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A sequential direct arylation/Suzuki–Miyaura cross-coupling transformation of unprotected 2'-deoxyadenosine affords a novel class of fluorescent analogues†

Thomas E. Storr,^{ab} Johanna A. Strohmeier,^b Christoph G. Baumann^{*b} and Ian J. S. Fairlamb^{*a}

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Novel rigid 8-biaryl-2'-deoxyadenosines with tuneable fluorescent properties can be accessed by an efficient sequential catalytic Pd⁰-coupling approach.

Fluorescent nucleosides are used widely as probes of enzymatic turnover and biomolecular structure, and as labels in high-throughput biotechnologies.¹ Common organic, *e.g.* pyrenyl or fluorescein, and inorganic metal-containing extrinsic fluorophores can be attached to either sugar² or nucleobase.³ Direct coupling of a conjugated aromatic group yields a more compact fluorescent analogue. Examples include aryl,⁴ heteroaryl⁵ or arylalkynyl⁶ nucleosides, but also modified nucleobase mimetics exhibiting unique fluorescent properties (Fig. 1).⁷

This communication describes the synthesis of novel 8-biaryl-2'-deoxyadenosines (*e.g.* **II**, Scheme 1) which function as *Rigid Organo-fluorescent Nucleosides* (RONs). These π -conjugated systems are accessible using our recently developed direct arylation methodology for unprotected adenine nucleosides, which facilitates the chemoselective installation of an aryl group at the 8-position.⁸ The use of a dihaloaromatic coupling partner would provide a secondary handle for further chemical manipulation, allowing addition of aryl groups *via* a classical cross-coupling (hereafter 'coupling') approach. Suzuki–Miyaura coupling has been used effectively with unprotected nucleosides⁹ and nucleotides,¹⁰ therefore it should be applicable

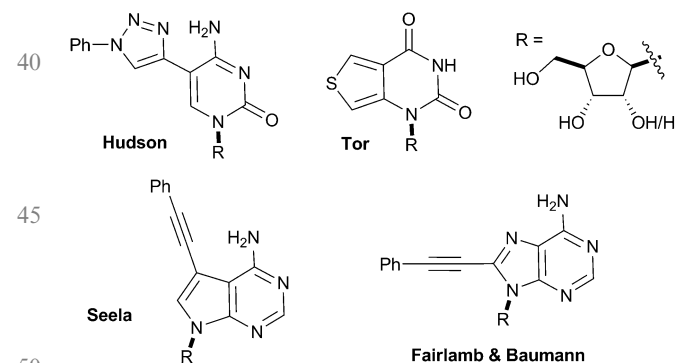


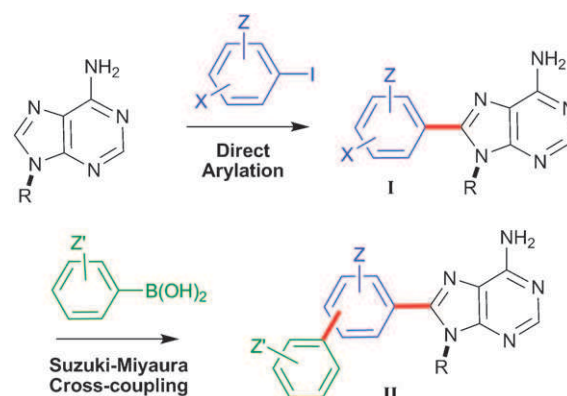
Fig. 1 Fluorescent nucleosides.

^a Department of Chemistry, University of York, York YO10 5DD, UK. E-mail: ijsf1@york.ac.uk

^b Department of Biology, University of York, York YO10 5YW, UK.

E-mail: cb17@york.ac.uk

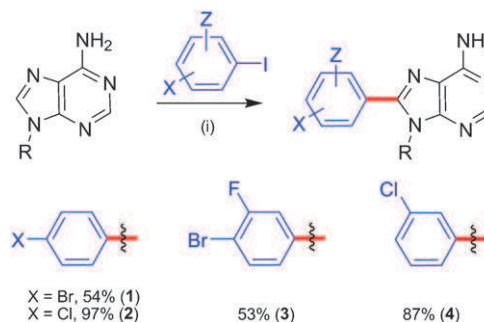
† Electronic supplementary information (ESI) available: Experimental details (including characterisation data for all compounds) and X-ray data for **5d** and **5i**, including cif files. CCDC [CCDC NUMBER(S)]. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc02043e



Scheme 1 Proposed targets and sequential direct arylation/Suzuki–Miyaura approach (R = 2'-deoxyribose).

to these substrates. This sequential coupling approach would provide a divergent synthetic route to differently substituted 8-biaryl-2'-deoxyadenosines (*via* **I**).

For the synthesis of target **I**, the use of diiodobenzene was dismissed as our prior findings indicated that double C–H arylation occurs.^{8a} However, we rationalised that an aromatic coupling partner possessing two sites with different chemical reactivity towards Pd⁰ might provide an elegant solution. Therefore, as a first step towards the selective synthesis of the intermediate compounds, we evaluated iodobromobenzenes and iodochlorobenzenes as direct arylation substrates (Scheme 2). Using our established direct arylation conditions,^{8b} both 4-bromo and 4-chloro-iodobenzene reacted with 2'-deoxyadenosine to give compounds **1** and **2** in 54% and 97% yields, respectively.



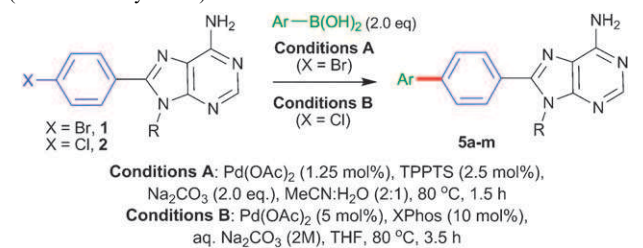
Scheme 2 Direct arylation of 2'-deoxyadenosine. Reagents and conditions: (i) ArI (2.0 eq.), Pd(OAc)₂ (5.0 mol%), CuI (3.0 eq.), piperidine (0.4 eq.), Cs₂CO₃ (2.5 eq.), DMF, 80 °C, 15 h (R = 2'-deoxyribose; Z = H or F).

3-Fluoro-4-bromiodobenzene was a robust substrate giving **3** in 53% yield, whilst 3-chloro-iodobenzene provided **4** in 87% yield.

With the 8-haloaryl-2'-deoxyadenosines (**1–4**) in hand we focussed on the Suzuki–Miyaura coupling methodology. We employed a Pd : TPPTS (tris-(3-sulphophenyl)phosphine trisodium salt = TPPTS) water soluble catalyst system. A slightly modified version of Shaughnessy's protocol was employed, specifically Pd(OAc)₂ (1.25 mol%), TPPTS (2.5 mol%), Na₂CO₃ (2.0 eq.), MeCN : H₂O (2 : 1), 80 °C, 1.5 h (hereafter Conditions A).^{9a,b} Interestingly, the employment of a catalyst preformation/preactivation step {Pd(OAc)₂, ligand, solvent and heating} led to a poor catalyst system resulting in incomplete reaction (Table 1; numbers in parentheses). This has implications for product isolation as it has a similar polarity to the starting material. The addition of the pre-catalyst and ligand with the solid reagents to a dry vessel (under an argon atmosphere) prior to addition of the solvent mixture worked most effectively (Table 1, all other yields).

The coupling of arylboronic acids with bromo analogue **1** using Conditions A proceeded well. Both electron-rich and electron-deficient arylboronic acids were efficient coupling partners (entries 1, 3, 5–7 and 9, Table 1). It is not surprising that chloro analogue **2** failed to serve as a substrate using Conditions A. Indeed, the difference in reactivity of C–Cl and C–Br bonds is apparent in the high yield observed for **5e** (81%, entry 5). We identified Buchwald's bulky electron-rich phosphine Xphos (2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl = Xphos) as an enhancing ligand.

Table 1 Suzuki–Miyaura couplings of **1** and **2** with arylboronic acids (R = 2'-deoxyribose)



Entry	Ar	Cpd	Yield/%	
			Conditions A (from 1)	Conditions B (from 2)
1	4-MeOC ₆ H ₄	5a	71 (38) ^a	88
2	4-MeC ₆ H ₄	5b	—	72
3	C ₆ H ₅	5c	89 (74) ^a	91 [81] ^b
4	4-FC ₆ H ₄	5d	—	92
5	4-ClC ₆ H ₄	5e	81 ^{c,d}	—
6	3,5-F ₂ C ₆ H ₃	5f	82	94 ^e
7	4-CF ₃ C ₆ H ₄	5g	77	88
8	3-CF ₃ C ₆ H ₄	5h	—	79
9	4-AcC ₆ H ₄	5i	89 ^c	76
10	4-CHOC ₆ H ₄	5j	—	84
11	2-Furyl	5k	—	71
12	2-Thienyl	5l	—	52 ^f
13	3-Thienyl	5m	—	63

^a Using a preformed catalyst (see main text for details). ^b Using PhBF₃K as a substitute for PhB(OH)₂. ^c 3 h reaction time. ^d Residual boronic acid starting material remaining. ^e 2 h reaction time. ^f 18 h reaction time.

Reactions were conducted using standard 'in-house' conditions, namely Pd(OAc)₂ (5 mol%), Xphos (10 mol%), aq. Na₂CO₃ (2 M), 80 °C, 3.5 h (hereafter Conditions B). Nine substituted biphen-4-yl-2'-deoxyadenosines were generated in good yields (entries 1–4, 6–10, Table 1) and three heteroaromatics were also coupled successfully (entries 11–13, Table 1). Using PhBF₃K as a substitute for PhB(OH)₂, a slightly lower yield of **5c** (entry 3, Table 1) was obtained with Conditions B. The structures of compounds **5d** and **5i** were determined by single crystal X-ray diffraction; **5d** is shown as a representative example in Fig. 2.

The crystal structure of **5d** shows that this nucleoside adopts a *syn*-C2'-*endo* conformation and exhibits an intramolecular H-bond, consistent with related 8-aryl-2'-deoxyadenosines.^{8b}

The Suzuki–Miyaura couplings using **3** (Conditions A) provided the 8-(2-fluoro-biphen-4-yl)-2'-deoxyadenosines **6a** and **6b** in good yields (Table 2, entries 1 and 2). 8-(Biphen-3-yl)-2'-deoxyadenosines **7a–c** were accessible from **4** and ArB(OH)₂ using Conditions B (Table 2, entries 3–5). Finally, the chloro-substituted analogue **5e** was subjected to Conditions B to give terphenyl analogue **8** in 76% yield (Scheme 3).

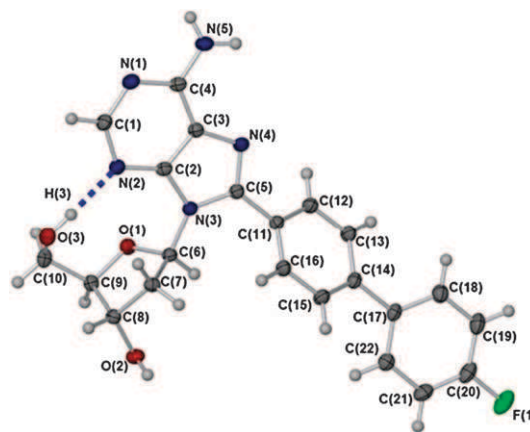
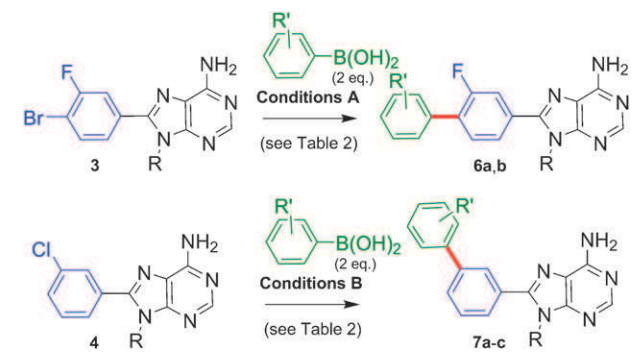
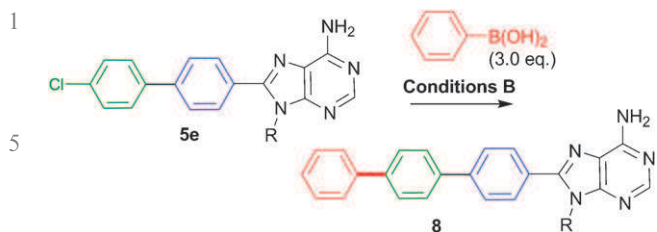


Fig. 2 Crystal structure of compound **5d** (using arbitrary numbering).

Table 2 Suzuki–Miyaura couplings of **3** and **4** with arylboronic acids



Entry	Substrate	Conditions	R'	Cpd	Yield/%
1	3	A	4'-MeO	6a	65
2	3	A	H	6b	93
3	4	B	4'-MeO	7a	88
4	4	B	H	7b	87
5	4	B	3',5'-F	7c	87



Scheme 3 Synthesis of terphenyl derivative **8**.

Table 3 Photophysical properties of 8-substituted-2'-deoxyadenosines in DMSO at 25 °C

Cpd	λ_{\max}/nm	$\epsilon \times 10^4/\text{M}^{-1} \text{cm}^{-1}$	$\lambda_{\text{em}}/\text{nm}$	Stokes shift/ cm^{-1}	Φ
5a	309	3.13	400	7362	0.65
5b	305	2.26	409	8337	0.68
5c	304	2.07	414	8740	0.69
5d	304	2.30	412	8623	0.69
5f	307	1.71	434	9532	0.72
5g	307	1.75	440	9846	0.75
5h	304	1.76	427	9475	0.77
5i	314	2.02	491	11 481	0.27
5j	318	2.53	399	6384	0.10
5k	320	2.71	407	6680	0.70
5l	322	2.25	419	7190	0.59
5m	307	2.14	403	7759	0.64
6a	310	2.21	408	7748	0.60
6b	304	1.89	420	9085	0.69
7a^a	275	3.30	393	10 918	—
7b^a	261	1.93	380	11 278	—
7c^a	260	1.98	383	12 352	—
8	315	3.14	424	8161	0.77
9^b	289	1.29	384	8560	0.81

^a Measurements determined using methanol solutions. ^b Compound **9** is 8-phenyl-2'-deoxyadenosine.^{8b}

The photophysical properties of all RONs (**5a–j**, **6a**, **6b**, **7a–c**, **8** and **9**) were determined (λ_{\max} , ϵ , λ_{em} and Φ are listed in Table 3). A sequential increase in the UV λ_{\max} and decrease in fluorescence lifetime is observed as the π -system is extended: phenyl (289 nm, 2.6 ns, **9**), biphen-4-yl (304 nm, 1.9 ns, **5c**) and terphenyl (315 nm, 1.7 ns, **8**). The biphen-3-yl derivatives (**7a–c**) possess unfavourable λ_{\max} values which overlap with biomolecular absorption bands.¹¹ In the **5a–m** series the λ_{\max} values are either similar to **5c** or shifted to longer wavelengths. The 8-aryl-2'-deoxyadenosines (**5a–h**, **5k–m**, **6a**, **b**, **8** and **9**) have excellent fluorescence quantum yields (0.59–0.81).

In summary, a library of novel RONs has been synthesised using an efficient sequential direct arylation/Suzuki–Miyaura coupling approach. The spectroscopic properties of RONs can be tuned by changing the terminal aryl group, in most cases without adversely affecting the quantum yield. Once incorporated into oligonucleotides using solid-phase synthesis, the RONs could be exploited as thymine specific base-discriminating fluorescent probes.^{10a}

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