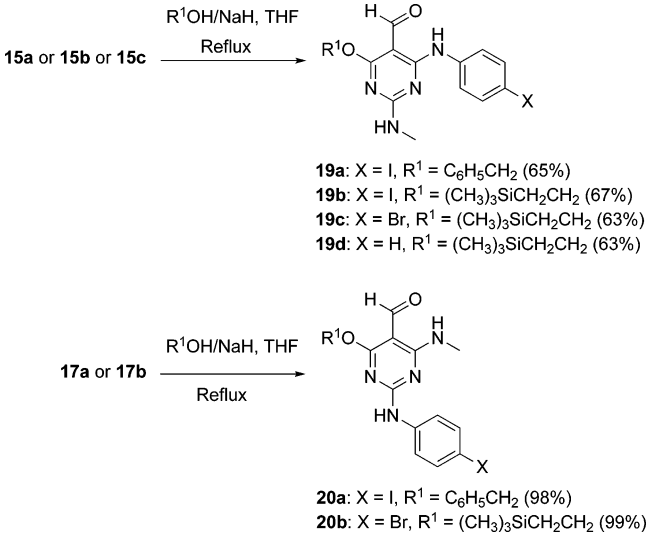
trichloropyrimidine-5-carbaldehyde (**8**) was treated with methylamine (2.0 equiv) in a solution of THF, CH_2Cl_2, or toluene at −78 °C. In these three different solvent environments, the desired product **16** was isolated in only 49%, 34%, and 1.3%[16] yield, respectively, thus highlighting the efficacy of PTC for these transformations.

Following the isolation of pyrimidine **16**, the second aromatic substitution reaction at position 2 was attempted using 4-bromoaniline as illustrated in Scheme 6, Condition A. Quite unexpectedly, only starting material was present after 24 h at rt in a 1:1 mixture of toluene/H_2O, TBAI (0.05 equiv), and $KHCO_3$ (1.2 equiv). Refluxing the reaction in a more polar solvent mixture (CH_2Cl_2/H_2O (2:1)) led to the same outcome. It was therefore evident that more forcing conditions were necessary to induce the transformation given the reduced electrophilicity of the pyrimidine ring (due to the electron-donating methylamine substituent) and the use of a relatively weak nucleophile.[17] Thus, the reaction was repeated in a 1:1 mixture of toluene/H_2O and refluxed for 24 h as illustrated in Scheme 6 (Condition B, X = Br). Although the yield of **17b** was more acceptable at 85%, these forcing conditions also generated imine **18b**, albeit in only 12% yield.

Repeating the reaction of 4-iodoaniline under identical conditions (Scheme 6, Condition B, X = I) led to **17a** in only 60% yield as a yellow solid, which was collected from the reaction mixture via filtration. A ^1H NMR spectrum of the remaining filtrate that had been extracted with EtOAc revealed the presence of imine **18a**. Our attempts to hydrolyze the imine using a 5% solution of HCl proved to be quite fruitful since the overall yield of **17a** was improved to 70%. Despite this more favorable yield, the additional hydrolysis step was not very convenient and thus other conditions were explored. In particular, a more polar solvent such as THF/H_2O was considered since this was expected to enhance the rate of the substitution reaction which in turn would permit a lower reaction temperature. Such conditions were predicted to be less conducive for imine formation because of the miscibility of THF and water. This rational proved valid as treatment of 2,4-dichloro-6-(methylamino)pyrimidine-5-carbaldehyde (**16**) with 4-iodoaniline (1.0 equiv) and $KHCO_3$ (1.2 equiv) in THF/H_2O (1:1) at rt provided 4-chloro-2-(4-iodophenylamino)-6-(methylamino)-pyrimidine-5-carbaldehyde (**17a**) in 85% yield (Condition C).

Installation of the 4-Alkoxy Substitutent. With the amine substituents at the 2- and 6-position of the pyrimidine ring

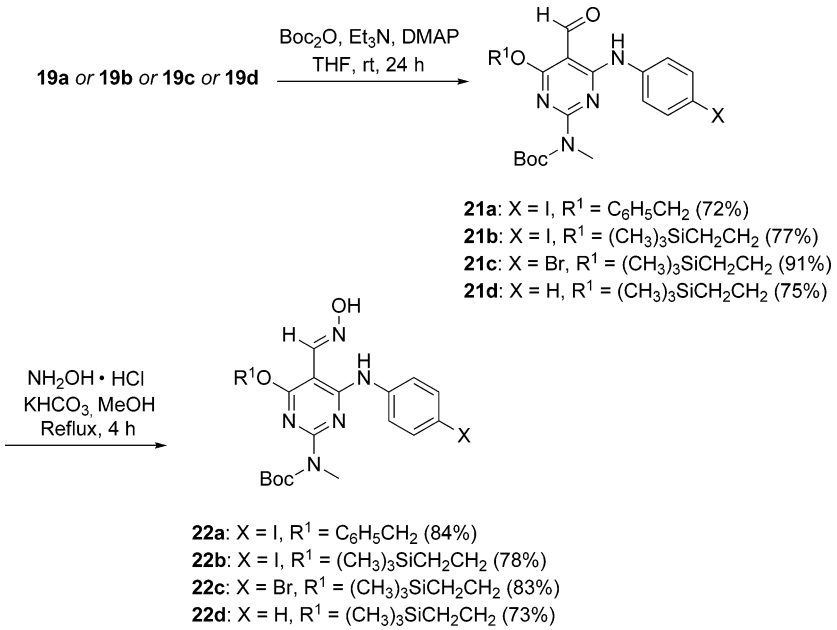
SCHEME 7. Installation of the 4−Alkoxy Substituent



(16) The disubstituted product, 4-chloro-2,6-bis(methylamino)pyrimidine-5-carbaldehyde, was isolated in 76% yield.

(17) Henderson, W. A., Jr.; Schultz, C. J. *J. Org. Chem.* **1962**, *27*, 4643−4646.

SCHEME 8. Synthetic Route to Hydroxylimines 22a−d



established, the installation of the 4-alkoxy moieties in **15a−c** and **17a/17b** was next attempted. This functional group was to become the carbonyl group in G∧C bases **4a/4b**, eventually playing a key role as a hydrogen bond acceptor in the self-assembly process.[6] All of the 4-chloro-2,6-disubstituted pyrimidine-5-carbaldehydes **15a−c** and **17a/17b** were readily transformed into their corresponding 4-alkoxy-2,6-disubstituted pyrimidine-5-carbaldehydes **19a−d** or **20a/20b** in the presence of 2-trimethylsilylethyl alkoxide or benzyl alkoxide under refluxing conditions (Scheme 7). The structures of **19a** and **19c** were confirmed by single-crystal X-ray diffraction analysis.

Attempted Synthesis of the G∧C Bases from Pyrimidines 19a−d. With a practical, scalable, and reproducible methodology for the preparation of 2(or 6)-arylaminopyrimidines **19a−d** and **20a/20b** in a regioselective manner, the preparation of the G∧C bases **4a**/**4b** was next embarked upon.[7b] The synthesis was thus initiated using compounds **19a−d**, by protecting the secondary methylamine groups with Boc_2O in the presence of Et_3N and DMAP (Scheme 8). The corresponding products **21a−d** were isolated in good yields. Subsequent treatment of aldehydes **21a−d** with the HCl salt of hydroxylamine in the presence of $KHCO_3$ furnished hydroxylimines **22a−d** in yields ranging from 73% to 84%. The structures of **21b** and **22c** were confirmed by single-crystal X-ray diffraction analysis.

These hydroxylimines **22a−d** were then converted to nitriles **23a−d** by refluxing in a solution of TFAA, Et_3N in THF as illustrated in Scheme 9. Unfortunately, moderate yields of the desired products were obtained due to the competing formation of bicyclic compounds **24a−c**, which we proposed formed via nucleophilic attack of an in situ formed amide anion onto the nitrogen atom of imine ester **25**.[18] The structure of the undesired cyclized adduct **24c** was confirmed by X-ray crystal analysis. Nitriles **23a−d** were then treated with *N*-chlorocarbonyl isocyanate and DMAP in a solution of CH_2Cl_2 to provide carbamides **26a−d** in good yields.

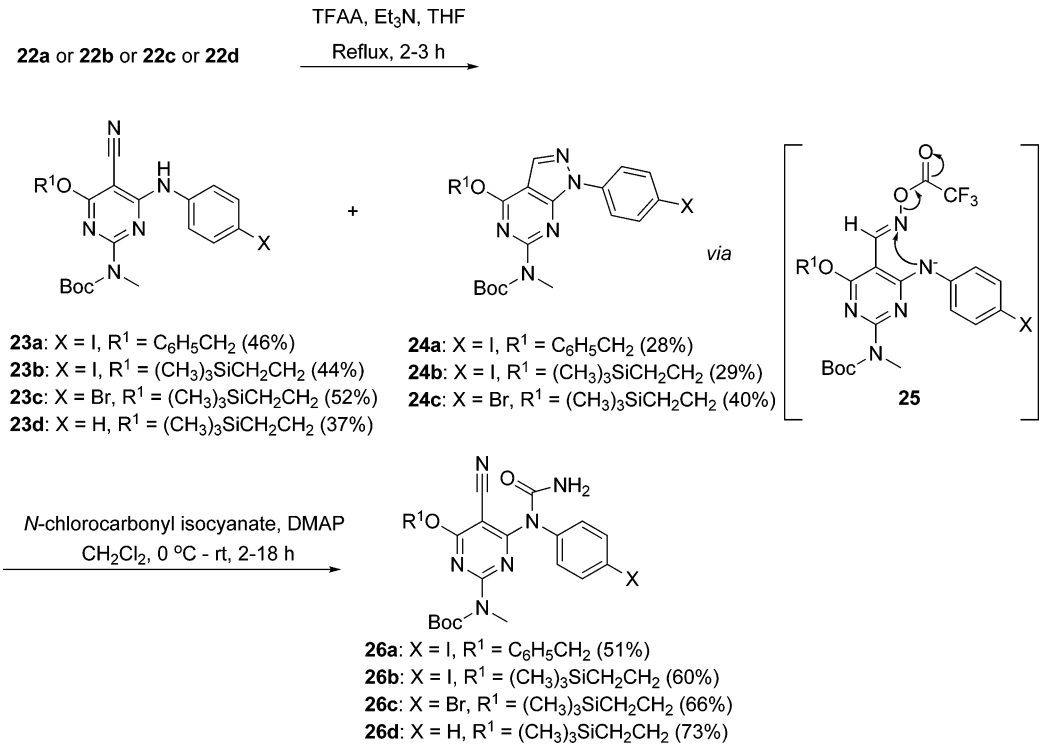
With use of carbamide **26c**, the cyclization reaction to generate the fused heterobicyclic structure **27c** was next explored as illustrated in Table 1. Unfortunately in the presence of NH_3 (entries 1−3, Table 1), a soft Lewis acid (entry 4, Table 1) or basic conditions (entries 5 and 6, Table 1), the cyclized adduct **27c** was not observed. Rather, the $CONH_2$ group was liberated to regenerate **23c**. Such was the case for the cyclization attempts with **26a** and **26d** as well. Given these observations, it is likely that the phenyl ring plays an important role in the dissociation of the carbamide by stabilizing the resulting amide species.

Synthesis of the G∧C Base from Compounds 20a/20b. In light of the challenges experienced with the cyclization described in Table 1, we were hopeful that pyrimidines **20a/20b**, which contained a more electron-rich methylamine substituent in lieu of the arylamine, would be less prone to liberate $CONH_2$ in the analogous cyclization reaction. Thus, the synthetic sequence was repeated using substrates **20a/20b** to provide **31a/31b** as described in Scheme 10. As anticipated, treatment of the crude carbamides **31a/31b** with 7 N ammonia in MeOH at rt afforded the desired cyclized adducts **32a/32b** in 88% and 65% yield, respectively (for the two steps beginning from **30a/30b**). The primary amines of the bicyclic products **32a/32b** were subsequently protected using Boc_2O under standard conditions to afford **33a/33b** in good yields. The structures of **33a** and **33b** were confirmed by single-crystal X-ray diffraction analysis.

Suzuki Cross-Coupling Reaction. Generation of Highly Functionalized Pyrimidine Substrates. Although the goal of preparing tricyclic compounds **33a/33b** was realized, it was important to have the flexibility to access electronically and structurally unique G∧C bases derived from **33a/33b**, in order to effectively study the self-assembly process. By employing the aromatic iodide or bromide of **33a** or **33b** as the coupling partner in a palladium-catalyzed cross-coupling reaction, it was suspected that such flexibility could be attained. Thus, a Suzkui cross-coupling reaction[19] of **33a** with a variety of commercially available boronic acids was performed. As presented in Table 2, the coupled adducts **34a−g** were assembled in moderate to excellent yields under the conditions described ($Pd_2(dba)_3$, P(*t*−Bu)$_3$, KF, THF, rt).[20] In entries 2 and 3, a side product of little

(18) A side product was also observed during the synthesis of **23d**, although it was only isolated in 1% yield and with insufficient purity for characterization purposes. ^{1}H NMR and ESI−mass spectral data strongly suggest the bicyclic product analogous to **24a−c**.

SCHEME 9. Synthetic Route to Nitriles 26a−d



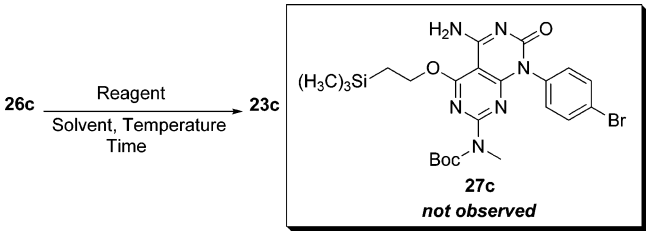
23a: X = I, R^1 = $C_6H_5CH_2$ (46%)
23b: X = I, R^1 = $(CH_3)_3SiCH_2CH_2$ (44%)
23c: X = Br, R^1 = $(CH_3)_3SiCH_2CH_2$ (52%)
23d: X = H, R^1 = $(CH_3)_3SiCH_2CH_2$ (37%)

24a: X = I, R^1 = $C_6H_5CH_2$ (28%)
24b: X = I, R^1 = $(CH_3)_3SiCH_2CH_2$ (29%)
24c: X = Br, R^1 = $(CH_3)_3SiCH_2CH_2$ (40%)

25

26a: X = I, R^1 = $C_6H_5CH_2$ (51%)
26b: X = I, R^1 = $(CH_3)_3SiCH_2CH_2$ (60%)
26c: X = Br, R^1 = $(CH_3)_3SiCH_2CH_2$ (66%)
26d: X = H, R^1 = $(CH_3)_3SiCH_2CH_2$ (73%)

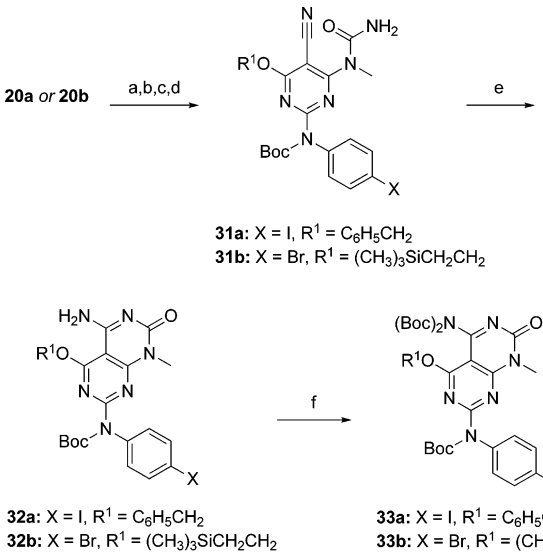
TABLE 1. Cyclization Attempts of Carbamide 26c to Generate 27c



entry	reagent	solvent	temp (°C)	time (h)
1	7 N NH_3 in MeOH		0 to rt	7
2	0.5 M NH_3	dioxane	rt	3
3	7 N NH_3 in MeOH/urea		rt	3
4	$PdCl_2(PPh_3)_2$, Et_3N	THF	rt	19
5	LiHMDS	THF	−78	4
6	NaH	THF	rt	1

consequence was also observed whereby one of the Boc protecting groups on the nitrogen atom had been removed (i.e., **35b/35c**). In any case, in addition to the interesting electronic or structural impact that the iodide atom on the aromatic amine of **33a** may have on the self-assembly process of the G∧C bases, it also serves as a proficient handle in which to prepare many unique derivatives for the purpose of our studies.

SCHEME 10. Synthetic Route to G∧C Base Precursors 33a/33b[a]



31a: X = I, R^1 = $C_6H_5CH_2$
31b: X = Br, R^1 = $(CH_3)_3SiCH_2CH_2$

32a: X = I, R^1 = $C_6H_5CH_2$
32b: X = Br, R^1 = $(CH_3)_3SiCH_2CH_2$

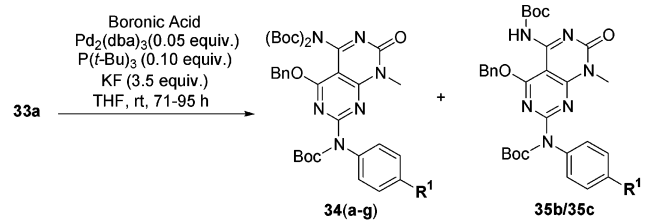
33a: X = I, R^1 = $C_6H_5CH_2$
33b: X = Br, R^1 = $(CH_3)_3SiCH_2CH_2$

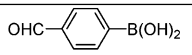
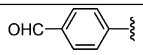
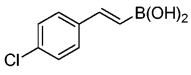
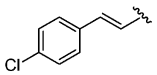
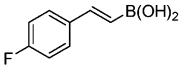
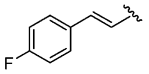
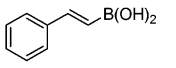
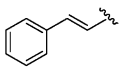
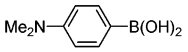
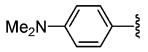
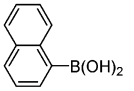
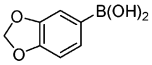
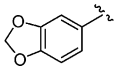
[a] Reagents and conditions: (a) Boc_2O, Et_3N, THF (**28a**, 90%; **28b**, 81%). (b) NH_2OH·HCl, $KHCO_3$, MeOH (**29a**, 68%, **29b**, 73%). (c) TFAA, Et_3N, THF (**30a**, 88%; **30b**, 81%). (d) *N*-Chlorocarbonyl isocyanate, DMAP, CH_2Cl_2. (e) 7 N NH_3, MeOH (**32a**, 88%, 2 steps; **32b**, 65%, 2 steps). (f) Boc_2O, Et_3N, DMAP (**33a**, 77%, **33b**, 92%).

Conclusion

An efficient, scalable, and high-yielding method for the regioselective synthesis of 4-alkoxy-2(or 6)-arylamino-6(or 2)−methylaminopyrimidine-5-carbaldehydes from 2,4,6-trichloropyrimidine-5-carbaldehyde (**8**) has been established. In a biphasic mixture (toluene/H_2O) containing a PTC catalyst (TBAI) and $KHCO_3$, the S_NAr reaction of compound **8** with aniline nucleophiles proceeds smoothly without the deleterious formation of imines and disubstituted products. A second S_NAr reaction using **12a−c** and methylamine generates 6-arylamino-2-methylaminopyrmidines **15a−c** in excellent yields. The other regioisomers **17a/17b** were also obtained in equally high yields by simply reversing the order of the nucleophilic addition under optimized reaction conditions. Furthermore, **15a−c** and **17a/17b** were readily transformed into their 4-alkoxy derivatives in a refluxing solution with the chosen alkoxide. We have also demonstrated that highly functionalized pyrimidine derivatives **33a/33b** can be constructed and these are capable of further functionalization using a Suzuki cross-coupling reaction.

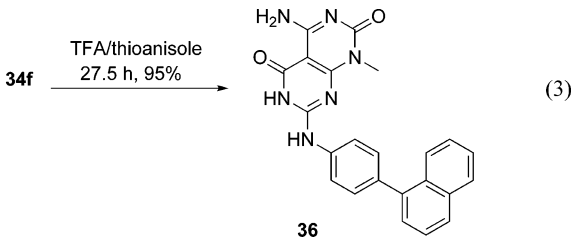
TABLE 2. Sukuki Cross-Coupling Reactions of 33a



entry	boronic acid	R^1	compound,yield (%)[a]
1			**34a,** 59
2			**34b,** 65 **35b,** 13
3			**34c,** 65 **35c,** 19
4			**34d,** 89
5			**34e,** 37[b]
6			**34f**, 90
7			**34g,** 47[c]

[a] Isolated yield. [b] 70% based on recovered starting material. [c] 60% based on recovered starting material

Future efforts will be focused on the transformation of the cross-coupled adducts **34a**−**g** into their respective G∧C bases via a global deprotection of the Boc and Bn groups. Preliminary results using **34f** (eq 3) are quite promising, providing **36** in 95% yield. The resulting deprotected adducts of **34a**−**g** will then be implemented in the self-assembly studies which will be reported in due course.



(3)

Experimental Section

Representative Example of the Nucleophilic Aromatic Substitution Reaction. 2,4-Dichloro-6-(4-iodophenylamino)pyrimidine-5-carbaldehyde (12a). A mixture of 2,4,6-trichloropyrimidine-5-carbaldehyde (**8**) (6.21 g, 29.4 mmol), $KHCO_3$ (3.53 g, 35.3 mmol), tetrabutylammonium iodide (542 mg, 1.47 mmol), and 4-iodoaniline (6.43 g, 29.4 mmol) in CH_2Cl_2/H_2O (200 mL/100 mL) was stirred at rt for 24 h. The organic layer was then separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was recrystallized with EtOAc to provide 11.49 g of **12a** ($C_{11}H_6Cl_2IN_3O$, 99%) as yellow needles. R_f 0.62 (SiO_2, 30% EtOAc/hexane). Mp 137.5−138 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 11.16 (NHC_6, br s, 1H), 10.35 (C_5H, s, 1H), 7.68 (C_8H, $C_{10}H$, d, ^3J = 8.5 Hz, 2H), 7.39 (C_7H, $C_{11}H$, d, ^3J = 8.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 190.7 (C_5), 166.5 (C_2), 162.8 (C_1), 159.3 (C_4), 138.2 (C_8, C_{10}), 136.0 (C_6), 124.2 (C_7, C_{11}), 107.1 (C_3), 90.0 (C_9). EI-MS: expected mass for M^+/z 392.89/394.89, obsd 392.80/394.80 (M^+/z, 28%/18%), 76 ($C_6H_4^+$, 100%). CI-MS: expected mass for M^+/z 392.89/394.89, obsd 393.45/395.50 (M^+, 100%). The structure of **12a** is confirmed by X-ray crystallography.

Representative Example of the Installation of the 4-Alkoxy Substituent. 4-(Benzyloxy)-6-(4-iodophenylamino)-2-(methylamino)pyrimidine-5-carbaldehyde (19a). Benzyl alcohol (2.2 mL, 21 mmol) was added dropwise to a stirred suspension of NaH (0.68 g, 95%, 27 mmol) in THF (70 mL) over a period of 30 min at rt under nitrogen atmosphere. After stirring for 15 min, the mixture was cooled to 0 °C and **15a** (4.03 g, 10.4 mmol) was added. The resulting mixture was warmed to rt and refluxed for 24 h. After cooling to 0 °C, the reaction mixture was carefully quenched with a saturated aqueous solution of NH_4Cl and the solvent was removed under reduced pressure. The residue was diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (1−2% EtOAc/hexane) provided 3.12 g of **19a** ($C_{19}H_{17}IN_4O_2$, 65%) as a brown solid. R_f 0.61 (SiO_2, 30% EtOAc/hexane). Mp 161−162 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 11.46 (C_6NH, s, br, 1H), 11.23 (C_6NH, s, br, 1H, minor isomer) (due to the possible hydrogen bond between C_5O and C_6NH, this compound displays two sets of peaks for certain protons), 10.00 (C_5H, s, 1H), 7.58−7.37 (C_7H−$C_{11}H$, $C_{15}H$−$C_{19}H$, m, 9H), 5.48 ($C_{12}NH$, s, br, 1H), 5.37 ($C_{13}H$, s, 2H), 3.01 ($C_{12}H$, d, ^3J = 3.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 186.4 (C_5), 171.3 (C_4), 163.0 (C_2), 161.3 (C_1), 138.7 (C_6), 137.5 (C_8, C_{10}), 136.3 (C_{14}), 128.5, 128.1, 127.8 (C_{15}−C_{19}), 123.5, 123.3 (C_7, C_{11}), 93.1 (C_3), 86.6 (C_9), 67.7 (C_{13}), 28.5 (C_{12}). ESI-MS: expected mass for [M + H^+]/z 461.05, obsd 460.9 ([M + H^+]/z, 100%). High-resolution ESI-MS: calcd mass 461.0475, actual mass 461.0474. The structure of **19a** is confirmed by X-ray crystallography.

Representative Example of the Monoprotection of the Secondary Amine. *tert*-Butyl 4-(Benzyloxy)-5-formyl-6-(4-iodophenylamino)pyrimidin-2-yl(methyl)carbamate (21a). Triethylamine (0.9 mL, 6.4 mmol) was added to a solution of **19a** (0.89 g, 1.9 mmol) and DMAP (74 mg, 0.60 mmol) in THF (20 mL) at rt under nitrogen atmosphere. After stirring for 5 min, Boc_2O (0.63 g, 2.8 mmol) was added and the resulting mixture was stirred at rt for 19 h. The reaction was then quenched with H_2O and the solvent was removed under reduced pressure. The residual solid was dissolved in EtOAc and washed with 10% aqueous citric acid, H_2O, 5% aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (1% EtOAc/hexane) provided 0.78 g of **21a** ($C_{24}H_{25}IN_4O_4$, 72%) as a white solid. R_f 0.14 (SiO_2, 5% EtOAc/hexane). Mp 117.5−118.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 11.23 (C_6NH, br s, 1H), 10.15 (C_5H, s, 1H), 7.61−7.53 (C_7H−$C_{11}H$, q, ^3J = 9.0 Hz, 4H), 7.44−7.33 ($C_{15}H$−$C_{19}H$, m, 5H), 5.49 ($C_{13}H$, s, 2H), 3.40 ($C_{12}H$, s, 3H), 1.55 ($C_{22}H$, s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 187.7 (C_5), 171.2 (C_4), 161.6 (C_2), 160.1 (C_1), 152.9 (C_{20}), 138.0 (C_6), 137.5 (C_8, C_{10}), 135.9 (C_{14}), 128.5 (C_{16}, C_{18}), 128.3 (C_{17}), 128.0 (C_{15}, C_{19}), 123.4 (C_7, C_{11}), 94.5 (C_3), 87.2 (C_9), 82.2 (C_{21}), 68.5 (C_{13}), 34.7 (C_{12}), 28.0 (C_{22}). ESI-MS: expected mass for [M + Na^+]/z 583.08, obsd 582.7 ([M + Na^+]/z, 100%), 482.8 ([M − Boc + Na^+]/z, 7%). Negative: 559.0 (31%), 459.0 (35%).

Representative Example of the Synthesis of the Hydroxylimine. *tert*-Butyl 4-(Benzyloxy)-5-((hydroxyimino)methyl)-6-(4-

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iodophenylamino)pyrimidin-2-yl(methyl)carbamate (22a). A solution of aldehyde **21a** (5.21 g, 9.29 mmol) in anhydrous methanol (100 mL) was treated with $KHCO_3$ (3.74 g, 37.4 mmol) and hydroxylamine hydrochloride (1.30 g, 18.7 mmol) at rt under nitrogen atmosphere. The mixture was then refluxed for 4 h. After cooling to rt, the reaction was quenched with H_2O and the solvent was removed under reduced pressure. The product was extracted with EtOAc and the combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to provide 4.49 g of **22a** ($C_{24}H_{26}IN_5O_4$, 84%) as a yellow solid. The material was used in the next step without further purification. R_f 0.54 (SiO_2, 30% EtOAc/hexane). Mp 143.5−145 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.99 (C_6NH, br s, 1H), 8.56 (C_5H, s, 1H), 7.58 (C_8H, C_{10}H, d, ^3J = 9.0 Hz, 2H), 7.51 (C_7H, C_{11}H, d, ^3J = 9.0 Hz, 2H), 7.42−7.34 (C_{15}H−C_{19}H, m, 5H), 7.08 (NOH, s, 1H), 5.42 (C_{13}H, s, 2H), 3.36 (C_{12}H, s, 3H), 1.51 (C_{22}H, s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 167.1 (C_4), 158.6 (C_2), 157.8 (C_1), 154.0 (C_{20}), 145.4 (C_5), 138.8 (C_6), 137.3 (C_8, C_{10}), 136.4 (C_{14}), 128.4 (C_{16}, C_{18}), 128.0 (C_{17}), 127.9 (C_{15}, C_{19}), 122.8 (C_7, C_{11}), 89.1 (C_3), 86.1 (C_9), 81.8 (C_{21}), 68.3 (C_{13}), 34.8 (C_{12}), 28.1 (C_{22}). ESI-MS: expected mass for [M + Na^+]/z 598.09, obsd 597.8 [M + Na^+]/z, 73%) 475.9 ([M − Boc + H^+]/z, 100%). Negative: 573.9 (100%).

Representative Example of the Synthesis of the Nitrile. *tert*-Butyl 4-(Benzyloxy)-5-cyano-6-(4-iodophenylamino)pyrimidin-2-yl(methyl)carbamate (23a). A solution of hydroxylimine **22a** (4.32 g, 7.51 mmol) and Et_3N (3.2 mL, 23 mmol) in THF (40 mL) at 0 °C was slowly treated with trifluoroacetic anhydride (1.7 mL, 12 mmol). After stirring for 15 min, the mixture was warmed to rt and then refluxed for 2 h. The reaction was quenched at rt with H_2O and the solvent was removed under reduced pressure. The residue was diluted with EtOAc, washed with H_2O, 10% aqueous citric acid, H_2O, 5% aqueous $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by flash chromatography on silica gel (3% EtOAc/hexane) provided 1.91 g of **23a** ($C_{24}H_{24}IN_5O_3$, 46%) as white solid. R_f 0.59 (SiO_2, 30% EtOAc/ hexane). Mp 152.4−154.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.59 (C_8H, C_{10}H, d, ^3J = 8.4 Hz, 2H), 7.46−7.32 (C_7H, C_{11}H, C_{15}H−C_{19}H, C_6NH, m, 8H), 5.48 (C_{13}H, s, 2H), 3.35 (C_{12}H, s, 3H), 1.51 (C_{22}H, s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 170.4 (C_4), 161.6 (C_1), 160.5 (C_2), 152.9 (C_{20}), 137.6 (C_8, C_{10}), 137.5 (C_6), 135.6 (C_{14}), 128.5 (C_{16}, C_{18}), 128.3 (C_{17}), 127.9 (C_{15}, C_{19}), 123.1 (C_7, C_{11}), 114.2 (C_5), 87.7 (C_9), 82.4 (C_{21}), 70.5 (C_3), 68.9 (C_{13}), 34.7 (C_{12}), 28.0 (C_{22}). ESI-MS: expected mass for [M + Na^+]/z 580.37, obsd ([M + Na^+]/z, 579.9, 100%). Negative: 556.1 (91%), 456.1 (49%).

***tert*-Butyl 4-(Benzyloxy)-1-(4-iodophenyl)-1*H*-pyrazolo[3,4-*d*]-pyrimidin-6-yl(methyl)carbamate (24a).** A 1.19 g yield of **24a** ($C_{24}H_{24}IN_5O_3$, 28%) was also isolated as a white solid. R_f 0.74 (SiO_2, 30% EtOAc/hexane). Mp 124−125.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.09 (C_8H, C_{10}H, d, ^3J = 8.7 Hz, 2H), 8.08 (C_5H, s, 1H), 7.78 (C_7H, C_{11}H, d, ^3J = 8.7 Hz, 2H), 7.51−7.35 (C_{15}H−C_{19}H, m, 5H), 5.60 (C_{13}H, s, 2H), 3.48 (C_{12}H, s, 3H), 1.54 (C_{22}H, s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 163.1 (C_4), 158.8 (C_1), 155.7 (C_{20}), 153.9 (C_2), 138.9 (C_6), 138.0 (C_8, C_{10}), 135.7 (C_{14}), 133.1 (C_5), 128.6, 128.5, 128.4 (C_{16}−C_{19}), 122.3 (C_7, C_{11}), 100.9 (C_3), 90.4 (C_9), 81.6 (C_{21}), 68.7 (C_{13}), 35.3 (C_{12}), 28.3 (C_{22}). ESI-MS: expected mass for [M + Na^+]/z 580.37, obsd ([M + Na^+]/z, 579.9, 100%). Negative: 556.1 (28%), 456.1 (100%).

Representative Example of the Synthesis of the Carbamide. *tert*-Butyl 4-(Benzyloxy)-5-cyano-6-(1-(4-iodophenyl)ureido)pyrimidin-2-yl(methyl)carbamate (26a). *N*-Chlorocarbonyl isocyanate (0.43 mL, 5.3 mmol) was added to a solution of **23a** (1.41 g, 2.53 mmol) and DMAP (709 mg, 5.8 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C. The contents of the flask were stirred at 0 °C for 75 min, followed by rt for 2 h. The reaction was quenched with 10% aqueous $NaHCO_3$ then diluted with H_2O and the product was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. After drying under high vacuum, 0.773 g of **26a** ($C_{25}H_{25}IN_6O_4$, 51%) was obtained as a white solid. R_f 0.13 (SiO_2, 30% EtOAc/hexane). Mp 149.5−150 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.75 (C_8H, C_{10}H, d, ^3J = 8.4 Hz, 2H), 7.35−7.29 (C_{15}H−C_{19}H, m, 5H), 7.04 (C_7H, C_9H, d, ^3J = 8.4 Hz, 2H), 5.44 (C_{13}H, s, 2H), 3.42 (C_{12}H, s, 3H), 1.54 (C_{22}H, s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 171.9 (C_4), 162.3 (C_2), 158.3 (C_1), 154.5 (C_{23}), 152.4 (C_{20}), 138.5 (C_6, C_8, C_{10}), 135.1 (C_{14}), 132.2 (C_7, C_{11}), 128.6 (C_{16}, C_{18}), 128.4 (C_{17}), 127.6 (C_{15}, C_{19}), 110.8 (C_5), 95.1 (C_9), 83.6 (C_{21}), 69.6 (C_3, C_{13}), 34.4 (C_{12}), 28.0 (C_{22}). ESI-MS: expected mass for [M + H^+]/z 601.10, obsd 600.7 ([M + H^+]/z, 100%), 500.9 ([M − Boc + H^+]/z, 35%), 1199.6 (dimer, 29%). Negative: 556.1 (100%).

Representative Example of the Suzuki Cross-Coupling Reaction. *tert*-Butyl 4-(Benzyloxy)-5-(di(*tert*-butoxycarbonyl)amino)-8-methyl-7-oxo-7,8-dihydropyrimido[4,5-*d*]pyrimidin-2-yl(4′-formylbiphenyl-4-yl)carbamate (34a). A screw-capped vial was charged with **33a** (291 mg, 0.363 mmol), 4-formylphenylboronic acid (109 mg, 0.726 mmol), potassium fluoride (74 mg, 1.3 mmol), and tris(dibenzylideneacetone)dipalladium(0) (17 mg, 0.018 mmol). THF (1.0 mL) was then added followed by tri-*tert*-butylphosphine (0.36 mL solution of 41 mg/2.0 mL THF). The vial was subsequently flushed with nitrogen and capped. After stirring at rt for 71 h, the mixture was diluted with Et_2O, filtered through a pad of Celite, and eluted with EtOAc and MeOH. The solution was concentrated in vacuo and the product was purified by flash column chromatography on silica gel (3−30% EtOAc/hexane) to provide 166 mg of **34a** ($C_{42}H_{46}N_6O_9$, 59%) as white foam. R_f 0.43 (SiO_2, 50% EtOAc/hexane). Mp 129−130 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 10.11 (C_{36}H, br s, 1H), 8.03 (C_{32}H, C_{34}H, d, ^3J = 8.4 Hz, 2H), 7.86 (C_8H, C_{12}H, d, ^3J = 8.1 Hz, 2H), 7.78 (C_{31}H, C_{35}H, d, ^3J = 8.4 Hz, 2H), 7.40 (C_9H, C_{11}H, d, ^3J = 8.1 Hz, 2H), 7.31−7.29 (C_{15}H, C_{17}H, C_{19}H, m, 3H), 7.23−7.20 (C_{16}H, C_{18}H, m, 2H), 5.37 (C_{13}H, s, 2H), 3.64 (C_6H, s, 3H), 1.57 (C_{22}H, s, 9H), 1.39 (C_{26}H, C_{29}H, s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 191.6 (C_{36}), 165.7 (C_4), 161.2, 160.8, 160.1 (C_1, C_2, C_5), 155.8 (C_{23}), 151.7 (C_{20}), 149.1 (C_{24}, C_{27}), 145.7 (C_{30}), 140.3 (C_{14}), 138.8 (C_7), 135.3 (C_{33}), 134.5 (C_{10}), 130.2 (C_{32}, C_{34}), 128.6 (C_9, C_{11}), 128.3, 128.2, 128.18 (C_{15}−C_{19}), 127.8 (C_8, C_{12}), 127.4 (C_{31}, C_{35}), 93.2 (C_3), 83.7 (C_{25}, C_{28}), 83.5 (C_{21}), 69.8 (C_{13}), 30.0 (C_6), 27.7 (C_{22}), 27.7 (C_{26}, C_{29}). ESI-MS: expected mass for [M + H^+]/z 779.34, obsd 778.9 ([M + H^+]/z, 5%), 800.8 ([M + Na^+]/z, 65%). High-resolution ESI-MS: calcd mass 779.3405, actual mass 779.3425.

4-Amino-1-methyl-7-(4-(naphthalen-1-yl)phenylamino)pyrimido[4,5-*d*]pyrimidine-2,5(1*H*,6*H*)-dione (36). Thioanisole (0.6 mL, 5 mmol) and TFA (9.4 mL, 127 mmol) were added to compound **34f** (300 mg, 0.374 mmol) under nitrogen atmosphere and the solution was stirred for 27.5 h. Et_2O was then added and the precipitate was centrifuged, collected, and washed with Et_2O to provide 189 mg of **36** ($C_{25}H_{20}F_3N_6O_{4.5}$, 95%) as a white solid. ^{1}H NMR (300 MHz, DMSO) δ (ppm): 10.49 (NH, s, 1H), 9.28 (NH, s, H), 8.64 (NH, s, 1H), 8.08−7.28 (C_8H, C_9H, C_{11}H, C_{12}H, C_{31}H−C_{33}H, C_{35}H−C_{38}H, m, 11H), 3.47 (C_6H, s, 3H). Due to the solubility in DMSO, no ^{13}C NMR was recorded. Anal. Calcd for $C_{25}H_{20}F_3N_6O_{4.5}$ (M + TFA + $^1/_2H_2O$): C, 56.29; H, 3.78: N, 15.75. Found: C, 56.64; H, 3.98: N, 15.37. High-resolution ESI-MS: calcd mass 411.1561, actual mass 411.1564.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds and single-crystal X-ray structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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