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Regiochemistry in Stille Couplings of 2,6-Dihalopurines

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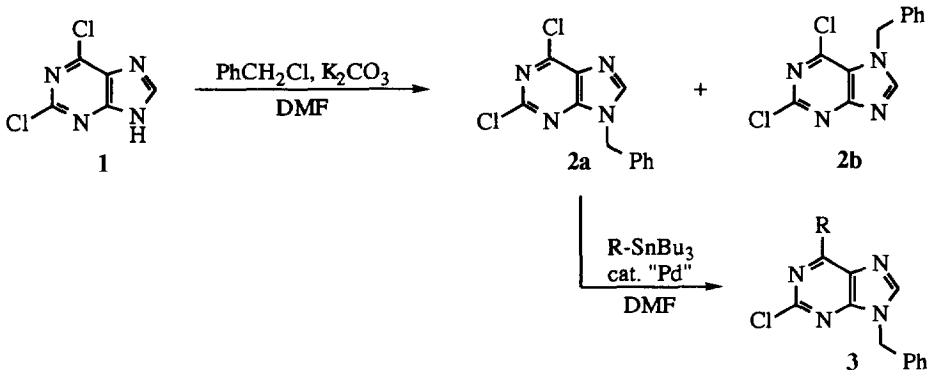
Abstract: The regiochemistry in Stille couplings of 2,6-dihalopurines have been studied. 2,6-Dichloropurines react selectively in the 6-position, and 6-chloro-2-iodopurines and 2-bromo-6-chloropurines in the 2-position. Copyright © 1996 Elsevier Science Ltd

Modified purines containing carbon substituents in the 2- 6- or 8-position are associated with interesting biological properties, such as antiviral effect,[1] anticancer effect,[1] antihypertensive effect[2] or cytokinin activity.[3] Pd-catalyzed coupling between halopurines and organotin reagents, the Stille reaction, is emerging as a popular reaction for *C* - *C* bond formation in the purine 2-,[4] 6,[4k,5] and 8-position.[4k,6] Transition metal catalyzed couplings employing organozinc,[5b,5d,7] organoaluminium[8] or Grignard reagents[9] have also been studied. The regioselectivity in these reaction has, however, attracted little attention.[5d]

It is well known that selective substitution in the purine 6-position easily can be achieved when 2,6-dichloropurines is reacted with oxygen,[10] nitrogen[10b,10d,11] and halogen nucleophiles.[12] Even 2-iodo-6-chloropurines reacts preferably in the 6-position with alcohols[4a,4b] and ammonia.[13] Calculations also indicate that the purine 6-position is more activated for nucleophilic attack than the 2-position.[14] Regioselectivity in *C* - *C* bond forming reactions have been studied to a much lesser extent. Sodium diethyl malonate is reported to attack the 6-position of a 2,6-dichloropurine,[15] selective arylation in the 2-position has been achieved by photolysis of 2-iodo-6-chloropurines in the presence of electron rich arenes,[16] and in a preliminary communication, we recently reported regioselective Pd-catalyzed couplings in the 6-position of 2,6-dichloropurines.[5d] In this paper, we are reporting our results from Stille couplings employing several 2,6-dihalopurines.

N-9 benzylated purines were chosen as model substances and 2,6-dichloropurine **1** was *N*-alkylated with benzyl chloride to give 9-benzyl-2,6-dichloropurine **2a** together with the 7-benzylated isomer **2b** in a 7 : 3 ratio, as judged by ^{1}H NMR spectroscopy of the crude product. The isomers were isolated in 72 % and 18 % yields, respectively (Scheme 1). The yield of **2a** is higher than reported earlier.[17]

Coupling in the 6-position, exclusively, was achieved when the 2,6-dichloropurine **2a** was treated with a wide variety of organotin reagents in the presence of 5 mol % Pd-catalyst (Scheme 1, Table 1). The structures of the coupling products **3** were established by long range HETCOR and COLOC NMR,[5d] and by comparing NMR spectra with those of the isomeric 2-substituted 6-chloropurines (*vide infra*). Alkynyl- alkenyl and thienyltin reagents coupled selectively when $(Ph_3P)_2PdCl_2$ was employed (Table 1, entries 1-4).



Scheme 1

Table 1. Pd-Catalyzed Coupling between 9-Benzyl-2,6-dichloropurine **2a** and Organotin Reagents.

Entry	R-$SnBu_3$	Catalyst	Time (h)	Temp (°C)	Yield (%), **3**
1	PhC≡C$SnBu_3$	$(Ph_3P)_2PdCl_2$	24	60	68, **3a**
2	*trans* PhCH=CH$SnBu_3$	"	24	80	56, **3b**
3	CH_2=C(OEt)$SnBu_3$	"	24	70	70, **3c**
4	(2-thienyl)$SnBu_3$	"	24	70	59, **3d**
5	(2-furyl)$SnBu_3$	"	2	65	-,[a] **3e**
6	"	"	24	60	n.r.
7	"	$[(2\text{-furyl})_3P]_4Pd$	22	60	-,[b] **3e**
8	"	"	22	50	88, **3e**
9	$PhSnBu_3$	$(Ph_3P)_2PdCl_2$	24	75	-,[c] **3f**
10	"	$[(2\text{-furyl})_3P]_4Pd$	23	70	-,[d] **3f**
11	"	"	35	65	81, **3f**

(a) A ca. 5 : 2 mixture of **3e** and **9f** was formed. (b) A ca. 17 : 2 mixture of **3e** and **9f** was formed. (c) A ca. 2 : 3 mixture of **3f** and 9-benzyl-2,6-diphenylpurine was formed. (d) A ca. 13 : 2 mixture of **3f** and 9-benzyl-2,6-diphenylpurine was formed.

The coupling with the 2-furyltin reagent in the presence of $(Ph_3P)_2PdCl_2$ was less selective (Table 1, entry 5). A ca 5 : 2 mixture of the desired product **3e** and the 2-furyl-6-chloropurine derivative **9f** (*vide infra*) was formed as judged by ^1H NMR of the crude product. When the reaction temperature was lowered only 5 degrees, no reaction took place at all (Table 1, entry 6). The regioselectivity was improved considerably by

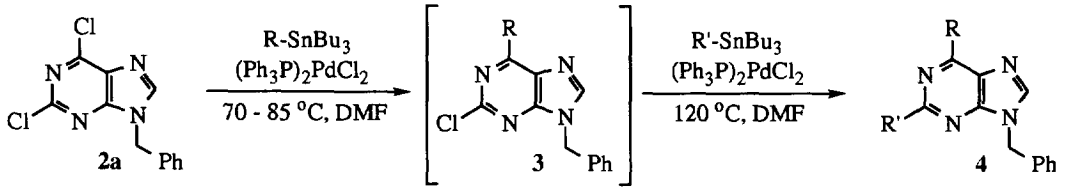
changing to the more reactive catalyst $[(2\text{-furyl})_3P]_4Pd$[18] (Table 1, entries 7-8). The latter catalyst allowed coupling at lower temperatures, and complete selectivity was achieved at 50 °C (Table 1, entry 8).

Coupling with $PhSnBu_3$ in the presence of $(Ph_3P)_2PdCl_2$ was also non-selective (Table 1, entry 9). A ca. 3 : 2 mixture of the desired compound **3f** and 9-benzyl-2,6-diphenylpurine was formed as jugded by the ^1H NMR and MS spectra of the crude product. Again, improved regioselectivity was achieved when $[(2\text{-furyl})_3P]_4Pd$ was employed at somewhat lower temperature (Table 1, entries 10-11). Slow, but selective, coupling took place at 65 °C (Table 1, entry 11). When the reaction mixture was stirred at this temerature for 48 h, some 2,6-diphenylpurine could be detected.

Attempts to introduce the vinyl substituent in the 6-position by coupling of the dichloropurine **2a** with vinyl(tributyl)tin failed. Although TLC and ^1H NMR indicated that the desired reaction took place, all attempts to isolate the product resulted in extensive polymerization. This result is not completely surprising. It is known that both 6-vinyl and 8-vinylpurines[4k,5c,6c] readily undergo addition of nucleophiles and a 2-chloro-6-vinylpurine is expected to be especially reactive. Some formation of unidentified products was also observed in the formation of the 6-alkynylpurine **3a**, but the 6-styrylpurine **3c** was formed cleanly.

The products **3** contain a 2-chloro substituent which easily can be manipulated further (*vide infra*). 6-Substituted 2-chloropurines are also associated with interesting medicinal[19] and agrochemical[20] properties, and a few naturally occurring purine nucleosides with a 2-chloro substituent have been isolated.[21]

The initially non selective coupling of the furyltin and phenyltin reagents with the 2,6-dichloropurine **2a** demonstrated that even 2-chloropurines may participate in Stille couplings, although less readily than 6-chloropurines. Furthermore, we have recently shown that 2-chloropurines react with zinc cyanide in the presence of Pd(0).[7] We therefore envisaged that it would be possible to utilize the difference in reactivity between the purine 2- and 6-position for selective introduction of two different substituents in one-pot Stille reactions (Scheme 2, Table 2).



Scheme 2

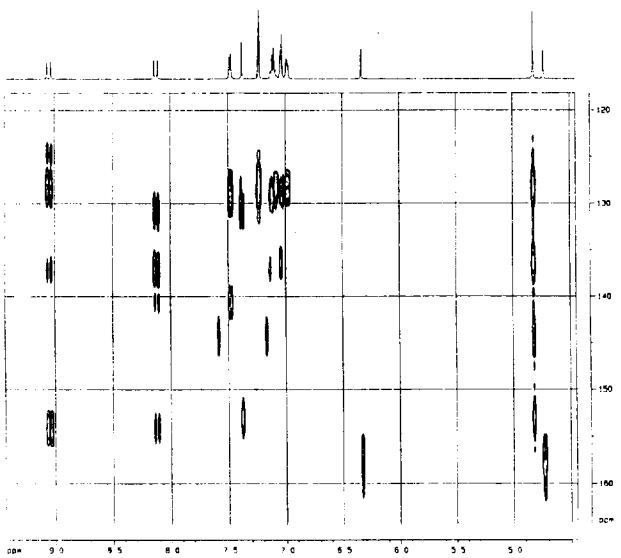
Table 2. One-Pot Stille Coupling between 9-Benzyl-2,6-dichloropurine **2a** and Two Organostannanes.

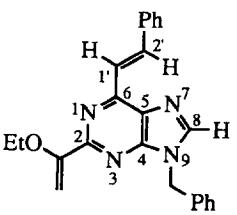
Entry	R-$SnBu_3$	R'-$SnBu_3$	Yield (%), **4**
1	*trans* PhCH=CHSnBu_3	CH_2=C(OEt)SnBu_3	57 **4a**
2	*trans* PhCH=CHSnBu_3	Ph$Sn Bu_3$	63 **4b**
3	CH_2=C(OEt)SnBu_3	*trans* PhCH=CHSnBu_3	69 **4c**
4	Ph$Sn Bu_3$	*trans* PhCH=CHSnBu_3	62 **4d**

The 2,6-dichloropurine **2a** was reacted with one equivalent of an organotin reagent in the presence of catalytic $(Ph_3P)_2PdCl_2$ at 70-85 °C until TLC showed the coupling in the 6-position to be complete, another

organotin compound was added and the temperature raised to 120 °C. In all cases examined, only the expected regioisomer of the disubstituted purine **4** was formed.

The structures of the styryl and ethoxyvinyl disubstituted purines **4a** and **4c** were proven by gradient accelerated HMBC spectroscopy (heteronuclear multiple bond correlation) optimized for 10 Hz coupling constants and gradient accelerated HMQC (heteronuclear multiple quantum correlation) spectroscopy. Benzene-d_6 was the solvent of choice for these experiments due to severe spectral crowding of the ^{1}H resonances in the chloroform spectra. As an illustrative example of a part of the gradient accelerated HMBC spectrum of **4a** is shown in Fig. 1.





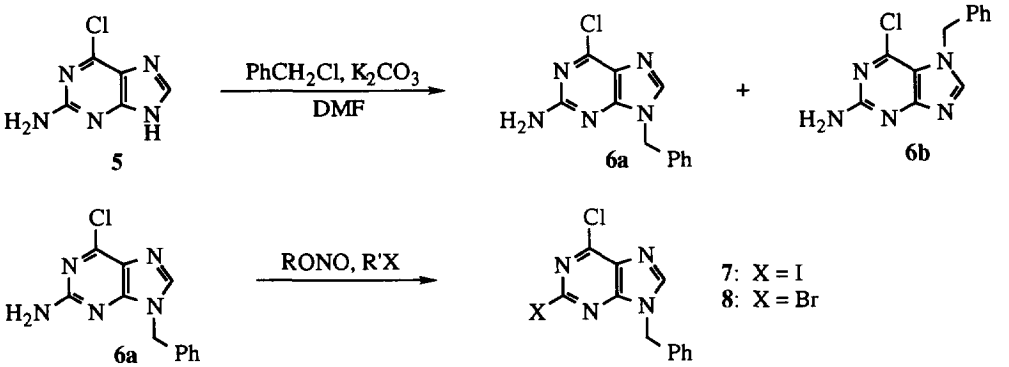
4a

Fig. 1

The ^{1}H shift of the benzylic protons at 4.82 ppm serves as an obvious starting point in the elucidation of the structure of **4a**. The benzylic protons correlates to C-4 (152.9 ppm) and C-8 (144.1 ppm) as well as to the *ipso* and *ortho* carbons in the phenyl group. The H-8 (7.38 ppm) - C-8 (144.1 ppm) direct correlation is found from the HMQC spectrum. H-8 again correlates to C-4 at 152.9 ppm and C-5 at 130.7 ppm. With the C-5 shift identified, the other long range correlation from C-5 to H–1' at 124.6 ppm (the innermost H) in the styryl side chain confirms that the styryl substituent is positioned at the 6-position in **4a**.

After developing a method for selective coupling in the 6-position of 2,6-dihalopurines, we wanted to explore the possibility of coupling in the 2-position, exclusively. The order of reactivity of aryl halides in palladium mediated cross couplings is generally found to be Ar-I › Ar-Br ›› Ar-Cl,[22] and we wished to examine the regioselectivity in coupling reactions of *N*-alkylated 2-iodo-6-chloropurine and 2-bromo-6-chloropurine. *N*-Benzylation of 2-amino-6-chloropurine **5** with benzyl chloride in DMF employing potassium carbonate as base, afforded the 9-benzylated purine **6a** the 7-benzylated isomer **6b** in a 7 : 2 ratio and the isolated yields were 73 % and 15 % respectively (Scheme 3).

The aminopurine **6a** was converted to the iodopurine **7** in 67 % yield by treatment with isopentyl nitrite, diiodomethane, iodine and CuI in THF (Scheme 3, Table 3). This method has previously been used for the preparation of other 2-iodopurines.[2b] Iodination employing *n*-pentyl nitrite and diiodomethane[23] gave only a moderate yield, 35 %, of the desired 2-iodopurine **7** and a substantially amount of 9-benzyl-6-chloro-2-pentyloxypurine was also formed in this reaction.



Scheme 3

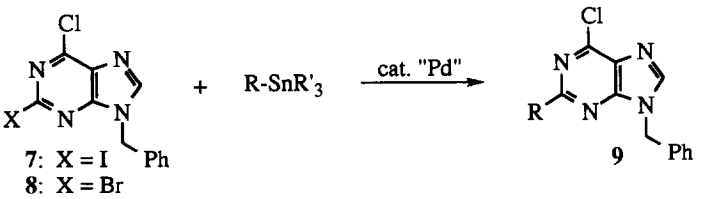
Table 3. Synthesis of 2-Halo-6-chloropurines **7** and **8**.

Entry	RONO	R'X	Co-reagents	Solvent	Temp. (°C)	Yield (%) **7**,**8**
1	*n*-pentylONO	CH_2I_2	—	—	85	35, **7**
2	*i*-pentylONO	CH_2I_2	CuI, I_2	THF	Δ	67, **7**
3	*n*-pentylONO	$CHBr_3$	—	—	85	28, **8**
4	*i*-pentylONO	$CHBr_3$	—	—	85	34, **8**
5	*i*-pentylONO	$CHBr_3$	CuBr, Br_2	THF	50	45, **8**

The 2-bromo-6-chloropurine **8** could also be prepared from the 2-aminopurine **6a**. Again, halogenation employing only *n*-pentylnitrite and bromoform[2b] gave a substantial amount of the 2-pentyloxypurine and the desired 2-bromopurine **8** could only be isolated in 28 % yield. Almost the same results were obtained with isopentylnitrite. When the reaction was carried out in THF using Br_2 and CuBr as co-reagents the yield of the purine **8** was raised to 45 %. The formation of some 9-benzyl-6-chloro-2-isopentyloxypurine was observed.

The 6-chloro-2-iodopurine **7** was coupled with organotin reagents, to give the products **9** (Scheme 4, Table 4). MS confirmed that that the products contained a chloro substituent and that coupling had taken place in the 2-position. The spectral data for the compounds **9** were also different from the data for the isomeric purines **3**. A reactive Pd-catalyst, like $[(2\text{-furyl})_3P]_4Pd$, and somewhat lower reaction temperature than in the couplings of **2a**, were required in most instances in order to achieve complete selectivity.

In contrast to 2-chloropurines, 6-chloropurines readily undergo substitution reactions when threathed with alcohols,[10] and the products **9** were prone to nucleophilic attack in the 6-position. When the crude products **9** were treated with potassium fluoride in methanol, in order to convert the co-product Bu_3SnCl to the corresponding tin fluoride, formation of the corresponding 6-methoxypurines were observed. Removal of the tributyltin chloride formed in the Stille reactions, was better done by dissolving the crude product in acetonitrile and extracting the tin chloride with hexane.



Scheme 4

Table 4. Pd-Catalyzed Coupling between the 6-Chloro-2-iodopurine **7** or the 2-Bromopurine **8** and Organostannanes.

Entry	X	R-SnR'$_3$	Catalyst	Time (h)	Temp (°C)	Yield (%), **9**
1	I	PhC≡CSnBu$_3$	[(2-furyl)$_3$P]$_4$Pd	2	65	-,[a]
2	I	"	"	2	40	79, **9a**
3	I	CH_2=CHSnBu$_3$	"	1	40	80, **9b**
4	I	*trans* PhCH=CHSnBu$_3$	"	5	60	65, **9c**
5	I	CH_2=C(OEt)SnBu$_3$	$(Ph_3P)_2PdCl_2$	16	60	76, **9d**
6	Br	CH_2=C(OEt)SnBu$_3$	[(2-furyl)$_3$P]$_4$Pd	5	50	76, **9d**
7	I	(2-thienyl)SnBu$_3$	"	2	60	80, **9e**
8	I	(2-furyl)SnBu$_3$	"	3	60	81, **9f**
9	I	(2-pyridyl)SnMe$_3$	"	22	65	73, **9g**
10	I	PhSnBu$_3$	"	24	60	73, **9h**
11	Br	PhSnBu$_3$	"	24	60	80, **9h**

a) Only 9-benzyl-2,6-di(phenylethynyl)purine was formed.

As shown in Table 4, a variety of substituents can be introduced in the 2-position by Pd-catalyzed coupling of the 2-iodo-6-chloropurine **7**. This method has a much broader scope than photolysis of 2-iodo-6-chloropurines, which only can be used for selective introduction of aryl and electron rich heteroaryl groups.[16] Both the 2-alkynyl- and 2-vinylpurine (Table 4, entries 2 and 3) were completely stable in contrast to the 6-substituted isomers (*vide supra*).

Also the 2-bromo-6-chloropurine **8** coupled with organotin reagents in the purine 2-position (Table 4, entries 6 and 11). The reactivity of the 2-bromopurine **8** appears to be comparable to that of the corresponding 2-iodopurine **7** in theese reactions.

The results presented herein demonstrates that the regioselectivity in Stille couplings of 2,6-halopurines is largely governed by the identity of the leaving group halogens. When the 2,6-dichloropurine **2a** is employed, the reaction takes place in the 6-position which is more activated for nucleophilic attack than the 2-position. With the 2-iodo- and 2-bromopurines **7** and **8**, coupling in the 2-position, the position carrying the best leaving

group, is achieved. The regiochemistry in the latter coupling reactions are opposite to that in nucleophilic substitution reactions with oxygen and nitrogen nucleophiles, which attack 2-iodo-6-chloropurines in the 6-position.[4a,4b,13]

EXPERIMENTAL

The ^{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 or a Varian XL-300 (manual), or at 200 MHz with a Varian Gemini 200 or a Bruker Avance DPX 200 instrument. The ^{13}C NMR spectra were recorded at 125, 75 or 50 MHz using the above mentioned instruments. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. Gradient accelerated (z gradient) ^{1}H ^{13}C HMBC[24] and ^{1}H {^{13}C} HMQC[25] spectra were recorded with the Bruker Avance DRX 500 spectrometer equipped with a 5 mm triple resonance (^{1}H, ^{13}C, ^{15}N) inverse detection probe (TXI) using the Bruker pulse programs; inv4gslplrnd (HMBC) and inv4gs (HMQC). The 10 mg samples were dissolved in 0.4 ml benzene-d_6. The F2 (^{1}H) acquisition parameters for the 10 Hz optimized HMBC spectra includes 8 scans per increment, a time domain of 2048 complex points with an acquisition time of 0.23 seconds and a sweep width of 9 ppm. The F1 acquisition parameters include 128 increments with a sweep width of 228 ppm. The total acquisition time is approximately 30 minutes. The spectrum in Fig. 1 was processed with a sine window function in both dimensions. The gradient accelerated HMQC spectra were recorded in 18 minutes with a time domain of 1024 complex points employing garp decoupling of the ^{13}C atoms with 128 increments in the F1 dimension and sine window function in both processing dimensions. Mass spectra were recorded with a VG Prospec instrument at 70 eV ionizing voltage 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, DCE from CaH_2 and DMF from barium oxide. *trans*-Phenylethenyl(tributyl)stannane,[26] 2-(tributylstannyl)thiophene[27] and 2-(trimethyl-stannyl)pyridine[28] were prepared according to literature procedures. All other reagents were commercially available and used as received.

9-Benzyl-2,6-dichloro-9H-purine (2a) and 7-benzyl-2,6-dichloro-7H-purine (2b). Potassium carbonate (3.40 g, 25 mmol) was added to a solution of 2,6-dichloro-1*H*-purine **1** (1.528 g, 5.5 mmol) in dry DMF (50 ml) and the mixture was stirred at ambient temperature under N_2. After 20 min, benzyl chloride (1.26 ml, 11 mmol) was added and the resulting mixture was stirred for 20 h, filtered and evaporated *in vacuo*. The products were separated by flash chromatography on silica gel eluting with EtOAc-acetone-hexane (1:2:10).
9-Benzyl-2,6-dichloro-9H-purine (2a): Yield 1.103 g (72 %) colourless powdery crystals. M.p. 149 - 150 °C (Lit.[17a] 148 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.43 (s, 2 H, CH_2), δ 7.3 - 7.4 (m, 5 H, Ph), 8.10 (s, 1 H, H-8). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 47.9 (CH_2), 128.0, 128.9 and 129.2 (CH in Ph), 130.5 (C-5), 133.9 (C in Ph), 145.5 (C-8), 151.6, 152.99, 153.04 (C-2/C-4/C-6). MS (E.I.): 282/280/278 (3/17/24, M^+), 91 (100).
7-Benzyl-2,6-dichloro-7H-purine (2b): Yield 275 mg (18 %) colourless needles. M.p. 157 - 158 °C (EtOAc). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 5.73 (s, 2 H, CH_2), 7.2 (m, 2 H, Ph), 7.3 - 7.4 (m, 3 H, Ph), 9.05 (s, 1 H, H-8). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 49.6 (CH_2), 121.9 (C-5), 126.6, 128.0 and 128.8 (CH in Ph), 136.3 (C in Ph), 143.2 (C-6), 151.2 (C-2), 152.9 (C-8), 163.4 (C-4). MS (E.I.): 282/280/278 (2/12/21, M^+), 91 (100).

Coupling of 9-Benzyl-2,6-dichloro-9H-purine (2a) with organostannanes. A mixture of 9-benzyl-2,6-dichloro-9*H*-purine **2a** (279 mg, 1.0 mmol), bis(triphenylphosphine)palladium(II) chloride (35 mg, 0.05 mmol) and organostannane (1.2 mmol) in dry DMF (3 ml) was heated under N_2 at the temperatures and for the times, given below and evaporated *in vacuo*. A sat. solution of potassium fluoride in methanol (20 ml) was added to the residue, the resulting mixture stirred at ambient temperature over night and evaporated *in vacuo* together with a small amount of silica gel. The residue was added on top of a silica gel column and the product were isolated by flash chromatography.

9-Benzyl-2-chloro-6-phenylethynyl-9H-purine (3a). 9-Benzyl-2,6-dichloro-9*H*-purine **2a** (126 mg, 0.45 mmol) and phenylethynyl(tributyl)stannane (0.19 ml, 0.54 mmol) were heated at 60 °C for 24 h, as described above. EtOAc-hexane (1:2) followed by EtOAc-hexan (2:3) were used for flash chromatography to give a yellow oil which was crystallized from acetone-hexane; yield 105 mg (68 %), colourless powdery crystals. M.p. 170 - 171 °C. (Found: C, 69.50; H, 3.67. Calc. for $C_{20}H_{13}ClN_4$: C, 69.67; H, 3.80 %). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.41 (s, 2 H, CH_2), 7.3 - 7.4 (m, 8 H, Ph), 7.7 (m, 2 H, Ph), 8.06 (s, 1 H, H-8). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 47.9 (CH_2), 83.4 and 99.8 (C≡), 120.3 (C in Ph), 127.3, 127.8, 128.2, 128.6, 129.6, and 132.0 (CH in Ph), 132.6 (C-5), 133.6 (C in Ph), 142.4 (C-6), 144.8 (C-8), 152.4, 153.3 (C-2/C-4). MS (E.I.): 346/345/344 (31/33/76, M^+), 343 (34), 317 (4), 309 (8), 282 (6), 267 (6), 183 (4), 113 (5), 91 (100), 65 (15).

*9-Benzyl-2-chloro-6-*trans*-(β-phenylethenyl)-9H-purine (3b).* 9-Benzyl-2,6-dichloro-9*H*-purine **2a** and *trans*-phenylethenyl(tributyl)stannane were heated at 80 °C for 24 h, as described above. EtOAc-hexane (3:7) was used for flash chromatography; yield 200 mg (56 %) colourless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.42 (s, 2 H, CH_2), 7.3 - 7.4 (m, 8 H, Ph), 7.63 (d, *J* 16.1 Hz, 1 H, CH=), 7.7 (m, 2 H, Ph), 8.00 (s, 1 H, H-8), 8.45 (d, *J* 16.1 Hz, 1 H, CH=). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 46.5 (CH_2), 121.5 (CH=), 127.5, 127.8, 127.9, 128.7, 128.8 and 129.8 (CH in Ph), 129.6 (C-5), 135.1 and 135.9 (C in Ph), 140.7 (CH=), 146.9 (C-8), 152.8 (C-2), 153.3 (C-4), 154.3 (C-6). MS (E.I.) : 348/346 (25/78, M^+), 257 (25), 255 (83), 219 (23), 140 (10), 91 (100), 65 (19). Hrms: found 346.0980, calc. for $C_{20}H_{15}ClN_4$ 346.0985.

9-Benzyl-2-chloro-6-(α-ethoxyethenyl)-9H-purine (3c). 9-Benzyl-2,6-dichloro-9*H*-purine **2a** and (1-ethoxyvinyl)tributyltin were heated at 70 °C for 24 h, as described above. EtOAc-hexane (1:3) was used for flash chromatography; yield 230 mg (70 %) pale yellow powdery crystals. M.p. 125 - 128 °C. (Found: C, 60.79; H, 4.78. Calc. for $C_{16}H_{15}ClN_4O$: C, 61.05; H, 4.80 %). ^{1}H NMR ($CDCl_3$, 300 MHz) : δ 1.49 (t, *J* 7.1 Hz, 3 H, CH_3), 4.08 (q, *J* 7.1 Hz, 2 H, CH_2), 4.92 (d, *J* 2.6 Hz, 1 H, CH=), 5.41 (s, 2 H , CH_2), 6.04 (d, *J* 2.6 Hz, 1 H, CH=), 7.3 (m, 5 H, Ph), 8.06 (s, 1 H, H-8). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (CH_3), 47.3 (CH_2Ph), 63.9 (CH_2O), 95.0 (CH_2=), 127.8 - 128.6 (CH in Ph), 129.0 (C-5), 134.4 (C in Ph), 145.1 (C-8), 153.7, 153.9, 154.0 (C-2/C-4/C-6), 155.0 (EtOC=). MS (E.I.): 316/315/314 (3/2/6, M^+), 299 (13), 272 (20), 271 (12), 270 (57), 179 (10), 91 (100), 65 (14).

9-Benzyl-2-chloro-6-(2-thienyl)-9H-purine (3d). 9-Benzyl-2,6-dichloro-9*H*-purine **2a** and 2-(tributylstannyl)thiophene were heated at 70 °C for 24 h, as described above. EtOAc-hexane (1:5) was used for flash chromatography; yield 195 mg (59 %) pale yellow powdery crystals. M.p. 193 - 195 °C. (Found: C, 58.71; H, 3.53. Calc. for $C_{16}H_{11}ClN_4S$: C, 58.80 H, 3.39 %). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.48 (s, 2 H, CH_2), 7.28 (m, 1 H, H-4'), 7.4 (m, 5 H, Ph), 7.92 (s, 1 H, H-8), 8.58 (m, 1 H, H-3'), 8.67 (m, 1 H, H-5'). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 46.4 (CH_2), 127.1 (C-5), 127.2, 128.3 and 128.5 (CH in Ph), 127.6 (C-4'), 132.4, 132.9 (C-3'/C-5'), 135.5 (C in Ph), 137.7 (C-2'), 146.7 (C-8), 150.1, 152.3, 153.3 (C-2/C-4/C-6). MS (E.I.): 328/327/326 (27/26/64, M^+), 325 (36), 291 (18), 92 (11), 91 (100).

9-Benzyl-2-chloro-6-(2-furyl)-9H-purine (3e). 9-Benzyl-2,6-dichloro-9*H*-purine **2a** (126 mg, 0.45 mmol) and 2-(tributylstannyl)furan (0.17 ml, 0.54 mmol) were heated at 50 °C for 22 h, as described above except that tetrakis[tri(2-furyl)phosphine]palladium(0) [generated *in situ* from tris(dibenzylideneacetone)dipalladium chloroform adduct (13 mg, 0.013 mmol) and tri(2-furyl)phosphine (23 mg, 0.10 mmol)] was used as catalyst. EtOAc-hexane (1:5) was used for flash chromatography; yield 123 mg (88 %) colourless powdery crystals. M.p. 167 - 169 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.38 (s, 2 H, CH_2), 6.6 (m, 1 H), 7.3 (m, 5 H, Ph), 7.7 (m, 1 H), 7.7 - 7.8 (m, 1 H), 8.00 (s, 1 H, H-8). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.2 (CH_2), 112.7 and 118.6 (CH in furyl), 127.0 (C-5), 127.8, 128.6 and 129.0 (CH in Ph), 134.5 (C in Ph), 144.8, 146.5 (CH in furyl/C-8), 147.1, 148.6 (C in furyl/C-6), 153.5, 154.3 (C-2/C-4). MS (E.I.): 312/311/310 (23/24/70, M^+), 309 (31), 293

(2), 281 (8), 275 (11), 245 (2), 233 (3), 219 (1), 91 (100), 65 (12). Hrms: found 310.0602, calc. for $C_{16}H_{11}ClN_4O$ 310.0621

9-Benzyl-2-chloro-6-phenyl-9H-purine (3f). 9-Benzyl-2,6-dichloro-9*H*-purine **2a** (126 mg, 0.45 mmol) and 2-phenyl(tributyl)tin (0.18 ml, 0.54 mmol) were heated at 65 °C for 35 h, as described above except that tetrakis[tri(2-furyl)phosphine]palladium(0) [generated *in situ* from tris(dibenzylideneacetone)dipalladium chloroform adduct (13 mg, 0.013 mmol) and tri(2-furyl)phosphine (23 mg, 0.10 mmol)] was used as catalyst. EtOAc-hexane (1:5) was used for flash chromatography; yield 117 mg (81 %) colourless powdery crystals. M.p. 150 - 151 °C. (Found: C, 67.49; H, 3.97. Calc. for $C_{18}H_{13}ClN_4$: C, 67.40; H, 4.08 %). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.35 (s, 2 H, CH_2), 7.2 - 7.4 (m, 5 H, Ph), 7.4 - 7.6 (m, 3 H, Ph), 7.97 (s, 1 H, H-8), 8.7 - 8.8 (m, 2 H, Ph). ^{13}C NMR (DMSO-d_6, 50 MHz) : δ 46.8 (CH_2), 127.7, 128.1, 128.86, 128.92, 129.6 and 129.8 (CH in Ph), 131.9 (C-5), 134.2 and 136.1 (C in Ph), 147.6 (H-8), 152.9, 154.4, 154.8 (C-2/C-4/C-6). MS (E.I.): 322/321/320 (19/32/57, M^+), 319 (47), 262 (13), 243 (10), 91 (100), 89 (8), 65 (18).

Coupling of 9-Benzyl-2,6-dichloro-9H-purine (2a) with two different organostannanes. A mixture of 9-benzyl-2,6-dichloro-9*H*-purine **2a** (279 mg, 1.0 mmol), bis(triphenylphosphine)palladium(II) chloride (35 mg, 0.05 mmol) and organostannane (1.2 mmol) in dry DMF (3 ml) was heated under N_2 at the temperatures and for the times given below. The second organostannane (1.2 mmol) was added and the reaction mixture was heated at 120 °C and evaporated *in vacuo*. A sat. solution of potassium fluoride in methanol (20 ml) was added to the residue, the resulting mixture stirred at ambient temperature over night and evaporated *in vacuo* together with a small amount of silica gel. The residue was added on top of a silica gel column and the product isolated by flash chromatography.

*9-Benzyl-2-(α-ethoxyethenyl)-6-*trans*-(β-phenylethenyl)-9H-purine (4a).* 9-Benzyl-2,6-dichloro-9*H*-purine **2a** was reacted with *trans*-phenylethenyl(tributyl)stannane at 80 °C for 5 h, before (1-ethoxyvinyl)tributyltin was added and the mixture stirred at 120 °C for 20 h. EtOAc-hexane (1:3) was used for flash chromatography. The product was crystallized from EtOAc-hexane; yield 196 mg (57 %) pale yellow needles. M.p. 141 - 143 °C. (Found: C, 75.26; H, 5.70. Calc. for $C_{24}H_{22}N_4O$: C, 75.37; H, 5.80 %). ^{1}H NMR (C_6D_6, 500 MHz): δ 1.39 (t *J* 7.0 Hz, 3 H, CH_3), 3.88 (q, *J* 7.0 Hz, 2 H, CH_2), 4.73 (d, *J* 0.9 Hz, 1 H, CH=), 4.82 (s, 2 H, CH_2), 6.33 (d, *J* 0.9 Hz, 1 H, CH=), 7.0 - 7.1 (m, 8 H, Ph), 7.38 (s, 1 H, H-8), 7.5 (m, 2 H, Ph), 8.13 (d, *J* 16.2 Hz, 1 H, =CH-Pur), 9.05 (d, *J* 16.2 Hz, 1 H, =CH-Ph). ^{13}C NMR (C_6D_6, 125 MHz): δ 14.8 (CH_3), 46.6 (CH_2N), 64.3 (CH_2O), 89.0 (CH_2=), 124.6 (=CH-Pur), 126.1 - 129.1 (CH in Ph), 130.7 (C-5), 136.2 and 137.0 (C in Ph), 140.5 (=CH-Ph), 144.1 (C-8), 152.9 (C-4), 153.0 (C-6), 156.9 (C-2), 159.5 (OC=). MS (E.I.): 382 (10, M^+), 367 (100), 353 (14), 338 (37) 91 (63), 71 (38).

*9-Benzyl-2-phenyl-6-*trans*-(β-phenylethenyl)-9H-purine (4b).* 9-Benzyl-2,6-dichloro-9*H*-purine **2a** was reacted with *trans*-phenylethenyl(tributyl)stannane at 85 °C for 3 h, before phenyl(tributyl)stannane was added and the mixture stirred at 120 °C for 20 h. EtOAc-hexane (1:3) was used for flash chromatography. The product was crystallized from toluene-hexane; yield 245 mg (63 %) colourless needles. M.p. 142 - 145 °C. (Found: C, 79.88; H, 5.20. Calc. for $C_{26}H_{20}N_4$: C, 80.39; H, 5.19 %). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.45 (s, 2 H, CH_2), 7.3 - 7.6 (m, 11 H, Ph), 7.7 - 7.9 (m, 3 H, Ph and CH=), 7.97 (s, 1 H, H-8), 8.52 (d, *J* 16.1 Hz, 1 H, CH=), 8.6 - 8.7 (m, 2 H, Ph). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 47.4 (CH_2), 122.4 (CH=), 127.3, 127.4, 127.7, 127.8, 128.0, 128.1, 128.4, 128.6 and 129.0 (CH in Ph), 130.3 (C-5), 134.8, 135.6 and 137.6 (C in Ph), 138.6 (CH=), 143.1 (C-8), 151.9, 152.5, 157.9 (C-2/C-4/C6). MS (E.I.): 388 (100, M^+), 355 (18), 340 (6), 326 (12), 311 (6), 297 (50), 243 (6), 140 (7), 91 (47). Hrms: found 388.1694, calc. for $C_{26}H_{20}N_4$ 388.1688.

*9-Benzyl-6-(α-ethoxyethenyl)-2-*trans*-(β-phenylethenyl)-9H-purine (4c).* 9-Benzyl-2,6-dichloro-9*H*-purine **2a** was reacted with (1-ethoxyvinyl)tributyltin at 70 °C for 4 h, before *trans*-phenylethenyl(tributyl)stannane was

added and the mixture stirred at 120 °C for 24 h. EtOAc-hexane (1:3) was used for flash chromatography. The product was crystallized from $CHCl_3$-hexane; yield 265 (69 %) colourless needles. M.p. 152 - 154 °C. (Found: C, 75.48; H, 5.75. Calc. for $C_{24}H_{22}N_4O$: C, 75.37; H, 5.80 %). ^1H NMR (C_6D_6, 500 MHz): δ 1.35 (t *J* 6.9 Hz, 3 H, CH_3), 3.80 (q, *J* 6.9 Hz, 2 H, CH_2), 4.72 (s, 2 H, CH_2), 4.89 (d, *J* 1.9 Hz, 1 H, CH=), 6.68 (d, *J* 1.9 Hz, 1 H, CH=), 6.8 - 7.1 (m, 8 H, Ph), 7.33 (s, 1 H, H-8), 7.3 - 7.4 (m, 2 H, Ph), 7.70 (d, *J* 15.9 Hz, 1 H, =CH-Pur), 8.43 (d, *J* 15.9 Hz, 1H, =CH-Ph). ^{13}C NMR (C_6D_6, 125 MHz): δ 14.7 (CH_3), 46.4 (CH_2N), 63.7 (CH_2O), 93.9 (CH_2=), 127.7 - 129.2 (CH in Ph and =CH-Pur), 129.6 (C-5), 136.2 (C in Ph), 136.9 (=CH-Ph), 137.1 (C in Ph), 144.2 (C-8), 152.5 (C-6), 153.5 (C-4), 157.4 (OC=), 159.3 (C-2). MS (E.I.): 382 (17, M^+), 367 (62), 338 (84), 321 (17), 292 (25), 247 (28), 91 (100).

*9-Benzyl-6-phenyl-2-(*trans*-β-phenylethenyl)-9H-purine (4d).* 9-Benzyl-2,6-dichloro-9*H*-purine **2a** was reacted with phenyl(tributyl)stannane at 70 °C for 24 h, before *trans*-phenylethenyl(tributyl)stannane was added and the mixture stirred at 120 °C for 24 h. EtOAc-hexane (1:4) was used for flash chromatography; yield 240 mg (62 %) colourless powdery crystals. M.p. 171 - 173 °C. (Found: C, 80.31; H, 5.13. Calc. for $C_{26}H_{20}N_4$: C, 80.39; H, 5.19 %). ^1H NMR ($CDCl_3$, 200 MHz): δ 5.46 (s, 2 H, CH_2), 7.3 - 7.7 (m, 9 H, Ph and CH=), 8.00 (s, 1 H, H-8), 8.14 (d, *J* 16.1 Hz, 1 H, CH=), 8.8 - 8.9 (m, 2 H, Ph). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 47.3 (CH_2), 126.9, 127.26, 127.34, 127.8, 127.9, 128.0, 128.1, 128.5, 128.8, 130.2, 134.8, 135.3, 135.8, 136.1, 143.2, 152.4, 153.6, 158.2. MS (E.I.): 388 (100, M^+), 377 (1), 362 (7), 297 (97), 255 (4), 91 (20).

2-Amino-9-benzyl-6-chloro-9H-purine (6a) and 2-amino-7-benzyl-6-chloro-7H-purine (6b). Potassium carbonate (2.49 g, 18 mmol) was added to a stirred solution of 2-amino-6-chloro-1*H*-purine **5** (1.027 g, 6.06 mmol) in dry DMF (50 ml) at ambient temperature under N_2. After 20 min, benzyl chloride (1.38 ml, 12 mmol) was added and the resulting mixture was stirred for 16 h, filtered and evaporated *in vacuo*. The products were separated by flash chromatography on silica gel eluting with $CHCl_3$-MeOH (20:1) followed by $CHCl_3$-MeOH (10:1).

2-Amino-9-benzyl-6-chloro-9H-purine (6a): Yield 1.147 g (73 %), colourless needles. M.p. 211 - 213 °C (Lit.[17a] 212 °C). ^1H NMR ($CDCl_3$, 200 MHz): δ 5.19 (br s, 2 H, NH_2), 5.29 (s, 2 H, CH_2), 7.3 - 7.4 (m, 5 H, Ph), 7.77 (s, 1 H, H-8). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 46.1 (CH_2), 123.2 (C-5), 127.1, 127.7 and 128.7 (CH in Ph), 136.6 (C in Ph), 143.2 (C-8), 149.5 (C-6), 154.1 (C-4), 159.9 (C-2). MS (E.I.): 261/259 (24/68, M^+), 91 (100).

2-Amino-7-benzyl-6-chloro-7H-purine (6b): Yield 234 mg (15 %), colourless prisms. M.p. dec. ca. 260 °C (Lit.[17a] >250 °C). ^1H NMR (DMSO-d_6, 200 MHz): δ 5.55 (s, 2 H, CH_2), 6.66 (br s, 2 H, NH_2), 7.1 (m, 2 H, Ph), 7.3 (m, 3 H, Ph), 8.55 (s, 1 H, H-8). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 49.0 (CH_2), 113.9 (C-5), 125.4, 126.7 and 127.7 (CH in Ph), 136.0 (C in Ph), 141.2 (C-6), 148.7 (C-8), 158.7 (C.2), 161.3 (C-4). MS (E.I.): 261/259 (13/40, M^+), 91 (100).

9-Benzyl-6-chloro-2-iodo-9H-purine (7). To a stirred solution of 2-amino-9-benzyl-6-chloro-9*H*-purine **6a** (1.131 g, 4.36 mmol) in dry THF (50 ml) at ambient temperature under N_2 was added copper(I) iodide (872 mg, 4.58 mmol), iodine (1.107 g, 4.36 mmol), diiodomethane (3.6 ml, 44.7 mmol) and isopentyl nitrite (1.8 ml, 13.4 mmol). The resulting mixture was heated at reflux for 75 min, cooled, filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography eluting with EtOAc-hexane (1:6) and (1:3) to remove iodine, and the product was eluted with EtOAc-hexane (2:3); yield 1.077 g (67 %), colourless prisms. M.p. 145 - 146 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 5.42 (s, 2 H, CH_2), 7.3 - 7.4 (m, 5 H, Ph), 8.01 (s, 1 H, H-8). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 47.9 (CH_2), 116.6 (C-2), 127.9, 128.8 and 129.1 (CH in Ph), 131.3 (C-5), 133.9 (C in Ph), 144.9 (C-8), 150.2, 152.5 (C-4/C-6). MS (E.I.): 373/372/371/370 (2/13/13/41, M^+), 369 (21), 293 (3), 279 (1), 252 (4), 243 (18), 207 (18), 127 (19), 91 (100), 65 (23). Hrms: found 369.9488, calc. for $C_{12}H_8ClIN_4$ 369.9482.

*9-Benzyl-2-bromo-6-chloro-9*H*-purine (8).* To a stirred solution of 2-amino-9-benzyl-6-chloro-9*H*-purine **6a** (400 mg, 1.54 mmol) in dry THF (10 ml) at ambient temperature under N_2 was added copper(I) bromide (287 mg, 2.00 mmol), bromine (310 mg, 1.94 mmol), bromoform (1.8 ml, 20 mmol) and isopentyl nitrite (0.8 ml, 5.9 mmol). The resulting mixture was heated at 50 °C for 20 h, cooled, filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography eluting with EtOAc-hexane (1:2); yield 222 mg (45 %). M.p. 160 - 162 °C. (Found: C, 44.38; H, 2.37. Calc. for $C_{12}H_8BrClN_4$: C, 44.54; H, 2.49 %). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.42 (s, 2 H, CH_2), 7.2 - 7.4 (m, 5 H, Ph), 8.03 (s, 1 H, H-8). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 48.0 (CH_2), 89.9, 127.9, 128.9, 129.2, 130.8, 133.9, 143.0, 145.3, 151.2. MS (E.I.): 324 (37, M^+), 243 (14), 91 (100), 65 (23).

*Coupling of 9-Benzyl-6-chloro-2-iodo-9*H*-purine (7) with organostannanes.* A mixture of 9-benzyl-6-chloro-2-iodo-9*H*-purine **7** (185 mg, 0.5 mmol), tetrakis[tri(2-furyl)phosphine]palladium (0) [generated *in situ* from tris(dibenzylideneacetone)dipalladium chloroform adduct (13 mg, 0.013 mmol) and tri(2-furyl)phosphine (23 mg, 0.10 mmol)] and organostannane (0.6 mmol) in dry DMF (3 ml) was heated under N_2 at the temperatures and for the times given below and evaporated *in vacuo*. The residue was dissolved in MeCN (30 ml) and washed with hexane (6 x 10 ml). The MeCN phase was evaporated *in vacuo* and the product purified by flash chromatography on silica gel.

*9-Benzyl-6-chloro-2-phenylethynyl-9*H*-purine (9a).* 9-Benzyl-6-chloro-2-iodo-9*H*-purine **7** (169 mg, 0.46 mmol) and phenylethynyl(tributyl)stannane (0.19 ml, 0.55 mmol) were heated at 40 °C for 2 h as described above. EtOAc-hexane (2:3) was used for flash chromatography; yield 126 mg (79 %) colourless nedles. M.p. 185 - 186 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.47 (s, 2 H, CH_2), 7.3 - 7.4 (m, 8 H, Ph), 7.7 (m, 2 H, Ph), 8.08 (s, 1 H, H-8). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 47.8 (CH_2), 87.6 and 87.9 (C≡), 121.2 (C in Ph), 128.0, 128.4, 128.9, 129.3, 129.7 (CH in Ph), 130.5 (C-5), 132.6 (CH in Ph), 134.3 (C in Ph), 145.7 (C-8), 146.0, 150.9, 151.9 (C-2/C-4/C-6). MS (E.I.): 346/344 (41/100, M^+), 309 (12), 267 (6), 253 (2), 226 (4), 182 (12), 127 (7), 91 (98), 65 (12). Hrms: found 344.0832, calc. for $C_{20}H_{13}ClN_4$ 344.0829.

*9-Benzyl-6-chloro-2-ethenyl-9*H*-purine (9b).* 9-Benzyl-6-chloro-2-iodo-9*H*-purine **7** and ethenyl(tributyl)-stannane were heated at 40 °C for 1 h as described above. 1,2-Dichloroethanewas used for flash chromatography; yield 112 mg (83 %) colourless nedles. M.p. 139 - 142 °C. (Found: C, 62.19; H, 4.24. Calc. for $C_{14}H_{11}ClN_4$: C, 62.11; H, 4.10 %). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.44 (s, 2 H, CH_2), 5.76 (dd, *J* 10.3 and 1.9 Hz, 1H, CH=), 6.69 (dd, *J* 17.3 and 1.9 Hz, 1H, CH=), 6.93 (dd, *J* 17.3 and 10.3 Hz, 1H, CH=), 7.3 - 7.4 (m, 5H, Ph), 8.03 (s, 1H, H-8). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 47.6 (CH_2), 124.1, 128.0, 128.7, 129.2, 129.9, 134.7, 135.4, 144.8, 150.6, 152.3, 159.0. MS (E.I.): 272/270 (57/22, M^+), 269 (41), 235 (7), 193 (7), 165 (6), 149 (15), 91 (100), 65 (17).

*9-Benzyl-6-chloro-2-*trans*-(β-phenylethenyl)-9*H*-purine (9c).* 9-Benzyl-6-chloro-2-iodo-9*H*-purine **7** and *trans*-phenylethenyl(tributyl)stannane were heated at 60 °C for 5 h as described above. 1,2-Dichloroethanewas used for flash chromatography; yield 113 mg (65 %) colourless nedles. M.p. 187 - 190 °C. (Found: C, 69.26; H, 4.49. Calc. for $C_{20}H_{15}ClN_4$: C, 69.26; H, 4.36 %). ^{1}H NMR ($CDCl_3$, 200 MHz): 5.43 (s, 2 H, CH_2), 7.27 (d, *J* 16.0 Hz, 1H, CH=), 7.3 - 7.4 (m, 8H, Ph), 7.6 (m, 2H, Ph), 7.99 (s, 1H, H-8), 8.03 (d, *J* 16.0 Hz, 1H, CH=). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 47.6 (CH_2), 126.4, 127.6, 127.9, 128.71, 128.73, 129.1, 129.2, 129.5, 134.8, 135.8, 138.4, 144.7, 150.6, 152.4, 159.6. MS (E.I.): 346 (97, M^+), 311 (11), 279 (11), 255 (52), 167 (20), 149 (54), 91 (100), 65 (21), 55 (24).

*9-Benzyl-6-chloro-2-(α-ethoxyethenyl)-9*H*-purine (9d).* 9-Benzyl-6-chloro-2-iodo-9*H*-purine **7** and (1-ethoxy-vinyl)tributyltin were heated at 60 °C for 16 h as described above except that bis(triphenyl-phosphine)palladium(II) chloride (18 mg, 0.025 mmol) was used as catalyst. EtOAc-acetone-hexane (1:2:9)

was used for flash chromatography; yield 119 mg (76 %) colourless powdery crystals. M.p. 114 - 117 °C. (Found: C, 60.85; H, 4.92. Calc. for $C_{16}H_{15}ClN_4O$: C, 61.05; H, 4.80 %). ^1H NMR ($CDCl_3$, 200 MHz): δ 1.51 (t, *J* 7.0 Hz, 3 H, CH_3), 4.06 (q, *J* 7.0 Hz, 2 H, CH_2), 4.67 (d, *J* 2.1 Hz, 1 H, CH=), 5.46 (s, 2 H , CH_2), 5.75 (d, *J* 2.1 Hz, 1H, CH=), 7.3 - 7.5 (m, 5 H, Ph), 8.05 (s, 1 H, H-8). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.5 (CH_3), 47.8 (CH_2Ph), 64.2 (CH_2O), 90.5 (CH_2=), 127.8, 128.4, 128.8 (CH in Ph), 129.9 (C-5), 134.2 (C in Ph), 144.8 (C-8), 150.1, 151.7, 155.7, 156.4 (C-2/C-4/C-6/OC=). MS (E.I.): 316/314 (3/10, M^+), 299 (48), 285 (7), 270 (29), 244 (8), 91 (100), 65 (14).

9-Benzyl-6-chloro-2-(2-thienyl)-9H-purine (9e). 9-Benzyl-6-chloro-2-iodo-9*H*-purine **7** and 2-(tributylstannyl)thiophene were heated at 60 °C for 2 h as described above. EtOAc-$CHCl_3$-hexane (1:3:3) was used for flash chromatography; yield 131 mg (80 %) colourless powdery crystals. M.p. 163 - 165 °C. (Found: C, 58.81; H, 3.43. Calc. for $C_{16}H_{11}ClN_4S$: C, 58.80; H, 3.39 %). ^1H NMR ($CDCl_3$, 200 MHz): δ 5.38 (s, 2 H, CH_2), 7.11 (m, 1 H, H-4') 7.3 - 7.4 (m, 5 H, Ph), 7.42 (m, 1 H), 7.96 (s, 1 H, H-8), 8.02 (m, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 47.8 (CH_2), 125.8, 128.15, 128.21, 128.7, 129.2, 129,4, 130.0, 134.7, 142.3, 144.5, 150.8, 152.3, 156.0. MS (E.I.): 326 (67, M^+), 291 (5), 249 (3), 182 (8), 121 (4), 91 (100), 65 (13).

9-Benzyl-6-chloro-2-(2-furyl)-9H-purine (9f). 9-Benzyl-6-chloro-2-iodo-9*H*-purine **7** (167 mg, 0.45 mmol) and 2-(tributylstannyl)furan (0.17 ml, 0.54 mmol) were heated at 60 °C for 3 h as described above. EtOAc-hexane (1:2) followed by EtOAc-hexane (2:3) was used for flash chromatography; yield 113 mg (81 %) colourless powdery crystals. M.p. 145 - 146 °C. (Found: C, 61.22; H, 3.47. Calc. for $C_{16}H_{11}ClN_4O$: C, 61.84; H, 3.57 %). ^1H NMR ($CDCl_3$, 200 MHz): δ 5.47 (s, 2 H, CH_2), 6.59 (m, 1 H, H-4'), 7.3 - 7.4 (m, 6 H, Ph and H-3'), 7.65 (m, 1H, H-2'), 8.00 (s, 1 H, H-8). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 47.5 (CH_2), 112.2, 113.8 (C-3'/C-4'), 127.9, 128.5, 129.0 (CH in Ph), 129.3 (C-5), 134.5 (C in Ph), 144.8, 145.0 (C-8/C-5'), 150.8, 151.1, 151.9, 152.2 (C-2/C-4/C-6/C-2'). MS (E.I.): 313/312/311/310 (3/22/20/63, M^+), 309 (29), 285 (4), 275 (4), 233 (3), 219 (4), 192 (3), 182 (6), 167 (2), 154 (2), 140 (3), 91 (100), 65 (18). Hrms: found 310.0608, calc. for $C_{16}H_{11}ClN_4O$ 310.0621.

9-Benzyl-6-chloro-2-(2-pyridyl)-9H-purine (9g). 9-Benzyl-6-chloro-2-iodo-9*H*-purine **7** and 2-(trimethylstannyl)pyridine were heated at 65 °C for 22 h as described above, except that dichloroethane was used as solvent. EtOAc-hexane (2:3) followed by EtOAc were used for flash chromatography; yield 117 mg (73 %) pale yellow needles. M.p. 154 - 155 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 5.58 (s, 2 H, CH_2), 7.3 - 7.6 (m, 6 H, Ph and Pyr), 7.8 - 7.9 (m, 1 H, Pyr), 8.07 (s, 1 H, H-8), 8.59 (d, *J* 8.0 Hz, 1 H, Pyr), 8.88 (d, *J* 4.2, 1 H, Pyr). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 47.9 (CH_2), 124.2 and 124.8 (CH in Pyr), 128.1, 128.8, 129.2 (CH in Ph), 130.8 (C-5), 134.5 (C in Ph), 137.0 (CH in Pyr), 145.6 (C-8), 150.1 (CH in Pyr), 151.5, 152.7, 153.9, 158.1 (C-2/C-4/C-6/C in Pyr). MS (E.I.): 324/323/322/321 (1/16/39/41, M^+), 310 (100), 285 (5), 259 (2), 244 (6), 230 (4), 195 (3), 182 (8), 168 (4), 105 (3), 91 (69), 65 (22). Hrms: found 321.0760, calc. for $C_{17}H_{12}ClN_5$ 321.0781.

9-Benzyl-6-chloro-2-phenyl-9H-purine (9h). 9-Benzyl-6-chloro-2-iodo-9*H*-purine **7** and phenyl(tributyl)-stannane were heated at 60 °C for 24 h as described above. EtOAc-$CHCl_3$-hexane (1:3:6) was used for flash chromatography, and the product was crystallized from $CHCl_3$-hexane, yield 115 mg (73 %) colourless needles. M.p. 158 - 160 °C. (Found: C, 67.14; H, 3.43. Calc. for $C_{18}H_{13}ClN_4$: C, 67.40 ; H, 4.08 %). ^1H NMR ($CDCl_3$, 200 MHz): δ 5.45 (s, 2 H, CH_2), 7.3 - 7.4 (m, 5 H, Ph), 7.4 - 7.5 (m, 3 H, Ph), 8.01 (s, 1 H, H-8), 8.5 - 8.6 (m, 2 H, Ph). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 48.0 (CH_2), 127.4 , 127.8, 127.9, 128.1, 128.5 and 129.2 (CH in Ph), 130.1 (C-5), 134.1 and 135.8 (C in Ph), 144.0 (C-8), 150.0, 151.7, 158.3 (C-2/C-4/C-6). MS (E.I.): 320 (85, M^+), 293 (5), 285 (7), 243 (6), 182 (12), 91 (100), 77 (5), 65 (12).

Coupling of 9-Benzyl-2-bromo-6-chloro-9H-purine (8) with organostannanes. A mixture of 9-benzyl-2-bromo-6-chloro-9*H*-purine **8** (185 mg, 0.5 mmol), tetrakis[tri(2-furyl)phosphine]palladium (0) [generated *in*

situ from tris(dibenzylideneacetone)dipalladium chloroform adduct (13 mg, 0.013 mmol) and tri(2-furyl)phosphine (23 mg, 0.10 mmol)] and organostannane (0.6 mmol) in dry DMF (3 ml) was heated under N_2 at the temperatures and for the times given below and evaporated *in vacuo*. The residue was dissolved in MeCN (30 ml) and washed with hexane (6 x 10 ml). The MeCN phase was evaporated *in vacuo* and the product purified by flash chromatography on silica gel.

9-Benzyl-6-chloro-2-(α-ethoxyethenyl)-9H-purine (9d). 9-Benzyl-2-bromo-6-chloro-9*H*-purine **8** and (1-ethoxyvinyl)tributyltin were heated at 50 °C for 5 h as described above. Yield 76 %.

9-Benzyl-6-chloro-2-phenyl-9H-purine (9h). 9-Benzyl-2-bromo-6-chloro-9*H*-purine **7** and phenyl(tributyl)-stannane were heated at 60 °C for 24 h as described above. Yield 80 %.

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