Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2021, **19**, 3124

Received 22nd February 2021,
Accepted 11th March 2021

DOI: 10.1039/d1ob00326g

rsc.li/obc

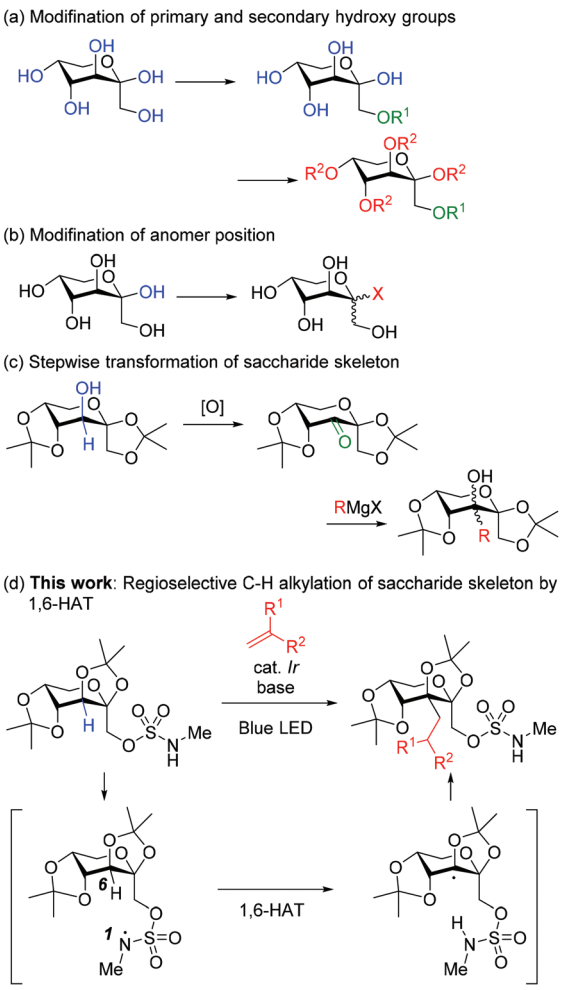
Regioselective C(sp^3)–H alkylation of a fructopyranose derivative by 1,6-HAT†

Yanru Li,[a] Shoto Miyamoto,[a] Takeru Torigoe[b,a] and Yoichiro Kuninobu *[b,a]

Regioselective C(sp^3)–H alkylation of a fructopyranose derivative using electron-deficient alkenes as alkylation reagents was achieved. The reaction proceeded *via* 1,6-hydrogen atom transfer under photoredox iridium catalysis. Several functional groups were introduced into the fructopyranose derivative.

Development of regioselective C(sp^3)–H transformations is an important issue in recent synthetic organic chemistry.[1,2] In many cases, C(sp^3)–H transformations have been developed using simple substrates. From a practical perspective, it is also important to realize regioselective C(sp^3)–H transformations of natural products, such as saccharides. One of the synthetic methods of saccharides is their modification, generally at the highly reactive primary and secondary hydroxy groups (Scheme 1a) and anomer positions (Scheme 1b).[3] Transformations of saccharide skeletons have also been reported. For example, alkyl, allyl, and phenyl groups can be introduced into saccharide skeletons by the oxidation of the saccharide hydroxy group and a subsequent Grignard reaction at the resulting carbonyl group. In this method, multiple steps are required to introduce substituents into the saccharide skeletons, and the stereochemistry at the reaction site is not determined (Scheme 1c).[4] Although direct C(sp^3)–H transformations of saccharide skeletons can be considered as an ideal method, examples of regioselective C(sp^3)–H transformations are still rare.

Hydrogen atom transfer (HAT) has received much attention as one of the most efficient methods to realize regioselective C(sp^3)–H transformations. Recently, Knowles[5] and Rovis[6] independently reported amide-directed photoredox-catalyzed C(sp^3)–H alkylation by 1,5-HAT using alkenes with an electron-withdrawing group as alkylation reagents. Later, Rovis *et al.* succeeded in the γ-position-selective C(sp^3)–H alkylation of



Scheme 1 Several transformations of saccharides.

[a]*Department of Molecular and Material Sciences, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, 6-1 Kasugakoen, Kasuga-shi, Fukuoka 816-8580, Japan*

[b]*Institute for Materials Chemistry and Engineering, Kyushu University, 6-1 Kasugakoen, Kasuga-shi, Fukuoka 816-8580, Japan.*

E-mail: kuninobu@cm.kyushu-u.ac.jp

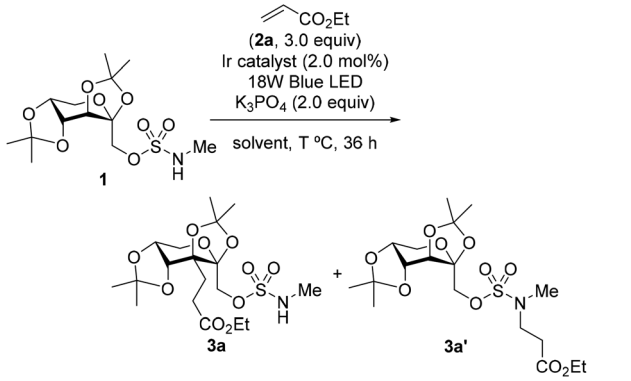
†Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new compounds. See DOI: 10.1039/d1ob00326g

carboxylic acid derivatives by 1,5-HAT under visible-light photoredox catalysis. They reported only one example of C(sp^3)–H alkylation of a saccharide derivative, and the yield of the alkylated product was moderate.[7,8]

Herein, we report regioselective C(sp^3)–H alkylation of a fructopyranose derivative by 1,6-HAT using a methylsulfamate group as the hydrogen atom abstraction moiety (Scheme 1d).[9] The generation of a carbon radical species by 1,6-HAT and subsequent trapping of the carbon radical intermediate with an alkene bearing an electron-withdrawing group produced an alkylated fructopyranose derivative.

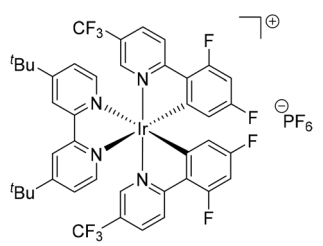
Fructopyranose derivative **1** was reacted with ethyl acrylate (**2a**, 3.0 equivalents) in the presence of [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (2.0 mol%) and K_3PO_4 (2.0 equiv.) under blue LED irradiation (Table 1). The reaction in DMF did not give the desired product **3a** (entry 1). Using benzotrifluoride ($PhCF_3$), chlorobenzene (PhCl), or dichloromethane (DCM), mixtures of the desired C–H alkylated product **3a** and undesired N–H alkylated product **3a′** were formed (entries 2–4). The alkylation proceeded regioselectively at the C–H bond of **1**, and **3a** was formed in 20% GC yield when the reaction was carried out in 1,2-dichloroethane (DCE, entry 5). A mixed solvent of DCE and H_2O (2 : 1) was suitable for this reaction, and **3a** was formed in 31% yield (entry 6). To improve the yield of **3a**, we investigated the reaction temperature (entries 7 and 8). Reaction at a lower temperature (15 °C) did not change the yield of **3a** (entry 7). On the other hand, the yield of **3a** was improved when the reaction was carried out at 60 °C, and **3a** was obtained in 46% yield (40% isolated yield, entry 8). The alkylation reaction did not proceed under dark conditions or without the iridium photocatalyst (entries 9 and 10). These results clearly show that the iridium photocatalyst and blue LED irradiation are indispensable to promote the alkylation reaction. The alkylation reaction did not proceed using 9-mesityl-10-methylacridinium perchlorate as an organic photocatalyst.

Table 1 Effect of solvents and temperatures for C(sp^3)–H alkylation of **1**



Entry	Solvent	T (°C)	Yield[a] (%) 3a	3a′
1[b]	DMF	25	<1	<1
2[b]	$PhCF_3$	25	8	22
3[b]	PhCl	25	15	10
4[b]	DCM	25	20	4
5[b]	DCE	25	20	1
6	DCE/H_2O (2/1)	25	31	<1
7	DCE/H_2O (2/1)	15	30	<1
8	DCE/H_2O (2/1)	60	46 (40)	<1
9[b,c]	DCE/H_2O (2/1)	25	<1	<1
10[b,d]	DCE/H_2O (2/1)	25	<1	<1

[a] GC yield. Isolated yield is reported in parentheses. [b] 48 h. [c] Dark. [d] Without [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6

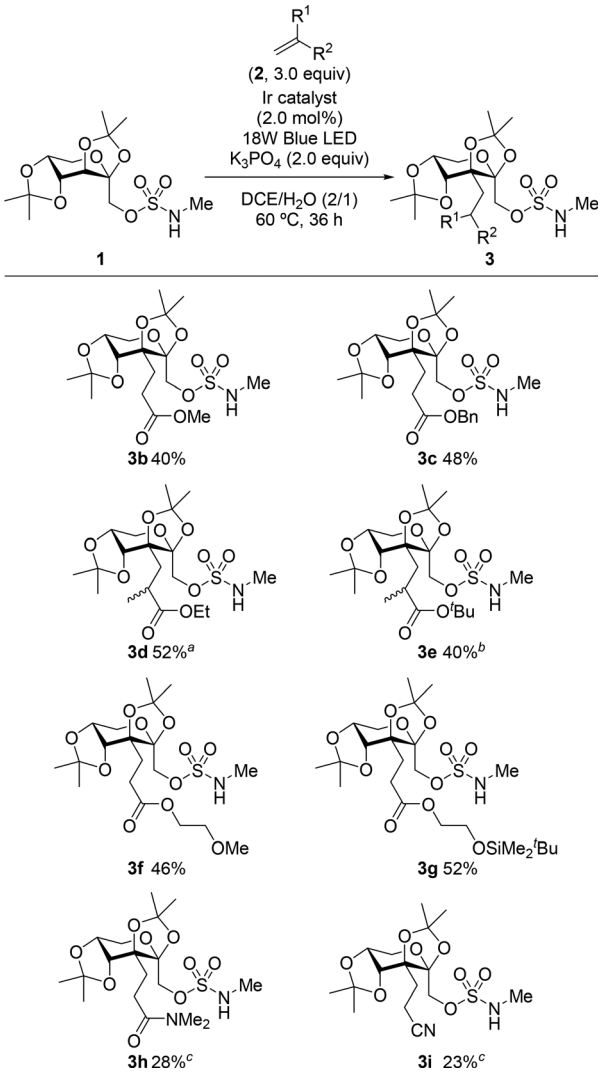


Ir catalyst = [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6

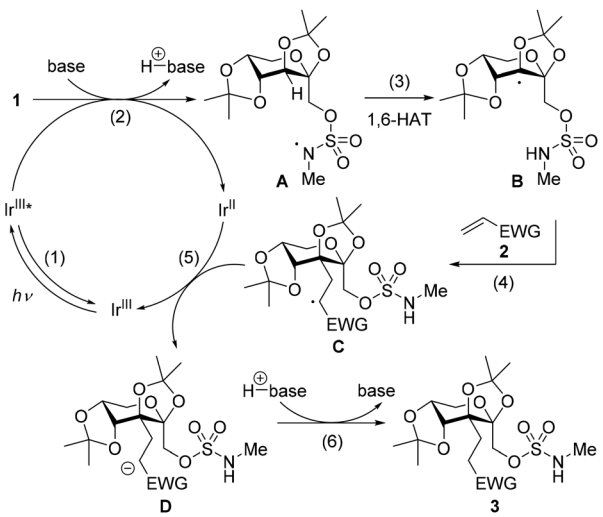
Under the optimized reaction conditions shown in Table 1 entry 5, we investigated the substrate scope of the alkylation reagents (Scheme 2). Treatment of fructopyranose derivative **1** with methyl acrylate (**2b**) or benzyl acrylate (**2c**) provided alkylated products **3b** and **3c** in 40% and 48% yields, respectively. The alkylation reaction also proceeded using methacrylates **2d** and **2e**, and the corresponding alkylated products **3d** and **3e** were obtained in 52% and 40% yields, respectively, as a mixture of diastereomers without inhibition from steric hindrance. Acrylates **2f** and **2g** bearing a methoxy or siloxy group were also suitable for this reaction and produced **3f** and **3g** in 46% and 52% yields, respectively, without deprotection of the methoxy and siloxy groups. The alkylation reaction also proceeded using acrylamide and acrylonitriles, and the corresponding alkylated products **3h** and **3i** were obtained in 28% and 23% yields, respectively.

The proposed mechanism for the regioselective C(sp^3)–H alkylation of fructopyranose derivative **1** is shown in Scheme 3: (1) excitation of the iridium photocatalyst (Ir^{III}) to Ir^{III}* species upon blue LED irradiation;[10] (2) formation of sulfamyl radical **A** through a proton-coupled electron transfer by the excited Ir^{III}* and a base, and the deactivation and reduction of Ir^{III}* species to Ir^{II};[5,6,11] (3) formation of carbon radical **B** by 1,6-HAT;[9] (4) reaction of the nucleophilic carbon radical with an alkene bearing an electron-withdrawing group to generate alkyl radical intermediate **C**; (5) reduction of radical intermediate **C** by Ir^{II} to give anionic intermediate **D** and regenerate Ir^{III}; and (6) subsequent protonation of **D** to produce alkylated product **3**.

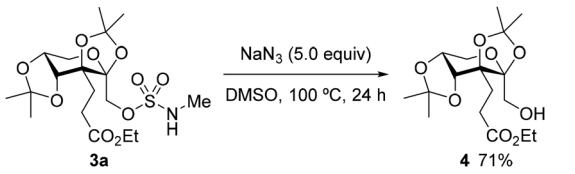
The *N*-methyl sulfamate group of the alkylated fructopyranose derivative **3a** can be converted to a hydroxy group (Scheme 4). Treatment of fructopyranose derivative **3a** with NaN_3 in DMSO at 100 °C for 24 h gave 71% yield of the deprotected product **4** (Scheme 4). Interestingly, the hydroxylation reaction proceeded whereas an azide group is generally introduced under these reaction conditions.[9c,12] This is possibly due to the steric hindrance of the fructopyranose skeleton.



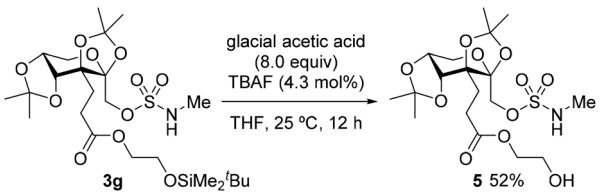
Scheme 2 Scope of alkenes. [a]Mixture of diastereomers (52 : 48). [b]25 °C, 48 h, mixture of diastereomers (76 : 24). [c]25 °C, 48 h.



Scheme 3 Proposed mechanism.



Scheme 4 Conversion of the *N*-methyl sulfamate group in alkylated fructopyranose derivative **3a** to a hydroxy group.



Scheme 5 Deprotection of a silyl group of **3g**.

The silyl group of the alkylated fructopyranose **3g** can be removed easily by treatment with TBAF, giving **5** bearing a free hydroxy group (Scheme 5). It is expected that a variety of functional groups and molecules can be introduced using the hydroxy group.

Conclusions

In summary, we successfully developed the regioselective C(sp^3)–H alkylation of a fructopyranose derivative by 1,6-HAT. Conventional functionalization of saccharides is achieved by the conversion of the highly reactive primary and secondary hydroxy groups and anomer positions. In contrast, these are maintained after C(sp^3)–H alkylation. Using this reaction, several functional groups can be introduced at the terminal position of the alkyl chains using several electron-deficient alkenes, even on a gram scale. The *N*-methyl sulfamate group, which abstracts a hydrogen atom from the fructopyranose derivative, can be converted to a hydroxy group. The silyl group of the siloxy group at the terminal position of the introduced alkyl chain can be removed easily using TBAF to give a free hydroxy group. It is expected that a variety of functional groups and molecules can be introduced into fructopyranose derivatives using the hydroxy groups. Because there have been few examples of C(sp^3)–H transformations of saccharides, the results of this work will provide useful insight into C–H transformations and sugar chemistry. In addition, it is expected that these results will lead to further development of saccharide chemistry because C(sp^3)–H transformations provide saccharide derivatives that cannot be produced by the transformations of the hydroxy groups and anomer positions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported in part by JSPS KAKENHI Grant numbers JP 17H03016, 18H04656, and 20H04824, the Takeda Science Foundation, The Mitsubishi Foundation, and the Yamada Science Foundation.

Notes and references

1 For several reviews, see: (*a*) M. C. White, *Science*, 2012, **335**, 807–809; (*b*) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754–8786; (*c*) H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh and A. Lei, *Chem. Rev.*, 2017, **117**, 9016–9085; (*d*) Z. Chen, M.-Y. Rong, J. Nie, X.-F. Zhu, B.-F. Shi and J.-A. Ma, *Chem. Soc. Rev.*, 2019, **48**, 4921–4942.

2 We reported several C(sp^3)–H transformations. See: (*a*) Y. Kuninobu, D. Asanoma and K. Takai, *Synlett*, 2010, 2883–2886; (*b*) Y. Kuninobu, T. Nakahara, H. Takeshima and K. Takai, *Org. Lett.*, 2013, **15**, 426–428; (*c*) Z. Wang, J. Ni, Y. Kuninobu and M. Kanai, *Angew. Chem., Int. Ed.*, 2014, **53**, 3496–3499; (*d*) N. Takemura, Y. Kuninobu and M. Kanai, *Org. Biomol. Chem.*, 2014, **12**, 2528–2532; (*e*) Z. Wang, Y. Kuninobu and M. Kanai, *Org. Lett.*, 2014, **16**, 4790–4793; (*f*) H.-L. Li and Y. Kuninobu, *Adv. Synth. Catal.*, 2020, **362**, 2637–2641; (*g*) Y. Yang, F. Cao, L. Yao, T. Shi, B. Tang, Y. Kuninobu and Z. Wang, *J. Org. Chem.*, 2020, **85**, 9713–9726.

3 *The Organic Chemistry of Sugars*, ed. D. E. Levy and P. Fugedi, CRC Press, Boca Raton, 2005.

4 C. Fayet and J. Gelas, *Carbohydr. Res.*, 1986, **155**, 99–106.

5 G. J. Choi, Q. Zhu, D. C. Miller, C. J. Gu and R. R. Knowles, *Nature*, 2016, **539**, 268–271.

6 J. C. K. Chu and T. Rovis, *Nature*, 2016, **539**, 272–275.

7 D.-F. Chen, J. C. K. Chu and T. Rovis, *J. Am. Chem. Soc.*, 2017, **139**, 14897–14900.

8 For several examples of regioselective C(sp^3)–H transformations by HAT, see: (*a*) K. Chen, J. M. Richter and P. S. Baran, *J. Am. Chem. Soc.*, 2008, **130**, 7247–7249; (*b*) T. Liu, M. C. Myers and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2017, **56**, 306–309; (*c*) I. C. S. Wan, M. D. Witte and A. J. Minnaard, *Chem. Commun.*, 2017, **53**, 4926–4929; (*d*) V. Dimakos, H. Y. Su, G. E. Garrett and M. S. Taylor, *J. Am. Chem. Soc.*, 2019, **141**, 5149–5153; (*e*) V. Dimakos, D. Gorelik, H. Y. Su, G. E. Garrett, G. Hughes, H. Shibayama and M. S. Taylor, *Chem. Sci.*, 2020, **11**, 1531–1537; (*f*) Y. Wang, H. M. Carder and A. E. Wendlandt, *Nature*, 2020, **578**, 403–408 For several recent reviews of regioselective C(sp^3)–H transformations by HAT, see: (*g*) X.-Q. Hu, J.-R. Chen and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2017, **56**, 1960–1962; (*h*) K. M. Nakafuku, *Synthesis*, 2018, **50**, 1569–1586; (*i*) A. L. G. Kanegusuku, T. Castanheiro, S. K. Ayer and J. L. Roizen, *Org. Lett.*, 2019, **21**, 6089–6095; (*j*) G. Kumar, S. Pradhan and I. Chatterjee, *Chem. – Asian J.*, 2020, **15**, 651–672; (*k*) H. Chen and S. Yu, *Org. Biomol. Chem.*, 2020, **18**, 4519–4532; (*l*) S. Sarkar, K. P. S. Cheung and V. Gevorgyan, *Chem. Sci.*, 2020, **11**, 12974–12993.

9 For examples of C(sp^3)–H transformations by 1,6-HAT using a sulfonamide group as a hydrogen abstraction moiety, see: (*a*) M. A. Short, J. M. Blackburn and J. L. Roizen, *Angew. Chem., Int. Ed.*, 2018, **57**, 296–299; (*b*) Z.-Y. Ma, L.–N. Guo, Y. You, F. Yang, M. Hu and X.-H. Duan, *Org. Lett.*, 2019, **21**, 5500–5504; (*c*) W. Shu, H. Zhang and Y. Huang, *Org. Lett.*, 2019, **21**, 6107–6111.

10 M. S. Lowry, J. I. Goldsmith, J. D. Slinker, R. Rohl, R. A. Pascal, G. G. Malliaras and S. Bernhard, *Chem. Mater.*, 2005, **17**, 5712–5719.

11 G. J. Choi and R. R. Knowles, *J. Am. Chem. Soc.*, 2015, **137**, 9226–9229.

12 In ref. 9c, the azidation was carried out using substrates with an *N*-Boc-methylsulfamate group. In our case, the hydroxylation proceeded in the case of both **3a** and *N*-Boc-**3a**. Therefore, the progress of hydroxylation instead of azidation was not due to non-protection of the nitrogen atom in **3a**.