HETEROCYCLES, Vol. 96, No. 9, 2018, pp. 1549 - 1569. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 9th July, 2018, Accepted, 15th August, 2018, Published online, 29th August, 2018
DOI: 10.3987/COM-18-13956

# SYNTHESIS OF 4-ARYL AND UNSYMMETRICAL 4,6-DIARYLPYRIMIDINES BY THE SUZUKI-MIYAURA CROSS-COUPLING REACTION

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To Kiyoshi Tomioka, an individualistic organic chemist who has enriched our field: Koki (古希)

**Abstract** – A two-step procedure for the synthesis of 4-arylpyrimidines from inexpensive 4,6-dichloropyrimidine *via* a Suzuki-Miyaura/hydrodechlorination reaction sequence is described. The reaction resulted in the predominant formation of mono-arylated product. The cross-coupling of 4-chloro-6-substituted pyrimidines with various aryl/heteroarylboronic acids also furnished 4,6-disubstituted pyrimidines in acceptable yields.

## INTRODUCTION

Pyrimidines represent a long-standing class of heterocycles with significance in areas of biologically active compounds (Figure 1),[1] e.g., imatinib (**1**), fluacrypyrim, rosuvastatin (**2**), AZD5438 (**3**),[1d] CDK9/CycT1 inhibitor (**4**),[2] and buparlisib (**5**),[3] materials with nonlinear optical (NLO)[4b] and photoluminescent (**6**)[4] properties, and ligands for the molecular recognition of metal cations (**7**)[5] and proteins.[6]

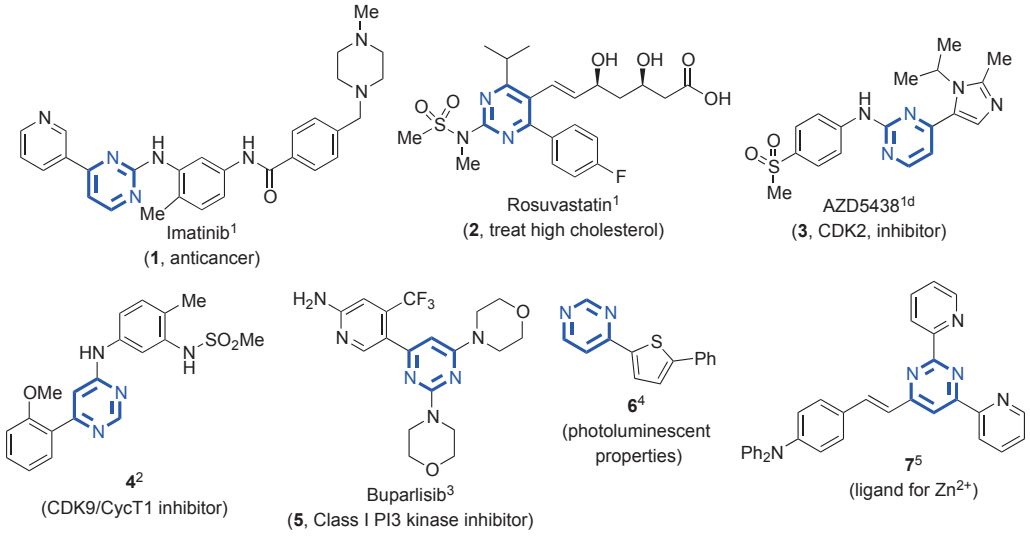



**Figure 1.** Some selective pyrimidine bioactive and material science molecules (**1**-**7**)

The traditional methods for the synthesis of arylated pyrimidines by de novo approaches[5,7] have been superseded by the discovery and extensive development of transition metal catalyzed cross-coupling[8a,9] and C-H activation/arylation reactions,[8] which take advantage of the commercial availability of relatively inexpensive chlorinated pyrimidines.[10] In these reactions, the $\pi$-electron deficiency of heteroaryl chlorides in general, and of pyrimidine chlorides in particular, facilitates oxidative addition to the C-Cl bond without the use of specialized ligands.[11] Of the available cross-coupling Name Reactions, the Suzuki-Miyaura reaction[8a,9] has witnessed the broadest utility. While the Suzuki-Miyaura reaction on polyhalogenated pyrimidines such as 2,4,5,6-tetrachloropyrimidine,[12] 2,4,6-trichloropyrimidine,[9b,11c,13] 2,4-dichloropyrimidines,[14] 2,5-dihalopyrimidines[15] and 4,6-dihalopyrimidines[16] with arylboronic acids coupling partners are known, bromo- and iodo-pyrimidines have received scant attention possibly due to their expense. Furthermore, selective mono-arylation of dihalopyrimidines has been studied: 2-chloro-4-bromopyrimidine undergoes the expected faster reaction at the C-Br bond but results in significant amounts of unreacted starting material.[15c] The 2,4-dibromo and 2,4-diiodo derivatives lead to equal mixtures of mono- and di-arylated products,[11c] but selective C-4 mono-arylation may be achieved by slow addition of a solution of the arylboronic acid in aqueous sodium carbonate into a solution of 2 equiv of 2,4-dichloropyrimidine in acetonitrile.[17]

An ongoing project in our laboratories required the establishment of a general methodology for the preparation of differentially and unsymmetrically 4,6-disubstituted pyrimidines **8** and 4-substituted pyrimidines **9** and **10** (Figure 2) with an emphasis on arylated pyrimidines. Herein we report studies on the preparation of series of diverse 4,6-disubstituted **8** and 4-substituted pyrimidines **10**, the latter group being obtained *via* reductive dehydrochlorination of 6-chloro-4-arylpyrimidine intermediates **9** which avoids the use of expensive 4-chloropyrimidine precursors.[10]

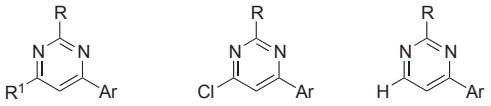
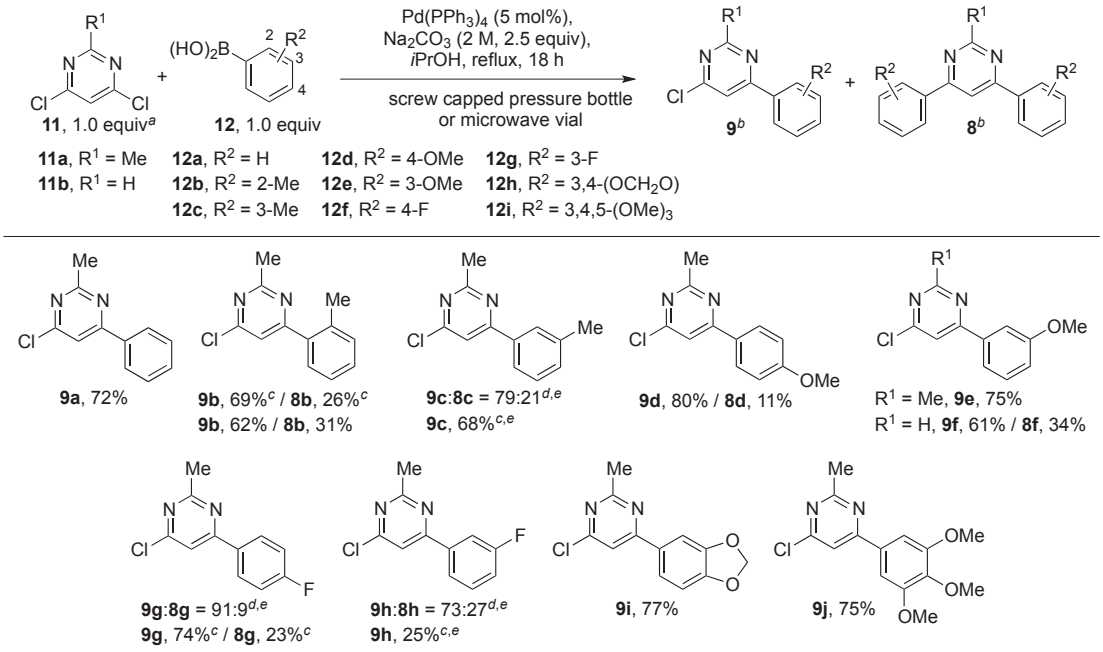



**Figure 2.** Target pyrimidines (**8-10**) in this work

## RESULTS AND DISCUSSION

To initiate our study, optimized conditions for mono-arylation using the Suzuki-Miyaura reaction were established on the dichloropyrimidine (**11a**) and 2-methyl-1-phenylboronic acid (**12b**) cross-coupling pair (see Table S1 in SI). Standard well-recognized coupling conditions ($Pd(PPh_3)_4/Na_2CO_3/i$PrOH) were used and thence applied for the preparation of a series of mono-chloro aryl-substituted pyrimidines: 4-phenyl (**9a**), isomeric tolyl (**9b**, **9c**), isomeric anisyl (**9d**, **9e**, **9f**), isomeric fluorophenyl (**9g**, **9h**), and two more highly oxygenated derivatives (**9i**, **9j**) (Table 1). Coupling reactions gave mono-arylated products with the exception of **9b**, **9c**, **9d**, **9f**, **9g**, and **9h** which afforded minor but significant amounts of diarylpyrimidines **8b**, **8c**, **8d**, **8f**, **8g**, and **8h**, respectively. Difficulty in separation of mono- (**9c**, **9g**, and **9h**) and di-arylated (**8c**, **8g**, and **8h**) materials required converting the mixtures to the hydrodechlorination products (**17**) which allowed facile separation of **8** from the resulting compound **17** (Table 3) (see SI). All reactions were carried out on 2 g scale. Of some note is the fact that cross-coupling proceeds in the case of **9b** despite the presence of an *ortho* substituent.

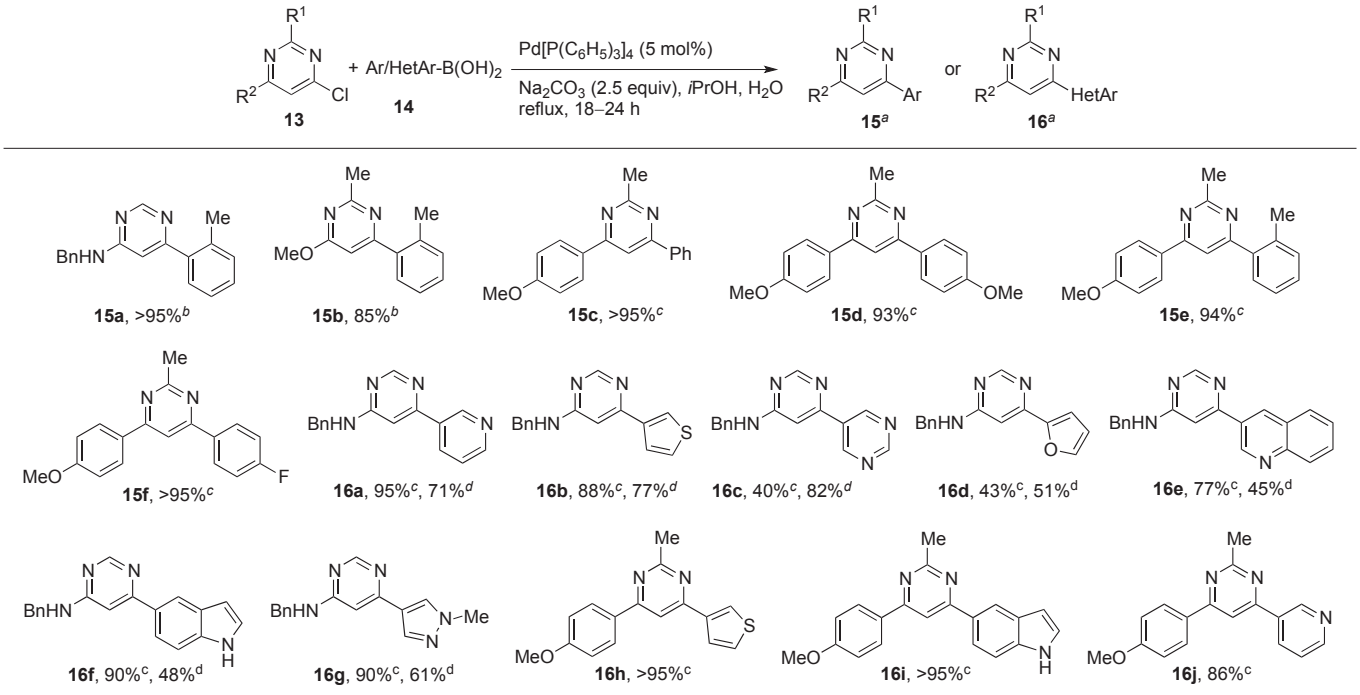
**Table 1.** Suzuki-Miyaura reaction of 4,6-dichloropyrimidine **11**




[a]All reactions were performed on 2 g scale unless otherwise indicated. [b]Yield of isolated product. [c]Reaction was performed on 200 mg scale. [d]Ratio of **9** and **8** by GC-MS analysis. [e]Mixture of **9** and **8** was isolated (see SI).

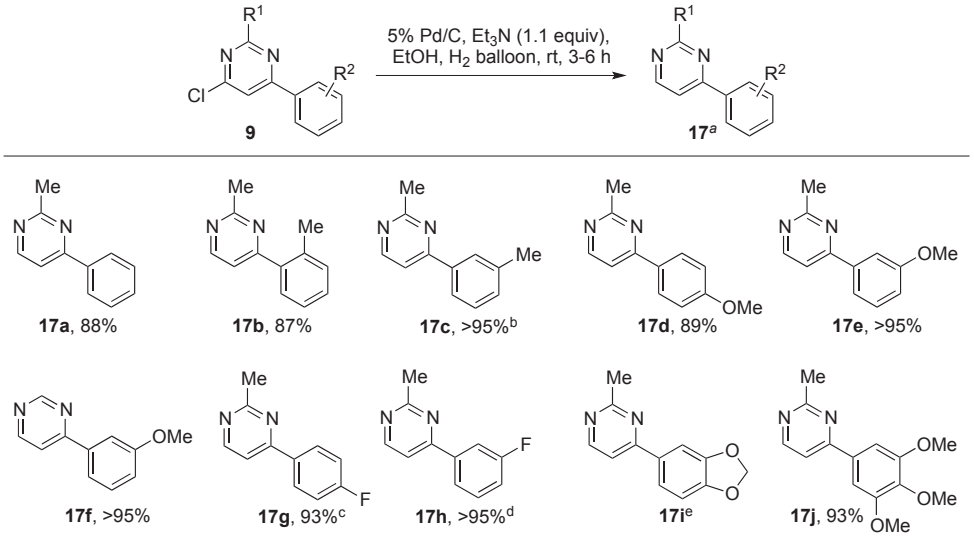
The availability of the 4-substituted 6-chloropyrimidines (**9**) provided the opportunity for the development of a general synthesis of unsymmetrical 4,6-substituted products **8** (Table 2) and a route for 4-monoarylpyrimidines **17** (Table 3). In the first task, a series of selected systems was explored (Table 2). Thus, using standard cross-coupling conditions, 4-amino (**15a**), 4-methoxy (**15b**) and a series of 4-aryl (**15c-f**) pyrimidines were prepared in high yields. Likewise, a number of available heteroarylboronic acids were subjected to the cross-coupling conditions to furnish an array of interesting 4-amino (**16a-g**) and 4-aryl-6-heteroarylpyrimidines (**16h-j**) (Table 2). In the 4-aryl-6-heteroaryl series, both $\pi$-excessive and $\pi$-deficient heterocyclic boronic acids underwent cross-coupling to afford products in good to excellent yields. In the second aim, a selected series of 4-aryl-6-chloropyrimidines were subjected to standard hydrogenation conditions to furnish monoarylated pyrimidines **17a-h** and **17j** generally in very good yields (Table 3). For reasons not understood, compound **9i** failed to undergo the dehydrochlorination reaction.

**Table 2.** Suzuki-Miyaura reaction of 4-chloro-6-substituted pyrimidines **13**




[a]Yield of isolated product. [b]1.1 equiv of organoborane (**14**), reflux conditions in sealed microwave vial. [c]1.3 equiv of organoborane (**14**), reflux conditions in sealed microwave vial. [d]1.0 equiv of organoborane (**14**), reflux conditions in a flask.

**Table 3.** Hydrodechlorination reaction of 6-chloropyrimidines derivatives **9**




[a]Yield of isolated product. [b]Mixture of **9c**:**8c** = 79:21 (GC-MS analysis) was used as SM. [c]Mixture of **9g**:**8g** = 91:9 (GC-MS analysis) was used as SM. [d]Mixture of **9h**:**8h** = 73:27 (GC-MS analysis) was used as SM. [e]SM was recovered in >90% yield.

In summary, this work has shown the value of the venerable[18] Suzuki-Miyaura cross-coupling strategy[8] for the provision of diverse mono-arylated 6-chloropyrimidine derivatives (Table 1) and thereby a conduit to the preparation of unsymmetrical 4,6-diarylated pyrimidines (Table 2). Hydrodechlorination of the 6-chloro derivatives provides an effective alternative route to 4-arylpyrimidines which avoids the use of the very expensive 4-chloropyrimidine starting material.[10] Scale up to gram quantities of most reactions has been demonstrated. The obtained products may be of value in consideration of biological activity (structural analogues of **3**,[1d] **4**,[2] and **5**[3] are kinase inhibitors) and electroluminescent properties.[19] The use of the synthesized pyrimidines in a related project in our laboratories will be reported in due course.

## EXPERIMENTAL

**General information:** Melting points were obtained on an Electrothermal IA9100 Melting Point Apparatus and are uncorrected. $^1$H and $^{13}$C spectra were recorded on Bruker Avance-400 MHz spectrometer. The chemical shifts of $^1$H and $^{13}$C NMR signals are quoted relative to internal C*H*Cl$_3$ ($\delta$ = 7.26) and *C*DCl$_3$ ($\delta$ = 77.0) or tetramethylsilane ($\delta$ = 0.0). Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), triplet (t), quartet (q), multiplet (m) and broad singlet (brs). The GC-MS analyses were performed on an Agilent 6890 GC coupled with an Agilent 5973 inert MS under EI conditions. High resolution mass spectra were obtained on a GCT Mass Spectrometer (Waters, Micromass) and a QSTAR XL hybrid mass Spectrometer (Applied Biosystems/MDS Sciex). IR spectra were recorded on a Bruker Alpha FT-IR spectrometer. Column chromatography was performed using silica gel (230-400 mesh) as the stationary phase. All reactions

were monitored by thin layer chromatography (TLC). All reagents and solvents were purchased from commercial sources and used without purification. *N*-Benzyl-6-chloropyrimidin-4-amine was prepared by a reported procedure.[20]

**General Procedure for the Synthesis of 6-Aryl-4-chloropyrimidines (9a-j):** To a degassed solution of 4,6-dichloropyrimidine (200 mg, 1.0 equiv) and arylboronic acid (1.0 equiv) in *i*PrOH (4 mL) in a 20 mL microwave vial was added an aqueous solution of 2M $Na_2CO_3$ (2.5 equiv) and $Pd(PPh_3)_4$ (5.0 mol%) under an argon atmosphere and the resulting heterogeneous solution was further degassed for 10 min. The vial was sealed and placed in an oil bath at 83 °C and the reaction mixture was refluxed for 18 h, cooled, diluted with $H_2O$ (20 mL) and the whole was extracted with EtOAc (3 X 30 mL). The combined organic extract was washed with brine, dried ($Na_2SO_4$), and evaporated under reduced pressure give an oil which was purified by gradient column chromatography on silica gel using EtOAc/hexanes as eluent to afford compounds **9a-j**.

**4-Chloro-2-methyl-6-phenylpyrimidine (9a):** Following the General Procedure and purification method using 4,6-dichloro-2-methylpyrimidine (2.0 g, 1.0 equiv), phenylboronic acid (1.5 g, 1.0 equiv), 2M $Na_2CO_3$ (15.4 mL, 2.5 equiv), and $Pd(PPh_3)_4$ (709 mg, 5 mol%) in *i*PrOH (40 mL) provided compound **9a** (1.82 g, 72% yield) as a pale yellow solid, mp 71–73 °C (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 2923, 2853, 1559, 1533, 1450, 747 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.06-8.03 (m, 2H), 7.54-7.47 (m, 4H), 2.77 (s, 3H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 169.2, 165.8, 161.6, 135.8, 131.4, 129.1, 127.4, 114.0, 26.1 ppm; HRMS (EI) calcd for $C_{11}H_9ClN_2$ [M] 204.0454, found 204.0446. The physical and spectral data were consistent with those previously reported.[21]

**4-Chloro-2-methyl-6-(2-methylphenyl)pyrimidine (9b):** *200 mg scale reaction:* Following the General Procedure and purification method using 4,6-dichloro-2-methylpyrimidine (200 mg, 1.0 equiv), 2-methylphenylboronic acid (167 mg, 1.0 equiv) provided compound **9b** (185 mg, 69% yield) and compound **8b** (45 mg, 26% yield).

*2 g scale reaction:* Following the General Procedure and purification method using 4,6-dichloro-2-methylpyrimidine (2.0 g, 1.0 equiv), 2-methylphenylboronic acid (1.67 g, 1.0 equiv), 2M $Na_2CO_3$ (15.4 mL, 2.5 equiv), and $Pd(PPh_3)_4$ (709 mg, 5 mol%) in *i*PrOH (40 mL) provided compound **9b** (1.66 g, 62% yield) and compound **8b** (529 mg, 31% yield).

Compound **9b**: Colorless oil; FT-IR (neat) $\nu_{max}$ 3096, 2962, 1604, 1394, 1153, 908, 753 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.41-7.38 (m, 1H), 7.37-7.33 (m, 1H), 7.29-7.26 (m, 2H), 2.77 (s, 3H), 2.41 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 168.9, 168.7, 160.9, 136.8, 136.1, 131.3, 129.9, 129.4, 126.2, 118.0, 25.9, 20.3 ppm; HRMS (EI) calcd for $C_{12}H_{11}ClN_2$ [M] 218.0611, found 218.0619.

Compound **8b:** Colorless solid, mp 83–85 °C (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3079, 2957, 2836,

1601-1394, 1238, 1045, 766 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.49-7.47 (m, 2H), 7.38-7.29 (m, 7H), 2.86 (s, 3H), 2.46 (s, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 167.7, 167.2, 138.4, 135.9, 131.1, 129.5, 129.4, 126.2, 117.9, 26.5, 20.4 ppm; HRMS (EI) calcd for $C_{19}H_{18}N_2$ [M] 274.1470, found 274.1481.

**4-Chloro-2-methyl-6-(3-methylphenyl)pyrimidine (9c) and 2-methyl-4,6-bis(3-methylphenyl)-pyrimidine (8c):** The General Procedure and purification method were followed using 4,6-dichloro-2-methylpyrimidine (2.0 g, 1.0 equiv), 3-methylphenylboronic acid (1.7 g, 1.0 equiv), 2M $Na_2CO_3$ (15.4 mL, 2.5 equiv), and $Pd(PPh_3)_4$ (709 mg, 5 mol%) in *i*PrOH (40 mL) to provide a mixture of **9c** and **8c** (2.36 g, **9c**:**8c** = 79:21, by GC-MS) as a colorless oil. This mixture was used without further purification in next hydrodechlorination step.

*200 mg scale reaction:* Following the General Procedure and purification method using 4,6-dichloro-2-methylpyrimidine (200 mg, 1.0 equiv), 3-methylphenylboronic acid (167 mg, 1.0 equiv) provided compound **9c** (181 mg, 68% yield) along with 74 mg of a mixture (**9c**:**8c** = 26:74 by GC-MS analysis).

Compound **9c**: Colorless oil; FT-IR (neat) $\nu_{max}$ 3060, 2863, 1556, 1535, 1393, 1147 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.86 (s, 1H), 7.80 (d, $J$ = 7.6 Hz, 1H), 7.51 (s, 1H), 7.37 (t, $J$ = 7.6 Hz, 1H), 7.29 (d, $J$ = 7.6 Hz, 1H), 2.77 (s, 3H), 2.43 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 169.1, 166.0, 161.5, 138.8, 135.7, 132.2, 128.9, 127.9, 124.5, 114.0, 26.1, 21.5 ppm; HRMS (EI) calcd for $C_{12}H_{11}ClN_2$ [M] 218.0611, found 218.0620.

**4-Chloro-6-(4-methoxyphenyl)-2-methylpyrimidine (9d) and 4,6-bis(4-methoxyphenyl)-2-methylpyrimidine (8d):** The General Procedure and purification method were followed using 4,6-dichloro-2-methylpyrimidine (2.0 g, 1.0 equiv), *p*-methoxyphenylboronic acid (1.9 g, 1.0 equiv), 2M $Na_2CO_3$ (15.4 mL, 2.5 equiv), and $Pd(PPh_3)_4$ (709 mg, 5 mol%) in *i*PrOH (40 mL) to provide compound **9d** (2.3 g, 80% yield) and compound **8d** (207 mg, 11% yield).

Compound **9d**: pale yellow solid, mp 74–75 °C (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3078, 2838, 1607, 1558, 1506, 1252, 1152, 1030, 985, 831 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.03 (d, $J$ = 8.8 Hz, 2H), 7.46 (s, 1H), 6.99 (d, $J$ = 8.8 Hz, 2H), 3.87 (s, 3H), 2.74 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 168.9, 165.3, 162.4, 161.3, 128.9, 128.1, 114.4, 112.9, 55.5, 26.1 ppm; HRMS (EI) calcd for $C_{12}H_{11}ClN_2O$ [M] 234.0560, found 234.0549.

Compound **8d**: Colorless solid, mp 159–160 °C (EtOAc/hexanes) (lit[22] mp 159–160 °C); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.08 (d, $J$ = 8.6 Hz, 4H), 7.74 (s, 1H), 7.00 (d, $J$ = 8.6 Hz, 4H), 3.86 (s, 6H), 2.81 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 168.2, 163.9, 161.7, 130.0, 128.7, 114.2, 108.3, 55.4, 26.5 ppm. The physical and spectral data were consistent with those reported.[22]

**4-Chloro-6-(3-methoxyphenyl)-2-methylpyrimidine (9e):** Following the General Procedure and

purification method using 4,6-dichloro-2-methylpyrimidine (2.0 g, 1.0 equiv), 3-methoxyphenylboronic acid (1.87 g, 1.0 equiv), 2M $Na_2CO_3$ (15.4 mL, 2.5 equiv), and $Pd(PPh_3)_4$ (709 mg, 5 mol%) in *i*PrOH (40 mL) provided compound **9e** (2.16 g, 75% yield) as a colorless solid, mp 69–71 ºC (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3079-3003, 2957-2836, 1601-1394, 1238, 766 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.62-7.61 (m, 1H), 7.59-7.57 (m, 1H), 7.51 (s, 1H), 7.40 (t, $J$ = 7.9 Hz, 1H), 7.07-7.04 (m, 1H), 3.89 (s, 3H), 2.77 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 169.1, 165.6, 161.5, 160.2, 137.2, 130.1, 119.7, 117.4, 114.1, 112.5, 55.5, 26.0 ppm; HRMS (EI) calcd for $C_{12}H_{11}ClN_2O$ [M] 234.0560, found 234.0551.

**4-Chloro-6-(3-methoxyphenyl)pyrimidine (9f) and 4,6-bis(3-methoxyphenyl)pyrimidine (8f):** Following the General Procedure and purification method using 4,6-dichloropyrimidine (2.0 g, 1.0 equiv), 3-methoxyphenylboronic acid (2.04 g, 1.0 equiv), 2M $Na_2CO_3$ (16.8 mL, 2.5 equiv), and $Pd(PPh_3)_4$ (775 mg, 5 mol%) in *i*PrOH (40 mL) provided compound **9f** (1.66 g, 61% yield) and compound **8f** (670 mg, 34% yield).

Compound **9f**: Colorless solid, mp 92–94 ºC (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3069, 3003, 2979, 2827, 1606, 1425, 1273, 1174, 788 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): 9.01 (s, 1H), 7.72 (s, 1H), 7.65 (s, 1H), 7.59 (d, $J$ = 7.7 Hz, 1H), 7.41 (t, $J$ = 8.0 Hz, 1H), 7.07 (dd, $J_1$ = 8.2 Hz, $J_2$ = 2.4 Hz, 1H), 3.89 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 165.5, 161.9, 160.3, 158.9, 136.7, 130.1, 119.6, 117.8, 117.3, 112.3, 55.5 ppm; HRMS (EI) calcd for $C_{11}H_9ClN_2O$ [M] 220.0403, found 220.0409. The physical and spectral data were consistent with those reported.[2]

Compound **8f**: Pale yellow solid, mp 77–78 ºC (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3136, 3000, 2956, 2833, 1571, 1427, 1265, 1040, 749 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 9.30 (s, 1H), 8.06 (s, 1H), 7.72 (t, $J$ = 2.1 Hz, 2H), 7.69-7.67 (m, 2H), 7.43 (t, $J$ = 8.0 Hz, 2H), 7.08-7.05 (m, 2H), 3.91 (s, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 164.5, 160.2, 159.1, 138.4, 130.0, 119.5, 117.0, 113.1, 112.3, 55.5 ppm; HRMS (EI) calcd for $C_{18}H_{16}N_2O_2$ [M] 292.1212, found 292.1216.

**4-Chloro-6-(4-fluorophenyl)-2-methylpyrimidine (9g) and 4,6-bis(4-fluorophenyl)-2-methylpyrimidine (8g):** The General Procedure and purification method were followed using 4,6-dichloro-2-methylpyrimidine (2.0 g, 1.0 equiv), 4-fluorophenylboronic acid (1.7 g, 1.0 equiv), 2M $Na_2CO_3$ (15.4 mL, 2.5 equiv), and $Pd(PPh_3)_4$ (709 mg, 5 mol%) in *i*PrOH (40 mL) to provide a mixture of compound **9g** and **8g** (2.07 g, **9g**:**8g** = 91:9, by GC-MS) which was forwarded to the hydrodechlorination step.

*200 mg scale reaction:* Following the General Procedure using 4,6-dichloro-2-methylpyrimidine (200 mg, 1.0 equiv), 4-fluorophenylboronic acid (172 mg, 1.0 equiv) and purification by flash chromatography using $Et_2O$/hexanes provided compound **9g** (202 mg, 74% yield) along with **8g** (40 mg, 23%).

Compound **9g**: colorless solid, mp 98–100 ºC ($Et_2O$/hexanes); FT-IR (neat) $\nu_{max}$ 3115, 3030, 2899, 1600,

1396, 1235, 840 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.09-8.06 (m, 2H), 7.50 (s, 1H), 7.21-7.16 (m, 2H), 2.76 (s, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 169.2, 164.9 (d, $J$ = 251 Hz), 164.6, 161.6, 131.9 (d, $J$ = 3 Hz), 129.5 (d, $J$ = 9 Hz), 116.2 (d, $J$ = 22 Hz), 113.6, 26.0 ppm; HRMS (EI) calcd for $C_{11}H_8ClFN_2$ [M] 222.0360, found 222.0368.

Compound **8g**: Pale yellow solid, mp 153.1–154.1 °C (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3074, 3045, 1600, 1580, 1507, 1227, 847 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.15-8.10 (m, 4H), 7.78 (s, 1H), 7.23-7.17 (m, 4H), 2.83 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 168.6, 164.5 (d, $J$ = 249.5 Hz), 163.8, 133.5 (d, $J$ = 3.3 Hz), 129.3 (d, $J$ = 8.7 Hz), 116.0 (d, $J$ = 21.6 Hz), 109.2, 26.5 ppm; HRMS (EI) calcd for $C_{17}H_{12}F_2N_2$ [M] 282.0969, found 282.0961.

**4-Chloro-6-(3-fluorophenyl)pyrimidine (9h):** Following the General Procedure and purification method using 4,6-dichloro-2-methylpyrimidine (2.0 g, 1.0 equiv), 3-fluorophenylboronic acid (1.72 g, 1.0 equiv), 2M $Na_2CO_3$ (15.4 mL, 2.5 equiv), and $Pd(PPh_3)_4$ (709 mg, 5 mol%) in *i*PrOH (40 mL) provided compound **9h**:**8h** (2.42 g, 73:27, by GCMS) which was forwarded to the hydrodechlorination step.

*200 mg scale reaction:* Following the General Procedure using 4,6-dichloro-2-methylpyrimidine (200 mg, 1.0 equiv), 3-fluorophenylboronic acid (172 mg, 1.0 equiv) and purification by flash chromatography using $Et_2O$/hexanes provided compound **9h** (69 mg, 25% yield) along with 158 mg of a mixture **9h**:**8h** = 58:42 (by GC-MS).

Compound **9h**: Colorless solid, mp 109–111 °C ($Et_2O$/hexanes); FT-IR (neat) $\nu_{max}$ 3077, 3015, 2955, 2853, 1560, 1395, 1210, 775 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.83-7.80 (m, 2H), 7.54 (s, 1H), 7.51-7.45 (m, 1H), 7.25-7.19 (m, 1H), 2.78 (s, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 169.3, 164.4 (d, $J$ = 11 Hz), 161.9, 161.7, 138.0 (d, $J$ = 7 Hz), 130.6 (d, $J$ = 8 Hz), 122.8 (d, $J$ = 3 Hz), 118.3 (d, $J$ = 21 Hz), 114.3 (d, $J$ = 23 Hz), 114.1, 25.9 ppm; HRMS (EI) calcd for $C_{11}H_8ClFN_2$ [M] 222.0360, found 222.0355. The physical and spectral data were consistent with those reported.[23]

Compound **8h**: Colorless solid, mp 150–152 °C (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3135, 3005, 2972, 1613, 1452, 1260, 762 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.89-7.82 (m, 5H), 7.51-7.46 (m, 2H), 7.23-7.18 (m, 2H), 2.86 (s, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 168.9, 163.8, 163.3 (d, $J$ = 245 Hz), 162.1, 139.6 (d, $J$ = 8 Hz), 130.5 (d, $J$ = 8 Hz), 122.8 (d, $J$ = 3 Hz), 117.7 (d, $J$ = 21 Hz), 114.3 (d, $J$ = 23 Hz), 109.9, 26.4 ppm; HRMS (EI) calcd for $C_{17}H_{12}F_2N_2$ [M] 282.0969, found 282.0958.

**4-(Benzo[*d*][1,3]dioxol-5-yl)-6-chloro-2-methylpyrimidine (9i):** Following the General Procedure and purification method, using 4,6-dichloro-2-methylpyrimidine (2.0 g, 1.0 equiv), 3,4-(methylenedioxy)phenylboronic acid (2.04 g, 1.0 equiv), 2M $Na_2CO_3$ (15.4 mL, 2.5 equiv), and $Pd(PPh_3)_4$ (709 mg, 5 mol%) in *i*PrOH (40 mL) provided compound **9i** (2.32 g, 77% yield) as a colorless solid, mp 148–149 °C (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3118, 3062, 2910, 1570, 1406, 1239, 933 $cm^{-1}$;

$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.62-7.58 (m, 2H), 7.42 (s, 1H), 6.91 (d, $J$ = 8.0 Hz, 1H), 6.05 (s, 2H), 2.74 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 168.9, 165.0, 161.4, 150.5, 148.6, 129.9, 122.2, 113.1, 108.6, 107.4, 101.8, 26.0 ppm; HRMS (EI) calcd for $C_{12}H_9ClN_2O_2$ [M] 248.0353, found 248.0361.

**4-Chloro-2-methyl-6-(3,4,5-trimethoxyphenyl)pyrimidine (9j):** Following the General Procedure and purification method, using 4,6-dichloro-2-methylpyrimidine (2.0 g, 1.0 equiv), phenylboronic acid (2.6 g, 1.0 equiv), 2M $Na_2CO_3$ (15.4 mL, 2.5 equiv), and $Pd(PPh_3)_4$ (709 mg, 5 mol%) in *i*PrOH (40 mL) provided compound **9j** (2.69 g, 75% yield) as a colorless solid, mp 113–115 $^o$C (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3098, 2998, 2834, 1588, 1392, 1126, 707 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.49 (s, 1H), 7.30 (s, 2H), 3.97 (s, 6H), 3.93 (s, 3H), 2.77 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 169.0, 165.3, 161.5, 153.6, 141.1, 131.0, 113.6, 104.6, 60.9, 56.3, 26.0 ppm; HRMS (EI) calcd for $C_{14}H_{15}ClN_2O_3$ [M] 294.0771, found 294.0759.

**Suzuki-Miyaura Cross-Coupling of *N*-Benzyl-6-chloropyrimidin-4-amine (13) with Aromatic Boronic Acids (14):**

***N*-Benzyl-6-(2-methylphenyl)pyrimidin-4-amine (15a):** Following the General Procedure and purification method, using *N*-benzyl-6-chloropyrimidin-4-amine (500 mg, 1.0 equiv), 2-methylphenylboronic acid (364 mg, 1.1 equiv), 2M $Na_2CO_3$ (3.0 mL, 2.5 equiv), and $Pd(PPh_3)_4$ (141 mg, 5 mol%) in *i*PrOH (10 mL) to provide compound **15a** (626 mg, >95% yield) as a colorless viscous oil; FT-IR (neat) $\nu_{max}$ 3407, 3247, 3027, 2966, 2869, 1592, 1411, 1354, 978 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.50 (s, 1H), 7.36-7.18 (m, 9H), 6.32 (s, 2H), 4.52 (s, 2H), 2.28 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 162.5, 158.1, 138.9, 135.7, 130.8, 129.1, 128.8, 127.6, 127.4, 125.8, 45.5, 20.1 ppm; HRMS (EI) calcd for $C_{18}H_{17}N_3$ [M] 275.1422, found 275.1433.

**4-Methoxy-2-methyl-6-(2-methylphenyl)pyrimidine (15b):** Following the General Procedure and purification method, using 4-chloro-6-methoxy-2-methylpyrimidine **S1** (1.0 g, 1.0 equiv), 2-methylphenylboronic acid (943 mg, 1.1 equiv), 2M $Na_2CO_3$ (7.9 mL, 2.5 equiv), and $Pd(PPh_3)_4$ (365 mg, 5 mol%) in *i*PrOH (20 mL) provided compound **15b** (1.15 g, 85% yield) as pale-yellow oil; FT-IR (neat) $\nu_{max}$ 3109, 3019, 2951, 1605, 1402, 1370, 1046, 760 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.38-7.36 (m, 1H), 7.32-7.23 (m, 3H), 6.61 (s, 1H), 4.00 (s, 3H), 2.68 (s, 3H), 2.37 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 169.9, 167.8, 167.7, 138.4, 135.8, 130.9, 129.2, 129.0, 125.9, 101.5, 53.6, 26.1, 20.2 ppm; HRMS (EI) calcd for $C_{13}H_{14}N_2O$ [M] 214.1106, found 214.1100.

**4-(4-Methoxyphenyl)-2-methyl-6-phenylpyrimidine (15c):** Following the General Procedure and purification method, using 4-chloro-6-(4-methoxyphenyl)-2-methylpyrimidine **9d** (200 mg, 1.0 equiv), phenylboronic acid (136 mg, 1.3 equiv), 2M $Na_2CO_3$ (1.1 mL, 2.5 equiv), and $Pd(PPh_3)_4$ (49 mg, 5 mol%) in *i*PrOH (4 mL) provided compound **15c** (225 mg, >95% yield) as a pale yellow solid, mp

103–105 °C (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3060, 3001, 2960, 2836, 1606, 1393, 1254, 833 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.09 (d, $J$ = 8.8 Hz, 4H), 7.80 (s, 1H), 7.51-7.49 (m, 3H), 7.01 (d, $J$ = 8.8 Hz, 4H), 3.86 (s, 3H), 2.84 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 168.4, 164.7, 164.3, 161.8, 137.7, 130.5, 129.8, 128.9, 128.8, 127.3, 114.3, 109.3, 55.4, 26.5 ppm; HRMS (EI) calcd for $C_{18}H_{16}N_2O$ [M] 276.1263, found 276.1270.

**4,6-Bis(4-methoxyphenyl)-2-methylpyrimidine (15d):** Following the General Procedure and purification method, using 4-chloro-6-(4-methoxyphenyl)-2-methylpyrimidine **9d** (200 mg, 1.0 equiv), 4-methoxyphenylboronic acid (169 mg, 1.3 equiv), 2M $Na_2CO_3$ (1.1 mL, 2.5 equiv), and $Pd(PPh_3)_4$ (49 mg, 5 mol%) in *i*PrOH (4 mL) provided compound **15d** (243 mg, 93% yield) as a colorless solid, mp 159–160 °C (EtOAc/hexanes) (lit[22] mp 159–160 °C); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.08 (d, $J$ = 8.6 Hz, 4H), 7.74 (s, 1H), 7.00 (d, $J$ = 8.6 Hz, 4H), 3.86 (s, 6H), 2.81 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 168.2, 163.9, 161.7, 130.0, 128.7, 114.2, 108.3, 55.4, 26.5 ppm. The physical and spectral data were consistent with those reported.[22]

**4-(4-Methoxyphenyl)-2-methyl-6-(2-methylphenyl)pyrimidine (15e):** The General Procedure and purification method was followed using 4-chloro-6-(4-methoxyphenyl)-2-methylpyrimidine **9d** (400 mg, 1.0 equiv), 2-methylphenylboronic acid (302 mg, 1.3 equiv), 2M $Na_2CO_3$ (2.1 mL, 2.5 equiv), and $Pd(PPh_3)_4$ (99 mg, 5 mol%) in *i*PrOH (8 mL) to provide compound **15e** (466 mg, 94% yield) as pale yellow solid, mp 67–68 °C (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3065, 2958, 2837, 1605, 1457, 1368, 1254, 1175, 1032, 836, 759 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.08 (d, $J$ = 8.8 Hz, 2H), 7.53 (s, 1H), 7.46-7.44 (m, 1H), 7.37-7.28 (m, 3H), 7.03-6.99 (m, 2H), 3.86 (s, 3H), 2.83 (s, 3H), 2.43 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 167.9, 167.7, 163.7, 161.9, 138.8, 135.9, 131.0, 129.7, 129.3, 129.2, 128.8, 126.1, 114.3, 113.0, 55.4, 26.5, 20.3 ppm; HRMS (ESI) calcd for $C_{19}H_{18}N_2O$ [M + H] 290.1419, found 290.1411.

**4-(4-Fluorophenyl)-6-(4-methoxyphenyl)-2-methylpyrimidine (15f):** Following the General Procedure and purification method, using 4-chloro-6-(4-methoxyphenyl)-2-methylpyrimidine **9d** (200 mg, 1.0 equiv), 4-fluorophenylboronic acid (156 mg, 1.3 equiv), 2M $Na_2CO_3$ (1.1 mL, 2.5 equiv), and $Pd(PPh_3)_4$ (49 mg, 5 mol%) in *i*PrOH (4 mL) provided compound **15f** (249 mg, >95% yield) as a colorless solid, mp 131–132 °C (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3062, 3049, 2971, 2839, 1599, 1414, 1227, 829 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.12-8.08 (m, 4H), 7.74 (s, 1H), 7.20-7.16 (m, 2H), 7.02-6.99 (m, 2H), 3.87 (s, 3H), 2.82 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 168.4, 164.4 (d, $J$ = 249 Hz), 164.3, 163.4, 161.9, 133.8, 129.7, 129.2 (d, $J$ = 8 Hz), 128.7, 115.9 (d, $J$ = 22 Hz), 114.3, 108.7, 55.4, 26.5 ppm; HRMS (EI) calcd for $C_{18}H_{15}FN_2O$ [M] 294.1168, found 294.1158.

**Suzuki-Miyaura Cross-Coupling of *N*-Benzyl-6-chloropyrimidin-4-amine (13) with Heteroaromatic Boronic Acids (14):**

**General Procedure: Method A:** In a microwave vial equipped with a stirbar was added a 0.05 M solution of the aryl chloride **13** (1 equiv) in *i*PrOH and boronic acid **14** (1.3 equiv) with stirring. The resulting solution was degassed with argon for 5 min before adding a 2M aqueous solution of $Na_2CO_3$ (2.5 equiv). The mixture was degassed for an additional 5 min before adding $Pd(PPh_3)_4$ (5 mol%), followed by an additional degassing cycle for 10 min before the vial was sealed and heated at 84 °C with stirring for 18 h. Upon consumption of the starting materials (TLC), the reaction mixture was cooled to rt and a solid impurity was removed by suction filtration. The mother liquor was then diluted with water and the whole was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), evaporated to dryness *in vacuo* and the residue was subjected to flash silica gel column chromatography (conditions *vide infra*) to give the pure product.

**Method B:** In a round bottom flask equipped with a stirbar was added with stirring a 0.05 M solution of the aryl chloride **13** (1 equiv) in *i*PrOH and boronic acid **14** (1.0 equiv). The resulting solution was degassed with argon for 5 min before adding a 2M aqueous solution of $Na_2CO_3$ (2.5 equiv). The mixture was degassed for an additional 5 min before adding $Pd(PPh_3)_4$ (5 mol%), followed by an additional degassing cycle for 10 min and heating at 84 °C under argon for 18 h. Upon consumption of the starting materials (TLC), the reaction mixture was cooled to rt and a solid impurity was removed by suction filtration. The mother liquor was then diluted with $H_2O$ and the whole was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to dryness *in vacuo* and the residue was subjected to flash silica gel column chromatography to give product **16**.

***N*-Benzyl-6-(pyridin-3-yl)pyrimidin-4-amine (16a):** Following the General Porcedure (Method A), using *N*-benzyl-6-chloropyrimidin-4-amine (100 mg, 0.455 mmol, 1.0 equiv) and pyridin-3-ylboronic acid (73 mg, 0.592 mmol), and purification by flash column chromatography (5% MeOH/EtOAc) afforded compound **16a** (113 mg, 95% yield).

Following the General Porcedure (Method B), using *N*-benzyl-6-chloropyrimidin-4-amine (200 mg, 1.0 equiv) and pyridin-3-ylboronic acid (119 mg, 1.0 equiv), and purification by flash column chromatography (30% EtOAc/hexanes) afforded compound **16a** (170 mg, 71% yield).

Compound **16a**: Colourless solid, mp 146-147 ºC (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3248, 3107, 3029, 2917, 2868, 1600, 1415, 700 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.17 (s, 1H), 8.66 (d, 1H, $J$ = 3.6 Hz), 8.56 (s, 1H), 8.33 (d, 1H, 7.3 Hz), 8.14 (t, 1H, $J$ = 6.0 Hz), 7.51 (t, $J$ = 3.9 Hz), 7.37-7.31 (m, 4H), 7.23 (t, 1H, 7.0 Hz), 7.10 (s, 1H), 4.61 (d, 2H, $J$ = 5.1 Hz) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 162.9, 158.6, 150.7, 147.6, 139.4, 133.9, 132.7, 128.3, 127.3, 126.8, 123.8, 101.5, 43.5 ppm; HRMS (EI) calcd for $C_{16}H_{14}N_4$ [M] 262.1218, found 262.1211.

***N*-Benzyl-6-(thiophen-3-yl)pyrimidin-4-amine (16b):** Following the General Procedure (Method A), using *N*-benzyl-6-chloropyrimidin-4-amine (100 mg, 0.455 mmol, 1.0 equiv) and 3-thienylboronic acid (76 mg, 0.592 mmol, 1.3 equiv) and purification by flash column chromatography (40% EtOAc/hexanes) afforded compound **16b** (107 mg, 88% yield).

Following the General Porcedure (Method B), using *N*-benzyl-6-chloropyrimidin-4-amine (200 mg, 1.0 equiv) and 3-thienylboronic acid (125 mg, 1.0 equiv) and purification by flash column chromatography (EtOAc/hexanes) afforded compound **16b** (188 mg, 77% yield).

Compound **16b**: Beige solid, mp 148–150 ºC (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3241, 3105, 3028, 2924, 1594, 1513, 1454, 1351, 1230, 1096, 979, 851, 696 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 8.58 (s, 1H), 7.98 (dd, *J* = 3.0 Hz, 1.2 Hz, 1H), 7.53 (dd, *J* = 5.01 Hz, 1.2 Hz, 1H), 7.39-7.28 (m, 6H), 6.58 (s, 1H), 5.47 (brs, 1H), 4.60 (d, *J* = 5.6 Hz, 2H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 163.1, 158.9, 140.6, 129.0, 127.8, 127.6, 126.6, 125.84, 125.81, 98.8, 76.4, 45.7 ppm; HRMS (EI) calcd for $C_{15}H_{13}N_3S$ [M] 267.0830, found 267.0835.

***N*-Benzyl-4,5'-bipyrimidin-6-amine (16c):** Following the General Porcedure (Method A), using *N*-benzyl-6-chloropyrimidin-4-amine (100 mg, 0.455 mmol, 1.0 equiv) and pyrimidin-5-ylboronic acid (73 mg, 0.592 mmol, 1.3 equiv), and purification by flash column chromatography (5% MeOH/EtOAc) afforded compound **16c** (48 mg, 40% yield).

Following the General Porcedure (Method B), using *N*-benzyl-6-chloropyrimidin-4-amine (200 mg, 0.455 mmol, 1.0 equiv) and pyrimidin-5-ylboronic acid (121 mg, 1.0 equiv), and purification by flash column chromatography (EtOAc/hexanes) afforded compound **16c** (196 mg, 82% yield).

Compound **16c**: Beige solid, mp 178–180 ºC (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3266, 3151, 3030, 2919, 2850, 1599, 1398, 722 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.32-9.28 (m, 2H), 8.57 (s, 1H), 8.18 (s, 1H), 7.64-7.54 (m, 1H), 7.34-7.13 (m, 4H), 5.75 (s, 1H), 4.61 (br s, 2H), 3.38 (s, 1H) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 159.1, 158.8, 154.9, 131.5, 131.4, 130.6, 128.8, 128.3, 127.3, 126.8, 102.0, 43.4 ppm; HRMS (EI) calcd for $C_{15}H_{13}N_5$ [M] 263.1171, found 263.1174.

***N*-Benzyl-6-(furan-2-yl)pyrimidin-4-amine (16d):** Following the General Porcedure (Method A), using *N*-benzyl-6-chloropyrimidin-4-amine (100 mg, 0.455 mmol, 1.0 equiv) and 2-furanylboronic acid (66 mg, 0.592 mmol) and purification by flash column chromatography (20–40% EtOAc/hexanes) afforded compound **16d** (49 mg, 43% yield).

Following the General Porcedure (Method B), using *N*-benzyl-6-chloropyrimidin-4-amine (100 mg, 1.0 equiv) and 2-furanylboronic acid (54 mg, 1.0 equiv) and purification by flash column chromatography (EtOAc/hexanes) afforded compound **16d** (58 mg, 51% yield).

Compound **16d**: Colourless solid, mp 159–160 ºC (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3215, 3138, 3028,

2996, 2870, 1612-1422, 1350, 774 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.41 (s, 1H), 8.03 (t, 1H, $J$ = 5.8 Hz), 7.86 (s, 1H), 7.33 (d, 4H, $J$ = 4.4 Hz), 7.24 (dq, 1H, $J$ = 8.5 Hz, 4.2 Hz), 7.10 (ad, 1H), 6.83 (brs, 1H), 6.65-6.64 (m, 1H), 4.58 (brs, 2H) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 162.6, 158.5, 151.9, 144.9, 139.4, 128.3, 127.2, 126.8, 112.2, 110.6, 98.2, 43.4 ppm; HRMS (EI) calcd for $C_{15}H_{13}N_3O$ [M] 251.1059, found 251.1066.

***N*-Benzyl-6-(quinolin-3-yl)pyrimidin-4-amine (16e):** Following the General Porcedure (Method A), using *N*-benzyl-6-chloropyrimidin-4-amine (100 mg, 0.455 mmol, 1.0 equiv) and 3-quinolinylboronic acid (102 mg, 0.592 mmol) and purification by flash column chromatography (60% EtOAc/hexanes) afforded compound **16e** (109 mg, 77 % yield).

Following the General Porcedure (Method B), using *N*-benzyl-6-chloropyrimidin-4-amine (100 mg, 1.0 equiv) and 3-quinolinylboronic acid (79 mg, 1.0) and purification by flash column chromatography (EtOAc/hexanes) afforded compound **16e** (64 mg, 45% yield).

Compound **16e**: Colourless solid, mp 99–100 ºC (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3246, 3204, 3029, 2979, 2917, 1595, 1453, 750 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.48 (s, 1H), 8.96 (s, 1H), 8.60 (s, 1H), 8.13-8.06 (m, 3H), 7.83-7.79 (m, 1H), 7.66 (t, 1H, $J$ =7.4 Hz), 7.37-7.32 (m, 4H), 7.24 (t, 2H, $J$ = 7.0 Hz), 4.64 (d, 2 H, $J$ = 5.7 Hz) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 158.7, 148.5, 148.1, 139.3, 133.4, 131.5, 131.4, 130.5, 129.9, 129.0, 128.8, 128.7, 128.3, 127.3, 127.20, 127.16, 126.8, 43.5 ppm; HRMS (EI) calcd for $C_{20}H_{16}N_4$ [M] 312.1375, found 312.1368.

***N*-Benzyl-6-(1H-indol-5-yl)pyrimidin-4-amine (16f):** Following the General Procedure (Method A), using *N*-benzyl-6-chloropyrimidin-4-amine (100 mg, 0.455 mmol, 1.0 equiv) and 1*H*-indol-5-ylboronic acid (96 mg, 0.592 mmol, 1.3 equiv) and purification by flash column chromatography (60–70% EtOAc/hexanes) afforded compound **16f** (123 mg, 90% yield).

Following the General Porcedure (Method B), using *N*-benzyl-6-chloropyrimidin-4-amine (100 mg, 1.0 equiv) and 1*H*-indol-5-ylboronic acid (74 mg, 1.0 equiv) and purification by flash column chromatography (EtOAc/hexanes) afforded compound **16f** (65 mg, 48% yield).

Compound **16f**: Colorless solid, mp 222–224 ºC (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3236, 3029, 2925, 1594, 1420, 741 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.29 (s, 1H), 8.51 (s, 1H), 8.29 (s, 1H), 7.83-7.78 (m, 2H), 7.49 (d, 1H, $J$ = 8.5 Hz), 7.41-7.32 (m, 4H), 7.24 (t, 1H, $J$ = 6.9 Hz), 7.02 (s, 1H), 6.55 (s, 1H), 4.62 (d, 2H, $J$ = 5.4 Hz); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 163.0, 161.7, 158.2, 139.7, 137.1, 128.3, 128.2, 127.8, 127.2, 126.8, 126.4, 119.7, 118.8, 111.5, 102.1, 99.6, 43.6 ppm; HRMS (EI) calcd for $C_{19}H_{16}N_4$ [M] 300.1375, found 300.1382.

***N*-Benzyl-6-(1-methyl-1H-pyrazol-4-yl)pyrimidin-4-amine (16g):** Following the General Porcedure (Method A), using *N*-benzyl-6-chloropyrimidin-4-amine (100 mg, 0.455 mmol, 1.0 equiv) and

1-methyl-1*H*-pyrazole-4-boronic acid pinacol ester (123 mg, 0.592 mmol, 1.3 equiv) and purification by flash column chromatography (10% MeOH/EtOAc) afforded compound **16g** (109 mg, 90% yield).

Following the General Porcedure (Method B), using *N*-benzyl-6-chloropyrimidin-4-amine (100 mg, 1.0 equiv) and 1-methyl-1*H*-pyrazole-4-boronic acid pinacol ester (95 mg, 1.0 equiv) and purification by flash column chromatography (MeOH/EtOAc) afforded compound **16g** (74 mg, 61% yield).

Compound **16g**: colourless solid, mp 155–156 °C (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3244, 3106, 3028, 2927, 2855, 1597-1413, 1205, 982 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.46 (s, 1H), 7.91-7.87 (m, 2H), 7.42-7.27 (m, 5H), 6.42 (s, 1H), 5.76 (br s, 1H), 4.57 (s, 2H), 3.91 (s, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 162.8, 158.5, 157.4, 137.9, 137.0, 129.9, 128.9, 127.8, 127.5, 122.1, 76.5, 45.6, 39.3 ppm; HRMS (EI) calcd for $C_{15}H_{15}N_5$ [M] 265.1327, found 265.1322.

**4-(4-Methoxyphenyl)-6-(thienyl-3-yl)pyrimidine (16h):** Following the General Porcedure (Method A), using 4-chloro-6-(4-methoxyphenyl)-2-methylpyrimidine (600 mg, 1.0 equiv) and 3-thienylboronic acid (426 mg, 1.3 equiv), and the resulting mixture was purified by flash chromatography (5→15% EtOAc/hexanes) to afford the product **16h** (700 mg, 97 % yield) as a pale-yellow solid, mp 104-106 °C (EtOAc:hexanes); FT-IR (neat) $\nu_{max}$ 3108, 2836, 1607, 1580, 1512, 1253, 1174, 834 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 8.14 (d, $J$ = 3 Hz, 1H), 8.08 (d, $J$ = 8.8 Hz, 2H), 7.73 (d, $J$ = 5.1 Hz, 1H), 7.66 (s, 1H), 7.43 (dd, $J$ = 5.0 Hz, 3.0 Hz, 1H), 7.02 (d, 8.8 Hz, 2H), 3.87 (s, 3H), 2.80 (s, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 168.6, 164.4, 161.9, 160.3, 140.9, 130.0, 128.88, 126.8, 126.4, 126.2, 114.4, 108.9, 55.5, 26.6 ppm; HRMS (EI) calcd for $C_{16}H_{14}N_2OS$ [M] 282.0827, found 282.0820.

**5-(6-(4-Methoxyphenyl)-2-methylpyrimidin-4-yl)-1*H*-indole (16i):** Following the General Porcedure (Method A), using 4-chloro-6-(4-methoxyphenyl)-2-methylpyrimidine (175 mg, 1.0 equiv) and 5-indolylboronic acid (156 mg, 1.3 equiv), and the resulting mixture was purified by flash chromatography (40% EtOAc/hexanes) to afford the product **16i** (232 mg, 98% yield) as a pale-yellow solid, mp 244–245 °C (EtOAc:hexane); FT-IR (neat) $\nu_{max}$ 3200, 3180, 3000, 2850, 1606, 1574, 1511, 1239, 1173 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 11.36 (s, 1H), 8.63 (s, 1H), 8.33-8.30 (m, 3H), 8.13 (dd, $J$ = 8.6 Hz, 1.3 Hz, 1H), 7.53 (d, $J$ = 8.6 Hz, 1H), 7.45 (m, 1H), 7.09 (d, $J$ = 8.8 Hz, 2H), 6.59 (s, 1H), 3.85 (s, 3H), 2.71 (s, 3H) ppm; $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 167.1, 165.0, 162.9, 161.4, 137.6, 129.2, 128.8, 127.9, 127.6, 126.6, 120.5, 119.9, 114.1, 111.6, 107.8, 102.3, 55.3, 26.3 ppm; HRMS (EI) calcd for $C_{20}H_{17}N_3O$ [M] 315.1372, found 315.1379.

**4-(4-Methoxyphenyl)-2-methyl-6-(pyridin-3-yl)pyrimidine (16j):** Following the General Porcedure (Method A), using 4-chloro-6-(4-methoxyphenyl)-2-methylpyrimidine (175 mg, 0.748 mmol) and 3-pyridineboronic acid (120 mg, 0.972 mmol) and purification by flash column chromatography (60% EtOAc/hexanes) afforded compound **16j** (179 mg, 86% yield) as a beige solid, mp 165–166 °C

(EtOAc:hexane); FT-IR (neat) $\nu_{max}$ 3155, 3005, 2919, 2839, 1610, 14121, 1248, 1029 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 9.28 (d, 1H, $J$ = 1.7 Hz), 8.72 (dd, 1H, $J$ = 4.8 Hz, 1.5 Hz), 8.42 (dt, 1H, $J$ = 8.0 Hz, 1.9 Hz), 8.11 (d, 2H, $J$ = 8.9 Hz), 7.82 (s, 1H), 7.44 (dd, 1H, $J$ = 7.9 Hz, 4.8 Hz), 7.02 (d, 2H, 8.9 Hz), 3.87 (s, 3H), 2.83 (s, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 168.9, 164.7, 162.2, 162.1, 151.4, 148.7, 134.8, 133.4, 129.5, 128.9, 123.8, 114.5, 109.2, 55.6, 26.6 ppm; HRMS (EI) calcd for $C_{17}H_{15}N_3O$ [M] 277.1215, found 277.1221.

**General Procedure for Hydrodechlorination Reaction of 6-Chloropyrimidines (9a-j):** A round bottom flask was evacuated, backfilled with argon and then charged sequentially with Pd/C (80 mg, 5 wt% on activated carbon), EtOH (4 mL), $Et_3N$ (1.1 equiv) and chloropyrimidine **9a-j** (200 mg, 1.0 equiv). The reaction vessel was evacuated and backfilled with hydrogen thrice and the reaction mixture was stirred for 4 h under hydrogen atmosphere at rt before passing through a pad of Celite followed by a wash with $CH_2Cl_2$. The filtrate was evaporated and the crude reaction mixture was purified by column chromatography on silica gel using EtOAc/hexanes as eluent to afford compounds **17a-j.**

**2-Methyl-4-phenylpyrimidine (17a):** Following the General Procedure and purification method, using the chloropyrimidine **9a** (1.8 g, 1.0 equiv), Pd/C (760 mg, 5 wt% on activated carbon) and $Et_3N$ (1.42 mL, 1.1 equiv) in EtOH (25 mL) afforded compound **17a** (1.33 g, 88% yield) as a colorless solid, mp 54–55 $^oC$ (EtOAc/hexanes) (lit[24] mp 55–56 $^oC$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.65 (d, $J$ = 5.3Hz, 1H), 8.08-8.06 (m, 2H), 7.50-7.48 (m, 4H), 2.80 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 168.4, 164.1, 157.5, 136.9, 130.8, 128.9, 127.2, 113.9, 26.3 ppm. The physical and spectral data were consistent with those reported.[24]

**2-Methyl-4-(2-methylphenyl)pyrimidine (17b):** Following the General Procedure and purification method, using the chloropyrimidine **9b** (200 mg, 1.1 equiv) afforded compound **17b** (146 mg, 87% yield) as a colorless oil; FT-IR (neat) $\nu_{max}$ 3099, 3022, 2961, 2858, 1604, 1392, 754 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.66 (d, $J$ = 5.2 Hz, 1H), 7.43-7.40 (m, 1H), 7.35-7.26 (m, 3H), 7.20 (d, $J$ = 5.2 Hz, 1H), 2.79 (s, 3H), 2.40 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 167.9, 167.2, 156.8, 137.9, 135.9, 131.1, 129.4, 129.3, 126.1, 117.9, 26.3, 20.3 ppm; HRMS (EI) calcd for $C_{12}H_{12}N_2$ [M] 184.1000, found 184.1006.

**2-Methyl-4-(3-methylphenyl)pyrimidine (17c) and 2-methyl-4,6-bis(3-methylphenyl)pyrimidine (8c):** Following the General Procedure and purification method, using the chloropyrimidine mixture (2.293 g, **9c**:**8c** = 79:21, by GCMS), Pd/C (876 mg, 5 wt% on activated carbon) and $Et_3N$ (1.63 mL, 1.1 equiv) in EtOH (25 mL) afforded compound **9c** (1.43 g, >95% yield) and compound **8c** (175 mg).

Compound **17c**: pale yellow oil; FT-IR (neat) $\nu_{max}$ 3035, 2922, 1572, 1548, 1435, 1312 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.61 (d, $J$ = 5.3 Hz, 1H), 7.89 (s, 1H), 7.81 (d, $J$ = 7.7 Hz, 1H), 7.43 (d, $J$ = 5.3

Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 2.79 (s, 3H), 2.42 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 168.3, 164.5, 157.3, 138.6, 136.9, 131.6, 128.8, 127.8, 124.3, 113.9, 26.3, 21.5 ppm; HRMS (EI) calcd for $C_{12}H_{12}N_2$ [M] 184.1000, found 184.1009.

Compound **8c**: Pale yellow solid, mp 65–67 °C (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3038, 2922, 1571, 1534, 1487, 793 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.95 (s, 2H), 7.89 (d, *J* = 7.7 Hz, 2H), 7.85 (s, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.31 (d, *J* = 7.7 Hz, 2H), 2.87 (s, 3H), 2.46 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 168.5, 164.9, 138.7, 137.5, 131.4, 128.8, 127.9, 124.4, 110.2, 26.6, 21.6 ppm; HRMS (EI) calcd for $C_{19}H_{18}N_2$ [M] 274.1470, found 274.1481.

**4-(4-Methoxyphenyl)-2-methylpyrimidine (17d):** Following the General Procedure and purification method, using the chloropyrimidine **9d** (2.0 g, 1.0 equiv), Pd/C (760 mg, 5 wt% on activated carbon) and $Et_3N$ (1.31 mL, 1.1 equiv) in EtOH (25 mL) afforded compound **17d** (1.53 g, 89% yield) as a colorless solid, mp 109–111 °C (EtOAc/hexanes) (lit[25] mp 110–112 °C); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.58 (d, *J* = 5.4 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 5.4 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 2.77 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 168.2, 163.5, 161.9, 157.1, 129.3, 128.7, 114.3, 113.0, 55.4, 26.3 ppm. The physical and spectral data were consistent with those previously reported.[25]

**4-(3-Methoxyphenyl)-2-methylpyrimidine (17e):** Following the General Procedure and purification method, using the chloropyrimidine **9e** (2.16 g, 1.0 equiv), Pd/C (750 mg, 5 wt% on activated carbon) and $Et_3N$ (1.41 mL, 1.1 equiv) in EtOH (25 mL) afforded compound **17e** (1.81 g, 98% yield) as a colorless solid, mp 33–35 °C (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3075, 3029, 2958, 2835, 1601, 1390, 1180 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.66 (d, *J* = 5.4 Hz, 1H), 7.67-7.65 (m, 1H), 7.63-7.60 (m, 1H), 7.49 (d, *J* = 5.4 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.06-7.03 (m, 1H), 3.90 (s, 3H), 2.80 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 168.3, 163.7, 160.1, 157.4, 138.3, 129.9, 119.5, 116.7, 114.0, 112.3, 55.4, 26.3 ppm; HRMS (EI) calcd for $C_{12}H_{12}N_2O$ [M] 200.0950, found 200.0941.

**4-(3-Methoxyphenyl)pyrimidine (17f):** Following the General Procedure and purification method, using the chloropyrimidine **9f** (1.5 g, 1.0 equiv), Pd/C (550 mg, 5 wt% on activated carbon) and $Et_3N$ (1.04 mL, 1.1 equiv) in EtOH (25 mL) afforded compound **17f** (1.24 g, 98% yield) as a colorless oil; FT-IR (neat) $\nu_{max}$ 3077, 3005, 2957, 2835, 1601, 1428, 1386, 1230, 770 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.26 (d, *J* = 1.4 Hz, 1H), 8.75 (d, *J* = 5.3 Hz, 1H), 7.71-7.68 (m, 2H), 7.64-7.61 (m, 1H), 7.42 (t, *J* = 8 Hz, 1H), 7.08-7.04 (m, 1H), 3.90 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 163.7, 160.2, 159.1, 157.5, 137.9, 130.0, 119.5, 117.2, 117.1, 112.1, 55.4 ppm; HRMS (EI) calcd for $C_{11}H_{10}N_2O$ [M] 186.0793, found 186.0799. The physical and spectral data were consistent with those reported.[26]

**4-(4-Fluorophenyl)-2-methylpyrimidine (17g) and 4,6-bis(4-fluorophenyl)-2-methylpyrimidine (8g):** Following the General Procedure and purification method, using the chloropyrimidine mixture (2.0 g,

**9g**:**8g** = 91:9, by GCMS) afforded compound **17g** (1.43 g, 93% yield) and compound **8g** (175 mg).

Compound **17g**: pale yellow solid, mp 69–70 ºC (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3119, 2933, 1600, 1548, 1441, 1232, 1168, 837 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.64 (d, $J$ = 5.4 Hz, 1H), 8.10-8.05 (m, 2H), 7.43 (d, $J$ = 5.4 Hz, 1H), 7.19-7.14 (m, 2H), 2.78 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 168.4, 164.5 (d, $J$ = 249 Hz), 162.8, 157.5, 133.0 (d, $J$ = 3 Hz), 129.1 (d, $J$ = 9 Hz), 115.9 (d, $J$ = 21 Hz), 113.5, 26.3 ppm; HRMS (EI) calcd for $C_{11}H_9FN_2$ [M] 188.0750, found 188.0741.

Compound **8g**: pale yellow solid, mp 153.1–154.1 ºC (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3074, 3045, 1600, 1580, 1507, 1227, 847 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.15-8.10 (m, 4H), 7.78 (s, 1H), 7.23-7.17 (m, 4H), 2.83 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 168.6, 164.5 (d, $J$ = 249.5 Hz), 163.8, 133.5 (d, $J$ = 3.3 Hz), 129.3 (d, $J$ = 8.7 Hz), 116.0 (d, $J$ = 21.6 Hz), 109.2, 26.5 ppm; HRMS (EI) calcd for $C_{17}H_{12}F_2N_2$ [M] 282.0969, found 282.0961.

**4-(3-Fluorophenyl)-2-methylpyrimidine (17h) and 4,6-bis(3-fluorophenyl)-2-methylpyrimidine (8h):** Following the General Procedure and purification method, using the chloropyrimidine mixture (2.3 g, **9h**:**8h** = 73:27, by GCMS), Pd/C (600 mg, 5 wt% on activated carbon) and $Et_3N$ (1.16 mL, 1.1 equiv) in EtOH (25 mL) afforded compound **17h** (1.39 g, 97% yield) and compound **8h** (490 mg).

Compound **17h**: colorless solid, mp 67–69 ºC (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3129, 3019, 2998, 2916, 1613, 1435, 1203, 768 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.68 (d, $J$ = 5.3 Hz, 1H), 7.84-7.81 (m, 2H), 7.49-7.44 (m, 2H), 7.22-7.17 (m, 1H), 2.80 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 168.6, 164.3 (d, $J$ = 245 Hz), 162.6, 157.7, 139.3 (d, $J$ = 8 Hz), 130.5 (d, $J$ = 8 Hz), 122.7 (d, $J$ = 3 Hz), 117.7 (d, $J$ = 21 Hz), 114.2 (d, $J$ = 23 Hz), 113.9, 26.3 ppm; HRMS (EI) calcd for $C_{11}H_9FN_2$ [M] 188.0750, found 188.0742.

Compound **8h**: colorless solid, mp 150–152 ºC (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3135, 3005, 2972, 2856, 1613, 1452, 1260, 762 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.89-7.82 (m, 5H), 7.51-7.46 (m, 2H), 7.23-7.18 (m, 2H), 2.86 (s, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 168.9, 163.8, 163.3 (d, $J$ = 245 Hz), 162.1, 139.6 (d, $J$ = 8 Hz), 130.5 (d, $J$ = 8 Hz), 122.8 (d, $J$ = 3 Hz), 117.7 (d, $J$ = 21 Hz), 114.3 (d, $J$ = 23 Hz), 109.9, 26.4 ppm; HRMS (EI) calcd for $C_{17}H_{12}F_2N_2$ [M] 282.0969, found 282.0958.

**2-Methyl-4-(3,4,5-trimethoxyphenyl)pyrimidine (17j):** Following the General Procedure and purification method, using the chloropyrimidine **9j** (2.5 g, 1.0 equiv), Pd/C (700 mg, 5 wt% on activated carbon) and $Et_3N$ (1.3 mL, 1.1 equiv) in EtOH (25 mL) afforded compound **17j** (2.06 g, 93% yield) as a colorless solid, mp 94–96 ºC (EtOAc/hexanes); FT-IR (neat) $\nu_{max}$ 3075, 2996, 2957, 2835, 1590, 1427, 1341, 1125, 767 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.64 (d, $J$ = 1.3 Hz, 1H), 7.45 (d, $J$ = 1.3 Hz, 1H), 7.33 (s, 2H), 3.97 (s, 6H), 3.92 (s, 3H), 2.80 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 168.3,

163.5, 157.4, 153.6, 140.6, 132.3, 113.6, 104.4, 60.9, 56.3, 26.3 ppm; HRMS (EI) calcd for $C_{14}H_{16}N_2O_3$ [M] 260.1161, found 260.1170.

**ACKNOWLEDGEMENTS**

We are grateful for support of this work by an NSERC CRD grant.

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