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Suzuki–Miyaura cross-coupling reaction of aryl and heteroaryl pinacol boronates for the synthesis of 2-substituted pyrimidines

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ABSTRACT

Suzuki–Miyaura cross-coupling reaction with 2-heteroarylboronic acids is generally challenging due to these acids easy decomposition. To overcome this problem, we developed a coupling method that uses 2-heteroaryl pinacol boronates in the presence of 1.0 mol % $Pd(OAc)_2$ and 2.0 mol % S-Phos with 4 equiv amount of LiOH in dioxane and H_2O at 80 °C for 30 min. This developed method allowed for the synthesis of a wide variety of 2-heteroaryl pyrimidines from 2-chloropyrimidyl derivatives in high yields, and is also useful in the preparation of various biaryl derivatives from heteroaryl chlorides.

1. Introduction

2-Aryl or 2-heteroaryl pyrimidines and their derivatives have recently been reported as inhibitors of tubulin polymerization,[1] class 1 phosphatidylinositide 3-kinases (PI3K),[2] checkpoint kinase 2 (CHK2),[3] and activin like kinase 5 (ALK5),[4] and as activators of cell type-specific NF-kB (Fig. 1).[5] The synthesis of these compounds via transition metal-catalyzed cross-coupling reaction provides an interesting challenge in medicinal chemistry, as it allows a single common intermediate to be diversified into a large number of related products. However, cross-coupling reaction of heteroaryl chlorides, including 2-chloropyrimidyl derivatives, is generally considered to be difficult,[6] because these substrates cannot only bind to the catalyst metal center and deactivate the catalytic activity,[7] but also react with the solvent by S_NAr-mechanism instead of the slower cross-coupling reaction.[8] Hence, practical methods that allow efficient cross-coupling reaction of heteroaryl chlorides are needed.

Suzuki–Miyaura cross-coupling reaction is arguably the most important and widely used method for construction of sp^2–sp^2 carbon–carbon bonds.[9] Recent pioneering advances in the development of efficient catalysts have significantly extended the scope of this reaction with various functionalized boronic acids.[10,11] Especially, problematic cross-coupling reactions with 2-heteroarylboronic acids, which are easily decomposed via protodeboronation, oxidation, and/or polymerization,[12] have been improved by two new methods: one is the use of palladium precatalyst,[13] and the other is masking of boronic acids to stabilize them as MIDA boronates,[14] trifluoroborate salts,[15] or cyclic triboronates.[16]

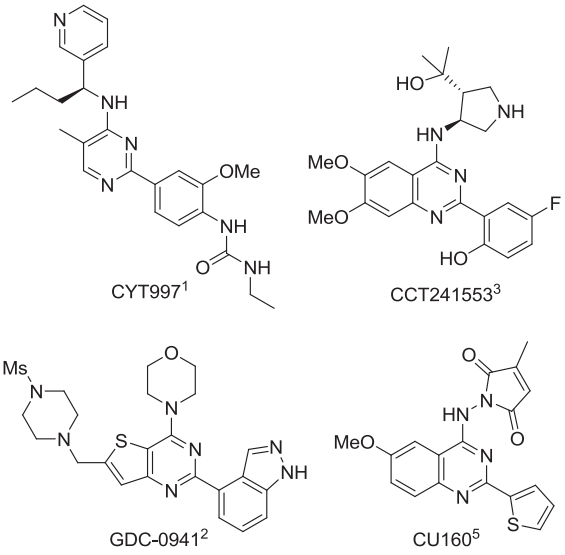

Fig. 1. Representative drug candidates of 2-aryl or 2-heteroaryl pyrimidines.

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Several approaches to the construction of various 2-aryl or 2-heteroaryl pyrimidines using Suzuki–Miyaura cross-coupling reaction with boronic acids or trifluoroborate salts have been reported.[7a,8,10c,12b,d,f,g,14] Some of these approaches focused on the use of a combination of *tert*-amyl alcohol and molecular sieves or an aqueous two-phase system in the presence of a weak base to suppress both side reactions, i.e., (1) S_NAr-reaction at the second position of the pyrimidine ring and (2) homocoupling reaction of the boronic acids.[17] However, the versatile coupling reactions with 2-chloropyrimidyl derivatives have not sufficiently been explored, even though a methodology for pharmaco-modulation of 2-functionalized pyrimidines is required. Therefore, to establish a more effective method for the synthesis of 2-aryl or 2-heteroaryl pyrimidines, we focused on stable boronates, such as MIDA boronates and trifluoroborate salts, because stable boronates would undergo minimal decomposition derived from homocoupling reaction and protodeboronation, leading to reaction completion. In the case of MIDA boronates, the challenging cross-coupling reaction with 2-heteroaryl, vinyl, and cyclopropyl MIDA boronates was considered feasible. As for the trifluoroboronate salts, they were seen as able to install heterocyclic building blocks, including the five-membered 2-heteroaryl ones, onto the aryl or heteroaryl chlorides. However, MIDA boronates and trifluoroborate salts have to be prepared from free boronic acids or boronic esters,[18,19] requiring long reaction time and/or high palladium loading for efficient coupling reaction.

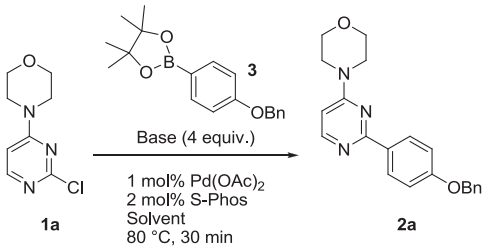
Considering these drawbacks, we turned our attention to the stable pinacol boronates as attractive building blocks. Pinacol boronates are not only commercially available, but can also be readily prepared by several established methods, such as alkylation of $B(OR)_3$ with aromatic lithium or magnesium reagents.[20] In particular, preparation of pinacol boronates using palladium catalyzed cross-coupling reaction[21] or transition metal-catalyzed direct C–H borylation[22] has great advantage over the use of other stable boronates. Therefore, we undertook a detailed examination of Suzuki–Miyaura cross-coupling using the convenient pinacol boronates. Actually, we examined various bases in aqueous condition to obtain reaction conditions that would suppress the undesired S_NAr-reaction. After selection of appropriate bases and optimization of the reaction conditions, we could drive the reaction to completion with high yield. This new method could be applied to the synthesis of various biaryl derivatives, including five-membered 2-heteroaryl and other heteroaryl structures. Moreover, the use of this new method allows us to overcome the problem of high palladium loading and long reaction time. Herein, we describe Suzuki–Miyaura cross-coupling reaction of heteroaryl chlorides with aryl or heteroaryl pinacol boronates, including the challenging five-membered 2-heteroaryl ones, for pharmaco-modulation of 2-aryl or 2-heteroaryl pyrimidines and their derivatives.

2. Results/discussion

Based on the reported aqueous reaction conditions,[14] we examined various bases in the presence of 1.0 mol % $Pd(OAc)_2$ and 2.0 mol % S-Phos in dioxane and H_2O at 80 °C for 30 min under N_2 (Table 1). As for the substrates for this coupling reaction, 4-morpholino-2-chloropyrimidine **1a** and 4-benzyloxyphenyl pinacol boronate **3** were used, because they are fundamental structures of the representative drug candidates CYT997[1] and CCT241553[3] illustrated in Fig. 1.

First, we used K_3PO_4[7a,13,14] as a base, since it is often used for Suzuki–Miyaura cross-coupling reaction. The reaction did not proceed to completion, and the isolated yield was insufficient (34%, entry 1) due to slow reaction rate. To find an appropriate base, we examined various weak bases, such as Li_2CO_3, Na_2CO_3,[12d,15c] K_2CO_3,[8,15a,b] Cs_2CO_3, CsF, KOAc, and Et_3N (Table 1). The results

Table 1
Effects of various bases and solvents on $Pd(OAc)_2$/S-Phos-catalyzed cross-coupling reaction[a]



Entry	Base	Solvent (v/v)	Yield (%)
1	K_3PO_4	Dioxane–H_2O (4:1)	34
2	Li_2CO_3	Dioxane–H_2O (4:1)	5
3	Na_2CO_3	Dioxane–H_2O (4:1)	22
4	K_2CO_3	Dioxane–H_2O (4:1)	41
5	Cs_2CO_3	Dioxane–H_2O (4:1)	46
6	CsF	Dioxane–H_2O (4:1)	9
7	KOAc	Dioxane–H_2O (4:1)	Trace
8	Et_3N	Dioxane–H_2O (4:1)	Trace
9	LiOH	Dioxane–H_2O (4:1)	99
10	NaOH	Dioxane–H_2O (4:1)	97
11	KOH	Dioxane–H_2O (4:1)	76
12	$Ca(OH)_2$	Dioxane–H_2O (4:1)	54
13	$Ba(OH)_2$	Dioxane–H_2O (4:1)	78
14	LiOH	Toluene–H_2O (4:1)	26
15	LiOH	*n*-Butanol–H_2O (4:1)	39
16	LiOH	DMF–H_2O (4:1)	87
17	LiOH	Dioxane	0
18	LiOH (1 equiv)	Dioxane–H_2O (4:1)	61
19	LiOH (2 equiv)	Dioxane–H_2O (4:1)	84
20	LiOH (3 equiv)	Dioxane–H_2O (4:1)	93

[a] 4-Morpholino-2-chloropyrimidine **1a** (1.0 equiv), pinacol boronate **3** (1.2 equiv), $Pd(OAc)_2$ (1 mol %), S-Phos (2 mol %), base (4 equiv), solvent (0.1 mM), 80 °C, 30 min; isolated yields, n=1.

were similar to that obtained with K_3PO_4, i.e., poor to moderate isolated yields (trace–46%, entries 2–8). Among the investigated bases (entries 1–8), Cs_2CO_3, which is considered to be the strongest base, was somehow better than the other bases. This finding indicated that the strength of the base might be important for this cross-coupling reaction. Based on this speculation, various metal hydroxides were examined.

As expected, LiOH[23] (99%, entry 9) and NaOH (97%, entry 10) effectively led to the desired coupling product **2a**, which was quantitatively produced within 30 min in excellent yield without S_NAr-reaction of the 2-chloropyrimidine **1a**[7,8] (see Supplementary data, Fig. S1). In the case of KOH (76%, entry 11), the yield was slightly less than that obtained with LiOH or NaOH, with occurrence of S_NAr-reaction of **1a**, probably due to KOH strong nucleophilicity. On the other hand, the reaction with $Ca(OH)_2$ (54%, entry 12) or $Ba(OH)_2$ (78%, entry 13), both of which are much milder bases than the alkali metal hydroxides, did not proceed to completion within 30 min despite suppression of the side reaction. Although the reaction was left to proceed for 2 h, the 2-chloropyrimidine **1a** was not completely consumed, giving the desire coupling product **2a** in almost the same yield [$Ca(OH)_2$: 71%, $Ba(OH)_2$: 73%]. These results indicate that the basicity and nucleophilicity of LiOH and NaOH not only promote the cross-coupling reaction, but also induce no side reactions, such as S_NAr-reaction of **1a** and homocoupling reaction of **3**.

As for the reaction solvent, it was investigated in the presence of LiOH, because LiOH is a much milder base than NaOH, and hence has advantages regarding suppression of S_NAr-reaction. The reaction using 1.0 mol % $Pd(OAc)_2$ and 2.0 mol % S-Phos with 4 equiv amount of LiOH in toluene and H_2O at 80 °C for 30 min did not proceed to completion, and the isolated yield was insufficient (26%, entry 14). Similarly, the use of *n*-butanol–H_2O led to the desired coupling product **2a** in low yield (39%, entry 15) due to S_NAr-

reaction of **1a** with *n*-butanol. In the case of DMF–H_2O, the yield was slightly less than that obtained with dioxane–H_2O, again due to occurrence of S_NAr-reaction of **1a** (87%, entry 16). Based on these findings, we concluded that dioxane–H_2O is the best solvent for this cross-coupling reaction. Next, to confirm the importance of H_2O[24] as a co-solvent, we conducted the reaction under anhydrous conditions[25] using 1 mol % $Pd(OAc)_2$ and 2 mol % S-Phos as a catalyst with 4 equiv amount of LiOH as a base in dioxane for 30 min. Surprisingly, the reaction in absence of H_2O did not produce to the desired product (0%, entry 17). From this result, we concluded that H_2O as a co-solvent is required for smooth progression of this coupling reaction.

Regarding the reaction temperature, we understood that 80 °C is necessary for smooth coupling reaction because the reaction did not proceed to completion at room temperature (7%) and even at 50 °C (29%).

Finally, we tried to optimize the reaction equivalent of LiOH. In the presence of 1 equiv amount of LiOH, the coupling product was obtained in moderate yield (61%, entry 18). When 2 or 3 equiv amount of LiOH was used, the 2-chloropyrimidine **1a** was not completely consumed, although the desired product was obtained in good to excellent yield (entry 19: 84%, entry 20: 93%). Taken together, these findings indicate that 1.0 mol % $Pd(OAc)_2$ and 2.0 mol % S-Phos with 4 equiv amount of LiOH in dioxane and H_2O at 80 °C for 30 min represent the ideal conditions for synthesis of 2-aryl pyrimidine derivatives by Suzuki–Miyaura cross-coupling reaction in a short time under low palladium loading.

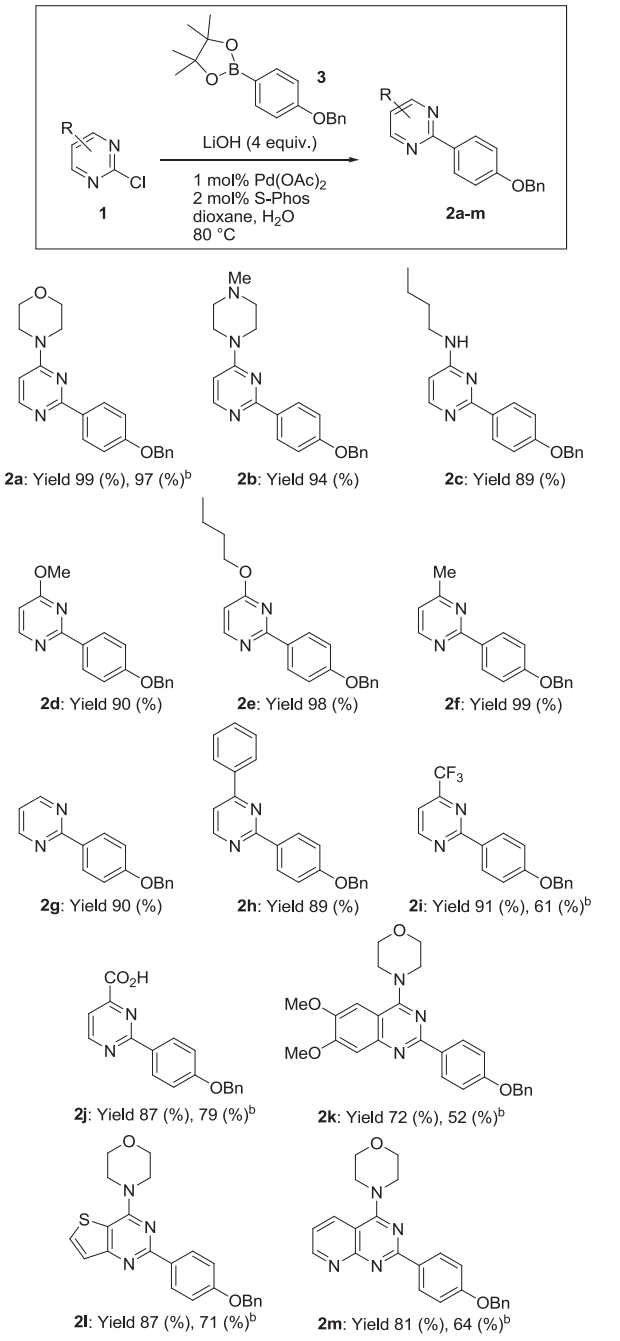
To examine the limitations of the selected conditions for Suzuki–Miyaura cross-coupling reaction, we used C4-substituted 2-chloropyrimidines or fused 2-chloropyrimidines, such as quinazoline, thieno[3,2-*d*]pyrimidine, and pyrido[2,3-*d*]pyrimidine as building blocks (Table 2). All reactions progressed smoothly with excellent yields (**2a**–**h**, 89–99%) in pyrimidines, which—like **1a**—have an electron-donating group at the C4-position. Interestingly, the desired coupling products were obtained in good to excellent yields (**2i**; 91%, **2j**; 87%) with compounds having an electron-withdrawing substituent, such as CF_3 or COOH. In the case of fused pyrimidine chlorides, the coupling reaction led to acceptable yields (**2k**–**m**, 72–87%), even though trace amounts of the corresponding S_NAr products were observed. As the 2-chloropyrimidines and fused 2-chloropyrimidines could be converted to the desired coupling products within 30 min, we believe that our reaction conditions would be useful for drug discovery, since 2-aryl-4-substituted pyrimidines are important motifs for medicinal chemistry research.

Next, we carried out the cross-coupling reaction of C4-substituted 2-chloropyrimidines having an electron-withdrawing substituent or fused 2-chloropyrimidines in the presence of NaOH as a base. Surprisingly, NaOH, which is stronger base than LiOH, was somehow worse than LiOH due to occurrence of S_NAr-reaction of **1a** (**2i**; 61%, **2j**; 79%, **2k**; 52%, **2l**; 79%, **2m**; 64%). The use of C4-substituted 2-chloropyrimidine having an electron-donating substituent gave almost the same reaction yield (**2a**; 97%). From these findings, we concluded that LiOH is ideal not only for the developed cross-coupling reaction, but also for the synthesis of various 2-pyrimidyl derivatives.

As Suzuki–Miyaura cross-coupling reaction with heteroaryl boronates generally gives poor yield, we considered using our optimized conditions for coupling reaction with heteroaryl pinacol boronates **5**, such as indolyl, pyrrolyl, pyrazolyl, furanyl, and thiophenyl pinacol boronate. As shown in Table 3, Suzuki–Miyaura cross-coupling reaction with 4-morpholino-2-chloropyrimidine **1a** and heteroaryl boronates, such as indolyl boronate or 3-heteroaryl boronate, gave the corresponding desired products (**4a**–**e**) in good yields within 30 min, although about 70% of the Boc group in **4b** was deprotected. Encouraged by these results, we extended our work to the synthesis of the 2-heteroaryl pyrimidines **4** from the 4-morpholino-2-chloropyrimidine **1a** and the five-membered 2-heteroaryl pinacol boronates, which are more challenging than other pinacol boronates because of easy decomposition via protodeboration in polar-protic reaction media. Fortunately, the selected boronates produced the desired coupling products in excellent yields (**4f**–**l**, 91–99%) with no side reactions.

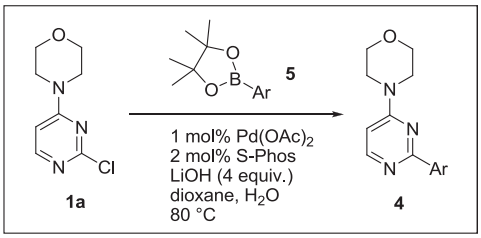
Next, we conducted the reaction with 2-furylboronic acid instead of the pinacol boronate **5** under the same reaction conditions.

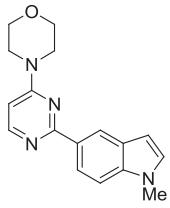
Table 2
Coupling of the 4-benzyloxyphenylboronic acid pinacol ester **3** to various 2-chloropyrimidines or fused 2-chloropyrimidines **1**[a]

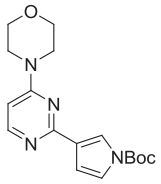


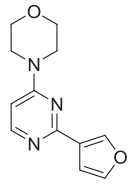
[a] 2-Chloropyrimidines **1** (1.0 equiv), pinacol boronate **3** (1.2 equiv), $Pd(OAc)_2$ (1 mol %), S-Phos (2 mol %), LiOH (4 equiv), dioxane–H_2O=4:1 (0.1 mM), 80 °C, 30 min; isolated yields, n=1.
[b] NaOH (4 equiv).

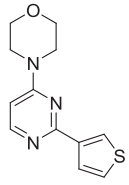
Table 3
Coupling of aryl or heteroaryl pinacol boronates **5** to the 4-morpholino-2-chloropyrimidine **1a**[a]

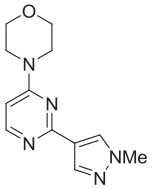


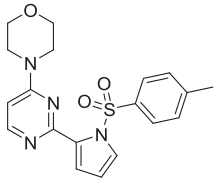

4a: Yield 86 (%)

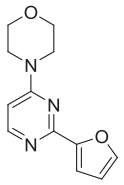

4b: Yield 23 (%)[b]

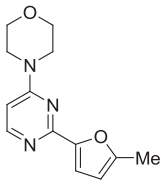

4c: Yield 95 (%)

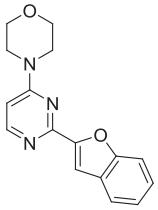

4d: Yield 94 (%)

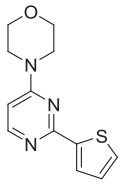

4e: Yield 80 (%)[c]

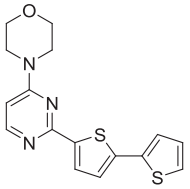

4f: Yield 99 (%)

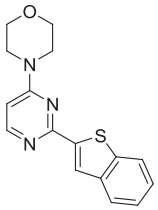

4g: Yield 91 (%)


4h: Yield 99 (%)


4i: Yield 91 (%)


4j: Yield 96 (%)


4k: Yield 99 (%)

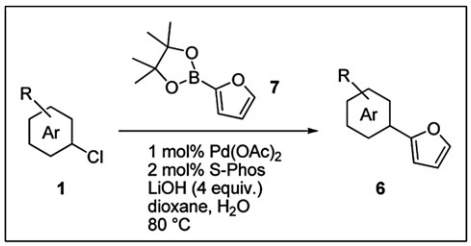

4l: Yield 93 (%)

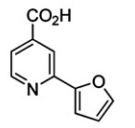
[a] 4-Morpholino-2-chloropyrimidine **1a** (1.0 equiv), pinacol boronate **5** (1.2 equiv), $Pd(OAc)_2$ (1 mol%), S-Phos (2 mol%), LiOH (4 equiv), dioxane–H_2O=4:1 (0.1 mM), 80 °C, 30 min; isolated yields, n=1.
[b] deBoc derivative was also isolated (yield=68%).
[c] 2 h.

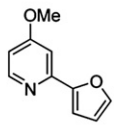
However, the target product **4g** was obtained in low yield (28%), indicating importance of the pinacol boronates. To understand these differences (pinacol boronate 91% vs boronic acid 28%), we evaluated the stability of the 2-furyl pinacol boronate and that of the 2-furylboronic acid under 4 equiv amount of LiOH in dioxane and H_2O at 80 °C. Interestingly, the 2-furyl pinacol boronate was gradually consumed over 30 min, whereas the 2-furylboronic acid was perfectly decomposed within 5 min (see Supplementary data, Fig. S2). These findings indicated the heteroaryl pinacol boronates were stable enough to provide the desired coupling products.

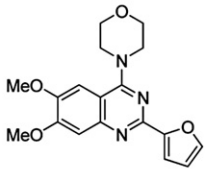
Heteroaryl chlorides **1**, such as 2-pyridine, 2-quinazoline, 2-thieno[3,2-*d*]pyrimidine, pyrido[2,3-*d*]pyrimidine, 2-quinoline, 2-quinoxaline, 2-furo[3,2-*c*]pyridine, and 2-thieno[3,2-*c*]pyridine chlorides, are attractive motifs in medicinal chemistry. Thus, we turned our attention to the scope and limitations of use of various heteroaryl chlorides. Suzuki–Miyaura cross-coupling reaction with the labile 2-furyl pinacol boronate **7** and a variety of heteroaryl chlorides was then investigated under our optimized conditions. As shown in Table 4, optimal reaction conditions were not limited to 2-heteroaryl chlorides and gave the corresponding coupling products in good to excellent yields within 30 min (**6a**–**i**, 74–99%).[26,27] Surprisingly, the challenging 2-furyl pinacol boronate **7** due to its instability could produce the corresponding coupling product (**6c**–**e**, 89–96%) more efficiently than the 4-benzyloxyphenyl pinacol boronate **3** (**2k**–**m**, 72–87%). Although a trace amount of the corresponding hydrolyzed product was observed in the 2-chloroquinoxaline **6g**, the developed method seems to have significant advantages in the production of biaryl compounds.

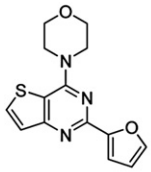
Table 4
Coupling of various heteroaryl chlorides **1** to the 2-furyl pinacol boronate **7**[a]

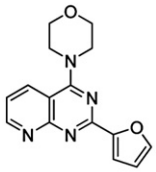


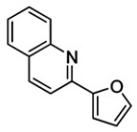

6a: Yield 99 (%)

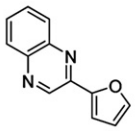

6b: Yield 86 (%)

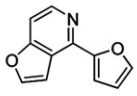

6c: Yield 89 (%)

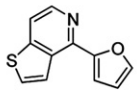

6d: Yield 96 (%)


6e: Yield 92 (%)


6f: Yield 95 (%)


6g: Yield 74 (%)


6h: Yield 96 (%)


6i: Yield 96 (%)

[a] Compound **1** (1.0 equiv), pinacol boronate **7** (1.2 equiv), $Pd(OAc)_2$ (1 mol%), S-Phos (2 mol%), LiOH (4 equiv), dioxane–H_2O=4:1 (0.1 mM), 80 °C, 30 min; isolated yields, n=1.

3. Conclusion

In summary, we succeeded in developing optimum conditions for Suzuki–Miyaura cross-coupling reaction of aryl or heteroaryl pinacol boronates, including the challenging five-membered 2-heteroaryl pinacol boronates, to construct 2-aryl or 2-heteroaryl pyrimidines from 2-chloropyrimidyl derivatives in high yields. These conditions, which are also useful in the preparation of

various biaryl derivatives from heteroaryl chlorides, allow for use of low palladium loading and short time coupling reaction. Other than providing efficient Suzuki–Miyaura cross-coupling reaction, the developed reaction protocol is very convenient in two aspects: (1) no anhydrous conditions are required; (2) a cheap base (LiOH) is used. Furthermore, the developed reaction protocol can easily be used at large scale. Further studies will focus on pharmaco-modulation of the 2-functionalized pyrimidines using the developed methodology.

4. Experimental section

4.1. General

Melting points were determined on a Stanford Research Systems *Opti Meit*. IR spectra were recorded on a JEOL *JIR-SPX60* spectrometer as ATR. NMR spectra were recorded on a JEOL *JNM-LA300* spectrometer. Chemical shifts are given in parts per million with tetramethylsilane used as internal standard for spectra obtained in DMSO-d_6, $CDCl_3$, and CD_3CN. All *J* values are given in hertz. High-resolution mass spectra (HRMS) were recorded on a Thermo Fisher Scientific LTQ orbitrap Discovery MS equipment. Reagents and solvents were used as obtained from commercial suppliers without further purification. Column chromatography was carried out using a Yamazen *W-prep* system, and performed using pre-packed silica-gel or amino silica-gel columns. Reaction progress was determined by TLC analysis on a silica-gel or amino silica-gel coated glass plate. Visualization was done with UV light (254 nm) or iodine. All reactions were carried out under a nitrogen atmosphere unless otherwise mentioned. UPLC was performed using a Waters *Acquity*™ system. The sample was dissolved in methanol solution, applied on a ACQUITY UPLC® BEH C18 column (2.1 mm×50 mm, 1.7 μm), and eluted at 1 mL/min with a 4 min gradient (from 10% B to 90% B: method A; from 50% B to 90% B: method B), where solvent A is water (0.1% TFA solution) and solvent B is methanol. The purity of all new compounds was determined by UPLC and was >95%.

4.2. General procedure for the synthesis of biaryl compounds

To a solution of 2-chloroheteroaryl compound **1** (0.50 mmol) in 1,4-dioxane (4.0 mL) were added pinacol boronate **3**, **5**, or **7** (0.60 mmol), $Pd(OAc)_2$ (1.1 mg, 5.0 μmol), S-Phos (4.1 mg, 10.0 μmol), and 2 M LiOH solution (1.0 mL, 2.0 mmol) at room temperature, and the mixture was stirred for 30 min at 80 °C under N_2 atmosphere. The reaction was quenched by adding water, and then the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed in vacuo, and the residue was purified by silica-gel column chromatography. The solvent was removed in vacuo, and the residue was triturated with Et_2O to give biaryl compounds.

*4.2.1. 4-(2-(4-(Benzyloxy)phenyl)pyrimidin-4-yl)morpholine (**2a**).* Yield=99% (white solid), mp 128–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.64 (m, 4H), 3.74 (m, 4H), 5.05 (s, 2H), 6.28 (d, *J*=6.2 Hz, 1H), 6.96 (d, *J*=8.8 Hz, 2H), 7.25–7.39 (m, 5H), 8.24 (d, *J*=6.2 Hz, 1H), 8.26 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 44.0, 69.9, 100.2, 114.5, 127.5, 128.0, 128.6, 129.6, 131.1, 136.7, 156.1, 160.1, 161.9, 163.3; IR (ATR): ν (cm^{-1}) 1589, 1566, 1544; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{22}N_3O_2$ $(M+H)^+$ 348.1707, found $(M+H)^+$ 348.1702 (Δ=−1.22 ppm); HPLC purity=99.4% (t_R=2.77 min, method A).

*4.2.2. 2-(4-(Benzyloxy)phenyl)-4-(4-methylpiperazin-1-yl)pyrimidine (**2b**).* Yield=94% (white solid), mp 94–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.33 (s, 3H), 2.48 (m, 4H), 3.73 (m, 4H), 5.10 (s, 2H), 6.34 (d, *J*=6.2 Hz, 1H), 7.01 (d, *J*=9.0 Hz, 2H), 7.30–7.44 (m, 5H), 8.26 (d, *J*=6.2 Hz, 1H), 8.32 (d, *J*=9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 43.6, 46.2, 54.6, 69.9, 100.3, 114.4, 127.5, 128.0, 128.6, 129.5, 131.3, 136.7, 156.1, 160.6, 161.6, 163.4; IR (ATR): ν (cm^{-1}) 1587, 1566, 1541; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{25}N_4O$ $(M+H)^+$ 361.2023, found $(M+H)^+$ 361.2022 (Δ=−0.22 ppm); HPLC purity=99.3% (t_R=2.05 min, method A).

*4.2.3. 2-(4-(Benzyloxy)phenyl)-N-butylpyrimidin-4-amine (**2c**).* Yield=89% (colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.86 (t, *J*=7.3 Hz, 3H), 1.33 (m, 2H), 1.48 (m, 2H), 3.24 (m, 2H), 5.02 (s, 2H), 6.06 (d, *J*=5.9 Hz, 1H), 6.94 (d, *J*=8.8 Hz, 2H), 7.23–7.37 (m, 5H), 8.15 (d, *J*=5.9 Hz, 1H), 8.24 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 13.8, 20.0, 31.3, 41.0, 69.9, 114.4, 114.5, 127.5, 127.9, 128.5, 129.5, 131.1, 136.7, 155.6, 160.5, 162.3, 163.6; IR (ATR): ν (cm^{-1}) 1589, 1570; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{24}N_3O$ $(M+H)^+$ 334.1914, found $(M+H)^+$ 334.1912 (Δ=−0.50 ppm); HPLC purity=99.9% (t_R=3.34 min, method A).

*4.2.4. 2-(4-(Benzyloxy)phenyl)-4-methoxypyrimidine (**2d**).* Yield=90% (white solid), mp 95–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.05 (s, 3H), 5.12 (s, 2H), 6.55 (d, *J*=5.9 Hz, 1H), 7.05 (d, *J*=9.0 Hz, 2H), 7.32–7.46 (m, 5H), 8.39 (d, *J*=9.0 Hz, 2H), 8.44 (d, *J*=5.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 53.4, 70.0, 105.4, 114.6, 127.5, 128.0, 128.6, 129.8, 130.4, 136.6, 157.3, 161.0, 164.0, 169.3; IR (ATR): ν (cm^{-1}) 1583, 1572, 1558; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{17}N_2O_2$ $(M+H)^+$ 293.1285, found $(M+H)^+$ 293.1281 (Δ=−1.27 ppm); HPLC purity=99.2% (t_R=3.56 min, method A).

*4.2.5. 2-(4-(Benzyloxy)phenyl)-4-butoxypyrimidine (**2e**).* Yield=98% (white solid), mp 49–50 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.92 (t, *J*=7.3 Hz, 3H), 1.44 (m, 2H), 1.73 (m, 2H), 4.40 (t, *J*=6.7 Hz, 2H), 5.06 (s, 2H), 6.46 (d, *J*=5.9 Hz, 1H), 6.98 (d, *J*=9.0 Hz, 2H), 7.25–7.39 (m, 5H), 8.30 (d, *J*=9.0 Hz, 2H), 8.36 (d, *J*=5.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 13.9, 19.2, 30.8, 66.0, 70.0, 105.5, 114.6, 127.5, 128.0, 128.6, 129.8, 130.5, 136.7, 157.2, 160.9, 164.0, 169.2; IR (ATR): ν (cm^{-1}) 1589, 1562; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{23}N_2O_2$ $(M+H)^+$ 335.1754, found $(M+H)^+$ 335.1752 (Δ=−0.51 ppm); HPLC purity=96.9% (t_R=3.52 min, method B).

*4.2.6. 2-(4-(Benzyloxy)phenyl)-4-methylpyrimidine (**2f**).* Yield=99% (white solid), mp 113–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.54 (s, 3H), 5.12 (s, 2H), 6.96 (d, *J*=5.1 Hz, 1H), 7.06 (d, *J*=9.0 Hz, 2H), 7.32–7.46 (m, 5H), 8.39 (d, *J*=9.0 Hz, 2H), 8.57 (d, *J*=5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.4, 69.9, 114.7, 117.9, 127.5, 128.0, 128.6, 129.7, 130.7, 136.7, 156.7, 160.8, 164.0, 167.0; IR (ATR): ν (cm^{-1}) 1589, 1560; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{17}N_2O$ $(M+H)^+$ 277.1335, found $(M+H)^+$ 277.1334 (Δ=−0.42 ppm); HPLC purity=99.9% (t_R=3.45 min, method B).

*4.2.7. 2-(4-(Benzyloxy)phenyl)pyrimidine (**2g**).* Yield=90% (white solid), mp 92–93 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.12 (s, 2H), 7.07 (d, *J*=9.0 Hz, 2H), 7.11 (dd, *J*=5.0, 5.0 Hz, 1H), 7.32–7.46 (m, 5H), 8.38 (d, *J*=9.0 Hz, 2H), 8.74 (d, *J*=5.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 70.0, 114.8, 118.4, 127.5, 128.0, 128.6, 129.8, 130.4, 136.6, 157.1, 161.0, 164.4; IR (ATR): ν (cm^{-1}) 1589, 1562; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{15}N_2O$ $(M+H)^+$ 263.1179, found $(M+H)^+$ 263.1176 (Δ=−0.93 ppm); HPLC purity=99.4% (t_R=3.48 min, method A).

*4.2.8. 2-(4-(Benzyloxy)phenyl)-4-phenylpyrimidine (**2h**).* Yield=89% (white solid), mp 110–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.14 (s, 2H), 7.10 (d, *J*=9.0 Hz, 2H), 7.33–7.52 (m, 9H), 8.20 (m, 2H), 8.54 (d, *J*=9.0 Hz, 2H), 8.77 (d, *J*=5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 70.0, 113.8, 114.7, 127.1, 127.5, 128.0, 128.6, 128.9, 129.9, 130.8(2), 136.7, 137.0, 157.7, 161.0, 163.7, 164.3; IR (ATR): ν (cm^{-1}) 1589, 1560; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{19}N_2O$

$(M+H)^+$ 339.1492, found $(M+H)^+$ 339.1488 (Δ=−1.23 ppm); HPLC purity=98.6% (t_R=3.71 min, method B).

*4.2.9. 2-(4-(Benzyloxy)phenyl)-4-(trifluoromethyl)pyrimidine (**2i**).* Yield=91% (white solid), mp 127–128 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.14 (s, 2H), 7.07 (d, *J*=9.0 Hz, 2H), 7.33–7.46 (m, 6H), 8.46 (d, *J*=9.0 Hz, 2H), 8.95 (d, *J*=5.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 70.0, 113.5(2), 114.9, 127.5, 128.1, 128.6, 129.0, 130.4, 136.5, 155.6, 159.4, 161.7, 165.2; IR (ATR): ν (cm^{-1}) 1589, 1560; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{14}N_2OF_3$ $(M+H)^+$ 331.1053, found $(M+H)^+$ 331.1050 (Δ=−0.70 ppm); HPLC purity=99.3% (t_R=3.61 min, method A).

*4.2.10. 2-(4-(Benzyloxy)phenyl)pyrimidine-4-carboxylic acid (**2j**).* Yield=87% (white solid), mp 160–161 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 5.14 (s, 2H), 7.14 (d, *J*=7.5 Hz, 2H), 7.30–7.46 (m, 5H), 7.62 (m, 1H), 8.44 (d, *J*=7.5 Hz, 2H), 8.86 (d, *J*=4.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 69.8, 115.0, 117.5, 128.1, 128.3, 128.8, 130.1, 130.8, 137.3, 158.5(2), 161.0, 163.6; IR (ATR): ν (cm^{-1}) 1589, 1560; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{15}N_2O_3$ $(M+H)^+$ 307.1077, found $(M+H)^+$ 307.1080 (Δ=0.92 ppm); HPLC purity=98.2% (t_R=3.44 min, method A).

*4.2.11. 4-(2-(4-(Benzyloxy)phenyl)-6,7-dimethoxyquinazolin-4-yl) morpholine (**2k**).* Yield=72% (white solid), mp 98–100 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.65 (m, 4H), 3.88 (m, 4H), 3.92 (s, 3H), 3.97 (s, 3H), 5.07 (s, 2H), 7.00 (d, *J*=9.2 Hz, 2H), 7.02 (s, 1H), 7.24 (s, 1H), 7.25–7.41 (m, 5H), 8.40 (d, *J*=9.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 50.3, 56.0, 56.2, 66.7, 69.9, 102.3, 107.8, 109.7, 114.5, 127.5, 127.9, 128.5, 129.5, 131.5, 136.8, 148.0, 150.1, 154.4, 158.4, 160.4, 164.0; IR (ATR): ν (cm^{-1}) 1589, 1560; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{28}N_3O_4$ $(M+H)^+$ 458.2074, found $(M+H)^+$ 458.2072 (Δ=−0.41 ppm); HPLC purity=97.0% (t_R=3.10 min, method A).

*4.2.12. 4-(2-(4-(Benzyloxy)phenyl)thieno[3,2-d]pyrimidin-4-yl)morpholine (**2l**).* Yield=87% (white solid), mp 129–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.87 (m, 4H), 4.04 (m, 4H), 5.12 (s, 2H), 7.04 (d, *J*=9.0 Hz, 2H), 7.38–7.46 (m, 6H), 7.70 (d, *J*=5.5 Hz, 1H), 8.40 (d, *J*=9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 46.3, 66.8, 69.9, 112.2, 114.5, 125.4, 127.5, 128.0, 128.6, 129.6, 131.3, 131.4, 136.8, 158.2, 160.2, 160.4, 162.9; IR (ATR): ν (cm^{-1}) 1527; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{22}N_3O_2S$ $(M+H)^+$ 404.1427, found $(M+H)^+$ 404.1418 (Δ=−2.40 ppm); HPLC purity >99.9% (t_R=3.04 min, method A).

*4.2.13. 4-(2-(4-(Benzyloxy)phenyl)pyrido[2,3-d]pyrimidin-4-yl)morpholine (**2m**).* Yield=81% (white solid), mp 157–158 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.87 (m, 4H), 3.89 (m, 4H), 5.12 (s, 2H), 7.05 (d, *J*=9.0 Hz, 2H), 7.24–7.45 (m, 6H), 8.15 (dd, *J*=8.3, 1.8 Hz, 1H), 8.59 (d, *J*=9.0 Hz, 2H), 8.99 (dd, *J*=4.4, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 50.2, 66.6, 70.0, 109.2, 114.4, 119.5, 127.5, 128.0, 128.6, 130.5, 130.7, 133.4, 136.6, 155.9, 161.3(2), 162.2, 165.1; IR (ATR): ν (cm^{-1}) 1591, 1564, 1533; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{23}N_4O_2$ $(M+H)^+$ 399.1816, found $(M+H)^+$ 399.1814 (Δ=−0.31 ppm); HPLC purity=97.7% (t_R=2.85 min, method A).

*4.2.14. 4-(2-(1-Methyl-1H-indol-5-yl)pyrimidin-4-yl)morpholine (**4a**).* Yield=86% (white solid), mp 126–128 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 3.70 (m, 8H), 3.80 (s, 3H), 6.53 (d, *J*=3.1 Hz, 1H), 6.67 (d, *J*=6.2 Hz, 1H), 7.35 (d, *J*=3.1 Hz, 1H), 7.46 (d, *J*=8.6 Hz, 1H), 8.21 (d, *J*=8.6 Hz, 1H), 8.30 (d, *J*=6.2 Hz, 1H), 8.60 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 32.6, 43.7, 65.9, 100.7, 101.6, 109.3, 120.6, 121.2, 127.9, 129.2, 130.5, 137.8, 156.1, 161.7, 163.6; IR (ATR): ν (cm^{-1}) 1577, 1566, 1543; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{19}N_4O$ $(M+H)^+$ 295.1553, found $(M+H)^+$ 295.1552 (Δ=−0.63 ppm); HPLC purity=99.4% (t_R=2.10 min, method A).

*4.2.15. tert-Butyl 3-(4-morpholinopyrimidin-2-yl)-1H-pyrrole-1-carboxylate (**4b**).* Yield=23% (brown solid), mp 130–131 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.57 (s, 9H), 3.63 (m, 4H), 3.66 (m, 4H), 6.64 (d, *J*=6.2 Hz, 1H), 6.80 (m, 1H), 7.27 (m, 1H), 7.80 (s, 1H), 8.20 (d, *J*=6.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 27.5, 43.6, 65.9, 84.4, 100.9, 111.7, 120.4, 120.6, 128.2, 148.1, 156.0, 160.0, 161.5; IR (ATR): ν (cm^{-1}) 1732, 1578, 1549; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{23}O_3N_4$ $(M+H)^+$ 331.1765, found $(M+H)^+$ 331.1763 (Δ=−0.60 ppm); HPLC purity >99.9% (t_R=2.59 min, method A).

*4.2.16. 4-(2-(Furan-3-yl)pyrimidin-4-yl)morpholine (**4c**).* Yield=95% (pale yellow solid), mp 85–86 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 3.64 (m, 4H), 3.67 (m, 4H), 6.67 (d, *J*=6.2 Hz, 1H), 6.95 (dd, *J*=1.8, 0.9 Hz, 1H), 7.73 (dd, *J*=1.8, 1.8 Hz, 1H), 8.21 (d, *J*=6.2 Hz, 1H), 8.29 (dd, *J*=1.8, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 43.6, 65.8, 101.2, 109.6, 127.4, 144.1, 144.3, 156.0, 159.3, 161.5; IR (ATR): ν (cm^{-1}) 1569, 1544; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{14}N_3O_2$ $(M+H)^+$ 232.1081, found $(M+H)^+$ 232.1078 (Δ=−0.96 ppm); HPLC purity=99.2% (t_R=1.30 min, method A).

*4.2.17. 4-(2-(Thiophen-3-yl)pyrimidin-4-yl)morpholine (**4d**).* Yield=94% (pale yellow solid), mp 109–110 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 3.67 (m, 8H), 6.69 (d, *J*=6.2 Hz, 1H), 7.57 (dd, *J*=5.0, 3.0 Hz, 1H), 7.74 (dd, *J*=5.0, 1.2 Hz, 1H), 8.25 (d, *J*=6.2 Hz, 1H), 8.26 (dd, *J*=3.0, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 43.6, 65.9, 101.3, 126.5, 127.3, 127.4, 142.2, 156.2, 160.0, 161.6; IR (ATR): ν (cm^{-1}) 1576, 1539; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{14}N_3OS$ $(M+H)^+$ 248.0852, found $(M+H)^+$ 248.0849 (Δ=−1.06 ppm); HPLC purity=99.7% (t_R=1.53 min, method A).

*4.2.18. 4-(2-(1-Methyl-1H-pyrazol-4-yl)pyrimidin-4-yl)morpholine (**4e**).* Yield=80% (white solid), mp 125–127 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 3.63 (m, 4H), 3.66 (m, 4H), 3.86 (s, 3H), 6.59 (d, *J*=6.2 Hz, 1H), 7.92 (s, 1H), 8.17 (d, *J*=6.2 Hz, 1H), 8.24 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 43.5, 65.8, 100.3, 122.9, 131.5, 138.5, 156.0, 159.6, 161.4; IR (ATR): ν (cm^{-1}) 1579, 1560, 1541; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{16}N_5O$ $(M+H)^+$ 246.1349, found $(M+H)^+$ 246.1346 (Δ=−1.38 ppm); HPLC purity=99.3% (t_R=1.11 min, method A).

*4.2.19. 4-(2-(1-Tosyl-1H-pyrrol-2-yl)pyrimidin-4-yl)morpholine (**4f**).* Yield=99% (white solid), mp 132–134 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.36 (s, 3H), 3.49 (m, 4H), 3.69 (m, 4H), 6.27 (d, *J*=6.2 Hz, 1H), 6.30 (dd, *J*=3.4, 3.4 Hz, 1H), 6.83 (m, 1H), 7.23 (d, *J*=8.3 Hz, 2H), 7.47 (m, 1H), 7.69 (d, *J*=8.3 Hz, 2H), 8.08 (d, *J*=6.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 21.6, 43.9, 66.5, 100.5, 111.2, 118.4, 126.4, 127.2, 129.2, 134.9, 137.5, 144.1, 155.1, 158.2, 161.4; IR (ATR): ν (cm^{-1}) 1587, 1568; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{21}N_4O_3S$ $(M+H)^+$ 385.1329, found $(M+H)^+$ 385.1326 (Δ=−0.75 ppm); HPLC purity=99.9% (t_R=2.26 min, method A).

*4.2.20. 4-(2-(Furan-2-yl)pyrimidin-4-yl)morpholine (**4g**).* Yield=91% (pale yellow solid), mp 131–132 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 3.66 (m, 8H), 6.62 (dd, *J*=3.5, 1.8 Hz, 1H), 6.69 (d, *J*=6.2 Hz, 1H), 7.16 (m, 1H), 7.82 (m, 1H), 8.23 (d, *J*=6.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 43.6, 65.8, 101.3, 112.0, 112.4, 144.9, 152.4, 156.0, 156.2, 161.4; IR (ATR): ν (cm^{-1}) 1573, 1543; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{14}N_3O_2$ $(M+H)^+$ 232.1081, found $(M+H)^+$ 232.1079 (Δ=−0.55 ppm); HPLC purity=99.2% (t_R=1.26 min, method A).

*4.2.21. 4-(2-(5-Methylfuran-2-yl)pyrimidin-4-yl)morpholine (**4h**).* Yield=99% (pale yellow solid), mp 75–78 °C; ^{1}H NMR

(300 MHz, DMSO-d_6): δ (ppm) 2.34 (s, 3H), 3.62 (m, 4H), 3.66 (m, 4H), 6.24 (d, J=3.3 Hz, 1H), 6.64 (d, J=6.2 Hz, 1H), 7.06 (d, J=3.3 Hz 1H), 8.19 (d, J=6.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 13.7, 43.6, 65.8, 100.9, 108.5, 113.7, 150.9, 154.1, 156.0, 156.2, 161.4; IR (ATR): ν (cm^{-1}) 1573, 1533; HRMS (ESI) m/z calcd for $C_{13}H_{16}N_3O_2$ (M+H)$^+$ 246.1237, found (M+H)$^+$ 246.1235 (Δ=−0.99 ppm); HPLC purity=98.3% (t_R=1.61 min, method A).

*4.2.22. 4-(2-(Benzofuran-2-yl)pyrimidin-4-yl)morpholine (**4i**).* Yield=91% (white solid), mp 177–178 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.71 (m, 4H), 3.80 (m, 4H), 6.39 (d, J=6.2 Hz, 1H), 7.24 (m, 1H), 7.34 (m, 1H), 7.57 (s, 1H), 7.62 (m, 2H), 8.34 (d, J=6.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 43.9, 66.5, 101.4, 108.5, 112.0, 121.8, 123.1, 125.7, 128.3, 154.0, 155.6, 156.2, 157.2, 161.6; IR (ATR): ν (cm^{-1}) 1568, 1547; HRMS (ESI) m/z calcd for $C_{16}H_{16}O_2N_3$ (M+H)$^+$ 282.1237, found (M+H)$^+$ 282.1235 (Δ=−0.81 ppm). HPLC purity=99.6% (t_R=2.14 min, method A).

*4.2.23. 4-(2-(Thiophen-2-yl)pyrimidin-4-yl)morpholine (**4j**).* Yield=96% (white solid), mp 107–108 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 3.65 (m, 4H), 3.67 (m, 4H), 6.69 (d, J=6.2 Hz, 1H), 7.14 (dd, J=5.0, 3.7 Hz, 1H), 7.65 (dd, J=5.0, 1.1 Hz, 1H), 7.83 (dd, J=3.7, 1.1 Hz, 1H), 8.21 (d, J=6.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 43.6, 65.8, 101.3, 128.0, 128.1, 129.8, 144.0, 156.1, 159.4, 161.3; IR (ATR): ν (cm^{-1}) 1578, 1533; HRMS (ESI) m/z calcd for $C_{12}H_{14}ON_3S$ (M+H)$^+$ 248.0852, found (M+H)$^+$ 248.0850 (Δ=−1.00 ppm); HPLC purity=99.1% (t_R=1.61 min, method A).

*4.2.24. 4-(2-(2,2′-Bithiophen-5-yl)pyrimidin-4-yl)morpholine (**4k**).* Yield=99% (yellow solid), mp 162–164 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.67 (m, 4H), 3.78 (m, 4H), 6.28 (d, J=6.2 Hz, 1H), 7.02 (m, 1H), 7.15 (d, J=3.9 Hz, 1H), 7.23 (m, 2H), 7.77 (d, J=3.9 Hz, 1H), 8.20 (d, J=6.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 43.9, 66.5, 100.3, 124.1, 124.3, 124.9, 127.9, 128.7, 137.4, 140.6, 142.5, 156.1, 160.1, 161.5; IR (ATR): ν (cm^{-1}) 1570, 1535; HRMS (ESI) m/z calcd for $C_{16}H_{16}N_3OS_2$ (M+H)$^+$ 330.0729, found (M+H)$^+$ 330.0728 (Δ=−0.53 ppm); HPLC purity=99.8% (t_R=2.69 min, method A).

*4.2.25. 4-(2-(Benzo[b]thiophen-2-yl)pyrimidin-4yl)-morpholine (**4l**).* Yield=93% (white solid), mp 163–164 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.67 (m, 4H), 3.79 (m, 4H), 6.32 (d, J=6.2 Hz, 1H), 7.33 (m, 2H), 7.81 (m, 2H), 8.15 (s, 1H), 8.26 (d, J=6.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 43.9, 66.5, 100.8, 122.5, 124.4, 124.6, 124.8, 125.3, 140.1, 141.4, 144.1, 156.1, 160.5, 161.5; IR (ATR): ν (cm^{-1}) 1570, 1537; HRMS (ESI) m/z calcd for $C_{16}H_{16}N_3OS$ (M+H)$^+$ 298.1009, found (M+H)$^+$ 298.1008 (Δ=−0.10 ppm); HPLC purity=99.3% (t_R=2.54 min, method A).

*4.2.26. 2-(Furan-2-yl)isonicotinic acid (**6a**).* Yield=99% (white solid), mp 226–227 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 6.67 (m, 1H), 7.20 (d, J=3.3 Hz, 1H), 7.69 (d, J=5.1 Hz, 1H), 7.89 (m, 1H), 8.08 (s, 1H), 8.74 (d, J=5.1 Hz, 1H), 13.8 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 109.8, 112.6, 116.9, 121.1, 139.3, 144.8, 149.5, 150.8, 152.4, 166.0; IR (ATR): ν (cm^{-1}) 1728, 1616, 1562; HRMS (ESI) m/z calcd for $C_{10}H_8NO_3$ (M+H)$^+$ 190.0499, found (M+H)$^+$ 190.0497 (Δ=−0.74 ppm); HPLC purity=99.3% (t_R=1.52 min, method A).

*4.2.27. 2-(Furan-2-yl)-4-methoxypyridine (**6b**).* Yield=86% (white solid), mp 34–36 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 3.87 (s, 3H), 6.64 (dd, J=3.4, 1.7 Hz, 1H), 6.87 (dd, J=5.7, 2.6 Hz, 1H), 7.09 (d, J=3.4 Hz, 1H), 7.23 (d, J=2.6 Hz, 1H), 7.82 (d, J=1.7 Hz, 1H), 8.37 (d, J=5.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 55.4, 103.9, 108.8, 109.1, 112.3, 144.1, 150.1, 151.0, 153.0, 165.9; IR (ATR): ν (cm^{-1}) 1605, 1577, 1558; HRMS (ESI) m/z calcd for $C_{10}H_{10}NO_2$ (M+H)$^+$ 176.0706, found (M+H)$^+$ 176.0704 (Δ=−1.23 ppm); HPLC purity=99.7% (t_R=1.00 min, method A).

*4.2.28. 4-(2-(Furan-2-yl)-6,7-dimethoxyquinazolin-4-yl)morpholine (**6c**).* Yield=89% (white solid), mp 165–167 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.68 (m, 4H), 3.91 (m, 4H), 3.96 (s, 3H), 3.99 (s, 3H), 6.52 (m, 1H), 7.05 (s, 1H), 7.24 (m, 1H), 7.37 (s, 1H), 7.59 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 50.2, 56.0, 56.2, 66.6, 102.9, 108.0, 109.9, 111.7, 112.2, 144.4, 148.3, 149.5, 152.0, 153.0, 154.6, 164.0; IR (ATR): ν (cm^{-1}) 1620, 1570, 1544; HRMS (ESI) m/z calcd for $C_{18}H_{20}N_3O_4$ (M+H)$^+$ 342.1448, found (M+H)$^+$ 342.1446 (Δ=−0.79 ppm); HPLC purity=99.7% (t_R=2.07 min, method A).

*4.2.29. 4-(2-(Furan-2-yl)thieno[3,2-d]pyrimidin-4-yl)morpholine (**6d**).* Yield=96% (white solid), mp 143–145 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 3.77 (m, 4H), 3.95 (m, 4H), 6.64 (dd, J=3.4, 1.7 Hz, 1H), 7.22 (dd, J=3.4, 0.8 Hz, 1H), 7.47 (d, J=5.7 Hz, 1H), 7.84 (dd, J=1.7, 0.8 Hz, 1H), 8.23 (d, J=5.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 45.8, 66.0, 111.7, 112.1(2), 124.6, 134.0, 144.7, 152.4, 152.9, 157.6, 162.0; IR (ATR): ν (cm^{-1}) 1541, 1520; HRMS (ESI) m/z calcd for $C_{14}H_{14}N_3O_2S$ (M+H)$^+$ 288.0801, found (M+H)$^+$ 288.0800 (Δ=−0.37 ppm); HPLC purity=98.8% (t_R=1.81 min, method A).

*4.2.30. 4-(2-(Furan-2-yl)pyrido[2,3-d]pyrimidin-4-yl)morpholine (**6e**).* Yield=92% (white solid), mp 178–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.86 (m, 8H), 6.53 (dd, J=3.5, 1.7 Hz, 1H), 7.25 (dd, J=8.3, 4.4 Hz, 1H), 7.41 (d, J=3.5 Hz, 1H), 7.60 (d, J=1.7 Hz, 1H), 8.12 (dd, J=8.3, 1.8 Hz, 1H), 8.96 (dd, J=4.4, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 50.0, 66.6, 109.3, 112.1, 114.6, 119.7, 133.8, 145.2, 152.4, 155.6, 156.0, 161.0, 165.1; IR (ATR): ν (cm^{-1}) 1583, 1562, 1533; HRMS (ESI) m/z calcd for $C_{15}H_{15}N_4O_2$ (M+H)$^+$ 283.1190, found (M+H)$^+$ 283.1187 (Δ=−0.95 ppm); HPLC purity=99.5% (t_R=1.36 min, method A).

*4.2.31. 2-(Furan-2-yl)quinoline (**6f**).* Yield=95% (white solid), mp 90–91 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 6.72 (dd, J=3.5, 1.8 Hz, 1H), 7.35 (m, 1H), 7.56 (m, 1H), 7.77 (m, 1H), 7.93 (m, 3H), 7.99 (d, J=8.4 Hz, 1H), 8.40 (d, J=8.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 110.7, 112.6, 117.4, 126.4, 126.9, 128.0, 128.6, 130.2, 137.1, 145.0, 147.5, 148.4, 153.1; IR (ATR): ν (cm^{-1}) 1598, 1556, 1500; HRMS (ESI) m/z calcd for $C_{13}H_{10}NO$ (M+H)$^+$ 196.0757, found (M+H)$^+$ 196.0754 (Δ=−1.28 ppm); HPLC purity=99.0% (t_R=1.65 min, method A).

*4.2.32. 2-(Furan-2-yl)quinoxaline (**6g**).* Yield=74% (orange solid), mp 102–103 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 6.79 (dd, J=3.6, 1.7 Hz, 1H), 7.58 (dd, J=3.6, 0.6 Hz, 1H), 7.81 (m, 2H), 8.05 (m, 3H), 9.38 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 112.9, 113.0, 128.8, 129.0, 129.7, 130.9, 140.6, 141.3, 142.6, 143.5, 146.3, 150.9; IR (ATR): ν (cm^{-1}) 1612, 1558, 1552; HRMS (ESI) m/z calcd for $C_{12}H_9N_2O$ (M+H)$^+$ 197.0709, found (M+H)$^+$ 197.0709 (Δ=−0.01 ppm); HPLC purity=99.4% (t_R=2.86 min, method A).

*4.2.33. 4-(Furan-2-yl)furo[3,2-c]pyridine (**6h**).* Yield=96% (yellow oil); ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 6.72 (m, 1H), 7.26 (d, J=3.5 Hz, 1H), 7.42 (m, 1H), 7.59 (d, J=5.7 Hz, 1H), 7.94 (m, 1H), 8.19 (d, J=2.0 Hz, 1H), 8.45 (d, J=5.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 105.8, 106.0, 110.3, 112.4, 119.2, 142.8, 144.4, 144.8, 147.3, 153.2, 159.8; IR (ATR): ν (cm^{-1}) 1593, 1560, 1531; HRMS (ESI) m/z calcd for $C_{11}H_8NO_2$ (M+H)$^+$ 186.0550, found (M+H)$^+$ 186.0546 (Δ=−1.77 ppm); HPLC purity=98.0% (t_R=1.08 min, method A).

*4.2.34. 4-(Furan-2-yl)thieno[3,2-c]pyridine (**6i**).* Yield=96% (yellow oil); ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 6.73 (m, 1H), 7.29 (d, J=3.5 Hz, 1H), 7.99 (m, 3H), 8.13 (m, 1H), 8.42 (m, 1H); ^{13}C NMR

(75 MHz, DMSO-d_6): δ (ppm) 111.0, 112.3, 116.6, 122.8, 129.4, 130.1, 142.1, 143.6, 144.8, 148.4, 153.8; IR (ATR): ν (cm^{-1}) 1587, 1533; HRMS (ESI) m/z calcd for $C_{11}H_8NOS$ $(M+H)^+$ 202.0321, found $(M+H)^+$ 202.0320 (Δ=−0.41 ppm); HPLC purity=99.7% (t_R=1.30 min, method A).

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Supplementary data

Kinetic studies of **1a**, 2-furyl pinacol boronate, and 2-furylboronic acid, and ^1H and ^{13}C NMR spectra for all new compounds. Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2011.10.057.

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