Multiple Regio- and Chemoselective Functionalizations of Pyrimidine Derivatives Using TMPMgCl·LiCl and TMP_2Mg·2 LiCl

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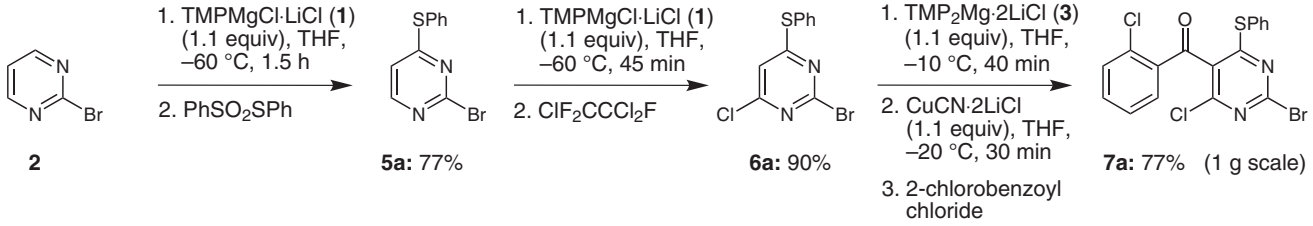
Abstract: The multiple successive regio- and chemoselective magnesiation of commercially available 2-bromopyrimidine at the C4, C6, and C5 positions allows the regioselective functionalization of all positions of the pyrimidine ring.

Key words: Grignard reagents, pyrimidines, regioselective magnesiation, magnesium bases

Procedure 1:



Scheme 1

Introduction

Pyrimidines are privileged structures in drug discovery and display a broad spectrum of biological activity.[1] Their direct functionalization by lithiation is difficult due to the electrophilic character of the ring, which readily undergoes the addition of various organometallics in positions 4 and 6.[2] This implies that low temperatures are required for the metalation of pyrimidines.[3] Recently, we have shown that 2,2,6,6-tetramethylpiperidin-1-ylmagnesium chloride–lithium chloride complex (TMPMgCl·LiCl, **1**)[4] allows full functionalization of the pyrimidine scaffold under mild conditions.[5] Herein, we wish to report a complementary metalation procedure of 2-bromopyrimidine (**2**) using 2,2,6,6-tetramethylpiperidin-1-ylmagnesium chloride–lithium chloride complex (TMPMgCl·LiCl, **1**) or bis(2,2,6,6-tetramethylpiperidin-1-yl)magnesium–bis(lithium chloride) complex[6] (TMP_2Mg·2LiCl, **3**) (Schemes 1 and 2) by successive magnesiations.

Scope and Limitations

A variety of pyrimidine derivatives can be easily prepared starting from commercially available 2-bromopyrimidine[7] (**2**). The treatment of **2** with TMPMgCl·LiCl (**1**, 1.1 equiv, –60 °C, 1.5 h) leads to the 4-magnesiated pyrimidine **4**, which can be trapped by electrophiles such as *S*-phenyl benzenethiosulfonate, iodine, or 1,1,2-trichloro-1,2,2-trifluoroethane furnishing the functionalized pyrimidines **5a–c** in 71–80%. The formation of a new C–C bond can be easily performed by a Negishi[8] or Sonogashira[9] cross-coupling reaction of in situ generated 2-bromo-4-iodopyrimidine (**5b**) giving 4-substituted pyrimidines **5d–f** in 56–67% (Scheme 3).

Further magnesiation is readily carried out at position 6 by the addition of TMPMgCl·LiCl (**1**) to selected 4-substituted-2-bromopyrimidines. Thus, the 2-bromo-4-(phenylsulfanyl)pyrimidine (**5a**) is magnesiated quantitatively with TMPMgCl·LiCl (**1**, 1.1 equiv, –60 °C, 45 min) and reacted with tosyl cyanide, 1,1,2-trichloro-1,2,2-trifluoroethane, or 1,2-dibromo-1,1,2,2-tetrachloroethane affording the expected 4,6-disubstituted 2-bromopyrimidines **6a–c** in 67–90% yield (Table 1, entries 1–3). Similarly, 2-bromo-4-iodopyrimidine (**5b**) is converted within one hour at –60 °C into the magnesiated species, which is trapped

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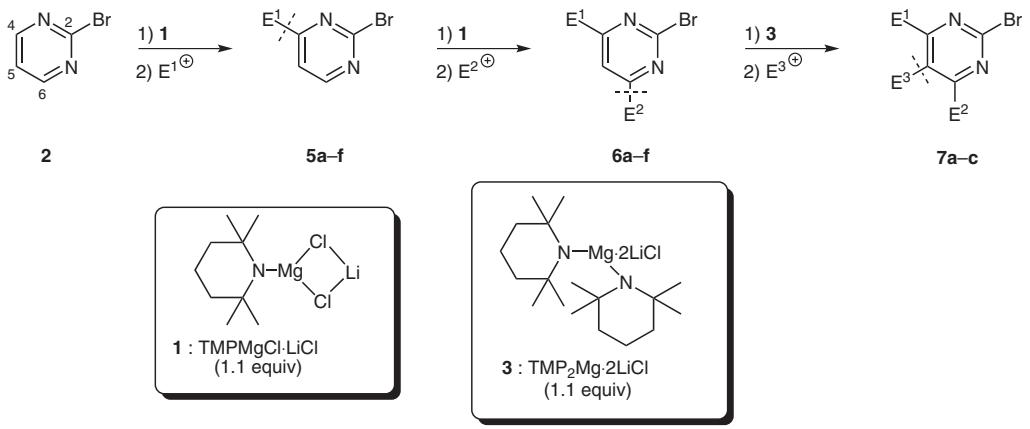
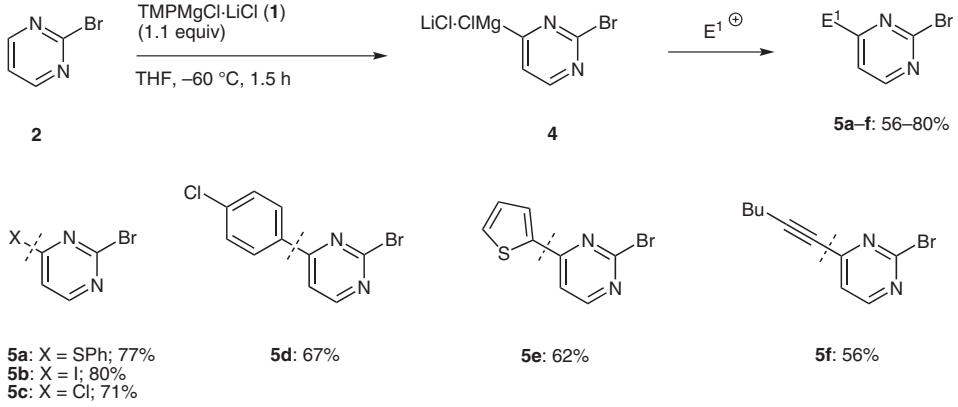


Scheme 2 Magnesiation of 2-bromopyrimidine (**2**) at positions 4, 6, and 5 using TMPMgCl·LiCl (**1**, 1.1 equiv) or $TMP_2Mg·2LiCl$ (**3**, 1.1 equiv)



Scheme 3 Magnesiation of 2-bromopyrimidine (**2**) at position 4 using TMPMgCl·LiCl (**1**, 1.1 equiv)

with iodine leading to 2-bromo-4,6-diiodopyrimidine (**6d**) in 82% yield (Table 1, entry 4).

Reaction with 1,2-dibromo-1,1,2,2-tetrachloroethane furnishes the bromopyrimidine **6e** in 67% yield (Table 1, entry 5). Trapping with trimethylsilyl cyanide provides the pyrimidine derivative **6f** in 89% (Table 1, entry 6). The last position (position 5) can also be magnesiated at –10 °C within 40 minutes using $TMP_2Mg·2LiCl$ (**3**, 1.1 equiv). Trapping with 2-chlorobenzoyl chloride (after transmetalation with CuCN·2LiCl),[10] allyl bromide (after successive transmetalations with $ZnCl_2$ and in the presence of a catalytic amount of CuCN·2LiCl) or *S*-methyl methanethiosulfonate leads to the fully substituted pyrimidines **7a–c** in 77–89% yield (Table 1, entries 7–9).

An efficient and convergent multiple regio- and chemoselective magnesiation of commercially available 2-bromopyrimidine using TMPMgCl·LiCl and $TMP_2Mg·2LiCl$ was demonstrated. In summary, we have extended our previous work to the scaled-up and optimized preparation of highly functionalized pyrimidines. This reaction could be performed with standard laboratory glassware and did not require the use of expensive chemicals or catalysts.

All reactions were carried out under argon atmosphere in dried glassware. All starting materials were purchased from commercial suppliers and used without further purification unless otherwise stated. THF was continuously refluxed and freshly distilled from Na benzophenone ketyl under N_2. Yields refer to isolated compounds estimated to be >95% pure as determined by ^1H NMR and capillary GC analysis.

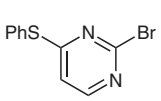
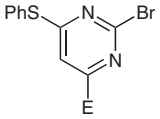
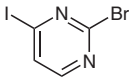
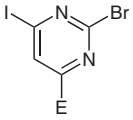
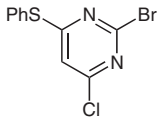
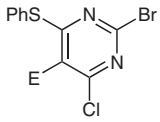
Isopropylmagnesium Chloride–Lithium Chloride

Mg turnings (110 mmol) and anhyd LiCl (100 mmol) were placed in an argon-flushed flask dried and THF (50 mL) was added. A soln of *i*-PrCl (100 mmol) in THF (50 mL) was slowly added at 25 °C. The reaction started within a few minutes. When the addition was finished, the mixture was stirred at 25 °C for 12 h. The grey soln of *i*-PrMgCl·LiCl was cannulated from the excess Mg to a different flask under argon. A yield of ca. 95–98% of *i*-PrMgCl·LiCl was obtained. The reagent was titrated prior to use by the method of Paquette,[11a] or the method developed in our laboratory.[12]

2,2,6,6-Tetramethylpiperidin-1-ylmagnesium Chloride–Lithium Chloride Complex (1)

A dry, N_2-flushed 250-mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with freshly titrated 1.2 M *i*-PrMgCl·LiCl in THF (100 mL, 120 mmol). 2,2,6,6-Tetramethylpiperidine (18.7 g, 132 mmol, 1.1 equiv) was added dropwise at 25 °C. The mixture was stirred at 25 °C until gas evolution was completed (ca. 24 h). The reagent was titrated prior to use [benzoic acid with 4-(phenylazo)diphenylamine as the indicator].[11b]

Table 1 Products Obtained by Magnesiations of Pyrimidines of Type **5** and **6** and Quenching with Electrophiles

Entry	Substrate of type **5** and **6**	Electrophile	Products	Yield[a] (%)
				
1	**5a**	$ClCF_2CCl_2F$	**6a** E = Cl	90
2	**5a**	TsCN	**6b** E = CN	67
3	**5a**	$BrCCl_2CCl_2Br$	**6c** E = Br	85
				
4	**5b**	I_2	**6d** E = I	82
5	**5b**	$BrCCl_2CCl_2Br$	**6e** E = Br	67
6	**5b**	Me_3SiCN	**6f** E = $SiMe_3$	89
				
7	**6a**	2-ClC_6H_4COCl[b]	**7a** E = 2-ClC_6H_4CO	77
8	**6a**	allyl bromide[c,d]	**7b** E = allyl	89
9	**6a**	$MeSO_2SMe$	**7c** E = SMe	80

[a] Yield of analytically pure product.
[b] Transmetalation with CuCN·2LiCl (1.1 equiv) was performed.
[c] Transmetalation with $ZnCl_2$ (1.1 equiv) was performed.
[d] Transmetalation with CuCN·2LiCl (5 mol%) was performed.

Bis(2,2,6,6-tetramethylpiperidin-1-yl)magnesium–Bis(lithium chloride) Complex (3)

A dry, argon flushed 250-mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with freshly distilled 2,2,6,6-tetramethylpiperidine (5.07 mL, 30 mmol) dissolved in THF (30 mL). This soln was cooled to –40 °C and 2.4 M BuLi in hexane (12.5 mL, 30 mmol) was added dropwise. When the addition was complete, the mixture was warmed to 0 °C and stirred at this temperature for 30 min. Freshly titrated 1.0 M TMPMgCl·LiCl (**1**) in THF (30 mL, 30 mmol) was then added dropwise to the mixture and it was stirred at 0 °C for 30 min, warmed to 25 °C, and stirred for 1 h. The solvents were then removed under vacuum to afford a yellowish solid. Freshly distilled THF was then slowly added with vigorous stirring until the salts were completely dissolved. The resulting soln of TMP_2Mg·2LiCl (**3**) was titrated prior to use at 0 °C [benzoic acid with 4-(phenylazo)diphenylamine as the indicator].[11b] A concentration of 0.6 M in THF was obtained.

1 M Zinc Chloride in Tetrahydrofuran Solution

A dry, argon-flushed 500-mL Schlenk flask, equipped with a magnetic stirrer and a glass stopper, was charged with $ZnCl_2$ (20.45 g, 150 mmol) and heated to 150 °C under high vacuum for 5 h. After cooling to 25 °C under argon, anhyd THF (150 mmol) was added and the mixture was stirred continuously until the salts had dissolved. The reagent $ZnCl_2$ (1 M in THF) appears as a colorless soln.

1 M Copper(I) Cyanide–Bis(lithium chloride) in Tetrahydrofuran Solution

A dry, argon-flushed 50-mL Schlenk flask, equipped with a magnetic stirrer and a glass stopper, was charged with LiCl (848 mg, 20 mmol) and heated to 130 °C under high vacuum for 1 h. After cooling to 25 °C under argon, CuCN (869 mg, 10 mmol) was added under an inert atmosphere inside a glove box. The Schlenk flask was further heated to 140 °C for 5 h under high vacuum and cooled to 25 °C. It was then charged with freshly distilled THF (20 mL) under an argon flush and wrapped with aluminum foil to protect it from light. The mixture was stirred vigorously until all the solid had gone into solution to furnish 1.0 M CuCN·2LiCl in THF.

2-Bromo-4-(phenylsulfanyl)pyrimidine (5a); Typical Procedure Using TMPMgCl·LiCl (1) or TMP_2Mg·2 LiCl (3)

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with 1.1 M TMPMgCl·LiCl (**1**) in THF (10 mL, 11 mmol) and cooled to –60 °C. 2-Bromopyrimidine (**2**, 1.60 g, 10 mmol) dissolved in THF (10 mL) was added and the mixture was stirred at –60 °C for 1.5 h. $PhSO_2SPh$ (3.0 g, 12 mmol) in THF (12 mL) was added dropwise at –60 °C, the resulting mixture was allowed to warm up rapidly to –30 °C and then slowly to 25 °C and stirred at this temperature for 15 min. Purification by flash chromatography (pentane–Et_2O, 4:1) afforded **5a** (2.07 g, 77%) as a white solid; mp 83.7–85.0 °C.

IR (ATR): 3060, 3021, 1542, 1509, 1473, 1443, 1396, 1314, 1158, 1144, 1092, 1067, 1020, 1001, 974, 828, 790, 757, 691, 675 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 5.4 Hz, 1 H), 7.45–7.60 (m, 5 H), 6.64 (d, *J* = 5.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6, 157.3, 151.9, 135.4, 130.5, 130.1, 126.7, 115.5.

MS (EI, 70 eV): *m/z* (%) = 267 (100), 265 (96) [(^{79}Br)M^+], 187 (79), 109 (17).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{10}H_7BrN_2S$: 265.9513; found: 265.9505.

2-Bromo-4-chloro-6-(phenylsulfanyl)pyrimidine (6a)

Following the typical procedure using 1.1 M TMPMgCl·LiCl (**1**) in THF (10 mL, 11 mmol) and 2-bromo-4-(phenylsulfanyl)pyrimidine (**5a**, 2.67 g, 10 mmol) in THF (10 mL) with stirring at –60 °C for 45 min. $ClCF_2CCl_2F$ (2.81 g, 15 mmol) was added dropwise at –60 °C; the mixture was allowed to warm up rapidly to –30 °C and slowly to –15 °C for 1 h. Purification by flash chromatography (pentane–CH_2Cl_2, 2:1) afforded **6a** (2.65 g, 90%) as a white solid; mp 66.8–67.9 °C.

IR (ATR): 3107, 1516, 1489, 1442, 1360, 1339, 1256, 1188, 1102, 1093, 970, 844, 801, 757, 692 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.51–7.59 (m, 5 H), 6.58 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 177.5, 161.0, 151.5, 135.6, 131.1, 130.5, 126.1, 114.9.

MS (EI, 70 eV): *m/z* (%) = 302 (69), 301 (100), 300 (50) [(^{79}Br)M^+], 265 (36), 221 (26).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{10}H_6BrClN_2S$: 299.9124; found: 299.9120.

[2-Bromo-4-chloro-6-(phenylsulfanyl)pyrimidin-5-yl](2-chlorophenyl)methanone (7a)

Following the typical procedure using 0.55 M TMP_2Mg·2LiCl (**3**) in THF (6 mL, 3.3 mmol) and cooled to –10 °C. 2-Bromo-4-chloro-6-(phenylsulfanyl)pyrimidine (**6a**, 0.91 g, 3.0 mmol) dissolved in THF (6 mL) was slowly added and the mixture was stirred at –10 °C for 40 min. The mixture was cooled to –20 °C, 1.0 M CuCN·2LiCl in THF (3.3 mL, 3.3 mmol) was added and the mixture

was stirred for 30 min. Then, 2-chlorobenzoyl chloride (1.05 g, 6.0 mmol) was added dropwise at –20 °C and the resulting mixture was stirred at 35 °C for 30 min. Purification by flash chromatography (pentane–CH_2Cl_2, 3:1) afforded the pyrimidine **7a** (1.02 g, 77%) as a white solid; mp 132.4–134.0 °C.

IR (ATR): 3065, 1678, 1584, 1520, 1476, 1438, 1318, 1282, 1218, 1197, 1140, 1106, 1055, 918, 819, 773, 750, 736, 717, 704, 688, 656 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.41–7.84 (m, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 189.6, 172.3, 156.3, 150.7, 135.4, 134.8, 134.6, 133.7, 132.1, 131.4, 130.3, 129.4, 128.3, 127.5, 126.2.

MS (70 eV, EI): *m/z* (%) = 438 (1) [(^{79}Br)M^+], 405 (100), 403 (69), 139 (18), 111 (14).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{17}H_9BrCl_2N_2OS$: 437.8996; found: 437.9003.

2-Bromo-4-iodopyrimidine (5b)

Following the typical procedure using 1.1 M TMPMgCl·LiCl (**1**) in THF (10 mL, 11 mmol) and 2-bromopyrimidine (**2**, 1.60 g, 10 mmol) in THF (10 mL) with stirring at –60 °C for 1.5 h. 1.0 M $ZnCl_2$ in THF (12 mL, 12 mmol) was added dropwise at –60 °C; the mixture was allowed to warm up slowly to 25 °C. I_2 (3.04 g, 12 mmol) dissolved in anhyd THF (12 mL) added dropwise and the mixture was stirred at 25 °C for 45 min. Purification by flash chromatography (pentane–CH_2Cl_2, 3:1) afforded **5b** (2.29 g, 80%) as a white solid; mp 103.5–104.7 °C.

IR (ATR): 3090, 3006, 1513, 1388, 1312, 1180, 1150, 976, 832, 750, 662 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 5.1 Hz, 1 H), 7.74 (d, *J* = 5.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.7, 151.2, 131.5, 129.9.

MS (70 eV, EI): *m/z* (%) = 286 (73), 284 (73) [(^{79}Br)M^+], 157 (100), 127 (26).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_4H_2BrIN_2$: 283.8446; found: 283.8438.

2-Bromo-4-chloropyrimidine (5c)

Following the typical procedure using 1.1 M TMPMgCl·LiCl (**1**) in THF (10 mL, 11 mmol) and 2-bromopyrimidine (**2**, 1.60 g, 10 mmol) in THF (10 mL) with stirring at –60 °C for 1.5 h. $ClCF_2CCl_2F$ (2.81 g, 15 mmol) was added dropwise at –60 °C; the mixture was allowed to warm up slowly to –45 °C and then stirred overnight at –45 °C. Purification by flash chromatography (pentane–CH_2Cl_2, 1:1) afforded **5c** (1.38 g, 71%) as a yellowish solid; mp 46.5–47.7 °C.

IR (ATR): 3090, 3048, 1720, 1526, 1404, 1318, 1189, 1161, 1092, 979, 859, 815, 789, 755, 680 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 5.3 Hz, 1 H), 7.35 (d, *J* = 5.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.1, 159.7, 152.2, 120.7.

MS (EI, 70 eV): *m/z* (%) = 194 (62), 192 (49) [(^{79}Br)M^+], 157 (10), 115 (37).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_4H_2BrClN_2$: 191.9090; found: 191.9075.

2-Bromo-4-(4-chlorophenyl)pyrimidine (5d)

Following the typical procedure using 1.1 M TMPMgCl·LiCl (**1**) in THF (10 mL, 11 mmol) and 2-bromopyrimidine (**2**, 1.60 g, 10 mmol) in THF (10 mL) with stirring at –60 °C for 1.5 h. 1.0 M $ZnCl_2$ in THF (12 mL, 12 mmol) was added dropwise at –60 °C; the mixture was allowed to warm up slowly to 25 °C for 3 h. $Pd(dba)_2$ (115 mg, 2 mol%) and $(2\text{-furyl})_3P$ (93 mg, 4 mol%) dissolved in THF (10 mL) and mixed with 1-chloro-4-iodobenzene (2.86 g, 12 mmol) were then transferred via cannula to the mixture. The resulting mixture was stirred at 50 °C for 1 h. Purification by flash chromatography (pentane–CH_2Cl_2; 2:1) afforded **5d** (1.81 g, 67%) as a yellowish solid; mp 130.5–132.7 °C.

IR (ATR): 3094, 1594, 1561, 1523, 1488, 1423, 1397, 1337, 1167, 1088, 1060, 1010, 982, 817, 802, 763, 723, 660, 628 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 5.3 Hz, 2 H), 8.02 (d, *J* = 8.6 Hz, 1 H), 7.63 (d, *J* = 5.3 Hz, 1 H), 7.47 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 159.7, 153.6, 138.3, 133.4, 129.6, 128.7, 115.2.

MS (70 eV, EI): *m/z* (%) = 270 (100), 268 (73) [(^{79}Br)M^+], 191 (50), 137 (17).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{10}H_6BrClN_2$: 267.9403; found: 267.9412

2-Bromo-4-(thiophen-2-yl)pyrimidine (5e)

Following the typical procedure using 1.1 M TMPMgCl·LiCl (**1**) in THF (10 mL, 11 mmol) and 2-bromopyrimidine (**2**, 1.60 g, 10 mmol) in THF (10 mL) with stirring at –60 °C for 1.5 h. 1.0 M $ZnCl_2$ in THF (12 mL, 12 mmol) was added dropwise at –60 °C; the mixture was allowed to warm up slowly to 25 °C for 3 h. $Pd(dba)_2$ (115 mg, 2 mol%) and $(2\text{-furyl})_3P$ (93 mg, 4 mol%) dissolved in THF (10 mL), and mixed with 2-iodothiophene (2.73 g, 13 mmol) were then transferred via cannula to the mixture. The resulting mixture was stirred at 20 °C for 30 min. Purification by flash chromatography (pentane–EtOAc, 4:1) afforded **5e** (1.49 g, 62%) as a yellowish solid; mp 127.4–129.1 °C.

IR (ATR): 3080, 3047, 1564, 1515, 1434, 1413, 1358, 1331, 1240, 1166, 1113, 999, 980, 852, 842, 762, 721, 674, 622 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 5.3 Hz, 1 H), 7.79–7.81 (dd, *J* = 1.1 Hz, *J* = 2.7 Hz, 1 H), 7.56–7.58 (dd, *J* = 1.1 Hz, *J* = 2.7 Hz, 1 H), 7.14–7.17 (dd, *J* = 4.8 Hz, *J* = 1.2 Hz, 1 H), 7.48 (d, *J* = 5.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6, 157.3, 151.9, 135.4, 130.5, 130.1, 126.7, 115.5.

MS (EI, 70 eV): *m/z* (%) = 242 (51), 240 (49) [(^{79}Br)M^+], 161 (100).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_8H_5BrN_2S$: 239.9357; found: 239.9353.

2-Bromo-4-(hex-1-ynyl)pyrimidine (5f)

Prepared from in situ generated 2-bromo-4-iodopyrimidine **5b** [starting from 2-bromopyrimidine (**2**, 1.6 g, 10 mmol)]. $Pd(dba)_2$ (114 mg, 2 mol%) and $(2\text{-furyl})_3P$ (93 mg, 4 mol%) dissolved in THF (10 mL) and mixed with CuI (40 mg, 0.2 mmol, 2 mol%) and Et_3N (70 mL) were transferred via cannula to the mixture. Hex-1-yne (0.98 g, 12 mmol) was then slowly added at 20 °C and the resulting mixture was stirred at the same temperature for 1 h. Purification by flash chromatography (pentane–CH_2Cl_2, 1:1) afforded **5f** (1.34 g, 56%) as a yellow oil.

IR (ATR): 2958, 2933, 2226, 1556, 1516, 1466, 1416, 1325, 1166, 1088, 980, 954, 843, 794, 779, 768, 739, 680 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 5.0 Hz, 1 H), 7.27 (d, *J* = 5.0 Hz, 1 H), 2.47 (t, *J* = 7.3 Hz, 2 H), 1.61 (p, *J* = 7.1 Hz, 2 H), 1.46 (s, *J* = 7.3 Hz, 2 H), 2.47 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.8, 153.5, 152.9, 122.0, 99.6, 78.0, 29.8, 22.0, 19.2, 13.5.

MS (EI, 70 eV): *m/z* (%) = 240 (28), 238 (27) [(^{79}Br)M^+], 211 (88), 209 (85), 198 (99), 196 (100), 116 (42).

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{10}H_{11}BrN_2$: 238.0106; found: 238.0101.

2-Bromo-6-(phenylsulfanyl)pyrimidine-4-carbonitrile (6b)
Following the typical procedure using 1.1 M TMPMgCl·LiCl (**1**) in THF (10 mL, 11 mmol) and 2-bromo-4-(phenylsulfanyl)pyrimidine (**5a**, 2.67 g, 10 mmol) in THF (10 mL) with stirring at –60 °C for 45 min. TsCN (2.72 g, 15 mmol) in THF (20 mL) was then added dropwise at –60 °C; the mixture was stirred at –30 °C for 2 h. Purification by flash chromatography (pentane–CH_2Cl_2, 1:1) afforded **6b** (1.96 g, 67%) as a white solid; mp 104.3–106.4 °C.

IR (ATR): 3107, 3057, 1593, 1542, 1494, 1476, 1444, 1379, 1285, 1219, 1174, 1133, 971, 875, 809, 753, 690 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.54–7.61 (m, 5 H), 6.88 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 179.0, 152.5, 141.0, 135.5, 131.5, 130.8, 125.3, 118.6, 114.2.

MS (70 eV, EI): *m*/*z* (%) = 292 (100), 291 (69) [(^{79}Br)M^+], 212 (99), 185 (29), 109 (40), 77 (10), 65 (30).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_6BrN_3S$: 290.9466; found: 290.9442.

2,4-Dibromo-6-(phenylsulfanyl)pyrimidine (6c)
Following the typical procedure using 1.1 M TMPMgCl·LiCl (**1**) in THF (5.5 mL, 5 mmol) and 2-bromo-4-(phenylsulfanyl)pyrimidine (**5a**, 1.51 g, 5 mmol) in THF (10 mL) with stirring at –60 °C for 45 min. $BrCCl_2CCl_2Br$ (2.44 g, 7.50 mmol) was slowly added; the mixture was allowed to warm up rapidly to –30 °C and then to warm up slowly to –15 °C for 1 h. Purification by flash chromatography (pentane–CH_2Cl_2, 3:1) afforded **6c** (1.47 g, 85%) as a white solid; mp 62.0–64.0 °C.

IR (ATR): 3093, 3055, 1512, 1476, 1440, 1352, 1245, 1177, 1092, 1026, 965, 921, 842, 806, 765, 743, 683 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.57 (m, 5 H), 6.75 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.8, 152.0, 150.5, 135.5, 131.0, 130.4, 126.0, 118.8.

MS (EI, 70 eV): *m*/*z* (%) = 345 (100), 344 (42) [(^{79}Br)M^+], 265 (75), 109 (37).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_6Br_2N_2S$: 343.8618; found: 343.8595.

2-Bromo-4,6-diiodopyrimidine (6d)
Following the typical procedure using 1.1 M TMPMgCl·LiCl (**1**) in THF (10 mL, 11 mmol) and 2-bromo-4-iodopyrimidine (**5b**, 2.84 g, 10 mmol) in THF (20 mL) with stirring at –60 °C for 1 h. 1.0 M $ZnCl_2$ in THF (12 mL, 12 mmol) was added dropwise at –60 °C; the mixture was allowed to warm up slowly to –20 °C for 1 h. I_2 (3.04 g, 12 mmol) in THF (12 mL) was slowly added at –20 °C and the resulting mixture was stirred for 60 min at –20 °C. The mixture was then quenched with sat. aq $Na_2S_2O_3$ (50 mL). Purification by flash chromatography (pentane–CH_2Cl_2, 4:1) afforded **6d** (3.35 g, 82%) as a white solid; mp 186.4–188.0 °C.

IR (ATR): 3101, 2925, 1465, 1344, 1305, 1228, 1109, 1091, 972, 840, 768, 721 cm^{-1}.

^1H NMR (400 MHz, THF-d_8): δ = 8.05 (s, 1 H).

^{13}C NMR (100 MHz, THF-d_8): δ = 149.8, 142.7, 130.2.

MS (70 eV, EI): *m*/*z* (%) = 412 (100), 410 (98) [(^{79}Br)M^+], 283 (65), 178 (48), 127 (55), 77 (25).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_4HBrI_2N_2$: 409.7412; found: 409.7400.

2,4-Dibromo-6-iodopyrimidine (6e)
Following the typical procedure using 1.1 M TMPMgCl·LiCl (**1**) in THF (5.5 mL, 5 mmol) and 2-bromo-4-iodopyrimidine (**5b**, 1.42 g, 5 mmol) in THF (10 mL) with stirring at –60 °C for 1 h. $BrCCl_2CCl_2Br$ (2.442 g, 7.5 mmol) was added dropwise at –78 °C; the mixture was allowed to warm up slowly to –60 °C for 1 h. Purification by flash chromatography (pentane–CH_2Cl_2, 3:1) afforded **6e** (1.22 g, 67%) as a white solid; mp 145.6–147.2 °C.

IR (ATR): 3101, 2925, 1476, 1352, 1323, 1235, 1096, 972, 858, 776, 737 cm^{-1}.

^1H NMR (400 MHz, THF-d_8): δ = 8.29 (s, 1 H).

^{13}C NMR (100 MHz, THF-d_8): δ = 152.7, 150.4, 136.1, 131.0.

MS (EI, 70 eV): *m*/*z* (%) = 364 (95), 362 (49) [(^{79}Br)M^+], 239 (46), 237 (100), 235 (50), 132 (35), 127 (39).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_4HBr_2IN_2$: 361.7551; found: 361.7562

2-Bromo-4-iodo-6-(trimethylsilyl)pyrimidine (6f)
Following the typical procedure using 1.1 M TMPMgCl·LiCl (**1**) THF (5.5 mL, 5 mmol) and 2-bromo-4-iodopyrimidine (**5b**, 1.42 g, 5 mmol) in THF (10 mL) with stirring at –60 °C for 1 h. Me_3SiCN (0.74 g, 6.0 mmol) was then added dropwise; the mixture was allowed to warm up slowly to –35 °C for 2 h. Purification by flash chromatography (pentane–CH_2Cl_2, 3:1) afforded **6f** (1.59 g, 89%) as a white solid; mp 64.3–66.6 °C.

IR (ATR): 2957, 2898, 1518, 1449, 1250, 1218, 1168, 1134, 1120, 1078, 970, 837, 776, 744, 728, 625 cm^{-1}.

^1H NMR (400 MHz, THF-d_8): δ = 8.03 (s, 1 H), 0.31 (s, 9 H).

^{13}C NMR (100 MHz, THF-d_8): δ = 182.8, 151.9, 137.1, 131.0, –2.7.

MS (70 eV, EI): *m*/*z* (%) = 358 (13), 356 (11) [(^{79}Br)M^+], 340 (22), 338 (15), 276 (62), 231 (100), 229 (98), 139 (41), 137 (39).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_7H_{10}BrIN_2Si$: 355.8841; found: 355.8829

5-Allyl-2-bromo-4-chloro-6-(phenylsulfanyl)pyrimidine (7b)
Following the typical procedure using 0.55 M TMP_2Mg·2LiCl (**3**) in THF (6 mL, 3.3 mmol) cooled to –10 °C. 2-Bromo-4-chloro-6-(phenylsulfanyl)pyrimidine (**6a**, 0.91 g, 3 mmol) in THF (6 mL) was slowly added and the mixture was stirred at –10 °C for 40 min. 1.0 M $ZnCl_2$ in THF (9 mL, 9 mmol) was then added dropwise at –10 °C and the mixture was stirred at this temperature for 30 min. Then, 1.0 M CuCN·2LiCl in THF (0.15 mL, 5 mol%) was added at –20 °C and the mixture was cooled down to –60 °C. Allyl bromide (0.72 g, 6 mmol) was added to the reaction and the resulting mixture was allowed to warm up slowly to –30 °C. Purification by flash chromatography (pentane–CH_2Cl_2, 3:1) afforded **7b** (0.91 g, 89%) as a white solid; mp 49.5–51.1 °C.

IR (ATR): 3052, 3011, 1638, 1522, 1480, 1442, 1435, 1418, 1309, 1280, 1211, 1190, 1009, 1084, 1022, 992, 978, 939, 900, 853, 790, 776, 748, 707, 688 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.43–7.52 (m, 5 H), 5.84–5.91 (m, 1 H), 5.18–5.21 (m, 2 H), 3.55 (dt, ^3J = 6.3 Hz, ^4J = 1.5 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.0, 159.4, 148.1, 135.4, 130.3, 130.0, 129.3, 126.8, 125.9, 118.2, 32.8.

MS (EI, 70 eV): *m*/*z* (%) = 340 (5) [(^{79}Br)M^+], 327 (100), 325 (72), 109 (10).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{10}BrClN_2S$: 339.9437; found: 339.9435.

2-Bromo-4-chloro-5-(methylsulfanyl)-6-(phenylsulfanyl)pyrimidine (7c)
Following the typical procedure using 0.55 M TMP_2Mg·2 LiCl (**3**) in THF (6 mL, 3.3 mmol) and cooling to –10 °C. 2-Bromo-4-chloro-6-(phenylsulfanyl)pyrimidine (**6a**, 0.91 g, 3 mmol) dissolved in THF (6 mL) was slowly added and the mixture was stirred at –10 °C for 40 min. $MeSO_2SMe$ (1.14 g, 9.0 mmol) was then added dropwise and the resulting mixture was stirred at 25 °C for 30 min. Pu-

rification by flash chromatography (pentane–CH_2Cl_2, 3:1) afforded **7c** (0.83 g, 80%) as a white solid; mp 64.5–66.3 °C.

IR (ATR): 3060, 2922, 1487, 1463, 1440, 1274, 1255, 1195, 1087, 1068, 1042, 1023, 1000, 972, 914, 828, 794, 744, 703, 686 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.45–7.51 (m, 5 H), 2.47 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 179.2, 164.0, 149.8, 135.2, 130.0, 129.3, 127.9, 124.7, 17.1.

MS (EI, 70 eV): *m*/*z* (%) = 348 (100), 346 (65) [(^{79}Br)M^+], 315 (31), 313 (27), 269 (14), 267 (27), 109 (25), 77 (19).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_8BrClN_2S_2$: 345.9001; found: 345.9014.

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