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Metal free C–H functionalization of diazines and related heteroarenes with organoboron species and its application in the synthesis of a CDK inhibitor, meriolin 1†

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Here, we report a metal-free cross-coupling reaction of diazines and related heteroarenes with organoboron species *via* C–H functionalization. The optimized conditions represent a metal-free method for the activation of aryl/heteroarylboronic acids, which undergo coupling with diazines and related heteroarenes. Optimized conditions also find application in the synthesis of a pyrimidine-based potent CDK inhibitor, **meriolin 1**.

Diazines, particularly pyrimidine and its benzofused derivatives have occupied an important and significant position in the chemical space because of their ubiquitous occurrence in natural,[1] pharmaceutical,[2] agro,[3] electronic and photonic products.[4] A few examples of pyrimidine containing pharmaceutical and photonic products are shown in Fig. 1.[4,5]

Considering the importance and applications of aryl substituted pyrimidines and their derivatives, the development of new synthetic methods for the preparation of functionalized pyrimidine is highly required. Historically, this was achieved *via* cross-coupling reactions by using pre-functionalized pyrimidine.[6] Recently, Verbitskiy *et al.*[7] developed the SN^H method for the functionalization of pyrimidines, which were found suitable with electron-rich heteroarenes. In the present decade, the direct C–H functionalization of electron-deficient heteroarenes[8] has received considerable attention, which is mainly exploited for azines (pyridine and its derivatives). Pyrimidine also represents an electron-deficient system and in comparison to pyridine, the presence of the second N-atom further significantly decreases the electron density, but this has been less explored under C–H functionalization methods. In the literature, three metal-catalyzed reports are available, where pyrimidine was used as a substrate (Fig. 2)[8a–c] but all these reported methods are highly specific to one example only. Very recently, Antonchick and co-workers[9] reported a metal-free method for the arylation of electron-deficient heteroarenes but again specific to quinoline only and with a pre-functionalized one at that, *i.e.*, quinoline *N*-oxide. In continuation of our work concerning functionalization of electron-deficient heteroarenes,[10] here we report a general method for the C–H functionalization of pyrimidine and its derivatives. The optimized method involves metal-free conditions for the activation of aryl boronic acids. Moreover, the optimized conditions work very well with other heteroarenes such as pyrazine, quinoxalines, quinoline, pyridine and quinazolines. In addition, we have also demonstrated its application in the synthesis of a marine-derived pyrimidine-based potent CDK inhibitor, **meriolin 1**.

To start, 5-bromo-2-chloropyrimidine **1** and phenylboronic acid **2** were selected as coupling partners. The initial reaction was performed under previously developed redox-based conditions[10a] involving iron(II) acetylacetonate [$Fe(acac)_2$] and $K_2S_2O_8$, but no coupling was observed (Table 1, entry 1). Next, the reaction was tried under Baran's conditions,[8a] and a cross-coupled product was observed in a yield of 15% (Table 1, entry 2). Next, when the reaction was tried with iron(II) acetylacetonate [$Fe(acac)_2$] and $K_2S_2O_8$ at 110 °C, the formation of coupled product **3a** was observed in a yield of 15% (Table 1, entry 3). Surprisingly, by changing the solvents to acetone : water, **3a** was observed in a yield of 53% (Table 1, entry 4). Further rise in the temperature increased the yield of **3a** to 61% (Table 1, entry 5). The coupling was observed at high temperatures, which in turn suggested that the metal salts might not be required for the activation of arylboronic acid. In this direction, series of reactions were performed under metal-free conditions (Table 1, entries 6–8) and to our delight, the acetone : water system at 160 °C also gave the coupled product **3a** in a yield of 63% (Table 1, entry 8).

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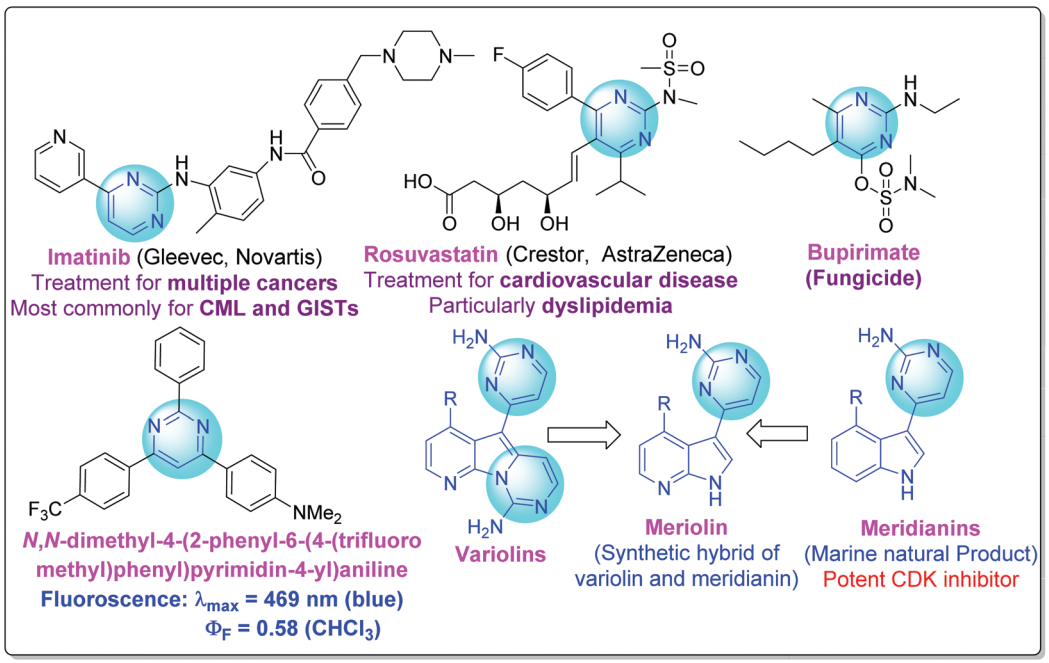


Fig. 1 Examples of pyrimidine containing products.

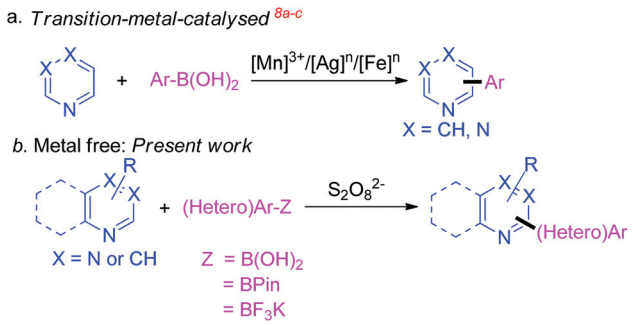


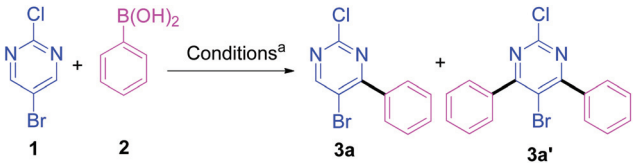
Fig. 2 C–H functionalization of electron-deficient heteroarenes.

When the reaction was conducted in water alone, 51% of coupled product **3a** was observed (Table 1, entry 9), however, at room temperature, no coupling was observed (Table 1, entry 10). Other solvent systems were also tried (Table 1, entries 11–17), but none gave any advantage. Among various reaction conditions, metal-free peroxysulfate ($K_2S_2O_8$) at 160 °C in acetone : water was found to be the best (Table 1, entry 8).

With the optimized reaction conditions in hand, investigation towards substrate scope was tried (Scheme 1). As shown in Scheme 1, both the substrates with varying substituents afforded the corresponding coupled products **3–11** in a moderate to good yields. In a few cases, trace amounts of biphenyl and bis-addition products were also detected as by-products (<10%). Under optimized conditions, 5-bromo-2-chloropyrimidine **1** reacted smoothly with various substituted aryl boronic acid and gave coupled products **3b–3d** in moderate to good yields. 5-Bromo-2-chloropyrimidine also reacted well with heteroarylboronic acids such as 2-aminopyrimidinyl-5-boronic acid and (6-methoxypyridin-3-yl)boronic acid, and gave the corresponding coupled products **3e** and **3f**. Other substituted pyrimidine derivatives such as 2-amino-5-bromopyrimidine when tried with phenylboronic acid, gave 67% of the corresponding coupled product **4a**. 2-Amino-5-bromopyrimidine upon reaction with *para*- and *meta*-substituted electron-rich arylboronic acids gave the corresponding coupled products (**4b–4e**) in moderate to good yields. On the other hand, *ortho*-substituted arylboronic acids and electron-withdrawing group containing arylboronic acids also underwent coupling but gave comparatively lower yields of the corresponding coupled products (**4f–4k**). When 5-bromopyrimidine and 2-aminopyrimidine were tried with phenylboronic acid, corresponding coupled products **5a** and **6a** were obtained in moderate yields. When un-substituted pyrimidine was tried with phenylboronic acid, 4th-substitued regio-isomer **7a** was observed in a yield of 37% along with a trace amount of the 2-substituted regio-isomer. Under optimized conditions, quinazoline also underwent coupling and provided the 4th-substituted regio-isomeric product **8a** in a yield of 38%. With pyrazine and 2,3-dimethylpyrazine, corresponding coupled products **9a** and **10a** were obtained in yields of 55 and 59%, respectively. Further, benzo-fused diazine such as 2-methylquinoxaline also underwent coupling with unsubstituted and substituted (3-methyl, 4-methyl and 4-bromo) phenylboronic acids, and gave the corresponding coupled products **11a–11d** in moderate to good yield.

Next, the optimized metal-free peroxysulfate-mediated conditions were further extended to azines also. Substituted pyridine and its benzofused derivatives **12** were explored, which

Table 1 Optimization studies[a]



Entry	Catalyst (mol%)	Solvent (v/v = 2 : 1)	PTC[b]	Acid	T[c] (°C)	T (h or min)	Yield[d] (%) 3a	3a′
1[e]	$Fe(acac)_2$ (20)	DCM : H_2O	TBAB	TFA	rt	24 h	—	—
2	$Ag(NO_3)_2$ (20)	DCM : H_2O	—	TFA	rt	24 h	15	—
3	$Fe(acac)_2$ (50)	DCM : H_2O			110	8 h	15	—
4	$Fe(acac)_2$ (50)	Acetone : H_2O			110	8 h	53	5
5	$Fe(acac)_2$ (50)	Acetone : H_2O			160	1 h	61	7
6		DCM : H_2O	TBAB	TFA	90	18 h	30	—
7		Acetone : H_2O			110	3 h	21	—
8		**Acetone : H_2O**			**160**	**45 min**	**63**	**8**
9		H_2O			160	3 h	51	10
10		Acetone : H_2O			rt	24 h	—	—
11		DCE : H_2O[b]			160	3 h	13	—
12		ACN : H_2O			160	3 h	15	—
13		EtOH : H_2O			160	3 h	11	—
14		DMSO : H_2O[b]			160	3 h	—	—
15		DMF : H_2O[b]			160	3 h	—	—
16		EAA : H_2O[b]			160	3 h	—	—
17		Acetylacetone : H_2O			160	3 h	—	—

Reaction conditions: [a] 5-Bromo-2-chloropyrimidine **1** (0.25 mmol), **2** (0.375 mmol), $K_2S_2O_8$ (0.75 mmol) and solvents (3 mL). [b] Phase-transfer catalyst, DCE = 1,2-dichloroethane, DMSO = dimethylsulfoxide, DMF = dimethylformamide, EAA = ethylacetoacetate. [c] Represent bath temperature (reactions were performed in a sealed tube, details are provided in Experimental section). [d] Isolated yields. [e] **2** (0.275 mmol) was used.

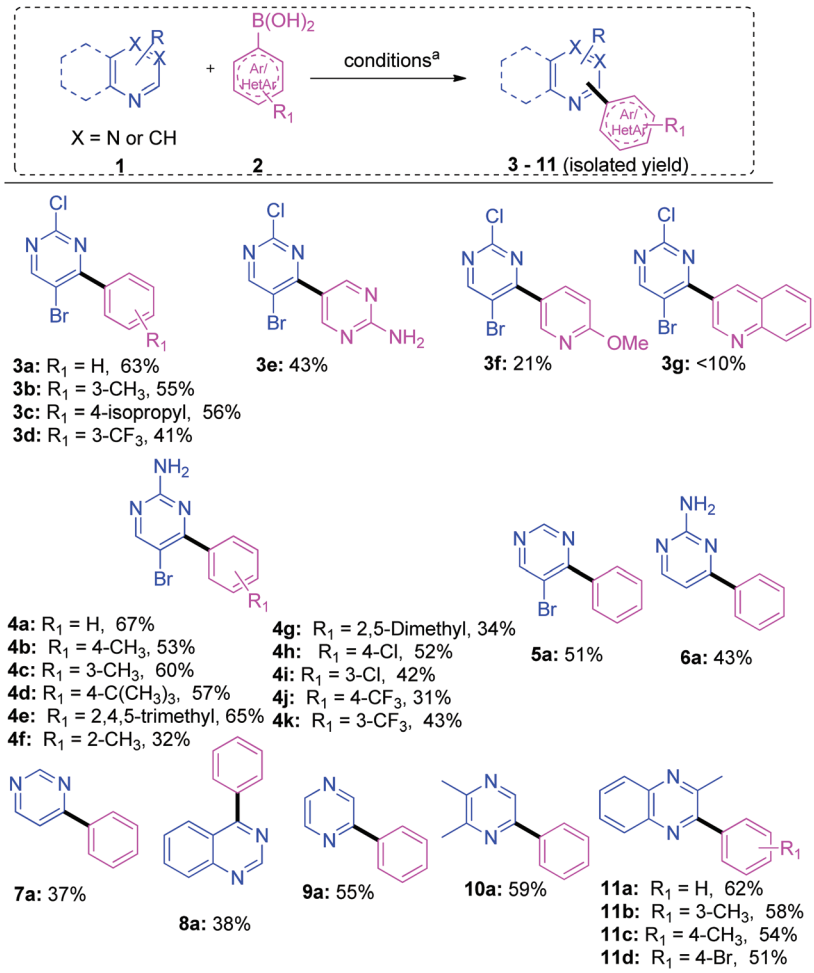
gave the single regio-isomeric products in good to moderate yields (Scheme 2). Both pyridines and quinolines reacted with phenylboronic acid under optimized conditions and furnished moderate to good yield of the corresponding coupled products (**13a–13d**).

Further, the reactivity of other organoboron species such as potassium organo trifluoroborate salts and arylboronic acid pinacol ester were also tested (Table 2). Phenylboronic acid pinacol ester underwent cross-coupling smoothly with 2-amino-5-bromopyrimidine and gave 2-amino-5-bromo-4-phenylpyrimidine in 55% yield (Table 2, entry 2). Similarly, phenyltrifluoroborate and 4-methylphenyltrifluoroborate also underwent coupling with 2-amino-5-bromopyrimidine and gave desired coupled products in good yield (Table 2, entries 3 and 4).

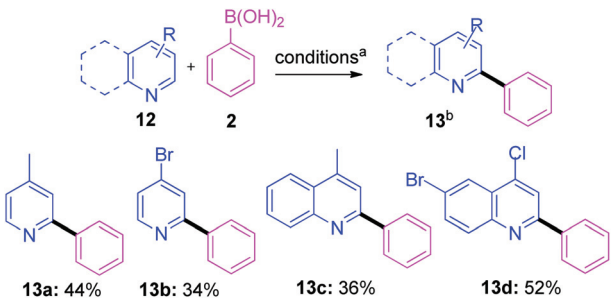
The control experiments in the presence of a free-radical scavenger such as (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) drastically suppressed the formation of coupled product **3a** (Scheme 3), suggesting the radical mechanism. Based on the present results and literature precedents,[8a,b] the following plausible mechanistic cascade is proposed for the present coupling reaction (Fig. 3). The peroxydisulfate upon heating generates the sulfate anion radical (**II**) which activates arylboronic acid **2** and generates aryl radical **III**. The aryl radical **III** then reacts further with *in situ* generated heteroarene salt **1′**[10b,11,12] and produces cationic radical intermediate **V**, which undergoes single electron transfer (SET) with either sulfate radical **II** or peroxy disulfate **I** to afford the protonated required product **3** along with either the sulfate ion (**IV**) or sulfate ion/sulfate radical pairs (**IV** or **II**). The generated sulfate radical (**II**) might further be involved in the propagation of chains, while hydrogen sulfate (**IV**) in the protonation of heteroarenes, which in turn avoid the use of an external acid.

As pyrimidine is present in a large number of natural and other products,[1–4] the optimized method finds application in the synthesis of such molecules. In the present case, the concept has been successfully demonstrated by synthesizing **meriolin 1**.[5d]

Meriolins represent a derivative of the 7-azaindole moiety, which was designed by Meijer and co-workers and given the name meriolin, as the structure represents two marine natural products variolin and meridianin.[12] The meriolins are known as highly potent CDK-based anti-cancer agents. Regarding the synthesis, four methods were reported in the literature[5d,13–15] (Fig. 4), wherein three involved palladium-based catalyses for the construction of final molecules. Here, we have developed a metal-free method for the construction of **meriolin 1** under optimized conditions. By using optimized conditions, when 2-aminopyrimidine **1** was treated with *N*-Boc protected 7-azaindole boronate ester **21a**, coupling and Boc-deprotection occurred in a single step and **meriolin 1** was obtained in an overall yield of 35% (Fig. 4). Other protected groups such as methyl (**21b**), tosyl (**21c**) and dimethyl carbamoyl (**21d**) were also tried but none gave any improvement. However, with tosyl



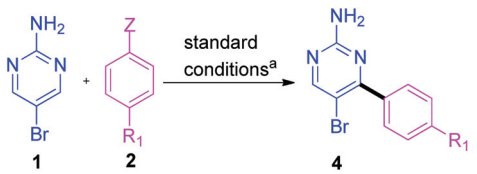
Scheme 1 Coupling of diverse diazines with un/substituted (hetero)arylboronic acids. [a] Reaction conditions: heteroarene **1** (0.25 mmol), **2** (0.375 mmol), $K_2S_2O_8$ (0.75 mmol), acetone/water (v/v = 2 : 1) at 160 °C (reactions were performed in a sealed tube), 45 min.

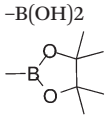


Scheme 2 Coupling of diverse azines with un/substituted phenylboronic acids. [a] Reaction conditions: azine **4** (0.25 mmol), **2** (0.375 mmol), $K_2S_2O_8$ (0.75 mmol), acetone/water (v/v = 2 : 1) at 160 °C (reactions were performed in a sealed tube), 45 min; [b] isolated yield.

and dimethyl carbamoyl, the starting materials *viz.* **21c** and **21d** were observed as such in the reaction mixture, which in turn suggested that the presence of these groups stabilizes the C–B bond and makes the substrates inactive for reaction.

Table 2 Coupling with different organoboron species[a]



Entry	(Z =)	(R_1 =)	**4** (isolated yield %)
1[b]	–B(OH)2	H	67
2		H	55
3	$-BF_3K$	H	51
4	$-BF_3K$	CH_3	54

Reaction conditions: [a] heteroarene **1** (0.25 mmol), **2** (0.375 mmol), acetone/water, $K_2S_2O_8$ (0.75 mmol), 160 °C (reactions were performed in a sealed tube), 1 h. [b] 45 min.

Scheme 3 Coupling in the presence of a radical scavenger.

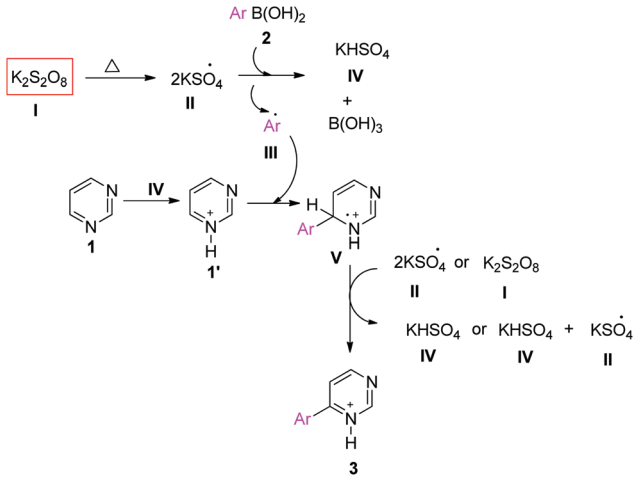


Fig. 3 Plausible mechanism.

Conclusions

In conclusion, we have developed a general, transition metal-free method for the generation of aryl/heteroaryl radicals, which undergo smooth coupling with less-explored electron-deficient heteroarenes such as a pyrimidine and its derivatives. In addition, optimized conditions also work with other substrates such as pyrazine, quinoxalines, pyridine, quinoline, and quinazolines. The optimized conditions avoid the need for an external strong acid. The present methodology was also successfully utilized for the synthesis of **meriolin 1**.

Experimental section

General information

All reactions were performed in an ace pressure tube bushing type, back seal, volume 100 mL, *L* × O.D. 17.8 cm × 38.1 mm (sealed tube). Analytical thin layer chromatography was performed using TLC pre-coated silica gel 60 F_{254} Merck (20 × 20 cm). TLC plates were visualized by exposing to UV light or by iodine vapors or immersion in an acidic staining solution of *p*-anisaldehyde followed by heating on a hot plate. The organic solvent was concentrated by rotary evaporation on a BUCHI-Switzerland R-120 rotary evaporator and a vacuum pump V-710. Flash column chromatography was performed on Merck flash silica gel of 230–400 mesh size. ^{1}H NMR spectra were recorded with Bruker 400 and 500 MHz NMR instruments. Chemical data for protons are reported in parts per million (ppm, scale) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent ($CDCl_3$: δ 7.26, or other solvents as mentioned). All the NMR spectra were processed in either MestReNova or Bruker software. Mass spectra were recorded with a HRMS instrument.

General procedure

Cross-coupling of electron deficient heteroarenes (diazines and azines) with organo boron species. To a 100 mL sealed tube were added heteroarenes **1** (0.25 mmol), aryl/heteroaryl boronic acid or aryl/heteroaryl boronic acid pinacol ester **2** (0.375 mmol), $K_2S_2O_8$ (0.75 mmol), and 3 mL of acetone/water (2 : 1). The tube was sealed with a back seal stopper, heated at 160 °C for 45 min–1 h. After completion of the reaction as monitored by TLC, the heating was stopped and the reaction mixture was allowed to cool down to room temperature. Then the reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a silica gel column using hexane/EtOAc.

Synthesis of bioactive synthetic hybrid meriolin 1. To a 100 mL sealed tube were added 2-aminopyrimidine **1** (0.25 mmol), 7-azaindole boronate ester **6** (0.375 mmol), and $K_2S_2O_8$ (0.75 mmol) in 6 ml of acetone/water (2 : 1). The tube was sealed with a back seal stopper, and heated at 160 °C for 2 h. After completion of the reaction as monitored by TLC, the heating was stopped and the reaction mixture was allowed to cool down to room temperature. Then the reaction mixture was diluted with dichloromethane and washed with saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a silica gel column using DCM/MeOH.

Spectral data of compounds

5-Bromo-2-chloro-4-phenylpyrimidine (3a). White solid (43 mg, 63%); **mp 105 °C**; TLC R_f = 0.6 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.84 (dd, *J* = 13.4, 7.3 Hz, 2H), 7.52 (q, *J* = 5.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.93, 162.2, 159.78, 135.59, 130.96, 129.41, 128.39, 117.20; HRMS (ESI+) (*m*/*z*) calcd for $C_{10}H_7{}^{79}BrClN_2$ [M + H] 268.9481 found 268.9467, calcd for $C_{10}H_7{}^{81}BrClN_2$ [M + H] 270.9461 found 270.9445.

5-Bromo-2-chloro-4-(*m*-tolyl)pyrimidine (3b). Yellow solid (38 mg, 55%); **mp 97 °C**; TLC R_f = 0.7 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.42–7.33 (m, 2H), 2.44 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.20, 162.18, 159.72, 138.36, 135.53, 131.73, 129.89, 128.20, 126.49, 117.26, 21.45; HRMS (ESI+) (*m*/*z*) calcd for

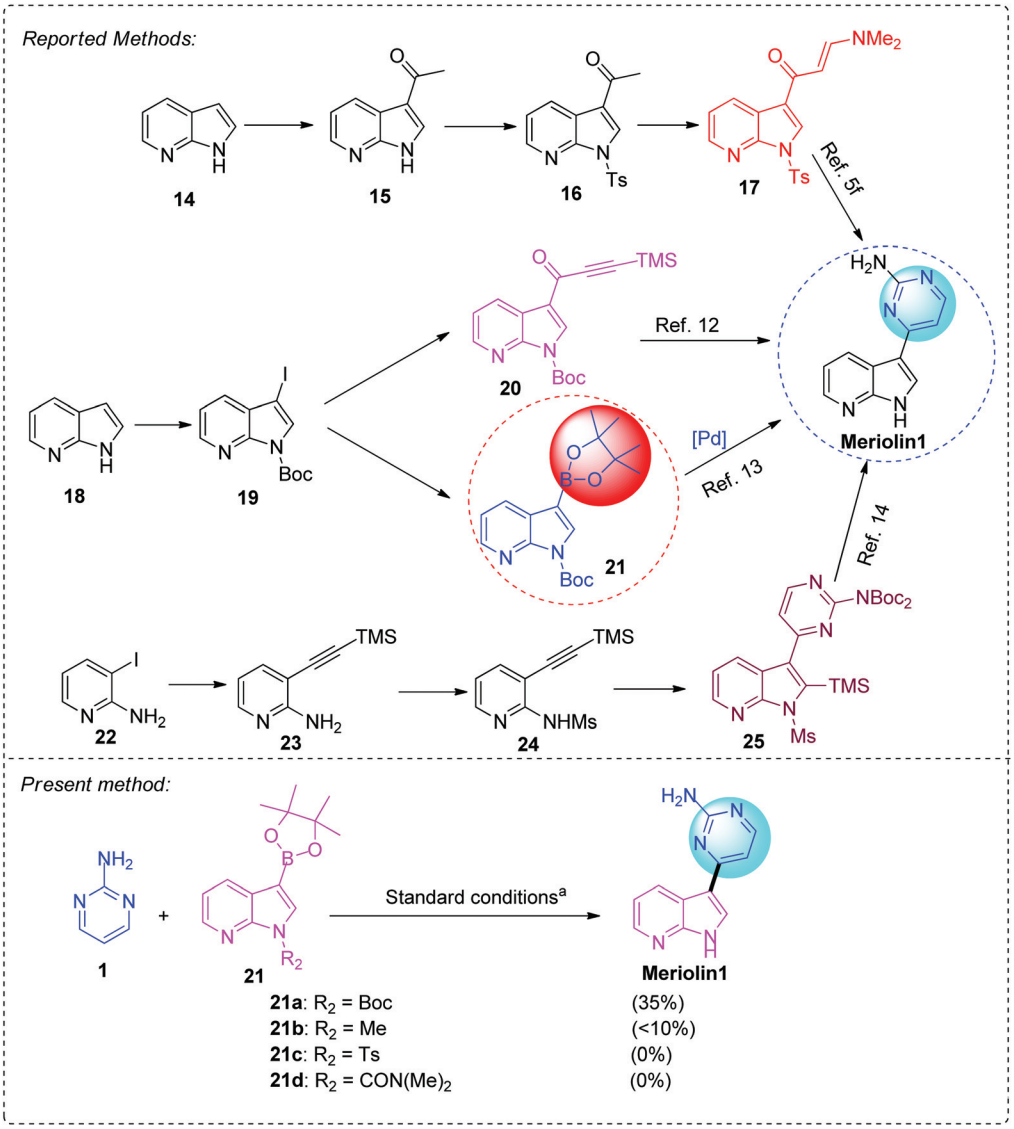


Fig. 4 Synthesis of **meriolin 1**. [a] Reaction conditions: 2-amino pyrimidine **1** (0.25 mmol), **21** (0.375 mmol), acetone/water, $K_2S_2O_8$ (0.75 mmol), 160 °C (reactions were performed in a sealed tube), 2 h.

$C_{11}H_9{}^{79}BrClN_2$ [M + H] 282.9638 found 282.9629, calcd for $C_{11}H_9{}^{81}BrClN_2$ [M + H] 284.9617 found 284.9603.

5-Bromo-2-chloro-4-(4-iso-propylphenyl)pyrimidine (3c). Colorless oil (51 mg, 56%); TLC R_f = 0.7 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 3.00 (dd, J = 13.8, 6.9 Hz, 1H), 1.29 (d, J = 6.9 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.79, 162.21, 159.68, 133.07, 129.54, 126.53, 125.45, 116.96, 34.16, 30.93, 23.75; HRMS (ESI+) (m/z) calcd for $C_{13}H_{13}{}^{79}BrClN_2$ [M + H] 310.9951 found 310.9927, calcd for $C_{13}H_{13}{}^{81}BrClN_2$ [M + H] 312.9930 found 312.9912.

5-Bromo-2-chloro-4-(3-(trifluoromethyl)phenyl)pyrimidine (3d). Colorless oil (31 mg, 41%); TLC R_f = 0.5 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.11 (s, 1H), 8.04 (d, J = 7.7 Hz, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.74, 164.04, 161.44, 137.66, 134.11, 132.30, 130.45, 129.04 (q, J = 3.60 Hz), 127.79 (q, J = 3.83 Hz), 125.09 (q, J = 272.34 Hz), 118.59; GC-MS (EI) m/z (relative intensity): 337.8 (M^+, 24.6), 257.1 (99.99), 230.0 (8.73), 194.0 (3.82), 176.0 (12.01), 145.1 (8.80), 100.1 (3.77), 69.1 (7.34).

5-Bromo-2-chloro-[4,5′-bipyrimidin]-2′-amine (3e). White solid (31 mg, 43%); **mp 123 °C**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 2H), 8.74 (s, 1H), 5.51 (s, 2H); ^{13}C NMR (101 MHz, mixture of $CDCl_3$ and CD_3OD) δ 159.10, 158.42, 157.96, 155.88, 155.56, 115.63, 111.92; HRMS (ESI+) (m/z) calcd for $C_8H_6{}^{79}BrClN_5$ [M + H] 285.9495 found 285.9481, calcd for $C_8H_6{}^{81}BrClN_5$ [M + H] 287.9475 found 287.9460.

5-Bromo-2-chloro-4-(6-methoxypyridin-3-yl)pyrimidine (3f). White solid (16 mg, 21%); **mp 117 °C**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, J = 2.2 Hz, 1H), 8.76 (s, 1H), 8.13 (dd, J = 8.7, 2.4 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 4.02 (s, 3H); ^{13}C NMR

(126 MHz, $CDCl_3$) δ 165.56, 164.14, 162.39, 159.83, 148.84, 139.62, 124.86, 116.67, 110.80, 54.03; HRMS (ESI+) (*m*/*z*) calcd for $C_{10}H_8{}^{79}BrClN_3O$ [M + H] 299.9539 found 299.9541, calcd for $C_{10}H_8{}^{81}BrClN_3O$ [M + H] 301.9519 found 301.9519.

5-Bromo-4-phenylpyrimidin-2-amine (4a). White solid (42 mg, 67%); **mp 153 °C**; TLC R_f = 0.6 (30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.72–7.66 (m, 2H), 7.49–7.45 (m, 3H), 5.25 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.24, 161.67, 160.88, 137.40, 129.90, 128.91, 128.16, 106.42; HRMS (ESI+) (*m*/*z*) calcd for $C_{10}H_9{}^{79}BrN_3$ [M + H] 249.9980 found 249.9965, calcd for $C_{10}H_9{}^{81}BrN_3$ [M + H] 251.9959 found 251.9945.

5-Bromo-4-(*p*-tolyl)pyrimidin-2-amine (4b). White solid (35 mg, 53%); **mp 149 °C**; TLC R_f = 0.7 (30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 5.34 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.16, 161.69, 160.79, 158.56, 134.54, 128.91, 128.84, 106.34, 21.47; HRMS (ESI+) (*m*/*z*) calcd for $C_{11}H_{11}BrN_3$ [M + H] 264.0136 found 264.0130.

5-Bromo-4-(*m*-tolyl)pyrimidin-2-amine (4c). Yellow solid (40 mg, 60%); **mp 139 °C**; TLC R_f = 0.7 (30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.51–7.43 (m, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.28 (s, 1H), 5.24 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.49, 161.68, 160.78, 158.55, 137.36, 130.62, 129.36, 127.99, 126.01, 106.44, 21.46; HRMS (ESI+) (*m*/*z*) calcd for $C_{11}H_{11}BrN_3$ [M + H] 264.0136 found 264.0122.

5-Bromo-4-(4-(*tert*-butyl)phenyl)pyrimidin-2-amine (4d). White solid (44 mg, 57%); **mp 145 °C**; TLC R_f = 0.7 (30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 5.21 (s, 2H), 1.35 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.03, 160.64, 159.80, 152.17, 133.44, 127.65, 124.11, 105.31, 33.82, 30.19; HRMS (ESI+) (*m*/*z*) calcd for $C_{14}H_{17}BrN_3$ [M + H] 306.0606 found 306.0594.

5-Bromo-4-(2,4,5-trimethylphenyl)pyrimidin-2-amine (4e). Red oil (48 mg, 65%); TLC R_f = 0.7 (30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.03 (s, 1H), 6.95 (s, 1H), 5.32 (s, 2H), 2.26 (s, 6H), 2.21–2.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.81, 161.60, 159.82, 137.69, 135.09, 133.93, 132.24, 131.61, 128.78, 108.16, 19.60, 19.25, 18.78; HRMS (ESI+) (*m*/*z*) calcd for $C_{13}H_{15}BrN_3$ [M + H] 292.0449 found 292.0428.

5-Bromo-4-(*o*-tolyl)pyrimidin-2-amine (4f). Colorless oil (21 mg, 32%); TLC R_f = 0.7 (30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.36–7.32 (m, 1H), 7.31–7.26 (m, 2H), 7.21–7.16 (m, 1H), 5.20 (s, 2H), 2.21 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.58, 161.50, 160.08, 137.61, 135.11, 130.36, 129.23, 127.78, 125.80, 108.18, 19.36; HRMS (ESI+) (*m*/*z*) calcd for $C_{11}H_{11}{}^{79}BrN_3$ [M + H] 264.0131 found 264.0128, calcd for $C_{11}H_{11}{}^{81}BrN_3$ [M + H] 266.0116 found 266.0108.

5-Bromo-4-(2,5-dimethylphenyl)pyrimidin-2-amine (4g). Yellow solid (24 mg, 34%); **mp 168 °C**; TLC R_f = 0.7 (30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.15 (s, 2H), 6.99 (s, 1H), 5.30 (s, 2H), 2.34 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.79, 161.56, 159.95, 137.48, 135.34, 131.93, 130.23, 129.97, 128.17, 108.13, 20.92, 18.83; HRMS (ESI+) (*m*/*z*) calcd for $C_{12}H_{13}BrN_3$ [M + H] 278.0293 found 278.0284.

5-Bromo-4-(4-chlorophenyl)pyrimidin-2-amine (4h). White solid (37 mg, 52%); **mp 163 °C**; TLC R_f = 0.7 (30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 8.6 Hz, 2H), 5.23 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.93, 161.66, 161.10, 136.14, 135.73, 130.46, 128.43, 106.17; HRMS (ESI+) (*m*/*z*) calcd for $C_{10}H_8BrClN_3$ [M + H] 283.9590 found 283.9601.

5-Bromo-4-(3-chlorophenyl)pyrimidin-2-amine (4i). Yellow solid (30 mg, 42%); **mp 121 °C**; TLC R_f = 0.7 (30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.70 (t, *J* = 1.7 Hz, 1H), 7.61 (dt, *J* = 7.4, 1.5 Hz, 1H), 7.46–7.38 (m, 2H), 5.25 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.74, 161.60, 161.13, 138.97, 134.23, 129.99, 129.45, 129.10, 127.18, 106.18; HRMS (ESI+) (*m*/*z*) calcd for $C_{10}H_8BrClN_3$ [M + H] 283.9590 found 283.9581.

5-Bromo-4-(4-(trifluoromethyl)phenyl)pyrimidin-2-amine (4j). White solid (34 mg, 42%); **mp 129 °C**; TLC R_f = 0.5 (30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.83 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 5.27 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.80, 160.59, 160.13, 139.69, 130.65 (q, *J* = 32.63 Hz), 128.39, 124.14 (q, *J* = 3.7 Hz), 122.81 (q, *J* = 272.46 Hz), 105.13; HRMS (ESI+) (*m*/*z*) calcd for $C_{11}H_8BrF_3N_3$ [M + H] 317.9854 found 317.9841.

5-Bromo-4-(3-(trifluoromethyl)phenyl)pyrimidin-2-amine (4k). Colorless oil (28 mg, 31%); TLC R_f = 0.5 (30% EtOAc/hexane); ^{1}H NMR δ (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.93 (s, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 5.18 (s, 2H); ^{13}C NMR δ 163.53, 161.70, 161.25, 158.54, 138.05, 132.32, 128.61, 126.53 (q, *J* = 3.79 Hz), 126.16 (q, *J* = 3.84 Hz), 123.86 (q, *J* = 272.35 Hz), 106.15; HRMS (ESI+) (*m*/*z*) calcd for $C_{11}H_8BrF_3N_3$ [M + H] 317.9854 found 317.9833.

5-Bromo-4-phenylpyrimidine (5a). Yellow solid (30 mg, 51%); **mp 113 °C**; TLC R_f = 0.5 (20% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.92 (s, 1H), 7.82 (dd, *J* = 6.7, 2.9 Hz, 2H), 7.51 (dd, *J* = 4.9, 1.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.34, 160.15, 156.91, 136.77, 130.35, 129.28, 128.31, 119.19; HRMS (ESI+) (*m*/*z*) calcd for $C_{10}H_8BrN_2$ [M + H] 234.9871 found 234.9857.

4-Phenylpyrimidin-2-amine (6a). White solid (18 mg, 43%); **mp 135 °C**; TLC R_f = 0.4 (30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 5.4 Hz, 1H), 8.01–7.96 (m, 2H), 7.47 (dd, *J* = 5.0, 1.8 Hz, 3H), 7.05 (d, *J* = 5.4 Hz, 1H), 5.52 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.56, 163.28, 158.67, 137.23, 130.61, 128.77, 127.06, 107.78; HRMS (ESI+) (*m*/*z*) calcd for $C_{10}H_{10}N_3$ [M + H] 172.0875 found 172.0857.

4-Phenylpyrimidine (7a).[8a] Yellow oil (15 mg, 37%); TLC R_f = 0.6 (30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.77 (d, *J* = 5.3 Hz, 1H), 8.10 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.73 (dd, *J* = 5.3, 1.1 Hz, 1H), 7.57–7.43 (m, 3H); HRMS (ESI+) (*m*/*z*) calcd for $C_{10}H_9N_2$ [M + H] 157.0766 found 157.0761.

4-Phenylquinazoline (8a). Red oil (20 mg, 38%); TLC R_f = 0.6 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.06 (m, 2H), 7.85 (m, 1H), 7.71 (m, 2H), 7.57–7.48 (m, 4H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.41, 153.61, 150.03, 136.02, 132.72, 129.05, 128.91, 127.84, 127.62, 126.73, 126.09, 122.13; HRMS (ESI+) (*m*/*z*) calcd for $C_{14}H_{11}N_2$ [M + H] 207.0922 found 207.0905.

2-Phenylpyrazine (9a).[10a] Light yellow solid (22 mg, 55%); **mp 119 °C**; TLC R_f = 0.5 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (d, *J* = 1.5 Hz, 1H), 8.61 (dd, *J* = 2.4, 1.6 Hz, 1H), 8.49 (d, *J* = 2.5 Hz, 1H), 8.03–7.99 (m, 2H), 7.50–7.45 (m, 3H); HRMS (ESI+) (*m*/*z*) calcd for $C_{10}H_9N_2$ [M + H] 157.0766 found 157.0764.

2,3-Dimethyl-5-phenylpyrazine (10a). Light yellow oil (27 mg, 59%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.98 (d, *J* = 7.3 Hz, 2H), 7.51–7.41 (m, 3H), 2.61 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.25, 151.95, 150.88, 139.70, 138.26, 130.65, 130.50, 128.12, 23.72, 23.21; HRMS (ESI+) (*m*/*z*) calcd for $C_{12}H_{13}N_2$ [M + H] 185.1079 found 185.1071.

2-Methyl-3-phenylquinoxaline (11a). Red oil (34 mg, 62%); TLC R_f = 0.6 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–7.95 (m, 2H), 7.68–7.62 (m, 2H), 7.60–7.55 (m, 2H), 7.47–7.40 (m, 3H), 2.70 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.93, 152.56, 141.24, 141.00, 139.02, 129.78, 129.27, 129.24, 129.03, 1128.95, 128.60, 128.32, 24.42; HRMS (ESI+) (*m*/*z*) calcd for $C_{15}H_{13}N_2$ [M + H] 221.1079 found 221.1082.

2-Methyl-3-(*m*-tolyl)quinoxaline (11b). Red oil (34 mg, 58%); TLC R_f = 0.7 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14–8.03 (m, 2H), 7.76–7.68 (m, 2H), 7.48–7.45 (m, 1H), 7.43–7.38 (m, 2H), 7.30 (dd, *J* = 4.5, 2.5 Hz, 1H), 2.77 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.18, 152.66, 141.19, 140.97, 138.95, 138.42, 129.78, 129.71, 129.58, 129.23, 129.22, 128.40, 128.29, 125.94, 24.39, 21.53; HRMS (ESI+) (*m*/*z*) calcd for $C_{16}H_{15}N_2$ [M + H] 235.1235 found 235.1227.

2-Methyl-3-(*p*-tolyl)quinoxaline (11c).[10a] Red oil (32 mg, 54%); TLC R_f = 0.7 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–7.93 (m, 2H), 7.69–7.60 (m, 2H), 7.51–7.45 (m, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 2.71 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.99, 152.61, 141.08, 139.02, 136.16, 129.58, 129.23, 129.21, 129.15, 128.91, 128.24, 24.41, 21.35; HRMS (ESI+) (*m*/*z*) calcd for $C_{16}H_{15}N_2$ [M + H] 235.1235 found 235.1227.

2-(4-Bromophenyl)-3-methylquinoxaline (11d). Yellow solid (38 mg, 51%); TLC R_f = 0.8 (10% EtOAc/hexane); **mp 89 °C**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13–8.04 (m, 2H), 7.78–7.71 (m, 2H), 7.70–7.63 (m, 2H), 7.58–7.51 (m, 2H), 2.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.73, 152.17, 141.24, 140.95, 137.81, 130.67, 129.53, 129.17, 128.29, 123.62, 117.31, 24.27; HRMS (ESI+) (*m*/*z*) calcd for $C_{15}H_{11}{}^{79}BrN_2$ [M + H] 299.0184 found 299.0168, calcd for $C_{15}H_{11}{}^{81}BrN_2$ [M + H] 301.0163 found 301.0149.

4-Methyl-2-phenylpyridine (13a).[8d] Colorless oil (19 mg, 44%); TLC R_f = 0.7 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.0 Hz, 1H), 7.90 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.48 (s, 1H), 7.42–7.33 (m, 3H), 6.99 (dd, *J* = 5.0, 0.7 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.35, 149.31, 148.01, 139.39, 128.91, 128.74, 127.01, 123.23, 121.74, 21.29; HRMS (ESI+) (*m*/*z*) calcd for $C_{12}H_{12}N$ [M + H] 170.0970 found 170.0965.

4-Bromo-2-phenylpyridine (13b).[8e] Colorless oil (20 mg, 34%); TLC R_f = 0.8 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 5.3 Hz, 1H), 8.00–7.93 (m, 2H), 7.90 (d, *J* = 1.4 Hz, 1H), 7.48 (dd, *J* = 12.5, 5.1 Hz, 3H), 7.41 (dd, *J* = 5.2, 1.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.93, 150.38, 138.07, 133.51, 129.64, 128.90, 127.03, 125.29, 123.97; HRMS (ESI+) (*m*/*z*) calcd for $C_{11}H_9BrN$ [M + H] 233.9918 found 233.9906.

4-Methyl-2-phenylquinoline (13c).[8f] Colorless oil (20 mg, 36%); TLC R_f = 0.8 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13–8.05 (m, 3H), 7.92 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.67–7.61 (m, 2H), 7.46 (m, 3H), 7.38 (m, 1H), 2.69 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.08, 147.13, 143.77, 138.83, 129.28, 128.30, 128.16, 127.75, 126.52, 126.25, 125.00, 122.58, 118.76, 17.98; HRMS (ESI+) (*m*/*z*) calcd for $C_{16}H_{14}N$ [M + H] 220.1126 found 220.1122.

6-Bromo-4-chloro-2-phenylquinoline (13d). White solid (41 mg, 52%); **mp 110 °C**; TLC R_f = 0.7 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 2.1 Hz, 1H), 8.12 (dd, *J* = 8.1, 1.5 Hz, 2H), 8.02 (d, *J* = 9.0 Hz, 1H), 7.97 (s, 1H), 7.82 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.54–7.49 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.54, 146.59, 140.93, 137.11, 133.07, 130.68, 129.04, 127.98, 126.42, 125.25, 120.37, 118.73, 117.83; HRMS (ESI+) (*m*/*z*) calcd for $C_{15}H_{10}{}^{79}BrClN$ [M + H] 317.9685 found 317.9672, calcd for $C_{15}H_{10}{}^{79}BrClN$ [M + H] 319.9665 found 319.9650.

***tert*-Butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate (21).**[13] ^{1}H NMR δ (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.18 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.98 (s, 1H), 7.14 (dd, *J* = 7.8, 4.8 Hz, 1H), 1.59 (s, 9H), 1.30 (s, 12H).

4-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)pyrimidin-2-amine (meriolin 1). Yellow solid (28 mg, 35%); **mp 222 °C**; TLC R_f = 0.5 (10% MeOH/DCM); ^{1}H NMR δ (500 MHz, DMSO) δ 12.20 (s, 1H), 8.93 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.35 (d, *J* = 2.1 Hz, 1H), 8.29 (dd, *J* = 4.6, 1.6 Hz, 1H), 8.14 (d, *J* = 5.3 Hz, 1H), 7.19 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.07 (d, *J* = 5.3 Hz, 1H), 6.52 (s, 2H); ^{13}C NMR δ (126 MHz, DMSO) δ 163.40, 162.04, 157.09, 149.19, 143.42, 130.72, 128.44, 117.78, 116.70, 112.42, 104.97; HRMS (ESI+) (*m*/*z*) calcd for $C_{11}H_{10}N_5$ [M + H] 212.0936 found 212.0918.

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