A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Stereoselective Electro-2-Deoxyglycosylation from Glycals

Authors: Xinshan Ye, Miao Liu, Kai-Meng Liu, De-Cai Xiong, Hanyu Zhang, Tian Li, Bohan Li, Xianjin Qin, and Jinhe Bai

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202006115

Link to VoR: https://doi.org/10.1002/anie.202006115

WILEY-VCH

10.1002/anie.202006115

WILEY-VCH

Stereoselective Electro-2-Deoxyglycosylation from Glycals

Miao Liu,[+] Kai-Meng Liu,[+] De-Cai Xiong,* Hanyu Zhang, Tian Li, Bohan Li, Xianjin Qin, Jinhe Bai and Xin-Shan Ye*

Dedicated to Professor Henry N. C. Wong on the occasion of his 70th birthday.

Abstract: We herein report a novel and highly stereoselective electro-2-deoxyglycosylation from glycals. This method is featured by the excellent stereoselectivity and scope as well as functional-group tolerance. This process could also be amenable to the modification of a wide range of natural products and drugs. Furthermore, a scalable synthesis of glycosylated podophyllotoxin and a one-pot trisaccharide synthesis through iterative electro-glycosylations have also been achieved.

Glycosylation reaction is the central topic in modern carbohydrate chemistry.[1] Due in large part to the fact that sugar attachments are essential for the biological activities of naturally occurring glycosylated natural products.[2] Moreover, glycosylated modification of a drug could very often drastically change its physical properties and thus significantly improve its pharmacological activity.[3] Among them, 2-deoxyglycosides are widely found as a single sugar motif or part of oligosaccharides, in aureolic acid antibiotics, cardiac glycosides, anthracyclines, avermectins, macrolides, pluramycins, angucyclines, enediynes and other biologically active compounds and drugs (Figure 1A).[4] Accordingly, the development of a highly effective 2-deoxyglycosylation method has been in high demand over the last decades. However, owing to the absence of any directing group at C2 position, the stereoselective construction of the labile 2-deoxyglycosidic bond has been a long-standing challenge.[5]

So far, many successful strategies have already been developed to give access to 2-deoxyglycosides in a direct, indirect, or de novo manner.[6-10] Of special note, 2-deoxyglycosylation of glycals with glycosyl acceptors proves to be one of the most atom-economic and straightforward approaches.[5] Accordingly, numbers of elegant methods (Figure 1B), including metal-catalyzed glycosylation,[11] organo-catalyzed glycosylation,[12] photo-catalyzed glycosylation,[13] have been established in recent years. *En route* to stereoselective 2-deoxyglycosylations, we gradually shift our focus to organic electrochemistry, an old but potentially ideal pursuit since it is green and sustainable.[14] Indeed, the beginning of this century has witnessed the renaissance of organic electrosynthesis as a valuable addition to the synthetic community.[15] The application of electrical current to catalyze glycosylation reactions could be traced back to Noyori's pioneer work in the late 1980s.[16] Later, Yoshida and co-workers successfully identified that thio-/seleno-/telluro- glycoside donors could also be activated and undergo glycosylation under different electrochemical conditions.[17,18] However, to the best of our knowledge, electro-2-deoxyglycosylation remains elusive to date. In continuation of our interest in the area of carbohydrate synthesis,[19] we envisage the possibility of the generation of 2-deoxyglycosides from glycals in an electro-induced fashion, and we report herein the results of our studies on electro-2-deoxyglycosylation.

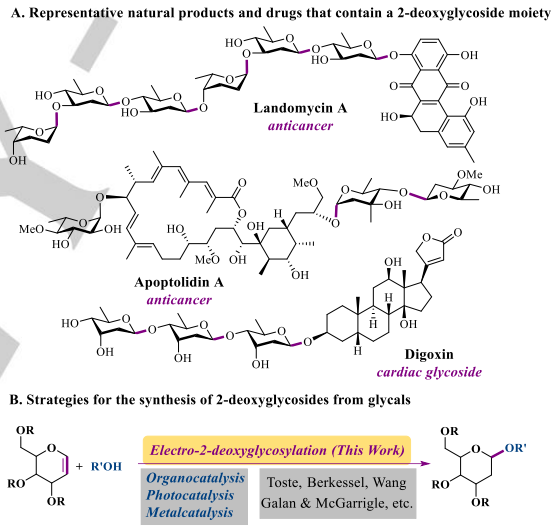


Figure 1. Selected bioactive 2-deoxyglycosides and glycosylation methods derived from glycals.

We commenced our investigation with a model reaction using galactal **1** as the donor and the alcohol **2** as the acceptor (Scheme 1 and Tables S1-S4). Upon extensive solvent screening, CH_2Cl_2 and dimethoxyethane (DME) were initially found to generate desired disaccharide **3** with exclusively α-selectivity, albeit in a 5% yield. The combination of DME and methyl nonafluorobutyl ether (MFE)[20] could slightly promoted the formation of desired disaccharide **3** along with less decomposition of the starting material **1** (Table S1). Later, the additives proved to be essential to our reaction outcome.[15b] After an extensive screening of numerous additives (entries 2-8, Scheme 1 and Table S2), alkyl bromides were found to be optimal, and saccharide **3** was obtained in 92% isolated yield when using 60 mol% of 3-bromopropionitrile (entry 6, Scheme 1). Whereas Bu_4NOTf was identified as the suitable electrolyte (entries 6, 12, Table S3), the carbon electrode and platinum electrode were chosen as the optimal anode and cathode,

[a] M. Liu,[+] K.-M. Liu,[+] Dr. D.-C. Xiong, H. Zhang, T. Li, B. Li, X. Qin, J. Bai, Prof. X.-S. Ye.
State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University,
Xue Yuan Road No. 38, Beijing 100191 (China)
E-mail: xinshan@bjmu.edu.cn, decai@bjmu.edu.cn
Dr. D.-C. Xiong
Shandong Key Laboratory of Carbohydrate Chemistry and Glycobiology, Shandong University, 27 Shanda Nanlu, Jinan, Shandong 250100 (China)
[+] These authors contributed equally to this work.

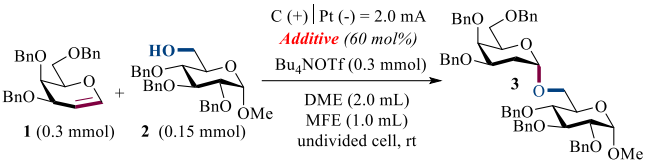
Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/anie.202006115

respectively (Table S4). Lastly, dichloromethane or DME alone could also be applied as reaction solvent (entries 15-16, Scheme 1), and we observed no conversion whatsoever in the absence of electrical current (entry 17, Scheme 1). Of particular note, all the reactions mentioned above were performed under constant current conditions (2.0 mA) in an undivided cell at ambient temperature.



Entry	Deviation from above	Yield (%)
1	-	8
2	CBr_4	60
3	$BrCCl_3$	65
4	$BrCH_2CO_2Et$	80
5	$BrCH_2CN$	79
6	$BrCH_2CH_2CN$	92
7	1.0 equiv of $BrCH_2CH_2CN$	91
8	0.3 equiv of $BrCH_2CH_2CN$	86
9	$BrCH_2CH_2CN$, 3.0 mA	71
10	$BrCH_2CH_2CN$, 1.0 mA	80
11	$BrCH_2CH_2CN$, 1.5 equiv of **1**	78
12	$BrCH_2CH_2CN$, 3.0 equiv of Bu_4NOTf	92
13	$BrCH_2CH_2CN$, Bu_4NBF_4	89
14	$BrCH_2CH_2CN$, RVC (+)/Pt (−)	89
15	$BrCH_2CH_2CN$, CH_2Cl_2 as solvent	91
16	$BrCH_2CH_2CN$, no MFE	88
17	$BrCH_2CH_2CN$, no electricity	n.d.

Scheme 1. Reaction Optimization.

With optimal conditions in hand, we next set out to investigate the reaction scope. As shown in Figure 2A, to our delight, under standard reaction conditions both secondary and tertiary alcohols could all successfully react with galactal **1** to deliver glycosides **4-7** in good yields with exclusive α-selectivity. Benzoyl and methyl protected galactals were also well-tolerated to give glycosides **8** and **9** in moderate to good yields. TBS-protected galactal proved to be sensitive under standard reaction conditions and gave glycoside **10** in 41% yield. Fortunately, the yield could be further improved to 75% upon using CH_2Cl_2 as the solvent along with the addition of β-pinene as a proton scavenger.[21] Moreover, glucal donor, which is commonly believed to be more challenging,[12b] in our case underwent 2-deoxyglycosylation smoothly and afforded disaccharide **11** as a single α-anomer in 72% yield. Arabinal was also identified as a suitable substrate, providing disaccharide **12** as a single β-anomer in a 80% yield. Reaction with different kinds of acceptors was also permissible and delivered the desired glycosides **13** and **14** in satisfactory yields. Lastly, thioglycosides were also well tolerated during the reaction, which indicates the possibility of potential one-pot orthogonal glycosylations.

Next, we applied our established protocol to the late-stage modification of natural products and drugs.[22] As shown in Figure 2B, late-stage glycosylated modification occurred smoothly under standard reaction conditions, thus afforded the desired products (**16-29**) in good to excellent yields. Of note, owing to the solubility issue, CH_2Cl_2 was also applied as the reaction solvent, as is the case for **26** and **27**. In all cases, excellent α-selectivity for galactal and β-selectivity for arabinal were observed, respectively. Meanwhile, it is worth mentioning that various functional groups including ketone (**23**), carboxylic acid (**24**), uracil (**25**), enoate (**26-27**) and 1,3-diene (**28-29**) moieties are all well tolerated during the reactions. And the scalability of this protocol was further demonstrated by an efficient synthesis of glycosylated podophyllotoxin **21** on a 934 mg scale in 75% isolated yield.

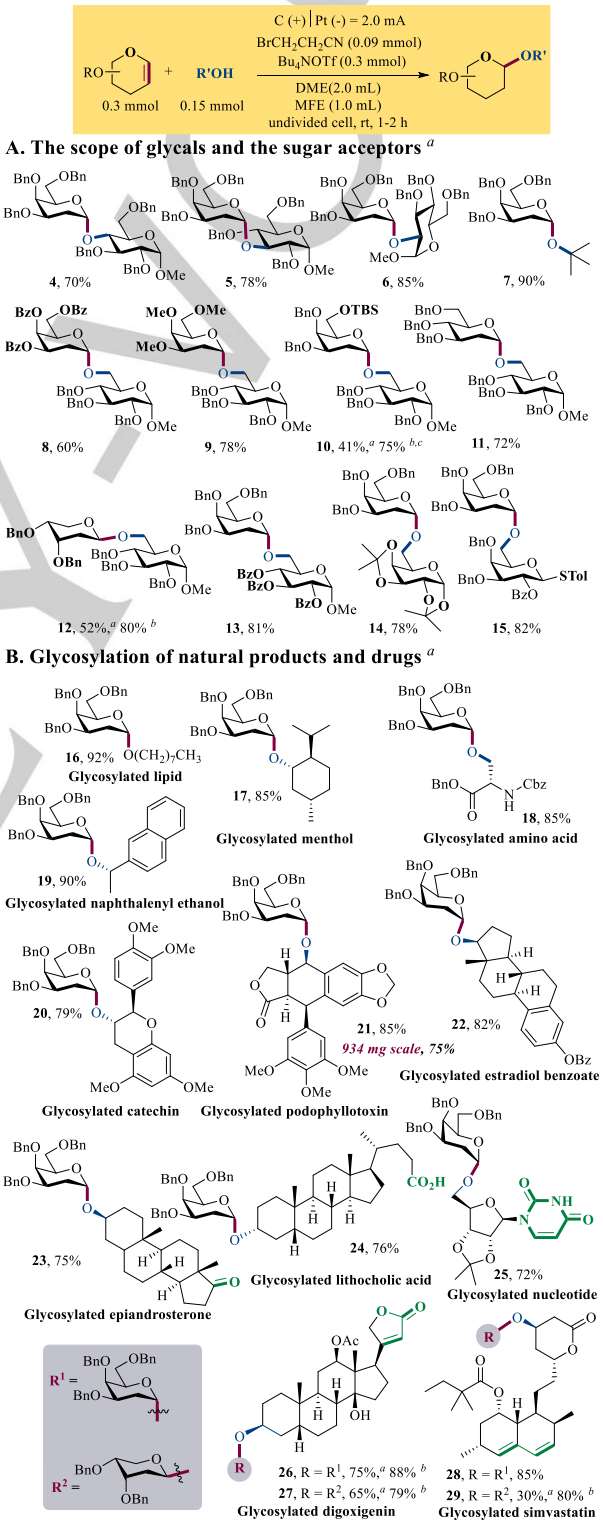


Figure 2. Substrate scope. The yields were isolated yields, the α/β ratios were determined by ^{1}H NMR. (a) Standard conditions: glycal (0.30 mmol), acceptor

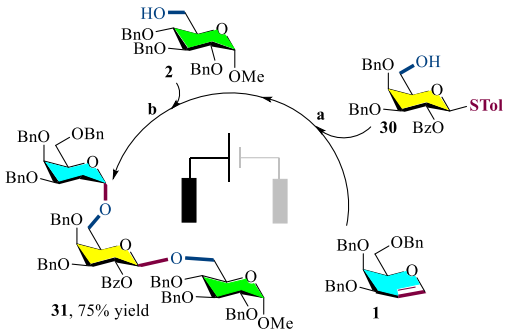
Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/anie.202006115

(0.15 mmol), Bu_4NOTf (2.0 equiv), $BrCH_2CH_2CN$ (0.09 mmol), DME (2.0 mL)/MFE (1.0 mL), 2.0 mA, rt. (b) CH_2Cl_2 as the solvent. (c) β-Pinene (0.15 mmol) was added.

Finally, to further extend the synthetic potential of this method, we performed a one-pot trisaccharide synthesis via iterative electro-glycosylations. As shown in Scheme 2, galactal **1** was first reacted with the acceptor **30** to furnish the disaccharide **15** within 2 h under the standard reaction conditions (2 mA in DME/MFE). Subsequent in-situ electro-glycosylation with acceptor **2** following Yoshida's[18a,c] protocol delivered the trisaccharide **31** in low yield (<10%) at room temperature. Fine-tuning Yoshida's reaction conditions by lowering the temperature to -50 °C increased the yield to 22%. Finally, the iterative electro-one-pot trisaccharide synthesis was successfully accomplished by conducting the second electro-glycosylation at -78 °C using CH_2Cl_2 as solvent, affording the desired trisaccharide **31** in 75% isolated yield.



Scheme 2. Iterative Electro-Glycosylation. Conditions: (a) **1** (0.30 mmol), **30** (0.15 mmol), $BrCH_2CH_2CN$ (0.09 mmol), CH_2Cl_2 (3.0 mL), 2.0 mA, rt. (b) **2** (0.08 mmol), 4.0 mA, -78 °C.

To shed light on the possible reaction mechanism (Figures 3A-C, Figures S1-5 and Tables S5-7), a series of mechanistic experiments were carefully designed and executed. Firstly, two deuterium labeling experiments proved a *syn*-addition of glycal with alcohol (Figure 3A and Figures S1-2). ^{1}H-NMR monitoring the reaction between **1** and CH_3OH in CD_2Cl_2 revealed just a 14% gradual loss of the mount of $BrCH_2CH_2CN$ at the most during the reaction (Figure S3 and Table S5). The CV of $BrCH_2CH_2CN$ was consistent with that of the full $Br^-/Br_3^-/Br_2$ reaction.[23] The CVs of the reactants depicted that the intensity of both the oxidation peaks and the reduction peak increases, especially a dramatic increase in the reduction peak current (Figure 3B and Figure S4). Then, Bu_4NBr, Bu_4NBr_3, Br_2 or $ClCH_2CH_2CN$ were used as an alternative additive, respectively. Only Br_2 gave the disaccharide in 20% yield. $ClCH_2CH_2CN$ alone could not facilitate this reaction either (Figure 3C and entries 3-6 in Table S6). Interestingly, the combination of $ClCH_2CH_2CN$ with Br_2 was able to generate the disaccharide in 52% yield (Table S6, entries 9-10). TEMPO inhibition and trapping experiments proved the presence of a propionitrile radical (entry 11 in Table S6, and Figure S5). Thus, we speculate an involvement of propionitrile radical, Br_2, and Br^- in this reaction.[24,25] Combining these observations with enol ether radical cation work reported previously,[26] a postulated mechanism is proposed in Figure 3D. Cathodic reduction of $BrCH_2CH_2CN$ generates propionitrile radical and Br^-, which could combine H^+ to give HBr. Covalent H-Br with weak acidity is considered to be a good hydrogen source in the hydrogen abstraction reaction.[27] Since enol radical cations and related nucleophilic addition reactions are well-evidenced,[26] anodic oxidation of glycal **A** affords radical cation **B**.[26e] The attack of **B** by a glycosyl acceptor produces intermediate **C**.[26c] The combined effects of a half-chair conformer[28] and the orientation of 3-substituent in the glycal radical cation might be responsible for the good stereoselectivity, for instance, the α-selectivity for disaccharide **11** and β-selectivity for disaccharide **12**. Br^- abstracts H^+ from **C** to produce HBr and radical **D**. Radical **D** abstracts hydrogen from HBr to give the glycoside **E** and a Br radical at the anode. The newly-formed C-H bond is mainly equatorial.[29] Two liberated Br radicals combine to form Br_2, which could diffuse back to the cathode and react with two propionitrile radicals to regenerate $BrCH_2CH_2CN$.

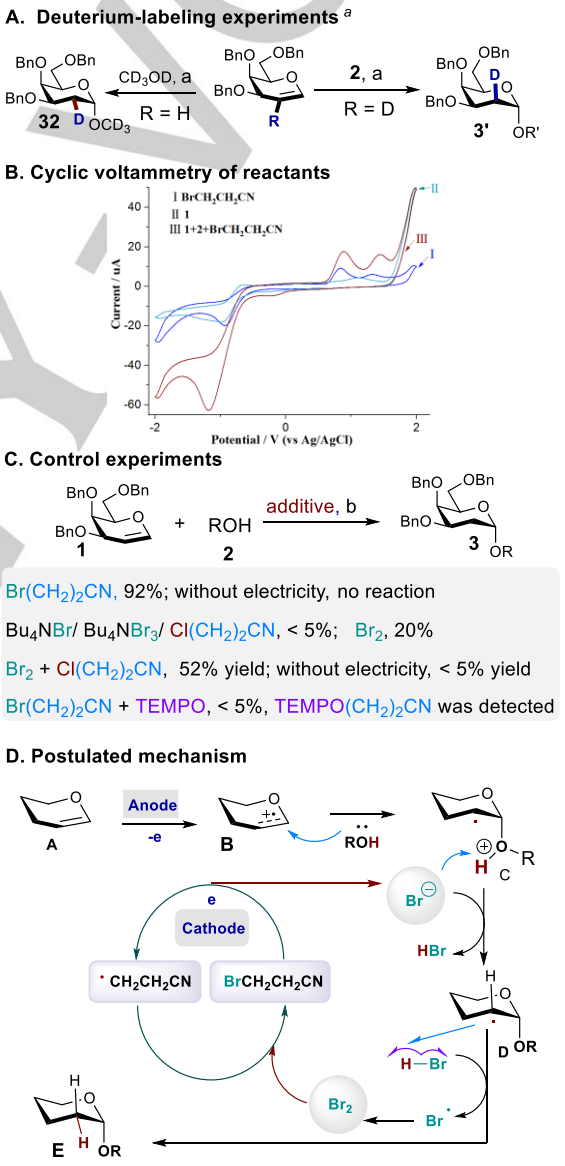


Figure 3. Mechanistic studies. (a) Standard conditions: glycal (0.30 mmol), acceptor (9.0 mmol for CD_3OD or 0.15 mmol for **2**), Bu_4NOTf (2.0 equiv), $BrCH_2CH_2CN$ (0.09 mmol), DME (2.0 mL)/MFE (1.0 mL), 2.0 mA, rt. (b) glycal (0.30 mmol), **2** (0.15 mmol), Bu_4NOTf (2.0 equiv), additive, DME (2.0 mL)/MFE (1.0 mL), 2.0 mA, rt. Cyclic voltammogram at 50 mV/s of (I) glycal **1**, (II) $BrCH_2CH_2CN$ and (III) **1**+ **2** + $BrCH_2CH_2CN$ in DME.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

To conclude, an unprecedented electro-2-deoxyglycosylation from glycals has been established in an undivided cell, using $BrCH_2CH_2CN$ as an additive. Accordingly, thirteen 2-deoxyglycosides covering a large set of challenging linkages were prepared in good yields and with excellent stereoselectivities. The glycosylation of fourteen natural products and drugs further demonstrates its great potential in carbohydrate-based drug discovery. A scalable synthesis of glycosylated podophyllotoxin and an iterative one-pot trisaccharide synthesis have also been achieved. Given the large abundance of 2-deoxyglycosides in natural products, this method might find wide applications in the field of glycochemistry and glycomedicines.

Acknowledgements

This work was financially supported by grants from the National Natural Science Foundation of China (Grant No. 21572012), the National Key R&D Program of China (2018YFA0507602), and the Open Projects Fund of Shandong Key Laboratory of Carbohydrate Chemistry and Glycobiology (No. 2019CCG01). We thank Mr. Lei Zhang for helpful discussions about cyclic voltammetry experiments. We are grateful to Profs. Houhua Li, Qian Wan, and Chengchu Zeng for their insightful discussions.

Keywords: carbohydrate• electrosynthesis • 2-deoxyglycoside • glycal • glycosylation

[1] a) L. Krasnova, C.-H. Wong, *J. Am. Chem. Soc.* **2019**, *141*, 3735-3754; b) C. S. Bennett, *Selective Glycosylations: Synthetic Methods and Catalysts: Synthetic Methods and Catalysts*; Wiley-VCH Verlag: 2017; c) S. C. Hung, M. M. L. Zulueta, *Glycochemical Synthesis: Strategies and Applications*; First ed.; Wiley & Sons: Hoboken, NJ, 2016; d) A. V. Demchenko, *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*; Wiley-VCH Verlag: Weinheim, Germany, 2008; e) X. Zhu, R. R. Schmidt, *Angew. Chem. Int. Ed.* **2009**, *48*, 1900-1934; *Angew. Chem.* **2009**, *121*, 1932-1967.

[2] a) B. La Ferla, C. Airoldi, C. Zona, A. Orsato, F. Cardona, S. Merlo, E. Sironi, G. D'Orazio, F. Nicotra, *Nat. Prod. Rep.* **2011**, *28*, 630-648; b) E. K. McCranie, B. O. Bachmann, *Nat. Prod. Rep.* **2014**, *31*, 1026-1042.

[3] a) R. W. Gantt, P. Peltier-Pain, J. S. Thorson, *Nat. Prod. Rep.* **2011**, *28*, 1811-1853; b) R. D. Goff, J. S. Thorson, *MedChemComm* **2014**, *5*, 1036-1047; c) L. Daley, Y. Guminski, P. Demerseman, A. Kruczynski, C. Etiévant, T. Imbert, B. T. Hill, C. Monneret, *J. Med. Chem.* **1998**, *41*, 4475-4485; d) Q.-L. He, I. Minn, Q. Wang, P. Xu, S. A. Head, E. Datan, B. Yu, M. G. Pomper, J. O. Liu, *Angew. Chem. Int. Ed.* **2016**, *55*, 12035-12039; *Angew. Chem*. **2016**, *128*, 12214-12218.

[4] a) S. I. Elshahawi, K. A. Shaaban, M. K. Kharel, J. S. A. Thorson, *Chem. Soc. Rev.* **2015**, *44*, 7591-697; b) R. M. Lederkremer, C. Marino, *Adv. Carbohydr. Chem. Biochem.* **2007**, *61*, 143-216.

[5] For reviews, see: a) C. S. Bennett, M. C. Galan, *Chem. Rev.* **2018**, *118*, 7931-7985; b) J. Zeng, Y. Xu, H. Wang, L. Meng, Q. Wan, *Sci. China: Chem*. **2017**, *60*, 1162-1179; c) S. Medina, M. C. Galan, *Carbohydr. Chem.* **2015**, *41*, 59-89; d) A. Borovika, P. Nagorny, *J. Carbohydr. Chem.* **2012**, *31*, 255-283; e) D. Hou, T. L. Lowary, *Carbohydr. Res.* **2009**, *344*, 1911-1940; f) C. H. Marzabadi, R. W. Franck, *Tetrahedron* **2000**, *56*, 8385-8417; g) J. Thiem, W. Klaffke, *Top. Curr. Chem*. **1990**, *154*, 285-333.

[6] For selected examples of direct synthesis, see: a) J. M. Nogueira, M. Bylsma, D. K. Bright, C. S. Bennett, *Angew. Chem. Int. Ed.* **2016**, *55*, 10088-10092; *Angew. Chem.* **2016**, *128*, 10242-10246. b) K. A. D'Angelo, M. S. Taylor, *J. Am. Chem. Soc.* **2016**, *138*, 11058-11066; c) H. Tanaka, A. Yoshizawa, T. Takahashi, *Angew. Chem. Int. Ed.* **2007**, *46*, 2505-2507; *Angew. Chem.* **2007**, *119*, 2557-2559; d) J. Zeng, R. Wang, S. Zhang, J. Fang, S. Liu, G. Sun, B. Xu, Y. Xu, D. Fu, W. Zhang, Y. Hu, Q. Wan, *J. Am. Chem. Soc.* **2019**, *141*, 8509-8515.

[7] For selected examples of indirect synthesis, see: a) W. R. Roush, C. E. Bennett, *J. Am. Chem. Soc.* **1999**, *121*, 3541-3542; b) K. Toshima, S. Mukaiyama, Y. Nozaki, H. Inokuchi, M. Nakata, K. Tatsuta, *J. Am. Chem. Soc.* **1994**, *116*, 9042-9051; c) D. Kahne, D. Yang, J. J. Lim, R. Miller, E. Paguaga, *J. Am. Chem. Soc.* **1988**, *110*, 8716-8717; f) D. Hou, H. A. Taha, T. L. Lowary, *J. Am. Chem. Soc.* **2009**, *131*, 12937-12948; g) X. Yang, B. Fu, B. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 12433-12435.

[8] For selected example of de novo synthesis, see: R. S. Babu, Q. Chen, S. W. Kang, M. Zhou, G. A. O'Doherty, *J. Am. Chem. Soc.* **2012**, *134*, 11952-11955.

[9] For selected examples of anomeric *O*-alkylation, see: a) J. P. Issa, C. S. Bennett, *J. Am. Chem. Soc.* **2014**, *136*, 5740-5744; b) D. Zhu, K. N. Baryal, S. Adhikari, J. Zhu, *J. Am. Chem. Soc.* **2014**, *136*, 3172-3175.

[10] Examples of anomeric *C*-alkyloxylation, see: K. M. Hoang, N. R. Lees, S. B. Herzon, *J. Am. Chem. Soc.* **2019**, *141*, 8098-8103.

[11] a) B. D. Sherry, R. N. Loy, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4510-4511; b) A. Sau, R. Williams, C. Palo-Nieto, A. Franconetti, S. Medina, M. C. Galan, *Angew. Chem. Int. Ed.* **2017**, *56*, 3640-3644; *Angew. Chem*. **2017**, *129*, 3694-3698. c) C. Palo-Nieto, A. Sau, M. C. Galan, *J. Am. Chem. Soc.* **2017**, *139*, 14041-14044.

[12] a) E. I. Balmond, D. M. Coe, M. C. Galan, E. M. McGarrigle, *Angew. Chem. Int. Ed.* **2012**, *51*, 9152-9155; *Angew. Chem.* **2012**, *124*, 9286-9289. b) E. I. Balmond, D. Benito-Alifonso, D. M. Coe, R. W. Alder, E. M. McGarrigle, M. C. Galan, *Angew. Chem. Int. Ed.* **2014**, *53*, 8190-8194; *Angew. Chem*. **2014**, *126*, 8329-8333. c) S. Das, D. Pekel, J. M. Neudorfl, A. Berkessel, *Angew. Chem. Int. Ed.* **2015**, *54*, 12479-12483; *Angew. Chem*. **2015**, *127*, 12656-12660. c) R. Williams, M. C. Galan, *Eur. J. Org. Chem.* **2017**, *2017*, 6247-6264.

[13] G. Zhao, T. Wang, *Angew. Chem. Int. Ed.* **2018**, *57*, 6120-6124; *Angew. Chem.* **2018**, *130*, 6228-6232.

[14] a) E. J. Horn, B. R. Rosen, P. S. Baran, *ACS Cent. Sci.* **2016**, *2*, 302-308; b) R. D. Little, K. D. Moeller, *Chem. Rev.* **2018**, *118*, 4483-4484.

[15] For selected reviews, see: a) M. Yan, Y. Kawamata, P. S. Baran, *Chem. Rev.* **2017**, *117*, 13230-13319; b) R. Francke, R. D. Little, *Chem. Soc. Rev.* **2014**, *43*, 2492-2521; c) C. Gütz, B. Klöckner, S. R. Waldvogel, *Org. Process Res. Dev.* **2016**, *20*, 26-32; d) Y. Jiang, K. Xu, C. Zeng, *Chem. Rev.* **2018**, *118*, 4485-4540; e) S. Tang, Y. Liu, A. Lei, *Chem* **2018**, *4*, 27-45; f) C. Ma, P. Fang, T.-S. Mei, *ACS Catal.* **2018**, *8*, 7179-7189; g) A. Wiebe, T. Gieshoff, S. Mçhle, E. Rodrigo, M. Zirbes, S. R. Waldvogel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5594-5619; *Angew. Chem*. **2018**, *130*, 5694-5721.

[16] R. Noyori, I. Kurimoto, *J. Org. Chem.* **1986**, *51*, 4320-4322.

[17] For selected reviews, see: a) A. Shimizu, R. Hayashi, J. Yoshida, *Chem. Rev.* **2018**, *118*, 4702-4730; b) S. Manmode, K. Matsumoto, T. Nokami, T. Itoh, *Asian J. Org. Chem.* **2018**, *7*, 1719-1729; c) J. Yoshida, K. Kataoka, R. Horcajada, A. Nagaki, *Chem. Rev.* **2008**, *108*, 2265-2299; d) T. Nokami, *Trends Glycosci. Glycotechnol.* **2019**, *31*, SE74-SE75.

[18] For selected examples, see: a) T. Nokami, A. Shibuya, H. Tsuyama, S. Suga, A. A. Bowers, D. Crich, J. Yoshida, *J. Am. Chem. Soc.* **2007**, *129*, 10922-10928; b) T. Nokami, R. Hayashi, Y. Saigusa, A. Shimizu, C.-Y. Liu, K.-K. Tony Mong, J. Yoshida, *Org. Lett.* **2013**, *15*, 4520-4523; c) T. Nokami, Y. Nozaki, Y. Saigusa, A. Shibuya, S. Manabe, Y. Ito, J. Yoshida, *Org. Lett.* **2011**, *13*, 1544-1547; d) T. Nokami, A. Shibuya, S. Manabe, Y. Ito, J. Yoshida, *Chem. Eur. J.* **2009**, *15*, 2252-2255; e) T. Nokami, H. Tsuyama, A. Shibuya, T. Nakatsutsumi, J. Yoshida, *Chem. Lett*. **2008**, *37*, 942-943; f) T. Nokami, Y. Isoda, N. Sasaki, A. Takaiso, S. Hayase, T. Itoh, R. Hayashi, A. Shimizu, J. Yoshida, *Org. Lett.* **2015**, *17*, 1525-1528; g) S. Yamago, K. Kokubo, O. Hara, S. Masuda, J. Yoshida, *J. Org. Chem.* **2002**, 67, 8584-8592.

[19] a) Y. Wu, D.-C. Xiong, S.-C. Chen, Y.-S.Wang, X.-S. Ye, *Nat. Commun.* **2017**, *8*, 14851; b) L. Sun, X. Wu, D.-C. Xiong, X.-S. Ye, *Angew. Chem. Int. Ed.* **2016**, *55*, 8041-8044; *Angew. Chem*. **2016**, *128*, 8173-8176. c) X.-F. Huang, L.-J. Huang, H.-S. Wang, X.-S. Ye, *Angew. Chem. Int. Ed.* **2004**, *43*, 5221-5224; *Angew. Chem*. **2004**, *116*, 5333-5336.

[20] J. Arai, *J. Appl. Electrochem.* **2002**, *32*, 1071-1079.

[21] X. Gu, L. Chen, X. Wang, X. Liu, Q. You, W. Xi, L. Gao, G. Chen, Y.-L. Chen, B. Xiong, J. Shen, *J. Org. Chem.* **2014**, *79*, 1100-1110.

[22] S. Bansal, S. Vyas, S. Bhattacharya, M. Sharma, *Nat. Prod. Rep.* **2013**, *30*, 1438-1454.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

[23] a) B. Bennett, J. Chang, A. J. Bard, *Electrochimica Acta*, **2016**, *219*, 1–9; b) L. S. Kang, M. H. Luo, C. M. Lam, L. M. Hu, R. D. Little, C. C. Zeng, *Green Chem.* **2016**, *18*, 3767-3774; c) I. Damljanovic , D. Stevanovic , M. Vukicevic, R. D. Vukicevic, *Carbohydr. Res.* **2011**, *346*, 2683-2687.

[24] We thank a reviewer for calling our attention to the presence of trace amount of bromide and control experiments by the addition of an alternative bromide source.

[25] We could rule out an acid-catalyzed glycosylation process (entry 12 in Table S6, Table S7, and *Ref*. 11b) and a bromoglycosylation-debromination pathway (see 7.3 in SI) by control experiments.

[26] a) K. D. Moeller, M. R. Marzabadi, D. G. New, M. Y. Chiang, S. Keith, *J. Am. Chem. Soc.* **1990**, *112*, 6123-6124; b) A. Sutterer, K. D. Moeller, *J. Am. Chem. Soc.* **2000**, *122*, 5636-5637; c) J. M. Campbell, H.-C. Xu, K. D. Moeller, *J. Am. Chem. Soc.* **2012**, *134*, 18338-18344; d) C.-Y. Cai, X.-M. Shu, H.-C. Xu, *Nat. Commun.* **2019**, *10,* 4953; e) CVs of glycals: T. Linker, D. Schanzenbach, E. Elamparuthi, T Sommermann, W. Fudickar, V. Gyóllai, L. Somsák, W. Demuth, M. Schmittel, *J. Am. Chem. Soc.* **2008**, *130*, 16003-16010.

[27] S. Sumino, A. Fusano, I. Ryu, *Org. Lett.* **2013**, *15*, 2826-2829.

[28] a) A. Nowacki, D. Walczak, B. Liberek, *Carbohydr. Res.* **2012**, *352*, 177–185; b) A. Nowacki, D. Walczak, B. Liberek, *Carbohydr. Res.* **2018**, *462*, 13–27.

[29] B. Giese, *Angew. Chem. Int. Ed.* **1989**, 28, 969-980; *Angew. Chem.* **1989**, 101, 993-1004.

WILEY-VCH

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/anie.202006115

WILEY-VCH

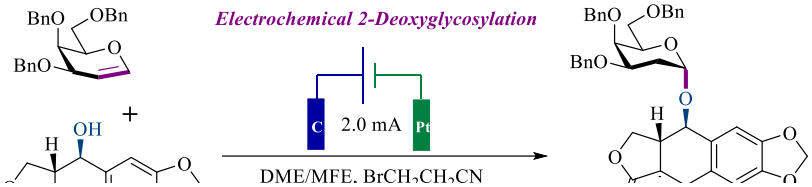
Layout 2:

COMMUNICATION

Miao Liu,[+] Kai-Meng Liu,[+] De-Cai Xiong, Hanyu Zhang, Tian Li, Bohan Li, Xianjin Qin, Jinhe Bai and Xin-Shan Ye**

Page No. – Page No.

Stereoselective Electro-2-Deoxyglycosylation from Glycals



WILEY-VCH

Accepted Manuscript

This article is protected by copyright. All rights reserved.