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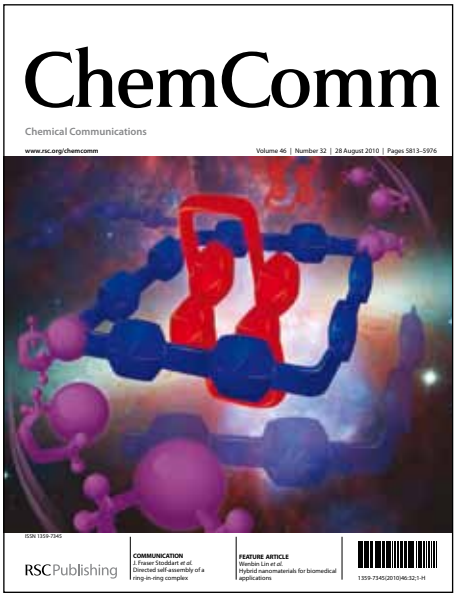

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Stereoselective copper-catalyzed Chan-Lam-Evans *N*-arylation of glucosamines with arylboronic acids at room temperature

Alexandre Bruneau, Jean-Daniel Brion, Mouad Alami* and Samir Messaoudi*

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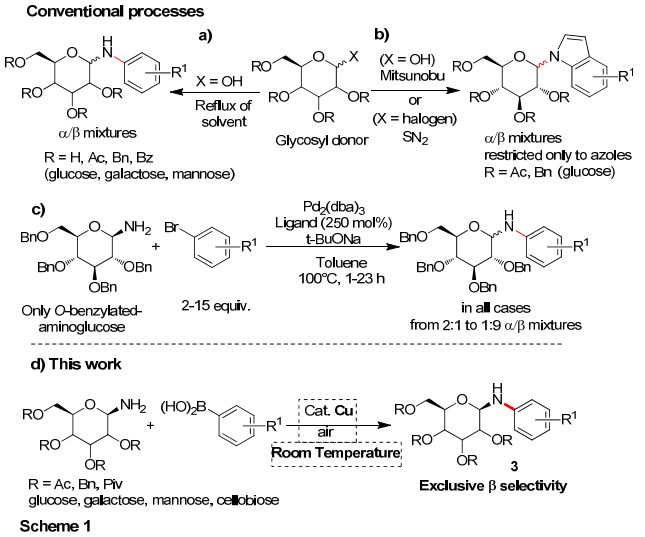
An efficient and practical *N*-arylation of glycosylamines with substituted aryl boronic acids has been established. Using $Cu(OAc)_2$ and pyridine at room temperature under air atmosphere, the protocol proved to be general, and a variety of aryl *N*-glycosides have been prepared in good to excellent yields with exclusive β selectivity.

Substituted *N*-glycosides are valuable synthetic targets due to their presence in compounds ranging from pharmaceuticals to materials.[1] One of the most important subfamilies of *N*-glycosides is (hetero)aryl *N*-glycosides whose derivatives show promising biological activities, including antiviral,[2] and anticancer[3] properties. While these derivatives clearly hold great potential in medicinal chemistry as well as in organic synthesis, the synthesis of aryl *N*-glycosides has never been thoroughly explored, since the stereoselective induction of nitrogen scaffolds at the anomeric position remains a particularly difficult task.[4] Usually, these derivatives are prepared by treating aniline derivatives with glycosyl hydroxides at high temperature (Scheme 1, path a).[5] Alternative routes to *N*-glycosidic bond formation consist on the use of N-H azoles as partners in (*i*) a Mitsunobu coupling glycosylation with glycosyl hydroxides (Scheme 1b),[6] or (*ii*) a nucleophilic substitution of the acetohaloglycoside precursor under basic conditions (Scheme 1b).[7] These procedures however, are cruelly limited in substrate scope with respect to nitrogen nucleophile[8] and (hetero)aryl *N*-glycosylamines were obtained in variable yields depending on the reactivity of the nitrogen nucleophile. In addition, reactions can be lengthy and undesired mixture of epimers α/β is occasionally observed.[4,5a] An appealing option to access aryl *N*-glycosides **3** would be the use of glycosylamines as nucleophiles in transition metal-catalyzed reactions. To our knowledge, only one report described the preparation of aryl *N*-glycosides by coupling of per-*O*-benzylated D-glucopyranosylamine with activated bromoarenes (Scheme 1c).[9] This report is very interesting since glycosylamines can act as a nucleophile in transition metal-catalyzed reactions. Unfortunately, the preparative interest of



Scheme 1

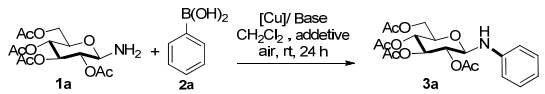
this transformation is limited since the reaction required the use of catalytic to stoichiometric amounts of Pd_2dba_3 (10 to 200 mol%), and a large excess of ligand (2.5 equiv) as well as aryl bromide (2 to 15 equiv) to obtain satisfactory yields of coupling products. Only per-*O*-benzylated D-glucopyranosylamine was used as a sugar partner, thus limited the scope of the reaction. Moreover, in all cases, a mixture of anomers (from 2:1 to 1:9 α/β) was observed due probably to the instability of glycosylamines at high temperature. Owing to the biological significance and existing restricted synthetic methodologies, there is an exigent need for a facile and efficient protocol to synthesize aryl *N*-glycosides **3**.

Since the initial reports of Chan and Lam,[10] the copper promoted coupling of amines with organoboronic acids has emerged as a powerful tool for C–N bond formation, and has found wide applications in organic synthesis because of the mildness of the reaction conditions. Although this coupling has been extensively studied with various nitrogen nucleophiles, to the best of our knowledge, there is no report describing the formation of aryl *N*-glycosides from aminoglycosides and arylboronic acids. Consequently, in continuation of our interest in C-heteroatom bond formation,[11] we report herein that *N*-arylation of glucosamines can be realized efficiently and stereoselectively using a catalytic amount of $Cu(OAc)_2$ at room temperature under air atmosphere (Scheme 1d).

Univ Paris-Sud, CNRS, BioCIS-UMR 8076, Laboratoire de Chimie Thérapeutique, LabEx LERMIT, Faculté de Pharmacie, 5 rue J.-B. Clément, Châtenay-Malabry, F-92296, France. Fax: + (33) 0146835828; Tel: + (33) 0146835887; E-mail: samir.messaoudi@u-psud.fr, mouad.alami@u-psud.fr

† Electronic Supplementary Information (ESI) available: General, experimental procedures for starting materials and ^1H and ^{13}C spectra for all new compounds. See DOI: 10.1039/b000000x/

Table 1 Survey of reaction conditions for the *N*-arylation of aminoglucose **1a** with **2a**[a]



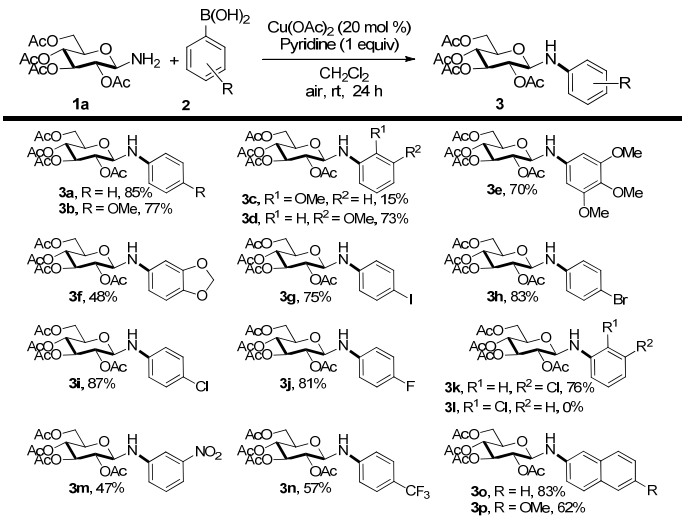
entry	[Cu]	Base	[c] Mol/L	Conv. (%)[b]	yield (%)[c]
1	$Cu(OAc)_2$	Pyridine	0.07	51[d]	19
2	$Cu(OAc)_2$	Pyridine	0.07	45	21
3	$Cu(OAc)_2$	Pyridine	0.14	65	53
4	$Cu(OAc)_2$	Pyridine	0.29	68	57
5	$Cu(OAc)_2$	Pyridine	0.58	85	65
6	$Cu(OAc)_2$	Pyridine	0.58	86[e]	72
7	$Cu(OAc)_2$	Collidine	0.58	28[e]	49
8	$Cu(OAc)_2$	Lutidine	0.58	40[e]	-
9	$Cu(OAc)_2$	Et_3N	0.58	40[e]	-
10	$Cu(OAc)_2$	K_2CO_3	0.58	54[e]	-
11	$Cu(OAc)_2$	Pyridine	0.58	82[e,f]	72
12	$Cu(OAc)_2$	Pyridine	0.58	66[e,g]	-
13	CuI	Pyridine	0.58	52[e,f]	-
14	$CuSO_4.5H_2O$	Pyridine	0.58	37[e,f]	-
15	CuTC	Pyridine	0.58	65[e,f]	-
16	$Cu(OAc)_2$	Pyridine	0.58	95[e,f]	80[h]
17	**$Cu(OAc)_2$**	**Pyridine**	**0.58**	**100[e,f]**	**85[i]**

[a] **1a** (1 equiv), phenylboronic acid **2a** (2 equiv), [Cu] (20 mol %), base (2 equiv), molecular sevies, CH_2Cl_2, 24 h, 20 °C. [b] Conversion was determined by ^1H NMR in the crude reaction mixture based on the chemical shift of the proton signal (ppm) at the C5-position of the sugar moiety (**1a**: δ = 3.69, **3a**: δ = 3.82). [c] Yield of isolated **3a**. [d] 1.5 equiv. of $Cu(OAc)_2$ were used. [e] The reaction was performed without molecular sieves as the additives. [f] Reaction with 1 equiv. of pyridine. [g] Reaction with 40 mol% of pyridine. [h] $PhB(OH)_2$ (2 equiv) were added in two portions at t = 0 and 3.5 h. [i] $PhB(OH)_2$ (2.5 equiv) were added in three portions at t = 0 (1 equiv), 3.5 h (0.75 equiv) and 7 h (0.75 equiv).

At the outset, we examined the coupling of peracetylated β-aminoglucose **1a** with phenylboronic acid **2a** under various source of copper catalysts, bases and solvents. Representative results from this study are summarized in Table 1. The reaction of **1a** (1 equiv) with **2a** (2 equiv) was first investigated under Chan and Lam's original procedure[10a,b] [$Cu(OAc)_2$ (1.5 equiv), pyridine (2 equiv), molecular sieves, CH_2Cl_2, 24 h at 20 °C] (Table 1, entry 1). Unfortunately, this protocol afforded an inseparable mixture of the expected β-aryl *N*-glycoside **3a**, together with diphenyl byproduct arising from an oxidative homo-coupling of phenylboronic acid[12]. After a tedious separation, **3a** was isolated in a low 19% yield. Next, we examined the catalytic version using 20 mol% of $Cu(OAc)_2$ under otherwise identical conditions. Although the reaction conversion was low compared to the stoichiometric version, the desired product **3a** was isolated in a similar yield (21%, entry 2). Increasing the concentration of β-aminoglucose **1a** from 0.07 to 0.29 M largely favors the formation of **3a** (entries 2-4) and the concentration c = 0.58 M was found to be the best compromise between solubility and efficiency of the reaction with the yield of **3a** increased up to 65% (entry 5). These results indicate clearly that the concentration of **1a** plays a critical role in the outcome of the C–N bond formation. Further optimization revealed that the presence of molecular sieves proved to be deleterious for the coupling of **1a** with **2a** since performing the reaction without molecular sieves led to the desired product **3a** in a good 72% yield (entry 6). The screening reaction was continued with respect to the base. Pyridine was found to be the best choice (compare entries 6 and 7-10), and the use of only 1 equivalent was sufficient, giving rise to **3a** in a good 72% yield (entry 11). One can note that under catalytic amount of pyridine (40 mol%), the reaction conversion drops down until 66% (entry 12). With respect to copper catalyst, no significant improvement of the yield of **3a** was observed (entries 13-15). Pleasingly, the yield of **3a** was improved up to 85% by employing 2.5 equivalent of phenylboronic acid added in three portions (entry 17). Under these optimal conditions, **3a** was formed as a single β-isomer without any anomerization.

Motivated by these results, we next explored the scope of the coupling reaction of β-aminoglucose **1a** with various arylboronic acids.[13] Gratifyingly, all the arylations proceeded cleanly and selectively in excellent yields. As depicted in Table 2, **1a** was readily coupled with aryl boronic acids having *para* and *meta* electron-donating or electron-withdrawing substituents to give *N*-glycosylated products in good to excellent yields with complete β-selectivity.

Table 2 Scope of arylboronic acids **2** for Cu-catalyzed *N*-arylation of aminoglucose **1a**[a]

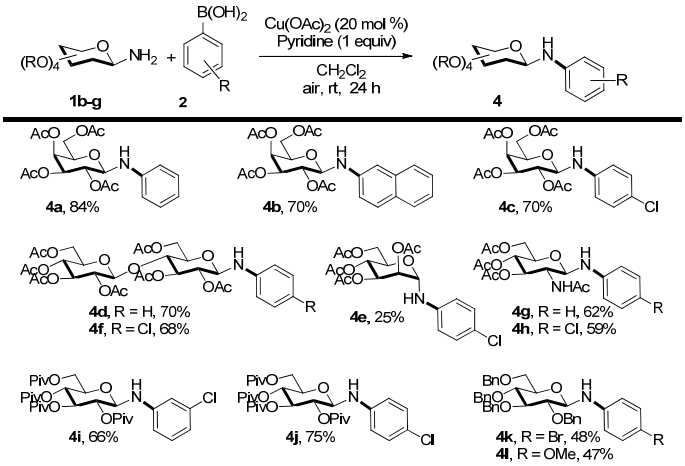


[a] Reactions of **1a** (1 equiv) with $ArB(OH)_2$ (2.5 equiv) were performed in flask at r.t. in CH_2Cl_2 by using $Cu(OAc)_2$ (20 mol %), Pyridine (1 equiv).

It was soon discovered that substitution *ortho* to boron had a dramatic influence on the reaction rate. The relatively hindered 2-methoxyphenylboronic acid gave only a 15% yield of the desired compound **3c**, while 2-chlorophenylboronic acid did not furnish **3n** even using a stiochiometric amount of $Cu(OAc)_2$. Interestingly, C-halogen bonds (e.g., I, Br, Cl, F) were tolerated in the *N*-glycosylation reaction affording compounds **3g-k** in yields ranging from 75 to 87%. The presence of halogen substituents in **3g-k** provided a handle for further structural diversifications using metal-catalyzed cross coupling reactions.

In a further set of experiments, we investigated the scope and generality of the method with respect to mono- and aminodisaccharides. As depicted in Table 3, coupling reactions proceeded cleanly in high yields without any side reaction such as anomerization of the resulting aryl-*N*-glycosides. The reaction is general with respect to the sugar configuration as *O*-acetylated 1-amino–β–D-galactose, *O*-acetylated 1-amino–α–D-mannose[14]

Table 3 Scope of glucosamines **1b-g** for *N*-arylation with **2**[a]

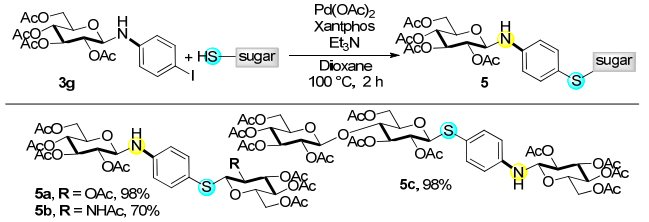


[a] Reactions of **1a** (1 equiv) with $ArB(OH)_2$ (2.5 equiv) were performed in flask at r.t. in CH_2Cl_2 by using $Cu(OAc)_2$ (20 mol %), Pyridine (1 equiv).

and 1-amino-*N*–acetyl-β–D-glucosamine give the corresponding products **4a-c**, **4e** and **4g,h** in moderate to good yields. The coupling procedure is not only limited to monoaminosaccharides but also works successfully with peracetylated β–D-disaccharide derived from D–cellobiose octaacetate. The exclusive 1,2-trans β–*N*-glycosides **4d**,**f** were obtained in 70% and 68% yields, respectively, and the stereochemistry of the 1–4' glycosidic bond remained intact. Importantly, there is no significant impact of protecting groups on the reactivity of the aminosugar derivatives since benzyl- or pivaloyl- protected carbohydrate react similarly than *O*-acetylated derivative **1a** furnishing the coupling products **4i-l** in yields ranging from 47 to 75%. Noteworthy, the coupling of unprotected 1-amino–β–glucose with phenylboronic acid failed, and the starting material was recovered unchanged.

With substantial amounts of **3g** in hand (Table 2), we focused our attention on demonstrating whether our method could be employed as a platform for molecular diversity. As shown in Table 4, the significant increase in molecular complexity achieved by otherwise simple and reliable transformations is quite appealing, thus giving access to structures that are difficult to obtain by other means. Notably, *N*-glycosyl phenylthioglycosides **5a-c**[15] bearing both C–N and C–S β–glycosidic bonds could easily be prepared *via* a Pd-catalyzed coupling reaction of **3g** with various thioglycosides.[11e]

Table 4 Pd-catalyzed *S*-glycosidation of **3g** with various thioglycosides **2**[a]



[a] For experimental conditions see reference (11e) or (ESI).

In summary, we have succeeded in achieving the coupling of *N*-glycosylamine derivatives with functionalized arylboronic acid at room temperature to furnish aryl *N*-aminoglycosides. To the best of our knowledge the $C(sp^2)$–N bond of aryl *N*-glycosides was formed, for the first time, directly by using *N*-glycosides as nucleophile partners in the presence of $Cu(OAc)_2$ as the catalyst system. Because of the mildness of the reaction conditions, the protocol developed is diastereoselective, functional-group tolerant, and proceeds in good to excellent yields. We believe that this methodology will find broad applications in organic synthetic chemistry as well as in combinatorial and pharmaceutical sciences.

Notes and references

1 (a) R. A. Dwek, *Chem. Rev.*1996, **96**, 683; (b) A. H. Adel, R. Abdel, S. H. El, A. El, R. S. Richard, *Carbohydr. Res*. 1999, **315**, 106; (c) D.M. Huryn, Okabe, M. *Chem. Rev.* 1992, **92**, 1745.

2 (a) A. L. Hopkins, J. Ren, J. Milton, R. J. Hazen, J. H. Chan, D. I. Stuart, D. K. Stammers, *J. Med. C*hem. 2004, **47**, 5912. (b) E. de Clerq, Antiviral Res. 2005, **67**, 56. (c) C. Mathe, G. Gosselin, *Antiviral Res.* 2006, **71**, 276.

3 (a) H. J. Knölker, K. R. Reddy, *Chem. Rev*. 2002, **102**, 4303; (b) F. Anizon, P. Moreau, M. Sancelme, A. Voldoire, M. Prudhomme, M. Ollier, D. Severe, J.-F. Riou, C. Bailly, D. Fabbro, T. Meyer, A.-M. Aubertin, *Bioorg. Med. Chem.* 1998, **6**, 1597; (c) C. Marminon, F. Anizon, P. Moreau, S. Leonce, A. Pierre, B. Pfeiffer, P. Renard, M. Prudhomme, *J. Med. Chem*. 2002, **45**, 1330.

4 M. Y. Fosso, V. P. N. Nziko, C. W. T. Chang, *J. Carbohydr. Chem*. 2012, **31**, 603.

5 (a) W. Du, Y. Hu, *Synth. Commun*. 2004, **34**, 2987. (b) N. Bridiau, M. Benmansour, M. D. Legoy, M. Maugard, *Tetrahedron*, 2007, **63**, 4178, (b) F. Erben, D. Kleeblatt, M. Sonneck, M. Hein, H. Feist, C. Fischer, A. Matin, J. Iqbal, M. Ploetz, J. Eberle, P. Langer, *Org. Biomol. Chem*., 2013, **11**, 3963.

6 (a) S. Messaoudi, F. Anizon, S. Léonce, A. Pierré, B. Pfeiffer, M. Prudhomme, *Eur. J. Med. Chem*. 2005, **40**, 961; (b) S. Messaoudi, F. Anizon, S. Léonce, A. Pierré, B. Pfeiffer, M. Prudhomme, *Tetrahedron* 2005, **61**, 7304; (c) H. Henon, S. Messaoudi, B. Hugon, F. Anizon, B. Pfeiffer, M. Prudhomme, *Tetrahedron* 2005, **61**, 5599.

7 (a) M. Ohkubo, T. Nishimura, H. Jona, M. Nakano, T. Honma, H. Morishima, *Tetrahedron* 1996, **52**, 8099; (b) M. Ohkubo, H. Kawamoto, T. Ohno, M. Nakano, H. Morishima, *Tetrahedron* 1997, **53**, 585; (c) S. Messaoudi, F. Anizon, B. Pfeiffer, R. Golsteyn, M. Prudhomme, *Tetrahedron Lett.* 2004, **45**, 4643.

8 Glycosyl amines are not stable enough to act as nucleophiles in SNAr to make *N*-glycosyl compounds.

9 N. Chida, *J. Synt. Org. Chem. Jpn*. 2008, **66**, 1105.

10 (a) D. M. T. Chan, K. L. Monaco, R. P. Wang , M. P. Winters, *Tetrahedron Lett*., 1998, **39** , 2933; (b) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan, A. Combs, *Tetrahedron Lett*. 1998, **39**, 2941; (c) D. A. Evans, J. L. Katz, T. R. West, *Tetrahedron Lett*. 1999, **39**, 2937; For review, see: (d) J. X. Qiao, P. Y. S. Lam, *Synthesis*, 2011, 829; (e) K. S. Rao, T.-S. Wu, *Tetrahedron* 2012, **68**, 7735.

11 (a) D. Audisio, S. Messaoudi, J.-F. Peyrat, J.-D. Brion, M. Alami, *Tetrahedron Lett*. 2007, **48**, 6928; (b) S. Messaoudi, D. Audisio, J.-D. Brion, M. Alami, *Tetrahedron* 2007, **63**, 10202; (c) D. Audisio, S. Messaoudi, J.-F. Peyrat, J.-D. Brion, M. Alami, *J. Org. Chem*. 2011, **76**, 4995; (d) S. Messaoudi, J.-D. Brion, M. Alami, *Adv. Synth. Catal*. 2010, **352**, 1677; (e) E. Brachet, J.-B. Brion, S. Messaoudi, M. Alami, *Adv. Synth. Catal*. 2013**, 355,** 477.

12 The arylboronic acids are well-known to dimerize under similar conditions, see: A. S. Demir, O. Reis, M. Emrullahoglu, *J. Org. Chem.* 2003, **68**, 10130.

13 The coupling of **1a** with heteroarylboronic acids (pyridin-3-ylboronic acid or benzofuran-2-ylboronic acid and thiophen-2-ylboronic acid) or with an aliphatic boronic acid (butylboronic acid) failed.

14 Attempts to prepare 1-amino-α–glucose failed. This later is unstable and isomerizes into the thermodynamically stable β-anomer. See: Y. Ichikawa, T. Nishiyama, M. Isobe, *J. Org. Chem*. 2001, **66**, 4200.

15 For recent reviews on glycoconjugates and applications see: a) Y. M. Chabre, R. Roy, *Chem. Soc. Rev.* 2013, **42**, 4657; b) M. Gingras, Y. M. Chabre, R. Roy, *Chem. Soc. Rev*. 2013, **42**, 4823; and references therein.