Regioselective Functionalization of Purine Derivatives at Positions 8 and 6 Using Hindered TMP-Amide Bases of Zn and Mg

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Abstract: A broad range of purine derivatives were efficiently metalated at positions 8 and 6 using TMP-amide bases. This provided polysubstituted purines in good to very good yields after subsequent trapping of the zinc or magnesium intermediates with various electrophiles.

Key words: purine derivatives, metalation, Negishi cross-coupling, magnesium, zinc

As a result of the large variety of biologically active compounds bearing a purine unit this scaffold became an important class of pharmacophores that has been extensively studied in the last decades.[2] Diverse combinatorial libraries of functionalized purines have been synthesized by direct C–H arylations[3] or heterocylizations.[4] Moreover, Pd- and Fe-mediated reactions can allow access to several simple 6,8-disubstituted and 2,6,8-trisubstituted purines.[5] In addition, the more challenging approach, that is, coupling of metalated purine derivatives with appropriate electrophiles, have been developed via magnesiation,[6] zincation,[7] or lithiation.[8] Recently, our group has described for the first time the successive and selective generation of magnesium and zinc organometallic intermediates at positions 6, 8, and 2 to furnish a large collection of novel and highly designed purine derivatives.[9] In the present work, we extend the study in the regioselective functionalization of purine scaffolds to the development of an efficient metalation protocol at positions 8 and 6 of a wide range of purine derivatives using hindered TMP-amide bases[10] (TMP = 2,2,6,6-tetramethylpiperidide).

First, the starting materials **1** used in this study were bearing a protecting group (PG) such as a methoxymethyl (MOM), a benzyl (Bn), or a 2,2,3,3-tetrahydropyranyl (THP) group (see Figure 1). Thus, a selective deprotonation at position 8 using either zinc- or magnesium-amide bases generated a metalated species of type **2** as depicted in Scheme 1. For example, purines **1a**, **1i**, and **1k** were readily zincated by using TMPZnCl·LiCl[11] within 30 minutes at 25 °C. Subsequent trapping with iodine (1.2 equiv) provided the corresponding iodinated compounds **3a**–**c** in 60–98% yields (Table 1, entries 1–3). Notably, if organomagnesium reagent TMPMgCl·LiCl[12] was used at –60 °C the yield was only slightly affected (entry 2). Bromination of purine **1i** and **1j** with 1,2-dibromo-1,1,2,2-tetrachloroethane proceeded under Barbier reaction conditions[13] at 0 °C using bisamide zinc base $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$.[14] The 8-brominated compounds **3d** and **3e** were obtained after 15 minutes in 82% and 75% yield, respectively (entries 4, 5). Remarkably, using the same conditions as described above compound **1f** was brominated to furnish the 2,6,8-trihalogenopurine **3f** bearing three different halogens in 87% yield (entry 6). Similarly, derivative **1i** reacted with *S*-phenyl benzenesulfonothioate under Barbier reaction conditions at 0 °C affording 8-phenylthiopurine **3g** in 60% yield (entry 7). Copper(I)-catalyzed allylation[15] (10 mol% CuCN·2LiCl) of derivative **1f** with 3-bromocyclohexene (–65 °C to 25 °C, 2 h) led to the allylated purine **3h** in 84% yield (entry 8).

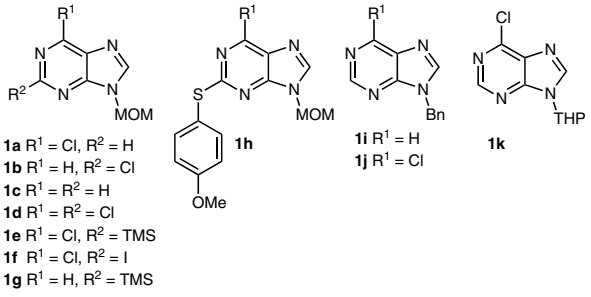
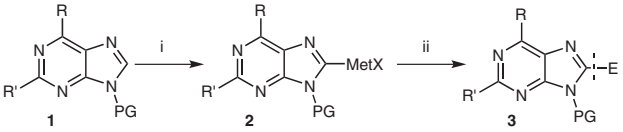


Figure 1 Array of protected purines examined in the study



Scheme 1 General reaction scheme for the selective metalation of purine derivatives of type **1** at position 8 and subsequent reaction with an electrophile: *Reagents and conditions*: (i) TMP-amide base; (ii) electrophile, 60–98%. See Table 1 for more details.

As shown in Scheme 2, the 8-zincated intermediates of type **4** underwent Pd-catalyzed Negishi cross-coupling reactions[16] with $Pd(dba)_2$ (2 mol%), (*o*-furyl)$_3$P (4 mol%), and various aryl iodides (1.2 equiv) within a few hours (2–14 h) to afford the 8-arylated purines of type **5** in 48–97% yields. For example, purine **1c** was readily metalated by using TMPZnCl·LiCl within 30 minutes at 25 °C. The organometallic intermediate reacted with either ethyl 4-iodobenzoate or 4-iodoanisole at 25 °C to provide the purine derivatives **5a** and **5b** in 97% and 61% yield, re-

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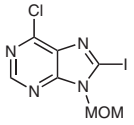
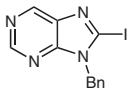
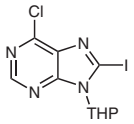
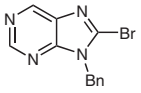
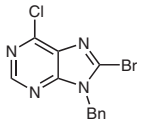
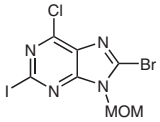
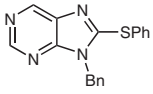
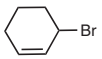
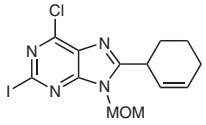
Table 1 Synthesis and Yields of Purine Derivatives of Type **3**

Entry	SM[a]	Electrophile	Product[b]
1	**1a**	I_2	 **3a** (98)[c]
2	**1i**	I_2	 **3b** (80)[c] (84)[d]
3	**1k**	I_2	 **3c** (60)[c]
4	**1i**	$(CCl_2Br)_2$	 **3d** (82)[e]
5	**1j**	$(CCl_2Br)_2$	 **3e** (75)[e]
6	**1f**	$(CCl_2Br)_2$	 **3f** (87)[e]
7	**1i**	$PhSO_2SPh$	 **3g** (60)[e]
8	**1f**		 **3h** (84)[f]

[a] Starting material.
[b] Yield (%) of isolated analytically pure product is given in parentheses.
[c] 1) TMPZnCl·LiCl (1.1 equiv), 25 °C, 30 min; 2) I_2 (1.2 equiv), 25 °C, 1 h.
[d] 1) TMPMgCl·LiCl (1.1 equiv), –60 °C, 15 min; 2) I_2 (1.2 equiv), –60 °C, 2.5 h.
[e] 1) Electrophile (1 equiv), 0 °C, 5 min; 2) $TMP_2Zn·2MgCl_2·2LiCl$ (1.2 equiv), 0 °C to 25 °C, 15 min.
[f] 1) $ZnCl_2$ (1 equiv), 25 °C, 5 min; 2) TMPMgCl·LiCl (1.13 equiv), –65 °C, 30 min; 3) CuCN·2LiCl (0.1 equiv), 3-bromocyclohexene (1.4 equiv), –65 °C to 25 °C, 2 h.

spectively (Table 2, entries 1, 2). Similarly, compound **1a** furnished the 8-arylated 6-chloropurines **5c** and **5d** in 91% and 95% yield, respectively (entries 3, 4). Noticeably, derivative **5e** was only detected in traces due to the deprotection of the THP group during the cross-coupling reaction. The unprotected arylated product was isolated instead in 75% yield (entry 5). Remarkably, functional groups like thioether and TMS are tolerated in position 2 during both the deprotonation and the Negishi cross-coupling reaction (entries 9–12). In the case of purine **1e**, the cross-coupling reaction was performed at 45 °C for 14 hours leading to the trisubstituted purine **5l** in 91% (entry 12). The same reaction was performed on 20 and 30 mmol scales furnishing the expected product **5l** in 70% and 85% yield, respectively. Unfortunately attempts with aryl bromides or heteroaryl halides as electrophiles for the Negishi cross-coupling reaction failed.

Table 2 Synthesis and Yields of Purine Derivatives of Type **5**

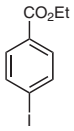
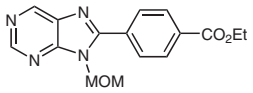
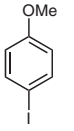
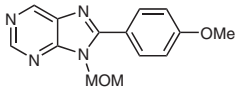
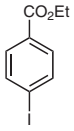
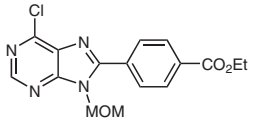
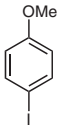
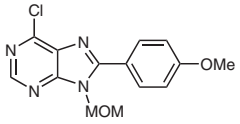
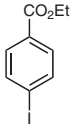
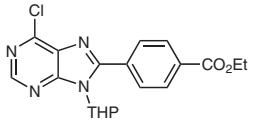
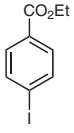
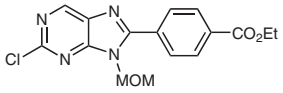
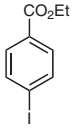
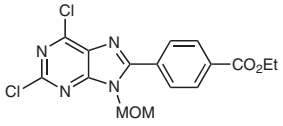
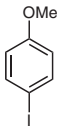
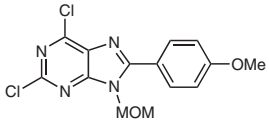
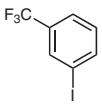
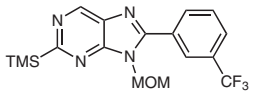
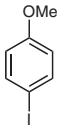
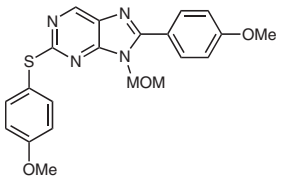
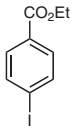
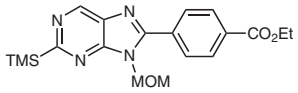
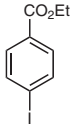
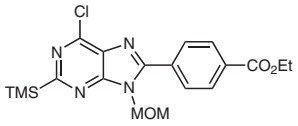
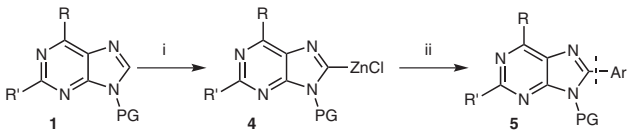
Entry	SM[a]	ArI	Product[b]
1	**1c**		 **5a** (97)[c]
2	**1c**		 **5b** (61)[c]
3	**1a**		 **5c** (91)[c]
4	**1a**		 **5d** (95)[c]
5	**1k**		 **5e** (traces)[d]
6	**1b**		 **5f** (58)[c]
7	**1d**		 **5g** (62)[c]

Table 2 Synthesis and Yields of Purine Derivatives of Type **5** (continued)

Entry	SM[a]	ArI	Product[b]
8	**1d**		 **5h** (71)[c]
9	**1g**		 **5i** (48)[c]
10	**1h**		 **5j** (85)[c]
11	**1g**		 **5k** (52)[c]
12	**1e**		 **5l** (91)[e]

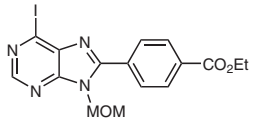
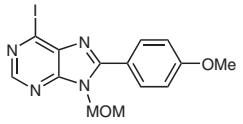
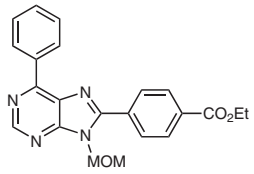
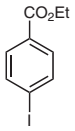
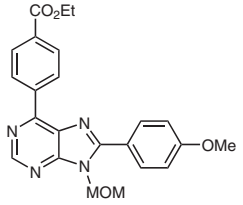
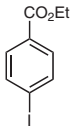
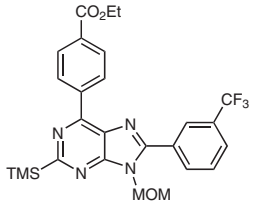
[a] Starting material.
[b] Yield (%) of isolated analytically pure product is given in parentheses.
[c] Obtained by palladium-catalyzed cross-coupling reaction using $Pd(dba)_2$ (2 mol%) and (*o*-furyl)$_3$P (4 mol%) at 25 °C for 2–14 h.
[d] The deprotected product was obtained instead in 75% yield.
[e] Obtained by palladium-catalyzed cross-coupling reaction using $Pd(dba)_2$ (2 mol%) and (*o*-furyl)$_3$P (4 mol%) at 45 °C for 14 h.



Scheme 2 General reaction scheme for the selective zincation of purine derivatives of type **1** at position 8 and subsequent Negishi cross-coupling reaction with an aryl iodide. *Reagents and conditions*: (i) TMPZnCl·LiCl (1.1 equiv), anhyd THF, 30 min, 25 °C; (ii) ArI (1.2 equiv), 48–97%. LiCl in **4** is omitted for clarity. See Table 2 for more details.

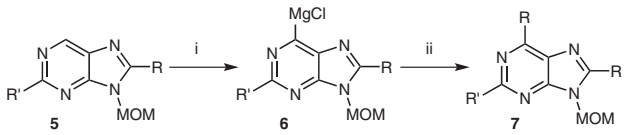
The deprotonation at position 6 of the purine scaffold was achieved with TMPMgCl·LiCl within 60 minutes at –20 °C leading to organomagnesium intermediates of type **6** as illustrated in Scheme 3. Thus, after subsequent iodolysis purine derivatives **5a** and **5b** furnished the corresponding 6-iodopurines **7a** and **7b** in 70% and 60% yield, respectively (Table 3, entries 1, 2). Negishi cross-coupling reactions of compound **5a** and **5b** with iodobenzene and ethyl 4-iodobenzoate in the presence of $Pd(dba)_2$ (2 mol%) and (*o*-furyl)$_3$P (4 mol%) gave the 6,8-bisarylated products **7c** and **7d** in 55% and 63% yield, respectively (entries 3, 4). Particularly, starting from derivative **5i** and using the same conditions described above a trisubstituted purine **7e** was obtained in 53% yield.

Table 3 Synthesis and Yields of Purine Derivatives of Type **7**

Entry	SM[a]	Electrophile	Product[b]
1	**5a**	I_2	 **7a** (70)
2	**5b**	I_2	 **7b** (60)
3	**5a**		 **7c** (63)[c]
4	**5b**		 **7d** (55)[c]
5	**5i**		 **7e** (53)[c]

[a] Starting material.
[b] Yield (%) of isolated analytically pure product is given in parentheses.
[c] Transmetalation with $ZnCl_2$ (1.3 equiv) then palladium-catalyzed cross-coupling reaction using $Pd(dba)_2$ (2 mol%) and (*o*-furyl)$_3$P (4 mol%) at 25 °C for 3–14 h.

In conclusion, a regioselective functionalization of a broad range of protected purine derivatives has been achieved successfully at positions 8 and 6 via zinc and magnesium intermediates providing a large variety of polysubstituted purines after subsequent trapping with



Scheme 3 General reaction scheme for the selective magnesiation of purine derivatives of type **5** at position 6 and subsequent reaction with an electrophile. *Reagents and conditions*: (i) TMPMgCl·LiCl (1.2 equiv), anhyd THF, 1 h, –20 °C; (ii) electrophile, 53–70%. LiCl in **6** is omitted for clarity. See Table 3 for more details.

various electrophiles. This study completes our previous work[9] by extending the scope of the purine scaffold and allows access now to a wide library of highly substituted compounds. Further studies concerning construction of new substituted derivatives are currently in progress.

All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes, which were used to transfer anhydrous solvents or reagents, were purged with argon prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under N_2. 2,2,6,6-Tetramethylpiperidine (TMPH) was distilled prior to use. Yields refer to isolated compounds estimated to be >95% pure as determined by ^{1}H NMR spectroscopy (25 °C) and capillary GC. NMR spectra were recorded on Bruker ARX-200, AC-300, or WH-400 using $CDCl_3$ as solvent. Standard abbreviations are used to indicate spin multiplicities. GC analyses were performed with instruments of type Hewlett-Packard 6890 or 5890 series II using a column of type HP 5. Column chromatography was performed using SiO_2 (0.040–0.063 mm, 230–400 mesh ASTM) from Merck. Melting points were measured using a Büchi B-540 apparatus and are uncorrected. Mass spectra and high-resolution mass spectra (HRMS) were recorded on Finnigan MAT 95Q or Finnigan MAT 90 instrument using electron impact (EI); where otherwise noted electrospray ionization (ESI) was used. TMPZnCl·LiCl,[11] TMPMgCl·LiCl,[12] $TMP_2Zn·2MgCl_2·2LiCl$,[14] CuCN·2LiCl,[17] $ZnCl_2$,[17] MOMCl solution in toluene[18] as well as purines **1a**,[19] **1e**,[9] **1i**,[20] **1j**,[21] and **1k**[22] were prepared according to literature procedures. The freshly prepared TMP-amide bases were titrated prior to use at 25 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator.

2-Chloro-9-(methoxymethyl)-9*H*-purine (1b)
A solution of MOMCl (30.0 mL, 2 M in toluene, 60 mmol, 2.3 equiv) was added dropwise to a solution of 2-chloro-9*H*-purine (4.0 g, 26 mmol, 1.0 equiv) and Et_3N (7.2 mL, 52 mmol, 2 equiv) in DME (300 mL) at 25 °C. The mixture was stirred at this temperature for 3 h, and then quenched with K_2CO_3 (ca. 10 g) and H_2O (200 mL). The aqueous layer was extracted with EtOAc (2 × 150 mL), then the combined organic layers were washed with H_2O (200 mL) and brine (300 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by column chromatography using CH_2Cl_2–EtOH (20:1) as eluent to lead to purine **1b**; yield: 3.0 g (58%); white solid; mp 113–115 °C.

^{1}H NMR ($CDCl_3$): δ = 9.01 (s, 1 H), 8.24 (s, 1 H), 5.61 (s, 2 H), 3.41 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 155.0, 153.5, 150.4, 145.9, 132.9, 74.1, 57.5.

MS (70 eV): *m*/*z* (%) = 200 (7), 198 (20), 170 (24), 169 (15), 168 (84), 167 (36), 52 (5), 45 (100).

HRMS: *m*/*z* calcd for $C_7H_7ClN_4O$: 198.0308; found: 198.0309.

9-(Methoxymethyl)-9*H*-purine (1c)
t-BuONO (0.50 mL, 4 mmol, 2 equiv) was added to a solution of 9-(methoxymethyl)-9*H*-purin-6-amine (0.56 g, 2 mmol, 1 equiv) in anhydrous THF (10 mL) at 25 °C. The mixture was heated under reflux conditions for 3 h, then *t*-BuONO (0.50 mL, 4 mmol, 2 equiv) was added again, and the mixture stirred for further 3 h. After cooling to 25 °C, the solvents were removed in vacuo, and the crude material was purified by column chromatography using a gradient elution (CH_2Cl_2–MeOH, 100:0, then 100:1 to 30:1) to provide purine **1c**; yield: 0.23 g (70%); pale yellow solid; mp 87–88 °C.

^{1}H NMR ($CDCl_3$): δ = 9.17 (s, 1 H), 9.01 (s, 1 H), 8.24 (s, 1 H), 5.64 (s, 2 H), 3.38 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 153.1, 148.8, 145.2, 133.8, 73.9, 57.3.

MS (70 eV): *m*/*z* (%) = 164 (8), 135 (11), 134 (100), 133 (38), 78 (5), 45 (86).

HRMS: *m*/*z* calcd for $C_7H_8N_4O$: 164.0698; found: 164.0697.

2,6-Dichloro-9-(methoxymethyl)-9*H*-purine (1d)[23]
A solution of MOMCl (7.50 mL, 2 M in toluene, 15 mmol, 1.5 equiv) was added dropwise to a solution of 2,6-dichloro-9*H*-purine (1.89 g, 10 mmol, 1.0 equiv) and K_2CO_3 (6.20 g, 45 mmol, 4.5 equiv) in DMF (20 mL) at 25 °C. The mixture was stirred at this temperature for 3 h, and then quenched with H_2O (20 mL). The aqueous layer was extracted with EtOAc (2 × 40 mL), then the combined organic layers were washed with H_2O (60 mL) and brine (60 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by column chromatography using a gradient elution (CH_2Cl_2–EtOH, 100:0 then 500:1 to 100:1) to provide purine **1d**; yield: 0.86 g (37%); white solid; mp 126–127 °C.

^{1}H NMR ($CDCl_3$): δ = 8.27 (s, 1 H), 5.61 (s, 2 H), 3.41 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 153.6, 152.1, 145.7, 130.6, 74.7, 57.6.

MS (70 eV): *m*/*z* (%) = 232 (9), 212 (9), 211 (12), 204 (40), 203 (20), 202 (62), 201 (21), 196 (12), 45 (100).

HRMS: *m*/*z* calcd for $C_7H_6Cl_2N_4O$: 231.9919; found: 231.9919.

6-Chloro-2-iodo-9-(methoxymethyl)-9*H*-purine (1f)
A solution of I_2 (0.95 g, 3.75 mmol, 1.5 equiv) in anhydrous THF (4 mL) was added dropwise to a solution of 6-chloro-9-(methoxymethyl)-2-(tributylstannyl)-9*H*-purine (1.22 g, 2.5 mmol, 1.0 equiv) in anhydrous THF (12 mL) at 25 °C. The mixture was stirred for 1 h, and then quenched with sat. aq $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL), then the combined organic layers were washed with H_2O (40 mL) and brine (60 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by column chromatography using pentane as eluent to furnish purine **1f**; yield: 0.73 g (90%); pale yellow solid; mp 128–130 °C.

^{1}H NMR ($CDCl_3$): δ = 8.17 (s, 1 H), 5.60 (s, 2 H), 3.42 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 152.9, 150.8, 145.0, 131.5, 117.2, 74.8, 57.7.

MS (70 eV): *m*/*z* (%) = 325 (9), 324 (28), 296 (33), 294 (100), 197 (7), 45 (16).

HRMS: *m*/*z* calcd for $C_7H_6ClIN_4O$: 323.9275; found: 323.9252.

9-(Methoxymethyl)-2-(trimethylsilyl)-9*H*-purine (1g)
Pd/C (0.25 g, 40 wt%) and ammonium formate (1.25 g, 19.8 mmol, 7.9 equiv) were successively added to a solution of purine **1e** (0.68 g, 2.5 mmol, 1.0 equiv) in MeOH (5 mL) at 45 °C. When the reaction started proceeding (intensive bubbling), the mixture was stirred for further 30 min until the starting material was completely converted as monitored on TLC (EtOAc). The solution was filtered through a pad of Celite. The pad was washed several times with EtOH and the combined filtrates were concentrated in vacuo. The crude material was dissolved in CH_2Cl_2 (100 mL) and the remaining ammonium formate was filtered off. The solvent was removed in vacuo and the resulting crude material was purified by column chromatography using EtOAc as eluent to afford purine **1g**; yield: 0.55 g (90%); pale yellow oil.

^{1}H NMR ($CDCl_3$): δ = 9.12 (s, 1 H), 8.14 (s, 1 H), 5.58 (s, 2 H), 3.32 (s, 3 H), 0.30 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 174.6, 150.9, 147.1, 144.7, 132.3, 73.6, 57.5, –1.9.

HRMS (ESI): *m*/*z* calcd for $C_{10}H_{16}N_4OSi + H^+$: 237.1166; found: 237.1166.

9-(Methoxymethyl)-2-[(4-methoxyphenyl)thio]-9*H*-purine (1h)
4-Methoxythiophenol (168 mg, 1.2 mmol, 1.2 equiv) was added to a solution of *t*-BuOK (224 mg, 2.0 mmol, 2 equiv) in NMP (2 mL) at 25 °C. The mixture was stirred for 5 min at 110 °C, then purine **1b** (193 mg, 1.0 mmol, 1.0 equiv) was added, and the resulting mixture was heated for 1 h at this temperature. After cooling to 25 °C, EtOAc (30 mL) was added and the organic layer was washed with H_2O (3 × 15 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by column chromatography using pentane–EtOAc (1:2) as eluent to afford purine **1h**; yield: 160 mg (53%); yellow oil.

^{1}H NMR ($CDCl_3$): δ = 8.87 (s, 1 H), 8.03 (s, 1 H), 7.55–7.50 (m, 2 H), 6.95–6.90 (m, 2 H), 5.37 (s, 2 H), 3.82 (s, 3 H), 3.23 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 167.2, 160.6, 152.8, 149.1, 144.2, 137.2, 131.1, 120.7, 114.6, 73.7, 57.7, 55.4.

MS (70 eV): *m*/*z* (%) = 304 (5), 303 (17), 302 (100), 301 (88), 272 (6), 271 (19), 259 (7), 257 (23), 139 (7), 45 (27).

HRMS: *m*/*z* calcd for $C_{14}H_{14}N_4O_2S$: 302.0837; found: 302.0829.

6-Chloro-8-iodo-9-(methoxymethyl)-9*H*-purine (3a)
Freshly prepared TMPZnCl·LiCl (0.92 mL, 1.2 M in THF, 1.1 mmol, 1.1 equiv) was added dropwise within 2 min to a solution of purine **1a** (199 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (1.5 mL) at 25 °C. The mixture was stirred for 30 min, then a solution of I_2 (305 mg, 1.2 mmol, 1.2 equiv) in anhydrous THF (4 mL) was added dropwise. The mixture was stirred for 1 h, and then quenched with sat. aq $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with Et_2O (2 × 30 mL), then the combined organic layers were washed with H_2O (40 mL) and brine (40 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by column chromatography using pentane–EtOAc (1:2) as eluent to furnish purine **3a**; yield: 317 mg (98%); beige solid; mp 125–127 °C.

^{1}H NMR ($CDCl_3$): δ = 8.71 (s, 1 H), 5.61 (s, 2 H), 3.42 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 153.5, 152.3, 149.6, 133.7, 107.4, 76.0, 57.6.

MS (70 eV): *m*/*z* (%) = 323 (20), 296 (28), 295 (9), 294 (94), 292 (8), 197 (7), 169 (29), 168 (9), 167 (100), 77 (7), 45 (66).

HRMS: *m*/*z* calcd for $C_7H_6ClIN_4O$: 323.9275; found: 323.9266.

9-Benzyl-8-iodo-9*H*-purine (3b)[24]
Method A: Freshly prepared TMPZnCl·LiCl (0.92 mL, 1.2 M in THF, 1.1 mmol, 1.1 equiv) was added dropwise within 2 min to a solution of purine **1i** (210 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (1.5 mL) at 25 °C. The mixture was stirred for 30 min, then a solution of I_2 (305 mg, 1.2 mmol, 1.2 equiv) in anhydrous THF (4 mL) was added dropwise. The mixture was stirred for 1 h, and then quenched with sat. aq $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), then the combined organic layers were washed with H_2O (40 mL) and brine (40 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by column chromatography using pentane–Et_2O (1:9) as eluent to furnish purine **3b**; yield: 270 mg (80%); white solid; mp 211–213 °C.

Method B: Freshly prepared TMPMgCl·LiCl (0.92 mL, 1.2 M in THF, 1.1 mmol, 1.1 equiv) was slowly added dropwise within 5 min to a solution of purine **1i** (210 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (4 mL) at –60 °C. The mixture was stirred for 15 min, then a solution of I_2 (305 mg, 1.2 mmol, 1.2 equiv) in anhydrous THF (3 mL) was added dropwise. The mixture was stirred for 2.5 h, and then quenched with sat. aq $Na_2S_2O_3$ (10 mL). After workup and purification as described above, purine **3b** was obtained as a white solid; yield: 284 mg (84%).

^{1}H NMR ($CDCl_3$): δ = 9.08 (s, 1 H), 8.95 (s, 1 H), 7.35–7.31 (m, 5 H), 5.48 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 152.8, 147.1, 136.4, 134.7, 128.9, 128.5, 127.9, 108.3, 49.0.

MS (70 eV): *m*/*z* (%) = 337 (5), 336 (41), 335 (18), 210 (16), 209 (100), 208 (9), 104 (6), 92 (7), 91 (84), 65 (16).

HRMS: *m*/*z* calcd for $C_{12}H_9IN_4$: 335.9872; found: 335.9859.

6-Chloro-8-iodo-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (3c)[25]
Freshly prepared TMPZnCl·LiCl (1.0 mL, 1.1 M in THF, 1.1 mmol, 1.1 equiv) was added dropwise within 2 min to a solution of purine **1k** (239 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (1.5 mL) at 25 °C. The mixture was stirred for 30 min, then a solution of I_2 (305 mg, 1.2 mmol, 1.2 equiv) in anhydrous THF (2 mL) was added dropwise. The mixture was stirred for 1 h, and then quenched with sat. aq $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), then the combined organic layers were washed with H_2O (40 mL) and brine (40 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by column chromatography using CH_2Cl_2 as eluent to afford purine **3c**; yield: 220 mg (60%); white solid; mp 143–145 °C.

^{1}H NMR ($CDCl_3$): δ = 8.68 (s, 1 H), 5.67 (dd, *J* = 11.4, 2.4 Hz, 1 H), 4.25–4.19 (m, 1 H), 3.79–3.71 (m, 1 H), 3.20–3.07 (m, 1 H), 2.20–2.13 (m, 1 H), 1.94–3.63 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 152.5, 151.6, 149.5, 134.3, 106.6, 87.4, 69.3, 28.8, 24.6, 23.3.

MS (70 eV): *m*/*z* (%) = 282 (27), 281 (6), 280 (100), 245 (27), 127 (6), 118 (7), 99 (7), 91 (6), 85 (6).

HRMS: *m*/*z* calcd for $C_{10}H_{10}ClIN_4O$: 363.9588; found: 363.9580.

Metalation at Position 8 of Purines Using $TMP_2Zn·2MgCl_2·2LiCl$ as Base and Subsequent Quench with Electrophile; General Procedure 1 (GP1)
Freshly prepared $TMP_2Zn·2MgCl_2·2LiCl$ (1.2 equiv) was added dropwise within 2 min to a solution of the desired purine (1.0 equiv) and the desired electrophile (1.0 equiv) in anhydrous THF (*c* = ca. 0.5 M) at 0 °C. The mixture was allowed to warm up to 25 °C over 15 min, and then quenched with sat. aq NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL), then the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by column chromatography.

9-Benzyl-8-bromo-9*H*-purine (3d)[26]
Starting from purine **1i** (210 mg, 1.0 mmol), following GP1 and using 1,2-dibromo-1,1,2,2-tetrachloroethane as electrophile, the desired purine **3d** was obtained after purification by column chromatography using a gradient elution (CH_2Cl_2–MeOH, 200:0, then 200:1 to 100:1); yield: 238 mg (82%); white solid; mp 130–131 °C.

^{1}H NMR ($CDCl_3$): δ = 9.05 (s, 1 H), 8.99 (s, 1 H), 7.37–7.31 (m, 5 H), 5.49 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 152.9, 152.5, 147.2, 134.5, 134.3, 134.2, 129.0, 128.5, 127.9, 47.6.

MS (70 eV): *m*/*z* (%) = 290 (36), 289 (20), 288 (37), 287 (16), 209 (100), 92 (13), 91 (87), 65 (28).

HRMS: *m*/*z* calcd for $C_{12}H_9BrN_4$: 288.0011; found: 287.9994.

9-Benzyl-8-bromo-6-chloro-9*H*-purine (3e)[27]
Starting from purine **1j** (245 mg, 1.0 mmol), following GP1 and using 1,2-dibromo-1,1,2,2-tetrachloroethane as electrophile, the desired purine **3e** was obtained after purification by column chromatography using a gradient elution (CH_2Cl_2–pentane, 5:1 to 7:1); yield: 240 mg (75%); white solid; mp 87–88 °C.

^{1}H NMR ($CDCl_3$): δ = 8.75 (s, 1 H), 7.36–7.31 (m, 5 H), 5.49 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 152.2, 152.1, 149.5, 134.5, 134.1, 134.0, 129.0, 128.7, 128.0, 48.3.

MS (70 eV): *m*/*z* (%) = 324 (15), 323 (7), 322 (11), 245 (14), 244 (6), 243 (45), 92 (6), 91 (100), 65 (9).

HRMS: *m*/*z* calcd for $C_{12}H_8BrClN_4$: 321.9621; found: 321.9617.

8-Bromo-6-chloro-2-iodo-9-(methoxymethyl)-9*H*-purine (3f)
Starting from purine **1f** (325 mg, 1.0 mmol), following GP1 and using 1,2-dibromo-1,1,2,2-tetrachloroethane as electrophile, the desired purine **3f** was obtained after purification by column chromatography using a gradient elution (EtOAc–pentane, 1:3 to 1:2); yield: 348 mg (87%); white solid; mp 144–146 °C.

^{1}H NMR ($CDCl_3$): δ = 5.60 (s, 2 H), 3.44 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 153.8, 149.0, 134.3, 131.6, 117.1, 74.9, 57.8.

MS (70 eV): *m*/*z* (%) = 404 (16), 402 (13), 376 (12), 374 (48), 372 (35), 323 (15), 295 (13), 293 (40), 45 (100).

HRMS: *m*/*z* calcd for $C_7H_5BrClIN_4$: 401.8380; found: 401.8376.

9-Benzyl-8-(phenylthio)-9*H*-purine (3g)
Starting from purine **1i** (420 mg, 2.0 mmol), following GP1 (the base was added dropwise within 1.5 h) and using $PhSO_2SPh$ as electrophile, the desired purine **3g** was obtained after purification by column chromatography using a gradient elution (CH_2Cl_2–MeOH, 400:1 to 100:1); yield: 380 mg (60%); white solid; mp 134–135 °C.

^{1}H NMR ($CDCl_3$): δ = 8.94 (s, 1 H), 8.93 (s, 1 H), 7.61–7.57 (m, 2 H), 7.46–7.41 (m, 3 H), 7.40–7.31 (m, 5 H), 5.50 (s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 155.6, 153.5, 151.7, 145.7, 134.9, 134.3, 134.2, 129.9, 129.8, 129.0, 128.4, 128.0, 127.2, 46.5.

MS (70 eV): *m*/*z* (%) = 319 (17), 318 (83), 317 (54), 227 (7), 209 (30), 167 (39), 92 (7), 91 (100), 65 (12).

HRMS: *m*/*z* calcd for $C_{18}H_{14}N_4S$: 318.0939; found: 318.0935.

6-Chloro-8-(cyclohex-2-en-1-yl)-2-iodo-9-(methoxymethyl)-9*H*-purine (3h)
A solution of $ZnCl_2$ (1.0 mL, 1 M in THF, 1.0 mmol, 1.0 equiv) was added to a solution of purine **1f** (325 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (1 mL) at 25 °C. The mixture was stirred for 5 min, then cooled to –65 °C prior to add freshly prepared TMPMgCl·LiCl (1.0 mL, 1.13 M in THF, 1.13 mmol, 1.13 equiv) dropwise within 2 min. The mixture was stirred for 30 min, then a solution of CuCN·2LiCl (0.1 mL, 1 M in THF, 0.1 mmol, 0.1 equiv) and 3-bromocyclohexene (225 mg, 1.4 mmol, 1.4 equiv) were successively added. The mixture was allowed to warm up to 25 °C over 2 h, and then quenched with sat. aq NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL), then the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by column chromatography using pentane–Et_2O (3:1) as eluent to furnish purine **3h**; yield: 340 mg (84%); white solid; 102–104 °C.

^{1}H NMR ($CDCl_3$): δ = 6.06–5.99 (m, 1 H), 5.79–5.73 (m, 1 H), 5.60 (s, 2 H), 3.97–3.88 (m, 1 H), 3.40 (s, 3 H), 2.24–2.10 (m, 3 H), 2.08–1.94 (m, 2 H), 1.79–1.64 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 161.8, 154.5, 149.0, 130.8, 130.8, 124.3, 115.7, 73.2, 57.4, 35.5, 28.1, 24.5, 21.2.

MS (70 eV): *m*/*z* (%) = 406 (13), 404 (39), 375 (13), 374 (28), 373 (19), 361 (28), 359 (23), 345 (14), 308 (15), 81 (14), 79 (14), 45 (100).

HRMS: *m*/*z* calcd for $C_{13}H_{14}ClIN_4O$: 403.9901; found: 403.9892.

Negishi Cross-Coupling Reactions; General Procedure 2 (GP2)
Freshly prepared TMPZnCl·LiCl (1.1 M in THF, 1.1 equiv) was added dropwise within 2 min to a solution of desired purine derivative (1 equiv) in anhydrous THF (*c* = ca. 0.7 M) at 25 °C. The reaction mixture was stirred for 30 min prior to adding successively $Pd(dba)_2$ (2 mol%), (*o*-furyl)$_3$P (4 mol%), and the desired aryl iodide (1.2 equiv). After the completion of the reaction (checked by GC-analysis of reaction aliquots quenched with sat. aq NH_4Cl, 2–14 h), the reaction mixture was quenched with sat. aq. NH_4Cl (10 mL) The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by column chromatography.

Negishi Cross-Coupling Reactions; General Procedure 3 (GP3)
The reaction was carried out as described above in GP2 except that the cross-coupling reaction was performed at 45 °C for 14 h.

Ethyl 4-[9-(Methoxymethyl)-9*H*-purin-8-yl]benzoate (5a)
Starting from purine **1c** (0.82 g, 5.0 mmol), following GP2 and using ethyl 4-iodobenzoate as aryl iodide, the desired purine **5a** was obtained after purification by column chromatography using EtOAc as eluent; yield: 1.51 g (97%); white solid; mp 117–119 °C.

^{1}H NMR ($CDCl_3$): δ = 9.34 (s, 1 H), 9.18 (s, 1 H), 8.24–8.19 (m, 4 H), 5.66 (s, 2 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 3.60 (s, 3 H), 1.43 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 165.7, 156.8, 154.4, 152.8, 147.7, 133.3, 133.1, 132.0, 130.1, 129.8, 73.5, 61.5, 57.9, 14.3.

MS (70 eV): *m*/*z* (%) = 312 (18), 283 (13), 282 (64), 281 (77), 267 (17), 253 (13), 209 (17), 133 (11), 45 (100).

HRMS: *m*/*z* calcd for $C_{16}H_{16}N_4O_3$: 312.1222; found: 312.1216.

9-(Methoxymethyl)-8-(4-methoxyphenyl)-9*H*-purine (5b)
Starting from purine **1c** (164 mg, 1.0 mmol), following GP2 and using 4-iodoanisole as aryl iodide, the desired purine **5b** was obtained after purification by column chromatography using Et_2O as eluent; yield: 165 mg (61%); white solid; mp 164–166 °C.

^{1}H NMR ($CDCl_3$): δ = 9.10 (s, 1 H), 8.97 (s, 1 H), 8.09–8.04 (m, 2 H), 7.09–7.04 (m, 2 H), 5.62 (s, 2 H), 3.89 (s, 3 H), 3.59 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 162.1, 156.8, 154.1, 152.3, 147.2, 133.6, 131.4, 120.9, 114.5, 73.2, 57.6, 55.5.

MS (70 eV): *m*/*z* (%) = 270 (100), 240 (61), 239 (94), 227 (18), 226 (11), 225 (25), 209 (10), 134 (11), 133 (12), 45 (81).

HRMS: *m*/*z* calcd for $C_{14}H_{14}N_4O_2$: 270.1117; found: 270.1109.

Ethyl 4-[6-Chloro-9-(methoxymethyl)-9*H*-purin-8-yl]benzoate (5c)
Starting from purine **1a** (199 mg, 1.0 mmol), following GP2 and using ethyl 4-iodobenzoate as aryl iodide, the desired purine **5c** was obtained after purification by column chromatography using pentane–EtOAc (5:1) as eluent; yield: 317 mg (91%); white solid; mp 142–144 °C.

^{1}H NMR ($CDCl_3$): δ = 8.77 (s, 1 H), 8.21–8.18 (m, 4 H), 5.63 (s, 2 H), 4.42 (q, *J* = 7.3 Hz, 2 H), 3.58 (s, 3 H), 1.42 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 165.7, 155.7, 154.2, 152.2, 150.6, 132.9, 132.0, 131.1, 130.0, 129.8, 73.9, 61.5, 57.8, 14.3.

MS (70 eV): *m*/*z* (%) = 348 (15), 346 (39), 317 (34), 316 (50), 315 (92), 314 (97), 300 (20), 286 (10), 271 (12), 243 (14), 45 (100).

HRMS: *m*/*z* calcd for $C_{16}H_{15}ClN_4O_3$: 346.0833; found 346.0823.

6-Chloro-9-(methoxymethyl)-8-(4-methoxyphenyl)-9*H*-purine (5d)
Starting from purine **1a** (1.19 g, 6.0 mmol), following GP2 and using 4-iodoanisole as aryl iodide, the desired purine **5d** was obtained after purification by column chromatography using a gradient elution (EtOAc–pentane, 1:1 to 2:1); yield: 1.74 g (95%); white solid; mp 157–159 °C.

^{1}H NMR ($CDCl_3$): δ = 8.74 (s, 1 H), 8.10 (d, *J* = 8.6 Hz, 2 H), 7.07 (d, *J* = 9.1 Hz, 2 H), 5.63 (s, 2 H), 3.91 (s, 3 H), 3.59 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 162.3, 157.0, 154.4, 151.5, 149.6, 131.6, 131.1, 120.3, 114.5, 73.9, 57.7, 55.5.

MS (70 eV): *m*/*z* (%) = 306 (29), 305 (16), 304 (100), 276 (11), 275 (16), 274 (35), 273 (39), 261 (13), 259 (12), 45 (65).

HRMS: *m*/*z* calcd for $C_{14}H_{13}ClN_4O_2$: 304.0727; found: 304.0721.

Ethyl 4-[2-Chloro-9-(methoxymethyl)-9*H*-purin-8-yl]benzoate (5f)

Starting from purine **1b** (199 mg, 1.0 mmol), following GP2 and using ethyl 4-iodobenzoate as aryl iodide, the desired purine **5f** was obtained after purification by column chromatography using pentane–EtOAc (4:1) as eluent; yield: 200 mg (58%); white solid; mp 142–143 °C.

^{1}H NMR ($CDCl_3$): δ = 9.02 (s, 1 H), 8.25–8.23 (m, 2 H), 8.20–8.18 (m, 2 H), 5.62 (s, 2 H), 4.44 (q, *J* = 7.2 Hz, 2 H), 3.61 (s, 3 H), 1.44 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 165.7, 156.4, 155.6, 154.7, 149.8, 133.1, 132.4, 132.0, 130.2, 129.7, 73.4, 61.5, 57.8, 14.3.

MS (70 eV): *m*/*z* (%) = 348 (17), 346 (48), 318 (24), 317 (41), 316 (59), 315 (79), 301 (16), 287 (13), 271 (14), 243 (21), 45 (100).

HRMS: *m*/*z* calcd for $C_{16}H_{15}ClN_4O_3$: 346.0833; found: 346.0824.

Ethyl 4-[2,6-Dichloro-9-(methoxymethyl)-9*H*-purin-8-yl]benzoate (5g)

Starting from purine **1d** (1.4 g, 6.0 mmol), following GP2 and using ethyl 4-iodobenzoate as aryl iodide, the desired purine **5g** was obtained after purification by column chromatography using pentane–EtOAc (2:1) as eluent; yield: 1.4 g (62%); beige solid; mp 149–151 °C.

^{1}H NMR ($CDCl_3$): δ = 8.25–8.18 (m, 4 H), 5.61 (s, 2 H), 4.44 (q, *J* = 7.2 Hz, 2 H), 3.61 (s, 3 H), 1.44 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 165.7, 156.4, 155.5, 153.1, 151.4, 133.3, 131.6, 130.3, 130.1, 129.9, 74.0, 61.5, 58.0, 14.3.

MS (70 eV): *m*/*z* (%) = 382 (13), 380 (19), 352 (13), 351 (20), 350 (21), 349 (26), 335 (6), 274 (5), 45 (100).

HRMS: *m*/*z* calcd for $C_{16}H_{14}Cl_2N_4O_3$: 380.0443; found: 380.0437.

2,6-Dichloro-9-(methoxymethyl)-8-(4-methoxyphenyl)-9*H*-purine (5h)[23]

Starting from purine **1d** (2.33 g, 10.0 mmol), following GP2 and using 4-iodoanisole as aryl iodide, the desired purine **5h** was obtained after purification by column chromatography using CH_2Cl_2 as eluent; yield: 2.40 g (71%); white solid; mp 179–181 °C.

^{1}H NMR ($CDCl_3$): δ = 8.08–8.03 (m, 2 H), 7.06–7.02 (m, 2 H), 5.57 (s, 2 H), 3.89 (s, 3 H), 3.59 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 162.4, 157.6, 155.7, 152.2, 150.1, 131.6, 130.3, 120.0, 114.6, 74.0, 57.8, 55.5.

MS (70 eV): *m*/*z* (%) = 340 (22), 338 (34), 310 (11), 309 (10), 308 (17), 307 (12), 295 (6), 293 (6), 133 (11), 45 (100).

HRMS: *m*/*z* calcd for $C_{14}H_{12}Cl_2N_4O_2$: 338.0337; found: 338.0327.

9-(Methoxymethyl)-8-[3-(trifluoromethyl)phenyl]-2-(trimethylsilyl)-9*H*-purine (5i)

Starting from purine **1g** (1.90 g, 8.0 mmol), following GP2 and using 1-iodo-3-(trifluoromethyl)benzene as aryl iodide, the desired purine **5i** was obtained after purification by column chromatography using pentane–EtOAc (3:1) as eluent; yield: 1.45 g (48%); white solid; mp 135–136 °C.

^{1}H NMR ($CDCl_3$): δ = 9.27 (s, 1 H), 8.46 (br s, 1 H), 8.36–8.34 (m, 1 H), 7.85–7.83 (m, 1 H), 7.73–7.69 (m, 1 H), 5.69 (s, 2 H), 3.64 (s, 3 H), 0.44 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 174.7, 154.4, 153.0, 146.7, 132.8 (q, $^3J_{C,F}$ = 1 Hz), 132.1, 131.7 (q, $^2J_{C,F}$ = 33 Hz), 129.7, 129.6, 127.7 (q, $^3J_{C,F}$ = 4 Hz), 126.7 (q, $^3J_{C,F}$ = 4 Hz), 123.7 (q, $^1J_{C,F}$ = 272 Hz), 73.1, 57.9, –1.8.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{19}F_3N_4OSi + H^+$: 381.1353; found: 381.1350.

9-(Methoxymethyl)-8-(4-methoxyphenyl)-2-[(4-methoxyphenyl)thio]-9*H*-purine (5j)

Starting from purine **1h** (302 mg, 1.0 mmol), following GP2 and using 4-iodoanisole as aryl iodide, the desired purine **5j** was obtained after purification by column chromatography using a gradient elution (EtOAc–pentane, 1:1 to 8:1); yield: 345 mg (85%); orange solid; mp 150–152 °C.

^{1}H NMR ($CDCl_3$): δ = 8.86 (s, 1 H), 7.99 (d, *J* = 8.6 Hz, 2 H), 7.57 (d, *J* = 8.6 Hz, 2 H), 7.02 (d, *J* = 9.1 Hz, 2 H), 6.96 (d, *J* = 8.6 Hz, 2 H), 5.35 (s, 2 H), 3.86–3.85 (m, 6 H), 3.35 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 166.0, 161.8, 160.4, 155.5, 154.9, 147.5, 137.2, 131.1, 130.7, 121.0, 120.8, 114.5, 114.4, 73.2, 57.7, 55.3, 55.3.

MS (70 eV): *m*/*z* (%) = 409 (40), 408 (100), 407 (79), 363 (39), 69 (36), 57 (52), 55 (47), 44 (48), 43 (35), 41 (44).

HRMS: *m*/*z* calcd for $C_{21}H_{20}N_4O_3S$: 408.1256; found: 408.1252.

Ethyl 4-[9-(Methoxymethyl)-2-(trimethylsilyl)-9*H*-purin-8-yl]benzoate (5k)[9]

Starting from purine **1g** (236 mg, 1.0 mmol), following GP2 and using ethyl 4-iodobenzoate as aryl iodide, the desired purine **5k** was obtained after purification by column chromatography using pentane–EtOAc (9:1) as eluent; yield: 200 mg (52%); white solid; mp 179–180 °C.

^{1}H NMR ($CDCl_3$): δ = 9.24 (s, 1 H), 8.20 (s, 4 H), 5.67 (s, 2 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 3.60 (s, 3 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 0.41 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 174.7, 165.8, 154.8, 153.0, 146.8, 132.9, 132.6, 132.2, 130.0, 129.6, 73.1, 61.4, 57.9, 14.3, –1.8.

MS (70 eV): *m*/*z* (%) = 384 (79), 383 (25), 369 (61), 351 (30), 350 (30), 338 (25), 337 (100), 89 (36), 73 (24), 45 (31).

HRMS: *m*/*z* calcd for $C_{19}H_{24}N_4O_3Si$: 384.1618; found: 384.1620.

Ethyl 4-[6-Chloro-9-(methoxymethyl)-2-(trimethylsilyl)-9*H*-purin-8-yl]benzoate (5l)[9]

Starting from purine **1e** (271 mg, 1.0 mmol), following GP3 and using ethyl 4-iodobenzoate as aryl iodide, the desired purine **5l** was obtained after purification by column chromatography using hexane–EtOAc (10:1) as eluent; yield: 380 mg (91%); white solid; mp 121–122 °C. The reaction was performed also on 20 and 30 mmol scales furnishing the desired purine **5l** in 70% and 85% yield, respectively.

^{1}H NMR ($CDCl_3$): δ = 8.20 (s, 4 H), 5.65 (s, 2 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 3.60 (s, 3 H), 1.41 (t, *J* = 7.1 Hz, 3 H), 0.40 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 175.3, 165.8, 154.9, 153.5, 149.5, 132.8, 132.3, 130.0, 129.9, 129.8, 73.8, 61.4, 58.0, 14.3, –1.9.

MS (70 eV): *m*/*z* (%) = 418 (55), 404 (100), 389 (64), 388 (51), 384 (100), 374 (72), 93 (57), 57 (46), 45 (83), 43 (56).

HRMS: *m*/*z* calcd for $C_{19}H_{23}ClN_4O_3Si$: 418.1228; found: 418.1225.

Ethyl 4-[6-Iodo-9-(methoxymethyl)-9*H*-purin-8-yl]benzoate (7a)

A solution of purine **5a** (312 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (10 mL) was added dropwise within 3 min to freshly prepared TMPMgCl·LiCl (1.3 mL, 0.94 M in THF, 1.2 mmol, 1.2 equiv) at –20 °C. The reaction mixture was stirred for 1 h prior to add a solution of I_2 (1.00 g, 3.9 mmol, 3.9 equiv) in anhydrous THF (2 mL). The resulting mixture was allowed to warm up to 0 °C over 3 h, and then quenched with sat. aq $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL), then the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by column chromatography using pentane–EtOAc

(1:1) as eluent to furnish purine **7a**; yield: 306 mg (70%); beige solid; mp 152–154 °C.

^{1}H NMR ($CDCl_3$): δ = 8.68 (s, 1 H), 8.24–8.20 (m, 4 H), 5.61 (s, 2 H), 4.44 (q, *J* = 7.3 Hz, 2 H), 3.59 (s, 3 H), 1.44 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 165.7, 155.1, 152.2, 150.5, 138.1, 133.0, 132.1, 130.1, 129.9, 121.6, 73.8, 61.5, 57.8, 14.3.

MS (70 eV): *m*/*z* (%) = 439 (14), 438 (62), 409 (17), 408 (100), 407 (88), 393 (17), 239 (11), 238 (14), 221 (11), 207 (16), 45 (70).

HRMS: *m*/*z* calcd for $C_{16}H_{15}IN_4O_3$: 438.0189; found: 438.0182.

6-Iodo-9-(methoxymethyl)-8-(4-methoxyphenyl)-9*H*-purine (7b)

A solution of purine **5b** (270 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF (10 mL) was added dropwise within 3 min to freshly prepared TMPMgCl·LiCl (1.3 mL, 0.94 M in THF, 1.2 mmol, 1.2 equiv) at –20 °C. The reaction mixture was stirred for 1 h prior to add a solution of I_2 (1.00 g, 3.9 mmol, 3.9 equiv) in anhydrous THF (2 mL). The resulting mixture was allowed to warm up to 0 °C over 3 h. and then quenched with sat. aq $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL), then the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by column chromatography using pentane–Et_2O (1:1) as eluent to furnish purine **7b**; yield: 238 mg (60%); beige solid; mp 156–158 °C.

^{1}H NMR ($CDCl_3$): δ = 8.63 (s, 1 H), 8.10–8.08 (m, 2 H), 7.08–7.06 (m, 2 H), 5.59 (s, 2 H), 3.90 (s, 3 H), 3.58 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 162.3, 156.3, 151.6, 150.6, 138.1, 131.7, 120.3, 120.2, 114.5, 73.9, 57.7, 55.5.

MS (70 eV): *m*/*z* (%) = 397 (15), 396 (100), 366 (21), 365 (23), 269 (12), 239 (11), 238 (9), 197 (7), 133 (12), 45 (30).

HRMS: *m*/*z* calcd for $C_{14}H_{13}IN_4O_2$: 396.0083; found: 396.0074.

Negishi Cross-Coupling Reactions; General Procedure 4 (GP4)

A solution of the desired purine derivative in anhydrous THF (*c* = ca. 0.1 M) was added dropwise within 3 min to freshly prepared TMPMgCl·LiCl (0.94 M in THF, 1.2 equiv) at –20 °C. The reaction mixture was stirred for 1 h prior to add a solution of $ZnCl_2$ (1 M in THF, 1.3 equiv). The resulting reaction mixture was allowed to warm up to 25 °C over 30 min, then $Pd(dba)_2$ (2 mol%), (*o*-furyl)$_3$P (4 mol%), and the desired aryl iodide (1.3 equiv) were successively added. After the completion of the reaction (checked by GC-analysis of reaction aliquots quenched with sat. aq NH_4Cl, 3–14 h), the reaction mixture was quenched with sat. aq NH_4Cl (10 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by column chromatography.

Ethyl 4-[9-(Methoxymethyl)-6-phenyl-9*H*-purin-8-yl]benzoate (7c)

Starting from purine **5a** (312 mg, 1.0 mmol), following GP4 and using 4-iodobenzene as aryl iodide, the desired purine **7c** was obtained after purification by column chromatography using pentane–EtOAc (5:1) as eluent; yield: 245 mg (63%); beige solid; mp 156–157 °C.

^{1}H NMR ($CDCl_3$): δ = 9.07 (s, 1 H), 8.94–8.92 (m, 2 H), 8.28–8.23 (m, 4 H), 7.61–7.43 (m, 3 H), 5.68 (s, 2 H), 4.45 (q, *J* = 7.0 Hz, 2 H), 3.62 (s, 3 H), 1.45 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 165.8, 155.1, 154.7, 154.2, 152.4, 135.2, 132.8, 132.6, 131.2, 130.5, 130.0, 129.9, 129.8, 128.7, 73.4, 61.4, 57.6, 14.3.

MS (70 eV): *m*/*z* (%) = 388 (26), 359 (9), 358 (46), 357 (100), 343 (10), 329 (13), 285 (6), 209 (9), 45 (23).

HRMS: *m*/*z* calcd for $C_{22}H_{20}N_4O_3$: 388.1535; found: 388.1529.

Ethyl 4-[9-(Methoxymethyl)-8-(4-methoxyphenyl)-9*H*-purin-6-yl]benzoate (7d)

Starting from purine **5b** (270 mg, 1.0 mmol), following GP4 and using ethyl 4-iodobenzoate as aryl iodide, the desired purine **7d** was obtained after purification by column chromatography using pentane–EtOAc (3:1) as eluent; yield: 230 mg (55%); beige solid; mp 158–159 °C.

^{1}H NMR ($CDCl_3$): δ = 9.05–9.01 (m, 3 H), 8.24–8.22 (m, 2 H), 8.18–8.14 (m, 2 H), 7.12–7.08 (m, 2 H), 5.68 (s, 2 H), 4.43 (q, *J* = 7.0 Hz, 2 H), 3.92 (s, 3 H), 3.62 (s, 3 H), 1.44 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 166.3, 162.1, 156.4, 155.6, 151.7, 151.7, 139.5, 132.1, 131.5, 131.1, 129.8, 129.7, 121.0, 114.5, 73.4, 61.1, 57.5, 55.5, 14.3.

MS (70 eV): *m*/*z* (%) = 419 (21), 418 (86), 389 (9), 388 (43), 387 (100), 373 (17), 359 (15), 315 (9), 300 (9), 159 (8), 45 (28).

HRMS: *m*/*z* calcd for $C_{23}H_{22}N_4O_4$: 418.1641; found 418.1640.

Ethyl 4-{9-(Methoxymethyl)-8-[3-(trifluoromethyl)phenyl]}-2-(trimethylsilyl)-9*H*-purin-6-yl)benzoate (7e)

Starting from purine **5i** (380 mg, 1.0 mmol), following GP4 and using ethyl 4-iodobenzoate as aryl iodide, the desired purine **7e** was obtained after purification by column chromatography using pentane–CH_2Cl_2 (5:4) as eluent; yield: 280 mg (55%); beige solid; mp 148–149 °C.

^{1}H NMR ($CDCl_3$): δ = 9.10–9.06 (m, 2 H), 8.52 (br s, 1 H), 8.45–8.42 (m, 1 H), 8.27–8.23 (m, 2 H), 7.87–7.84 (m, 1 H), 7.76–7.71 (m, 1 H), 5.72 (s, 2 H), 4.44 (q, *J* = 7.2 Hz, 2 H), 3.66 (s, 3 H), 1.45 (t, *J* = 7.2 Hz, 3 H), 0.49 (s, 9 H).

^{13}C NMR ($CDCl_3$): δ = 174.0, 166.5, 154.6, 153.9, 150.8, 140.4, 133.0 (q, $^4J_{C,F}$ = 1 Hz), 131.9, 131.7 (q, $^2J_{C,F}$ = 33 Hz), 130.0, 129.8, 129.7, 129.7, 129.6, 127.5 (q, $^3J_{C,F}$ = 4 Hz), 126.8 (q, $^3J_{C,F}$ = 4 Hz), 123.8 (q, $^1J_{C,F}$ = 272 Hz), 73.2, 61.1, 57.8, 14.3, –1.7.

HRMS (ESI): *m*/*z* calcd for $C_{26}H_{27}F_3N_4O_3Si + H^+$: 529.1877; found: 529.1872.

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