CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Chiral Benzazaborole-Catalyzed Regioselective Sulfonylation of Unprotected Carbohydrate Derivatives

Authors: Satoru Kuwano, Yusei Hosaka, and Takayoshi Arai

To be cited as: *Chem. Eur. J.* 10.1002/chem.201903443

Link to VoR: http://dx.doi.org/10.1002/chem.201903443

Supported by
ACES

WILEY-VCH

10.1002/chem.201903443

WILEY-VCH

COMMUNICATION

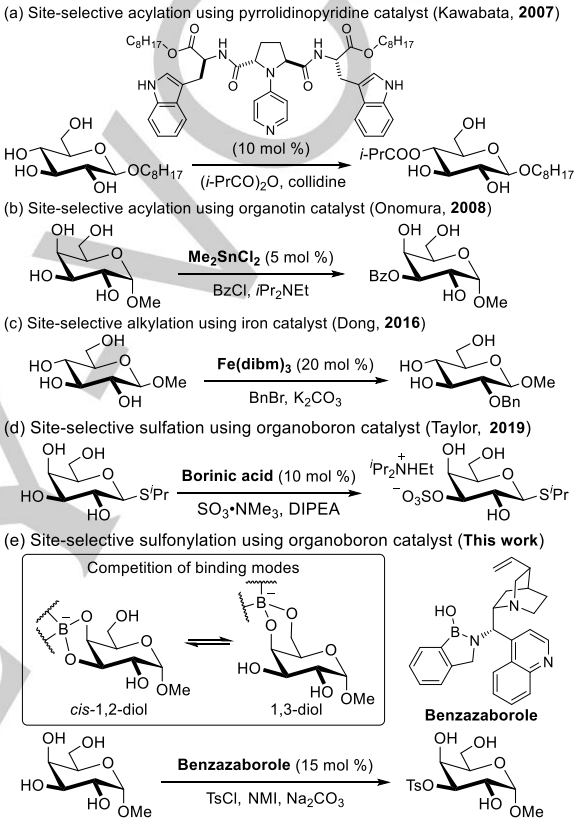
Chiral Benzazaborole-Catalyzed Regioselective Sulfonylation of Unprotected Carbohydrate Derivatives

Satoru Kuwano,*[a] Yusei Hosaka,[a] and Takayoshi Arai*[a]

Abstract: Chiral benzazaborole-catalyzed regioselective sulfonylations of unprotected carbohydrate derivatives have been developed. This methodology enables direct regioselective functionalization of the secondary OH group in carbohydrate in the presence of the primary OH group. Using the chiral organoboron catalysis, kinetic resolution of the carbohydrate derivatives was also achieved.

Carbohydrate derivatives play essential roles in various physiological and pathological events such as cell adhesion, fertilization, and cancer cell metastases.[1] For the synthesis of various carbohydrates, practical methods involving the catalyst-controlled regioselective functionalization of one specific OH group have been extensively investigated and developed.[2] After the pioneering works such as the development of *N*-methylimidazole[3] and 4-pyrrolidinopyridine[4,5] catalysts by Miller and Kawabata, respectively, several outstanding nucleophilic catalysts have been developed for the activation of electrophiles (Scheme 1a).[6] The other approach is the catalyst-controlled activation of carbohydrates so that they can themselves act as nucleophiles. Onomura *et al.* reported the organotin-catalyzed regioselective acylation through tin-alkoxide formation (Scheme 1b).[7] Although organotin catalysts are widely used, their inherent potential toxicity poses a problem sometimes.[8] Recently, Dong *et al.* reported the iron-catalyzed alkylation of polyols, thus avoiding the use of tin-based catalysts (Scheme 1c).[9,10]

Organoboron catalysts are among the most nontoxic compounds.[11] In 2011, Taylor *et al.* demonstrated that borinic acids serve as elegant catalysts for the regioselective acylation of minimally protected carbohydrate derivatives through nucleophile activation.[12,13] However, to the best of our knowledge, a general method using organoborons for the regioselective functionalization of unprotected carbohydrates has not been reported.[14,15,16] This is because the organoboron catalyst binds to both *cis*-1,2-diol and 1,3-diol moieties (Scheme 1e).[12,14] Herein, we describe the chiral benzazaborole-catalyzed regioselective sulfonylation of unprotected carbohydrates.[17] Sulfonylated carbohydrates are used as electrophiles in the synthesis of biologically interesting pseudosugars and building blocks.[18]



Scheme 1. Regioselective functionalization of unprotected carbohydrate derivatives.

Organoboron species **1** were evaluated as catalysts for the regioselective sulfonylation of *α*-D-galactopyranoside **2a** (Table 1).[19] While phenyl boronic acid **1a**, benzoxaborole **1b**, benzazaborole **1c**, and ethanolamine ester of borinic acid (**1d**) provided varying degrees of rate enhancement, formations of 6-*O*-tosylated product **4a** was observed (entries 1–4). In contrast, heterocyclic borinic acid **1e** promoted tosylation at the 3-position, and 3-*O*-tosylated product **3a** was produced in 19% yield (entry 5). To our delight, the use of chiral benzazaborole **1f** was effective for the regioselective sulfonylation with assistance of NMI,[20] and product **3a** was predominantly furnished in 71% yield (entry 6).[21] The high catalytic activity of **1f** would be derived by the electron-donation from nitrogen atom onto the boron center. Introduction of a methoxy substituent on the quinoline ring did not improve the chemical yield (entry 7).

[a] Dr. S. Kuwano, Y. Hosaka, Prof. Dr. T. Arai
Soft Molecular Activation Research Center (SMARC)
Chiba Iodine Resource Innovation Center (CIRIC)
Molecular Chirality Research Center (MCRC)
Synthetic Organic Chemistry, Department of Chemistry, Graduate School of Science, Chiba University
1-33 Yayoi, Inage, Chiba 263-8522 (Japan)
E-mail: skuwano@chiba-u.jp
tarai@faculty.chiba-u.jp

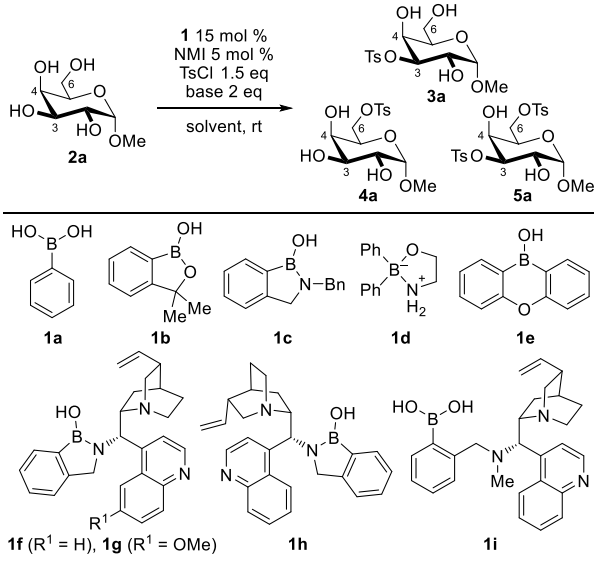
Supporting information for this article is given via a link at the end of the document.

10.1002/chem.201903443

WILEY-VCH

COMMUNICATION

Table 1: Optimization of reaction conditions.

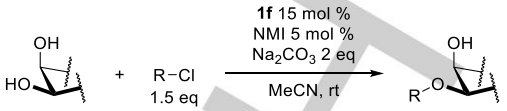


Entry	1	Solvent	base	3a[a] (%)	4a[a] (%)	5a[a] (%)
1	**1a**	MeCN	Na_2CO_3	2	11	2
2	**1b**	MeCN	Na_2CO_3	7	16	6
3	**1c**	MeCN	Na_2CO_3	2	12	2
4	**1d**	MeCN	Na_2CO_3	1	37	24
5	**1e**	MeCN	Na_2CO_3	19	6	27
6	**1f**	MeCN	Na_2CO_3	71	1	18
7	**1g**	MeCN	Na_2CO_3	60	<1	22
8	**1h**	MeCN	Na_2CO_3	31	<1	20
9	**1i**	MeCN	Na_2CO_3	9	13	9
10	**1f**	MeCN	Li_2CO_3	23	<1	4
11	**1f**	MeCN	K_2CO_3	52	<1	17
12	**1f**	MeCN	$NaHCO_3$	34	3	7
13	**1f**	MeCN	Et_3N	11	23	14
14	**1f**	MeCN	DIPEA	33	5	5
15	**1f**	EtCN	Na_2CO_3	58	<1	18
16	**1f**	DCM	Na_2CO_3	29	<1	21
17	**1f**	THF	Na_2CO_3	23	<1	2
18	**1f**	toluene	Na_2CO_3	13	<1	<1
19	**1f**	EtOAc	Na_2CO_3	10	<1	4
20	none	MeCN	Na_2CO_3	<1	<1	<1

[a] NMR yield.

When benzazaborole **1h** was employed as a pseudo-enantiomer of **1f**, the yield of **3a** decreased to 31% (entry 8). This result indicated a matching/mismatching between the chirality of the *cis*-1,2-diol moiety on the carbohydrates and chiral catalysts. The use of chiral 2-aminomethyl phenyl boronic acid **1i** did not increase the reactivity and selectivity (entry 9). Examination of the base effect revealed that Na_2CO_3 was the optimal choice for this reaction (entries 10–14). Among the tested solvents, acetonitrile gave the best result (entries 15–19). In the absence of organoboron catalyst, reaction did not proceed at all (entry 20).

Table 2: Chiral benzazaborole **1f**-catalyzed regioselective fuctionalization of carbohydrate derivatives having *cis*-1,2-diol moiety.



Entry	Substrate	Product	Yield (%)[a]
1	**2a**	**3a**	71[d]
2	**2b**	**3b**	70[e]
3	**2c**	**3ca**: R = Ts **3cb**: R = 4-$NO_2C_6H_4SO_2$ **3cc**: R = 3,5-$CF_3C_6H_3SO_2$	84[f]
4[b]			88
5[b]			82
6	**2d**	**3d**	60
7	**2e**	**3e**	88
8	**2f**	**3f**	98
9	**6a**	**7a**	>99
10[c]	**2a**	**3aa**	81
11[b]	**2b**	**8b**: R = 2-$CF_3C_6H_4CO$	67
12[b]	**2c**	**8c**: R = 2-$CF_3C_6H_4CO$	62

[a] Isolated yield. [b] Reaction was performed in the absence of NMI. [c] TsCl (4 eq), Na_2CO_3 (4 eq), and MS3A were used. [d] 18% of ditosylate were produced. [e] 15% of ditosylate were produced. [f] 8% of ditosylate were produced.

With the optimized conditions in hand, we next explored the substrate scope of the **1f**-catalyzed regioselective sulfonylation of

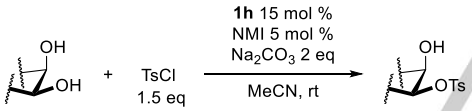
10.1002/chem.201903443

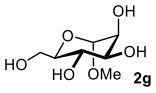
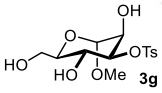
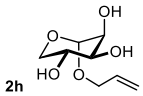
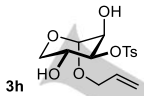
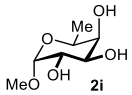
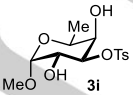
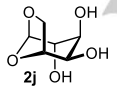
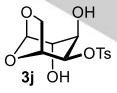
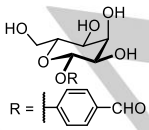
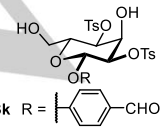
COMMUNICATION

carbohydrate derivatives (Table 2). Besides the *α*-anomer of a galactose derivative (**2a**), the *β*-anomer (**2b**) also gave monosulfonate ester **3b** in good yield (entry 2). Thioglycoside **2c**, which was utilized as a glycosyl donor, was smoothly converted into the corresponding monosulfonate esters, and various sulfonate esters were obtained in 82%–88% yields (entries 3–5). *N*-Boc protected D-galactosamine derivative **2d** could also be employed in this regioselective reaction in the presence of a free 6-OH group (entry 6). Derivatives of L-arabinose and L-rhamnose, which do not have a free primary OH group, readily afforded products **3e** and **3f** in high yields (entries 7 and 8). This method was suitable for the regioselective sulfonation of triol **6a** prepared from quinic acid, a carbohydrate-like structure present in numerous bioactive natural products (entry 9). Upon the addition of excess sulfonyl chloride, **2a** was converted into disulfonate ester **3aa** in 81% yield (entry 10). In addition to the regioselective sulfonylation, the catalyst system was applicable to regioselective acylation of unprotected carbohydrates (entries 11 and 12).

When D-mannose derivative **2g** was applied to the **1f**-catalyzed regioselective sulfonylation, the corresponding product **3g** was obtained in only 24% yield. Because the *cis*-1,2-diolmoiety of **2g** has enantiomeric stereochemistry relative to D-galactose derivative **2a**, a pseudo- enantiomeric catalyst **1h** was selected for the "matched" pair. In the presence of benzazaborole **1h**, mannopyranoside **2g** was smoothly converted into sulfonate ester **3g** in good yield (Table 3, entry 1). The use of **1h** was effective for the regioselective sulfonylation of carbohydrate derivatives possessing the same *cis*-1,2-stereochemistry as **2g**. Derivatives of D-lyxose **2h** and L-fucose **2i** were quantitatively transformed to the corresponding products **3h** and **3i** (entries 2 and 3). The reaction using 1,6-anhydrogalactopyranose **2j** resulted in monosulfonylation at the C4 position of an unbridged galactopyranoside (entry 4). Monosaccharide Helicid, which contains a *cis,cis*-1,2,3-triol and formyl group, gave disulfonate ester **3k** in good yield when using three equivalents of TsCl (entry 5). Interestingly, the free primary OH group was not functionalized, and the formyl group was tolerated under the reaction conditions.

Table 3: Chiral benzazaborole **1h**-catalyzed regioselective sulfonylation of carbohydrate derivatives having "enantiomeric" *cis*-1,2-diol moiety.

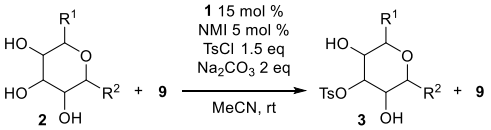


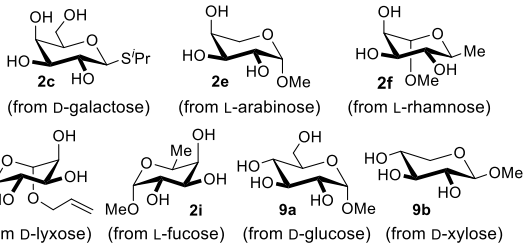
Entry	Substrate	Product	Yield (%)[a]
1	 **2g**	 **3g**	66
2	 **2h**	 **3h**	>99
3	 **2i**	 **3i**	>99
4[b]	 **2j**	 **3j**	84
5[c]	 **2k** R =	 **3k** R =	74

[a] Isolated yield. [b] TsCl (2 eq) was used. [c] TsCl (3 eq) and Na_2CO_3 (3 eq) were used.

To expand the utility of the benzazaborole-catalyzed regioselective sulfonylation, we applied this reaction to the kinetic resolution of carbohydrate derivatives. In general, separation of structurally similar carbohydrates by simple methods such as silica gel column chromatography and recrystallization is difficult because of the similar polarity and solubility of these compounds. Recently, enzyme, Sn-, and Cu-catalyzed methods have been developed for the aforesaid separation,[22] but there is no report on the use of an organocatalyst for this purpose. First, the kinetic resolution of D-galactose derivative **2c** and D-glucose derivative **9a** was investigated (Table 4, entry 1). When a mixture of **2c** and **9a** was stirred in the presence of benzazaborole **1f**, **2c** was selectively converted to sulfonate ester **3ca** in 80% yield. Remarkably, the primary OH group in D-glucopyranoside was not tosylated, and 99% of the unreacted **9a** was recovered. Our method could also be used for the resolution of L-arabinose derivative **2e** and D-xylose derivative **9b**, or L-rhamnose derivative **2f** and D-glucose derivative **9a** (entries 2 and 3). In addition, the resolutions of D-lyxose derivative **2h** and D-glucose derivative **9a**,

Table 4: Chiral benzazaborole-catalyzed kinetic resolution of carbohydrate derivatives.

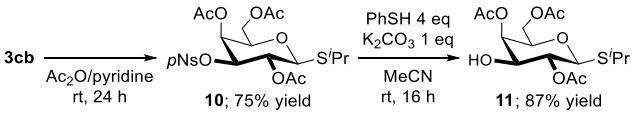




Entry	2	9	1	Yield of 3 (%)[a]	Recovered 9 (%)[a]
1	**2c**	**9a**	**1f**	80	99
2	**2e**	**9b**	**1f**	84	88
3	**2f**	**9a**	**1f**	97	98
4	**2h**	**9a**	**1h**	97	95
5	**2i**	**9b**	**1h**	99	94

[a] Isolated yield.

or L-fucose derivative **2i** and D-xylose derivative **9b** were effectively promoted when using **1h** (entries 4 and 5).



Scheme 2. Ns group as orthogonal protective group.

Finally, deprotection of Ns group in **10** was examined (Scheme 2). Use of PhSH and K_2CO_3 in MeCN gave deprotected compound **11** in good yield, and side reactions (substitution, elimination, or 1,2-acyl migration) were not observed in the mild basic conditions.

In conclusion, we have developed a chiral benzazaborole-catalyzed regioselective sulfonylation of unprotected carbohydrate derivatives. This methodology enables direct regioselective functionalization of the secondary OH groups in the carbohydrate derivatives in the presence of the primary OH groups. This organoboron catalysis could also be used for the kinetic resolution of carbohydrate derivatives.

Acknowledgements

This work was financially supported by Toray Award in Synthetic Organic Chemistry, Japan, and JSPS KAKENHI Grant Number 19K15553.

Keywords: chiral benzazaborole • organoboron catalyst • regioselective sulfonylation • carbohydrate derivatives • cooperative catalysis

[1] For examples, see: a) T. Feizi, *Nature* **1985**, *314*, 53; b) H.-J. Gabius, S. Gabius *Lectins and Cancer* (Springer-Verlag: New York, **1991**.); c) P. R. Crocker, T. Feizi, *Curr. Opin. Struct. Biol.* **1996**, *6*, 679; d) G. S. Kansas, *Blood* **1996**, *88*, 3259; e) S. Liedtke, H. Geyer, M. Wuhrer, R. Geyer, G. Frank, R. Gerardy-Schahn, U. Zahringer, M. Schachner, *Glycobiology* **2001**, *11*, 373; f) S. Brodesser, P. Sawatzki, T. Kolter, *Eur. J. Org. Chem.* **2003**, *11*, 2021.

[2] a) D. Lee, M. S. Taylor, *Synthesis* **2012**, *44*, 3421; b) W. Muramatsu, *Trends Glycosci. Glycotechnol*. **2016**, *28*, J1; c) Y. Ueda, T. Kawabata, *Top. Curr. Chem.* **2015**, *372*, 203; d) M. W. Giuliano, S. J. Miller, *Top. Curr. Chem.* **2015**, *372*, 157; e) C. R. Shugrue, S. J. Miller, *Chem. Rev.* **2017**, *117*, 11894; f) V. Dimakos, M. S. Taylor, *Chem. Rev.* **2018**, *118*, 11457.

[3] K. S. Griswold, S. J. Miller, *Tetrahedron* **2003**, *59*, 8869.

[4] T. Kawabata, W. Muramatsu, T. Nishio, T. Shibata, H. Schedel, *J. Am. Chem. Soc.* **2007**, *129*, 12890.

[5] a) Y. Ueda, W. Muramatsu, K. Mishiro, T. Furuta, T. Kawabata, *J. Org. Chem.* **2009**, *74*, 8802; b) H. Takeuchi, K. Mishiro, Y. Ueda, Y. Fujimori, T. Furuta, T. Kawabata, *Angew. Chem., Int. Ed.* **2015**, *54*, 6177; c) Y. Ueda, T. Furuta, T. Kawabata, *Angew. Chem., Int. Ed.* **2015**, *54*, 11966; d) M. Yanagi, A. Imayoshi, Y. Ueda, T. Furuta, T. Kawabata, *Org. Lett.* **2017**, *19*, 3099.

[6] a) G. Xiao, G. A. Cintron-Rosado, D. A. Glazier, B. Xi, C. Liu, P. Liu, W. Tang, *J. Am. Chem. Soc.* **2017**, *139*, 4346; b) *Heterocycles* **2019**, *98*, 304.

[7] a) F. Iwasaki, T. Maki, O. Onomura, W. Nakashima, Y. Matsumura, *J. Org. Chem.* **2000**, *65*, 996; b) Y. Demizu, Y. Kubo, H. Miyoshi, T. Maki, Y. Matsumura, N. Moriyama, O. Onomura *Org. Lett.* **2008**, *10*, 5075.

[8] a) W. Muramatsu, S. Tanigawa, Y. Takemoto, H. Yoshimatsu, O. Onomura, *Chem. Eur. J.* **2012**, *18*, 4850; b) W. Muramatsu, *J. Org. Chem.* **2012**, *77*, 8083; c) W. Muramatsu, H. Yoshimatsu, *Adv. Synth. Catal.* **2013**, *355*, 2518; d) M. Giordano, A. Iadonisi, *J. Org. Chem.* **2014**, *79*, 213; e) H. Xu, Y. Lu, Y. Zhou, B. Ren, Y. Pei, H. Dong, Z. Pei, *Adv. Synth. Catal.* **2014**, *356*, 1735; f) W. Muramatsu, *Org. Lett.* **2014**, *16*, 4846.

[9] B. Ren, O. Ramström, Q. Zhang, J. Ge, H. Dong, *Chem. Eur. J.* **2016**, *22*, 2481.

[10] a) B. Ren, J. Lv, Y. Zhang, J. Tian, H. Dong, *ChemCatChem* **2017**, *9*, 950; b) B. Ren, N. Yan, L. Gan, *RSC Adv.* **2017**, *7*, 46257.

[11] a) K. Ishihara, H. Yamamoto, *Eur. J. Org. Chem.* **1999**, 527; b) K. Ishihara in *Lewis Acids in Organic Synthesis Vol. 1* (Eds.: H. Yamamoto, Wiley-VCH, Weinheim, **2000**, pp. 89−190); c) K. Ishihara, H. Yamamoto in *Modern Aldol Reactions* (Eds.: R. Mahrwald, Wiley-VCH, Weinheim, **2004**, pp. 25−68).

[12] D. Lee, M. S. Taylor, *J. Am. Chem. Soc.* **2011**, *133*, 3724.

[13] a) L. Chan, M. S. Taylor, *Org. Lett.* **2011**, *13*, 3090; b) C. Gouliaras, D. Lee, L. Chan, M. S. Taylor, *J. Am. Chem. Soc.* **2011**, *133*, 13926; c) D. Lee, C. L. Williamson, L. Chan, M. S. Taylor, *J. Am. Chem. Soc.* **2012**, *134*, 8260; d) E. Dimitrijevic, M. S. Taylor, *Chem. Sci.* **2013**, *4*, 3298; e) S. O. Bajaj, E. U. Sharif, N. G. Akhmedov, G. A. O'Doherty, *Chem. Sci.* **2014**, *5*, 2230; f) K. A. D'Angelo, M. S. Taylor, *J. Am. Chem. Soc.* **2016**, *138*, 11058; g) S. Izumi, Y. Kobayashi, Y. Takemoto, *Org. Lett.* **2019**, *21*, 665.

[14] For pioneering example using organoboron compounds, see: a) K. Oshima, Y. Aoyama, *J. Am. Chem. Soc.* **1999**, *121*, 2315; b) R.-Z. Li, H. Tang, L. Wan, X. Zhang, Z. Fu, J. Liu, S. Yang, D. Jia, D. Niu, *Chem.* **2017**, *3*, 834.

[15] Boronic acid-catalyzed glycosylation via S_Ni-type strategy, see: M. Tanaka, A. Nakagawa, N. Nishi, K. Iijima, R. Sawa, D. Takahashi, K. Toshima, *J. Am. Chem. Soc.* **2018**, *140*, 3644.

[16] Diarylborinic acid-catalyzed, site-selective sulfation of carbohydrate derivatives was reported during the preparation of our manuscript (Scheme1d). see: D. Gorelik, Y. C. Lin, A. I. Briceno-Strocchia, M. S. Taylor, *J. Org. Chem.* **2019**, *84*, 900.

[17] a) X. Sun, H. Lee, S. Lee, K. L. Tan, *Nat. Chem.* **2013**, *5*, 790; b) C. L. Allen, S. J. Miller, *Org. Lett.* **2013**, *15*, 6178; c) I.-H. Chen, K. G. M. Kou, D. N. Le, C. M. Rathbun, V. M. Dong, *Chem. Eur. J.* **2014**, *20*, 5013.

[18] a) S. J. Danishefsky, M. P. DeNinno, S. Chen, *J. Am. Chem. Soc.* **1988**, *110*, 3929; b) Y. Tsuda, M. Nishimura, Y. Ito, *Chem. Pharm. Bull.* **1991**, *39*, 1983; c) S. R. Sanapala, S. S. Kulkarni, *J. Am. Chem. Soc.* **2016**, *138*, 4938.

[19] For chiral boronic acid catalyst, see; a) K. Arnold, B. Davies, D. Hérault, A. Whiting, *Angew. Chem. Int. Ed.* **2008**, *47*, 2673; b) D. Lee, S. G. Newman, M. S. Taylor, *Org. Lett.* **2009**, *11*, 5486; c) T. Hashimoto, A. O. Gálvez, K. Maruoka, *J. Am. Chem. Soc.* **2015**, *137*, 16016; d) N. Hayama, T. Azuma, Y. Kobayashi, Y. Takemoto, *Chem. Pharm. Bull.* **2016**, *64*, 704; e) N. Hayama, R. Kuramoto, T. Földes, K. Nishibayashi, Y. Kobayashi, I. Pápai, Y. Takemoto, *J. Am. Chem. Soc.* **2018**, *140*, 12216.

[20] a) S. Kuwano, Y. Hosaka, T. Arai, *Org. Biomol. Chem.* **2019**, *17*, 4475; b) N. Mannville, H. Alite, F. Haeffner, A. H. Hoveyda, M. L. Snapper, *Nat. Chem.*, **2013**, *5*, 768.

[21] DATB catalyst having an azaborine ring, see; a) H. Noda, M. Furutachi, Y. Asada, M. Shibasaki, N. Kumagai, *Nat. Chem.* **2017**, *9*, 571; b) H. Noda, Y. Asada, M. Shibasaki, N. Kumagai, *J. Am. Chem. Soc.* **2019**, *141*, 1546.

[22] a) J. García, A. Díaz-Rodríguez, S. Fernandez, Y. S. Sanghvi, M. Ferrero, V. Gotor, *J. Org. Chem.* **2006**, *71*, 9765; b) J. Maity, G. Shakya, S. K. Singh, V. T. Ravikumar, V. S. Parmar, A. K. Prasad, *J. Org. Chem.* **2008**, *73*, 5629; c) W. Muramatsu, Y. Takemoto, *J. Org. Chem.* **2013**, *78*, 2336; d) C. L. Allen, S. J. Miller, *Org. Lett.* **2013**, *15*, 6178.

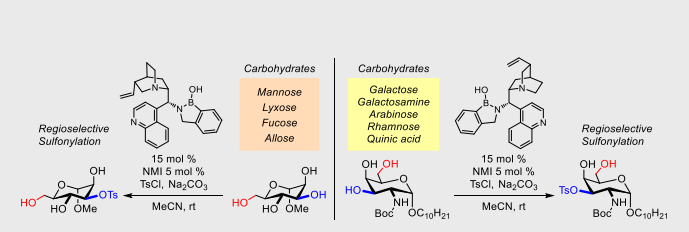
10.1002/chem.201903443

WILEY-VCH

COMMUNICATION

Entry for the Table of Contents

COMMUNICATION



Regioselective functionalization: Chiral benzazaborole-catalyzed regioselective sulfonylations of unprotected carbohydrate derivatives have been developed. This methodology enables direct regioselective functionalization of the secondary OH groups in carbohydrates in the presence of the primary OH groups. Using the chiral organoboron catalysis, kinetic resolution of the carbohydrate derivatives was also achieved.

S. Kuwano, Y. Hosaka, T. Arai**

Page No. – Page No.

Chiral Benzazaborole-Catalyzed Regioselective Sulfonylation of Unprotected Carbohydrate Derivatives