CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Re-Engineering Chemical Glycosylation: Direct, Metal-Free Anomeric O-Arylation of Unactivated Carbohydrates

Authors: Nicola Lucchetti and Ryan Gilmour

To be cited as: *Chem. Eur. J.* 10.1002/chem.201804416

Link to VoR: http://dx.doi.org/10.1002/chem.201804416

Supported by
ACES

WILEY-VCH

10.1002/chem.201804416

COMMUNICATION

WILEY-VCH

Re-Engineering Chemical Glycosylation: Direct, Metal-Free Anomeric *O*-Arylation of Unactivated Carbohydrates

Dr. Nicola Lucchetti, and Prof. Dr. Ryan Gilmour*

Abstract: To sustain innovation in glycobiology, effective routes to well-defined carbohydrate probes must be developed. For over a century, glycosylation has been dominated by formation of the anomeric C(sp^3)–O acetal junction in glycostructures. A dissociative mechanistic spectrum spanning S_N1 and S_N2 is frequently operational thereby complicating efficiency. By re-engineering this venerable process, an orthogonal disconnection allows the acetal to be forged directly from the reducing sugar without the need for substrate pre-functionalisation. Engagement with stable aryliodonium salts facilitates a formal O–H functionalisation reaction. This allows lactols to undergo mild, metal-free *O*-arylation at ambient temperature. The efficiency of the transformation has been validated using a variety of pyranoside and furanoside monosaccharides in addition to biologically relevant *di*- and *tri*-saccharides (up to 85%). Fluorinated mechanistic probes that augment the anomeric effect have been employed. It is envisaged that this strategy will prove expansive for the construction of complex acetals under substrate-based stereocontrol.

The functional virtuosity of complex carbohydrates is reflected in their structural diversity.[1] Central to the energy, architectural and molecular recognition aspects of cell biology, glycostructures continue to provide a rich source of innovation for the design of novel pharmaceuticals and materials:[2] This is particularly prominent in phenolic glycosides such as the antibiotic *Vancomycin*.[3] However, exploring and harnessing carbohydrate function is frequently compromised by synthetic challenges.[4] In contrast to peptides and nucleic acids, the efficiency with which complex sugars are produced biosynthetically cannot easily be emulated in a laboratory paradigm. An amalgamation of regio- and stereo-selectivity complications, further compounded by complex conformational equilibria, render carbohydrate coupling protocols less general than the aforementioned biomolecule classes. Whilst advances in automation have significantly alleviated the synthesis bottleneck,[5] innovative coupling methods to construct the acetal junction intrinsic to carbohydrates must be developed in parallel. When considering glycostructures of translational relevance to medicine, phenolic glycosides have emerged as venerable blueprints. Exploited for over a century as anti-inflammatory agents,[6] aryl capped glycosides based on *β-Phlorizin* have emerged as powerful and selective SGLT2 inhibitors for the clinical management of type II diabetes.[7] This motif also features in *Bimosiamose* for the treatment of psoriasis and asthma,[8] a plenum of myelin-associated glycoprotein (MAG) antagonists,[9] and in the natural product *Rumexoside* (Figure 1, top). Indeed, a recent survey of U.S. FDA approved drugs containing oxygen heterocycles by Njardarson and co-workers revealed that pyranoses and furanoses are the top two most frequently employed motifs.[10] Reconciling the pre-eminence of glycosylated molecules in human medicine with the dearth of effective strategies for their construction is exemplified by a recent study by Schepartz and Miller on the rapid *O*-glycosylation.[11] Consequently, strategies to facilitate the efficient synthesis of diverse aryl glycosides have been intensively pursued.[12] Predicated on retrosynthetic analysis of the anomeric C(sp^3)–O bond (Figure 1, upper centre, disconnection A), a plethora of protocols for aromatic *O*-glycosylation has been developed. These strategies traverse the *Umpolung* spectrum proceeding via postulated glycosyl cations,[4] radicals and carbenes (Figure 1, lower centre).[13] Furthermore significant advances in translating chemical glycosylation to a catalysis paradigm have enriched the field.[4,14]

To complement the existing glycosylation ordnance, it was envisaged that re-engineering the acetal linkage via strategic disconnection B (Figure 1, lower) would provide an attractive alternative for aryl glycoside formation. This O–H functionalisation reaction would mitigate the need for substrate-pre-functionalisation / activation sequences and allow reducing sugars to be used directly. A stereoretentive reaction would also allow chirality encoded at C1 to be translated to the product. Herein, a direct, metal-free, *O*-arylation of *mono*-, *di*- and *tri*-saccharides at the lactol position is validated using simple aryliodonium salts as the electrophilic partner (Figure 1, lower).

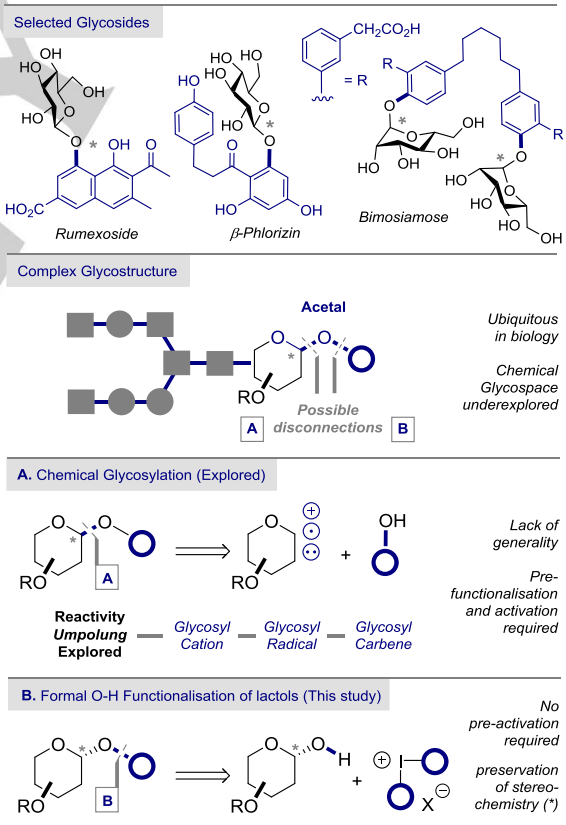


Figure 1. Top: Examples of pharmaceutically relevant aryl glycosides. Upper centre: A generic glycostructure indicting the two possible disconnections of the acetal junction. Lower centre: A conceptual overview of glycosylation strategies based on strategic disconnection A. Bottom: A conceptual alternative via an O–H functionalisation exploiting aryliodonium reagents (disconnection B).

Aryl-λ^3-iodane salts[15,16] have emerged as powerful and versatile arylating reagents.[17] Pertinent examples include Olofsson's elegant functionalisation of diaryliodonium salts to decorate the periphery of sugars,[18a] and Toste's diastereoselective acetalisation with chiral

[*] Dr. Nicola Lucchetti, Prof. Dr. Ryan Gilmour
Organisch Chemisches Institut
Westfälische Wilhelms-Universität Münster
Corrensstraße 40, 48149 Münster (Germany)
E-mail: ryan.gilmour@uni-muenster.de
Homepage: http://www.uni-muenster.de/Chemie.oc/gilmour/

Supporting information for this article is given via a link at the end of the document.

10.1002/chem.201804416

diaryliodonium phosphates.[19] Cognisant that these reagents undergo facile O–H functionalisation of various alcohols, we sought to explore the competence of aryl iodonium salts for the functionalisation of the hemi-acetal of unactivated, reducing sugars. As a starting point for this study, commercially available diphenyliodonium hexafluorophosphate **2a** was investigated as a model electrophile for the arylation of 2,3,4,6-*tetra*-*O*-benzylated-D-glucopyranose **1a** (Table 1).

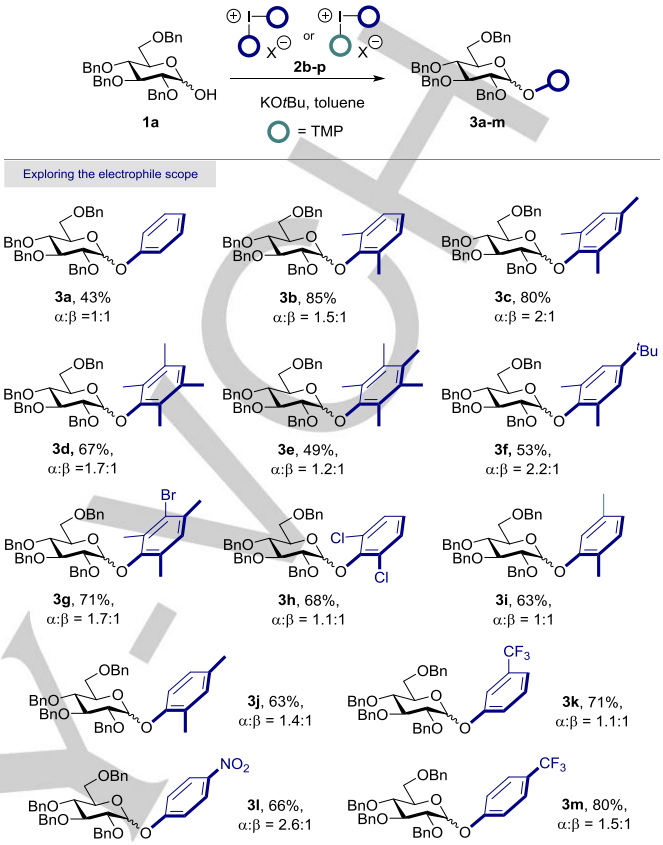
Table 1. Direct *O*-arylation of *tetra*-*O*-benzylated-D-glucopyranose **1a** using **2a**.[a]

Entry	Solvent	Base (eq.)	Yield [%][b]
1	toluene	KO*t*Bu (1.5)	39
2	toluene	K_2CO_3 (1.5)	0
3	toluene	NaH (1.5)	9
4	toluene	NaO*t*Bu (1.5)	<5
5	DCE	KO*t*Bu (1.5)	21
6	CH_3CN	KO*t*Bu (1.5)	<5
7	CH_2Cl_2	KO*t*Bu (1.5)	35
8[c]	toluene	KO*t*Bu (1.5)	37
9[d]	toluene	KO*t*Bu (1.5)	43

[a] Standard conditions: **1a** (1 eq.) and **2a** (1 eq.), 0.09 mmol scale. [b] Isolated yields following flash column chromatography. [c] T = 40 °C. [d] = [TMPIPh]OTs (**2aa**) used as the diaryliodonium salt.

Gratifyingly, arylation of lactol **1a** with **2a** in the presence of KO*t*Bu (1.5 equiv.) at ambient temperature in toluene afforded the desired compound **3a** in 39% yield (entry 1). Employing alternative inorganic bases such as K_2CO_3, NaH and NaO*t*Bu proved detrimental to reaction efficiency (entries 2-4). Generally, switching reaction media to CH_3CN or DCE did not improve the outcome (entries 5-7).[20] However, dichloromethane furnished **3a** in a comparable yield to toluene (35%, entry 7). No change in conversion or in the anomeric composition of the product (α:β) was observed by elevating the temperature to 40 °C (entry 8). Furthermore, an excess of arylating agent proved to be unnecessary and thus a 1:1 stoichiometry was optimal (see SI for details). In an attempt to improve the reaction efficiency, the optimised conditions identified in Table 1 were repeated using more electron-rich diaryliodonium salts. Inspired by studies from Stuart and co-workers,[17g,21] the 2,4,6-trimethoxyphenyl (TMP) group was exploited as a prosthetic ligand at the iodine(III) centre. This structural alteration led to a slight increase in yield (43%, entry 9). With a preliminary validation of concept having been demonstrated, attention was then focused on exploring the scope of this transformation (Scheme 1). This operationally simple protocol was performed at ambient temperature and the anomeric ratio (α:β) of the products was determined by ^{1}H NMR ($^3J_{HH}$-coupling constant) analysis. Symmetrical or unsymmetrical (TMP) diaryliodonium salts were employed as necessary (see SI for full preparative details). Gratifyingly, the 2,6-disubstituted arenes, known to facilitate reductive elimination, were well tolerated in the title transformation and furnished the desired aryl glycosides **3b-e** in good yields (49-85%). As expected, the *α*-anomers predominated giving a first indication that the reaction was stereoretentive (*vide infra*).

Scheme 1. Direct *O*-Arylation of carbohydrates: Exploring diaryliodonium scope.[a]

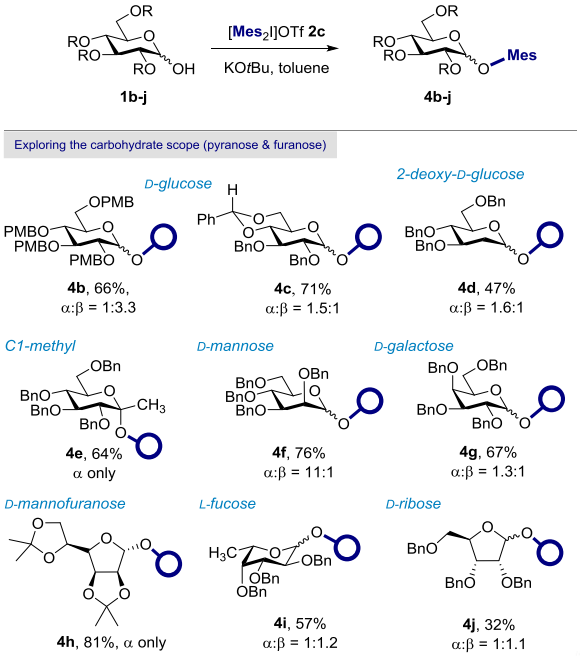


[a] Reactions were performed in toluene on a 0.15 mmol scale at ambient temperature. The α:β ratio of the products was determined by ^{1}H NMR spectroscopy. The α:β ratios of the starting materials are provided in the SI.

Increasing the steric demand of the arylating reagent had little effect on the transformation with **3f** being formed in 53% yield (α:β = 2.2:1). Importantly, the method was compatible with the presence of halides within the aromatic core (**3g**, 71% yield). This is advantageous for downstream functionalisation. The 2,6-dichloro derivative underwent smooth *O*-arylation to deliver **3h** in 68% yield. The scope was not limited to *ortho,ortho'*-disubstituted diaryliodonium salts. Indeed, 2,5- and 2,4-dimethylphenyl ethers were also isolated in good yields (**3i,j** both in 63% yields). In view of the importance of the CF_3 group in drug discovery,[22] the 3- and 4-trifluoromethylated derivatives **3k** and **3m** were prepared (71% and 80% yield, respectively). Finally, the 4-nitrophenyl substituted glucose **3l** was prepared in 66% yield (α:β = 2.6:1). Having investigated the electrophile scope, a series of reducing sugars were explored as nucleophilic coupling partners (Scheme 2). Modifying the protecting group electronics from benzyl (Bn) to *p*-methoxybenzyl (PMB) **4b** led to comparable yields (66%) but with an inversion in anomeric ratio (α:β 1:3.3 *versus* 2:1 for **3c**). This single example is intriguing in that the intrinsic α-selectivity of the lactol is inverted to favour the β-glycoside. The conformationally restricted substrate containing a benzylidene acetal was also well tolerated (**4c**, 71%, α:β 1.5:1), as was the 2-deoxy-system **4d** (47%, α:β 1.6:1). Installation of the sterically more cumbersome α-methly substituent did not impede the reaction and **4e** was isolated in 64% yield. Epimerisation at C2 to generate the D-mannose system was also well tolerated and furnished the glycoside **4f** in 76% yield (α:β 11:1). Interestingly, the C4 epimer D-galactose performed slightly less well with **4g** being isolated in 67% (α:β 1.3:1). The D-mannofuranose species **4h** was isolated in 81% yield exclusively as the α-anomer.

Finally, the L-fucose derivative **4i** was obtained in 57% yield, whilst the arylated D-ribose **4j** was obtained in 32% yield (anomeric ratio α:β = 1:1.1).

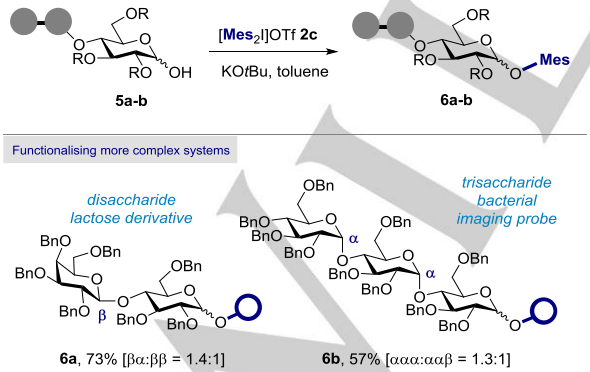
Scheme 2. *O*-Arylation of pyranoses and furanoses utilising aryliodonium salt **2c**.[a]



[a] Reaction were performed in toluene on a 0.15 mmol scale at ambient temperature. The α:β ratio was determined by ^{1}H NMR spectroscopy.

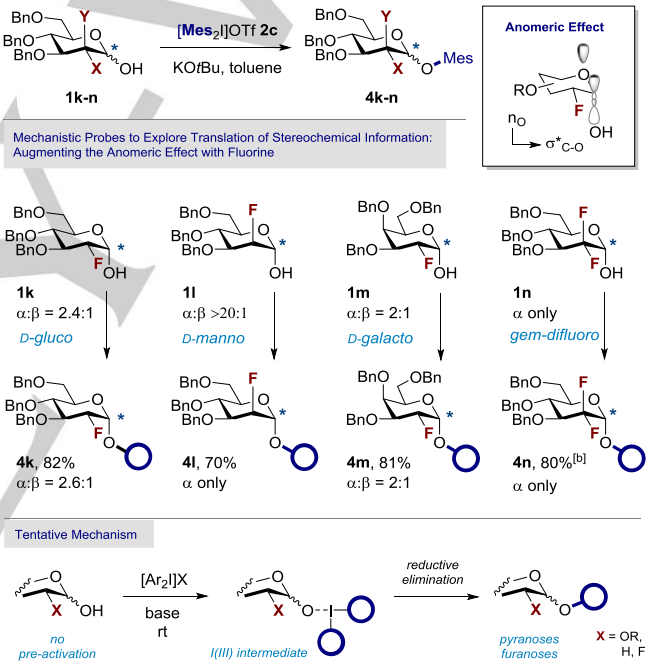
To validate this alternative to chemical glycosylation on more complex glycostructures, a representative O−H functionalisation using **2c** was performed on a biologically relevant *di*- and *tri*-saccharide (Scheme 3). Exposing the lactose derivative **5a** to the optimised arylation conditions at ambient temperature smoothly furnished the desired glycoside **6a** in 73% yield (βα:ββ 1.4:1). Furthermore the trisaccharide **6b**, commonly employed in bacterial imaging,[23] was isolated in 57% yield (ααα:ααβ 1.3:1)

Scheme 3. Extending the *O*-arylation to more complex carbohydrates.



Having established a broad substrate scope for the transformation, the conservation of stereochemistry was interrogated (Scheme 4). To that end, a series of fluorinated substrates were prepared to augment the anomeric effect.[24] The presence of the electron withdrawing group at C2 ensures that the equilibrium favours the α-anomer of the reducing sugar: This in turn should be mirrored in the product composition in the case of a stereoretentive process. Furthermore, 2-fluoro sugars remain privileged tools for mechanistic enzymology and in stereoselective glycosylation.[25] Interestingly, classic trichloroacetimidate activation of **1a** with a Lewis acid (TMSOTf) favours formation of the β-glycoside.[25c] However, with this protocol the predominant α-composition of the lactol is transmitted to the product (α:β 2.4:1 *versus* 2.6:1 for **1k** and **4k** respectively). In the D-mannose case **1l** → **4l**, complete stereoretention was again observed (α only). This feature of the process was further confirmed with the D-galactose system: **1m** → **4m**, α:β 2:1 → 2:1), and finally with the *geminal*-difluoro system: **1n** → **4n**, α → α). Interestingly, the trichloroacetimidate donor of the latter substrate (**1n**) is completely recalcitrant to classic glycosylation conditions[25c] and thus this method provides a handle to install C2 *gem*-difluorinated building blocks into structures of interest. Collectively, these data are consistent with a mechanistic framework that proceeds via an I(III) intermediate that is not prone to epimerisation prior to reductive elimination (Scheme 4, lower).

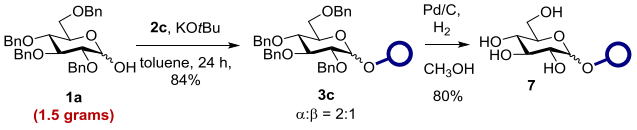
Scheme 4. Top: Exploring the stereoretentive nature of the *O*-arylation using fluorinated probes to enhance the anomeric effect. Bottom: Tentative mechanism.[a]



[a] Reaction were performed in toluene on a 0.15 mmol scale at ambient temperature. [b] Reaction were performed in toluene on a 0.22 mmol scale at ambient temperature. The α:β ratio was determined by ^{1}H NMR spectroscopy.

Finally, the utility of the method towards scale-up was explored on a 1.5 g scale (Scheme 5). The desired aryl ether **3a** was isolated in an increased 84% yield upon stirring for 24 h without any erosion in the anomeric ratio (α:β = 2:1). Global deprotection under hydrogenolysis conditions (H_2, Pd/C, methanol at ambient temperature), furnished **7** in 80% yield.

Scheme 5. Representative scale-up and global deprotection.



In summary, a mild, one-pot, procedure for the efficient and scalable synthesis of *O*-functionalised carbohydrates is disclosed. Predicated on a stereoretentive O−H functionalisation of the reducing sugar (lactol)

this alternative disconnection to conventional glycosylation constitutes a facile and expansive platform for the preparation of aryl glycosides. Promoted by easily accessible electrophilic iodine(III) reagents, the process does not require the classic pre-functionalisation / activation sequence inherent to classical glycosylation methods. Validated for both pyranosyl and furanosyl substrates, the reaction is compatible with a variety of arylating agents and tolerates a range of protecting groups and substituents. The process is particularly suited to the synthesis of fluorinated glycostructures where the stereoelectronic effects of the 2-fluoro substituent can be incorporated into the reaction design to promote formation of α-configured products. Given the generality of this enabling technology, we envisage that it will find application in the preparation of complex acetals in a broader sense.

Acknowledgements

This work was supported by the WWU Münster, the DFG (SFB 858, and Excellence Cluster "*Cells in Motion*") and the European Research Council (ERC-2013-StG Starter Grant to RG).

Keywords: acetal • arylation • fluorine • stereoretention • sugars

[1] a) *Nature Insight: Glycochemistry and Glycobiology* **2007**, *446*, 999-1051; b) N. S. Sampson, M. Mrksich, C. R. Bertozzi, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 12870-12871; c) C. R. Bertozzi, L. L. Kiessling, *Science* **2001**, *291*, 2357-2364; d) T. J. Boltje, T. Buskas, G.-J. Boons, *Nature Chem.* **2009**, *1*, 611-622; e) D. B. Werz, R. Ranzinger, S. Herget, A. Adibekian, C.-W. Von der Lieth, P. H. Seeberger, *ACS Chem. Biol*. **2007**, *2*, 685-691; f) A. Adibekian, P. Stallforth, M.-L. Hecht, D. B. Werz, P. Gagneux, P. H. Seeberger, *Chem. Sci.* **2010**, *2*, 337-344; g) P. H. Seeberger, in *Essentials of Glycobiology* (3rd edition). Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press; 2015-2017. Chapter 2.

[2] B. Ernst, J. L. Magnani, *Nat. Rev. Drug Discov*. **2009**, *8*, 661-677.

[3] G. M. Sheldrick, P. G. Jones, O. Kennard, D. H. Williams, G. A. Smith, *Nature* **1978**, *271*, 223-225.

[4] For recent reviews on chemical glycosylation, see: a) M. M. Nielsen, C. M. Pedersen, *Chem. Rev*. **2018**, DOI: 10.1021/acs.chemrev.8b00144; b) P. O. Adero, H. Amarasekara, P. Wen, L. Bohe, D. Crich, *Chem. Rev*. **2018**, DOI: 10.1021/acs.chemrev.8b00083; c) M. Panza, S. G. Pistorio, K. J. Stine, A. V. Demchenko, *Chem. Rev*. **2018**, DOI: 10.1021/acs.chemrev.8b00051; d) H.-Y. Wang, S. A. Blaszczyk, G. Xiao, W. Tang, *Chem. Soc. Rev*. **2018**, *47*, 681-701; e) W.-L. Leng, H. Yao, J.-X. He, X.-W. Liu, *Acc. Chem. Res.* **2018**, *51*, 628-639; f) P. Peng, R. R. Schmidt, *Acc. Chem. Res*. **2017**, *50*, 1171-1183; g) B. Yu, J. Sun, X. Yang, *Acc. Chem. Res.* **2012**, *45*, 1227-1236; h) D. Benito-Alifonso, M. C. Galan, in *Selective Glycosylation: Synthetic Methods and Catalysts* (Ed. C. Bennet) Wiley-VCH Verlag GmbH & Co. KGaA, pp. 155-172 (**2017**).

[5] a) O. J. Plante, E. R. Palmacci, P. H. Seeberger, *Science*, **2001**, *291*, 1523-1527; b) A. Pardo-Vargas, M. Delbianco, P. H. Seeberger, *Curr. Opin. Chem. Biol*. **2018**, *46*, 48-55; c) L. Wen, G. Edmunds, C. Gibbons, J. Zhang, M. R. Gadi, H. Zhu, J. Fang, X. Liu, Y. Kong, P. G. Wang, *Chem. Rev*. **2018**, DOI**:** 10.1021/acs.chemrev.8b00066.

[6] A. Michael, *Am. Chem. J*. **1879**, *1*, 305–312.

[7] a) C. Sheridan, *Nat. Biotechnol*. **2012**, *30*, 899-900; b) A. Sadurni, G. Kehr, M. Ahlqvist, H. Peilot Sjögren, C. Kankkonen, L. Knerr, R. Gilmour, *Chem. Eur. J*. **2018**, *24*, 2832-2836.

[8] T. P. Kogan, B. Dupré, H. Bui, K. L. McAbee, J. M. Kassir, I. L. Scott, X. Hu, P. Vanderslice, P. J. Beck, R. A. F. Dixon, *J. Med. Chem*. **1998**, *41*, 1099–1111.

[9] D. Schwizer, H. Gäthje, S. Kelm, M. Porro, O. Schwardt, B. Ernst, *Bioorg. Med. Chem*. **2006**, *14*, 4944-4957.

[10] M. D. Delost, D. T. Smith, B. J. Anderson, T. J. Njardarson, *J. Med. Chem.* **2018**, DOI: 10.1021/acs.jmedchem.8b00876.

[11] T. J. Wadzinki, A. Steinauer, L. Hie, G. Pelletier, A. Schepartz, S. J. Miller, *Nat. Chem.* **2018**, *10*, 644-652.

[12] K. Kitamura, Y. Ando, T. Matsumoto, K. Suzuki, *Chem. Rev*. **2018**, *118*, 1495-1598.

[13] A. Vasella, K. Briner, N. Soundarajan, M. S. Platz, *J. Org. Chem*. **1991**, *56*, 4741-4744.

[14] For recent reviews, see: a) X. Li, J. Zhu, *J. Carbohydr. Chem.* **2012**, *31*, 284-324; b) M. J. McKay, H. M. Nguyen, *ACS Catal.* **2012**, *2*, 1563-1595; c) X. Li, J. Zhu, *Eur. J. Org. Chem.* **2016**, 4724-4767.

[15] For recent reviews, see: a) R. D. Richardson, T. Wirth, *Angew. Chem. Int. Ed.* **2006**, *45*, 4402-4404; *Angew. Chem*. **2006**, *118*, 4510-4512; b) M. Ochiai, K. Miyamoto, *Eur. J. Org. Chem.* **2008**, 4229-4239; c) M. Uyanik, K. Ishihara, *Chem. Commun*. **2009**, 2086-2099; d) T. Dohi, Y. Kita, *Chem. Commun*. **2009**, 2073-2085; d) A. Yoshimura, V. V. Zhdankin, *Chem. Rev*. **2016**, *116*, 3328-3435.

[16] a) E. A. Merritt, B. Olofsson, *Angew. Chem. Int. Ed.* **2009**, *48*, 9052-9070; *Angew. Chem.* **2009**, *121*, 9214-9234; b) B. Olofsson, *Top. Curr. Chem*. **2015**, *343*, 135-136; c) M. Wang, S. Chen, X. Jiang, *Chem. Asian J*. **2018** DOI: 10.1002/asia.201800609; c) G. Grelier, B. Darses, P. Dauban, *Beilstein J. Org. Chem.* **2018**, *14*, 1508-1528.

[17] For examples of hypervalent iodine mediated *O*-arylation, see a) J. R. Crowder, E. E. Glover, M. F. Grundon, H. X. Kaempfen, *J. Chem. Soc.* **1963**, 4578-4585; b) T. B. Petersen, R. Khan, B. Olofsson, *Org. Lett.* **2011**, *13*, 3462-3465; c) H. Gao, Q.-L. Xu, C. Keene, L. Kürti, *Chem. Eur. J.* **2014**, *20*, 8883-8887; d) R. Ghosh, E. Stridfeldt, B. Olofsson, *Chem. Eur. J*. **2014**, *20*, 8888-8892; e) R. Ghosh, B. Olofsson, *Org. Lett.* **2014**, *16*, 1830-1832; f) S. K. Sundalam, D. R. Stuart, *J. Org. Chem*. **2015**, *80*, 6456-6466; g) T. L. Seidl, S. K. Sundalam, B. McCullough, D. R. Stuart, *J. Org. Chem.* **2016**, *81*, 1998-2009; h) E. Stridfeldt, E. Lindstedt, M. Reitti, J. Blid, P.-O. Norrby, B. Olofsson, *Chem. Eur. J*. **2017**, *23*, 13249-13258; i) M. Reitti, R. Gurubrahaman, M. Walther, E. Lindstedt, B. Olofsson, *Org. Lett.* **2018**, *20*, 1785-1788; j) X.-H. Li, A.-H. Ye, C. Liang, D.-L. Mo, *Synthesis* **2018**, *50*, 1699-1710.

[18] a) G. L. Tolnai, U. J. Nilsson, B. Olofsson, *Angew. Chem. Int. Ed.* **2016**, *55*, 11226-11230; *Angew. Chem.* **2016**, *128*, 11392-11396; b) Also see Y. Otsuka, T. Yamamoto, K. Fukase, *Synlett* **2018**, *29*, 1510-1516.

[19] B. Ye, J. Zhao, K. Zhao, J. M. McKenna, F. D. Toste, *J. Am. Chem. Soc*. **2018**, DOI: 10.1021/jacs.8b05962.

[20] Full experimental details are provided in the Supporting Information.

[21] For selected examples reporting TMP as a "*dummy*" ligand, see: a) E. Lindstedt, M. Reitti, B. Olofsson, *J. Org. Chem.* **2017**, *82*, 11909-11914; b) V. Carreras, A. H. Sandtorv, D. R. Stuart, *J. Org. Chem.* **2017**, *82*, 1279-1284; c) For a review, see: D. R. Stuart, *Chem. Eur. J*. **2017**, *23*, 15852-15863.

[22] a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev*. **2008**, *37*, 320-330; b) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881-1886.

[23] A. Axer, S. Hermann, G. Kehr, D. Clases, U. Karst, L. Fischer-Riepe, J. Roth, M. Fobker, M. Schäfers, R. Gilmour, A. Faust, *ChemMedChem* **2018**, *13*, 241-250.

[24] C. Thiehoff, Y. P. Rey, R. Gilmour, *Isr. J. Chem*. **2017**, *57*, 92-100.

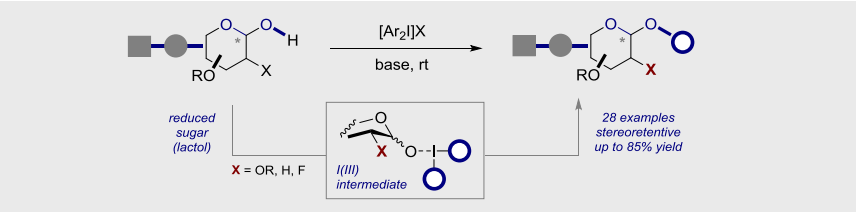
[25] For selected examples see: a) I. P. Street, J. B. Kempton, S. G. Withers, *Biochemistry* **1992**, *31*, 9970-9978; b) S. A. Allman, H. H. Jensen, B. Vijayakrishnan, J. A. Garnett, E. Leon, Y. Liu, D. C. Anthony, N. R. Sibson, T. Feizi, S. Matthews, B. G. Davis, *ChemBioChem* **2009**, *10*, 2522-2529; c) C. Bucher, R. Gilmour, *Angew. Chem. Int. Ed*. **2010**, *49*, 8724-8728; *Angew. Chem*. **2010**, *122*, 8906-8910; d) E. Durantie, C. Bucher, R. Gilmour, *Chem. Eur. J*. **2012**, *18*, 8208-8215; e) T. J. Kieser, N. Santschi, L. Nowack, G. Kehr, T. Kuhlmann, S. Albrecht, R. Gilmour, *ACS Chem. Neurosci*. **2018**, *9*, 1159-1165.

10.1002/chem.201804416

WILEY-VCH

Entry for the Table of Contents

COMMUNICATION



*Nicola Lucchetti, Ryan Gilmour**

Page No. – Page No.

Re-Engineering Chemical Glycosylation: Direct, Metal-Free Anomeric *O*-Arylation of Unactivated Carbohydrates

By re-engineering classic glycosylation, an orthogonal disconnection allows the acetal to be forged directly from the reducing sugar without the need for substrate pre-organisation. Engagement with stable aryliodonium salts facilitates a formal O−H functionalisation reaction of the lactol. This constitutes a mild, metal-free *O*-arylation at ambient temperature. The efficiency of the transformation has been validated using a variety of pyranoside and furanoside monosaccharides in addition to biologically relevant *di*- and *tri*-saccharides.