ChemPubSoc Europe

DOI: 10.1002/ejoc.201501568

EurJOC European Journal of Organic Chemistry

Communication

Regioselective Sulfation

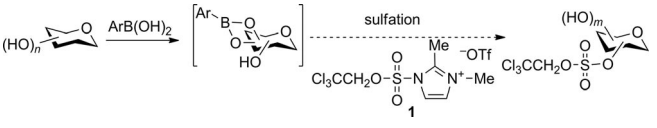
# Regioselective, Tin-Free Sulfation of Unprotected Hexopyranosides by Using Phenylboronic Acid

Kenji Fukuhara,[a] Naoyuki Shimada,[a] Takashi Nishino,[a] Eisuke Kaji,*[a] and Kazuishi Makino*[a]

**Abstract:** Regioselective, tin-free sulfation of a number of unprotected glycopyranosides derived from L-fucose, L-rhamnose, D-arabinose, D-glucose, D-galactose, and D-trehalose was achieved by using phenylboronic acid for masking the hydroxy groups and a 2,2,2-trichloroethyl-protected sulfurylimidazolium salt as the sulfating reagent. The formation of phenylborate ester remarkably improved the solubility of the carbohydrates in organic solvents and indicated high reactivity and regioselectivity in the sulfation reactions. This methodology was successfully adapted to result in a one-pot procedure that did not require separation or purification of the reaction intermediates.

## Introduction

Sulfated carbohydrates have been found to play important roles in a wide range of biological events such as blood coagulation, pathogen infection, tumor growth and metastasis, neurite outgrowth, and amyloidogenesis.[1] Their biological activities are affected by the positions and the degree of sulfation as well as the nature of the carbohydrate backbone. To better understand these biologically important roles, structurally homogeneous forms of sulfated carbohydrates are in great demand. This has led to the development of several synthetic methods for the synthesis of sulfated carbohydrates. Sulfated carbohydrates have conventionally been synthesized by treating precursors in which only the hydroxy groups to be sulfated are unprotected with a sulfur trioxide–amine complex such as $SO_3$–pyridine, $SO_3$–triethylamine, or $SO_3$–trimethylamine in a later synthetic stage.[2] This synthetic approach requires an extensive protection/deprotection process by using orthogonal protecting groups, which results in a lengthy and impractical synthetic procedure and a lower overall yield. To overcome this problem, direct regioselective sulfation reactions involving the reaction of a sulfur trioxide–amine complex with unprotected carbohydrates by formation of stannylene acetals have been investigated.[3,4] Although this pathway is an effective method that allows the sulfation of a specific hydroxy group, the unavoidable use of toxic and environmentally hazardous organotin reagents, such as $Bu_2SnO$, in stoichiometric quantities is a definite limitation for practical syntheses. Therefore, there still remains room for improvement in the available methods for regioselective sulfation of carbohydrates. Recently, we and others demonstrated the regioselective glycosylation of fully unprotected hexopyranoside by molecular recognition of the hydroxy groups at specific positions by arylboronic acids.[5–7] In this context, we report here a highly regioselective tin-free sulfation based on the masking of hydroxy groups with phenylboronic acid (Scheme 1).




Scheme 1. Regioselective *O*-sulfation of unprotected carbohydrates by using arylboronic acid.

In the syntheses of sulfated carbohydrates, the choice of sulfating reagent is another challenge. A conventional method for the direct transformation of hydroxy groups into sulfate groups is the use of sulfur trioxide–amine complexes. However, incomplete sulfation of the free hydroxy groups and problems are often encountered during the isolation of a highly polar sulfated product from the reaction mixture. Moreover, further chemical transformations of nonprotected sulfated carbohydrates are difficult. To overcome these problems, protected sulfurylimidazolium salts (SISs) with a 2,2,2-trichloroethyl (TCE) group were developed by Taylor's group as a new class of sulfating reagents.[8,9] This reliable TCE-protected reagent enables not only easy handling, separation, and purification of the sulfated product, but also permits a broad range of synthetic strategies to be applied to sulfated carbohydrates, as the protected sulfate groups are introduced at an early synthetic stage. We therefore chose Taylor's reagent **1**[8d] as a sulfating reagent for regioselective sulfation reactions by using phenylboronic acid.

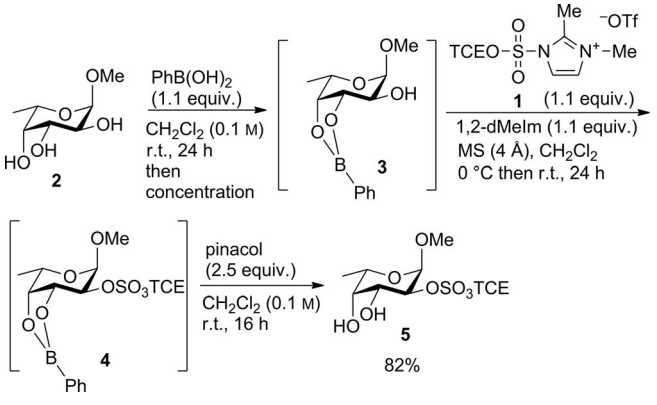
## Results and Discussion

We initially examined the sulfation of methyl α-L-fucopyranoside (**2**), which bears three contiguous secondary hydroxy

[a] *Department of Pharmaceutical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 108-8641, Japan*
*E-mail: makinok@pharm.kitasato-u.ac.jp*
*http://www.pharm.kitasato-u.ac.jp/medicinal/Welcome.html*

*Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201501568.*

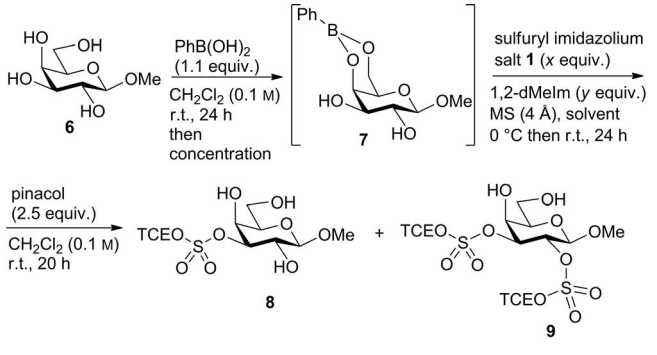
groups in different orientations (Scheme 2).[6,10,11] Treatment of a suspension of methyl α-L-fucopyranoside (**2**) in $CH_2Cl_2$ with 1.1 equiv. of phenylboronic acid at room temperature for 24 h afforded a clear colorless solution of 3,4-*O*-phenyboronate ester **3** without the addition of any other additives. Clearly, the formation of cyclic boronate esters of nonprotected carbohydrates remarkably improves their solubility in organic solvents. After removal of the solvent, the residue was treated with 1.1 equiv. of the sulfurylimidazolium salt **1** in the presence of 1.1 equiv. of 1,2-dimethylimidazole (1,2-dMeIm) and molecular sieves (MS) (4 Å) in $CH_2Cl_2$ for 24 h. Subsequent treatment with 2.5 equiv. of pinacol to remove the boronate ester[12] gave the 2-*O*-monosulfated product **5** as a single regioisomer in 82 % yield.




Scheme 2. Regioselective sulfation of methyl α-L-fucopyranoside (**2**) by using phenylboronic acid.

Encouraged by this result, we examined the regioselective sulfation of methyl β-D-galactopyranoside (**6**), which bears four hydroxy groups, including a primary hydroxy group (Table 1). The treatment of methyl β-D-galactopyranoside (**6**) with phenylboronic acid, followed by sulfation with sulfurylimidazolium salt **1** (1.1 equiv.) and 1,2-dMeIm (1.1 equiv.) in $CH_2Cl_2$ under the conditions employed in Scheme 1 gave both the 3-*O*-monosulfated product **8** and the 2,3-*O*-disulfated product **9** in 63 % and 12 % yield, respectively, after treatment with pinacol (Entry 1).

Table 1. Regioselective sulfation of methyl β-D-galactopyranoside (**6**) by using phenylboronic acid.

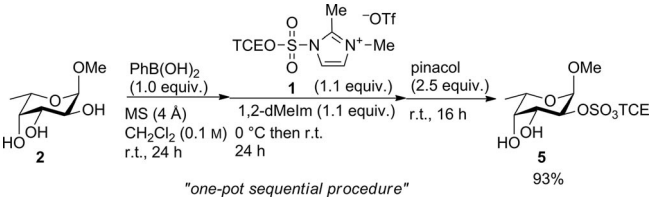



| Entry | Solvent | Sulfuryl imidazolium salt **1** (*x* equiv.) | 1,2-dMeIm (*y* equiv.) | Yield (%) **8** | **9** |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 1.1 | 1.1 | 63 | 12 |
| 2 | THF | 1.1 | 1.1 | 80 | – |
| 3 | $CH_2Cl_2$ | 5.0 | 5.0 | – | 82 |

The regioselectivity observed for the sulfation of the 4,6-*O*-boronate ester **7** is consistent with that reported during glycosylation reactions in which arylboronic acid was used to temporarily mask hydroxy groups.[6] A hydroxy group in which both substituents at adjacent positions are oriented equatorially is less reactive, due to steric hindrance. Conversely, if at least one of the adjacent substituents is oriented axially, a hydroxy group is more reactive, because there would be sufficient space to permit reaction. Changing the solvent from $CH_2Cl_2$ to THF provided the 3-*O*-monosulfated product **8** as the sole product in 80 % yield (Entry 2). In contrast, the 2,3-*O*-disulfated product **9** could be obtained in 82 % yield as a sole product when an excess of sulfurylimidazolium salt **1** (5.0 equiv.) and 1,2-dMeIm (5.0 equiv.) in $CH_2Cl_2$ was used (Entry 3). These results indicate that the use of $CH_2Cl_2$ as a solvent increases the reactivity in the sulfation reaction for boronate esters, when compared to THF.[8d]

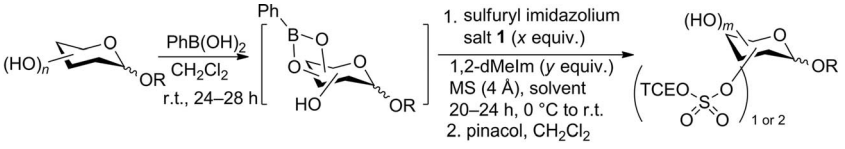
Under the optimized conditions, we applied the sulfation reaction, following the regioselective masking of the hydroxy groups with phenylboronic acid, to several nonprotected carbohydrates (Table 2). The monosulfation of methyl α-D-glucopyranoside (**10**), methyl α-L-rhamnopyranoside (**12**), and methyl β-D-arabinopyranoside (**14**) was accomplished with complete regioselectivity and high yield to provide **11** (72 %), **13** (76 %), and **15** (72 %), respectively (Entries 1, 2 and 3). α-D-Galactopyranoside **16** bearing an allyl side-chain, serving as a latent leaving group, at the anomeric position[13] was exclusively sulfated at the C3 hydroxy group to give **17** in 74 % yield (Entry 4). The regioselective sulfation of propargyl α-D-galactopyranoside (**16**), suitable as a substrate for the Huisgen cycloaddition in click chemistry,[14] was synthesized in 70 % yield without loss of the terminal alkyne (Entry 5).[15] The use of an excess amount of sulfurylimidazolium salt **1** in reactions with methyl α-D-glucopyranoside (**10**) and methyl α-D-galactopyranoside (**21**) in $CH_2Cl_2$ gave the 2,3-*O*-disulfated products **20** in 76 % yield and **22** in 85 % yield, respectively (Entries 6 and 7). The 2,2′-*O*-selective disulfation of D-trehalose (**23**), included as a structurally complicated substrate with very poor solubility in organic solvents, was achieved in 69 % yield (Entry 8).

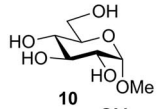
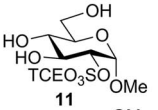
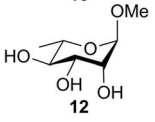
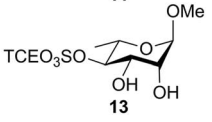
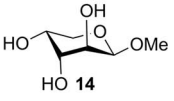
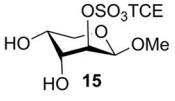
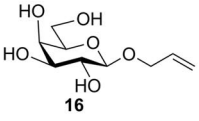
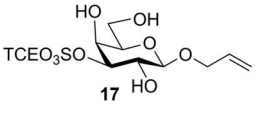
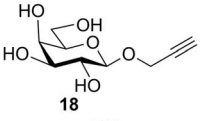
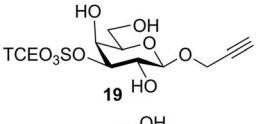
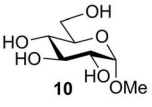
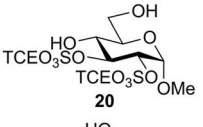
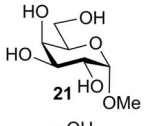
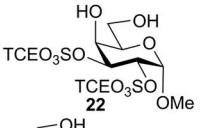
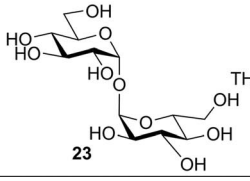
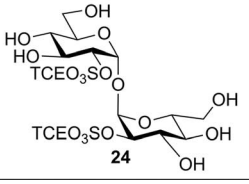
To demonstrate the utility of our methodology, a one-pot sequential procedure was applied to the regioselective sulfation of an unprotected carbohydrate by means of the transient masking of hydroxy groups with phenylboronic acid (Scheme 3). After methyl α-L-fucopyranoside (**2**) was stirred with 1.0 equiv. of phenylboronic acid in the presence of MS (4 Å) in




Scheme 3. Regioselective sulfation of methyl α-L-fucopyranoside (**2**) by using phenylboronic acid in a one-pot sequential procedure.

Table 2. Regioselective sulfation of unprotected carbohydrates by using phenylboronic acid.




| Entry | Substrate | Solvent | *x*; *y* (equiv.) | Product | Yield (%) |
|---|---|---|---|---|---|
| 1 |  **10** | THF | 1.1; 1.1 |  **11** | 72 |
| 2 |  **12** | $CH_2Cl_2$ | 1.1; 1.1 |  **13** | 76 |
| 3 |  **14** | $CH_2Cl_2$ | 1.1; 1.1 |  **15** | 66 |
| 4 |  **16** | THF | 3.0; 3.0 |  **17** | 74 |
| 5 |  **18** | THF | 1.1; 1.1 |  **19** | 70 |
| 6 |  **10** | $CH_2Cl_2$ | 5.0; 5.0 |  **20** | 63 |
| 7 |  **21** | $CH_2Cl_2$ | 3.0; 3.0 |  **22** | 85 |
| 8 |  **23** | THF | 4.0; 10.0 |  **24** | 69 |

$CH_2Cl_2$, 1,2-dimethylimidazole (1.1 equiv.) and sulfurylimidazolium salt **1** were added to the mixture, followed by treatment with pinacol (2.5 equiv.), to give methyl 2-*O*-(2,2,2-trichloroethyl)sulfo-α-L-fucopyranoside (**5**) in 93 % yield.[16] Note that this procedure did not involve any concentrations and extractions during the sequential reactions.

## Conclusions

We have demonstrated an efficient method for the regioselective sulfation of unprotected carbohydrates by using phenylboronic acid. This methodology is applicable to fully unprotected carbohydrates, including those which display very poor solubility in organic solvents. By this method, not only can simple monosaccharides be regioselectively sulfated, but structurally complicated disaccharides like D-trehalose are also suitable substrates. Studies on further applications of our methodology to the synthesis of complex sulfoglycolipids are now in progress.

## Experimental Section

**Representative Procedure for the Regioselective Sulfation of Methyl α-L-Fucopyranoside (2). Methyl 2-*O*-(2,2,2-Trichloroethyl)sulfo-α-L-fucopyranoside (5):** A suspension of methyl α-L-fucopyranoside (**2**) (35.6 mg, 0.20 mmol, 1.0 equiv.) and phenylboronic acid (26.4 mg, 0.22 mmol, 1.1 equiv.) in $CH_2Cl_2$ (2.0 mL, 0.10 M) was stirred at room temperature under $N_2$ for 24 h. After concentration under reduced pressure, MS (4 Å) (350 mg) and 1,2-dimethylimidazole (1.0 M in $CH_2Cl_2$, 0.22 mL, 0.22 mmol, 1.1 equiv.) were added. The resultant mixture was stirred at 0 °C under $N_2$ for 10 min, and then sulfurylimidazolium salt **1**[8d] (100.6 mg, 0.22 mmol,

1.1 equiv.) was added. The reaction mixture was warmed to room temperature and stirred for 24 h. The reaction mixture was filtered through a Celite pad®, which was further rinsed with $CH_2Cl_2$. The combined filtrates were washed with aqueous HCl (0.5 M in $H_2O$), followed by water. The organic layer was dried with $Na_2SO_4$ and concentrated under reduced pressure. The residue was dissolved in $CH_2Cl_2$ (2.0 mL) and treated with pinacol (59.2 mg, 0.50 mmol, 2.5 equiv.) at room temperature for 16 h. After the mixture had been concentrated under reduced pressure, the residue was purified by silica gel column chromatography ($CHCl_3$/AcOEt, 3:1) to give methyl 2-*O*-(2,2,2-trichloroethyl)sulfo-α-L-fucopyranoside (**5**) as a colorless white solid (63.7 mg, 0.16 mmol, 82 % yield).

## *Acknowledgments*

This work was partially supported by a Kitasato University Research Grant for Young Researchers. We thank Dr. K. Nagai and Ms. M. Sato at Kitasato University for instrumental analyses.

**Keywords:** Sulfation · Boronic acid · Regioselectivity · Carbohydrates

[1] a) A. Varki, R. D. Cummings, J. D. Esko, H. H. Freeze, P. Stanley, C. R. Bertozzi, G. W. Hart, M. E. Etzler, *Essentials of Glycobiology*, 2nd ed., Cold Spring Harbor Laboratory Press, Woodbury, NY, **2009**; b) T. Toida, A. Chaidedgumjorn, R. J. Linhardt, *Trends Glycosci. Glycotechnol.* **2003**, *15*, 29–46.

[2] For a recent review on the chemical sulfation of small molecules, see: R. A. Al-Horani, U. R. Desai, *Tetrahedron* **2010**, *66*, 2907–2918.

[3] a) B. Guilbert, N. J. Davis, S. L. Flitsch, *Tetrahedron Lett.* **1994**, *35*, 6563–6566; b) B. Guilbert, N. J. Davis, M. Pearce, R. T. Aplin, S. L. Flitsch, *Tetrahedron: Asymmetry* **1994**, *5*, 2163–2178; c) A. Lubineauc, R. Lemoine, *Tetrahedron Lett.* **1994**, *35*, 8795–8796; d) B. Abad-Romero, K. Mereiter, H. Sixta, A. Hofinger, P. Kosma, *Carbohydr. Res.* **2009**, *344*, 21–28.

[4] The sulfation reaction with $SO_3$–$Et_3N$ for the formation of the stannylene acetal of the boronate ester of methyl hexopyranoside was reported: S. Langston, B. Bernet, A. Vasella, *Helv. Chim. Acta* **1994**, *77*, 2341–2353.

[5] Glycosylation reactions on the polystyrylboronic acid solid support were reported as pioneer works: a) G. Belogi, T. Zhu, G.-J. Boons, *Tetrahedron Lett.* **2000**, *41*, 6965–6968; b) G. Belogi, T. Zhu, G.-J. Boons, *Tetrahedron Lett.* **2000**, *41*, 6969–6972; c) D. Crich, S. Sun, *J. Am. Chem. Soc.* **2002**, *124*, 8867–8869.

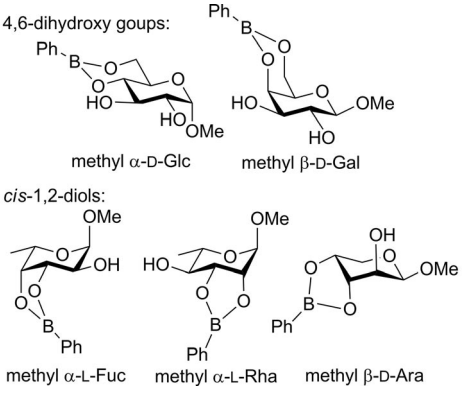
[6] a) E. Kaji, T. Nishino, K. Ishige, Y. Ohya, Y. Shirai, *Tetrahedron Lett.* **2010**, *51*, 1570–1573; b) T. Nishino, Y. Ohya, R. Murai, T. Shirahata, D. Yamamoto, K. Makino, E. Kaji, *Heterocycles* **2012**, *84*, 1123–1140; c) E. Kaji, D. Yamamoto, Y. Shirai, K. Ishige, Y. Arai, T. Shirahata, K. Makino, T. Nishino, *Eur. J. Org. Chem.* **2014**, 3536–3539.

[7] T. H. Fenger, R. Madsen, *Eur. J. Org. Chem.* **2013**, 5923–5933.

[8] a) Y. Liu, I. F. Lien, S. Ruttgaizer, P. Dove, S. D. Taylor, *Org. Lett.* **2004**, *6*, 209–212; b) L. Ingram, S. D. Taylor, *Angew. Chem. Int. Ed.* **2006**, *45*, 3503–3506; *Angew. Chem.* **2006**, *118*, 3583; c) A. M. Ali, S. D. Taylor, *Angew. Chem. Int. Ed.* **2009**, *48*, 2024–*2026*; *Angew. Chem.* **2009**, *121*, 2058; d) L. J. Ingram, A. Desoky, A. M. Ali, S. D. Taylor, *J. Org. Chem.* **2009**, *74*, 6479–6485; e) A. Y. Desoky, S. D. Taylor, *J. Org. Chem.* **2009**, *74*, 9406–9412; f) A. Y. Desoky, J. H. Hendel, L. J. Ingram, S. D. Taylor, *Tetrahedron* **2011**, *67*, 1281–1287.

[9] For seminal work on the introduction of protected sulfate groups into carbohydrates, see: a) C. L. Penney, A. Perlin, *Carbohydr. Res.* **1981**, *93*, 241–246; b) A. D. Proud, J. C. Prodger, S. L. Flitsch, *Tetrahedron Lett.* **1997**, *38*, 7243–7246.

[10] Molecular recognition between carbohydrate and phenylboronic acid has been widely investigated by us and others.[6,11] In general, phenylboronic acid recognizes the hydroxy groups at the C4 and C6 positions and/or the *cis*-1,2-diol in the nonprotected methyl hexopyranoside and regioselectively forms a cyclic boronate ester.




[11] a) R. J. Ferrier, *Methods Carbohydr. Chem.* **1972**, *6*, 419–426; b) R. J. Ferrier, *Adv. Carbohydr. Chem. Biochem.* **1978**, *35*, 31–80; c) P. J. Duggan, E. M. Tyndall, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1325–1339.

[12] Unexpectedly, the cyclic phenylboronate ester of sulfated pyranosides is stable under the workup procedure, which involves neutral water and aqueous acid, or purification by silica gel chromatography. However, a simple treatment of the cyclic phenylboronate ester of sulfated methyl α-L-fucopyranoside (**2**) with pinacol under neutral conditions afforded the desired 2-*O*-monosulfated product **5**.

[13] P. Wang, P. Haldar, Y. Wang, H. Hu, *J. Org. Chem.* **2007**, *72*, 5870–5873.

[14] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; *Angew. Chem.* **2001**, *113*, 2056.

[15] For a report on propargyl glycosides as stable glycosyl donors, see: S. Hotha, S. Kashyap, *J. Am. Chem. Soc.* **2006**, *128*, 9620–9621.

[16] Water generated as a byproduct in the formation of the phenylboronate ester could be sufficiently removed by MS (4 Å) before the sulfation reaction. Therefore, the degradation of Taylor's reagent **1** by water was suppressed, and the yield was improved in the one-pot sequential procedure.

Received: December 14, 2015
Published Online: January 26, 2016