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6-Halopurines in Palladium-Catalyzed Coupling with Organotin and Organozinc Reagents

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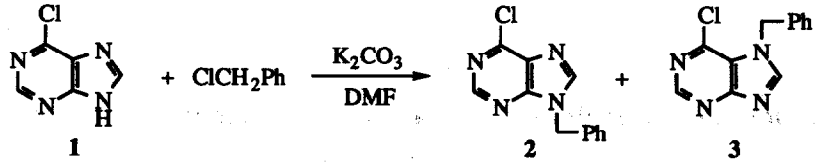
Abstract: *N*-9 and *N*-7 benzylated 6-halopurines readily participate in palladium catalyzed cross coupling reactions with organotin and organozinc derivatives. In most instances the 6-chloropurines can be used. Organostannanes are excellent reagents for the introduction of alkenyl and aryl substituents, but organozinc compounds are the reagents of choice for the introduction of alkyl groups.

We recently reported that 6-chloropurines participate in palladium catalyzed cross coupling reactions with organostannanes, allowing smooth introduction of alkenyl- and aryl substituents in the purine 6-position.[1] No protection of the relatively acidic purine ring *NH* function was required. This reaction, the so called Stille reaction,[2] has been extensively applied for carbon - carbon bond formation in heterocycles,[3] but the reaction has received little attention in purine chemistry. Apart from the work described above, coupling of *N*-9 alkylated 2-iodopurines has been studied[4] and recently a few examples of *N*-9 alkylated 6-iodo- and 8-bromopurines as substrates appeared.[4e] Our finding that readily available 6-chloropurines are reactive enough to participate in Stille type reactions and the fact that diverse biological effects are reported for modified purine nucleosides, led us to explore the reactivity of *N*-alkylated 6-chloropurines in palladium catalyzed cross couplings.

We herein report on the reactivity of both *N*-9 and *N*-7 benzylated 6-chloropurines in the Stille reaction. Furthermore, we report, to the best of our knowledge, the first examples of couplings between halopurines and organozinc reagents.

RESULTS AND DISCUSSION

6-Chloropurine **1**[5] was *N*-alkylated with benzyl chloride in the presence of potassium carbonate. DMF was the solvent of choice (Scheme 1).

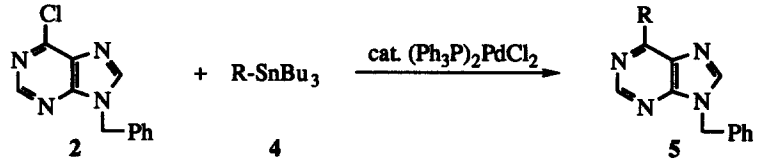


1 2 3

Scheme 1

Both the *N*-9 and *N*-7 benzylated isomers were formed with the latter as the minor isomer. The ^{1}H NMR spectrum of the crude product showed the isomer distribution to be 2 : 3; 7 : 3, and the products **2** and **3** were isolated in 66 % and 25 % yields, respectively, by flash chromatography. The yield of the *N*-9 benzylated isomer **2** was higher than previously reported when DMSO[6] or DMA[7] have been employed as solvent. In contrast to *N*-benzylation of 6-chloropurine under Mitsunobu conditions,[8] no *N*-3 alkylated product was formed as judged by ^{1}H NMR of the crude product.

9-Benzyl-6-chloropurine **2** was coupled with a number of organostannanes **4** (Scheme 2, Table 1). Bis(triphenylphosphine)palladium(II) chloride was found to be a suitable catalyst, and in most cases, DMF was the preferred solvent.



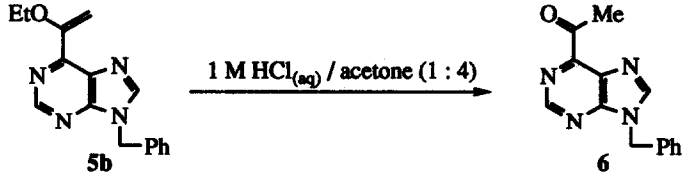
2 4 5

Scheme 2

High yields (75 - 87 %) of alkenyl- and arylpurines **5a** - **5e** were obtained when the reaction mixtures were heated to 80 - 110 °C. In the reaction with the styryltin reagent **4c**, a 8 : 92 mixture of *cis*- and *trans* organostannane was employed, but only the *trans* coupling product **5c** was formed as judged by ^{1}H NMR of the crude product.

Alkenyl- and aryltin reagents generally display high reactivity in Stille type reactions, but the transfer of sp^3-carbons are known to be much less feasible.[2] The benzyltin reagent **4f** participated in the coupling reaction to give 6,9-dibenzylpurine **5f** in 48 % yield when the reaction was carried out in refluxing DMF and the even less reactive tetrabutyltin **4g** gave 18 % of the *n*-butylpurine **5g** under the same reaction conditions.

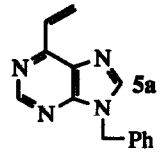
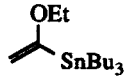
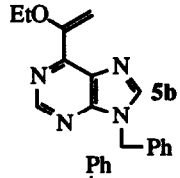
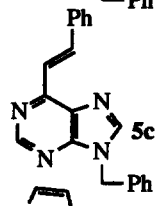
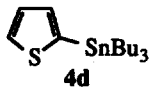
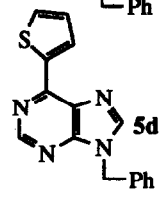
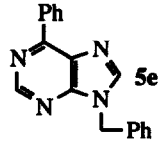
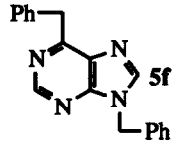
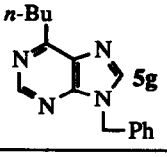
The enol ether **5b** was hydrolyzed under mild conditions to give the corresponding ketone **6** in 88 % yield (Scheme 3). This reaction sequence constitutes a convenient method for the introduction of an acyl group in the purine 6-position.



5b 6

Scheme 3

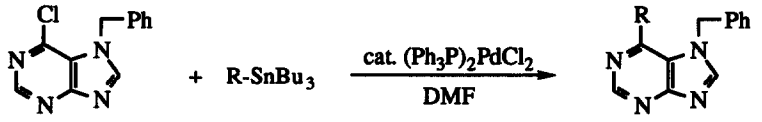
Table 1. Palladium Catalyzed Coupling of 9-Benzyl-6-chloropurine with Organostannanes.

Stannane 4	Solvent	Temp. (°C)	Time (h)	Product 5	Yield (%)
 **4a**	DCE	Δ	3.5	 **5a**	87
 **4b**	DMF	100	4.5	 **5b**	81
$PhCH{=}CHSnBu_3$ **4c**	DMF	100	24	 **5c**	76
 **4d**	DMF	100	16	 **5d**	87
$PhSnBu_3$ **4e**	DMF	110	7.0	 **5e**	75
$PhCH_2SnBu_3$ **4f**	DMF	Δ	18	 **5f**	48
Bu_4Sn **4g**	DMF	Δ	21	 **5g**	18

N-7 alkylated purines have received much less attention than their *N*-9 alkylated isomers due to the similarity of 9-alkylpurines with naturally occurring nucleosides, but very recently, high antiviral activity of an *N*-7 alkylated purine derivative was reported.[9] Both 9- and 7-benzylated 6-chloropurines have been reacted with a number of oxygen-, nitrogen-, and sulfur nucleophiles in substitution reactions, but no

consistent or significant differences in reactivity were noted.[6a] To our knowledge, there are no reports on transition metal catalyzed cross coupling of *N*-7 alkylated halopurines with organometallic reagents.

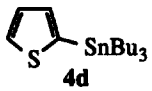
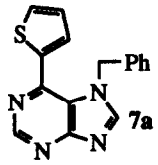
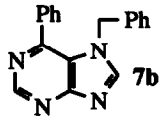
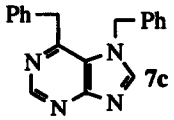
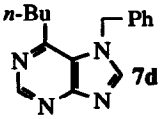
We subjected 7-benzyl-6-chloropurine **3** to the same set of reaction conditions as described above for the *N*-9 alkylated isomer **2** (Scheme 4, Table 2).



3 **4** **7**

Scheme 4

Table 2. Palladium Catalyzed Coupling of 7-Benzyl-6-chloropurine with Organostannanes.

Stannane **4**	Temp. (°C)	Time (h)	Product **7**	Yield (%)
 **4d**	100	16	 **7a**	90
$PhSnBu_3$ **4e**	110	4.0	 **7b**	93
$PhCH_2SnBu_3$ **4f**	Δ	4.0	 **7c**	62
Bu_4Sn **4g**	Δ	3.5	 **7d**	65[a]

a) 7-Benzylpurine[8] was also formed.

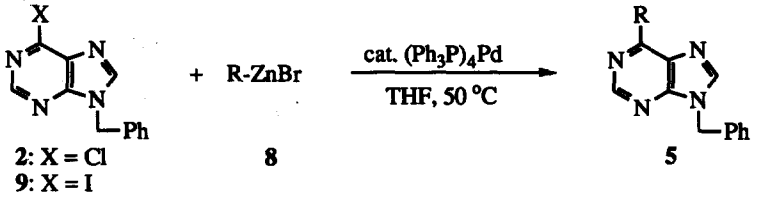
In all cases examined, the coupling with organostannanes **4** occurred more readily with the 7-substituted purine **3** than with the 9-substituted isomer **2**, and the 6-substituted products **7** were isolated in higher yields compared to couplings with the purine **2**. Especially, the reactivity towards tetrabutyltin is noteworthy. 7-Benzyl-6-*n*-butylpurine **7d** was isolated in 65 % yield after reflux in DMF for just 3.5 h. Some reduction of the chloropurine **3** accompanied this reaction.

Even though the 6-position in the *N*-7 benzylated purine **3** was believed to be more sterically hindered than the 6-position in the isomer **2**, this appeared to have no significant effect on the reactions with the organostannanes examined. An electron deficient purine 6-position should favor attack of Pd(0).[10] The dipole moments of the purines **2** and **3** have been measured in dioxane and the value for the 7-substituted compound **3** is higher than for the isomer **2**.[11] The difference between the two isomers is, however, small compared to calculated dipole moments for the 9-H and 7-H tautomers of purine.[12] Calculations of electron densities in purines indicate that the 9-H tautomer of purine is more π-electron deficient in the 6-position than the 7-H tautomer, and that the latter is more σ-electron deficient in the 6-position.[12] The same trends are reported for 7-methyl- and 9-methylpurine.[13] Determining the factors controlling the relative reactivity of the purines **2** and **3** in the Stille reaction is also complicated by the fact that the exact nature of the purine-palladium complexes involved in the reaction are not known. Addition of chlorodiazines to palladium(0) species give different amounts of mononuclear and binuclear complexes depending on the steric and electronic effects influencing the ligating abilities of the heterocyclic nitrogen atoms.[14]

Having shown Pd-catalyzed coupling of chloropurines **2** and **3** with alkenyl- and arylpurines to be an excellent method for the introduction of unsaturated carbon substituents into the purine 6-position, we were searching for a more convenient way of introducing simple alkyl substituents. 6-Alkylpurines are of biological interest, for instance high cytotoxic activity are reported for 6-methyl-9-β-D-ribofuranosyl-purine,[15] and 6-(2-phenetyl)purine exhibits cytokinin activity comparable to kinetin.[16]

Organozinc reagents are known to transfer alkyl groups more readily than organostannanes. These reagents generally promote rapid palladium catalyzed cross coupling, and competing side reactions, like β-hydride elimination of alkyl groups from the palladium complexes, are often minimized.[17] High chemo-regio- and stereoselectivity have been obtained in cross coupling reactions employing this class of compounds and they are known to tolerate a wide variety of functional groups in either or both coupling partners.[18] Successful *C-C* bond formations in the pyrimidine 2- and 4-position employing organozinc derivatives and palladium catalysis have been reported,[19] but to our knowledge, the same technique has never been applied in purine chemistry.

9-Benzyl-6-chloropurine **2** was reacted with a variety of organozinc reagents **8** in the presence of tetrakis(triphenylphosphine)palladium(0) at 50 °C in THF (Scheme 5, Table 3). No reaction took place at ambient temperature or without catalyst.



2: X = Cl
9: X = I

8

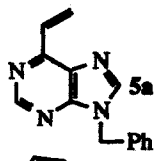
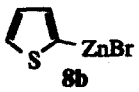
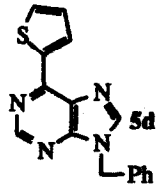
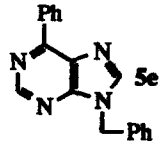
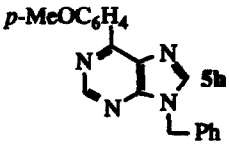
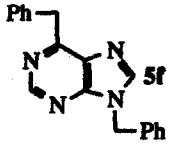
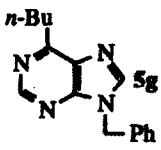
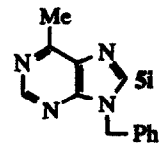
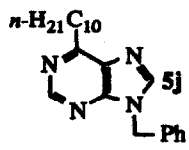
5

Scheme 5

The organozinc derivatives **8** were generated *in situ* from the corresponding lithium- or Grignard reagents and zinc bromide. The chloropurine **2** reacted with phenyl- benzyl- and alkylzinc reagents to give coupling products **5** in high yields (77 - 91 %). The reaction appeared to be excellent for the introduction of unreactive alkyl substituents into the purine 6-position. This is in contrast to the Stille reaction where only a low yield of the 6-butylpurine **5g** was obtained after prolonged reflux in DMF.

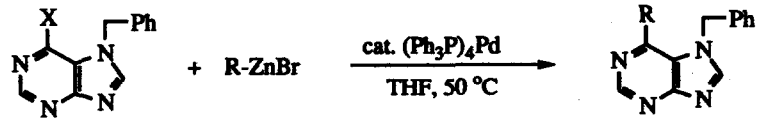
Work-up and purification of the coupling products were simpler when organozinc derivatives were used compared to organostannanes. The by-products formed in the reactions with the zinc reagents are water soluble zinc salts, whereas complete removal of tributyltin halides formed in Stille reactions can be quite tedious. The use of organozinc reagents instead of organostannanes also avoids the presence of toxic stannyl compounds.

Table 3. Palladium Catalyzed Coupling of 9-Benzyl-6-halopurines with Organozinc derivatives.

R-ZnBr 8	Halopurine	Time (h)	Product 5	Yield (%)
8a	9	2.0	 5a	62
 8b	9	2.0	 5d	78
PhZnBr 8c	2	0.25	 5e	77
 8d	2	16	 5h	82
$PhCH_2ZnBr$ 8e	2	1.0	 5f	91
n-BuZnBr 8f	2	3.0	 5g	84
MeZnBr 8g	2	0.5	 5i	90
$n\text{-}C_{10}H_{21}ZnBr$ 8h	2	16	 5j	83

Coupling of the 6-chloropurine 2 with vinyl- and 2-thienylzinc bromide on the other hand, resulted in complex mixtures where only traces of the desired products could be detected. Switching to 9-benzyl-6-iodopurine 9[7] as substrate, allowed coupling with vinyl- and thienylzinc reagents. The use of a more reactive halopurine apparently speeded up the desired coupling and suppressed unwanted side reactions. The rate of oxidative addition of a Pd(0) complex to an aryl halide is generally Ar-I>Ar-Br>Ar-Cl,[2b,20] and when reactive transmetallation reagents, like organozinc derivatives, are employed, it is likely that the oxidative addition of Pd(0) is the rate determining step.[21]

Coupling of organozinc reagents 8 with 7-benzyl-6-chloropurine 3 were also investigated (Scheme 6, Table 4).



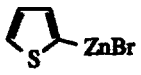
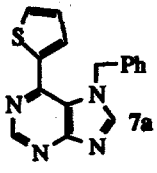
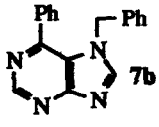
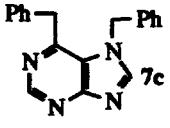
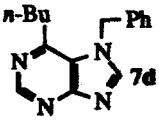
3: X = Cl
10: X = I

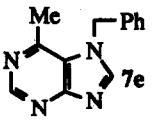
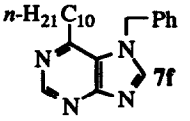
8

7

Scheme 6

Table 4. Palladium Catalyzed Coupling of 7-Benzyl-6-halopurines with Organozinc derivatives.

R-ZnBr 8	Halopurine	Time (h)	Product 7	Yield (%)
 8b	10	2.0	 7a	60
PhZnBr 8c	3	0.5	 7b	84
$PhCH_2ZnBr$ 8e	3	2.5	 7c	82
n-BuZnBr 8f	3	2.0	 7d	24[a]
8f	10	0.5	7d	33[b]

R-ZnBr **8**	Halopurine	Time (h)	Product **7**	Yield (%)
MeZnBr **8g**	**3**	1.0	 **7e**	73
n-$C_{10}H_{21}$ZnBr **8h**	**3**	2.0	 **7f**	20[c]

a) 7-Benzylpurine,[8] 54 % was formed. b) 7-Benzylpurine,[8] 56 % was formed.
c) 7-Benzylpurine,[8] 50 % was formed.

In the reactions with phenyl- benzyl- and methylzinc bromide, only slightly lower reactivity was noted and the coupling products **7** could still be isolated in high yields (73 - 84 %). Reaction with the less stable thienylzinc reagent **8b** required the more reactive 6-iodopurine **10**,[8] which was prepared in 85 % yield from the corresponding chloropurine **3** using the same procedure as for the preparation of the iodopurine **9**.[7]

Employing n-butyl- and n-decylzinc bromide, reagents with hydrogen in the β-position, resulted in low yields of the desired products **7d** and **7f**. β-Hydride elimination probably took place, which led to reduction of the chloropurine **3**. A substantial amount of 7-benzylpurine[8] was isolated. These results are in sharp contrast to the results of the coupling between the same organozinc species **8f** and **8h** and the 9-alkylated purine **2** where the desired cross coupling products **5g** and **5j** were isolated in more than 80 % yields (Table 3). The yields of the cross coupling products **7d** and **7f** were not significantly improved when the more reactive iodopurine **10** was used. In fact, the n-butylpurine **7d** was prepared in a higher yield employing the Stille reaction (Table 2).

In summary, we have shown that N-9 and N-7 benzylated 6-halopurines readily participate in palladium catalyzed cross coupling reactions with organotin and organozinc derivatives. In most instances, the 6-chloropurines can be used. Organostannanes are excellent reagents for the introduction of alkenyl and aryl substituents, but organozinc compounds are generally the reagents of choice for the introduction of alkyl groups. The low toxicity of the zinc species and the simple work-up procedures involved when these reagents are used, also make organozinc derivatives extremely attractive reagents for carbon-carbon bond formation in purines.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded at 300 MHz with a Varian XL-300 (manual) or at 200 MHz with a Varian Gemini 200 instrument. The ^{13}C NMR spectra were recorded at 75 or 50 MHz using the above mentioned instruments. Mass spectra were recorded at 70 eV ionizing voltage and are presented as *m/z* (% rel. int.). THF was distilled from sodium / benzophenone, dichloroethane from calcium hydride and DMF from barium oxide. 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. 6-Chloropurine,[5] 9-benzyl-6-iodopurine,[7] styryl(tributyl)tin,[22] 2-thienyl(tributyl)tin[23] and benzyl(tributyl)tin[24] were prepared according to literature procedures. All other reagents were commercially available and used as received.

9-Benzyl-6-chloropurine (2) and 7-Benzyl-6-chloropurine (3). Potassium carbonate (4.145 g, 30 mmol) was added to a stirring solution of 6-chloropurine (1.545 g, 10 mmol) in dry DMF (75 ml) at ambient temperature under N_2. After 20 min. benzyl chloride (1.75 ml, 15 mmol) was added, the resulting mixture was stirred for 22 h, filtered and evaporated. The isomers were separated by flash chromatography on silica gel using EtOAc/hexane [2:1 followed by 3:1] for elution.

9-Benzyl-6-chloropurine (2). Yield 1.613 g (66 %) colourless needles. M.p. 86-87 °C (Lit.[6] 86-87 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.47 (s, 2H), 7.3-7.4 (m, 5H), 8.11 (s, 1H, H-8), 8.80 (s, 1H, H-2). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 48.2 (CH_2), 127.3, 128.2 and 128.6 (CH in Ph), 130.5 (C-5), 133.7 (C in Ph), 144.2 (C-8), 150.1 (C-6), 150.9 (C-4), 151.3 (C-2). MS (EI): 246/244 (51/17, M^+), 91 (100).

7-Benzyl-6-chloropurine (3): Yield 611 mg (25 %) colourless needles. M.p. 153-154 °C (Lit.[6] 152-153 °C). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 5.75 (s, 2H), 7.1-7.2 (m, 2H, Ph), 7.3-7.4 (m, 3H, Ph), 8.81 (s, 1H, H-8), 9.00 (s, 1H, H-2). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 49.3 (CH_2), 121.2 (C-5), 125.6, 127.0 and 127.9 (CH in Ph), 135.7 (C in Ph), 141.2 (C-6), 150.2 (C-8), 150.7 (C-2), 160.5 (C-4). MS (EI): 246/244 (33/11, M^+), 91 (100).

Coupling of chloropurines (2) and (3) with organostannanes (4). A mixture of chloropurine **2** or **3** (245 mg, 1.0 mmol), bis(triphenylphosphine)palladium(II) chloride (35 mg, 0.05 mmol) and organostannane **4** in dry DMF (2 ml) was heated under N_2 at the temperatures and for the times given in Tables 1 and 2, and evaporated. A sat. solution of potassium fluoride in methanol (20 ml) was added to the residue, the resulting mixture stirred at ambient temperature for ca. 4 h and evaporated 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-6-vinylpurine (5a). Compound **5a** was prepared from 9-benzyl-6-chloropurine **2** and tributyl(vinyl)tin **4a** (1.4 mmol) as described above. Dichloroethane (3 ml) was used as solvent. EtOAc/acetone/hexane (1:2:3) was used for flash chromatography; yield 207 mg (87 %) colourless powdery crystals. M.p. 76-79 °C. (Found: C, 70.84; H, 5.17. Calc. for $C_{14}H_{12}N_4$: C, 71.17 H, 5.12 %). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.37 (s, 2H), 5.88 (dd, *J* 10.8 and 1.8 Hz, 1H), 6.96 (dd, *J* 17.5 and 1.8 Hz, 1H), 7.2-7.3 (m, 6H), 7.97 (s, 1H), 8.87 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.1, 126.3, 127.7, 128.4, 129.0, 130.8, 132.0, 135.0, 144.2, 152.0, 152.5, 153.5. MS (EI): 236 (98, M^+), 235 (100), 220, (2), 209 (8), 208 (8), 182 (2), 159 (7), 145 (7), 91 (82), 65 (18).

9-Benzyl-6-(α-ethoxyvinyl)purine (5b). Compound **5b** was prepared from 9-benzyl-6-chloropurine **2** and ethoxyvinyl(tributyl)tin **4b** (1.5 mmol) as described above. EtOAc/acetone/hexane (2:4:7) was used for flash chromatography; yield 227 mg (81 %) colourless powdery crystals. M.p. 112-115 °C. (Found: C, 68.85; H, 5.92. Calc. for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75 %). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.53 (t, *J* 7.0 Hz, 3H), 4.11 (q, *J* 7.0 Hz, 2H), 4.97 (d, *J* 2.5 Hz, 1H), 5.47 (s, 2H), 6.15 (d, *J* 2.5 Hz, 1H), 7.3-7.4 (m, 5H), 8.07 (s, 1H), 9.06 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0, 46.9, 63.4, 94.4, 127.5, 128.2, 128.8, 130.0, 134.8, 144.2, 151.7, 151.98, 152.02, 155.1. MS (EI): 280 (9, M^+), 265 (31), 236 (75), 209 (8), 189 (11), 168 (5), 147 (4), 145 (24), 91 (100), 65 (15).

9-Benzyl-6-(trans-β-styryl)purine (5c). Compound **5c** was prepared from 9-benzyl-6-chloropurine **2** and styryl(tributyl)tin **4c** (1.5 mmol) as described above. EtOAc/hexane (2:1) was used for flash chromatography; yield 240 mg (76 %) colourless powdery crystals. M.p. 132-134 °C. (Found: C, 76.82; H, 5.12. Calc. for $C_{20}H_{16}N_4$: C, 76.90; H, 5.16 %). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.44 (s, 2H), 7.3-7.4 (m, 8H), 7.7-7.8 (m, 3H), 8.05 (s, 1H), 8.42 (d, *J* 16.2, 1H), 8.96 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.8, 122.3, 127.8, 127.9, 128.5, 128.8, 129.1, 129.4, 130.9, 135.1, 136.0, 139.9, 143.9, 151.9, 152.6, 153.8. MS (EI): 312 (55, M^+), 311 (100), 221 (28), 168 (1), 156 (1), 140 (8), 128 (6), 115 (10), 104 (3), 91 (49).

9-Benzyl-6-(2-thienyl)purine (5d). Compound **5d** was prepared from 9-benzyl-6-chloropurine **2** and 2-thienyl(tributyl)tin **4d** (1.5 mmol) as described above. EtOAc/hexane (1:1) was used for flash

chromatography; yield 256 mg (87 %) colourless powdery crystals. M.p. 198-200 °C. (Found: C, 65.65; H, 4.13. Calc. for $C_{16}H_{12}N_4S$: C, 65.73; H, 4.14 %). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.47 (s, 2H), 7.2-7.3 (m, 6H), 7.62 (m, 1H), 8.07 (s, 1H), 8.68 (m, 1H), 8.93 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.3, 127.8, 128.6, 128.8, 129.1, 130.8, 132.7, 135.1, 139.9, 144.1, 150.1, 152.1, 152.6, one C was hidden. MS (EI): 292 (100, M^+), 291 (83), 264 (10), 247 (9), 215 (11), 149 (5), 146 (6), 95 (7), 91 (92), 65 (17).

9-Benzyl-6-phenylpurine (5e). Compound **5e** was prepared from 9-benzyl-6-chloropurine **2** and phenyl(tributyl)tin **4e** (1.5 mmol) as described above. EtOAc/hexane (1:1) was used for flash chromatography; yield 215 mg (75 %) colourless powdery crystals. M.p. 124-125 °C (Lit.[7] 121-123 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.50 (s, 2H), 7.3-7.4 (m, 5H), 7.5-7.6 (m, 3H), 8.11 (s, 1H), 8.8 (m, 2H), 9.07 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 47.2, 127.7, 128.5, 128.6, 129.1, 129.8, 130.8, 131.1, 135.0, 135.1, 144.3, 152.2, 152.5, 154.5. MS (EI): 286 (97, M^+), 285 (100), 257 (11), 209 (16), 195 (18), 91 (72), 89 (11), 79 (12), 78 (12), 77 (12).

6,9-Dibenzylpurine (5f). Compound **5f** was prepared from 9-benzyl-6-chloropurine **2** and benzyl(tributyl)tin **4f** (1.5 mmol) as described above. EtOAc/hexane (1:1) followed by (2:1) was used for flash chromatography and the product was crystallized from EtOAc/hexane (1:20); yield 143 mg (48 %) colourless powdery crystals. M.p. 84-86 °C . (Found: C, 75.82; H, 5.07. Calc. for $C_{19}H_{16}N_4$: C, 75.98; H, 5.37 %). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.53 (s, 2H), 5.42 (s, 2H), 7.2-7.3 (m, 8H), 7.5 (m, 2H), 8.03 (s, 1H), 8.93 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 39.4, 47.3, 126.6, 127.9, 128.5, 128.7, 129.1, 129.3, 132.3, 135.0, 137.8, 143.9, 151.2, 152.7, 160.7. MS (EI): 300 (40, M^+), 299 (45), 237 (7), 223 (52), 209 (40), 182 (5), 154 (6), 128 (6), 91 (100), 65 (17).

9-Benzyl-6-(n-butyl)purine (5g). Compound **5g** was prepared from 9-benzyl-6-chloropurine **2** and *n*-butyl(tributyl)tin **4g** (1.7 mmol) as described above. EtOAc/acetone/hexane (1:2:3) was used for flash chromatography; yield 47 mg (18 %) colourless powdery crystals. M.p. 35-37 °C . (Found: C, 72.01; H, 7.00. Calc. for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81 %). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.96 (t, *J* 7.3 Hz, 3H), 1.46 (m, 2H), 1.89 (m, 2H), 3.22 (t, *J* 7.8 Hz, 2H), 5.44 (s, 2H), 7.3 (m, 5H), 8.01 (s, 1H), 8.92 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.2, 23.1, 30.9, 33.2, 47.4, 127.5, 128.2, 128.8, 132.1, 134.8, 143.0, 150.3, 152.1, 162.6, MS (EI): 266 (1, M^+), 251 (3), 237 (13), 225 (15), 224 (100), 223 (16), 147 (6), 91 (77), 65 (12).

7-Benzyl-6-(2-thienyl)purine (7a). Compound **7a** was prepared from 7-benzyl-6-chloropurine **3** and 2-thienyl(tributyl)tin **4d** (1.5 mmol) as described above. EtOAc/MeOH (10:1) was used for flash chromatography; yield 264 mg (90 %) colourless powdery crystals. M.p. 142-144 °C. (Found: C, 65.56; H, 3.95. Calc. for $C_{16}H_{12}N_4S$: C, 65.73; H, 4.14 %). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.46 (s, 2H), 6.76 (m, 2H), 7.1-7.3 (m, 5H), 7.58 (d, *J* 5.0 Hz, 1H), 8.32 (s, 1H), 9.11 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 50.8, 122.3, 126.4, 127.2, 128.2, 128.8, 129.5, 129.6, 134.4, 137.8, 145.8, 149.7, 152.5, 162.1. MS (EI): 292 (184, M^+), 291 (55), 277 (5), 264 (6), 259 (7), 247 (7), 215 (6), 201 (5), 91 (100), 65 (16).

7-Benzyl-6-phenylpurine (7b). Compound **7b** was prepared from 7-benzyl-6-chloropurine **3** and phenyl(tributyl)tin **4e** (1.4 mmol) as described above. MeOH/$CHCl_3$ (1:10) was used for flash chromatography; yield 268 mg (93 %) colourless powdery crystals. M.p. 152-154 °C. (Found: C, 75.24; H, 4.99. Calc. for $C_{18}H_{14}N_4$: C, 75.51; H, 4.93 %). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.22 (s, 2H), 6.5-6.6 (m, 2H), 7.1-7.2 (m, 3H), 7.4-7.5 (m, 5H), 8.13 (s, 1H), 9.16 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 51.0, 122.7, 126.3, 128.2, 128.4, 128.7, 128.8, 129.8, 134.3, 136.0, 149.4, 152.5, 152.8, 161.9. MS (EI): 286 (82, M^+), 285 (77), 258 (6), 209 (13), 195 (7), 128 (9), 114 (5), 91 (100), 89 (8), 65 (17).

6,7-Dibenzylpurine (7c). Compound **7c** was prepared from 7-benzyl-6-chloropurine **3** and benzyl(tributyl)tin **4f** (1.6 mmol) as described above. MeOH/$CHCl_3$ (1:15) was used for flash chromatography; yield 188 mg (62 %) colourless powdery crystals. M.p. 156-158 °C. (Found: C, 76.05; H, 5.28. Calc. for $C_{19}H_{16}N_4$: C,

75.98; H, 5.37 %). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.24 (s, 2H), 5.33 (s, 2H), 6.9-7.0 (m, 3H), 7.2-7.4 (m, 7H), 8.16 (s, 1H), 9.01 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 40.5, 50.7, 124.1, 125.8, 127.0, 128.1, 128.7, 129.0, 129.5, 135.2, 137.3, 148.8, 152.8, 153.1, 161.6. MS (EI): 300 (100, M^+), 299 (70), 285 (11), 223 (11), 209 (18), 208 (11), 167 (14), 128 (8), 91 (79), 65 (18).

7-Benzyl-6-(n-butyl)purine (7d). Compound **7d** was prepared from 7-benzyl-6-chloropurine **3** and *n*-butyl(tributyl)tin **4g** (1.7 mmol) as described above. MeOH/EtOAc/acetone/hexane (1:1:2:3) was used for flash chromatography; yield 174 mg (65 %) colourless powdery crystals. M.p. 94-96 °C. (Found: C, 71.89; H, 6.74. Calc. for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.84 (t, *J* 7.3 Hz, 3H), 1.28 (m, 2H), 1.53 (m, 2H), 2.87 (m, 2H), 5.62 (s, 2H), 7.0 (m, 2H), 7.3-7-4 (m, 3H), 8.25 (s, 1H), 9.01 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.6, 22.5, 30.9, 34.0, 51.1, 123.4, 125.8, 128.5, 129.2, 135.1, 148.7, 152.9, 155.4, 161.0. MS (EI): 266 (4, M^+), 251 (5), 237 (16), 225 (15), 224 (100), 223 (36), 196 (4), 147 (7), 91 (70), 65 (11).

6-Acetyl-9-benzylpurine (6). 9-Benzyl-6-(α-ethoxyvinyl)purine **5b** (266 mg, 0.95 mmol) was added to acetone/1 M HCl (aq) 4:1 (5.0 ml) and the mixture was stirred at ambient temperature for 24 h, before water (10 ml) was added and the mixture extracted with ether (3 x 10 ml) and EtOAc (2 x 20 ml). The combined organic extracts were washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel eluting with MeOH/$CHCl_3$ (1:20); yield 212 mg (88 %) colourless powdery crystals. M.p. 124-126 °C. (Found: C, 66.66; H, 5.15. Calc. for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.91 (s, 3H), 5.51 (s, 2H), 7.3-7.4 (m, 5H), 8.27 (s, 1H), 9.14 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.9, 47.4, 127.7, 128.9, 129.0, 130.6, 134.6, 147.4, 148.6, 152.0, 154.3, 198.9. MS (EI): 252 (66, M^+), 237 (1), 224 (21), 211 (11), 210 (39), 209 (44), 182 (15), 119 (11), 91 (100), 65 (19).

Coupling of the halopurines (2), (3), (9) and (10)with organozinc reagents (8). A 1 M solution of anhydrous zinc bromide in dry THF (1.2 ml, 1.2 mmol) was added dropwise to a stirred solution of the desired Grignard or lithium reagent (1.2 mmol) in dry THF (4 ml) under N_2 at -78 °C. After 1 h, the cooling bath was removed and the reaction mixture allowed to reach ambient temperature before tetrakis(triphenylphosphine)-palladium(0) (58 mg, 0.05 mmol) in THF (2 ml) and halopurine (1.0 mmol) in THF (4 ml) were added. The resulting mixture was heated at 50 °C for the times given in Tables 3 and 4, and cooled. Sat. aq. ammonium chloride (10 ml) was added and the aq. phase extracted with EtOAc (4 x 25 ml). The combined organic extracts were washed with brine (2 x 20 ml) dried ($MgSO_4$) and evaporated. The product was purified by flash chromatography on silica gel.

9-Benzyl-6-vinylpurine (5a). Vinylzinc bromide **8a** was generated from vinylmagnesium bromide and reacted with 9-benzyl-6-iodopurine **9** as described above; yield 146 mg (62 %). Chromatography conditions and data, see above.

9-Benzyl-6-(2-thienyl)purine (5d). 2-Thienylzinc bromide **8b** was generated from 2-bromothiophene via 2-lithiothiophene and reacted with 9-benzyl-6-iodopurine **9** as described above; yield 168 mg (58 %). Chromatography conditions and data, see above.

9-Benzyl-6-phenylpurine (5e). Phenylzinc bromide **8c** was generated from bromobenzene via phenyllithium and reacted with 9-benzyl-6-chloropurine **2** as described above; yield 220 mg (77 %). Chromatography conditions and data, see above.

6,9-Dibenzylpurine (5f). Benzylzinc bromide **8e** was generated from benzylmagnesium bromide and reacted with 9-benzyl-6-chloropurine **2** as described above; yield 273 mg (91 %). Chromatography conditions and data, see above.

9-Benzyl-6-(n-butyl)purine (5g). *n*-Butylzinc bromide **8f** was generated from *n*-butyllithium and reacted with 9-benzyl-6-chloropurine **2** as described above; yield 223 mg (84 %). Chromatography conditions and data, see above.

9-Benzyl-6-(p-methoxyphenyl)purine (5h). *p*-Methoxyphenylzinc bromide **8d** was generated from *p*-bromoanisole via *p*-methoxyphenyllithium and reacted with 9-benzyl-6-chloropurine **2** as described above; EtOAc/hexane (1:1) was used for flash chromatography; yield 259 mg (82 %) colourless powdery crystals. M.p. 150-151 °C (Lit.[7] 148-151 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.88 (s, 3H), 5.45 (s, 2H), 7.07 (d, *J* 9.0 Hz, 2H), 7.3 (m, 5H), 8.06 (s, 1H), 8.82 (d, *J* 9.0 Hz, 2H), 9.00 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 47.2, 55.3, 114.0, 127.7, 128.5, 129.1, 130.2, 131,6, 135.1, 143.8, 152.2, 154.2, 162.1, two C were hidden. MS (EI): 316 (82, M^+), 315 (88), 300 (5), 272 (5), 225 (8), 149 (10), 91 (62), 71 (8), 65 (13).

9-Benzyl-6-methylpurine (5i). Methylzinc bromide **8g** was generated from methylmagnesium bromide and reacted with 9-benzyl-6-chloropurine **2** as described above. MeOH/EtOAc (3:17) was used for flash chromatography; yield 201 mg (90 %) colourless powdery crystals. M.p. 75-77 °C. (Found: C, 69.44; H, 5.18. Calc. for $C_{13}H_{12}N_4$: C, 69.62; H, 5.39 %). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.88 (s, 3H), 5.44 (s, 2H), 7.3 (m, 5H), 8.02 (s, 1H), 8.90 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.4, 47.2, 127.8, 128.6, 129.1, 132.9, 135.1, 143.5, 150.6, 152.5, 159.3. MS (EI): 224 (86, M^+), 223 (100), 209 (11), 196 (15), 167 (8), 147 (13), 104 (10), 91 (83), 89 (10), 65 (23).

9-Benzyl-6-(n-decyl)purine (5j). *n*-Decylzinc bromide **8h** was generated from *n*-decylmagnesium bromide and reacted with 9-benzyl-6-chloropurine **2** as described above. EtOAc/hexane (1:1) was used for flash chromatography: yield 291 mg (83 %) colourless powdery crystals. M.p. 45-47 °C. (Found: C, 75.68; H, 8.53. Calc. for $C_{22}H_{30}N_4$: C, 75.39; H, 8.63 %). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.87 (t, *J* 7.3 Hz, 3H), 1.2-1.5 (m, 14 H), 1.8-2.0 (m, 2H), 3.21 (m, 2H), 5.44 (s, 2H), 7.3 (m, 5H), 8.01 (s, 1H), 8.92 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 22.6, 28.6, 29.3, 29.4, 29.48, 29.53, 29.6, 31.8, 33.2, 47.2, 127.8, 128.5, 129.1, 132.5, 135.2, 143.4, 150.7, 152.6, 163.1. MS (EI): 350 (6, M^+), 335 (1), 321 (1), 307 (2), 293 (2), 237 (17), 225 (16), 224 (100), 223 (25), 91 (49).

7-Benzyl-6-(2-thienyl)purine (7a). 2-Thienylzinc bromide **8b** was generated from 2-bromothiophene via 2-lithiothiophene and reacted with 7-benzyl-6-iodopurine **10** as described above; yield 176 mg (60 %). Chromatography conditions and data, see above.

7-Benzyl-6-phenylpurine (7b). Phenylzinc bromide **8c** was generated from bromobenzene via phenyllithium and reacted with 7-benzyl-6-chloropurine **3** as described above; yield 240 mg (84 %). Chromatography conditions and data, see above.

6,7-Dibenzylpurine (7c). Benzylzinc bromide **8e** was generated from benzylmagnesium bromide and reacted with 7-benzyl-6-chloropurine **3** as described above; yield 246 mg (82 %). Chromatography conditions and data, see above.

7-Benzyl-6-(n-butyl)purine (7d). *n*-Butylzinc bromide **8f** was generated from *n*-butyllithium and reacted with 7-benzyl-6-chloropurine **3** as described above; yield 64 mg (24%). Chromatography conditions and data, see above.

7-Benzyl-6-methylpurine (7e). Methylzinc bromide **8g** was generated from methylmagnesium bromide and reacted with 7-benzyl-6-chloropurine **3** as described above. MeOH/$CHCl_3$ (1:7) was used for flash chromatography; yield 163 mg (73 %) colourless powdery crystals. M.p. 180-183 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.64 (s, 3H), 5.63 (s, 2H), 7.0-7.1 (m, 2H), 7.3-7.4 (m, 3H), 8.25 (s, 1H), 8.95 (s, 1H). ^{13}C

NMR ($CDCl_3$, 50 MHz): δ 21.4, 50.9, 124.2, 125.6, 128.6, 129.3, 135.1, 148.4, 151.1, 153.0, 160.6. MS (EI): 224 (54, M^+), 223 (37), 167 (3), 149 (10), 128 (8), 120 (5), 117 (7), 91 (100), 65 (12); Hrms calcd for $C_{13}H_{12}N_4$: 224.1062; found 224.1081.

7-Benzyl-6-(n-decyl)purine (7f). *n*-Decylzinc bromide **8h** was generated from *n*-decylmagnesium bromide and reacted with 7-benzyl-6-chloropurine **3** as described above. MeOH/$CHCl_3$ (1:16) was used for flash chromatography: yield 70 mg (20 %) colourless powdery crystals. M.p. 84-86 °C. (Found: C, 75.53; H, 8.48. Calc. for $C_{22}H_{30}N_4$: C, 75.39; H, 8.63 %). ^1H NMR ($CDCl_3$, 200 MHz): δ 0.88 (t, *J* 7.3 Hz, 3H), 1.2-1.4 (m, 14 H), 1.5-1.7 (m, 2H), 2.87 (m, 2H), 5.59 (s, 2H), 7.0 (m, 2H), 7.4 (m, 3H), 8.22 (s, 1H), 9.03 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 22.6, 29.1, 29.2, 29.3, 29.4, 29.48, 29.52, 31.8, 34.4, 51.2, 123.6, 125.9, 128.7, 129.4, 135.1, 148.7, 153.1, 155.4, 161.2. MS (EI): 350 (4, M^+), 237 (16), 225 (17), 224 (100), 223 (12), 150 (27), 104 (20), 91 (76), 83 (16), 69 (11).

7-Benzyl-6-iodopurine(10).[8] 7-Benzyl-6-chloropurine **3** (349 mg, 1.41 mmol) was added during 20 min. to a 57 % aq. solution of hydrogen iodide (2.0 ml) at -5 °C. The resulting mixture was stirred at -5 °C for 2.0 h, filtered and the solid washed with a small portion of ice water. Water (50 ml) was added to the solid, the mixture cooled to 10 °C and the pH adjusted to ca. 8. The solid was filtered of, dried and the crude product purified by flash chromatography on silica gel eluting with EtOAc/MeOH (9:1); yield 403 mg (85 %) pale yellow powdery crystals. M.p. 138 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 5.77 (s, 2H), 7.1-7.2 (m, 2H), 7.4 (m, 3H), 8.25 (s, 1H), 8.76 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 49.4, 108.6, 126.9, 128.4, 128.8, 129.3, 134.7, 149.6, 152.6, 159.1. MS (EI): 336 (44, M^+), 225 (1), 209 (100), 181 (7), 155 (9), 127 (8), 116 (7), 91 (92), 89 (5), 65 (18).

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