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Regiochemistry in the Pd-Mediated Coupling between 6,8-Dihalopurines and Organometallic Reagents

Jens M. J. Nolsøe, Lise-Lotte Gundersen* and Frode Rise

Department of Chemistry, University of Oslo, PO Box 1033, Blindern, N-0315 Oslo, Norway

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The regiochemistry in the Pd-mediated coupling between 6,8-dihalopurines and organometallic reagents has been examined. When 6,8-dichloropurines were reacted, highly selective coupling in the purine 6-position was obtained and the regiochemical outcome was completely reversed when a better leaving group (Br or I) was introduced at C-8.

Palladium-catalysed coupling reactions between 6- or 8-halopurines and organometallic reagents have become widely used in the synthesis of modified purines and purine nucleosides including compounds with various biological properties.[1–3] In our study of C–C bond forming reactions on halopurines,[2,3] we have previously demonstrated that selective substitution can be achieved when 2,6-dihalopurines are reacted with organometallic reagents in the presence of a Pd-catalyst.[3] Couplings on 2,6-dichloropurines took place in the more electrophilic 6-position exclusively, and the regioselectivity was completely reversed when a better leaving group (Br or I) was introduced into the purine 2-position. In this paper we report our results from Pd-catalysed cross-coupling reactions on 6,8-dihalopurines.

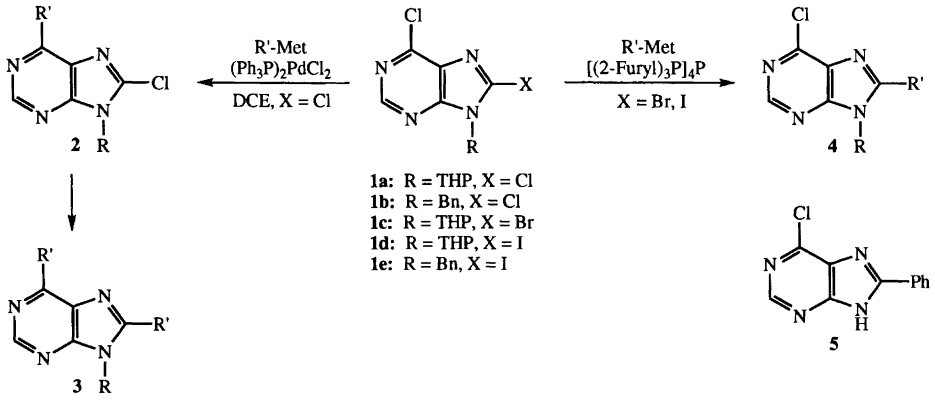
The difference in reactivity between 6- and 8-halopurines towards nucleophilic reagents is generally not very profound. For instance, 8-chloro-9-methylpurine reacts faster with sodium ethoxide than the 6-chloro isomer,[4] but the reactivity is reversed when the chloropurines are treated with piperidine, suggesting that the rate of substitution in the 8-position is quite sensitive to the size of the nucleophile.[5] The same trend is seen in nucleophilic displacements on *N*-9 alkylated 6,8-dichloropurines. 8-Substituted purines are often the only or major product formed in reactions with small nucleophiles such as sodium hydroxide, sodium ethoxide or ammonia,[6] but poor selectivity is observed for instance in the reaction between a 6,8-dichloropurine riboside and cyclopentylamine, which may be attributed to the larger steric requirement of the nucleophile.[7] However, the factors determining the regiochemistry in these reactions appear to be complex, and there are also reports on completely selective substitution in the purine 6-position when *N*-9 alkylated 6,8-dichloropurines are treated with various nucleophiles.[8] We therefore expected comparable behaviour at C-6 and C-8 in coupling reactions of 6,8-dihalopurines with two identical leaving groups.

We chose to examine the reactivity of the dihalopurines **1** (Scheme 1) towards organometallic reagents in the presence of a Pd-catalyst. The THP-protected dihalopurines **1a**, **1c** and **1d** were readily available by lithiation of the corresponding 6-chloropurine followed by treatment with an appropriate halogen donor as we have previously reported,[9] but all attempts to lithiate 9-benzyl-6-chloropurine and treat the product with electrophiles failed. Instead we prepared compound **1b** and **1e** in high yields by halogenation of 9-benzyl-6-chloropurine with an excess of *N*-chlorosuccinimide (NCS) or *N*-iodosuccinimide (NIS).

When the 6,8-dichloropurines **1a** and **1b** were subjected to Pd-catalysed couplings with organotin reagents, the major products were the 6-substituted compounds **2**, and the regioisomer **4** could not be detected (Scheme 1, Table 1). However, introduction of an alkynyl-, alkenyl- or aryl-substituent into the purine 6-position appears to increase the reactivity at C-8, and minor amounts of the disubstituted purines **3** were generally formed, according to the ^{1}H NMR and MS spectra of the crude products. Among the catalytic systems examined, we obtained best selectivity and conversion of the starting material **1a** and **1b** when bis(triphenylphosphine)palladium(0) chloride was employed in dichloroethane (DCE) and the catalyst was added in three portions. For introduction of a phenyl substituent the more reactive tin reagent phenyltrimethyltin was used in order to ensure a reasonable reaction rate.

The 6-chloro-8-iodopurines **1d** and **1e** as well as the 8-bromo compound **1c**, were also subjected to couplings with organotin and organozinc reagents (Scheme 1,

* To whom correspondence should be addressed.



Scheme 1.

Table 1. Palladium-catalysed coupling between dichloropurines **1a** and **1b** and organometallic reagents.

Entry	X	R	R'-Met	*T*/°C	*t*/h	Yield[a] (%) **2**	**2**:**3**[b]
1	Cl	THP	Ph–C≡C–$SnBu_3$	60	24	50, **2a**	79:21
2	Cl	THP	CH_2=C(OEt)$SnBu_3$	60	24	60, **2b**	96:4
3	Cl	Bn	CH_2=C(OEt)$SnBu_3$	60	20	63, **2c**	93:7
4	Cl	THP	(2-Thienyl)$SnBu_3$	75	30	63, **2d**	88:12
5	Cl	Bn	(2-Thienyl)$SnBu_3$	60	30	41, **2e**	87:13
6	Cl	THP	$PhSnMe_3$	Δ	27	58, **2f**	89:11
7	Cl	Bn	$PhSnMe_3$	Δ	24	58, **2g**	84:16

[a]Yield of isolated compounds. [b]From ^{1}H NMR spectroscopy of the crude product.

Table 2). Complete regioselectivity was easily obtained in all reactions examined when the reactive catalyst tetrakis[tri(2-furyl)phosphine]palladium(0)[10] was used, and in contrast with the dichloropurines **1a** an **1b**, the reaction took place in the 8-position to give compounds **4**. Disubstituted purines **3** were not detected. *N*,*N*-Dimethylformamide (DMF) was generally employed as solvent in the Stille coupling and tetrahydrofuran (THF) was used in the reactions with organozinc reagents. As reported before,[11] vinylpurines may be highly reactive and we found that the vinylpurines **4c** and **4d** were prone to decomposition when coupling in DMF was attempted. In these instances DCE was the solvent of choice. When the THP-protected compounds **1c** and **1d** were allowed to react with phenyltributyltin, for an unknown reason the the THP-group was almost completely cleaved off during the reaction and compound **5** was isolated. THP-cleavage also took place when phenyltrimethyltin was used, but deprotection of *N*-9 could not be observed in any of the other coupling reactions performed.

Table 2. Palladium-catalysed coupling between dihalopurines **1c**–**1e** and organometallic reagents.

Entry	X	R	R'-Met	Solvent	*T*/°C	*t*/h	Yield[a] (%) **4** or **5**
1	Br	THP	Ph–C≡C–$SnBu_3$	DMF	60	3.5	67, **4a**
2	I	Bn	Ph–C≡C–$SnBu_3$	DMF	75	3.5	67, **4b**
3	Br	THP	CH_2=CH$SnBu_3$	DCE	55	1.5	61, **4c**
4	I	THP	CH_2=CH$SnBu_3$	DCE	70	1	76, **4c**
5	I	Bn	CH_2=CH$SnBu_3$	DCE	70	19	76, **4d**
6	Br	THP	CH_2=C(OEt)$SnBu_3$	DMF	55	3.5	80, **4e**
7	I	THP	CH_2=C(OEt)$SnBu_3$	DMF	70	7	76, **4e**
8	I	Bn	CH_2=C(OEt)$SnBu_3$	DMF	70	9	72, **4f**
9	Br	THP	(2-Thienyl)$SnBu_3$	DMF	45	2.5	66, **4g**
10	I	THP	(2-Thienyl)$SnBu_3$	DMF	60	3	64, **4g**
11	I	Bn	(2-Thienyl)$SnBu_3$	DMF	60	5	70, **4h**
12	Br	THP	$PhSnBu_3$	DMF	80	18	61, **5**
13	I	THP	$PhSnBu_3$	DMF	85	18	66, **5**
14	I	Bn	$PhSnBu_3$	DMF	85	18	75, **4i**
15	Br	THP	CH_3ZnBr	THF	60	6	51, **4j**
16	I	THP	CH_3ZnBr	THF	60	4	77, **4j**
17	I	Bn	CH_3ZnBr	THF	60	4	68, **4k**

[a]Yield of isolated compounds.

As previously reported for 2,6-dihalopurines, we have now demonstrated that the regioselectivity in Pd-catalysed couplings of 6,8-dihalopurines is largely governed by the identity of the halogens and in these reactions substituents can be directed exclusively to the position bearing the best leaving group. When similar coupling reactions are performed on 6,8-dichloropurines, reaction in the purine 6-position is favoured.

Experimental

^{1}H NMR spectra were recorded at 500 MHz with a Bruker Avance DRX 500 instrument, at 300 MHz with a Bruker Avance DPX 300 instrument or at 200 MHz with a Bruker Avance DPX 200 instrument. ^{13}C NMR spectra were recorded at 125, 75 or 50 MHz using the above-mentioned spectrometers. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. Mass spectra were recorded at 70 eV ionising voltage with a VG Prospec instrument, and are presented as *m/z* (% rel. int.). Elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, Germany. Melting points are uncorrected. Silica gel for flash chromatography was purchased from Merck, Darmstadt, Germany (Merck No. 9385). THF was distilled from sodium–benzophenone, dichloroethane from CaH_2 and DMF from BaO. Zinc bromide was dried at 125 °C under high vacuum for 2–4 h, weighed out and dissolved in dry THF to give a 1 M solution which was stored under N_2. All other reagents were commercially available and used as received.

Starting material available by literature procedures. 9-Benzyl-6-chloro-9*H*-purine,[2b] 6,8-dichloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine,[9] 8-bromo-6-chloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine[9] and 6-chloro-8-iodo-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine.[9]

*9-Benzyl-6,8-dichloro-9*H*-purine* (**1b**). A mixture of 9-benzyl-6-chloro-9*H*-purine (0.200 g, 0.82 mmol) and *N*-chlorosuccinimide (1.09 g, 8.20 mmol) in dry DCE (20 ml) was heated at reflux under N_2 in the dark for 36 h and without protection from light for an additional 24 h and concentrated to ca. 4 ml. The resulting mixture was heated again at reflux for 30 h. Sat. aq $NaHSO_3$ (10 ml) was added, the phases were separated and the aqueous layer was extracted with dichloromethane (2 × 60 ml). The combined organic solutions were dried and evaporated *in vacuo*, and the product was isolated by flash chromatography on silica gel eluting with hexane followed by EtOAc–hexane 1:40, 1:20 and 1:4; yield 201 mg (88%), yellow crystals. M.p. 172–175 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.41 (s, 2 H, CH_2), 7.27 (m, 5 H, Ph), 8.69 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 49.1, 129.6, 130.4, 130.7, 132.2, 135.6, 146.0, 151.2, 153.9, 154.2. MS (EI): 278 (M^+, 27), 243 (18), 91 (100), 77 (3), 65 (15). HRMS: Found 278.0123, calc. for $C_{12}H_8Cl_2N$: 278.0126.

*9-Benzyl-6-chloro-8-iodo-9*H*-purine* (**1e**). A mixture of 9-benzyl-6-chloro-9*H*-purine (300 mg, 1.23 mmol) and *N*-iodosuccinimide (1.38 g, 6.15 mmol) in dry THF (20 ml) was heated at reflux under N_2 for 72 h and evaporated *in vacuo*. The residue was dissolved in dichloromethane (50 ml) and sat. aq. $NaHSO_3$ was added until the solution became colourless. After evaporation *in vacuo*, the product was isolated by flash chromatography on silica gel eluting with hexane followed by EtOAc–hexane 1:4 and 1:2; yield 425 mg (94%). M.p. 134–136 °C. Anal.: C, H. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.46 (s, 2 H, CH_2), 7.32 (m, 5 H, Ph), 8.69 (s, 1 H, H-8). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 49.8, 108.3, 128.0, 128.7, 129.05, 133.9, 134.3, 149.4, 152.1, 153.1. MS (EI): 370 (34, M^+), 243 (62), 91 (100), 77 (1), 65 (2).

General procedure for Stille coupling of 6,8-dichloropurines (**1a**) *and* (**1b**). A mixture of 6,8-dichloropurine **1a** or **1b** (0.41 mmol), organotin reagent (0.49 mmol) and bis(triphenylphosphine)palladium(0) chloride (14 mg, 21 μmol) in DCE (4 ml) was heated under N_2 for the times and temperatures given below. After 30 min and again after 1 h, additional bis(triphenylphosphine)-palladium(0) chloride (7 mg, 10 μmol) in DCE (0.5 ml) was added. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in acetonitrile (75 ml) and washed with hexane (5 × 10 ml). The acetonitrile solution was evaporated *in vacuo* and the product was isolated by flash chromatography on silica gel.

*8-Chloro-9-(tetrahydro-2*H*-pyran-2-yl)-6-phenylethynyl-9*H*-purine* (**2a**). 6,8-Dichloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **1a** and phenylethynyl(tributyl)tin were heated in DCE at 60 °C for 24 h as described above. Hexane followed by EtOAc–hexane 1:30, 1:14, 1:7 and 1:4 were used for flash chromatography; yield 70 mg (50%), pale yellow powdery crystals. M.p. 122–124 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.6–1.7 (m, 1 H, THP), 1.7–1.8 (m, 2 H, THP), 1.9 (m, 1 H, THP), 2.0–2.1 (m, 1 H, THP), 2.9–3.0 (m, 1 H, THP), 3.7–3.8 (m, 1 H, THP), 4.2 (m, 1 H, THP), 5.87 (dd, J_1 8.9 Hz, J_2 2.4 Hz, 1 H, H-2 in THP), 7.3–7.4 (m, 3 H, Ph), 7.6 (m, 2 H, Ph), 8.70 (s, 1 H, H-8). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.1, 24.7, 29.3, 69.2, 78.3, 84.1, 97.7, 120.1, 128.6, 130.5, 131.4, 132.1, 138.9, 150.6, 151.2, 152.2. MS (EI): 338 (8, M^+), 254 (100), 165 (12), 139 (17), 85 (35). HRMS: Found 338.0935, calc. for $C_{18}H_{15}ClN_4O$: 338.0934.

*8-Chloro-6-(α-ethoxyethenyl)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine* (**2b**). 6,8-Dichloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **1a** and 1-ethoxyethenyl(tributyl)tin were heated in DCE at 60 °C for 24 h as described above. Hexane followed by EtOAc–hexane 1:30, 1:14, 1:7 and 1:4 were used for flash chromatography; yield 76 mg (60%), colourless powdery crystals. M.p. 103–105 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.41 (t, *J* 7.0 Hz, 3 H, CH_3), 1.4–1.5 (m, 1 H, THP), 1.5 (m, 1 H, THP), 1.6 (m, 1 H, THP), 1.7–1.8 (m, 1 H, THP),

2.0–2.1 (m, 1 H, THP), 2.8–3.0 (m, 1 H, THP), 3.6–3.7 (m, 1 H, THP), 3.98 (q, *J* 7.0 Hz, 2 H, CH_2), 4.85 (d, *J* 2.7 Hz, 1 H, $=CH_2$), 5.69 (dd, J_1 11.3 Hz, J_2 2.4 Hz, 1 H, H-2′ in THP), 5.96 (d, *J* 2.7 Hz, 1 H, $=CH_2$), 8.89 (s, 1 H, H-2). ^{13}CNMR ($CDCl_3$, 75 MHz): δ 14.1, 23.0, 24.5, 28.7, 63.6, 69.1, 83.7, 94.9, 129.1, 142.9, 150.6, 151.9, 152.6, 154.6. MS (EI): 310/308 (1/0.3, M^+), 279 (8), 226 (12), 225 (13), 224 (30), 223 (7), 211 (14), 209 (40), 182 (36), 181 (15), 180 (100), 179 (11), 85 (18). HRMS: Found 308.1024, calc. for $C_{14}H_{17}ClN_4O_2$: 308.1040.

*9-Benzyl-8-chloro-6-(α-ethoxyethenyl)-9*H*-purine* (**2c**). 9-Benzyl-6,8-dichloro-9*H*-purine **1b** (0.40 mmol) and 1-ethoxyethenyl(tributyl)tin were heated in DCE at 60 °C for 20 h as described above. Hexane followed by EtOAc–hexane 1:30, 1:14 and 1:7 were used for flash chromatography; yield 79 mg (63%), pale yellow powdery crystals. M.p. 99–101 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.46 (t, *J* 7.0 Hz, 3 H, CH_3), 4.03 (q, *J* 7.0 Hz, 2 H, CH_2O), 4.89 (d, *J* 2.7 Hz, 1 H, $=CH_2$), 5.41 (s, 2 H, CH_2N), 6.02 (d, *J* 2.7 Hz, 1 H, $=CH_2$), 7.2–7.3 (m, 5 H, Ph), 8.96 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.2, 46.7, 63.6, 94.8, 127.7, 128.3, 128.8, 129.2, 134.3, 143.6, 150.6, 152.3, 152.9, 154.8. MS (EI): 314 (4, M^+), 270 (74), 223 (8), 179 (6), 91 (100). HRMS: Found 314.0900, calc. for $C_{16}H_{15}ClN_4O$: 314.0934.

*8-Chloro-9-(tetrahydro-2*H*-pyran-2-yl)-6-(2-thienyl)-9*H*-purine* (**2d**). 6,8-Dichloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **1a** and 2-thienyl(tributyl)tin were heated in DCE at 75 °C for 30 h as described above. Hexane followed by EtOAc–hexane 1:30, 1:14, 1:7 and 4:1 were used for flash chromatography; yield 83 mg (63%) colourless powdery crystals. M.p. >162 °C (decomp). Anal.: C, H. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.6–1.9 (m, 4 H, THP), 2.1 (m, 1 H, THP), 2.9–3.0 (m, 1 H, THP), 3.7 (m, 1 H, THP), 4.1–4.2 (m, 1 H, THP), 5.73 (dd, J_1 11.3 Hz, J_2 2.4 Hz, 1 H, H-2 in THP), 7.18 (dd, J_1 5.0 Hz, J_2 3.8 Hz, 1 H, H-4 in thienyl), 7.55 (dd, J_1 5.0 Hz, J_2 1.1 Hz, 1 H, H-5 in thienyl), 8.55 (dd, J_1 3.8 Hz, J_2 1.1 Hz, 1 H, H-3 in thienyl), 8.81 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.2, 24.6, 28.8, 69.2, 83.9, 127.6, 128.8, 130.8, 132.9, 139.4, 142.4, 148.9, 152.3, 152.6. MS (EI): 320 (2, M^+), 236 (80), 201 (9), 84 (30), 44 (100).

*9-Benzyl-8-chloro-6-(2-thienyl)-9*H*-purine* (**2e**). 9-Benzyl-6,8-dichloro-9*H*-purine **1b** (0.40 mmol) and 2-thienyl(tributyl)tin were heated in DCE at 75 °C for 30 h as described above. Hexane followed by EtOAc–hexane 1:30, 1:14, 1:7 and 1:4 were used for flash chromatography; yield 54 mg (41%) pale yellow powdery crystals. M.p. 134–136 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.42 (s, 2 H, CH_2), 7.20 (dd, J_1 4.9 Hz, J_2 3.8 Hz, 1 H, thienyl), 7.3 (m, 5 H, Ph), 7.57 (dd, J_1 4.9 Hz, J_2 1.0 Hz, 1 H, thienyl), 8.57 (dd, 1 H, J_1 3.8 Hz, J_2 1.0 Hz, 1 H, thienyl), 8.84 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 46.7, 127.7, 127.8, 128.4, 128.8, 128.9, 130.9, 132.9, 134.6, 139.4, 143.1, 148.8, 152.7, 152.8. MS (EI): 328/326 (20/61, M^+), 291 (24), 263 (3), 249 (6), 173 (2), 172 (2), 163 (2), 91 (100), 89 (3), 65 (16). HRMS: Found 326.0394, calc. for $C_{16}H_{11}ClN_4S$: 326.0393.

*8-Chloro-6-(phenyl)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine* (**2f**). 6,8-Dichloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **1a** and phenyl(trimethyl)tin were heated at reflux in DCE for 27 h as described above. Hexane followed by EtOAc–hexane 1:30, 1:14, 1:7 and 1:4 were used for flash chromatography; yield 75 mg (58%) colourless powdery crystals. M.p. 117–119 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.6–1.7 (m, 1 H, THP), 1.7–1.8 (m, 1 H, THP), 1.8–1.9 (m, 2 H, THP), 2.1 (m, 1 H, THP), 2.9–3.1 (m, 1 H, THP), 3.7–3.8 (m, 1 H, THP), 4.1–4.2 (m, 1 H, THP), 5.77 (dd, J_1 11.3 Hz, J_2 2.5 Hz, 1 H, H-2 in THP), 7.5–7.6 (m, 3 H, Ph), 8.7 (m, 2 H, Ph), 8.96 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.2, 24.6, 26.8, 69.3, 83.9, 128.9, 129.6, 129.8, 131.0, 135.0, 142.6, 152.3, 153.1, 153.6. MS (EI): 314 (4, M^+), 230 (100), 195 (94), 141 (15), 84 (24). HRMS: Found 314.0927, calc. for $C_{16}H_{15}ClN_4O$: 314.0934.

*9-Benzyl-8-chloro-6-phenyl-9*H*-purine* (**2g**). 9-Benzyl-6,8-dichloro-9*H*-purine **1b** (0.40 mmol) and phenyl(trimethyl)tin were heated at reflux in DCE for 24 h as described above. Hexane followed by EtOAc–hexane 1:30, 1:14, 1:7 and finally 1:4 were used for flash chromatography; yield 75 mg (58%) colourless powdery crystals. M.p. 133–134 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.45 (s, 2 H, CH_2), 7.3–7.4 (m, 5 H, Ph), 7.5 (m, 3 H, Ph), 8.7 (m, 2 H, Ph), 9.00 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 46.7, 127.8, 128.4, 128.6, 128.9, 129.6, 129.9, 131.1, 134.6, 135.0, 143.2, 152.6, 153.3, 153.5. MS (EI): 322/320 (22/67, M^+), 285 (30), 243 (12), 229 (6), 91 (100), 89 (5), 65 (16). HRMS: Found 320.0849, calc. for $C_{18}H_{13}ClN_4$: 320.0829.

General procedure for Stille coupling of 6,8-dihalopurines (**1c**)–(**1e**). A mixture of 6,8-dihalopurine **1c**–**1e** (0.41 mmol), organotin reagent (0.49 mmol) and tetrakis[tri(2-furyl)phosphine]palladium(0) (5 mol%) [generated *in situ* from tris(dibenzylideneacetone)dipalladium chloroform adduct and tri(2-furyl)phosphine] in the solvent described below (4 ml) was heated under N_2 for the times and temperatures given below. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in acetonitrile (75 ml) and washed with hexane (5 × 10 ml). The acetonitrile solution was evaporated *in vacuo* and the product was isolated by flash chromatography on silica gel or by crystallisation.

*6-Chloro-8-phenylethynyl-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine* (**4a**). 6-Chloro-8-iodo-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **1d** and phenylethynyl(tributyl)tin were heated in DMF at 60 °C for 3.5 h as described

above. Hexane followed by EtOAc–hexane 1:40, 1:20, 1:14, 1:7 and 1:4 were used for flash chromatography; yield 93 mg (67%) colourless crystals. M.p. 140–142 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.6–1.7 (m, 1 H, THP), 1.7–1.8 (m, 2 H, THP), 1.9 (m, 1 H, THP), 2.0–2.1 (m, 1 H, THP), 2.9–3.0 (m, 1 H, THP), 3.7–3.8 (m, 1 H, THP), 4.2 (m, 1 H, THP), 5.87 (dd, J_1 8.9 Hz, J_2 2.4 Hz, 1 H, H-2′ in THP), 7.3–7.4 (m, 3 H, Ph), 7.6 (m, 2 H, Ph), 8.70 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.1, 24.7, 29.3, 69.2, 78.3, 84.1, 97.7, 120.1, 128.6, 130.5, 131.4, 132.1, 138.9, 150.6, 151.2, 152.2. MS (EI): 338 (14, M^+), 255 (100), 219 (9), 192 (6), 127 (14), 85 (42). HRMS: Found 338.0944, calc. for $C_{18}H_{15}ClN_4O$: 338.0934.

*9-Benzyl-6-chloro-8-phenylethynyl-9*H*-purine* (**4b**). 9-Benzyl-6-chloro-8-iodo-9*H*-purine **1e** and phenylethynyl(tributyl)tin were heated in DMF at 75 °C for 3.5 h as described above. Hexane followed by EtOAc–hexane 1:40, 1:20, 1:14, 1:7 and 1:4 were used for flash chromatography; yield 95 mg (67%) colourless crystals. M.p. 165–167 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.50 (s, 2 H, CH_2) 7.1–7.2 (m, 3 H, Ph), 7.3–7.4 (m, 5 H, Ph), 7.5 (m, 2 H, Ph), 8.65 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.6, 77.9, 98.2, 119.9, 128.0, 128.5, 128.7, 128.9, 130.6, 131.4, 132.2, 134.9, 139.6, 150.5, 151.6, 152.5. MS (EI): 343 (100, M^+), 307 (6), 267 (5), 172 (10), 117 (9), 91 (79). HRMS: Found 344.0806, calc. for $C_{20}H_{13}ClN_4$: 344.0829.

*6-Chloro-8-ethenyl-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine* (**4c**). 6-Chloro-8-iodo-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **1d** and ethenyl(tributyl)tin were heated in DCE at 70 °C for 1 h as described above. Hexane followed by EtOAc–hexane 1:40, 1:20, 1:14, 1:7 and 1:4 were used for flash chromatography; yield 83 mg (76%) colourless oil. Similar treatment of 8-bromo-6-chloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **1c** with ethenyl(tributyl)tin in DCE at 70 °C for 1.5 h gave 66 mg (61%) of the title compound **4c**. ^{1}H NMR (C_6D_6, 300 MHz): δ 0.9 (m, 1 H, THP), 1.0–1.1 (m, 2 H, THP), 1.1–1.2 (m, 2 H, THP), 1.3–1.4 (m, 2 H, THP), 1.8–1.9 (m, 1 H, THP), 3.1 (m, 1 H, THP), 3.7 (m, 1 H, THP), 5.40 (dd, J_1 10.7 Hz, J_2 1.9 Hz, 1 H, =CH_2), 5.64 (dd, J_1 11.2 Hz, J_2 2.5 Hz, 1 H, H-2 in THP), 6.78 (dd, J_1 17.2 Hz, J_2 1.9 Hz, 1 H, =CH_2), 6.98 (dd, J_1 17.2 Hz, J_2 10.7 Hz, 1 H, CH=), 8.55 (s, 1 H, H-2). ^{13}C NMR (C_6D_6, 75 MHz): δ 22.9, 24.8, 31.2, 68.8, 82.9, 125.0, 125.5, 131.6, 150.3, 151.4, 152.4, 152.8. MS (EI): 264 (2, M^+), 180 (100), 145 (35), 84 (27). HRMS: Found 264.0789, calc. for $C_{12}H_{13}ClN_4O$: 264.0779.

*9-Benzyl-6-chloro-8-ethenyl-9*H*-purine* (**4d**). 9-Benzyl-6-chloro-8-iodo-9*H*-purine **1e** and ethenyl(tributyl)tin were heated in DCE at 70 °C for 19 h as described above. Hexane followed by EtOAc–hexane 1:40, 1:14 and finally 1:4 were used for flash chromatography; yield 83 mg (76%) colourless crystals. M.p. 126–128 °C. Anal.: C, H. ^{1}H NMR (C_6D_6, 200 MHz): δ 4.80 (s, 2 H, CH_2), 5.20 (dd, J_1 10.9 Hz, J_2 1.6 Hz, 1 H, CH_2=), 6.73 (dd, J_1 10.9 Hz, J_2 17.0 Hz, 1 H, CH=), 6.64 (dd, J_1 17.0 Hz, J_2 1.6 Hz, 1 H, CH_2=), 6.7–6.8 (m, 2 H, Ph), 6.9–7.0 (m, 3 H, Ph), 8.59 (s, H, H-2). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 46.6, 122.5, 127.2, 127.8, 128.8, 129.5, 131.7, 135.4, 150.2 152.0, 153.5, 153.6. MS (EI): 270 (53, M^+), 255 (6), 243 (4), 91 (100), 77 (5), 65 (17).

*6-Chloro-8-(α-ethoxyethenyl)-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine* (**4e**). 6-Chloro-8-iodo-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **1d** and 1-ethoxyethenyl(tributyl)tin were heated in DMF at 70 °C for 7 h as described above. Hexane followed by EtOAc–hexane 1:40, 1:20, 1:14, 1:7 and 1:4 were used for flash chromatography; yield 96 mg (76%) pale yellow powdery crystals. Similar treatment of 8-bromo-6-chloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **1c** with 1-ethoxyethenyl(tributyl)tin in DMF at 55 °C for 3.5 h gave 101 mg (80%) of the title compound **4e**. M.p. 148–151 °C. Anal.: C, H. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.38 (t, J 7.0 Hz, 3 H, CH_3), 1.5–1.6 (m, 2 H, THP), 1.8 (m, 2 H, THP), 2.0–2.1 (m, 1 H, THP), 2.9–3.0 (m, 1 H, THP), 3.6 (m, 1 H, THP), 3.95 (q, J 7.0 Hz, 2 H, CH_2), 4.1–4.2 (m, 1 H, THP), 4.67 (d, J 3.0 Hz, 1 H, =CH_2), 5.10 (d, J 3.0 Hz, 1 H, =CH_2), 5.74 (dd, J_1 11.1 Hz, J_2 2.3 Hz, 1 H, H-2 in THP), 8.67 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 75 Hz): δ 14.1, 23.1, 24.5, 28.9, 64.1, 69.0, 85.2, 93.1, 130.9, 150.6, 150.7, 151.3, 151.5, 152.5. MS (EI): 308 (5, M^+), 279 (16), 225 (38), 209 (73), 180 (100), 168 (39), 85 (51).

*9-Benzyl-6-chloro-8-(α-ethoxyethenyl)-9*H*-purine* (**4f**). 9-Benzyl-6-chloro-8-iodo-9*H*-purine **1e** and 1-ethoxyethenyl(tributyl)tin were heated in DMF at 70 °C for 9 h as described above. Hexane followed by EtOAc–hexane 1:8, 1:6, 1:4 and finally 1:2 were used for flash chromatography; yield 90 mg (72%) colourless crystals. M.p. 90–91 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24 (t, J 7.0 Hz, 3 H, CH_3), 3.84 (q, J 7.0 Hz, 2 H, CH_2), 4.54 (d, J 3.0 Hz, 1 H, CH=), 5.30 (d, J 3.0 Hz, 1 H, CH=), 5.65 (s, 2 H, CH_2), 7.0–7.2 (m, 5 H, Ph), 8.64 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.5, 48.4, 64.7, 93.1, 127.2, 128.3, 129.0, 131.1, 136.4, 147.5, 150.7, 151.7, 152.3, 153.8. MS (EI): 314 (18, M^+), 269 (35), 243 (32), 91 (100), 77 (5), 65 (18). HRMS: Found 314.0929, calc. for $C_{16}H_{15}ClN_4O$: 314.0934.

*6-Chloro-9-(tetrahydro-2*H*-pyran-2-yl)-8-(2-thienyl)-9*H*-purine* (**4g**). 6-Chloro-8-iodo-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **1d** and 2-thienyl(tributyl)tin were heated in DMF at 60 °C for 3.5 h as described above. Hexane followed by EtOAc–hexane 1:40, 1:20, 1:14, 1:7 and 1:4 were used for flash chromatography; yield 85 mg (64%) pale yellow powdery crystals. Similar treatment of 8-bromo-6-chloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **1c** with 2-thienyl(tributyl)tin in DMF at 45 °C for 2.5 h gave 87 mg (66%) of the title compound

4g. M.p. 110–112 °C. Anal.: C, H. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.6–1.9 (m, 4 H, THP), 2.1 (m, 1 H, THP), 2.9–3.0 (m, 1 H, THP), 3.7 (m, 1 H, THP), 4.1–4.2 (m, 1 H, THP), 5.73 (dd, J_1 11.3 Hz, J_2 2.4 Hz, 1 H, H-2 in THP), 7.18 (dd, J_1 5.0 Hz, J_2 3.8 Hz, 1 H, H-4 in thienyl), 7.55 (dd, J_1 5.0 Hz, J_2 1.1 Hz, 1 H, H-5 in thienyl), 8.55 (dd, J_1 3.8 Hz, J_2 1.1 Hz, 1 H, H-3 in thienyl), 8.81 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.2, 24.5, 28.3, 68.8, 84.2, 127.9, 130.3, 130.9, 131.4, 131.6, 149.9, 150.6, 151.2, 153.2. MS (EI, 15 eV): 320 (38, M^+), 236 (100), 84 (16).

*9-Benzyl-6-chloro-8-(2-thienyl)-9*H*-purine* (**4h**). 9-Benzyl-6-chloro-8-iodo-9*H*-purine **1e** and 2-thienyl(tributyl)tin were heated in DMF at 60 °C for 5 h as described above. The product was purified by crystallisation from dichloromethane–hexane; yield 89 mg (70%) yellow crystals. M.p. 150–153 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.71 (s, 2 H, CH_2), 7.1 (m, 6 H, Ph and H-4 in thienyl), 7.48 (dd, J_1 3.8, J_2 1.0 Hz, 1 H, H-3 in thienyl), 7.52 (dd, J_1 5.0, J_2 1.0 Hz, 1 H, H-5 in thienyl), 8.66 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 47.8, 126.6, 128.5, 128.6, 129.5, 130.5, 130.7, 130.8, 131.2, 135.4, 150.1, 150.9, 152.1, 154.4. MS (EI): 326 (63, M^+), 291 (8), 249 (9), 91 (100). HRMS: Found 326.0393, calc. for $C_{16}H_{11}ClN_4S$: 326.0389.

*9-Benzyl-6-chloro-8-phenyl-9*H*-purine* (**4i**). 9-Benzyl-6-chloro-8-iodo-9*H*-purine **1e** and phenyl(tributyl)tin were heated in DMF at 85 °C for 18 h as described above. Hexane followed by EtOAc–hexane 1:40, 1:30, 1:20, 1:14 and 1:4 were used for flash chromatography; yield 97 mg (75%) colourless crystals. M.p. 128–130 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.59 (s, 2 H, CH_2), 7.0–7.8 (m, 10 H, Ph), 8.79 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.5, 126.5, 128.1, 128.4, 128.8, 128.9, 129.3, 131.0, 131.3, 135.3, 150.0, 151.6, 153.6, 156.3. MS (EI): 320 (44, M^+), 285 (1), 258 (1), 243 (1), 91 (100), 77 (1), 65 (2). HRMS: Found 320.0844, calc. for $C_{18}H_{13}ClN_4$: 320.0829.

*6-Chloro-8-phenyl-9*H*-purine* (**5**). 6-Chloro-8-iodo-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **1d** (0.41 mmol) and phenyl(tributyl)tin were heated in DMF at 85 °C for 18 h as described above. Hexane followed by EtOAc–hexane 1:40, 1:30, 1:20, 1:14, and finally 1:4 were used for flash chromatography; yield 62 mg (66%) colourless crystals. Similar treatment of 8-bromo-6-chloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **1c** with phenyl(tributyl)tin in DMF at 80 °C for 18 h gave 57 mg (61%) of the title compound **5**. M.p. 260–262 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.5–7.7 (m, 3 H, Ph), 8.1–8.3 (m, 2 H, Ph), 8.71 (s, 1 H, H-2), 14.3 (br s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 127.4, 128.4, 129.1, 131.6, 151.4, 154.5 (br). MS (EI): 230 (100, M^+), 195 (42), 149 (8), 119 (7), 104 (14). HRMS: Found 230.0360, calc. for $C_{11}H_7ClN_4$: 230.0359.

General procedure for coupling of 6,8-dihalopurines (**1**) *with organozinc reagents.* A 1 M solution of anhydrous zinc bromide in THF (0.49 ml, 0.49 mmol) was added dropwise to a stirred solution of methylmagnesium chloride (0.49 mmol) in dry THF (4 ml) under N_2 at −78 °C. After 1 h, the cooling bath was removed and the mixture was allowed to reach ambient temperature before the 6,8-dihalopurine **1** (150 mg, 0.41 mmol), tris(dibenzylideneacetone)dipalladium chloroform adduct (10 mg, 10.3 μmol) and tri(2-furyl)phosphine (19 mg, 82 mmol) were added. The resulting mixture was stirred at 60 °C for 2 h and cooled. Sat. aq. NH_4Cl (10 ml) was added and the aqueous phase extracted with EtOAc (4 × 25 ml). The combined organic extracts were washed with brine (2 × 20 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The product was isolated by flash chromatography on silica gel.

*6-Chloro-8-methyl-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine* (**4j**). 6-Chloro-8-iodo-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **1d** and methylzinc bromide were heated at 60 °C for 4 h as described above. Hexane followed by EtOAc–hexane 1:40, 1:20, 1:14, 1:7, 1:4 and 1:1 were used for flash chromatography; yield 80 mg (77%) pale yellow oil. Similar treatment of 8-bromo-6-chloro-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **1c** with methylzinc bromide for 6 h gave 53 mg (51%) of the title compound **4j**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.5–1.6 (m, 3 H, THP), 1.7 (m, 1 H, THP), 1.8 (m, 1 H, THP), 2.0 (m, 1 H, THP), 2.70 (s, 3 H, CH_3), 3.6–3.7 (m, 1 H, THP), 4.1 (m, 1 H, THP), 5.66 (dd, J_1 8.8 Hz, J_2 2.5 Hz, 1 H, H-2 in THP), 8.54 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.1, 22.9, 24.6, 29.9, 69.0, 83.1, 130.4, 148.7, 150.8, 152.4, 155.1. MS (EI): 252 (5, M^+), 218 (40), 168 (100), 133 (51), 109 (27), 84 (48). HRMS: Found 252.0781, calc. for $C_{11}H_{13}ClN_4O$: 252.0778.

*9-Benzyl-6-chloro-8-methyl-9*H*-purine* (**4k**). 9-Benzyl-6-chloro-8-iodo-9*H*-purine **1e** and methylzinc bromide were heated 60 °C for 4 h as described above. Hexane followed by EtOAc–hexane 1:6, 1:4 and finally 1:2 were used for flash chromatography; yield 71 mg (68%) pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.53 (s, 3 H, CH_3), 5.37 (s, 2 H, CH_2), 7.1–7.3 (m, 5 H, Ph), 8.63 (s, 1 H, H-2). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.6, 46.4, 127.0, 128.4, 129.1, 130.5, 134.6, 148.9, 151.3, 153.2, 155.3. MS (EI): (45, M^+), 243 (19), 91 (100), 77 (5), 65 (15). HRMS: Found 260.0649, calc. for $C_{13}H_{11}ClN_4$: 260.0643.

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