

Direct N^9 -arylation of purines with aryl halides†

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Cite this: *Chem. Commun.*, 2014, 50, 4997Received 12th November 2013,
Accepted 10th February 2014

DOI: 10.1039/c3cc48642g

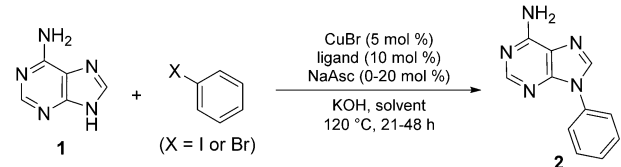
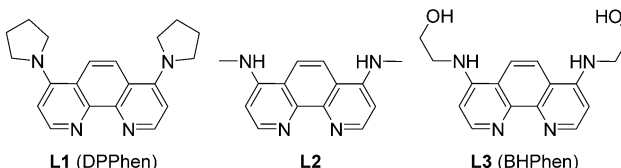
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An efficient method for N -arylation of purines is reported. The N -arylation is catalysed by Cu(I) and 4,7-bis(2-hydroxyethylamino)-1,10-phenanthroline (BHPen) in aqueous DMF or ethanol. The reaction generally proceeds with high selectivity for the N^9 -position.

Purine is a ubiquitous heterocyclic scaffold of fundamental importance, and is considered to be a privileged structure in medicinal chemistry.¹ Purine-based compounds, including N^9 -aryl purines, exhibit a wide range of biological and pharmaceutical activities,² such as antiviral,³ antibacterial⁴ and anti-cancer⁵ effects. In light of their importance, there is a surprising paucity of efficient methods for N -arylation of purines. Despite the many methods for metal-catalysed C–N bond formation,⁶ only few examples involving purines are reported. Arylboronic acids and diaryliodonium salts have been used to achieve a Cu-mediated regioselective N^9 -arylation or N^7 -arylation of various purine derivatives in moderate to very good yields under relatively mild conditions,⁷ but these reactions often have a narrow substrate scope and N^9 -arylguanines have only been prepared by the arylation of protected or masked nucleobases.^{7b,d} Aryl halides are abundantly available and are generally more stable than boronic acids and diaryliodonium salts; however, only three publications describe the N -arylation of purines with aryl halides, all in moderate yields.^{2b,8} Based on the hypothesis that electron-rich 1,10-phenanthroline ligands improve the performance by better stabilisation of the proposed Cu(III)-intermediate in the catalytic cycle, we recently found that 4,7-dipyrrolidinyl-1,10-phenanthroline (**L1**, DPPhen) catalyse N -arylation of various N -heterocycles with aryl halides in water. This system was also able to N -arylate adenine, 2,6-diaminopurine and theophylline, albeit only in moderate yields.⁹ Herein, we report a more general method for the direct synthesis of N -arylated purines with high and predictable

selectivity for the N^9 - or N^7 -position over other potential coupling positions and complete selectivity over other nucleophilic sites including aromatic amines. The method is exemplified with various purines and a broad selection of aryl halides.

Table 1 Reaction optimisation^a

						
						
Entry	Ligand	X	Solvent ^b	NaAsc (mol %)	Ratio PhX/1	Yield ^c (%)
1	L1	I	EtOH–H ₂ O	—	1 : 1.2	46
2	L1	I	EtOH–H ₂ O	5	1 : 1.2	40
3	L1	I	EtOH–H ₂ O	10	1 : 1.2	70
4	L1	I	EtOH–H ₂ O	20	1 : 1.2	58
5	L1	I	EtOH–H ₂ O	10	1.5 : 1	83
6	L1	I	BuOH–H ₂ O	10	1.5 : 1	79
7	L1	I	EtOH	10	1.5 : 1	42
8	L1	Br	EtOH–H ₂ O	10	2 : 1	75
9	None	I	EtOH–H ₂ O	10	2 : 1	5
10	L2	Br	EtOH–H ₂ O	10	2 : 1	77
11	L3	Br	EtOH–H ₂ O	10	2 : 1	91
12	L3	I	EtOH–H ₂ O	10	1.5 : 1	90
13	L3^d	I	EtOH–H ₂ O	10	1.5 : 1	78
14	L3^e	I	EtOH–H ₂ O	10	1.5 : 1	64
15	L3	Br	EtOH–H ₂ O	10	1.5 : 1	85
16	L3	I	DMSO–H ₂ O	10	1.5 : 1	84
17	L3	Br	DMSO–H ₂ O	10	1.5 : 1	86
18	L3	I	DMF–H ₂ O	10	1.5 : 1	90
19	L3	Br	DMF–H ₂ O	10	1.5 : 1	87

^a Reaction conditions: **1** (0.50–0.75 mmol), aryl halide (PhX, 0.50–1.00 mmol), KOH (1.0 mmol), CuBr (5 mol %), ligand **L1**–**L3** (10 mol %), sodium ascorbate (NaAsc, 0–20 mol %), solvent (1 mL), 120 °C, 21 h (X = I) or 48 h (X = Br). ^b Solvent ratio was 4 : 1 (v/v). ^c Yield of isolated product. ^d 7.5 mol % **L3**. ^e 15 mol % **L3**.

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† Electronic supplementary information (ESI) available: Experimental procedures and full spectroscopic data for all new compounds. See DOI: 10.1039/c3cc48642g



Direct *N*-arylation of guanine and hypoxanthine are reported for the first time.

The coupling of adenine (**1**) with iodobenzene was selected for optimisation, initially using CuBr and ligand **L1** with KOH as base in EtOH/H₂O (4 : 1) at 120 °C (Table 1). EtOH/H₂O was chosen since it readily produces a homogeneous mixture at this temperature. These conditions exclusively afforded the *N*⁹-arylated isomer in 46% yield with no trace of coupling at the *N*⁷- or 6-amino positions (entry 1). This complete regioselectivity is in accordance with selectivity observed in copper catalysed *N*-arylation of annelated imidazoles.¹⁰ Speculating that the moderate yield might be caused by *in situ* oxidation of Cu(I) to Cu(II), sodium ascorbate was added to the reaction mixture. This indeed improved the yield, with a 2 : 1 molar ratio between sodium ascorbate and copper giving the best results (entries 2–4). A ratio of 1.5 : 1 between iodobenzene and adenine provided the desired product in 83% yield (entry 5). Less polar reaction media, such as 1-butanol and water or pure ethanol, did not result in improved performance (entries 6 and 7), and more polar systems led to solubility problems.

Coupling with two equivalents of bromobenzene also gave good yield (entry 8), but we felt that the reaction could be improved further by reducing the amount of aryl halide. The phenanthroline ligand is critical for the reaction, as only trace amounts of the coupling product are observed when it is removed (entry 9). Ligand screening indicated poor general performance of bipyridines but superior performance of 4,7-dimethylaminophenanthroline **L2** compared to **L1** (see Table S1, ESI†). This can be rationalised by avoidance of steric interactions between the 4,7-substituents and the central phenanthroline ring for **L2** and thereby higher planarity and increased electron donating effect of the amine substituents. Inspired by this result, we designed and synthesised phenanthroline ligand **L3** with 2-hydroxyethylamino substituents. Interestingly, while ligand **L2** afforded a yield similar to **L1** in the optimised protocol (entry 10), **L3** represented a substantial improvement, providing the desired product in excellent yield (entry 11). This may be ascribed to further increased electron donation from the 2-hydroxyethylamino substituents because of intramolecular hydrogen bonds between the amino nitrogen atoms and the hydroxyl groups, and possibly also to improved solubility properties.

Changing the ratio between copper and ligand to 1 : 1.5 gave a moderate drop in yield (entry 13), whereas a 1 : 3 ratio gave a pronounced drop (entry 14). This is in accordance with previous observations and is probably due to sequestering of copper by the excess ligand.⁹ Variation of the solvent system showed that DMSO/H₂O and DMF/H₂O also afforded very good yields at an aryl halide/adenine ratio of 1.5 : 1 for both iodobenzene and bromobenzene (entries 12 and 15–19), indicating a high robustness of the reaction. Of these, DMF/H₂O was chosen as the medium for further investigation of the scope of the reaction, as it consistently gave high yields, produced a lower vapour pressure than EtOH/H₂O, and was more readily removed than DMSO. It is well known that DMF/H₂O can decompose to form dimethylamine when heated under basic conditions.¹¹

Table 2 Coupling of various aryl halides to adenine^a

 1	+	 (X = I or Br)	$\xrightarrow[\text{KOH, DMF/H}_2\text{O (4:1), 120 }^\circ\text{C, 21-48 h}]{\text{CuBr (5 mol \%), L3 (10 mol \%), NaAsc (10 mol \%)}}$	 3a-p
 3a : 89% (X = I)	 3b : 88% (X = I) 76% (X = Br)	 3c : 66% ^b (X = I)	 3d : 77% (X = I)	 3e : 83% (X = I)
 3f : 81% (X = I)	 3g : 2% (X = I)	 3h : 7% (X = I)	 3i : 82% (X = Br)	 3j : 81% (X = Br)
 3k : 76% (X = Br)	 3l : 63% ^b (X = Br)	 3m : 77% (X = Br)	 3n : 84% (X = Br)	 3o : 82% (X = Br)
				 3p : 79% ^c (X = Br)

^a Reaction conditions: **1** (0.50 mmol), aryl halide (0.75 mmol), KOH (1.0 mmol), CuBr (5 mol%), **L3** (10 mol%), NaAsc (10 mol%), DMF/H₂O (1 mL, 4 : 1 v/v), 120 °C, 21 h (X = I) or 48 h (X = Br). Yield of isolated product. ^b Incomplete solubility of the reactant and product in the reaction medium. ^c EtOH/H₂O (1 mL, 4 : 1 v/v) was used as solvent. With DMF/H₂O as solvent, the aliphatic *N*-formyl derivative of **3p** was isolated in 79% yield.

While some dimethylamine indeed was observed in the reaction mixture, it did not interfere with the reaction, further supporting the robustness of this method.

The substrate scope of the *N*-arylation was investigated by coupling adenine with aryl iodides and aryl bromides carrying various electron donating or withdrawing polar or non-polar substituents (Table 2). Alcohol, phenol, amine, carboxylic acid, cyano, trifluoromethyl, nitro, ketone and fluoro groups were all well tolerated and gave good to very good yields. However, substrates carrying substituents in the *ortho* position (**3g** and **3h**) were poorly tolerated, probably because of unfavourable steric interactions with the Cu-ligand complex. 2-Bromopyridine, 5-bromo-2-methylpyridine and 3-bromothiophene coupled readily to yield **3i**, **3j** and **3k**, respectively, indicating that heteroaryl halides are also suitable *N*-arylation substrates.¹² When 4-bromophenethylamine was used as the substrate, formyl transfer from DMF was observed, resulting in isolation of the aliphatic formamide derivative of **3p** as the only product in 79% yield. Switching to EtOH/H₂O as reaction medium gave the expected primary amine **3p** in 79% yield.

To further explore its scope, the protocol was investigated with various purine coupling partners (Table 3). Purine (**4a**) couples with iodo- and bromobenzene with a high selectivity for the *N*⁹- over the *N*⁷-position. This is rationalised by *N*³ exerting a directing effect on the catalytic complex. Coupling of 2,6-diaminopurine (**4b**) with iodo- and bromobenzene gave



Table 3 Coupling of various aryl halides to adenine^{a,b}

X = I: 5a : 62% (7%) X = Br: 5a : 64% (3%)	X = I: 5b : 94% X = Br: 5b : 60%	X = I: 6c : 79% ^c X = Br: 6c : 78%
X = I: 6d : 12% ^c X = Br: 6d : 10%	X = I: 5e : 60% (21%) ^d X = Br: 5e : 59% (13%) ^d	X = I: 5f : 43% (14%) ^{d,e} X = Br: 5f : 48% (11%) ^{d,f}

^a Reaction conditions: **4a-f** (0.50 mmol), aryl halide (PhX, 0.75 mmol), KOH (1.0 mmol), CuBr (5 mol%), L3 (10 mol%), NaAsc (10 mol%), DMF/H₂O (1 mL, 4:1 v/v), 120 °C, 21 h (X = I) or 48 h (X = Br). ^b Isolated yields, yields of the other (*N*⁷) regioisomers are given in parentheses. ^c *t* = 48 h. ^d No added NaAsc; the solvent was DMSO/H₂O (1 mL, 4:1 v/v). ^e *t* = 6 h. ^f *t* = 32 h.

94% and 60% yields, respectively, but with complete selectivity for the *N*⁹-position over the three other potential coupling positions in the molecule (*N*⁷ and the two amino groups). The exclusive selectivity for the *N*⁹- over the *N*⁷-position in both adenine and 2,6-diaminopurine indicates that the 6-amino group blocks *N*⁷-arylation. In contrast, theophylline (**4c**) couples with iodo- and bromobenzene to give 79% and 78% yields, respectively, of the exclusively *N*⁷-arylated product, which can be rationalised by steric hindrance of the *N*⁹-position by the *N*³-methyl substituent. The reaction of 8-methyltheophylline (**4d**) with iodo- and bromobenzene results in the isolation of the *N*⁷-arylated product in only 10–12% yield, indicating detrimental steric interactions between the *C*⁸-methyl and the Cu-ligand complex.

Guanine (**4e**) and hypoxanthine (**4f**) both couple with iodo- and bromobenzene with a lower preference for the *N*⁹-position over the *N*⁷-position compared to purine, reflecting a directing effect on the *N*⁷-position by the adjacent carbonyl group. The preference for the *N*⁹-position was enhanced by changing the solvent to DMSO/H₂O and omitting sodium ascorbate. For both purines, this resulted in a ratio of isolated *N*⁹/*N*⁷-arylated product of 3:1 with iodobenzene and 9:2 with bromobenzene. In the case of hypoxanthine, arylation at *N*¹ in addition to *N*⁹ was seen, and the reaction time was shortened to prevent over-arylation, resulting in somewhat lower yields compared to guanine, where no diarylated products were observed.

In conclusion, we have identified *N*⁴,*N*⁷-bis(2-hydroxyethyl)-1,10-phenanthroline-4,7-diamine (L3, BHPPhen) as an enabling ligand for selective, direct copper-catalysed arylation of various common purines with aryl iodides and aryl bromides in moderate to excellent yields. Direct coupling of guanine and hypoxanthine with aryl halides were achieved for the first time. This is also the first report of direct coupling of purines with aryl bromides.

Coupling of purines with aryl chlorides and sterically hindered aryl halides remains a challenge. A notable aspect is the predictable and generally high selectivity observed for arylation of one specific position in the presence of several other potential alkylation positions. Arylation at the *N*⁹-position was generally preferred, but this preference was altered in a predictable manner by the presence of adjacent groups. The robustness of the reaction is demonstrated not only by the broad substrate scope, but also by a good performance in several different solvent systems. Although DMF/H₂O was chosen as the standard for the reactions reported herein, the EtOH/H₂O system might be more suitable for up-scaling, where the cost and environmental impact become important factors.

We are grateful for financial support from the Danish Council for Independent Research, Technology and Production, Grants 274-08-056 and 09-070364.

Notes and references

- (a) H. Rosemeyer, *Chem. Biodiversity*, 2004, **1**, 361; (b) M. E. Welsch, S. A. Snyder and B. R. Stockwell, *Curr. Opin. Chem. Biol.*, 2010, **14**, 347.
- (a) M. Legraverend and D. S. Grierson, *Bioorg. Med. Chem.*, 2006, **14**, 3987; (b) N. Kato, T. Sakata, G. Breton, K. G. Le Roch, A. Nagle, C. Andersen, B. Bursulaya, K. Henson, J. Johnson, K. A. Kumar, F. Marr, D. Mason, C. McNamara, D. Plouffe, V. Ramachandran, M. Spooner, T. Tuntland, Y. Zhou, E. C. Peters, A. Chatterjee, P. G. Schultz, G. E. Ward, N. Gray, J. Harper and E. A. Winzeler, *Nat. Chem. Biol.*, 2008, **4**, 347; (c) F. Di Virgilio, *Cancer Res.*, 2012, **72**, 5441.
- L. Aguado, H. J. Thibaut, E.-M. Priego, M.-L. Jimeno, M.-J. Camarasa, J. Neyts and M.-J. Pérez-Pérez, *J. Med. Chem.*, 2009, **53**, 316.
- A. K. Bakkestuen, L.-L. Gundersen and B. T. Utenova, *J. Med. Chem.*, 2005, **48**, 2710.
- N. Kode, L. Chen, D. Murthy, D. Adewumi and S. Phadtare, *Eur. J. Med. Chem.*, 2007, **42**, 327.
- (a) I. P. Beletskaya and A. V. Cheprakov, *Organometallics*, 2012, **31**, 7753; (b) T. R. M. Rauws and B. U. W. Maes, *Chem. Soc. Rev.*, 2012, **41**, 2463; (c) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054.
- (a) A. K. Bakkestuen and L.-L. Gundersen, *Tetrahedron Lett.*, 2003, **44**, 3359; (b) M. F. Jacobsen, M. M. Knudsen and K. V. Gothelf, *J. Org. Chem.*, 2006, **71**, 9183; (c) L. Tao, Y. Yue, J. Zhang, S.-Y. Chen and X.-Q. Yu, *Helv. Chim. Acta*, 2008, **91**, 1008; (d) R. Keder, H. Dvořáková and D. Dvořák, *Eur. J. Org. Chem.*, 2009, 1522; (e) H.-Y. Niu, C. Xia, G.-R. Qu, Q. Zhang, Y. Jiang, R.-Z. Mao, D.-Y. Li and H.-M. Guo, *Org. Biomol. Chem.*, 2011, **9**, 5039; (f) I. Čerňa, R. Pohl, B. Klepetářová and M. Hocek, *J. Org. Chem.*, 2008, **73**, 9048; (g) S. Ding, N. S. Gray, Q. Ding and P. G. Schultz, *Tetrahedron Lett.*, 2001, **42**, 8751; (h) E. Kiselgof, D. B. Tulshian, L. Arik, H. Zhang and A. Fawzi, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2119; (i) I. Dreier, S. Kumar, H. Søndergaard, M. L. Rasmussen, L. H. Hansen, N. H. List, J. Kongsted, B. Vester and P. Nielsen, *J. Med. Chem.*, 2012, **55**, 2067.
- (a) J. C. Antilla, J. M. Baskin, T. E. Barder and S. L. Buchwald, *J. Org. Chem.*, 2004, **69**, 5578; (b) M. N. Soltani Rad, S. Behrouz, M. M. Doroodmand and N. Moghtaderi, *Synthesis*, 2011, 3915.
- J. Engel-Andreasen, B. Shimpukade and T. Ulven, *Green Chem.*, 2013, **15**, 336.
- (a) S. Ueda and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2012, **51**, 10364; (b) N. T. Jui and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2013, **52**, 11624.
- (a) A. Agarwal and P. M. S. Chauhan, *Synth. Commun.*, 2004, **34**, 2925; (b) L. Čechová, P. Jansa, M. Šála, M. Dračinský, A. Holý and Z. Janeba, *Tetrahedron*, 2011, **67**, 866; (c) T. P. Petersen, A. F. Larsen, A. Ritzén and T. Ulven, *J. Org. Chem.*, 2013, **78**, 4190.
- A control reaction without CuBr gave only 7% conversion after 48 h, indicating that nucleophilic aromatic substitution only makes a minor contribution to the yield of **3i**.

