Direct C–H borylation and C–H arylation of pyrrolo[2,3-*d*]pyrimidines: synthesis of 6,8-disubstituted 7-deazapurines†

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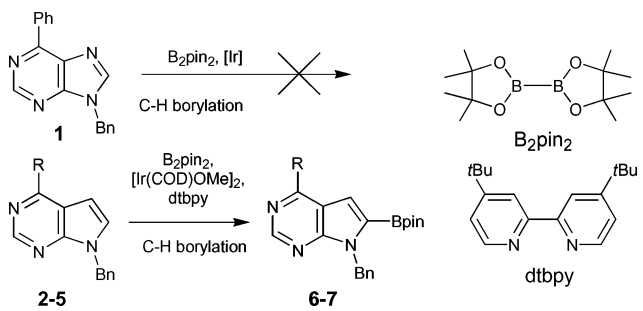
Novel direct C–H borylations of 7-deazapurines to position 8 by B_2pin_2 under Ir catalysis were followed by Suzuki cross-couplings with aryl halides and other functional group transformations to give diverse 8-substituted 7-deazaadenines.

2,6,9- or 6,8,9-Trisubstituted, as well as and 2,6,8,9-tetrasubstituted purines display a wide range of biological activities,[1] *i.e.* inhibition of protein kinases,[2] or tubulin polymerization,[3] and antagonist effects to receptors,[4] *etc.* 6-Arylpurines are of particular importance due to anti-HCV, cytostatic and antimycobacterial activities.[5] 7-Deazapurines (pyrrolo[2,3-*d*]-pyrimidines) are often used as surrogates of purine bases and also many of them display interesting biological effects.[6] However, compared to purines, this class of heterocycles is under explored. In our previous synthetic and medicinal chemistry studies of di-, tri- and tetrasubstituted purines we have heavily utilized regioselective cross-coupling reactions of di- and trihalopurines.[7] Later on, we have for the first time developed novel direct C–H arylation[8] reactions in purine bases[9] and nucleosides[10] and, most recently, we used a combination of regioselective cross-couplings, Cu-catalyzed N-arylations and direct C–H arylations for the efficient consecutive synthesis of small libraries of tri and tetrasubstituted purines.[11] Now we wished to explore the utility of another reaction from the family of C–H activations: Ir-catalyzed direct C–H borylation[12] in modifications of purines and 7-deazapurines. Such reactions should lead to hetarylboronates suitable for further functional group transformations by the Suzuki cross-coupling or Cu-catalyzed aminations. So far, not only have such reactions not been reported on these two heterocyclic systems, but also the corresponding hetarylboronates or -boronic acids are unknown.

Ir-catalyzed C–H borylation[12] of aromatic compounds is a one-step method to generate aryl boronates. The most active catalyst for this transformation is generated from di-*tert*-butylbipyridine and $[Ir(COD)(OMe)]_2$. 9-Benzyl-6-phenylpurine (**1**) was chosen as the first model substrate for studying the C–H borylation (Scheme 1). We have employed the above mentioned catalytic system under diverse conditions (from r.t. to 80 °C and MW irradiation). Unfortunately, no formation of 8-borylated purine was observed (mostly just the starting compound was recovered accompanied by minor byproducts). The most plausible explanation of this lack of reactivity is the formation of a stable complex of purine with Ir catalyst at N7. Another problem might be the limited stability[13] of the purine-8-boronate that may undergo protodeborylation back to the starting compound.

Therefore, our further efforts focused on 7-deazapurines (lacking the N7 coordination site). The model starting compound of choice was 9- benzyl-6-phenyl-7-deazapurine (**2**, 7-benzyl-4-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine). The reaction of **2** with bispinacolatodiboron in presence of di-*tert*-butylbipyridine and $[Ir(COD)(OMe)]_2$ proceeded well to give selectively 8-borylated product **6** in high yield (85%, Table 1, entry 1)‡. The regioselectivity was in accord with the literature examples[14] of borylation of indoles at position 2 and was unequivocally proved by X-ray diffraction analysis of **6** (Fig. 1).[15]

Next, we have tried the C–H borylation of 9-benzyl-7-deazaadenine **3** and its N-[(dimethylamino)methylidene]-protected derivative **4** under the same conditions. However, no C–H borylation was observed (entries 2,3). Another interesting substrate was 9-benzyl-6-chloro-7-deazapurine (**5**) suitable for further functional group transformations at position 6. In this case, the C–H borylation worked reasonably well to give the desired product **7** in moderate (but acceptable) 53% yield (entry 4). Then we have attempted hydrolysis of the boronate ester **6** to more reactive boronic acid. The hydrolysis proceeded quantitatively but the final free boronic acid was rather unstable and readily decomposed.



Scheme 1

Table 1 Direct C–H borylation of deazapurines

Entry	Starting compound	R	Yield (%)
1	**2**	Ph-	**6** (85%)[a]
2	**3**	NH_2	no reaction[a]
3	**4**	$(CH_3)_2NCH{=}N$-	no reaction[a]
4	**5**	Cl	**7** (53%)[b]

[a] 1.2 equiv. B_2pin_2, 5 mol% $[Ir(COD)OMe]_2$, 10 mol% dtbpy, THF, 80 °C, 20 h. [b] 1.5 equiv. B_2Pin_2, 8 mol% $[Ir(COD)(OMe)]_2$, 16 mol% dtbpy.

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† Electronic supplementary information (ESI) available: Experimental details and characterization data. CCDC reference numbers 703631 (**6**) and 703632 (**8b**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b900218a

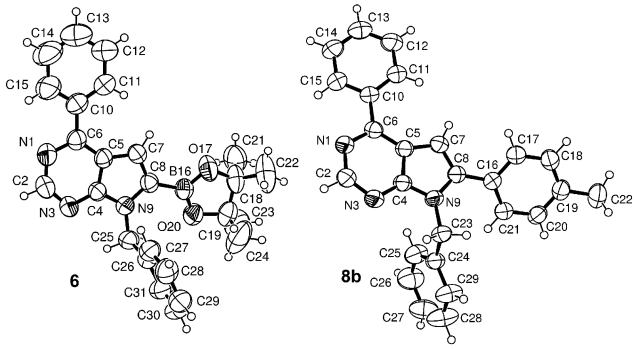
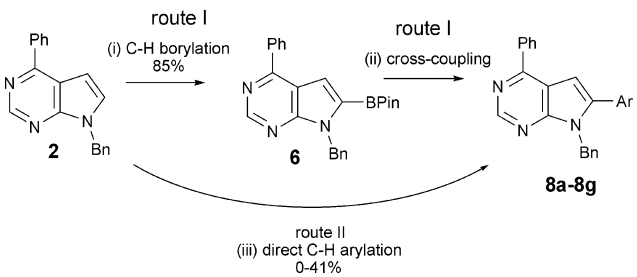
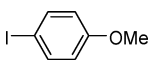
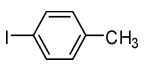
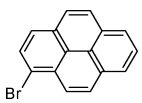
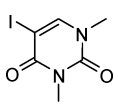
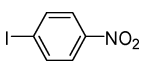
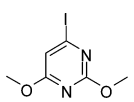


Fig. 1 ORTEP drawing with the atom numbering scheme. Thermal ellipsoids are drawn at the 50% probability level.



Scheme 2 *Reagents and conditions*: i) B_2pin_2, $[Ir(COD)OMe]_2$, dtbpy, THF, 80 °C, 20 h; ii) Ar-X, $Pd(dppf)Cl_2$, K_2CO_3, DMF, 90 °C, 1 h; iii) Ar-X, $Pd(OAc)_2$, Cs_2CO_3, CuI, DMF, 160 °C, 60 h.

Table 2 Synthesis of 8-arylated deazapurines by C–H activation

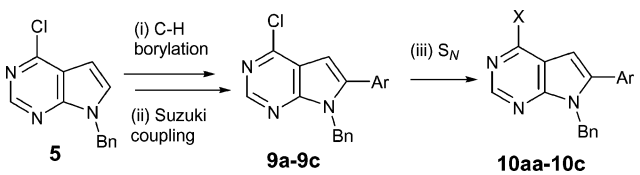
Entry	Ar-X	Product	Route I – coupling[a] (overall yield)[b]	Route II (yield)
1		**8a**	87%[a] (74%)[b]	39%
2		**8b**	90%[a] (76%)[b]	41%
3		**8c**	79%[a] (67%)[b]	35%
4		**8d**	95%[a] (81%)[b]	traces
5		**8e**	92%[a] (78%)[b]	0%
6		**8f**	91%[a] (77%)[b]	0%
7		**8g**	92%[a,c] (78%)[b,c]	0%

[a] Cross coupling. [b] Overall yield after two steps (C–H borylation and cross coupling). [c] Overall yield after acidic deprotection to free uracil **8h**.

Having access to the boronates, we have further explored their synthetic applications. The most obvious use was in the Suzuki cross-coupling reaction. Thus the reactions of the boronate **6** with diverse aryl halides were performed under conditions previously optimized[16] for other hetarylboronates ($Pd(dppf)Cl_2$ and K_2CO_3 in DMF) (Scheme 2). Generally, all the aryl halides (diverse aryl iodides and 2-bromopyrene) reacted well to give the desired 8-aryl products **8a–8g** in very high yields (Table 2). One example (**8b**) was also characterized by X-ray diffraction.[15] Interesting products **8e** and **8g** arose from the coupling with methylated 5- or 6-iodouracils (entries 4 and 6) as novel types of Janus-nucleobases[17] or fleximers.[18]

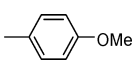
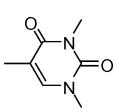
In the case of compound **8g**, the acid hydrolysis gave the free 9-benzyl-6-phenyl-8-(uracil-6-yl)-7-deazapurine **8h**. The overall yields of the 6,8-diaryl-7-deazapurines over the two steps (C–H borylation and cross-coupling, Table 2 - Route I) were very good (67–81%). As a complementary alternative method, we have also tried direct C–H arylation of **2** with the same aryl halides under the conditions optimized[9] for arylation of purines (Table 2, Route II). However, these reactions did not proceed well giving very low yields (entries 1–3) or no reaction what so ever (entries 4–7). Comparison of the two routes to diaryl-7-deazapurines **8** revealed that the two step sequence (Route I) is much more efficient (Table 2).

Finally, we were interested in the synthesis of 8-aryl-7-deazaadenines. As the direct C–H activations of 7-deazaadenine **3** were unsuccessful, we have envisaged the use of the 6-chloro derivative that can be readily transformed to 6-amino compounds (Table 3). The two-step arylation (C–H borylation followed by the Suzuki coupling) of 9-benzyl-6-chloro-7-deazapurine (**5**) with three different aryl iodides proceeded with acceptable 31–42% overall yields (the yield of the first step was the moderate



Scheme 3 *Reagents and conditions*: i) B_2pin_2, $[Ir(COD)OMe]_2$, dtbpy, THF, 80 °C, 20 h; ii) Ar-X, $Pd(dppf)Cl_2$, K_2CO_3, DMF, 90 °C, 1 h; (iii) a) NH_3/MeOH, 120 °C, overnight b,c) R-NH_2, butanol, reflux, overnight d) phenol, KO*t*-Bu, K_2CO_3, DMF, 110 °C, 16 h.

Table 3 Two-step synthesis of 6,8-disubstituted 7-deazapurines

Entry	Ar	Product (yield)	X	Product (yield)
1		**9a** (42%)	NH_2	**10aa** (83%)
2			NH-Ph	**10ab** (65%)
3			NH-Bn	**10ac** (77%)
4			O-Ph	**10ad** (93%)
5		**9b** (31%)	NH_2	**10b** (85%)
6		**9c** (36%)	NH_2	**10c** (79%)

54% as mentioned above). The follow-up aminations of the 6-chloro-7-deazapurines with methanolic ammonia gave the 8-aryl-7-deazaadenines **10aa**, **10b** and **10c** in very good yields (Scheme 3, Table 3). Other nucleophilic substitutions were also pursued with 6-chloro-7-deazapurine **9a**. Its reactions with aniline, benzylamine, as well as with sodium phenolate gave the corresponding 6-N- or 6-O-substituted products **10ab**, **10ac** and **10ad**, respectively.

In conclusion, the Ir-catalyzed C–H borylation of 7-deazapurines proceeded selectively in position 8. The follow-up Suzuki cross-coupling reactions can be efficiently used for the introduction of aryl groups to position 8. This is the first efficient methodology for 8-arylation of important 7-deazapurines (so far the 8-substituted 7-deazapurines were only prepared by multistep heterocyclizations[6]). The methodology can be combined with nucleophilic substitutions of 6-chloro-7-deazapurines to give an efficient way to synthesise diverse 6-substituted 8-aryl-7-deazapurines.

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Notes and references

‡ General procedure for C–H borylation. 7-Deazapurines **2** or **5** (2 mmol, 1 equiv.), bispinacolatodiboron (0.609 g, 2.4 mmol, 1.2 equiv.), $[Ir(COD)OMe]_2$ (66 mg, 0.1 mmol, 5 mol%) and 4,4′-di-*tert*-butyl-2,2′-bipyridine (54 mg, 0.2 mmol, 10 mol%) were dissolved in dry THF (15 ml) under Ar. The solution was heated at 80 °C in a septum-sealed flask for 20 hours. The solvent was evaporated and the residue was purified by silica gel flash chromatography (hexane/EtOAc 5:1→ ethyl acetate/hexanes 1:1) to give product **6** (698 mg, 85%) or **7** (390 mg, 53%). Compound **6**: M.p. 128–134 °C.^{1}H NMR (600 MHz, $CDCl_3$): 1.28 (s, 12H, CH_3); 5.81 (s, 2H, CH_2); 7.17–7.26 (m, 5H, H-*o,m,p*-Bn); 7.46 (s, 1H, H-5); 7.50 (m, 1H, H-*p*-Ph); 7.54 (m, 2H, H-*m*-Ph); 8.16 (m, 2H, H-*o*-Ph); 9.02 (s, 1H, H-2). ^{13}C NMR (151 MHz, $CDCl_3$): 24.65 ($(CH_3)_2C$); 47.17 (CH_2Ph); 84.39 ($C(CH_3)_2$); 113.54 (CH-5); 115.44 (C-4a); 127.14 (CH-*p*-Bn); 127.28 (CH-*o*-Bn); 128.25 (CH-*m*-Bn); 128.71 (CH-*m*-Ph); 129.06 (CH-*o*-Ph); 130.10 (CH-*p*-Ph); 132.15 (C-6); 138.16 (C-*i*-Ph); 138.79 (C-*i*-Bn); 152.94 (CH-2); 154.25 (C-7a); 158.73 (C-4). IR ($CHCl_3$): 2983, 1562, 1525, 1468, 1449, 1428, 1382, 1374, 1335, 1139. HRMS (ESI) calculated for $C_{25}H_{26}BN_3O_2$: 412.2191; found: 412.2192. Compound **7**: M.p. 172–175 °C.^{1}H NMR (500 MHz, $CDCl_3$): 1.28 (s, 12H, CH_3); 5.75 (s, 2H, CH_2); 7.16–7.25 (m, 6H, H-5 and H-*o,m,p*-Bn); 8.68 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$): 24.62 ((CH_3)$_2$C); 47.60 (CH_2Ph); 84.56 ($C(CH_3)_2$); 112.23 (CH-5); 117.21 (C-4a); 127.22 (CH-*o*-Bn); 127.34 (CH-*p*-Bn); 128.30 (CH-*m*-Bn); 132.79 (C-6); 138.12 (C-*i*-Bn); 151.91 (CH-2); 153.28 and 153.42 (C-4 and C-7a). IR ($CHCl_3$): 2984, 1579, 1541, 1525, 1469, 1430, 1374, 1355, 1330, 1259, 1177, 1137. HRMS (ESI) calculated for $C_{19}H_{21}BClN_3O_2$: 370.1499; found: 370.1488.

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