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Regio- and Chemoselective Metalation of Chloropyrimidine Derivatives with TMPMgCl·LiCl and $TMP_2Zn{\cdot}2\,MgCl_2{\cdot}2\,LiCl$**

Marc Mosrin and Paul Knochel*[a]

Abstract: Efficient zincation and magnesiation of chlorinated pyrimidines can be performed at convenient temperatures (e.g., 25 and 55 °C) by using TMPMgCl·LiCl and $TMP_2Zn{\cdot}2\,MgCl_2{\cdot}2\,LiCl$ (TMP = 2,2,6,6-tetramethylpiperidyl) as effective bases. Quenching of the resulting zincated or magnesiated pyrimidines with various electrophiles furnishes highly functionalized pyrimidines in 51–93% yield. Oxidative aminations were carried out, thus leading to aminated pyrimidines. By using this methodology, we have also prepared pharmaceutically relevant pyrazolopyrimidines and the fungicide Mepanipyrim.

Keywords: chemoselectivity · magnesium · metalation · pyrimidines · regioselectivity · zinc

Introduction

Pyrimidines are important heterocyclic scaffolds and their derivatives occupy a privileged position among substances with pharmaceutical or agrochemical applications.[1] The direct functionalization of these heterocycles by lithiation is difficult due to the high reactivity of the ring toward the addition of organometallic reagents,[2] which implies that low temperatures are quite often required for the metalation of pyrimidines.[3] Quéguiner and Radinov[4] reported the regioselective lithiation of polychloropyrimidines by using classical lithium amide bases. The sole example of a pyrimidine deprotonation at the C2 position was reported by Kanamoto and co-workers:[5] 4-(*tert*-butoxycarbonyl)amino-2-(trimethylsilyl)pyrimidine was obtained in 11% yield after deprotonation with lithium 2,2,6,6-tetramethylpiperidine and trapping with trimethylsilyl chloride (TMSCl). Recently, we have shown that TMPMgCl·LiCl[6] (**1**; TMP = 2,2,6,6-tetramethylpiperidyl) allows direct functionalization of the pyrimidine rings, including uracil and thiouracil derivatives.[7] Herein, we report the extension of this method with chloropyrimidines as the starting materials. These complementary procedures for the metalation of pyrimidine use reagent **1** and $TMP_2Zn{\cdot}2\,MgCl_2{\cdot}2\,LiCl$[8] (**2**) and enable selective functionalization at all of the positions of the pyrimidine ring under mild conditions starting from inexpensive commercial compounds. Applications of this method to the synthesis of biologically relevant molecules will also be presented.

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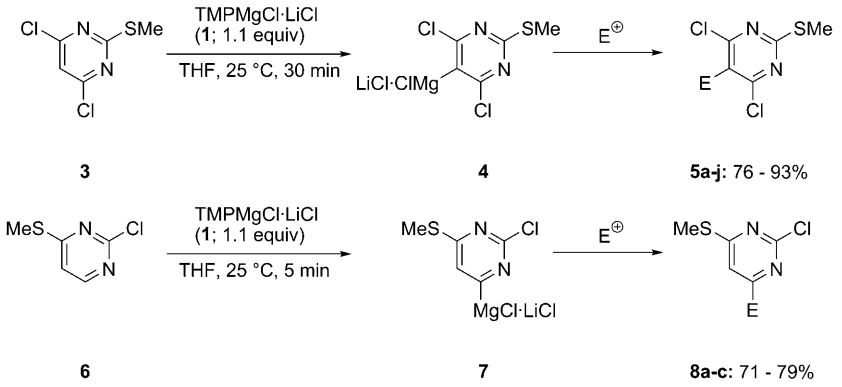
[**] TMP = 2,2,6,6-tetramethylpiperidyl.

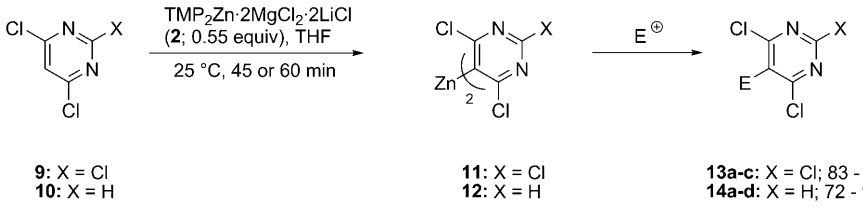
Results and Discussion

We first investigated the metalation of 4,6-dichloro-2-(methylthio)pyrimidine (**3**). Thus, the treatment of **3** with reagent **1** (1.1 equiv, 25 °C, 30 min) leads to a 5-magnesiated pyrimidine **4** (Scheme 1). Trapping with various electrophiles, such as PhCHO, $NCCO_2Et$, CH_3I, $(BrCCl_2)_2$, Me_3SiCN, or iodomethyl pivalate, leads to 5-substituted pyrimidines **5a–f** in 76–92% yield (Table 1, entries 1–6). Acylations can also be readily performed after transmetalation with CuCN·2 LiCl.[9] Quenching of the metalated species with 4-fluorobenzoyl chloride, 3,3-dimethylbutanoyl chloride, PhCOCl, and furan-2-carbonyl chloride furnishes 5-ketopyrimidine derivatives **5g–j** in 84–93% yield (Table 1, entries 7–10). The metalation of 2-chloro-4-(methylthio)pyrimidine (**6**) can also be selectively achieved at position 6 with **1** (1.1 equiv, 25 °C, 5 min), thus providing the magnesium reagent **7** (Scheme 1). Iodination by reaction with I_2 leads to the iodopyrimidine derivative **8a** in 71% yield (Table 1, entry 11). Reaction with $(BrCCl_2)_2$ furnishes the bromopyrimidine **8b** in 79% yield (Table 1, entry 12). Chlorination using $F_2ClCCCl_2F$ leads to the chloropyrimidine **8c** in 72% yield (Table 1, entry 13).

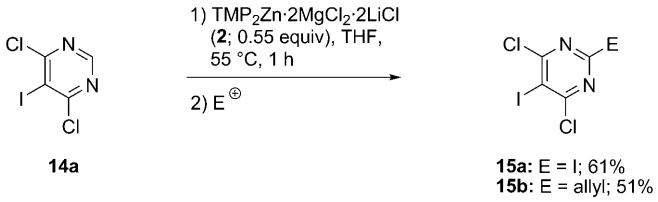
We extended this approach to the functionalization of other polychloropyrimidines and treated 2,4,6-trichloropyri-



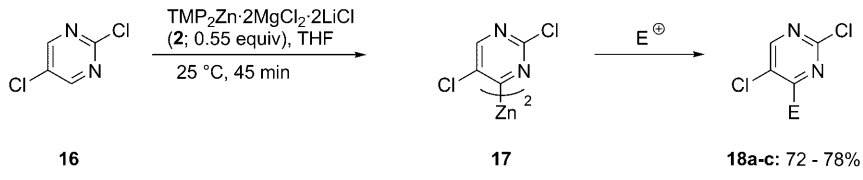
Scheme 1. Chemoselective magnesiation of 4,6-dichloro-2-(methylthio)pyrimidine (**3**) at C5 and 2-chloro-4-(methylthio)pyrimidine (**6**) at C6 by using reagent **1** (1.1 equiv) and trapping with electrophiles (E).



Scheme 2. Regio- and chemoselective metalation of 2,4,6-trichloropyrimidine (**9**) and 4,6-dichloropyrimidine (**10**) at C5 by using reagent **2** (0.55 equiv) and trapping with electrophiles.



Scheme 3. Chemoselective metalation and trapping of 5-iodo-4,6-dichloropyrimidine (**14a**) at C2 by using reagent **2** (0.55 equiv).

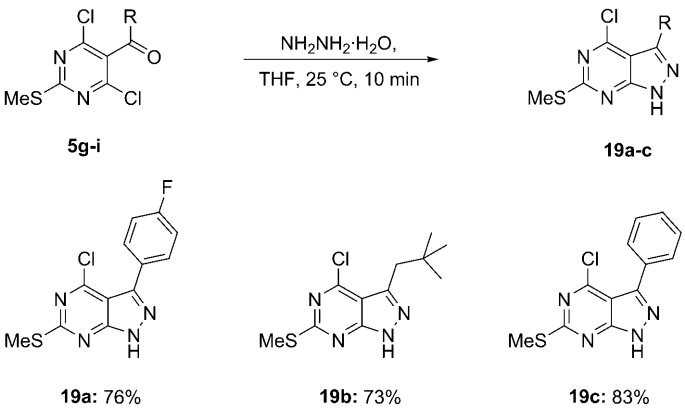


Scheme 4. Regio- and chemoselective metalation of 2,5-dichloropyrimidine (**16**) at C4 by using reagent **2** (0.55 equiv) and trapping with electrophiles.

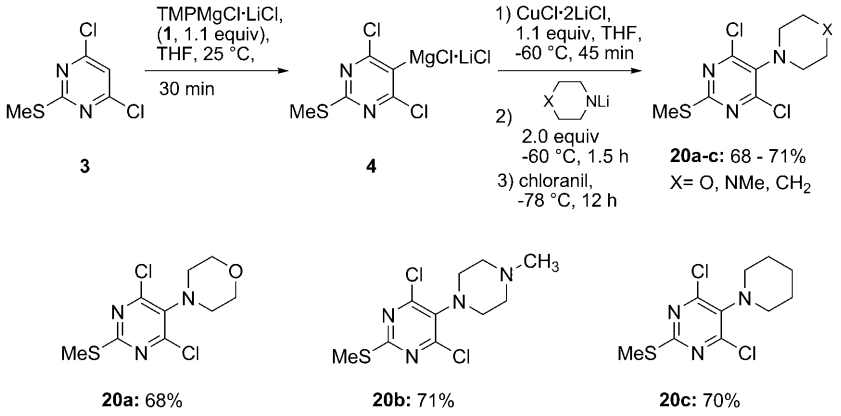
midine (**9**) and 4,6-dichloropyrimidine (**10**) with reagent **2** (0.55 equiv, 25 °C; Scheme 2). The treatment of **9** with **2** (0.55 equiv) provides the corresponding zinc reagent **11** after 60 min at 25 °C. Trapping with typical electrophiles (I_2, allyl bromide (after the addition of a catalytic amount of CuCN·2 LiCl), and propionyl chloride (after transmetalation with CuCN·2 LiCl)[9]) furnishes 5-substituted pyrimidines **13a–c** in 83–90 % yield (Table 2, entries 1–3). Smooth deprotonation of **10** can also be carried out under mild conditions with reagent **2** (0.55 equiv) and affords the zinc species **12** at 25 °C within 45 minutes. Quenching with I_2, PhCOCl (after transmetalation with CuCN·2 LiCl),[9] 3-bromocyclohexene (after the addition of a catalytic amount of CuCN·2 LiCl), and chloranil[10] affords the 5-functionalized pyrimidines **14a–d** in 72–91 % yield (Table 2, entries 4–7). A further metalation is also achieved at C2 by the addition of reagent **2** (0.55 equiv) to 5-substituted pyrimidines (Scheme 3). Thus, 4,6-dichloro-5-iodopyrimidine (**14a**) was converted into the 2-zincated species at 55 °C within 1 h and was iodinated by reaction with I_2, thus leading to the 2-iodopyrimidine (**15a**) in 61 % yield (Table 2, entry 8). Reaction with allyl bromide (after the addition of a catalytic amount of CuCN·2 LiCl) furnishes the allyl derivative **15b** in 51 % yield (Table 2, entry 9). The metalation of 2,5-dichloropyrimidine (**16**) can also be performed under mild conditions (Scheme 4). Thus, the treatment of **16** with reagent **2** (0.55 equiv) provides the corresponding zinc reagent **17** after 45 min at 25 °C. Trapping with I_2 provides the iodopyrimidine **18a** in 72 % yield (Table 2, entry 10). The formation of a new C–C bond can also be readily achieved by a Negishi cross-coupling,[11] thus giving the 4-substituted pyrimidines **18b** and **18c** in 78 and 73 % yield, respectively (Table 2, entries 11 and 12).

This method is of great utility for the preparation of pharmaceutically active heterocycles such as pyrazolopyrimidines.[12] The treatment of 5-ketopyrimidine derivatives **5g–i** with $NH_2NH_2·H_2O$ at 25 °C allows the formation of the pyrazolopyrimidines **19a–c** in 73–83 % yield (Scheme 5).

Aminopyrimidines are also well known for displaying a large spectrum of biological activity.[13] Recently, we developed an amination method that tolerates a broad range of functionalized groups and is not sensitive to the steric hindrance in the substrates.[14] By using this method, amination reactions can also be carried out starting from compound **3**. The deprotonation of **3** with reagent **1** (1.1 equiv, 25 °C, 30 min) after transmetalation with CuCl·2 LiCl leads to the



Scheme 5. Synthesis of the pyrazolopyrimidines **19a–c**.



Scheme 6. Amination reactions starting from 4,6-dichloro-2-(methylthio)pyrimidine (**3**), thus furnishing aminopyrimidine derivatives **20a–c**.

addition of the lithium amide species and chloranil to the 5-aminated pyrimidines **20a–c** in 68–71% yield (Scheme 6).

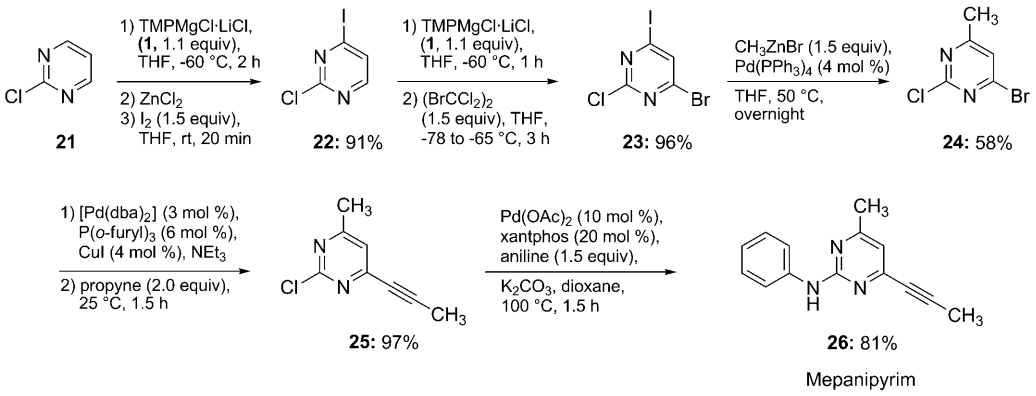
To demonstrate the robustness of our metalation method, we performed the synthesis of the fungicide Mepanipyrim[15] (**26**; Scheme 7). The treatment of 2-chloropyrimidine (**21**) with reagent **1** (1.1 equiv, −60°C, 2 h) after transmetalation with $ZnCl_2$ and quenching with I_2 leads to the 4-iodopyrimidine **22** in 91% yield. Subsequent magnesiation of **22** at position 6 can be readily achieved with reagent **1** (1.1 equiv, −60°C, 1 h) and provides 2-chloro-4-bromo-6-iodopyrimidine (**23**) in 96% yield after trapping with $(BrCCl_2)_2$. The Negishi cross-coupling[11] furnishes the 4-methylpyrimidine derivative **24** in 58% yield. The Sonogashira reaction[16] of **24** then affords the 6-alkynylpyrimidine **25** in 97% yield. Finally, a Buchwald–Hartwig Pd-catalyzed amination[17] allows the substitution of the chlorine atom at position 2 to give Mepanipyrim **26** in 81% yield.

Conclusion

In summary, we have reported the efficient metalation of chlorinated pyrimidines that proceeds at convenient temperatures with **1** and **2** as effective bases. Quenching of the resulting magnesiated or zincated pyrimidines with various electrophiles has been performed in satisfactory yields. This method displays a large scope of applicability and allows functionalization of all the positions of a pyrimidine unit. It may find broad application in the synthesis of pharmaceutically and agrochemically relevant molecules. Extension of this methodology to the preparation of new materials is currently under investigation in our laboratories.

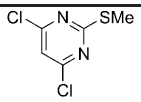
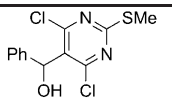
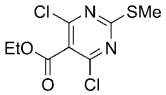
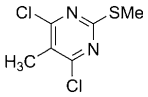
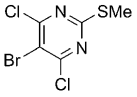
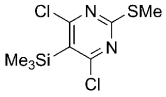
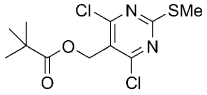
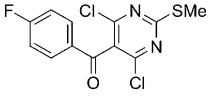
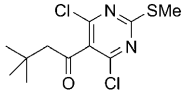
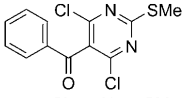
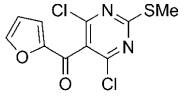
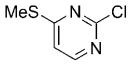
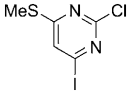
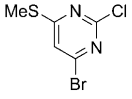
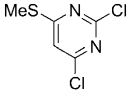
Experimental Section

General: All the reactions were carried out in an argon atmosphere in flame-dried glassware. Syringes that were used to transfer anhydrous solvents or reagents were purged with argon prior to use. THF was continuously heated to reflux and freshly distilled from sodium benzophenone



Scheme 7. Synthesis of the fungicide Mepanipyrim **26**.

Table 1. Products obtained by the magnesiation of **3** and **6** with reagent **1** and reactions with electrophiles.

Entry	Substrate		T [°C]	t [min]	E^+	Product		Yield [%][a]
1		**3**	25	30	PhCHO		**5a**	90
2		**3**	25	30	$NCCO_2Et$		**5b**	86
3		**3**	25	30	CH_3I		**5c**	92
4		**3**	25	30	$(BrCCl_2)_2$		**5d**	89
5		**3**	25	30	Me_3SiCN		**5e**	79
6		**3**	25	30	iodomethyl pivalate		**5f**	76
7		**3**	25	30	4-fluorobenzoyl chloride		**5g**	93[b]
8		**3**	25	30	3,3-dimethylbutyryl chloride		**5h**	84[b]
9		**3**	25	30	benzoyl chloride		**5i**	90[b]
10		**3**	25	30	furan-2-carbonyl chloride		**5j**	86[b]
11		**6**	25	5	I_2		**8a**	71
12		**6**	25	5	$(BrCCl_2)_2$		**8b**	79
13		**6**	25	5	FCl_2CCClF_2		**8c**	72

[a] Yield of the isolated analytically pure product. [b] Transmetalation with CuCN·2LiCl (1.1 equiv) was performed.

ketyl under nitrogen. The yields refer to the yields of isolated compounds estimated to be >95% pure as determined by ^{1}H NMR spectroscopic (25°C) and capillary GC analysis. Column chromatographic purification was performed on SiO_2 (0.040–0.063 mm, 230–400 mesh ASTM) from Merck if not specially indicated.

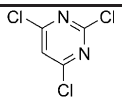
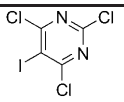
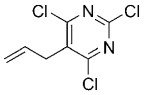
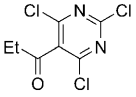
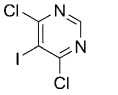
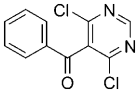
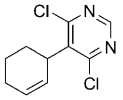
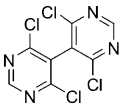
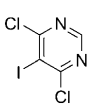
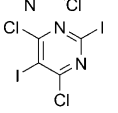
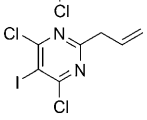
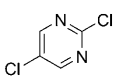
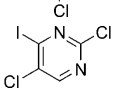
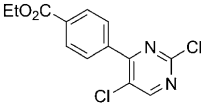
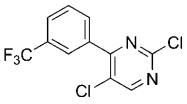
Typical procedure 1 (TP2): **preparation of TMPMgCl·LiCl (1)**: A dry, argon-flushed 250-mL flask equipped with a magnetic stirrer and a septum was charged with freshly titrated *i*-PrMgCl·LiCl (100 mL, 1.2 M, 120 mmol) in THF to which 2,2,6,6-tetramethylpiperidine (TMPH; 18.7 g, 132 mmol, 1.1 equiv) was added dropwise at 25°C. The reaction mixture was stirred at 25°C until gas evolution was completed (ca. 48 h). The fresh solution of **1** in THF was titrated at 25°C with benzoic acid and 4-(phenylazo)diphenylamine as the indicator.

Typical procedure 2 (TP2): **preparation of $TMP_2Zn·2MgCl_2·2LiCl$ (2)**: Freshly titrated **1** (100 mmol, 1.00 M, 100 mL) in THF was added dropwise to $ZnCl_2$ (53.0 mmol, 7.22 g), which had been dried in an argon-flushed Schlenk flask in vacuo at 140°C for 4 h and then cooled to 25°C. The resulting mixture was stirred for 15 h at 25°C. The freshly prepared solution of **2** in THF was titrated prior to use at 0°C with benzoic acid and 4-(phenylazo)diphenylamine as the indicator. A concentration of 0.5 M in THF was obtained.

Typical procedure 3 (TP3): **general procedure for the metalation**: A dry, argon-flushed 10-mL Schlenk tube equipped with a magnetic stirrer and a septum was charged with **1** (1.2 M, 0.92 mL, 1.1 mmol, 1.1 equiv) in THF or **2** (0.79 M, 1.39 mL, 0.55 mmol, 0.55 equiv) in THF. The pyrimidine substrate (1.0 mmol) in THF (2 mL) was added dropwise at temperature T_1. The completion of the metalation was checked by GC analysis of aliquots of the reaction mixture quenched with a solution of I_2 in THF. The electrophile or its solution in THF was added at temperature T_2. After completion of the reaction (checked by GC analysis of aliquots of the reaction mixture quenched with saturated aqueous NH_4Cl), the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with diethyl ether (5× 30 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo. The crude residue was purified by filter column chromatography (CH_2Cl_2/pentane).

4,6-Dichloro-2-(methylthio)pyrimidin-5-yl)-phenylmethanol (5a): 4,6-Dichloro-2-(methylthio)pyrimidine (**3**; 292 mg, 1.5 mmol) dissolved in dry THF (3 mL) was added dropwise at 25°C to a solution of **1** (1.14 M, 1.45 mL, 1.65 mmol) in THF and stirred at the same temperature for 30 min according to TP3. Benzaldehyde (239 mg, 2.25 mmol) in dry THF (3 mL) was slowly added at 25°C and the resulting mixture was stirred for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (5×30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:3) furnished **5a** as a colorless solid (405 mg, 90%). M.p. 83.9–84.6°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.36 (m, 5H), 6.52 (s, 1H), 3.48 (bs, 1H), 2.57 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0, 160.8, 139.5, 128.2, 127.5, 126.7, 125.0, 70.2, 14.2 ppm; MS (70 eV, EI): m/z (%): 300 [^{35}Cl−M^+] (100), 223 (29); IR (attenuated total reflection (ATR)): $\tilde{\nu}$ = 3561, 3447, 2925, 1538, 1478, 1339, 1308, 1259, 1171, 1111, 1021, 876, 814, 727, 711, 639 cm^{-1}; HRMS (EI): m/z: calcd for $C_{12}H_{10}{}^{35}Cl_2N_2O^{32}S$: 299.9891; found: 299.9878.

Table 2. Products obtained by the zincation of **6**, **7**, and **16** with reagent **2** and reactions with electrophiles.

Entry	Substrate		T [°C]	t [min]	E^+	Product		Yield [%][a]
1		**9**	25	60	I_2		**13a**	83
2		**9**	25	60	allyl bromide		**13b**	90[c]
3		**9**	25	60	propionyl chloride		**13c**	86[b]
4		**10**	25	45	I_2		**14a**	91
5		**10**	25	45	benzoyl chloride		**14b**	86[b]
6		**10**	25	45	3-bromo-1-cyclohexene		**14c**	72[c]
7		**10**	25	45	chloranil		**14d**	82
8		**14a**	55	60	I_2		**15a**	61
9		**14a**	55	0	allyl bromide		**15b**	51[c]
10		**16**	25	45	I_2		**18a**	72
11		**16**	25	45	ethyl 4-iodobenzoate		**18b**	78[d]
12		**16**	25	45	3-iodobenzo trifluoride		**18c**	73[d]

[a] Yield of isolated analytically pure product. [b] Transmetalation with CuCN·2 LiCl (1.1 equiv) was performed. [c] Transmetalation with CuCN·2 LiCl (5 mol %) was performed. [d] Obtained by Pd-catalyzed cross-coupling.

4,6-Dichloro-2-(methylthio)pyrimidine-5-carboxylic acid ethyl ester (5b): Compound **3** (292 mg, 1.5 mmol) dissolved in dry THF (3 mL) was added dropwise at 25 °C to a solution of **1** (1.14 M, 1.45 mL, 1.65 mmol) in THF and stirred at the same temperature for 30 min according to TP3. Ethyl cyanoformate (298 mg, 3 mmol) was slowly added at 25 °C and the resulting mixture was stirred for 20 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (5 × 30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by fast flash column chromatography (CH_2Cl_2/pentane 1:5) furnished **5b** as a colorless solid (345 mg, 86 %). M.p. 63.6–65.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.42 (q, 2 H, J = 6 Hz), 2.56 (s, 3 H), 1.38 ppm (t, J = 6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 162.5, 157.9, 121.9, 62.9, 14.5, 13.9 ppm; MS (70 eV, EI): m/z (%): 266 [^{35}Cl−M^+] (100), 238 (55), 221 (53); IR (ATR): $\tilde{\nu}$ = 2982, 2932, 1735, 1550, 1479, 1374, 1346, 1320, 1293, 1217, 1067, 1008, 860, 825, 780 cm^{-1}; HRMS (EI): m/z: calcd for $C_8H_8{}^{35}Cl_2N_2O_2{}^{32}S$: 265.9684; found: 265.9689.

4,6-Dichloro-5-methyl-2-(methylthio)-pyrimidine (5c): Compound **3** (292 mg, 1.5 mmol) in dry THF (3 mL) was added dropwise at 25 °C to a solution of **1** (1.14 M, 1.45 mL, 1.65 mmol) in THF and stirred at the same temperature for 30 min according to TP3. Iodomethane (426 mg, 3 mmol) was then slowly added at 25 °C and the resulting mixture was stirred for 20 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (5 × 30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:1) furnished **5c** as a colorless solid (287 mg, 92 %). M.p. 60.2–62.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.48 (s, 3 H), 2.32 ppm (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 161.1, 122.7, 15.4, 14.2 ppm; MS (70 eV, EI): m/z (%): 208 [^{35}Cl−M^+] (100), 162 (31), 127 (20); IR (ATR): $\tilde{\nu}$ = 2930, 2480, 1545, 1480, 1383, 1343, 1316, 1292, 1222, 1190, 1116, 1010, 973, 862, 792, 756, 694 cm^{-1}; HRMS (EI): m/z: calcd for $C_6H_6{}^{35}Cl_2N_2O_2{}^{32}S$: 207.9629; found: 207.9620.

4,6-Dichloro-5-bromo-2-(methylthio)-pyrimidine (5d): Compound **3** (292 mg, 1.5 mmol) dissolved in dry THF (3 mL) was added dropwise at 25 °C to a solution of **1** (1.14 M, 1.45 mL, 1.65 mmol) in THF and stirred at the same temperature for 30 min according to TP3. 1,2-Dibromotetrachloroethane (489 mg, 2.25 mmol) dissolved in dry THF (3 mL) was then slowly added at 25 °C and the resulting mixture was stirred for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (5 × 30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:7) furnished **5d** as a colorless solid (365 mg, 89 %). M.p. 83.9–84.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.51 ppm (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.2, 161.1, 113.4, 14.7 ppm; MS (70 eV, EI): m/z (%): 272 [^{79}Br^{35}Cl−M^+] (60); IR (ATR): $\tilde{\nu}$ = 2925, 1517, 1470, 1424, 1377, 1326, 1272, 1179, 852, 809, 747 cm^{-1}; HRMS (EI): m/z: calcd for $C_5{}^{79}Br{}^{35}Cl_2N_2{}^{32}S$: 271.8577; found: 271.8562.

4,6-Dichloro-2-(methylthio)-5-trimethylsilanyl-pyrimidine (5e): Compound **3** (292 mg, 1.5 mmol) in dry THF (3 mL) was added dropwise at 25 °C to a solution of **1** (1.14 M, 1.45 mL, 1.65 mmol) in THF and stirred at the same temperature for 30 min according to TP3. Trimethylsilylcyanide (179 mg, 1.8 mmol) was then slowly added at 25 °C and the resulting mixture was stirred for 20 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (5 × 30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent

was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:3) furnished **5e** as a colorless solid (317 mg, 79%). M.p. 82.5–84.0°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.52 (s, 3H), 0.46 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.4, 166.9, 124.0, 14.0, 1.8 ppm; MS (70 eV, EI): *m/z* (%): 266 [^{35}Cl−M^+] (56), 251 (100), 178 (18), 166 (23), 95 (24); IR (ATR): $\tilde{\nu}$=2956, 2930, 2894, 1509, 1455, 1323, 1284, 1246, 1163, 1034, 845, 799, 778, 701, 636 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_8H_{12}{}^{35}Cl_2N_2{}^{28}S^{32}Si$: 265.9867; found: 265.9825.

[4,6-Dichloro-2-(methylthio)pyrimidin-5-yl]methyl pivalate (5f): Compound **3** (195 mg, 1.0 mmol) in dry THF (2 mL) was added dropwise at 25°C to a solution of **1** (1.1 M, 1.0 mL, 1.7 mmol) in THF and stirred at the same temperature for 30 min according to TP3. Iodomethyl pivalate (339 mg, 1.4 mmol) was then slowly added at −15°C and the resulting mixture was allowed to warm slowly to 25°C over 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (5×30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:3) furnished **5f** as a colorless solid (235 mg, 76%). M.p. 58.3–60.7°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 5.20 (s, 2H), 2.56 (s, 3H), 1.19 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=177.9, 173.6, 162.5, 120.8, 60.1, 39.0, 27.1, 14.5 ppm; MS (70 eV, EI): *m/z* (%): 308 [^{35}Cl−M^+] (100), 210 (62), 208 (53), 57 (76); IR (ATR): $\tilde{\nu}$= 2976, 2928, 2873, 1723, 1552, 1481, 1458, 1426, 1397, 1382, 1369, 1339, 1317, 1302, 1280, 1227, 1189, 1142, 1122, 1032, 993, 974, 916, 868, 793, 770 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{11}H_{14}{}^{35}Cl_2N_2O_2{}^{28}S$: 308.0153; found: 308.0135.

[4,6-Dichloro-2-(methylthio)pyrimidin-5-yl](4-fluorophenyl)methanone (5g): Compound **3** (292 mg, 1.5 mmol) in dry THF (3 mL) was added dropwise at 25°C to a solution of **1** (1.14 M, 1.45 mL, 1.65 mmol) in THF and stirred at the same temperature for 30 min according to TP3. CuCN·2LiCl (1.0 M, 1.7 mL, 1.7 mmol) in THF was slowly added at −20°C and the reaction mixture was stirred at the same temperature for 30 min. 4-Fluorobenzoyl chloride (476 mg, 3 mmol) was added dropwise at −20°C and the resulting mixture was allowed to warm slowly to 25°C overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (5×30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:5) furnished **5g** as a colorless solid (441 mg, 93%). M.p. 133.5–135.0°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.85–7.88 (m, 2H), 7.18–7.20 (m, 2H), 2.61 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=187.7, 174.6, 167.7, 165.9, 157.9, 132.4 (d, *J*(C,F)=9.7 Hz), 131.4 (d, *J*(C,F)=3.0 Hz), 125.4, 116.7 (d, *J*(C,F)=22.2 Hz), 14.4 ppm; MS (70 eV, EI): *m/z* (%): 316 [^{35}Cl−M^+] (68), 221 (10), 123 (100), 95 (36), 75 (10); IR (ATR): $\tilde{\nu}$=3071, 2929, 2469, 2359, 1668, 1591, 1547, 1502, 1475, 1409, 1351, 1320, 1291, 1233, 1220, 1185, 1154, 1104, 1093, 969, 919, 848, 814, 774, 750, 684, 663, 637, 624 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{12}H_7{}^{35}Cl_2FN_2O^{32}S$: 315.9640; found: 315.9632.

1-[4,6-Dichloro-2-(methylthio)pyrimidin-5-yl]-3,3-dimethylbutan-1-one (5h): Compound **3** (975 mg, 5 mmol) in dry THF (5 mL) was added dropwise at 25°C to a solution of **1** (1.1 M, 5.0 mL, 5.5 mmol) in THF and stirred at the same temperature for 30 min according to TP3. CuCN·2 LiCl (1.0 M, 5.5 mL, 5.5 mmol) in THF was slowly added at −20°C and the reaction mixture was stirred at the same temperature for 30 min. 3,3-Dimethylbutanoyl chloride (1.35 g, 10 mmol) was added dropwise at −20°C and the resulting mixture was stirred at 25°C for 60 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL), extracted with diethyl ether (5×50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:7) furnished **5h** as a colorless solid (1.23 g, 84%). M.p. 95.0–96.0°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.75 (s, 2H), 2.57 (s, 3H), 1.12 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=197.6, 173.7, 156.6, 128.0, 55.9, 31.0, 29.3, 14.4 ppm; MS (70 eV, EI): *m/z* (%): 292 [^{35}Cl−M^+] (7), 238 (23), 236 (35), 223 (66), 221 (100), 57 (10); IR (ATR): $\tilde{\nu}$=2955, 2929, 2897, 2871, 1715, 1541, 1475, 1425, 1380, 1359, 1327, 1304, 1275, 1249, 1217, 1180, 1154, 1127, 996, 906, 853, 806, 777 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{11}H_{14}{}^{35}Cl_2N_2O^{32}S$: 292.0204; found: 292.0201.

4,6-Dichloro-2-methyl(thiopyrimidin-5-yl)-phenylmethanone (5i): Compound **3** (292 mg, 1.5 mmol) in dry THF (3 mL) was added dropwise at 25°C to a solution of **1** (1.14 M, 1.45 mL, 1.65 mmol) in THF and stirred at the same temperature for 30 min according to TP3. CuCN·2 LiCl (1.0 M, 1.6 mL, 1.6 mmol) in THF was slowly added at −20°C and the reaction mixture was stirred at the same temperature for 30 min. Benzoyl chloride (421 mg, 3 mmol) was added dropwise at −20°C and the resulting mixture was stirred at 25°C for 60 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (5×30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:6) furnished **5i** as a colorless solid (402 mg, 90%). M.p. 135.1–136.2°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.81–7.83 (m, 2H), 7.62–7.66 (m, 1H), 7.46–7.52 (m, 2H), 2.59 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=189.2, 174.2, 157.8, 134.8, 129.5, 129.1, 125.7, 14.4 ppm; MS (70 eV, EI): *m/z* (%): 298 [^{35}Cl−M^+] (100), 221 (26), 105 (78), 77 (33); IR (ATR): $\tilde{\nu}$=3318, 3060, 2925, 1667, 1594, 1535, 1473, 1450, 1344, 1308, 1284, 1230, 1173, 1096, 915, 848, 822, 771, 706, 680 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{12}H_8{}^{35}Cl_2N_2O^{32}S$: 297.9734; found: 297.9739.

[4,6-Dichloro-2-(methylthio)pyrimidin-5-yl](furan-2-yl)methanone (5j): Compound **3** (390 mg, 2.0 mmol) in dry THF (3 mL) was added dropwise at 25°C to a solution of **1** (1.1 M, 2.0 mL, 2.2 mmol) in THF and stirred at the same temperature for 30 min according to TP3. CuCN·2LiCl (1.0 M, 2.2 mL, 2.2 mmol) in THF was slowly added at −20°C and the reaction mixture was stirred at the same temperature for 30 min. Furan-2-carbonyl chloride (522 mg, 4 mmol) was added dropwise at −20°C and the resulting mixture was allowed to warm slowly to 25°C overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (5×30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:4) furnished **5j** as a colorless solid (498 mg, 86%). M.p. 122.8–124.4°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.71 (m, 1H), 7.28 (m, 1H), 7.65–7.67 (m, 1H), 2.63 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=176.2, 174.6, 158.1, 151.3, 148.7, 124.9, 121.2, 113.3, 14.5 ppm; MS (70 eV, EI): *m/z* (%): 290 (62), 288 [^{35}Cl−M^+] (100), 221 (12), 95 (55); IR (ATR): $\tilde{\nu}$=3140, 3119, 2929, 2464, 1649, 1562, 1536, 1475, 1454, 1446, 1394, 1344, 1320, 1265, 1264, 1222, 1183, 1154, 1122, 1109, 1075, 1030, 1014, 945, 887, 874, 832, 819, 790, 766, 740, 661, 619, 584 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{10}H_6{}^{35}Cl_2N_2O_2{}^{32}S$: 287.9527; found: 287.9530.

2-Chloro-4-iodo-6-(methylthio)pyrimidine (8a): 2-Chloro-4-(methylthio)-pyrimidine (**6**; 161 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added dropwise at 25°C to a solution of **1** (1.1 M, 1.0 mL, 1.1 mmol) in THF and stirred at the same temperature for 5 min according to TP3. Iodine (381 mg, 1.5 mmol) in dry THF (2 mL) was then added dropwise at 25°C and the resulting mixture was stirred for 45 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL), extracted with diethyl ether (5×30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:5) furnished **8a** as a colorless solid (203 mg, 71%). M.p. 97.9–99.6°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.53 (s, 1H), 2.53 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.8, 158.7, 127.1, 126.4, 12.8 ppm; MS (70 eV, EI): *m/z* (%): 286 [^{35}Cl−M^+] (100), 123 (13), 98 (53), 83 (16); IR (ATR): $\tilde{\nu}$=3080, 3008, 2930, 1517, 1496, 1468, 1414, 1359, 1336, 1320, 1287, 1241, 1194, 1117, 1098, 1031, 964, 946, 838, 822, 809, 750, 708, 659, 602 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_5H_4{}^{35}ClIN_2S$: 285.8828; found: 285.8812.

4-Bromo-2-chloro-6-(methylthio)pyrimidine (8b): Compound **6** (161 mg, 1.0 mmol) in dry THF (2 mL) was added dropwise at 25°C to a solution of **1** (1.1 M, 1.0 mL, 1.1 mmol) in THF and stirred at the same temperature for 5 min according to TP3. $(BrCl_2C)_2$ (429 mg, 1.5 mmol) dissolved in dry THF (2 mL) was added dropwise at 25°C and the resulting mixture was stirred for 45 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (5×30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:4) furnished **8b** as a colorless solid (189 mg, 79%).

M.p. 86.8–88.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 (s, 1H), 2.56 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9, 159.5, 150.7, 120.0, 13.0 ppm; MS (70 eV, EI): *m/z* (%): 238 [^{35}Cl−M^+] (28), 194 (11), 58 (69), 44 (12), 43 (100); IR (ATR): $\tilde{\nu}$ = 3090, 2997, 2925, 1529, 1481, 1416, 1367, 1321, 1261, 1207, 1189, 1101, 967, 905, 848, 832, 778, 747, 708, 605 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_5H_4{}^{79}Br^{35}ClN_2S$: 237.8967; found: 237.8958.

2,4-Dichloro-6-(methylthio)pyrimidine (8c): Compound **6** (161 mg, 1.0 mmol) in dry THF (2 mL) was added dropwise at 25 °C to a solution of **1** (1.1 M; 1.0 mL, 1.1 mmol) in THF and stirred at the same temperature for 5 min according to TP3. $F_2ClCCCl_2F$ (281 mg, 1.5 mmol) in dry THF (2 mL) was added dropwise at 25 °C and the resulting mixture was stirred for 45 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (5×30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:4) furnished **8c** as a colorless solid (140 mg, 72 %). M.p. 80.1–81.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.11 (s, 1H), 2.57 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.3, 160.0, 159.8, 116.1, 13.0 ppm; MS (70 eV, EI): *m/z* (%): 194 [^{35}Cl−M^+] (100), 148 (36), 113 (26), 87 (32); IR (ATR): $\tilde{\nu}$ = 3090, 3002, 2930, 1532, 1483, 1414, 1372, 1321, 1261, 1215, 1197, 1099, 969, 889, 851, 820, 809, 750, 716, 683, 603 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_5H_4{}^{35}Cl_2N_2S$: 193.9472; found: 193.9467.

2,4,6-Trichloro-5-iodo-pyrimidine (13a): 2,4,6-Trichloropyrimidine (**9**; 186 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added dropwise at 25 °C to a solution of **2** (0.79 M; 1.39 mL, 0.55 mmol) in THF and stirred at the same temperature for 1 h according to TP3. Iodine (381 mg, 1.5 mmol) dissolved in dry THF (2 mL) was then added dropwise at 25 °C and the resulting mixture was stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL), extracted with diethyl ether (5×30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:7) furnished **13a** as a colorless solid (256 mg, 83 %). M.p. 97.0–98.0 °C; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6, 159.3, 96.5 ppm; MS (70 eV, EI): *m/z* (%): 308 [^{35}Cl−M^+] (100), 273 (25), 127 (18), 85 (11); IR (ATR): $\tilde{\nu}$ = 1477, 1270, 1208, 1182, 1009, 851, 806, 752 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_4{}^{35}Cl_3IN_2$: 307.8172; found: 307.8162.

5-Allyl-2,4,6-trichloro-pyrimidine (13b): Compound **9** (186 mg, 1.0 mmol) in dry THF (2 mL) was added dropwise at 25 °C to a solution of **2** (0.79 M; 1.39 mL, 0.55 mmol) in THF and stirred at the same temperature for 1 h according to TP3. CuCN·2 LiCl (1.0 M, 5 drops) in THF was added at −20 °C, followed by the slow addition of allyl bromide (242 mg, 2.0 mmol) at −60 °C, and the resulting mixture was allowed to slowly warm to −20 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (5×30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:6) furnished **13b** as a colorless solid (201 mg, 90 %). M.p. 39.2–40.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.75–5.88 (m, 1H), 5.08–5.18 (m, 2H), 3.61 ppm (dt, ^3J = 6.4, ^4J = 1.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0, 157.1, 130.2, 129.3, 118.5, 33.5 ppm; MS (70 eV, EI): *m/z* (%): 222 [^{35}Cl−M^+] (100), 187 (33), 151 (62), 125 (35), 90 (43); IR (ATR): $\tilde{\nu}$ = 3087, 2934, 1635, 1533, 1501, 1435, 1330, 1287, 1215, 1185, 1123, 1095, 993, 930, 907, 875, 790 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_7H_5{}^{35}Cl_3N_2$: 221.9518; found: 221.9494.

1-(2,4,6-Trichloro-pyrimidin-5-yl)-propan-1-one (13c): Compound **9** (186 mg, 1.0 mmol) in dry THF (2 mL) was added dropwise at 25 °C to a solution of **2** (0.79 M; 1.39 mL, 0.55 mmol) in THF and stirred at the same temperature for 1 h according to TP3. CuCN·2 LiCl (1.0 M; 1.2 mL, 1.2 mmol) in THF was added at −20 °C and the reaction mixture was stirred for 30 min at the same temperature. Propionyl chloride (0.231 g, 2.5 mmol) was added dropwise at −20 °C and the resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (5×30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:5) furnished **13c** as a colorless solid (205 mg, 86 %). M.p. 74.3–75.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.83 (q, J = 7.2 Hz, 2H), 1.19 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.2, 159.2, 158.3, 131.7, 36.8, 7.2 ppm; MS (70 eV, EI): *m/z* (%): 238 [^{35}Cl−M^+] (2), 209 (100), 120 (8); IR (ATR): $\tilde{\nu}$ = 2987, 2941, 2894, 1718, 1538, 1501, 1403, 1305, 1210, 1155, 1065, 946, 835, 657 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_7H_5{}^{35}Cl_3N_2O$: 237.9467; found: 237.9482.

4,6-Dichloro-5-iodo-pyrimidine (14a): 4,6-Dichloropyrimidine (**10**; 745 mg, 5.0 mmol) dissolved in dry THF (10 mL) was added dropwise at 25 °C to a solution of **2** (0.79 M; 6.96 mL, 2.75 mmol) in THF and stirred at the same temperature for 45 min according to TP3. Iodine (1.78 g, 7.0 mmol) dissolved in dry THF (5 mL) was slowly added at 25 °C and the resulting mixture was stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and saturated aqueous $Na_2S_2O_3$ (20 mL), extracted with diethyl ether (5×50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:4) furnished **14a** as a colorless solid (1.25 g, 91 %). M.p. 134.9–136.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.65 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 156.8, 98.9 ppm; MS (70 eV, EI): *m/z* (%): 274 [^{35}Cl−M^+] (100), 239 (27), 97 (12), 83 (12), 57 (21); IR (ATR): $\tilde{\nu}$ = 2923, 2855, 1900, 1499, 1386, 11341, 1296, 1214, 1080, 1014, 790, 763, 745 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_4H^{35}Cl_2IN_2$: 273.8561; found: 273.8565.

(4,6-Dichloropyrimidin-5-yl)(phenyl)methanone (14b): Compound **10** (149 mg, 1.0 mmol) in dry THF (2 mL) was added dropwise at 25 °C to a solution of **2** (0.79 M; 1.39 mL, 0.55 mmol) in THF and stirred at the same temperature for 45 min according to TP3. CuCN·2 LiCl (1.0 M; 1.1 mL, 1.1 mmol) in THF was slowly added at −20 °C and the reaction mixture was stirred at the same temperature for 30 min. Benzoyl chloride was slowly added at −20 °C and the resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (5×30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:4) furnished **14b** as a colorless solid (215 mg, 86 %). M.p. 106.0–108.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.90 (s, 1H), 7.51–7.82 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.7, 158.6, 158.3, 135.2, 134.3, 132.0, 129.5, 129.4 ppm; MS (70 eV, EI): *m/z* (%): 252 [^{35}Cl−M^+] (21), 167 (11), 149 (100), 105 (40), 77 (39); IR (ATR): $\tilde{\nu}$ = 3329, 3061, 2957, 1726, 1668, 1593, 1581, 1531, 1511, 1453, 1404, 1386, 1348, 1317, 1256, 1242, 1236, 1184, 1162, 1071, 999, 924, 826, 794, 766, 698, 681, 674, 605 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{11}H_6{}^{35}Cl_2N_2O$: 251.9857; found: 251.9850.

4,6-Dichloro-5-(cyclohex-2-enyl)pyrimidine (14c): Compound **10** (149 mg, 1.0 mmol) in dry THF (2 mL) was added dropwise at 25 °C to a solution of **2** (0.79 M; 1.39 mL, 0.55 mmol) in THF and stirred at the same temperature for 45 min according to TP3. CuCN·2 LiCl (1 M; 0.05 mL, 5 mol %) in THF was slowly added at −20 °C. 3-Bromocyclohexene (322 mg, 2.0 mmol) was slowly added at −30 °C. The resulting mixture was allowed to warm slowly to 0 °C for 4 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL), extracted with diethyl ether (5×30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:4) furnished **14c** as a colorless oil (165 mg, 72 %). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.59 (s, 1H), 5.85–5.87 (m, 1H), 5.50–5.52 (m, 1H), 5.15–5.19 (m, 1H), 4.14–4.20 (m, 2H), 2.13–2.09 (m, 3H), 1.85–1.97 ppm (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 155.3, 135.4, 128.6, 126.2, 38.4, 25.7, 24.2, 22.5 ppm; MS (70 eV, EI): *m/z* (%): 230 (55), 228 [^{35}Cl−M^+] (81), 215 (26), 213 (44), 202 (19), 200 (29), 193 (20), 139 (31), 112 (21), 54 (100); IR (ATR): $\tilde{\nu}$ = 3025, 2933, 2861, 2836, 2363, 2340, 1531, 1509, 1447, 1408, 1377, 1351, 1329, 1307, 1214, 1162, 1127, 1046, 980, 882, 848, 809, 779, 721, 617, 560 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{10}H_{10}{}^{35}Cl_2N_2$: 228.0221; found: 228.0226.

4,4′,6,6′-Tetrachloro-5,5′-bipyrimidine (14d): Compound **10** (149 mg, 1.0 mmol) in dry THF (2 mL) was added dropwise at 25 °C to a solution of **2** (0.79 M; 1.39 mL, 0.55 mmol) in THF and stirred at the same temperature for 45 min according to TP3. Chloranil (295 mg, 1.2 mmol) dissolved in dry THF (7 mL) was slowly added at −40 °C for 1 h. The resulting mixture was allowed to warm slowly to 25 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL), extracted with di-

ethyl ether (5×30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2) furnished **14d** as a colorless solid (121 mg, 82%). M.p. 149.0–150.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.93 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.4, 158.9, 126.6 ppm; MS (70 eV, EI): *m/z* (%): 296 (100), 294 [^{35}Cl−M^+] (86), 207 (19), 205 (18), 149 (35), 57 (14); IR (ATR): $\tilde{\nu}$ = 3382, 3303, 2928, 1692, 1531, 1507, 1402, 1370, 1288, 1228, 1164, 988, 811, 771, 727, 571 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_8H_2{}^{35}Cl_4N_4$: 293.9034; found: 293.9045.

4,6-Dichloro-2,5-diiodo-pyrimidine (15a): 4,6-Dichloro-5-iodo-pyrimidine (**14a**) 275 mg, 1.0 mmol) in dry THF (3 mL) was added dropwise at 25 °C to a solution of **2** (0.79 M; 1.39 mL, 0.55 mmol) and stirred at 55 °C for 1 h according to TP3. Iodine (508 mg, 2.0 mmol) in dry THF (4 mL) was slowly added at 25 °C and the resulting mixture was stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (5×50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:4) furnished **15a** as a colorless solid (241 mg, 61%). M.p. 148.4–150.0 °C; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 123.6, 98.7 ppm; MS (70 eV, EI): *m/z* (%): 400 [^{35}Cl−M^+] (100), 273 (71), 127 (14); IR (ATR): $\tilde{\nu}$ = 2950, 2913, 2850, 2628, 2417, 1739, 1460, 1344, 1264, 1249, 1196, 1172, 1001, 806, 745 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_4{}^{35}Cl_2I_2N_2$: 399.7528; found: 399.7529.

5-Allyl-4,6-dichloro-2-iodopyrimidine (15b): Compound **14a** (275 mg, 1.0 mmol) in dry THF (3 mL) was added dropwise at 25 °C to a solution of **2** (0.79 M; 1.39 mL, 0.55 mmol) in THF and stirred at 55 °C for 1 h according to TP3. CuCN·2 LiCl (1.0 M, 5 drops) in THF was added at −20 °C, followed by the slow addition of allyl bromide (242 mg, 2.0 mmol) at −78 °C. The resulting mixture was allowed to slowly warm to −10 °C and stirred for 4 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (5×30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:3) furnished **15b** as a colorless solid (160 mg, 51%). M.p. 74.3–75.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.75–5.88 (m, 1H), 5.08–5.18 (m, 2H), 3.56 ppm (dt, ^3J = 6.4, ^4J = 1.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.2, 130.1, 130.0, 121.8, 118.5, 33.7 ppm; MS (70 eV, EI): *m/z* (%): 314 [^{35}Cl−M^+] (100), 187 (59), 151 (13), 99 (12), 58 (30), 43 (69); IR (ATR): $\tilde{\nu}$ = 3087, 3018, 2971, 2923, 2855, 1739, 1726, 1636, 1528, 1478, 1433, 1370, 1341, 1325, 1283, 1228, 1206, 1185, 1156, 1114, 1093, 985, 922, 904, 853, 808, 785, 777, 558 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_7H_5{}^{35}Cl_2IN_2$: 313.8874; found: 313.8869.

2,5-Dichloro-4-iodopyrimidine (18a): 2,5-Dichloropyrimidine (**16**; 149 mg, 1.0 mmol) dissolved in dry THF (2 mL) was added dropwise at 25 °C to a solution of **2** (0.79 M; 1.39 mL, 0.55 mmol) in THF and stirred at the same temperature for 45 min according to TP3. Iodine (381 mg, 1.5 mmol) in dry THF (2 mL) was added dropwise at 25 °C and the resulting mixture was stirred for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL), extracted with diethyl ether (5×30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:5) furnished **18a** as a colorless solid (203 mg, 72%). M.p. 118.8–120.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.39 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.8, 155.4, 137.5, 134.0 ppm; MS (70 eV, EI): *m/z* (%): 274 [^{35}Cl−M^+] (100), 149 (61), 147 (90), 120 (31), 43 (30); IR (ATR): $\tilde{\nu}$ = 3075, 3018, 2992, 1883, 1721, 1537, 1514, 1494, 1470, 1362, 1336, 1284, 1192, 1171, 1135, 1034, 944, 812, 752, 659 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_4H^{35}Cl_2IN_2$: 273.8561; found: 273.8554.

Ethyl 4-(2,5-dichloropyrimidin-4-yl)benzoate (18b): Compound **16** (149 mg, 1.0 mmol) in dry THF (2 mL) was added dropwise at 25 °C to a solution of **2** (0.79 M; 1.39 mL, 0.55 mmol) in THF and stirred at the same temperature for 45 min according to TP3. Ethyl 4-iodobenzoate (359 mg, 1.3 mmol, 1.3 equiv) was added to [Pd(dba)$_2$] (17 mg, 3 mol%; dba = dibenzylideneacetone) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) in THF (2 mL). This mixture was transferred by cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 45 min and quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (5×30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:1) furnished **18b** as a yellowish solid (232 mg, 78%). M.p. 86.4–87.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 (s, 1H), 8.16 (d, J = 8.2 Hz, 2H), 7.94 (d, J = 8.2 Hz, 2H), 4.41 (q, J = 7.2 Hz, 2H), 1.41 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 164.1, 160.0, 159.0, 138.1, 132.6, 129.5 (2), 127.9, 61.4, 14.3 ppm; MS (70 eV, EI): *m/z* (%): 296 [^{35}Cl−M^+] (29), 268 (64), 253 (100), 223 (34), 126 (13); IR (ATR): $\tilde{\nu}$ = 3033, 2992, 2935, 2915, 1718, 1610, 1574, 1545, 1520, 1499, 1486, 1463, 1442, 1401, 1362, 1336, 1315, 1272, 1194, 1170, 1130, 1106, 1095, 1037, 1016, 944, 861, 840, 786, 763, 724, 701, 652 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{13}H_{10}{}^{35}Cl_2N_2O_2$: 296.0119; found: 296.0117.

2,5-Dichloro-4-(3-(trifluoromethyl)phenyl)pyrimidine (18c): Compound **16** (149 mg, 1.0 mmol) in dry THF (2 mL) was added dropwise at 25 °C to a solution of **2** (0.79 M; 1.39 mL, 0.55 mmol) in THF and stirred at the same temperature for 45 min according to TP3. 3-Iodobenzotrifluoride (354 mg, 1.3 mmol, 1.3 equiv) was added to [Pd(dba)$_2$] (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL). This mixture was transferred by cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 45 min and then quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (5×30 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2/pentane 1:4) furnished **18c** as a colorless solid (232 mg, 73%). M.p. 45.2–46.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.69 (d, J = 5.1 Hz, 1H), 7.62–8.16 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.4, 160.1, 159.1, 135.0, 132.7 (2), 131.1 (q, J(C,F) = 32.3 Hz), 129.1, 127.8 (q, J(C,F) = 3.7 Hz), 126.4 (q, J(C,F) = 3.7 Hz), 123.7 ppm (q, J(C,F) = 272.5 Hz); MS (70 eV, EI): *m/z* (%): 292 [^{35}Cl−M^+] (84), 257 (100), 231 (24), 204 (15), 149 (15), 44 (24); IR (ATR): $\tilde{\nu}$ = 3090, 3048, 1616, 1547, 1524, 1486, 1449, 1401, 1336, 1324, 1310, 1252, 1198, 1166, 1103, 1071, 1036, 1000, 946, 909, 882, 810, 791, 776, 699, 656, 630 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{11}H_5{}^{35}Cl_2F_3N_2$: 291.9782; found: 291.9786.

4-Chloro-3-(4-fluorophenyl)-6-(methylthio)-1*H*-pyrazolo [3,4-*d*]pyrimidine (19a): Hydrazine (64% in water; 0.12 mL, 2.4 mmol) was added to a solution of **5g** (0.317 g, 1.0 mmol) in THF (2 mL) at 25 °C. The resulting mixture was stirred at the same temperature for 10 min and quenched with saturated aqueous Na_2CO_3 (10 mL), extracted with diethyl ether (5×20 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2) furnished **19a** as a colorless solid (224 mg, 76%). M.p. 225.7–227.2 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.77 (m, 2H), 7.32–7.36 (m, 2H), 2.58 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 168.6, 163.8, 161.4, 156.3, 153.0, 144.0, 131.9 (d, J(C,F) = 8.6 Hz), 127.8, 115.2 (d, J(C,F) = 31.7 Hz), 106.9, 13.8 ppm; MS (70 eV, EI): *m/z* (%): 294 [^{35}Cl−M^+] (100), 213 (35); IR (ATR): $\tilde{\nu}$ = 3187, 3156, 3076, 3029, 2982, 2918, 1739, 1597, 1531, 1520, 1467, 1420, 1399, 1367, 1322, 1304, 1267, 1217, 1156, 1151, 1098, 1069, 1022, 982, 972, 956, 869, 832, 816, 806, 785, 740, 692, 645, 602, 561 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{12}H_8{}^{35}ClFN_4{}^{32}S$: 294.0142; found: 294.0130.

4-Chloro-6-(methylthio)-3-neopentyl-1*H*-pyrazolo [3,4-*d*]pyrimidine (19b): Hydrazine (64% in water; 0.17 mL, 3.4 mmol) was added to **5h** (0.294 g, 1.0 mmol) in THF at 25 °C. The resulting mixture was stirred at the same temperature for 10 min and quenched with saturated aqueous Na_2CO_3 (10 mL), extracted with diethyl ether (5×20 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2) furnished **19b** as a colorless solid (199 mg, 73%). M.p. 130.9–132.4 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.88 (s, 2H), 2.55 (s, 3H), 0.94 ppm (s, 9H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 168.1, 155.6, 152.9, 143.5, 108.5, 31.9, 29.3, 13.8 ppm; MS (70 eV, EI): *m/z* (%): 270 [^{35}Cl−M^+] (12), 214 (100), 57 (24); IR (ATR): $\tilde{\nu}$ = 3203, 3156, 3119, 2960, 2929, 2902, 2860, 2359, 2332, 1739, 1594, 1533, 1483, 1462, 1449, 1412, 1362, 1330, 1291, 1267, 1238, 1209, 1199, 1143, 1101, 1069, 1006, 969, 890, 856, 811, 774, 750, 632, 616, 553 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{11}H_{15}{}^{35}ClN_4{}^{32}S$: 270.0706; found: 270.0703.

4-Chloro-6-(methylthio)-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (19c): Hydrazine (64% in water; 0.17 mL, 3.4 mmol) was added to **5i** (0.298 g,

1.0 mmol) in THF (2 mL) at 25 °C. The resulting mixture was stirred at the same temperature for 10 min and was quenched with saturated aqueous Na_2CO_3 (10 mL), extracted with diethyl ether (5×20 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash column chromatography (CH_2Cl_2) furnished **19c** as a colorless solid (229 mg, 83%). M.p. 201.0–202.3 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.70–7.72 (m, 2H), 7.46–7.50 (m, 3H), 2.57 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 168.5, 156.4, 153.1, 144.9, 131.3, 129.8, 129.0, 128.1, 106.9, 13.9 ppm; MS (70 eV, EI): *m/z* (%): 276 [^{35}Cl−M^+] (100), 195 (40), 77 (11); IR (ATR): $\tilde{\nu}$ = 3101, 3023, 2977, 2853, 1612, 1532, 1509, 1463, 1408, 1367, 1321, 1253, 1228, 1155, 1083, 1018, 977, 876, 863, 786, 765, 701, 636 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{12}H_9{}^{35}ClN_4{}^{32}S$: 276.0236; found: 276.0215.

4,6-Dichloro-5-(morpholin-1-yl)-2-(methylthio)pyrimidine (20a): Compound **3** (195 mg, 1.0 mmol) in dry THF (3 mL) was added dropwise at 25 °C to a solution of **1** (1.14 M; 1.45 mL, 1.65 mmol) in THF and stirred at the same temperature for 30 min according TP3. CuCl·2 LiCl (1.0 M, 1.1 mL, 1.1 mmol) in THF was slowly added at −50 °C and the reaction mixture was stirred at the same temperature for 45 min. *N*-Lithium morpholide (2 mmol; prepared by adding *n*BuLi (2 mmol) to morpholine (0.5 M, 174 mg, 2 mmol) in THF at 0 °C and stirring for 30 min) was added dropwise and the reaction mixture was further stirred for 90 min at −50 °C. The reaction mixture was cooled to −78 °C, and chloranil (295 mg, 1.2 mmol) in dry THF (7 mL) was added slowly over 45 min. The resulting mixture was stirred at −78 °C for 12 h. Diethyl ether (10 mL) was added to the crude reaction mixture, which was filtered through celite, thoroughly washed with diethyl ether, and the filtrate was washed with aqueous NH_4OH (2.0 M, 2×10 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (CH_2Cl_2) furnished **20a** as a colorless solid (191 mg, 68%). M.p. 127.5–130.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77–3.80 (m, 4H), 3.09–3.12 (m, 4H), 2.52 ppm (s, 3H, SCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3, 160.7 (2), 134.9, 67.7 (2), 49.7 (2), 14.9 ppm; MS (70 eV, EI): *m/z* (%): 279 [^{35}Cl−M^+] (70), 244 (14), 223 (64), 221 (100), 188 (23); IR (ATR): $\tilde{\nu}$ = 2966, 2886, 2855, 1536, 1463, 1381, 1323, 1302, 1273, 1176, 1105, 1068, 1036, 968, 923, 852, 805, 768, 689, 591, 568 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_9H_{11}{}^{35}Cl_2N_3O^{32}S$: 279.0000; found: 278.9981.

4,6-Dichloro-5-(4-methylpiperazin-1-yl)-2-(methylthio)pyrimidine (20b): Compound **3** (195 mg, 1.0 mmol) in dry THF (3 mL) was added dropwise at 25 °C to a solution of **1** (1.14 M; 1.45 mL, 1.65 mmol) in THF and stirred at the same temperature for 30 min according to TP3. CuCl·2 LiCl (1.0 M, 1.1 mL, 1.1 mmol) in THF was slowly added at −50 °C and the reaction mixture was stirred at the same temperature for 45 min. *N*-Lithium 4-methylpiperazide (2 mmol; prepared by adding *n*BuLi (2 mmol) to 4-methylpiperazine (0.5 M, 200 mg, 2 mmol) in THF at 0 °C and stirring for 30 min) was added dropwise and the mixture was further stirred for 90 min at −50 °C. The reaction mixture was cooled to −78 °C, and chloranil (295 mg, 1.2 mmol) in dry THF (7 mL) was added slowly over 45 min. The resulting mixture was stirred at −78 °C for 12 h. Diethyl ether (10 mL) was added to the crude reaction mixture, which was filtered through celite, thoroughly washed with diethyl ether, and the filtrate was washed with aqueous NH_4OH (2.0 M, 2×10 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (CH_2Cl_2) furnished **20b** as a colorless solid (208 mg, 71%). M.p. 82.7–83.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.11 (m, 4H), 2.49 (m, 4H), 2.49 (s, 3H), 2.31 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.7, 160.3, 135.1, 55.4, 49.1, 46.4, 14.6 ppm; MS (70 eV, EI): *m/z* (%): 294 (27), 292 [^{35}Cl−M^+] (53), 245 (46), 244 (13), 243 (100), 229 (17), 193 (11), 170 (15), 147 (6), 120 (5), 42 (5); IR (ATR): $\tilde{\nu}$ = 2928, 2843, 2836, 2784, 2759, 1539, 1463, 1401, 1379, 1299, 1271, 1154, 1136, 1071, 1006, 964, 927, 845, 801, 779, 767, 729, 613, 571 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{10}H_{14}N_4{}^{35}Cl^{32}S$: 292.0316; found: 292.0302.

4,6-Dichloro-5-(piperidin-1-yl)-2-(methylthio)pyrimidine (20c): Compound **3** (195 mg, 1.0 mmol) dissolved in dry THF (3 mL) was added dropwise at 25 °C to a solution of **1** (1.14 M; 1.45 mL, 1.65 mmol) in THF and stirred at the same temperature for 30 min according to TP3. CuCl·2 LiCl (1.0 M, 1.1 mL, 1.1 mmol) in THF was slowly added at −50 °C and the reaction mixture was stirred at the same temperature for 45 min. *N*-Lithium piperidide (2 mmol; prepared by adding *n*BuLi (2 mmol) to piperidine (0.5 M, 171 mg, 2 mmol) in THF at 0 °C and stirring for 30 min) was added dropwise and the mixture was further stirred for 90 min at −50 °C. The reaction mixture was cooled to −78 °C, and chloranil (295 mg, 1.2 mmol) in dry THF (7 mL) was added slowly over 45 min. The resulting mixture was stirred at −78 °C for 12 h. Diethyl ether (10 mL) was added to the crude reaction mixture, which was filtered through Celite, thoroughly washed with diethyl ether, and the filtrate was washed with aqueous NH_4OH (2.0 M, 2×10 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (CH_2Cl_2) furnished **20c** as a colorless solid (195 mg, 70%). M.p. 91.9–93.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.01–3.05 (m, 4H), 2.53 (s, 3H), 1.53–1.70 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 160.5, 136.6, 51.0, 26.7, 24.2, 14.9 ppm; MS (70 eV, EI): *m/z* (%): 277 [^{35}Cl−M^+] (50), 276 [M−1]$^+$ (100), 221 (12), 188 (12), 55 (11), 41 (17); IR (ATR): $\tilde{\nu}$ = 2931, 2849, 1537, 1462, 1388, 1344, 1323, 1286, 1255, 1176, 1113, 1064, 1032, 1019, 964, 915, 852, 824, 801, 765, 680, 573 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{10}H_{13}{}^{35}Cl_2N_3{}^{32}S$: 277.0207; found: 277.0181.

2-Chloro-4-iodopyrimidine (22): 2-Chloropyrimidine (**21**; 684 mg, 6.0 mmol) dissolved in THF (6 mL) was treated with a solution of **1** (1.1 M, 6.0 mL, 6.6 mmol) in THF at −60 °C for 2 h. Transmetalation with $ZnCl_2$ (1.0 M, 6.6 mL, 6.6 mmol) in THF was performed and the resulting mixture was allowed to warm slowly to room temperature. Iodine (2.284 g, 9.0 mmol) in dry THF (9 mL) was added dropwise and the resulting mixture was stirred for 1 h at 25 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and saturated aqueous $Na_2S_2O_3$ (30 mL), extracted with diethyl ether (5×50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash chromatography on silica gel (CH_2Cl_2/pentane 1:4) furnished **22** as a colorless solid (1.31 g, 91%). M.p. 111.3–112.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, J = 5.1 Hz, 1H), 7.72 ppm (d, J = 5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1, 158.0, 131.2, 130.2 ppm; MS (70 eV, EI): *m/z* (%): 240 (47) [^{35}Cl−M^+], 127 (17), 115 (22), 113 (64), 86 (16), 58 (39), 52 (15), 43 (100); IR (ATR): $\tilde{\nu}$ = 3094, 1511, 1395, 1342, 1318, 1227, 1192, 1165, 1133, 979, 834, 776, 758, 666, 578 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_4H_2{}^{35}Cl^{127}IN_2$: 239.8951; found: 239.8950.

4-Bromo-2-chloro-4-iodopyrimidine (23): Compound **22** (1.21 g, 5 mmol) dissolved in THF (10 mL) was slowly added at −60 °C to a solution of **1** (1.1 M; 5.5 mL, 5 mmol) in THF and the mixture was stirred at the same temperature for 1 h. $BrCl_2CCCl_2Br$ (2.442 g, 7.5 mmol) was added dropwise at −78 °C and the resulting mixture was allowed to warm slowly to −65 °C for 3 h. Purification by flash chromatography (pentane/CH_2Cl_2; 3:1) afforded pyrimidine **23** (1.53 g, 96%) as a colorless solid. M.p. 145.9–147.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 152.6, 134.5, 129.6 ppm; MS (EI, 70 eV) *m/z* (%): 320 (44), 318 (33) [^{79}Br−M^+], 193 (67), 191 (51), 130 (20), 127 (20), 86 (10), 14 (62), 62 (13), 58 (77), 43 (100); IR (ATR): $\tilde{\nu}$ = 3108, 1486, 1357, 1338, 1267, 1241, 1098, 977, 845, 806, 745, 587 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_4H^{79}Br^{35}Cl^{127}IN_2$: 317.8056; found: 317.8058.

4-Bromo-2-chloro-6-methylpyrimidine (24): $ZnCl_2$ (1.0 M, 6 mL, 6 mmol) in THF was added dropwise to a stirred solution of CH_3MgCl (2.93 M, 1.95 mL, 5.65 mmol) in THF at −20 °C. After the reaction mixture was stirred for 15 min at this temperature, it was warmed slowly to 25 °C. A solution of **23** (1.28 g, 4.0 mmol) and [Pd(PPh$_3$)$_4$] (200 mg, 4 mol%) in THF (8 mL) was added, and the resulting mixture was stirred at 50 °C overnight. The mixture was cooled to 25 °C and quenched with saturated aqueous NH_4Cl (50 mL), extracted with diethyl ether (5×50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash chromatography (pentane/CH_2Cl_2 4:1) afforded pyrimidine **24** (483 mg, 58%) as a colorless solid. M.p. 80.6–82.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (s, 1H), 2.50 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 160.0, 153.5, 123.5, 23.6 ppm; MS (EI, 70 eV): *m/z* (%): 208 (29), 206 (24) [^{79}Br−M^+], 129 (29), 127 (81), 86 (28), 66 (100), 64 (15), 62 (28), 55 (16), 51 (21), 43 (15); IR (ATR):

$\tilde{\nu}$ = 3124, 3082, 2955, 2918, 2850, 1721, 1552, 1515, 1462, 1430, 1404, 1370, 1354, 1296, 1251, 1228, 1188, 1130, 1040, 1011, 974, 911, 893, 861, 795, 750, 692, 600 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_5H_4{}^{79}Br^{35}ClN_2$: 205.9246; found: 205.9240.

2-Chloro-4-methyl-6-(prop-1-ynyl)pyrimidine (25): A mixture of NEt_3 (7 mL), CuI (12 mg, 4 mol%), $[Pd(dba)_2]$ (25 mg, 2 mol%), P(o-furyl)$_3$ (21 mg, 4 mol%), and **24** (312 mg, 1.5 mmol) in THF (2 mL) was added to recondensed propyne (81 mg, 2.0 mol). The reaction mixture was stirred at 25°C for 1.5 h and quenched with saturated aqueous NH_4Cl (30 mL), extracted with diethyl ether (3×50 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash chromatography (pentane/CH_2Cl_2 3:1) afforded pyrimidine **25** (241 mg, 97%) as a colorless solid. M.p. 127.4–128.8°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.07 (s, 1H), 2.47 (s, 3H), 2.08 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 160.9, 153.0, 121.0, 93.8, 77.3, 23.8, 4.5 ppm; MS (EI, 70 eV): *m/z* (%): 168 (17), 166 (50) [$^{35}Cl-M^+$], 58 (37), 44 (17), 43 (100); IR (ATR): $\tilde{\nu}$ = 3066, 2971, 2923, 2248, 2227, 1562, 1502, 1417, 1386, 1351, 1246, 1193, 1185, 1051, 982, 916, 893, 811, 764, 568 cm^{-1}; HRMS (EI): calcd for $C_8H_7{}^{35}ClN_2$: 166.0298; found: 166.0297.

4-Methyl-*N*-phenyl-6-(prop-1-ynyl)pyrimidin-2-amine (26): A Schlenk flask was flushed with nitrogen and charged with xantphos (11 mg, 20 mol%) and dry dioxane (3 mL). After purging the flask with dry argon, $Pd(OAc)_2$ (58 mg, 10 mol%) was added to the reaction mixture, which was stirred under nitrogen for 10 min. In another Schlenk flask, **25** (84 mg, 0.5 mmol), aniline (70 mg, 0.75 mmol), and K_2CO_3 (1.38 g, 10 mmol) were added to dry dioxane (4 mL). The solution of $Pd(OAc)_2$/xantphos[16] was transferred by cannula and the resulting mixture was subsequently heated to 100°C under argon with vigorous stirring for 1.5 h. After cooling, the solid material was filtered off and washed with CH_2Cl_2. The solvent was evaporated, and the crude product was purified by flash chromatography (CH_2Cl_2), thus affording pyrimidine **26** (91 mg, 81%) as a colorless solid. M.p. 125.5–127.0°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61–7.64 (m, 2H), 7.30–7.33 (m, 2H), 7.21 (bs, 1H), 6.98–7.03 (m, 1H), 6.63 (s, 1H), 2.38 (s, 3H), 2.07 pm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 159.7, 151.3, 139.5, 128.8, 122.3, 119.0, 114.1, 89.9, 78.5, 24.0, 4.4 ppm; MS (EI, 70 eV): *m/z* (%): 223 (53) [$^{35}Cl-M^+$], 222 (100), 77 (8), 43 (11); IR (ATR): $\tilde{\nu}$ = 3266, 3193, 3124, 3066, 2960, 2908, 2850, 2237, 1602, 1576, 1539, 1494, 1457, 1136, 1380, 1365, 1338, 1246, 1199, 1183, 1069, 1030, 996, 969, 890, 864, 824, 787, 750, 692, 621, 608, 590 cm^{-1}; HRMS (EI): calcd for $C_{14}H_{13}N_3$: 223.1109; found: 223.1109.

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