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Intramolecular cycloaddition of azomethine ylides activated by aromatic rings: scope and limitations

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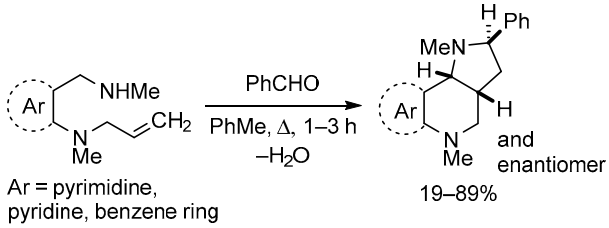


Simple aromatic substituents in the substrate molecule, including pyrimidine, pyridine, and benzene rings, directly facilitated the intramolecular cycloaddition of azomethine ylide to alkene. All of these aromatic substituents aided the formation of azomethine ylides, which then underwent highly diastereospecific sequential cycloaddition. It was shown that both the presence of an electron-deficient aromatic ring and a substituent at *ortho* position of the aromatic ring relative to the aminomethyl group enhanced the reactivity of azomethine ylides towards cycloaddition.

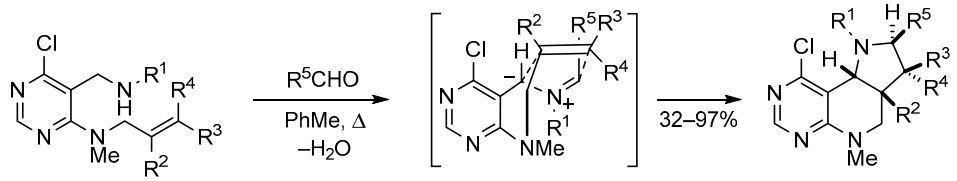
Keywords: azomethine ylide, aromatic ring, 1,3-dipolar cycloaddition, facilitating group, intramolecular reactions, stereocontrol.

The 1,3-dipolar cycloaddition, defined as a reaction of a dipolarophile with a 1,3-dipolar compound, is a classic tool in organic chemistry[1] and offers a reliable synthetic access to five-membered heterocyclic rings.[2] In particular, the reaction of azomethine ylides with alkenes is a powerful method for the preparation of substituted pyrrolidines,[3] which are important building blocks in the synthesis of many natural products and pharmaceuticals.[4] Intramolecular azomethine ylide reactions can provide direct access to polycyclic scaffolds of considerable complexity with high to complete stereocontrol.[5] Despite the abundance of literature related to cycloadditions of azomethine ylides stabilized by electron-withdrawing groups,[3] only a few cases of azomethine ylide reactions have been reported involving amines fused with an aromatic ring that may serve as a direct facilitating group.[6]

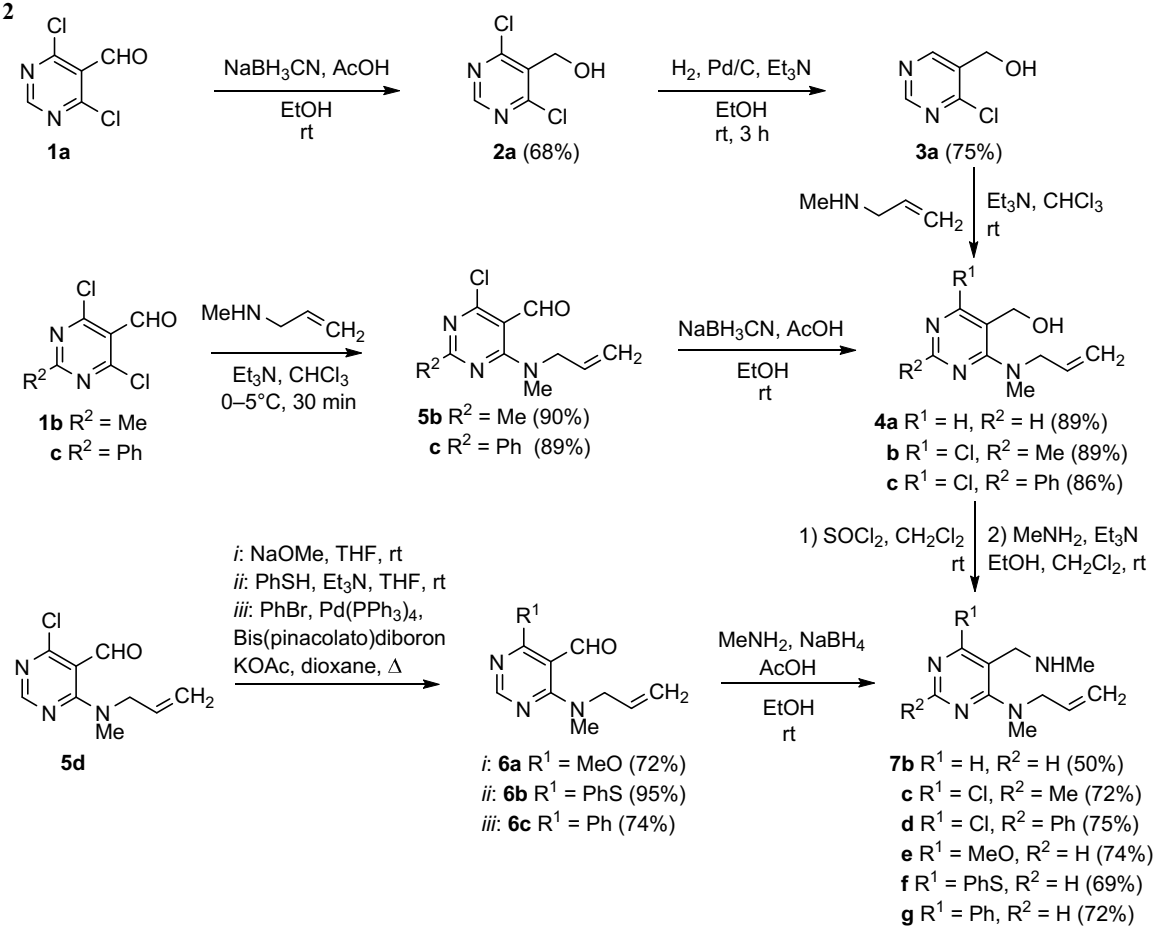
Recently, we reported a highly stereoselective intramolecular cycloaddition of azomethine ylide activated by pyrimidine ring (Scheme 1).[7] The stereochemical outcome of this reaction is rationalized by an S-shaped azomethine ylide intermediate. To the best of our knowledge, this is the first reported intramolecular cycloaddition of an azomethine ylide activated by a simple aromatic ring.[6] Although the preliminary scope of the intramolecular cycloaddition of azomethine ylide activated by pyrimidine ring was studied in our initial report, the effect of aromatic ring remained to be investigated. Thus, a further investigation of the activating effect of substituents including pyrimidine, pyridine, and benzene rings is warranted. Herein, the results of the investigation are presented.

Azomethine ylide cycloaddition in a pyrimidine system. To expand the scope of this new synthetic method, a series of substituted pyrimidines **7b**–**g** were prepared as depicted in Scheme 2. The treatment of starting material **1a** with $NaBH_3CN$ followed by hydrogenation of the hydroxymethyl derivative **2a** on Pd/C catalyst yielded compound **3a**.

Scheme 1



Scheme 2



1a

2a (68%)

3a (75%)

1b R^2 = Me
c R^2 = Ph

5b R^2 = Me (90%)
c R^2 = Ph (89%)

4a R^1 = H, R^2 = H (89%)
b R^1 = Cl, R^2 = Me (89%)
c R^1 = Cl, R^2 = Ph (86%)

5d

i: **6a** R^1 = MeO (72%)
ii: **6b** R^1 = PhS (95%)
iii: **6c** R^1 = Ph (74%)

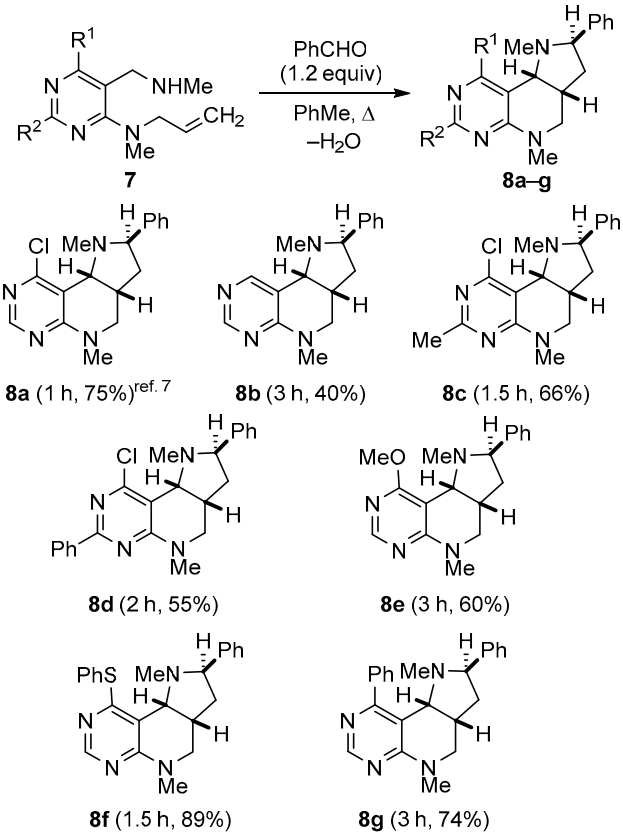
7b R^1 = H, R^2 = H (50%)
c R^1 = Cl, R^2 = Me (72%)
d R^1 = Cl, R^2 = Ph (75%)
e R^1 = MeO, R^2 = H (74%)
f R^1 = PhS, R^2 = H (69%)
g R^1 = Ph, R^2 = H (72%)

Condensation of compound **3a** with *N*-methylprop-2-en-1-amine formed the intermediate **4a**. Intermediates **4b** and **4c** could be obtained from the starting materials **1b** and **1c**, respectively. The nucleophilic substitution reactions of aryl chlorides **1b**,**c** with *N*-methylprop-2-en-1-amine furnished compounds **5b**,**c**. Reduction of aldehydes **5b**,**c** with $NaBH_3CN$ gave intermediates **4b**,**c**. The alcohols **4a**–**c** were converted to the respective secondary amines **7b**–**d** in a two-step process involving chlorination of intermediates **4a**–**c** using $SOCl_2$, followed by the addition of methanamine. Compounds **7e**–**g** could be obtained from the starting material **5d**. Coupling of compound **5d** with a nucleophile (NaOMe and PhSH) or PhBr gave intermediates **6a**–**c**, which after condensation with *N*-methylprop-2-en-1-amine afforded the respective compounds **7e**–**g**.

Compounds **7b**–**g** were studied in cyclization reactions with benzaldehyde under our previously reported conditions of refluxing in toluene with a Dean–Stark trap, in order to investigate the effects of substituents at the pyrimidine ring and to increase the diversity of products (Scheme 3).

As shown in Scheme 3, the reactions of substituted pyrimidines **7a**–**g** with benzaldehyde produced the desired products **8a**–**g** in moderate to good yields. In the previous work, we have shown that the substrate **7a** (R^1 = Cl, R^2 = H) reacted with benzaldehyde to give the product **8a** in 75% yield as a pair of enantiomers.[7] However, with R^1 = H and R^2 = H, only 40% yield of product **8b** was obtained.

Scheme 3



7

8a–g

8a (1 h, 75%)[ref. 7]

8b (3 h, 40%)

8c (1.5 h, 66%)

8d (2 h, 55%)

8e (3 h, 60%)

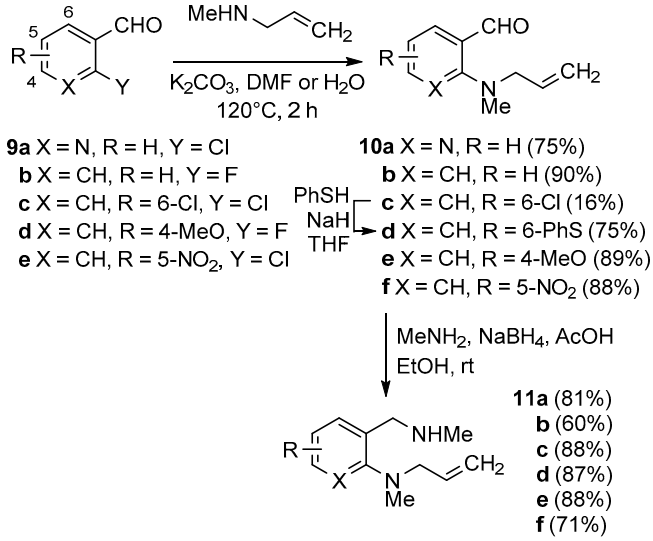
8f (1.5 h, 89%)

8g (3 h, 74%)

The results suggested that the *ortho*-Cl substituent of substrate **7a** had a significant influence on the ease of intramolecular cycloaddition. The 2-methyl-substituted compound **7c** and 2-phenyl-substituted compound **7d** gave a lower yield of the final products **8c**,**d** compared to the substrate **7a**. These results indicated that the reaction was sensitive to electronic effects and an electron-rich aromatic ring was unfavorable for this azomethine ylide cycloaddition. A further survey of the electronic effects revealed that the steric influence seems to be an important factor for enhancing the reactivity (compounds **7e**–**g** *vs* compound **7b**). All of the products **8b**–**g** were characterized as configured with the phenyl group and the two bridgehead hydrogen atoms on the same side of the newly formed pyrrolidine ring, based on the comparison of their ^{1}H NMR spectra with those of compound **8a**, which had been unambiguously characterized by X-ray structural analysis in our previous report.[7]

Azomethine ylide cycloaddition in pyridine and benzene systems. As expected, the precursors **11a**–**f** were prepared *via* a two- or three-step sequence as depicted in Scheme 4. Condensation of compounds **9a**–**c** with *N*-methylprop-2-en-1-amine in the presence of K_2CO_3 as a base formed the respective products **10a**–**c**, while products **10e**,**f** were obtained analogously from compounds **9d**,**e**. Compound **10d** was obtained by reacting the benzaldehyde derivative **10c** with PhSH. Reductive amination of aldehydes **10a**–**f** with methanamine gave the precursors **11a**–**f**.

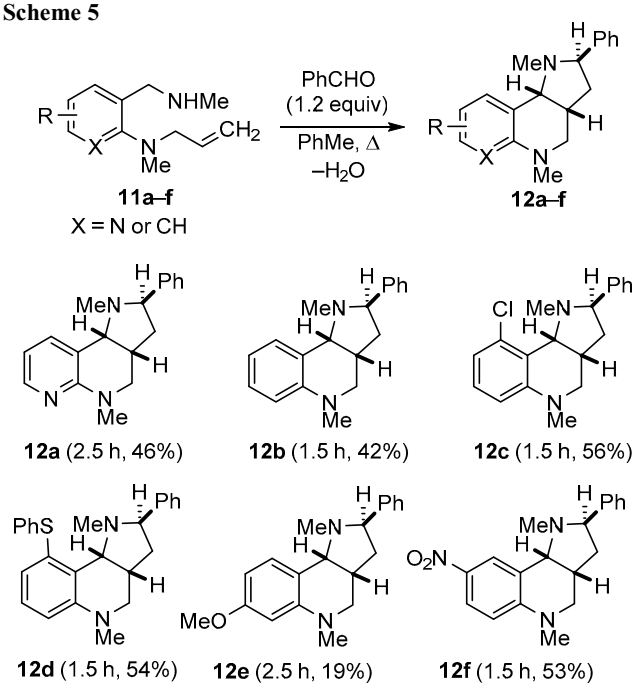
Scheme 4



Precursors **11a**–**f** were studied in reaction with benzaldehyde under the conditions described above to further investigate the electronic effects due to the aromatic ring (the *ortho* substituent effect), and to increase the diversity of products (Scheme 5).

As shown in Scheme 5, pyridin-3-ylmethanamine **11a** and several substituted anilines **11b**–**f** reacted with benzaldehyde to produce the desired products **12a**–**f** in moderate yields. The reaction seemed very sensitive to the electronic effects of aromatic ring since higher yields were obtained when anilines **11** with electron-withdrawing

Scheme 5



groups were employed (compounds **11f** *vs* **11b** *vs* **11e**). The presence of an *ortho* substituent in anilines **11c**,**d** led to higher yields of the final products **12c**,**d** compared to the reactions of analogous aniline **11b**. These results further validated the assumption that the presence of *ortho* substituents relative to the aminomethyl group enhanced the reactivity of azomethine ylides towards cycloaddition.

In conclusion, we have obtained new data about intramolecular cycloadditions of azomethine ylides activated by aromatic rings, including pyrimidine, pyridine, and benzene. The utility of this reaction sequence has been demonstrated by the synthesis of tricyclic derivatives containing fused piperidine and pyrrolidine rings. The reactions were completely stereocontrolled and yielded products in moderate to good yields. The reactivity of azomethine ylides in cycloaddition reactions was enhanced by both the presence of electron-deficient aromatic rings and the presence of *ortho* substituent relative to the aminomethyl group.

Experimental

^{1}H and ^{13}C NMR spectra were acquired on a Varian Mercury (300 MHz) NMR spectrometer with TMS as internal standard and $CDCl_3$ as solvent unless otherwise stated. HRMS analysis was performed on an Agilent 1290-micrOTOF-Q II mass spectrometer (ESI). Melting points were determined on an XT5 melting point apparatus and are uncorrected. Acetonitrile and dichloromethane were dried over CaH_2 and distilled. Toluene was dried over Na and distilled. All other commercial reagents were purchased from Energy Chemical and Sigma-Aldrich, and were used without additional purification.

(4,6-Dichloropyrimidin-5-yl)methanol (2a).[8] A stirred solution of 4,6-dichloro-5-formylpyrimidine (**1a**) (5.00 g, 28.2 mmol) in EtOH (50 ml) was treated with $NaBH_3CN$ (2.66 g, 42.3 mmol), followed by AcOH (5 ml). After

complete consumption of the starting material **1a**, as indicated by TLC, saturated aqueous $NaHCO_3$ (14 ml) was added to quench the reaction. The volatiles were removed *in vacuo*, and saturated aqueous $NaHCO_3$ (200 ml) was added. The mixture was extracted with EtOAc (2 × 200 ml), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (5:1 petroleum ether–EtOAc, v/v) afforded the desired product **2a** as a white solid. Yield 3.44 g (68%), mp 93–95°C (mp 88–90°C[8]). ^{1}H NMR spectrum, δ, ppm: 2.18 (1H, br. s, OH); 4.96 (2H, s, CH_2); 8.74 (1H, s, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 57.7; 131.3; 157.1; 161.7.

(4-Chloropyrimidin-5-yl)methanol (3a). Triethylamine (3 ml) and 10% Pd/C (330 mg) were added to a stirred solution of compound **2a** (3.33 g, 18.6 mmol) in EtOH (30 ml). The mixture was stirred for 3 h under a hydrogen atmosphere provided by a balloon. The Pd/C catalyst was then removed by filtration and the resulting clear solution was concentrated *in vacuo*. Purification by flash chromatography (4:1 to 1:1 petroleum ether–EtOAc, v/v) afforded the starting material **2a** (1.43 g) and the desired product **3a** as a white solid. Yield 1.15 g (75%), mp 62–63°C. ^{1}H NMR spectrum, δ, ppm: 2.76 (1H, s, OH); 4.85 (2H, s, CH_2); 8.85 (1H, s, H Ar); 8.94 (1H, s, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 57.9; 133.7; 156.8; 157.2; 158.2. Found, *m*/*z*: 145.0167 $[M+H]^+$. $C_5H_6ClN_2O$. Calculated, *m*/*z*: 145.0163.

{4-[Allyl(methyl)amino]pyrimidin-5-yl}methanol (4a). A stirred solution of compound **3a** (1.10 g, 7.6 mmol) in $CHCl_3$ (10 ml) was treated with *N*-methylprop-2-en-1-amine (1.08 g, 15.2 mmol), followed by Et_3N (1.6 ml, 11.4 mmol). The resulting solution was stirred for 12 h at room temperature, then washed with saturated aqueous $NaHCO_3$ (10 ml). The aqueous phase was extracted with CH_2Cl_2 (2×15 ml). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (2:1 to 1:5 petroleum ether–EtOAc, v/v) afforded the desired product **4a**. Yield 1.21 g (89%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm: 2.94 (1H, br. s, OH); 3.22 (3H, s, CH_3); 4.27–4.30 (2H, m, $C\underline{H}_2CH=CH_2$); 4.56 (2H, s, $C\underline{H}_2OH$); 5.13–5.24 (2H, m, $CH_2CH=C\underline{H}_2$); 5.86–5.96 (1H, m, $CH_2C\underline{H}=CH_2$); 8.01 (1H, s, H Ar); 8.50 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 37.6; 54.1; 61.0; 116.5; 117.3; 133.6; 156.5; 156.9; 162.0. Found, *m*/*z*: 180.1139 $[M+H]^+$. $C_9H_{14}N_3O$. Calculated, *m*/*z*: 180.1131.

Synthesis of compounds 5b,c (General method). A solution of *N*-methylprop-2-en-1-amine (2.00 g, 28.2 mmol) and Et_3N (4.07 ml, 29.4 mmol) in $CHCl_3$ (20 ml) was added dropwise to a stirred solution of compound **1b** or **1c** (28.2 mmol) in $CHCl_3$ (40 ml) at 0°C. The resulting solution was stirred for 0.5 h at 0–5°C, then washed with H_2O (30 ml) and saturated aqueous $NaHCO_3$ (30 ml), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography (20:1 to 5:1 petroleum ether–EtOAc, v/v) afforded the desired product **5b**,**c**.

4-[Allyl(methyl)amino]-6-chloro-2-methylpyrimidine-5-carbaldehyde (5b). Yield 5.73 g (90%), white solid, mp 55–56°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.52 (3H, s, $ArCH_3$); 2.89 (3H, s, NCH_3); 4.30 (2H, d, *J* = 5.7, $C\underline{H}_2CH=CH_2$); 5.19–5.28 (2H, m, $CH_2CH=C\underline{H}_2$); 5.80–5.90 (1H, m, $CH_2C\underline{H}=CH_2$); 10.33 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 26.1; 40.0; 54.6; 107.7; 118.7; 132.2; 161.4; 164.7; 168.1; 187.2. Found, *m*/*z*: 226.0751 $[M+H]^+$. $C_{10}H_{13}ClN_3O$. Calculated, *m*/*z*: 226.0742.

4-[Allyl(methyl)amino]-6-chloro-2-phenylpyrimidine-5-carbaldehyde (5c). Yield 7.22 g (89%), white solid, mp 81–82°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.97 (3H, s, NCH_3); 4.40 (2H, d, *J* = 6.0, $C\underline{H}_2CH=CH_2$); 5.24–5.31 (2H, m, $CH_2CH=C\underline{H}_2$); 5.88–5.99 (1H, m, $CH_2C\underline{H}=CH_2$); 7.43–7.52 (3H, m, H Ar); 8.38–8.42 (2H, m, H Ar); 10.39 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 40.1; 54.9; 108.3; 118.8; 128.6; 129.2; 132.0; 132.4; 135.9; 161.7; 163.3; 165.5; 187.2. Found, *m*/*z*: 288.0899 $[M+H]^+$. $C_{15}H_{15}ClN_3O$. Calculated, *m*/*z*: 288.0898.

Synthesis of compounds 4b,**c** (General method). A stirred solution of compound **5b**,**c** (2 mmol) in EtOH (5 ml) was treated with $NaBH_3CN$ (189 mg, 3.0 mmol), followed by AcOH (0.5 ml). After complete consumption of the starting material **5b** or **5c**, as indicated by TLC, saturated aqueous $NaHCO_3$ (1.0 ml) was added to quench the reaction. The volatiles were removed *in vacuo*, and saturated aqueous $NaHCO_3$ (20 ml) was added. The mixture was extracted with EtOAc (2×20 ml), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (5:1 to 3:1 petroleum ether–EtOAc, v/v) afforded the desired product **4b** or **4c**.

{4-[Allyl(methyl)amino]-6-chloro-2-methylpyrimidin-5-yl}methanol (4b). Yield 405 mg (89%), white solid, mp 75–76°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.08 (1H, br. s, OH); 2.48 (3H, s, $ArCH_3$); 3.16 (3H, s, NCH_3); 4.21 (2H, d, *J* = 5.1, $C\underline{H}_2CH=CH_2$); 4.64 (2H, s, $C\underline{H}_2OH$); 5.24–5.30 (2H, m, $CH_2CH=C\underline{H}_2$); 5.88–5.98 (1H, m, $CH_2C\underline{H}=CH_2$). ^{13}C NMR spectrum, δ, ppm: 25.5; 38.1; 55.3; 58.2; 110.9; 117.1; 133.8; 161.9; 165.0; 165.6. Found, *m*/*z*: 228.0902 $[M+H]^+$. $C_{10}H_{15}ClN_3O$. Calculated, *m*/*z*: 228.0898.

{4-[Allyl(methyl)amino]-6-chloro-2-phenylpyrimidin-5-yl}methanol (4c). Yield 498 mg (86%), white solid, mp 75–76°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.95 (1H, br. s, OH); 3.27 (3H, s, NCH_3); 4.29 (2H, d, *J* = 5.1, $C\underline{H}_2CH=CH_2$); 4.70 (2H, s, $C\underline{H}_2OH$); 5.27–5.33 (2H, m, $CH_2CH=C\underline{H}_2$); 5.95–6.04 (1H, m, $CH_2C\underline{H}=CH_2$); 7.41–7.46 (3H, m, H Ar); 8.35–8.39 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 38.2; 55.5; 58.6; 111.7; 117.3; 128.4; 128.5; 131.0; 133.8; 136.8; 161.8; 162.8; 165.1. Found, *m*/*z*: 290.1065 $[M+H]^+$. $C_{15}H_{17}ClN_3O$. Calculated, *m*/*z*: 290.1055.

Synthesis of compounds 7b–d (General method). A stirred solution of compound **4b–d** (1.64 mmol) in CH_2Cl_2 (10 ml) was treated with $SOCl_2$ (0.48 ml, 6.6 mmol) at room temperature. After complete consumption of the starting material, as indicated by TLC, the volatiles were removed *in vacuo*. The obtained crude chlorinated product was dissolved in CH_2Cl_2 (5 ml), and this solution was added dropwise at room temperature to a 30% solution of methylamine in ethanol (3 ml) diluted with CH_2Cl_2 (5 ml). After complete consumption of the chlorinated product, as indicated by TLC, the reaction mixture was washed with saturated aqueous $NaHCO_3$ (10 ml). The aqueous layer was

extracted with CH_2Cl_2 (10 ml). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (from 3:1 v/v petroleum ether–EtOAc to 100% EtOAc) afforded the desired products **7b**–**d**.

***N*-Allyl-*N*-methyl-5-[(methylamino)methyl]pyrimidin-4-amine (7b)**. Yield 158 mg (50%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.08 (1H, br. s, NH); 2.46 (3H, s, NHC$\underline{H}_3$); 3.17 (3H, s, NCH_3); 3.62 (2H, s, NHC$\underline{H}_2$); 4.29–4.32 (2H, m, C$\underline{H}_2$CH=CH_2); 5.15–5.24 (2H, m, CH_2CH=C$\underline{H}_2$); 5.85–5.96 (1H, m, CH_2C$\underline{H}$=CH_2); 8.11 (1H, s, H Ar); 8.54 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.0; 37.5; 52.2; 54.3; 112.2; 116.2; 134.2; 156.8; 157.7; 162.6. Found, *m*/*z*: 193.1451 $[M+H]^+$. $C_{10}H_{17}N_4$. Calculated, *m*/*z*: 193.1448.

***N*-Allyl-6-chloro-*N*,2-dimethyl-5-[(methylamino)methyl]-pyrimidin-4-amine (7c)**. Yield 284 mg (72%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.64 (1H, br. s, NH); 2.45 (3H, s, $ArCH_3$); 2.46 (3H, s, NHC$\underline{H}_3$); 3.12 (3H, s, NCH_3); 3.55 (2H, s, NHC$\underline{H}_2$); 4.27 (2H, d, *J* = 4.8, C$\underline{H}_2$CH=CH_2); 5.21–5.28 (2H, m, CH_2CH=C$\underline{H}_2$); 5.87–5.97 (1H, m, CH_2C$\underline{H}$=CH_2). ^{13}C NMR spectrum, δ, ppm: 25.6; 36.7; 37.7; 49.2; 55.4; 111.1; 116.7; 134.4; 161.4; 165.0; 165.6. Found, *m*/*z*: 241.1224 $[M+H]^+$. $C_{11}H_{18}ClN_4$. Calculated, *m*/*z*: 241.1215.

***N*-Allyl-6-chloro-*N*-methyl-5-[(methylamino)methyl]-2-phenylpyrimidin-4-amine (7d)**. Yield 372 mg (75%), pale-yellow solid, mp 89–90°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.76 (1H, br. s, NH); 2.49 (3H, s, NHC$\underline{H}_3$); 3.24 (3H, s, NCH_3); 3.65 (2H, s, NHC$\underline{H}_2$); 4.36 (2H, d, *J* = 4.5, C$\underline{H}_2$CH=CH_2); 5.25–5.34 (2H, m, CH_2CH=C$\underline{H}_2$); 5.95–6.05 (1H, m, CH_2C$\underline{H}$=CH_2); 7.41–7.46 (3H, m, H Ar); 8.34–8.38 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.8; 37.8; 49.5; 55.5; 112.2; 116.8; 128.3; 128.4; 130.7; 134.5; 137.1; 161.3; 162.3; 165.6. Found, *m*/*z*: 303.1384 $[M+H]^+$. $C_{16}H_{20}ClN_4$. Calculated, *m*/*z*: 303.1371.

4-[Allyl(methyl)amino]-6-methoxypyrimidine-5-carbaldehyde (6a). Sodium hydride (14.2 mmol, 60% dispersion in mineral oil) was added to a solution of MeOH (0.57 ml, 14.2 mmol) in THF (10 ml), followed by compound **5d** (1.50 g, 7.1 mmol). The resulting solution was stirred for 0.5 h at room temperature. The volatiles were removed *in vacuo* and EtOAc (40 ml) was added. The organic layers were washed with saturated aqueous $NaHCO_3$ (20 ml) and brine (15 ml), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) afforded the desired product **6a**. Yield 1.065 g (72%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.92 (3H, s, NCH_3); 4.04 (3H, s, OCH_3); 4.25 (2H, d, *J* = 5.1, C$\underline{H}_2$CH=CH_2); 5.16–5.25 (2H, m, CH_2CH=C$\underline{H}_2$); 5.81–5.95 (1H, m, CH_2C$\underline{H}$=CH_2); 8.27 (1H, s, H Ar); 10.24 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 39.9; 54.5; 54.7; 99.5; 118.1; 132.9; 137.0; 158.4; 172.8; 186.6. Found, *m*/*z*: 208.1089 $[M+H]^+$. $C_{10}H_{14}N_3O_2$. Calculated, *m*/*z*: 208.1081.

4-[Allyl(methyl)amino]-6-(phenylsulfanyl)pyrimidine-5-carbaldehyde (6b).[9] A solution of compound **5d** (846 mg, 4.0 mmol) in THF (20 ml) was treated with PhSH (0.62 ml, 6.0 mmol) followed by Et_3N (0.83 ml, 6.0 mmol). The resulting solution was stirred for 2 h at room temperature. The volatiles were removed *in vacuo* and EtOAc (20 ml) was added. The organic layers were washed with saturated aqueous $NaHCO_3$ (10 ml), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification by flash chromatography (10:1 petroleum ether–EtOAc, v/v) afforded the desired product **6b**. Yield 1.08 g (95%), pale-yellow solid, mp 57–58°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.10 (3H, s, NCH_3); 4.23 (2H, d, *J* = 5.1, C$\underline{H}_2$CH=CH_2); 5.24–5.32 (2H, m, CH_2CH=C$\underline{H}_2$); 5.85–5.94 (1H, m, CH_2C$\underline{H}$=CH_2); 7.43–7.46 (3H, m, H Ar); 7.52–7.57 (2H, m, H Ar); 8.23 (1H, s, H Ar); 10.23 (1H, s, CHO).

4-[Allyl(methyl)amino]-6-phenylpyrimidine-5-carbaldehyde (6c). $Pd(PPh_3)_4$ (316 mg, 0.27 mmol), KOAc (1.60 g, 16.3 mmol), and bromobenzene (0.86 ml, 8.2 mmol) were added under nitrogen atmosphere to a stirred solution of bis(pinacolato)diboron (4.06 g, 16 mmol) in 1,4-dioxane (100 ml). The resulting mixture was stirred for 10 h at reflux. After cooling to room temperature, compound **5d** (1.50 g, 7.1 mmol) and saturated aqueous Na_2CO_3 solution (16 ml) were added. The resulting mixture was stirred for 12 h at reflux. The volatiles were removed *in vacuo*, and saturated aqueous $NaHCO_3$ solution (40 ml) was added. The aqueous layer was extracted with EtOAc (2×20 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (5:1 petroleum ether–EtOAc, v/v) afforded the desired product **6c**. Yield 1.33 g (74%), pale-yellow solid, mp 36–37°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.07 (3H, s, NCH_3); 4.38 (2H, d, *J* = 5.7, C$\underline{H}_2$CH=CH_2); 5.24–5.30 (2H, m, CH_2CH=C$\underline{H}_2$); 5.89–5.98 (1H, m, CH_2C$\underline{H}$=CH_2); 7.48–7.56 (3H, m, H Ar); 7.71–7.75 (2H, m, H Ar); 8.63 (1H, s, H Ar); 9.78 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 39.9; 54.5; 111.3; 118.5; 128.7; 130.8; 132.5; 134.8; 136.9; 158.1; 161.2; 173.0; 188.5. Found, *m*/*z*: 254.1296 $[M+H]^+$. $C_{15}H_{16}N_3O$. Calculated, *m*/*z*: 254.1288.

Synthesis of compounds 7e–g (General method). A 30% solution of methanamine in ethanol (4 ml) was added to a stirred solution of compound **6a**–**c** (2.5 mmol) in EtOH (8 ml), followed by AcOH (1 drop). The resulting solution was stirred for 2.5 h at room temperature. $NaBH_4$ (190 mg, 5.0 mmol) was then added, and the mixture was stirred for 0.5 h at room temperature. Saturated aqueous $NaHCO_3$ solution (1.0 ml) was added to quench the reaction. The volatiles were removed *in vacuo*, and saturated aqueous $NaHCO_3$ solution (20 ml) was added again. The mixture was extracted with EtOAc (2×20 ml). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc) afforded the desired product **7e**–**g**.

***N*-Allyl-6-methoxy-*N*-methyl-5-[(methylamino)methyl]-pyrimidin-4-amine (7e)**. Yield 411 mg (74%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.16 (1H, br. s, NH); 2.45 (3H, s, NHC$\underline{H}_3$); 3.05 (3H, s, NC$\underline{H}_3$); 3.52 (2H, s, NHC$\underline{H}_2$); 3.94 (3H, s, OCH_3); 4.15 (2H, d, *J* = 3.3, C$\underline{H}_2$CH=CH_2); 5.20–5.29 (2H, m, CH_2CH=C$\underline{H}_2$); 5.87–5.99 (1H, m, CH_2C$\underline{H}$=CH_2); 8.28 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.8; 37.7; 46.4; 53.9; 55.9; 101.4; 116.5; 134.9; 155.0; 165.7; 169.3. Found, *m*/*z*: 223.1561 $[M+H]^+$. $C_{11}H_{19}N_4O$. Calculated, *m*/*z*: 223.1553.

***N*-Allyl-*N*-methyl-5-[(methylamino)methyl]-6-(phenylsulfanyl)pyrimidin-4-amine (7f)**. Yield 518 mg (69%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.57 (1H, br. s, NH); 2.52 (3H, s, NHC$\underline{H}_3$); 3.10 (3H, s, NC$\underline{H}_3$); 3.68 (2H, s, NHC$\underline{H}_2$); 4.26 (2H, d, *J* = 5.1, C$\underline{H}_2$CH=CH$_2$); 5.24–5.31 (2H, m, CH$_2$CH=C$\underline{H}_2$); 5.91–6.00 (1H, m, CH$_2$C$\underline{H}$=CH$_2$); 7.40–7.43 (3H, m, H Ar); 7.50–7.54 (2H, m, H Ar); 8.28 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.7; 37.5; 49.3; 55.5; 113.8; 116.4; 128.8; 129.0; 129.6; 134.5; 134.9; 155.3; 163.9; 168.1. Found, *m*/*z*: 301.1487 [M+H]$^+$. $C_{16}H_{21}N_4S$. Calculated, *m*/*z*: 301.1481.

***N*-Allyl-*N*-methyl-5-[(methylamino)methyl]-6-phenylpyrimidin-4-amine (7g)**. Yield 483 mg (72%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.48 (1H, br. s, NH); 2.13 (3H, s, NHC$\underline{H}_3$); 3.14 (3H, s, NC$\underline{H}_3$); 3.57 (2H, s, NHC$\underline{H}_2$); 4.27 (2H, d, *J* = 5.1, C$\underline{H}_2$CH=CH$_2$); 5.23–5.31 (2H, m, CH$_2$CH=C$\underline{H}_2$); 5.89–6.02 (1H, m, CH$_2$C$\underline{H}$=CH$_2$); 7.41–7.55 (5H, m, H Ar); 8.60 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.0; 38.0; 49.4; 55.7; 115.5; 117.0; 128.5; 128.6; 128.9; 134.4; 139.7; 155.4; 165.2; 167.1. Found, *m*/*z*: 269.1773 [M+H]$^+$. $C_{16}H_{21}N_4$. Calculated, *m*/*z*: 269.1761.

Synthesis of compounds 10a,e,f (General method). A stirred solution of compound **9a**,**d**,**e** (13 mmol) in DMF (20 ml) was treated with *N*-methylprop-2-en-1-amine (1.11 g, 15.6 mmol), followed by K_2CO_3 (2.70 g, 19.5 mmol). The resulting solution was stirred for 2 h at 120°C. After cooling to room temperature, water (120 ml) was added, and the mixture was extracted with EtOAc (2×40 ml). The combined organic layers were washed with water (30 ml), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography (20:1 petroleum ether–EtOAc, v/v) afforded the desired product **10a**,**e**,**f**.

2-[Allyl(methyl)amino]nicotinaldehyde (10a).[10] Yield 1.72 g (75%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.04 (3H, s, CH$_3$); 4.12–4.14 (2H, m, C$\underline{H}_2$CH=CH$_2$); 5.23–5.31 (2H, m, CH$_2$CH=C$\underline{H}_2$); 5.90–6.00 (1H, m, CH$_2$C$\underline{H}$=CH$_2$); 6.80 (1H, dd, *J* = 7.5, *J* = 4.8, H Ar); 7.96 (1H, dd, *J* = 7.2, *J* = 1.5, H Ar); 8.32 (1H, dd, *J* = 4.8, *J* = 2.1, H Ar); 9.99 (1H, s, CHO).

2-[Allyl(methyl)amino]-4-methoxybenzaldehyde (10e).[11] Yield 2.37 g (89%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.84 (3H, s, NCH$_3$); 3.75 (2H, d, *J* = 5.7, C$\underline{H}_2$CH=CH$_2$); 3.86 (3H, s, OCH$_3$); 5.21–5.31 (2H, m, CH$_2$CH=C$\underline{H}_2$); 5.87–6.00 (1H, m, CH$_2$C$\underline{H}$=CH$_2$); 6.52–6.58 (2H, m, H Ar); 7.77 (1H, d, *J* = 8.4, H Ar); 10.10 (1H, s, CHO).

2-[Allyl(methyl)amino]-5-nitrobenzaldehyde (10f).[11] Yield 2.52 g (88%), yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.06 (3H, s, NCH$_3$); 4.00–4.03 (2H, m, C$\underline{H}_2$CH=CH$_2$); 5.25–5.37 (2H, m, CH$_2$CH=C$\underline{H}_2$); 5.86–5.96 (1H, m, CH$_2$C$\underline{H}$=CH$_2$); 6.99 (1H, d, *J* = 8.7, H Ar); 8.22 (1H, dd, *J* = 9.0, *J* = 2.4, H Ar); 8.62 (1H, d, *J* = 2.7, H Ar); 10.02 (1H, s, CHO).

2-[Allyl(methyl)amino]benzaldehyde (10b).[11] 2-Fluorobenzaldehyde (**9b**) (10 ml, 94.4 mmol) was added to a stirred solution of K_2CO_3 (13 g, 94.4 mmol) in water (100 ml), followed by the addition of *N*-methylprop-2-en-1-amine (8 g, 113 mmol). The resulting solution was stirred for 36 h at reflux. After cooling to room temperature, the reaction mixture was extracted with Et_2O (2×15 ml). The combined Et_2O layers were washed with 10% aqueous HCl (60 ml), and the aqueous layer was washed with Et_2O (15 ml). The aqueous layer was made basic with 10% aqueous NaOH to pH 10 and extracted with EtOAc (3×20 ml). The combined EtOAc layers were washed with brine (30 ml), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography (50:1 petroleum ether–EtOAc, v/v) afforded the desired product **10b**. Yield 14.9 g (90%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.85 (3H, s, NCH$_3$); 3.73 (2H, d, *J* = 5.7, C$\underline{H}_2$CH=CH$_2$); 5.20–5.25 (2H, m, CH$_2$CH=C$\underline{H}_2$); 5.84–5.90 (1H, m, CH$_2$C$\underline{H}$=CH$_2$); 6.99–7.10 (2H, m, H Ar); 7.42–7.49 (1H, m, H Ar); 7.77 (1H, dd, *J* = 7.8, *J* = 1.8, H Ar); 10.26 (1H, s, CHO).

2-[Allyl(methyl)amino]-6-chlorobenzaldehyde (10c). A stirred solution of 2,6-dichlorobenzaldehyde (**9c**) (3.5 g, 20 mmol) in DMF (20 ml) was treated with *N*-methylprop-2-en-1-amine (7 g, 98 mmol), followed by K_2CO_3 (4 g, 29 mmol). The resulting solution was stirred for 2 h at 120°C. After cooling to room temperature, water (120 ml) was added, and the mixture was extracted with EtOAc (3×30 ml). The combined organic layers were washed with water (30 ml) and concentrated *in vacuo*. The crude residue was dissolved in 10% aqueous HCl (20 ml) and washed with Et_2O (2×20 ml). The aqueous layer was made basic with 10% aqueous NaOH to pH 10 and extracted with EtOAc (2×30 ml). The combined EtOAc layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (30:1 petroleum ether–EtOAc, v/v) afforded the desired product **10c**. Yield 684 mg (16%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.83 (3H, s, CH$_3$); 3.73 (2H, d, *J* = 5.7, C$\underline{H}_2$CH=CH$_2$); 5.19–5.30 (2H, m, CH$_2$CH=C$\underline{H}_2$); 5.85–5.95 (1H, m, CH$_2$C$\underline{H}$=CH$_2$); 6.94–6.98 (2H, m, H Ar); 7.30 (1H, t, *J* = 8.1, H Ar); 10.33 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 41.2; 60.5; 117.3; 118.2; 122.1; 123.6; 133.6; 133.7; 137.1; 155.4; 189.4. Found, *m*/*z*: 210.0685 [M+H]$^+$. $C_{11}H_{13}ClNO$. Calculated, *m*/*z*: 210.0680.

2-[Allyl(methyl)amino]-6-(phenylsulfanyl)benzaldehyde (10d). A solution of PhSH (0.182 ml, 1.8 mmol) in THF (10 ml) was treated with NaH (1.8 mmol, 60% dispersion in mineral oil), followed by the addition of compound **10c** (315 mg, 1.5 mmol). The resulting solution was stirred for 6 days at room temperature. The volatiles were removed *in vacuo*, and EtOAc (20 ml) was added. The organic layers were washed with saturated aqueous $NaHCO_3$ solution (10 ml) and brine (10 ml), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) afforded the desired product **10d**. Yield 318 mg (75%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.84 (3H, s, CH$_3$); 3.71 (2H, d, *J* = 5.7, C$\underline{H}_2$CH=CH$_2$); 5.21–5.30 (2H, m, CH$_2$CH=C$\underline{H}_2$); 5.82–5.96 (1H, m, CH$_2$C$\underline{H}$=CH$_2$); 6.41 (1H, d, *J* = 8.1, H Ar); 6.84 (1H, d, *J* = 8.1, H Ar); 7.17 (1H, t, *J* = 8.1, H Ar); 7.40–7.45 (3H, m, H Ar); 7.53–7.57 (2H, m, H Ar); 10.40 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 41.5; 62.1; 115.3; 118.2; 120.2; 124.5; 129.1; 129.7; 132.4; 133.2; 134.0; 135.5; 144.6;

157.6; 191.2. Found, *m/z*: 284.1111 $[M+H]^+$. $C_{17}H_{18}NOS$. Calculated, *m/z*: 284.1104.

Synthesis of compounds 11a–f (General method). A stirred solution of compound **10a**–**f** (2.5 mmol) in EtOH (8 ml) was treated with a 30% solution of methylamine in ethanol (4 ml), followed by AcOH (1 drop). The resulting solution was stirred for 2.5 h at room temperature. $NaBH_4$ (190 mg, 5.0 mmol) was added, and the mixture was stirred for 0.5 h at room temperature. Saturated aqueous $NaHCO_3$ solution (1.0 ml) was added to quench the reaction. The volatiles were removed *in vacuo*, and saturated aqueous $NaHCO_3$ solution (20 ml) was added, after which the mixture was extracted with EtOAc (2×20 ml). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc) afforded the desired product **11**.

***N*-Allyl-*N*-methyl-3-[(methylamino)methyl]pyridin-2-amine (11a)**. Yield 387 mg (81%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.81 (1H, br. s, NH); 2.43 (3H, s, $NHC\underline{H}_3$); 2.82 (3H, s, $NC\underline{H}_3$); 3.72 (2H, s, $NHC\underline{H}_2$); 3.75 (2H, d, *J* = 5.7, $C\underline{H}_2CH=CH_2$); 5.16–5.31 (2H, m, $CH_2CH=C\underline{H}_2$); 5.87–5.98 (1H, m, $CH_2C\underline{H}=CH_2$); 6.87 (1H, dd, *J* = 7.5, *J* = 4.8, H Ar); 7.61 (1H, dd, *J* = 7.5, *J* = 1.8, H Ar); 8.18 (1H, dd, *J* = 4.8, *J* = 2.1, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.2; 38.9; 52.0; 57.7; 116.8; 117.3; 126.0; 135.4; 138.0; 146.0; 161.9. Found, *m/z*: 192.1498 $[M+H]^+$. $C_{11}H_{18}N_3$. Calculated, *m/z*: 192.1495.

***N*-Allyl-*N*-methyl-2-[(methylamino)methyl]aniline (11b)**. Yield 285 mg (60%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.80 (1H, br. s, NH); 2.43 (3H, s, $NHC\underline{H}_3$); 2.66 (3H, s, $NC\underline{H}_3$); 3.49 (2H, d, *J* = 6.3, $C\underline{H}_2CH=CH_2$); 3.80 (2H, s, $NHC\underline{H}_2$); 5.13–5.28 (2H, m, $CH_2CH=C\underline{H}_2$); 5.82–5.91 (1H, m, $CH_2C\underline{H}=CH_2$); 7.02–7.12 (2H, m, H Ar); 7.19–7.33 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 35.8; 41.5; 52.2; 60.5; 117.2; 120.7; 123.7; 127.7; 129.9; 134.6; 135.5; 152.1. Found, *m/z*: 191.1547 $[M+H]^+$. $C_{12}H_{19}N_2$. Calculated, *m/z*: 191.1543.

***N*-Allyl-3-chloro-*N*-methyl-2-[(methylamino)methyl]-aniline (11c)**. Yield 494 mg (88%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.28 (1H, br. s, NH); 2.43 (3H, s, $NHC\underline{H}_3$); 2.68 (3H, s, $NC\underline{H}_3$); 3.90 (2H, d, *J* = 5.4, $C\underline{H}_2CH=CH_2$); 3.94 (2H, s, $NHC\underline{H}_2$); 5.15–5.30 (2H, m, $CH_2CH=C\underline{H}_2$); 5.80–5.91 (1H, m, $CH_2C\underline{H}=CH_2$); 7.00 (1H, dd, *J* = 7.8, *J* = 1.5, H Ar); 7.06–7.17 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.1; 41.4; 48.7; 60.8; 117.3; 119.2; 124.5; 128.4; 132.7; 135.2; 135.8; 154.5. Found, *m/z*: 225.1160 $[M+H]^+$. $C_{12}H_{18}ClN_2$. Calculated, *m/z*: 225.1153.

***N*-Allyl-*N*-methyl-2-[(methylamino)methyl]-3-(phenylsulfanyl)aniline (11d)**. Yield 649 mg (87%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.20 (1H, br. s, NH); 2.41 (3H, s, $NHC\underline{H}_3$); 2.69 (3H, s, $NC\underline{H}_3$); 3.59 (2H, d, *J* = 6.3, $C\underline{H}_2CH=CH_2$); 4.01 (2H, s, $NHC\underline{H}_2$); 5.15–5.29 (2H, m, $CH_2CH=C\underline{H}_2$); 5.83–5.95 (1H, m, $CH_2C\underline{H}=CH_2$); 6.99–7.31 (8H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.4; 41.6; 49.3; 61.0; 117.2; 120.2; 126.7; 128.2 (2C); 129.0; 129.3; 130.3; 135.6; 136.3; 136.7; 153.9. Found, *m/z*: 299.1587 $[M+H]^+$. $C_{18}H_{23}N_2S$. Calculated, *m/z*: 299.1576.

***N*-Allyl-5-methoxy-*N*-methyl-2-[(methylamino)methyl]-aniline (11e)**. Yield 485 mg (88%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.19 (1H, br. s, NH); 2.42 (3H, s, $NHC\underline{H}_3$); 2.64 (3H, s, $NC\underline{H}_3$); 3.49 (2H, d, *J* = 5.7, $C\underline{H}_2CH=CH_2$); 3.74 (2H, s, $NHC\underline{H}_2$); 3.79 (3H, s, OCH_3); 5.14–5.27 (2H, m, $CH_2CH=C\underline{H}_2$); 5.79–5.92 (1H, m, $CH_2C\underline{H}=CH_2$); 6.58 (1H, d, *J* = 8.1, H Ar); 6.66 (1H, s, H Ar); 7.22 (1H, d, *J* = 8.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.0; 41.4; 51.9; 55.3; 60.5; 107.5; 107.7; 117.2; 126.9; 130.9; 135.5; 153.4; 159.4. Found, *m/z*: 221.1657 $[M+H]^+$. $C_{13}H_{21}N_2O$. Calculated, *m/z*: 221.1648.

***N*-Allyl-*N*-methyl-2-[(methylamino)methyl]-4-nitroaniline (11f)**. Yield 418 mg (71%), yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.71 (1H, br. s, NH); 2.47 (3H, s, $NHC\underline{H}_3$); 2.83 (3H, s, $NC\underline{H}_3$); 3.75 (2H, d, *J* = 5.7, $C\underline{H}_2CH=CH_2$); 3.78 (2H, s, $NHC\underline{H}_2$); 5.23–5.32 (2H, m, $CH_2CH=C\underline{H}_2$); 5.80–5.94 (1H, m, $CH_2C\underline{H}=CH_2$); 7.00 (1H, d, *J* = 9.0, H Ar); 8.05 (1H, dd, *J* = 8.7, *J* = 2.7, H Ar); 8.27 (1H, d, *J* = 3.0, H Ar).^{13}C NMR spectrum, δ, ppm: 36.5; 40.2; 52.2; 59.2; 117.9; 118.4; 123.4; 125.9; 132.9; 134.2; 141.7; 157.6. Found, *m/z*: 236.1399 $[M+H]^+$. $C_{12}H_{18}N_3O_2$. Calculated, *m/z*: 236.1394.

Synthesis of compounds 8b–g and 12a–f (General method). A stirred solution of compound **7b**–**g** or **11a**–**f** (0.5 mmol) in toluene (2 ml) was treated with benzaldehyde (61 μl, 0.6 mmol). The resulting solution was heated in an azeotropic distillation apparatus for 1.5–3 h under N_2 atmosphere. The volatiles were removed *in vacuo*. Purification by flash column chromatography (5:1 to 2:1 petroleum ether–EtOAc, v/v) afforded the desired product **8** or **12**.

(2*R,3a*R**,9b*R**)-1,5-Dimethyl-2-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[2',3':4,5]pyrido[2,3-*d*]pyrimidine (8b)**. Yield 56 mg (40%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.03 (3H, s, 1-CH_3); 2.16–2.35 (2H, m, 3-CH_2); 2.61–2.69 (1H, m, 3a-CH); 3.18 (3H, s, 5-CH_3); 3.28–3.42 (2H, m, 4-CH_2); 3.97 (1H, d, *J* = 5.4, 9b-CH); 4.13 (1H, dd, *J* = 7.8, *J* = 6.0, 2-CH); 7.24–7.38 (5H, m, H Ar); 7.94 (1H, s, H Ar); 8.52 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 34.1; 35.2; 36.0; 37.5; 51.7; 60.0; 65.3; 112.0; 127.4; 128.5; 128.7; 142.6; 154.8; 157.6; 160.1. Found, *m/z*: 281.1769 $[M+H]^+$. $C_{17}H_{21}N_4$. Calculated, *m/z*: 281.1761.

(2*R,3a*R**,9b*R**)-9-Chloro-1,5,7-trimethyl-2-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[2',3':4,5]pyrido[2,3-*d*]-pyrimidine (8c)**. Yield 109 mg (66%), pale-yellow solid, mp 161–163°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.12 (3H, s, 1-CH_3); 2.21–2.26 (2H, m, 3-CH_2); 2.46–2.54 (4H, m, 3a-CH, 7-CH_3); 3.14–3.47 (5H, m, 5-CH_3, 4-CH_2); 4.26–4.31 (1H, m, 2-CH); 4.53 (1H, s, 9b-CH); 7.26–7.48 (5H, m, H Ar).^{13}C NMR spectrum, δ, ppm: 25.8; 33.5; 35.7; 36.5; 37.9; 51.0; 58.4; 65.0; 127.4; 128.3; 128.5; 129.8; 142.8; 159.2; 160.7; 166.3. Found, *m/z*: 329.1536 $[M+H]^+$. $C_{18}H_{22}ClN_4$. Calculated, *m/z*: 329.1528.

(2*R,3a*R**,9b*R**)-9-Chloro-1,5-dimethyl-2,7-diphenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[2',3':4,5]pyrido[2,3-*d*]-pyrimidine (8d)**. Yield 108 mg (55%), pale-yellow solid, mp 154–155°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.16 (3H, s, 1-CH_3); 2.20–2.30 (2H, m, 3-CH_2); 2.42–2.60 (1H, m, 3a-CH); 3.25–3.34 (1H, m) and 3.40–3.65 (1H, m, 4-CH_2); 3.34 (3H, s, 5-CH_3); 4.20–4.34 (1H, m, 2-CH); 4.60 (1H, d, *J* = 4.5, 9b-CH); 7.32–7.45 (8H, m, H Ar);

8.38–8.41 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 33.7; 35.8; 36.7; 38.2; 51.2; 58.5; 65.3; 106.7; 127.3; 128.2; 128.3; 128.4; 128.5; 130.7; 137.4; 143.4; 160.1; 160.8; 162.4. Found, *m*/*z*: 391.1690 $[M+H]^+$. $C_{23}H_{24}ClN_4$. Calculated, *m*/*z*: 391.1684.

(2*R,3a*R**,9b*R**)-9-Methoxy-1,5-dimethyl-2-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[2',3':4,5]pyrido[2,3-*d*]-pyrimidine (8e)**. Yield 93 mg (60%), pale-yellow solid, mp 103–104°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.03 (3H, s, 1-CH_3); 2.11–2.33 (2H, m, 3-CH_2); 2.44–2.50 (1H, m, 3a-CH); 3.17 (3H, s, 5-CH_3); 3.19–3.36 (2H, m, 4-CH_2); 3.89 (3H, s, OCH_3); 4.18 (1H, t, *J* = 7.8, 2-CH); 4.41 (1H, d, *J* = 4.5, 9b-CH); 7.28–7.39 (5H, m, H Ar); 8.27 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 33.8; 35.8; 36.7; 38.1; 51.7; 53.4; 55.9; 65.5; 127.2; 128.0; 128.4; 128.5; 143.2; 156.1; 161.3; 167.5. Found, *m*/*z*: 311.1874 $[M+H]^+$. $C_{18}H_{23}N_4O$. Calculated, *m*/*z*: 311.1866.

(2*R,3a*R**,9b*R**)-1,5-Dimethyl-2-phenyl-9-(phenylsulfanyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[2',3':4,5]pyrido[2,3-*d*]-pyrimidine (8f)**. Yield 173 mg (89%), pale-yellow powder, mp 99–100°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.21–2.25 (5H, m, 1-CH_3, 3-CH_2); 2.46–2.52 (1H, m, 3a-CH); 3.20 (3H, s, 5-CH_3); 3.22–3.41 (2H, m, 4-CH_2); 4.26 (1H, t, *J* = 8.4, 2-CH); 4.61 (1H, d, *J* = 4.2, 9b-CH); 7.29–7.32 (1H, m, H Ar); 7.36–7.43 (7H, m, H Ar); 7.50–7.53 (2H, m, H Ar); 8.28 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 34.1; 36.6; 36.8; 38.4; 51.1; 58.8; 65.7; 127.2; 127.9; 128.5; 128.6; 129.1; 129.8; 130.5; 134.8; 143.7; 156.6; 158.6; 165.9. Found, *m*/*z*: 389.1799 $[M+H]^+$. $C_{23}H_{25}N_4S$. Calculated, *m*/*z*: 389.1794.

(2*R,3a*R**,9b*R**)-1,5-Dimethyl-2,9-diphenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[2',3':4,5]pyrido[2,3-*d*]pyrimidine (8g)**. Yield 132 mg (74%), pale-yellow solid, mp 156–157°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.95–2.00 (1H, m) and 2.19–2.26 (1H, m, 3-CH_2); 2.03 (3H, s, 1-CH_3); 2.44–2.52 (1H, m, 3a-CH); 3.27 (3H, s, 5-CH_3); 3.33–3.42 (2H, m, 4-CH_2); 4.11 (1H, t, *J* = 6.9, 2-CH); 4.51 (1H, d, *J* = 3.3, 9b-CH); 7.20–7.33 (5H, m, H Ar); 7.40–7.49 (3H, m, H Ar); 7.90 (2H, d, *J* = 6.6, H Ar); 8.62 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 35.1; 36.7; 38.6; 39.8; 51.2; 58.9; 67.1; 108.0; 127.0; 127.1; 128.1; 128.4; 129.0; 129.4; 138.4; 144.5; 156.9; 160.4; 163.3. Found, *m*/*z*: 357.2087 $[M+H]^+$. $C_{23}H_{25}N_4$. Calculated, *m*/*z*: 357.2074.

(2*R,3a*R**,9b*R**)-1,5-Dimethyl-2-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*][1,8]naphthyridine (12a)**. Yield 64 mg (46%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.02 (3H, s, 1-CH_3); 2.22–2.27 (2H, m, 3-CH_2); 2.79–2.87 (1H, m, 3a-CH); 3.10 (3H, s, 5-CH_3); 3.23 (2H, d, *J* = 5.7, 4-CH_2); 3.93 (1H, t, *J* = 7.2, 2-CH); 4.10 (1H, d, *J* = 6.3, 9b-CH); 7.54 (1H, dd, *J* = 7.5, *J* = 4.8, H Ar); 7.23–7.36 (6H, m, H Ar); 8.10 (1H, dd, *J* = 5.4, *J* = 1.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 35.7; 35.8; 37.3; 38.3; 53.6; 62.6; 66.1; 111.7; 115.5; 127.2; 128.2; 128.3; 138.4; 142.6; 146.9; 158.5. Found, *m*/*z*: 280.1816 $[M+H]^+$. $C_{18}H_{22}N_3$. Calculated, *m*/*z*: 280.1808.

(2*R,3a*R**,9b*R**)-1,5-Dimethyl-2-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline (12b)**. Yield 58 mg (42%), pale-yellow solid, mp 69–70°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.02 (3H, s, 1-CH_3); 2.25–2.34 (2H, m, 3-CH_2); 2.86 (3H, s, 5-CH_3); 2.93–3.07 (3H, m, 3a-CH, 4-CH_2); 3.90 (1H, t, *J* = 6.9, 2-CH); 4.13 (1H, d, *J* = 6.3, 9b-CH); 6.69–6.75 (2H, m, H Ar); 7.08 (1H, d, *J* = 7.8, H Ar); 7.16–7.22 (1H, m, H Ar); 7.26–7.36 (5H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.2; 37.8; 39.2; 40.0; 56.8; 62.5; 67.1; 112.1; 116.9; 122.8; 127.1; 127.2; 128.3; 128.4; 131.4; 143.1; 150.0. Found, *m*/*z*: 279.1865 $[M+H]^+$. $C_{19}H_{23}N_2$. Calculated, *m*/*z*: 279.1856.

(2*R,3a*R**,9b*R**)-9-Chloro-1,5-dimethyl-2-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline (12c)**. Yield 88 mg (56%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.07 (3H, s, 1-CH_3); 2.24–2.33 (2H, m, 3-CH_2); 2.79–2.82 (1H, m, 3a-CH); 2.90 (3H, s, 5-CH_3); 3.01 (2H, d, *J* = 5.4, 4-CH_2); 4.09–4.14 (1H, m, 2-CH); 4.79 (1H, s, 9b-CH); 6.64 (1H, d, *J* = 8.1, H Ar); 6.79 (1H, d, *J* = 7.8, H Ar); 7.09 (1H, t, *J* = 8.1, H Ar); 7.41–7.44 (5H, m, H Ar).^{13}C NMR ($CDCl_3$) spectrum, δ, ppm: 36.4; 37.9; 40.0; 40.3; 56.1; 58.6; 67.8; 110.3; 118.5; 120.8; 127.0; 127.9; 128.4; 128.7; 136.5; 143.9; 151.0. Found, *m*/*z*: 313.1472 $[M+H]^+$. $C_{19}H_{22}ClN_2$. Calculated, *m*/*z*: 313.1466.

(2*R,3a*R**,9b*R**)-1,5-Dimethyl-2-phenyl-9-(phenylsulfanyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline (12d)**. Yield 104 mg (54%), pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.10 (3H, s, 1-CH_3); 2.21–2.27 (2H, m, 3-CH_2); 2.71–2.77 (1H, m, 3a-CH); 2.91 (3H, s, 5-CH_3); 2.99–3.03 (2H, m, 4-CH_2); 4.02–4.18 (1H, m, 2-CH); 4.85 (1H, s, 9b-CH); 6.62–6.66 (2H, m, H Ar); 7.07 (1H, t, *J* = 7.5, H Ar); 7.21–7.35 (10H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 37.0; 38.3; 40.0; 40.1; 56.2; 59.3; 67.9; 110.6; 121.3; 123.8; 126.7; 126.9; 127.8; 128.4; 128.5; 129.1; 131.0; 136.9; 137.7; 144.0; 150.2. Found, *m*/*z*: 387.1893 $[M+H]^+$. $C_{25}H_{27}N_2S$. Calculated, *m*/*z*: 387.1889.

(2*R,3a*R**,9b*R**)-7-Methoxy-1,5-dimethyl-2-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline (12e)**. Yield 29 mg (19%), pale-yellow solid, mp 104–105°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.02 (3H, s, 1-CH_3); 2.23–2.28 (2H, m, 3-CH_2); 2.85 (3H, s, 5-CH_3); 2.89–2.97 (1H, m, 3a-CH); 3.00–3.08 (2H, m, 4-CH_2); 3.80 (3H, s, OMe); 3.87 (1H, t, *J* = 7.4, 2-CH); 4.13 (1H, d, *J* = 8.4, 9b-CH); 6.27–6.30 (2H, m, H Ar); 7.00 (1H, d, *J* = 8.4, H Ar); 7.25–7.35 (5H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 36.0; 37.4; 39.2; 39.9; 55.2; 56.4; 62.0; 66.9; 98.8; 101.2; 115.3; 127.0; 128.2; 128.3; 132.1; 143.1; 150.9; 159.9. Found, *m*/*z*: 309.1976 $[M+H]^+$. $C_{20}H_{25}N_2O$. Calculated, *m*/*z*: 309.1961.

(2*R,3a*R**,9b*R**)-1,5-Dimethyl-8-nitro-2-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline (12f)**. Yield 86 mg (53%), yellow solid, mp 159–160°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.04 (3H, s, 1-CH_3); 2.17–2.35 (2H, m, 3-CH_2); 2.67–2.78 (1H, m, 3a-CH); 3.07 (3H, s, 5-CH_3); 3.24–3.39 (2H, m, 4-CH_2); 4.03 (1H, d, *J* = 6.0, 9b-CH); 4.10 (1H, dd, *J* = 7.8, *J* = 6.6, 2-CH); 6.62 (1H, d, *J* = 9.0, H Ar); 7.24–7.36 (5H, m, H Ar); 7.94 (1H, d, *J* =2.7, H Ar); 8.07 (1H, dd, *J* = 9.0, *J* = 2.4, H Ar). ^{13}C NMR spectrum, δ, ppm: 34.9; 35.3; 37.5; 39.4; 53.8; 61.8; 65.4; 110.0; 125.4; 127.3; 127.5; 127.6; 128.3; 128.9; 136.4; 142.5; 152.3. Found, *m*/*z*: 324.1715 $[M+H]^+$. $C_{19}H_{22}N_3O_2$. Calculated, *m*/*z*: 324.1707.

The Supplementary information file containing NMR spectra of all new compounds is available at http://link.springer.com/journal/10593.

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References

1. (a) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984, Vol. 2, p. 277. (b) Tkachuk, A. V.; Kurbatov, S. V.; Burov, O. N.; Kletskii, M. E.; Morozov, P. G.; Minkin, V. I. *Chem. Heterocycl. Compd.* **2014**, *50*, 26. [*Khim. Geterotsikl. Soedin.* **2014**, 32.]
2. (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (b) Harwood, L. M.; Vickers, R. J. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A.; Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002, p. 169. (c) Najera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105.
3. (a) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (b) Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem. Rev.* **2008**, *108*, 3174. (c) Burrell, A. J. M.; Coldham, I. *Curr. Org. Synth.* **2010**, *7*, 312. (d) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6784. (e) Narayan, R.; Potowski, M.; Jia, Z.; Antonchick, A. P.; Waldmann, H. *Acc. Chem. Res.* **2014**, *47*, 1296. (f) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2014**, *50*, 12434.
4. (a) Witherup, K. M.; Ransom, R. W.; Graham, A. C.; Bernard, A. M.; Salvatore, M. J.; Lumma, W. C.; Anderson, P. S.; Pitzenberger, S. M.; Varga, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6682. (b) Merritt, J. R.; Liu, J.; Quadros, E.; Morris, M. L.; Liu, R.; Zhang, R.; Jacob, B.; Postelnek, J.; Hicks, C. M.; Chen, W.; Kimble, E. F.; Rogers, W. L.; O'Brien, L.; White, N.; Desai, H.; Bansal, S.; King, G.; Ohlmeyer, M. J.; Appell, K. C.; Webb, M. L. *J. Med. Chem.* **2009**, *52*, 1295. (c) Ueda, J.; Takagi, M.; Shin-ya, K. *J. Nat. Prod.* **2009**, *72*, 2181. (d) Vartak, A. P.; Nickell, J. R.; Chagkutip, J.; Dwoskin, L. P.; Crooks, P. A. *J. Med. Chem.* **2009**, *52*, 7878. (e) Xue, F.; Kraus, J. M.; Labby, K. J.; Ji, H.; Mataka, J.; Xia, G.; Li, H.; Delker, S. L.; Roman, L. J.; Martásek, P.; Poulos, T. L.; Silverman, R. B. *J. Med. Chem.* **2011**, *54*, 6399. (f) Lorthiois, E.; Breitenstein, W.; Cumin, F.; Ehrhardt, C.; Francotte, E.; Jacoby, E.; Ostermann, N.; Sellner, H.; Kosaka, T.; Webb, R. L.; Rigel, D. F.; Hassiepen, U.; Richert, P.; Wagner, T.; Maibaum, J. *J. Med. Chem.* **2013**, *56*, 2207. (g) Krogsgaard-Larsen, N.; Storgaard, M.; Møller, C.; Demmer, C. S.; Hansen, J.; Han, L.; Monrad, R. N.; Nielsen, B.; Tapken, D.; Pickering, D. S.; Kastrup, J. S.; Frydenvang, K.; Bunch, L. *J. Med. Chem.* **2015**, *58*, 6131.
5. (a) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765. (b) Coldham, I.; Burrell, A. J. M.; Guerrand, H. D. S.; Oram, N. *Org. Lett.* **2011**, *13*, 1267. (c) Purushothaman, S.; Prasanna, R.; Raghunathan, R. *Tetrahedron Lett.* **2013**, *54*, 6450. (d) Vidadala, S. R.; Golz, C.; Strohmann, C.; Daniliuc, C.-G.; Waldmann, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 651. (e) Zhang, W.; Wang, J.; Luo, X.; Meng, X.; Li, Z. *Tetrahedron Lett.* **2016**, *57*, 1981.
6. (a) Wang, B.; Mertes, M. P.; Mertes, K. B.; Takusagawa, F. *Tetrahedron Lett.* **1990**, *31*, 5543. (b) Ardill, H.; Fontaine, X. L. R.; Grigg, R.; Henderson, D.; Montgomery, J.; Sridharan, V.; Surendrakumar, S. *Tetrahedron* **1990**, *46*, 6449. (c) Parmar, N. J.; Pansuriya, B. R.; Labana, B. M.; Kant, R.; Gupta, V. K. *RSC Adv.* **2013**, *3*, 17527. (d) Mantelingu, K.; Lin, F.; Seidel, D. *Org. Lett.* **2014**, *16*, 5910. (e) Kumar, C. S. P.; Harsha, K. B.; Sandhya, N. C.; Ramesha, A. B.; Mantelingu, K.; Rangappa, K. S. *New J. Chem.* **2015**, *39*, 8397.
7. Xie, H.; Xiang, J.; Dang, Q.; Bai, X. *Synlett* **2012**, *23*, 585.
8. Darout, E.; McClure, K. F.; Mascitti, V. *Tetrahedron* **2012**, *68*, 4596.
9. Yang, F.; Zheng, L.; Xiang, J.; Dang, Q.; Bai, X. *ACS Comb. Sci.* **2010**, *12*, 476.
10. Zhang, Y.; Zheng, L.; Yang, F.; Zhang, Z.; Dang, Q.; Bai, X. *Tetrahedron* **2015**, *71*, 1930.
11. Zhang, Y.; Yang, F.; Zheng, L.; Dang, Q.; Bai, X. *Org. Lett.* **2014**, *16*, 6041.