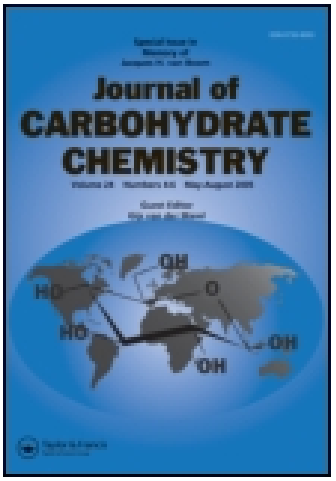
This article was downloaded by: [University of Sussex Library]
On: 11 February 2015, At: 08:36
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lcar20

Copper-Catalyzed Synthesis of N-aryl-D-Glucosamines from Arylboronic Acids

Chuanzhou Tao [a b], Feng Liu [a c], Bin Xu [a], Zhiling Cao [a b], Huiyan Wang [a] & Weiwei Liu [a c]

[a] School of Chemical Engineering, Huaihai Institute of Technology, Lianyungang, 222005, P.R. of China

[b] Jiangsu Marine Resources Development Research Institute, Lianyungang, 222005, P.R. of China

[c] School of Chemical Engineering, China University of Mining and Technology, XuZhou, 221116, P.R. of China

Published online: 11 Oct 2013.

To cite this article: Chuanzhou Tao, Feng Liu, Bin Xu, Zhiling Cao, Huiyan Wang & Weiwei Liu (2013) Copper-Catalyzed Synthesis of N-aryl-D-Glucosamines from Arylboronic Acids, Journal of Carbohydrate Chemistry, 32:7, 411-423, DOI: 10.1080/07328303.2013.816851

To link to this article: http://dx.doi.org/10.1080/07328303.2013.816851

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

Journal of Carbohydrate Chemistry, 32:411–423, 2013
Copyright © Taylor & Francis Group, LLC
ISSN: 0732-8303 print / 1532-2327 online
DOI: 10.1080/07328303.2013.816851

Taylor & Francis
Taylor & Francis Group

Copper-Catalyzed Synthesis of N-aryl-D-Glucosamines from Arylboronic Acids

Chuanzhou Tao,[1,2] Feng Liu,[1,3] Bin Xu,[1] Zhiling Cao,[1,2] Huiyan Wang,[1] and Weiwei Liu[1,3]

[1]School of Chemical Engineering, Huaihai Institute of Technology, Lianyungang 222005, P.R. of China
[2]Jiangsu Marine Resources Development Research Institute, Lianyungang 222005, P.R. of China
[3]School of Chemical Engineering, China University of Mining and Technology, XuZhou 221116, P.R. of China

A convenient catalytic protocol was developed to synthesize *N*-aryl-D-glucosamines from the corresponding arylboronic acids. C—N cross-coupling between arylboronic acids and 1,3,4,6-tetra-*O*-benzyl-*β*-D-glucosamine was realized by copper catalyst under mild conditions. Subsequent deprotection of the benzyl ethers gave the *N*-arylation products, *N*-aryl-D-glucosamines.

Keywords *N*-aryl-D-glucosamine; Arylboronic acid; Copper catalysis; Cross-coupling

Downloaded by [University of Sussex Library] at 08:36 11 February 2015

INTRODUCTION

D-Glucosamine and its *N*-substituted derivatives are found in numerous biologically active molecules such as cell surface *N*-glycoproteins, proteoglycans, glycosylphosphatidylinositol (GPI) anchors, glycosphingolipids, lipopolysaccharides, and chitin/chitosan.[1] Synthetic chemists also used these molecules as ligands or organocatalysts to introduce chirality in catalytic asymmetric reactions.[2] Recently, *N*-arylation derivatives from D-glucosamine (Fig. 1) were disclosed with many utilities such as a predictive method in ecotoxicology,[3a,3b]

Received April 5, 2013; accepted June 15, 2013.
Address correspondence to Chuanzhou Tao, School of Chemical Engineering, Huaihai Institute of Technology, Lianyungang 222005, P.R. of China, and Jiangsu Marine Resources Development Research Institute, Lianyungang 222005, P.R. of China E-mail: taocz@hhit.edu.cn.; and Weiwei Liu, School of Chemical Engineering, Huaihai Institute of Technology, Lianyungang 222005, P.R. of China, and School of Chemical Engineering, China University of Mining and Technology, XuZhou 221116, P.R. of China. E-mail: liuww323@yahoo.com.cn

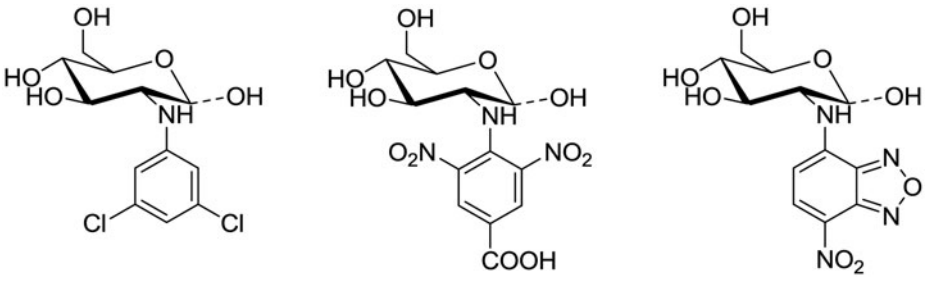


Figure 1: *N*-aryl-*D*-glucosamine derivatives.

Downloaded by [University of Sussex Library] at 08:36 11 February 2015

cancer cell detection,[3c] a metabolic indicator for FACS analysis,[3d] and measurement of glucose uptake in a single cell of living *E. coli*.[3e,3f] However, chemical modifications of D-glucosamine at the *N*-position mainly rely on acylation,[4] Schiff-base formation,[5] azidation,[6] and alkylation.[7] *N*-Arylation of D-glucosamine has rarely been realized due to synthetic difficulty. Only in a few examples was *N*-arylation of D-glucosamine accomplished by the S_NAr reaction between D-glucosamine and ary halides containing a strong electron-withdrawing group.[3,8]

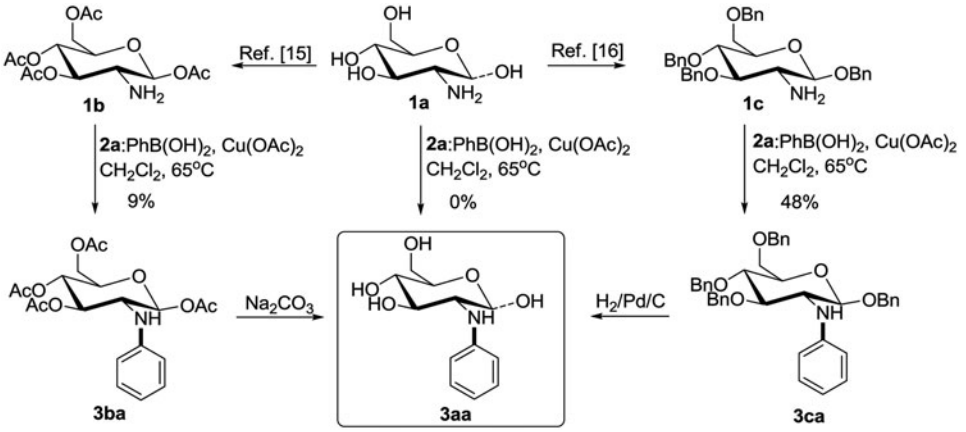
Very recently, we developed a general protocol for synthesis of *N*-aryl-D-glucosamines by the copper-catalyzed cross-coupling between aryl halides and D-glucosamine.[9,10] With aryl halides as arylation reagents, a number of functionalized *N*-aryl-1,3,4,6-tetra-*O*-benzyl-β-D-glucosamines were synthesized, which were subsequently deprotected to give *N*-aryl-D-glucosamines. The reaction represents a major advance in the *N*-aryl-D-glucosamines synthesis. However, aryl halides carrying an *ortho*-substituent failed to participate in the reaction. The cross-coupling had to be carried out at high temperature (130°C) and protected with inert gas. Besides, ligands were critical to the transformations.

Herein we report a convenient and mild protocol for synthesis of *N*-aryl-D-glucosamines via copper-catalyzed cross-coupling between arylboronic acids and D-glucosamine under ligand-free conditions, where aryl boronic acids were used as arylation reagents instead of aryl halides. Copper-catalyzed cross-couplings between arylboronic acids and N/O/S-nucleophiles (phenol, aniline, or thiophenol) are known as Chan-Evans-Lam–modified Ullmann condensation, and the advantage of this reaction is that much milder reaction conditions can be allowed such as lower temperature and aerobic environment.[10g,11,12] Importantly, *N*-*ortho*-substituent-aryl-D-glucosamines could also be obtained through the present method. The fact that many aryl boronic acids are now commercially available makes this protocol more practically appealing.[13]

Downloaded by [University of Sussex Library] at 08:36 11 February 2015

RESULTS AND DISCUSSION

We commenced our study with phenylboronic acid (**2a**) as model substrate, $Cu(OAc)_2$ as catalyst, and CH_2Cl_2 as solvent (Scheme. 1). Initially, D-glucosamine (**1a**) was selected as substrate to directly couple with phenylboronic acid (**2a**). Nevertheless, we could not obtain the *N*-arylation product **3aa** from D-glucosamine (**1a**). We speculated that the hydroxyl groups, especially 1-hydroxyl, have influence on the cross-coupling reaction. Then, we turned to the substrates from *O*-protected-D-glucosamines.



Scheme 1: Copper-catalyzed arylation of *D*-glucosamines with arylboronic acids.

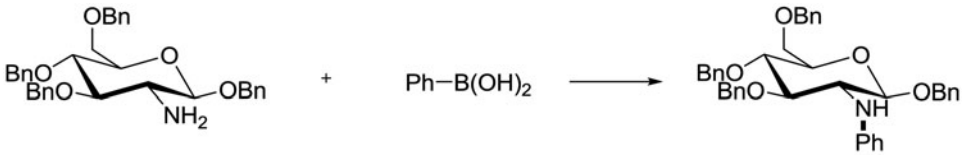
It is well known that acetyl is a versatile group for protecting hydroxyl in carbohydrate chemistry and can be removed under mild conditions.[14] If 1,3,4,6-tetra-*O*-acetyl-β-D-glucosamine (**1b**) was used as a surrogate of D-glucosamine, it would probably cross-couple with phenyl boronic acid (**2a**) to produce *N*-aryl-1,3,4,6-tetra-*O*-acetyl-β-D-glucosamine, which would easily be converted into *N*-aryl-D-glucosamines with base. This hypothesis prompted us to examine a roundabout process for synthesis of *N*-aryl-D-glucosamines catalyzed by copper (Sch. 1). The surrogate 1,3,4,6-tetra-*O*-acetyl-β-D-glucosamine (**1b**) was synthesized according to the literature.[15] With our standard conditions, however, the reaction was reluctant and only 9% of the product was obtained. On the other hand, as another protecting group for hydroxyl, benzyl may be more stable in the catalytic system (Sch. 1). So we turned to the benzyl-protected D-glucosamine and 1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine (**1c**)[16] was used as a model substrate. Gratifyingly, the designed product (**3ca**) was obtained with 48% yield. It is noteworthy that many classic methods[14,17] are known to deprotect the benzyl group from alcohol. For

Downloaded by [University of Sussex Library] at 08:36 11 February 2015

instance, hydrogenolysis with H_2/Pd/C can readily remove benzyl groups to release the hydroxyl groups of glucosamine.

Subsequently, to optimize the reaction condition, 1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine and phenyl boronic acid were selected as model substrates. It is reported that the undesired phenol and homocoupled biphenyl ether byproducts could be formed via copper-catalyzed C—O coupling with H_2O and phenol.[18] So, the molecular sieves were introduced into the reaction mixture to reduce the amount of H_2O. As shown in Table 1, under a ligand-free and base-free condition, different solvents were screened including polar solvents DMF and MeOH and less polar solvents $CHCl_3$, $ClCH_2CH_2Cl$, PhCl, CH_3CN, and toluene (entries 1–8). However, lower yields were obtained even when the reaction temperature was raised to 130°C. To our satisfaction, 65% yield was achieved when a CH_2Cl_2 and CH_3CN (2/1) mixture was used as cosolvent (entry 9). Nonetheless, other cosolvents such as toluene and CH_3CN slightly increased the yield (entry 10). With CH_2Cl_2 and CH_3CN as the solvent, we screened the copper sources including cuprous and cupric salts (entries 11–14).

Table 1: Copper-catalyzed phenylation of 1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine with phenylboronic acid[a]



1c **2a** **3ca**

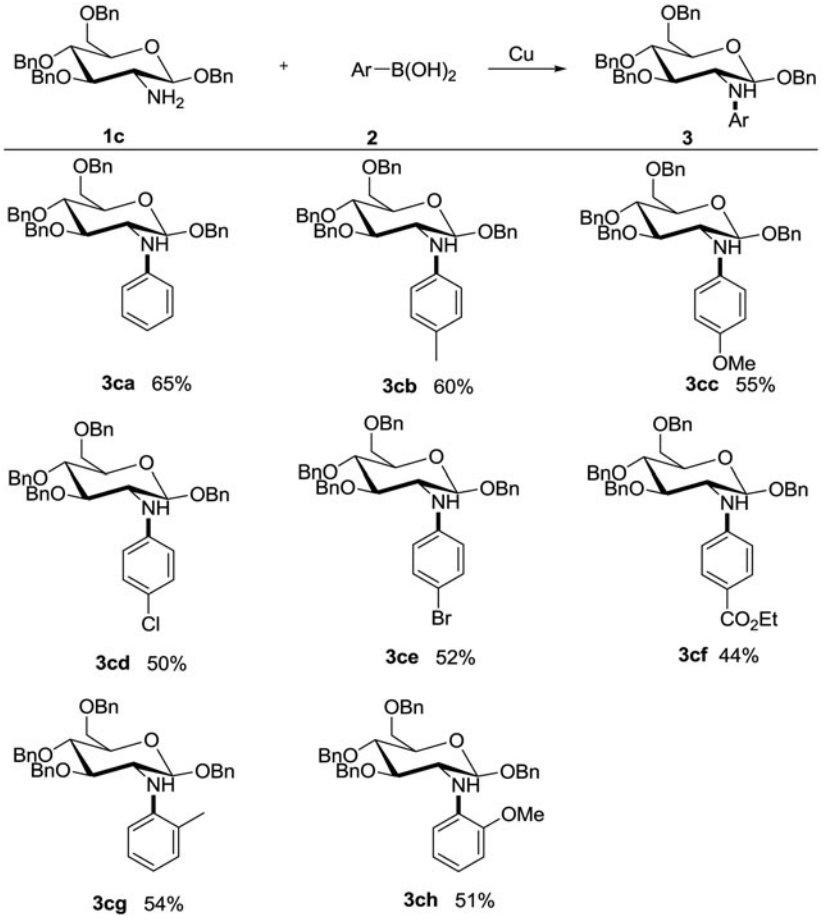
Entry	Catalyst	Solvent	Temp/°C	Yield%[b]
1	$Cu(OAc)_2$	CH_2Cl_2	65	48
2	$Cu(OAc)_2$	$CHCl_3$	65	39
3	$Cu(OAc)_2$	$ClCH_2CH_2Cl$	80	36
4	$Cu(OAc)_2$	PhCl	130	39
5	$Cu(OAc)_2$	Toluene	110	45
6	$Cu(OAc)_2$	CH_3CN	80	33
7	$Cu(OAc)_2$	DMF	120	29
8	$Cu(OAc)_2$	CH_3OH	65	15
9	$Cu(OAc)_2$	CH_2Cl_2/CH_3CN	65	65
10	$Cu(OAc)_2$	Toluene/CH_3CN	120	49
11	$CuSO_4$	CH_2Cl_2/CH_3CN	65	0
12	CuO	CH_2Cl_2/CH_3CN	65	0
13	CuI	CH_2Cl_2/CH_3CN	65	27
14	CuBr	CH_2Cl_2/CH_3CN	65	32

[a]Conditions: **1c** 0.5 mmol; **2a** 1.5 mmol; catalyst 20 mol%; 4ÅMS 400 mg; solvent = 3.0 mL (V_{sol}: V_{MeCN} = 2:1); O_2, 24 h.
[b]Isolated yield.

Downloaded by [University of Sussex Library] at 08:36 11 February 2015

The yields indicated that $Cu(OAc)_2$ was the best catalyst. Therefore, our optimal condition for the coupling of arylboronic acid and 1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine was as follows: 20 mol% $Cu(OAc)_2$ as the catalyst relative to 1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine, and CH_2Cl_2 and CH_3CN mixture as the cosolvent at 65°C.

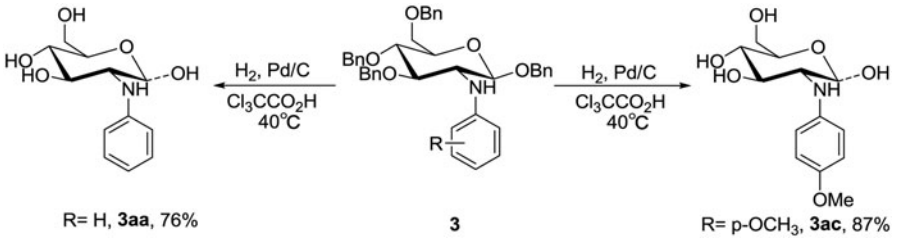
With the optimized catalytic system $Cu(OAc)_2/CH_2Cl_2/CH_3CN$, we next examined whether the same catalytic system can be applied to the coupling of 1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine with various arylboronic acids having different electronic and steric properties. It was found that both electron-rich and electron-deficient arylboronic acids can be smoothly converted to the desired products with satisfactory isolated yields (Sch. 2). It is noteworthy that



Scheme 2: Copper-catalyzed N-arylation of 1,3,4,6-tetra-O-benzyl-β-D-glucosamine (**1c**) with arylboronic acids (**2**).

arylboronic acids carrying an ortho-substituent were also found to readily participate in the reaction. For instance, 2-methylphenyl boronic acid could give an isolated yield of 54%, and the yield for 2-methoxylphenyl boronic acid is 51%.

Certainly, the above arylation products can now easily be converted to the target *N*-aryl-D-glucosamines. Hydrogenolysis catalyzed by Pd/C was employed to release the hydroxyl of *N*-aryl-1,3,4,6-tetra-*O*-benzyl-*β*-D-glucosamine. As shown in Scheme 3, under the standard conditions,[17] *N*-phenyl-*D*-glucosamine (**3aa**) and *N*-(4-methoxyl phenyl)-*D*-glucosamine (**3ac**) were obtained with high yields (76% and 87%, respectively).



Scheme 3: Deprotection of *N*-aryl-1,3,4,6-tetra-*O*-benzyl-*β*-*D*-glucosamines.

CONCLUSIONS

To conclude, we have developed a mild and convenient catalytic protocol for the synthesis of *N*-aryl-*D*-glucosamines. 1,3,4,6-tetra-*O*-benzyl-*β*-D-glucosamine is used as D-glucosamine surrogate and $Cu(OAc)_2$ was used as catalyst to achieve the C—N coupling. The efficiency and functional-group tolerance of this procedure have been demonstrated by synthesis of various functionalized *N*-aryl-1,3,4,6-tetra-*O*-benzyl-*β*-D-glucosamines. Furthermore, *N*-*ortho*-substituent-aryl-1,3,4,6-tetra-*O*-benzyl-*β*-D-glucosamines were also synthesized with the standard conditions. Finally, free *N*-aryl-*D*-glucosamines were easily obtained by deprotection of the benzyl protecting group. Given the fact that D-glucosamine derivatives play an important role in biomedical research and chiral molecule design, we anticipate that the method described in the present report will find applications in a number of fields such as pharmaceutical research and organic material synthesis.

EXPERIMENTAL

General Experimental Procedures

The solvents were distilled from CaH_2. All chemicals were obtained from commercial source and used without further purification. Flash column

Downloaded by [University of Sussex Library] at 08:36 11 February 2015

chromatography was performed on silica 230–400 mesh. Melting points were determined on a Yanaco melting point apparatus and were uncorrected. IR spectra were recorded on a Bruker Tensor 27 spectrometer with KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance 400 spectrometer at ambient temperature in DMSO-d^6 or D_2O. Chemical shifts are reported in ppm relative to TMS. HRMS analysis was performed on a Mariner ESI-TOF and Finnigan LCQ advantage Max Series MS System.

Downloaded by [University of Sussex Library] at 08:36 11 February 2015

Copper-catalyzed Coupling of arylboronic (2) with 1,3,4,6-tetra-O-benzyl-β-D-glucosamine (1c): General procedure

A 100-mL oven-dried round-bottom flask, containing a magnetic stirring bar, was charged with $Cu(OAc)_2$ (18 mg, 20 mol%), $ArB(OH)_2$ **2** (1.5 mmol, 3 eq.), and 4Å MS (400 mg). The solvent of CH_2Cl_2/CH_3CN (3.0 mL = 2.0 mL + 1.0 mL) was injected and the suspension was stirred for 10 min at rt. Then, 1,3,4,6-tetra-*O*-benzyl-β-*D*-glucosamine **1c** (270 mg, 0.5 mmol) was added. The reaction vessel was flushed with O_2, sealed, and stirred at 65°C for 24 h. The resulting mixture was cooled to rt and filtered through a pad of silica gel with the help of CH_2Cl_2 (30 mL). The filtrate was concentrated and the residue was purified by column chromatography (silica gel, EtOAc-PE) to afford the product **3**.

(2R,3R,4R,5S,6R)-2,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-N-phenyltetrahydro-2H-pyran-3-amine (3ca)

m.p. = 114–117°C. IR (KBr) ν: 3548, 3478, 3414, 1636, 1620, 1111, 1072, 620. ^{1}H NMR (400 MHz, DMSO) δ 7.40–7.27 (m, 8H), 7.25–7.14 (m, 10H), 7.11–7.03 (m, 4H), 6.74 (d, J = 7.8 Hz, 2H), 6.54 (t, J = 7.0 Hz, 1H), 5.62 (d, J = 9.0 Hz, 1H), 4.81–4.71 (m, 3H), 4.65 (d, J = 10.8 Hz, 1H), 4.61–4.51 (m, 4H), 4.48 (d, J = 7.9 Hz, 1H), 3.76–3.63 (m, 3H), 3.59–3.51 (m, 2H), 3.47–3.37 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 149.08, 138.50, 138.32, 138.28, 137.84, 128.64, 128.23, 128.20, 127.98, 127.97, 127.73, 127.70, 127.58, 127.52, 127.42, 127.28, 127.16, 127.01, 115.70, 112.78, 102.56, 84.17, 77.99, 74.13, 74.09, 73.91, 72.36, 70.04, 68.92, 59.66. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{40}H_{41}O_5NNa$: 638.2877; found: 638.2872.

(2R,3R,4R,5S,6R)-2,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-N-p-tolyltetrahydro-2H-pyran-3-amine (3cb)

m.p. = 115–116°C. IR (KBr) ν: 3548, 3477, 3417, 1636, 1617, 1565, 1415, 1123, 1111, 1069, 617. ^{1}H NMR (400 MHz, DMSO) δ 7.39–7.27 (m, 8H), 7.25–7.16 (m, 10H), 7.14–7.07 (m, 2H), 6.89 (d, J = 8.2 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 4.84–4.70 (m, 3H), 4.66 (d, J = 10.9 Hz, 1H), 4.62–4.51

(m, 4H), 4.48 (d, J = 8.0 Hz, 1H), 3.79–3.60 (m, 3H), 3.60–3.50 (m, 2H), 3.41–3.36 (m, 1H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 146.85, 138.57, 138.33, 138.30, 137.87, 129.09, 128.23, 128.20, 127.97, 127.73, 127.69, 127.58, 127.51, 127.42, 127.28, 127.17, 127.03, 124.11, 124.09, 113.00, 102.66, 84.19, 78.01, 74.09, 74.07, 73.91, 72.37, 70.05, 68.95, 60.17, 20.08. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{41}H_{44}O_5N$: 630.3214; found: 630.3212.

Downloaded by [University of Sussex Library] at 08:36 11 February 2015

(2R,3R,4R,5S,6R)-2,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-N-(4-methoxyphenyl)tetrahydro-2H-pyran-3-amine (3cc)

m.p. = 107–109°C. IR (KBr) ν: 3548, 3474, 3417, 1637, 1618, 1562, 1516, 1451, 1244, 1116, 1070, 742, 694. ^{1}H NMR (400 MHz, DMSO) δ 7.40–7.15 (m, 18H), 7.15–7.09 (m, 2H), 6.70 (s, 4H), 4.83–4.64 (m, 4H), 4.62–4.50 (m, 4H), 4.47 (d, J = 8.0 Hz, 1H), 3.79–3.59 (m, 6H), 3.54 (d, J = 5.2 Hz, 2H), 3.29 (dd, J = 9.3, 8.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 150.77, 143.36, 138.60, 138.33, 138.30, 137.88, 128.24, 128.22, 128.00, 127.99, 127.72, 127.71, 127.60, 127.53, 127.43, 127.30, 127.19, 127.04, 114.38, 113.93, 102.79, 84.23, 78.03, 74.07, 73.90, 72.37, 70.09, 68.95, 60.84, 55.36. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{41}H_{44}O_6N$: 646.3163; found: 646.3165.

(2R,3R,4R,5S,6R)-2,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-N-(4-chlorophenyl)tetrahydro-2H-pyran-3-amine (3cd)

m.p. = 118–120°C. IR (KBr) ν: 3445, 3343, 3029, 2895, 2862, 1600, 1517, 1492, 1450, 1114, 1070, 995, 813, 749, 697. ^{1}H NMR (400 MHz, DMSO) δ 7.39–7.27 (m, 8H), 7.24–7.15 (m, 8H), 7.16 (dd, J = 7.0, 2.5 Hz, 2H), 7.12–7.05 (m, 4H), 6.74 (d, J = 8.9 Hz, 2H), 4.82–4.70 (m, 3H), 4.67 (d, J = 10.9 Hz, 1H), 4.60–4.52 (m, 4H), 4.47 (d, J = 8.1 Hz, 1H), 3.80–3.52 (m, 5H), 3.46–3.37 (m, 1H). ^{13}C NMR (100 MHz, DMSO) δ 148.07, 138.46, 138.32, 138.25, 137.78, 128.30, 128.24, 128.22, 128.00, 127.73, 127.67, 127.60, 127.55, 127.43, 127.34, 127.24, 127.01, 118.85, 114.15, 102.47, 84.01, 78.01, 74.18, 74.10, 73.95, 72.38, 70.11, 68.88, 59.64. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{40}H_{41}O_5N^{35}Cl$: 650.2667; found: 650.2668; calcd for $C_{40}H_{41}O_5N^{37}Cl$: 652.2638; found: 652.2639.

(2R,3R,4R,5S,6R)-2,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-N-(4-bromophenyl)tetrahydro-2H-pyran-3-amine (3ce)

m.p. = 127–129°C. IR (KBr) ν: 3345, 3061, 3029, 2895, 2866, 1578, 1485, 1450, 1069, 809, 745, 694. ^{1}H NMR (400 MHz, DMSO) δ 7.40–7.27 (m, 8H), 7.27–7.12 (m, 12H), 7.08 (dd, J = 6.6, 3.0 Hz, 2H), 6.70 (d, J = 8.9 Hz, 2H), 5.91 (d, J = 9.1 Hz, 1H), 4.83–4.63 (m, 4H), 4.62–4.50 (m, 4H), 4.46 (d, J = 8.0 Hz, 1H), 3.78–3.50 (m, 5H), 3.40 (dd, J = 17.6, 9.0 Hz, 1H). ^{13}C NMR (100 MHz,

DMSO) δ 148.49, 138.44, 138.31, 138.24, 137.77, 131.12, 128.23, 128.21, 127.99, 127.73, 127.68, 127.67, 127.59, 127.54, 127.43, 127.33, 127.23, 127.01, 115.52, 114.76, 102.44, 84.00, 77.99, 74.17, 74.09, 73.93, 72.36, 70.09, 68.87, 59.55. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{40}H_{40}O_5NNa^{79}Br$: 716.1982; found: 716.1992; calcd for $C_{40}H_{40}O_5NNa^{81}Br$: 718.1970; found: 718.1990.

Ethyl 4-((2R,3R,4R,5S,6R)-2,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-3-ylamino)benzoate (3cf)

m.p. = 115–116°C. IR (KBr) ν: 3468, 3420, 3353, 3029, 2900, 2866, 1700, 1610, 1537, 1274, 1175, 1111, 1069, 752, 694. ^{1}H NMR (400 MHz, DMSO) δ 7.69 (d, J = 8.9 Hz, 2H), 7.40–7.26 (m, 8H), 7.22–7.14 (m, 10H), 7.06 (dd, J = 7.4, 2.1 Hz, 2H), 6.77 (d, J = 8.9 Hz, 2H), 4.84–4.63 (m, 4H), 4.62–4.47 (m, 5H), 4.22 (q, J = 7.1 Hz, 2H), 3.81–3.52 (m, 6H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ 165.86, 153.15, 138.35, 138.31, 138.21, 137.72, 130.77, 128.25, 128.23, 128.01, 127.99, 127.76, 127.64, 127.61, 127.57, 127.44, 127.35, 127.26, 127.00, 116.33, 111.70, 102.04, 83.71, 77.96, 74.23, 74.14, 73.98, 72.39, 70.05, 68.84, 59.48, 58.69, 14.38. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{43}H_{46}O_7N$: 688.3268; found: 688.3266.

(2R,3R,4R,5S,6R)-2,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-N-o-tolyltetrahydro-2H-pyran-3-amine (3cg)

Liquid, IR (KBr) ν: 3433, 3003, 2978, 2936, 2853, 1578, 1424, 1043, 1014, 649, 620. ^{1}H NMR (400 MHz, DMSO) δ 7.49 (dd, J = 5.1, 1.8 Hz, 1H), 7.43–7.35 (m, 6H), 7.33–7.28 (m, 3H), 7.26–7.18 (m, 7H), 7.17–7.12 (m, 4H), 7.09 (dd, J = 7.8, 1.7 Hz, 1H), 7.03 (dd, J = 7.2, 2.3 Hz, 1H), 6.84 (dd, J = 10.9, 4.4 Hz, 1H), 4.83 (m, 3H), 4.64–4.55 (m, 5H), 4.48 (dd, J = 11.0, 2.0 Hz, 1H), 3.89 (dd, J = 11.9, 9.3 Hz, 1H), 3.83–3.68 (m, 4H), 3.63 (t, J = 9.2 Hz, 1H), 2.08 (s, 3H). ^{13}C NMR (100 MHz, DMSO) δ 146.24, 138.32, 138.25, 138.16, 137.78, 137.75, 129.20, 128.26, 128.24, 128.03, 128.01, 127.95, 127.73, 127.66, 127.62, 127.61, 127.12, 126.96, 126.36, 121.24, 115.93, 110.95, 102.54, 82.82, 79.18, 74.00, 73.65, 72.41, 70.36, 69.71, 68.77, 58.65, 30.62. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{41}H_{43}O_6NNa$: 652.3043; found: 652.3033.

(2R,3R,4R,5S,6R)-2,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-N-(2-methoxyphenyl)tetrahydro-2H-pyran-3-amine (3ch)

Liquid, IR (KBr) ν: 3419, 3062, 3030, 2928, 2866, 1643, 1578, 1452, 1419, 1111, 1027, 734, 693. ^{1}H NMR (400 MHz, DMSO) δ 7.39–7.15 (m, 18H), 7.07 (dt, J = 4.6, 3.2 Hz, 2H), 6.91–6.80 (m, 2H), 6.74 (td, J = 7.7, 1.2 Hz, 1H), 6.56 (td, J = 7.7, 1.5 Hz, 1H), 4.85–4.51 (m, 9H), 3.85 (dd, J = 17.4, 8.2 Hz, 1H), 3.80–3.66 (m, 4H), 3.64–3.51 (m, 2H), 3.40 (dd, J = 17.7, 8.5 Hz, 1H), 3.29 (dd,

Downloaded by [University of Sussex Library] at 08:36 11 February 2015

J = 9.4, 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO) δ 163.69, 146.31, 138.48, 138.33, 138.29, 137.87, 128.24, 128.20, 128.00, 127.96, 127.70, 127.67, 127.61, 127.58, 127.42, 127.27, 127.11, 126.98, 120.89, 115.70, 110.87, 109.92, 102.28, 83.80, 78.06, 74.10, 74.08, 73.83, 72.37, 69.96, 68.95, 59.96, 55.41. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{41}H_{43}O_6N$+Na: 668.2983; found: 668.2987.

Deprotection of *N*-aryl-1,3,4,6-tetra-*O*-benzyl-β-D-glucosamine (3): General procedure

Under hydrogen atmosphere, a solution of **3** (0.5 mmol) in CH_3OH and EtOAc (4 mL + 2 mL) was stirred in the presence of Pd/C (10%, 100 mg) and trichloroacetic acid (80 mg, 0.5 mmol) at 40°C. After 40 h the reaction mixture was cooled to rt and filtered through a pad of silica gel with the help of CH_3OH. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, $CHCl_3$—CH_3OH) to afford the deprotected product.

(2R,3R,4R,5S,6R)-6-(Hydroxymethyl)-3-(phenylamino)tetrahydro-2H-pyran-2,4,5-triol (3aa)

IR (KBr) ν: 3383, 2975, 2927, 2898, 1644, 1450, 1412, 1382, 1088, 1049, 880, 637. ^{1}H NMR (400 MHz, D_2O) δ 7.68–7.38 (m, 5H), 5.05 (s, 0.81H), 4.90–4.84 (m, 0.35H), 4.11 (t, J = 9.7 Hz, 0.85H), 4.00–3.62 (m, 4.15H), 3.55 (t, J = 9.6 Hz, 1.04H), 3.51–3.32 (m, 0.77H). ^{13}C NMR (100 MHz, D_2O) δ 136.70, 136.23, 132.91, 132.71, 131.82, 130.71, 125.17, 125.13, 94.95, 90.38, 78.43, 74.09, 73.17, 72.78, 72.48, 72.22, 66.59, 66.24, 63.04, 62.88. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{12}H_{17}O_5NNa$: 278.0999; found: 278.0993.

(2R,3R,4R,5S,6R)-6-(Hydroxymethyl)-3-(4-methoxyphenylamino) tetrahydro-2H-pyran-2,4,5-triol (3ac)

IR (KBr) ν: 3411, 2936, 2840, 1600, 1577, 1512, 1445, 1260, 1031, 759. ^{1}H NMR (400 MHz, D_2O) δ 7.45 (t, J = 9.4 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 5.01 (s, 0.83H), 4.08 (t, J = 9.8 Hz, 0.84H), 3.96–3.58 (m, 7.45H), 3.51 (t, J = 9.5 Hz, 1.1H), 3.35 (s, 1.8H). ^{13}C NMR (100 MHz, D_2O) δ 162.23, 128.18, 127.89, 127.08, 118.08, 117.96, 94.17, 90.20, 78.42, 74.07, 72.78, 72.44, 72.21, 72.03, 66.99, 66.67, 62.98, 62.86, 58.30, 51.45. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{13}H_{19}O_6N$: 286.1285; found: 286.1293.

ACKNOWLEDGMENTS

We are grateful to the Priority Academic Program Development of Jiangsu Higher Education Institutions, Scientific and Technological Research Project of Lianyungang (CG1004), Open-end Funds of Jiangsu Key Laboratory of

Downloaded by [University of Sussex Library] at 08:36 11 February 2015

Marine Biotechnology (2009HS02), Open-end Funds of Jiangsu Marine Resources R & D Institute (JSIMR10C05), China Postdoctoral Science Foundation (20110491383) and Project of Natural Science Foundation of Jiangsu Education Committee (10KJB150001).

REFERENCES

1. (a) Varki, A.; Cummings, D. C.; Esko, J. D.; Freeze, H. H.; Stanley, P.; Bertozzi, C. R.; Hart, G. W.; Etzler, M. E. In *Essentials of Glycobiology,* 2nd ed.; Cold Spring Habor Laboratory Press: New York, **2009**. (b) Gandhi, N. S.; Mancera, R. L. The structure of glycosaminoglycans and their interactions with proteins. *Chem. Biol. Drug Des.* **2008**, *72*, 455–482. (c) Paulick, M. G.; Bertozzi, C. R. The glycosylphosphatidylinositol anchor: a complex membrane-anchoring structure for proteins. *Biochemistry* **2008**, *47*, 6991–7000. (d) Wang, L.-X.; Huang, W. Enzymatic transglycosylation for glycoconjugate synthesis. *Curr. Opin. Chem. Biol.* **2009**, *13*, 592–600. (e) Bryant, C. E.; Spring, D. R.; Gangloff, M.; Gay, N. J. The molecular basis of the host response to lipopolysaccharide. *Nat. Rev. Microbiol.* **2010**, *8*, 8–14. (f) Taube, S.; Jiang, M.; Wobus, C. E. Glycosphingolipids as receptors for non-enveloped viruses. *Viruses* **2010**, *2*, 1011–1049. (g) Liu, L.; Bennett, C. S.; Wong, C.-H. Advances in glycoprotein synthesis. *Chem. Commun.* **2006**, 21–33.

2. (a) Tollabi, M.; Framery, E.; Goux-Henry, C.; Sinou, D. Palladium-catalyzed asymmetric allylic alkylation using chiral glucosamine-based monophosphines. *Tetrahedron: Asymmetry*. **2003**, *14*, 3329–3333. (b) Glegoła, K.; Framer, E.; Goux-Henry, C.; Pietrusiewicz, K. M.; Sinou, D. Influence on the enantioselectivity in allylic alkylation of the anomeric position of the phosphine-amide ligands derived from D-glucosamine. *Tetrahedron* **2007**, *63*, 7133–7141. (c) Glegoła, K.; Johannesen, S. A.; Thim, L.; Goux-Henry, C.; Skrydstrup, T.; Framery, E. Simple D-glucosamine-based phosphine-imine and phosphine-amine ligands in Pd-catalyzed asymmetric allylic alkylations. *Tetrahedron Lett.* **2008**, *49*, 6635–6638. (d) Agarwal, J.; Peddinti, R. K. Glucosamine-based primary amines as organocatalysts for the asymmetric aldol reaction. *J. Org. Chem.* **2011**, *76*, 3502–3505.

3. (a) Winkler, R.; Sandermann, H. Jr. *N*-Glucosyl conjugates of chlorinated anilines: spontaneous formation and cleavage. *J. Agric. Food Chem.* **1992**, *40*, 2008–2012. (b) Margret, B.; Christiane, R.; Brigitte, T.; Thomas, J.; Burkhard, S. Uptake, translocation, and metabolism of 3,4-dichloroaniline in soybean and wheat plants. *Z. Naturforsch. C*, **1995**, *49*, 719–726. (c) Hidenori, T.; Hiroshi, I.; Masahiro, K. **2012**, Method for detecting cancer cell. *WO2012086802*. (d) Hisakage, F.; Shiho, O.; Mikako, S.; Hideaki, M. Utilization of fluorescent glucose analog 2-NBDG as a metabolic indicator for FACS analysis during ES cell differentiation. *Electrochemistry*, **2012**, *80*, 299–301. (e) Yamamoto, T.; Nishiuchi, Y.; Teshima, T.; Matsuoka, H.; Yamada, K. Synthesis of 2-NBDLG, a fluorescent derivative of L-glucosamine; the antipode of D-glucose tracer 2-NBDG. *Tetrahedron Lett.* **2008**, *49*, 6876–6878. (f) Jung, M. E.; Dong, T. A.; Cai, X.-L. Improved synthesis of 4-amino-7-nitrobenz-2,1,3-oxadiazoles using NBD fluoride (NBD-F). *Tetrahedron Lett.* **2011**, *52*, 2533–2535.

4. (a) Cheuk, N. G. S.; Wang, G. J. Synthesis and characterization of D-glucosamine-derived low molecular weight gelators. *Tetrahedron* **2010**, *66*, 5962–5971. (b) Vendrell, M.; Samanta, A.; Yun, S.-W. Synthesis and characterization of a cell-permeable near-infrared fluorescent deoxyglucose analogue for cancer cell imaging. *Org. Biomol. Chem.* **2011**, *9*, 4760–4762.

5. (a) Mensah, E. A.; Yu, F.; Nguyen, H. M. Nickel-catalyzed stereoselective glycosylation with C(2)-*N*-substituted benzylidene D-glucosamine and galactosamine

Downloaded by [University of Sussex Library] at 08:36 11 February 2015

trichloroacetimidates for the formation of 1,2-cis-2-amino glycosides. applications to the synthesis of heparin disaccharides, GPI anchor pseudodisaccharides, and α-GalNAc. *J. Am. Chem. Soc.*, **2010**, *132*, 14288–14302. (b) Pérez, E. M. S.; ávalos, M.; Babiano, R. Schiff bases from d-glucosamine and aliphatic ketones. *Carbohydr. Res*. **2010**, *345*, 23–32. (c) Cheng, A.; Hendel, J. L.; Colangelo, K. Convenient temporary methyl imidate protection of *N*-acetylglucosamine and glycosylation at O-4. *J. Org. Chem.* **2008**, *73*, 7574–7579.

6. Emmadi, M.; Kulkarni, S. S. Rapid transformation of D-mannose into orthogonally protected D-glucosamine and D-galactosamine thioglycosides. *J. Org. Chem.* **2011**, *76*, 4703–4709.

7. Liberek, B.; Melcer, A.; Osuch, A.; Wakiec, R.; Milewski, S.; Wisniewski, A. N-Alkyl derivatives of 2-amino-2-deoxy-D-glucose. *Carbohydr. Res.* **2005**, *340*, 1876–1884.

8. (a) Horton, D. The anomeric 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-D-glucopyranoses. *J. Org. Chem.* **1964**, *29*, 1776–1782. (b) Bindschädler, P.; Dialer, L. O.; Seeberger, P. H. Synthesis of differentially protected glucosamine building blocks and their evaluation as glycosylating agents. *J. Carbohyd. Chem.* **2009**, *28*, 395–420.

9. Tao, C.-Z.; Liu, F.; Liu, W.-W.; Zhu, Y.-M.; Li, Y.-F.; Liu, X.-L.; Zhao, J. Synthesis of *N*-aryl-D-glucosamines through copper-catalyzed C–N coupling. *Tetrahedron Lett.* **2012**, *53*, 7093–7096.

10. Our other work about copper-catalyzed reactions: (a) Tao, C.-Z.; Liu, F.; Zhu, Y.-M.; Liu, W.-W.; Cao, Z.-L. Copper-catalyzed aerobic oxidative synthesis of aryl nitriles from benzylic alcohols and aqueous ammonia. *Org. Biomol. Chem.* **2013**, *11*, 3349–3354. (b) Tao, C.-Z.; Lv, A.-F.; Zhao, N.; Yang, S.; Liu, X.-L.; Zhou, J.; Liu, W.-W.; Zhao, J. Ligand-free copper-catalyzed synthesis of diaryl thioethers from aryl halides and thioacetamide. *Synlett* **2011**, 134–138. (c) Tao, C.-Z.; Liu, W.-W.; Lv, A.-F.; Sun, M.-M.; Tian, Y.; Wang, Q.; Zhao, J. Room-temperature copper-catalyzed synthesis of primary arylamines from aryl halides and aqueous ammonia. *Synlett* **2010**, 1355–1358. (d) Tao, C.-Z.; Liu, W.-W.; Sun, J.-Y. Cao, Z.-L.; Li, H.; Zhang, Y.-F. 3-Acetyl-coumarin as a practical ligand for copper-catalyzed C-N coupling reactions at room temperature. *Synthesis* **2010**, 1280–1284. (e) Tao, C.-Z.; Liu, W.-W.; Sun, J.-Y. Copper-catalyzed synthesis of phenols from aryl halides and 4-methoxylbenzyl alcohol. *Chin. Chem. Lett.* **2009**, *20*, 1170–1174. (f) Tao, C.-Z.; Li, J.; Fu, Y.; Liu, L.; Guo, Q.-X. Copper-catalyzed synthesis of primary arylamines from aryl halides and 2,2,2-trifluoroacetamide. *Tetrahedron Lett.* **2008**, *49*, 70–75. (g) Tao, C.-Z.; Cui, X.; Li, J.; Liu, A.-X.; Liu, L.; Guo, Q.-X. Copper-catalyzed synthesis of aryl azides and 1-aryl-1,2,3-triazoles from boronic acids. *Tetrahedron Lett.* **2007**, *48*, 3525–3529. (h) Tao, C.-Z.; Li, J.; Cui, X.; Fu, Y.; Guo, Q.-X. Cu-catalyzed cross couplings under ligandless conditions. *Chin. Chem. Lett.* **2007**, *18*, 1199–1202.

11. Review: Ley, S. V.; Thomas, A. W. Modern synthetic methods for copper-mediated C(aryl)–O, C(aryl)–N, and C(aryl)–S bond formation. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449.

12. Recent articles about Chan-Evans-Lam-modified Ullmann condensation reactions: (a) Quach, T. D.; Batey, R. A. Ligand- and base-free copper(II)-catalyzed C−N bond formation: cross-coupling reactions of organoboron compounds with aliphatic amines and anilines. *Org. Lett.* **2003**, *5*, 4397–4400. (b) Zhang, L.-L; Zhang, G.-Y.; Zhang, M. L.; Cheng, J. $Cu(OTf)_2$-mediated Chan-Lam reaction of carboxylic acids to access phenolic esters. *J. Org. Chem.* **2010**, *75*, 7472–7474. (c) Wu, H.; Hynes, J. Jr. Copper-catalyzed chlorination of functionalized arylboronic acids. *Org. Lett.* **2010**, *12*, 1192–1195. (d) Xu, J.-M; Wang, X.-Y.; Shao, C.-W.; Su, D.-Y.; Cheng, G.-L.; Hu, Y.-F. Highly efficient synthesis of phenols by copper-catalyzed oxidative hydroxylation of arylboronic acids at room temperature in water. *Org. Lett.* **2010**, *12*, 1964–1967. (e) Xu, H.-J.; Zhao, Y.-Q.; Feng, T.; Feng, Y.-S. Chan–Lam-Type S-arylation of thiols

Downloaded by [University of Sussex Library] at 08:36 11 February 2015

with boronic acids at room temperature. *J. Org. Chem.* **2012**, *77*, 2878–2884. (f) Li, J.-H.; Bébastien, S.; Neuville, L.; Zhu, J.-P. Copper catalyzed *N*-arylation of amidines with aryl boronic acids and one-pot synthesis of benzimidazoles by a Chan–Lam–Evans *N*-arylation and C–H activation/C–N bond forming process. *Org. Lett.* **2012**, *14*, 5980–5983.

13. (a) Dai, J.-J.; Liu, J.-H.; Luo, D.-F.; Liu, L. Pd-catalysed decarboxylative Suzuki reactions and orthogonal Cu-based *O*-arylation of aromatic carboxylic acids. *Chem. Commun.* **2011**, *47*, 677–679. (b) Yang, C.-T.; Zhang, Z.-Q.; Liu, Y.-C.; Liu, L. Copper-catalyzed cross-coupling reaction of organoboron compounds with primary alkyl halides and pseudohalides. *Angew. Chem. Int. Ed.* **2011**, *50*, 3904–3907. (c) Zhu, C.; Li, G.-Q.; Ess, D. H.; Falck, J. R.; Kürti, L. Elusive metal-free primary amination of arylboronic acids: synthetic studies and mechanism by density functional theory. *J. Am. Chem. Soc.* **2012**, *134*, 18253–18256. (d) Qi, Q.-Q.; Shen, Q.-L.; Lu, L. Copper-mediated aerobic fluoroalkylation of arylboronic acids with fluoroalkyl iodides at room temperature. *J. Am. Chem. Soc.* **2012**, *134*, 6548–6551. (e) Li, X.-J.; Zhang, J.-L; Geng, Y.; Jin Z. Nickel-catalyzed suzuki–miyaura coupling of heteroaryl ethers with arylboronic acids. *J. Org. Chem.* **2013**, *78*, 5078–5084.

14. Wuts, P. G. M.; Greene, T. W. in *"Greene's Protective Groups in Organic Synthesis."* 4nd ed., John Wiley & Sons, **2007**.

15. Silva, D. J.; Wang, H.-M.; Allanson, N. M.; Jain, R. K.; Sofia, M. J. Stereospecific solution- and solid-phase glycosylations. synthesis of β-linked saccharides and construction of disaccharide libraries using phenylsulfenyl 2-deoxy-2-trifluoroacetamido glycopyranosides as glycosyl donors. *J. Org. Chem.* **1999**, *64*, 5926–5929.

16. Aly, M. R. E.; Schmidt, R. R. New diacylamino protecting groups for glucosamine. *Eur. J. Org. Chem.* **2005**, 4382–4392.

17. (a) Heathcock, C. H.; Ratcliffe, R. Stereoselective total synthesis of the guaiazulenic sesquiterpenoids .alpha.-bulnesene and bulnesol. *J. Am. Chem. Soc.* **1971**, *93*, 1746–1757. (b) Czech, B. P.; Bartsch, R. A. Effect of amines on *O*-benzyl group hydrogenolysis. *J. Org. Chem.* **1984**, *49*, 4076–4078. (c) Sajiki, H.; Hirota, K. A novel type of PdMC-catalyzed hydrogenation using a catalyst poison: Chemoselective inhibition of the hydrogenolysis for *O*-benzyl protective group by the addition of a nitrogen-containing base. *Tetrahedron* **1998**, *54*, 13981–13996.

18. (a) Quach, T. D.; Batey, R. A. Copper(II)-catalyzed ether synthesis from aliphatic alcohols and potassium organotrifluoroborate salts. *Org. Lett.* **2003**, *5*, 1381–1384. (b) Yamamoto, Y.; Takizawa, M.; Yu, X.-Q.; Miyaura, N. Cyclic triolborates: air- and water-stable ate complexes of organoboronic acids. *Angew. Chem. Int. Ed.* **2008**, *47*, 928–931. (c) Tzschucke, C. C.; Murphy, J. M.; Hartwig, J. F. Arenes to anilines and aryl ethers by sequential Iridium-catalyzed borylation and copper-catalyzed coupling. *Org. Lett.* **2007**, *9*, 761–764.

Downloaded by [University of Sussex Library] at 08:36 11 February 2015