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Visible-Light-Induced Photoacid Catalysis: Application in Glycosylation with *O*-Glycosyl Trichloroacetimidates

Gaoyuan Zhao,[a,†] Juncheng Li,[a] and Ting Wang *[a]

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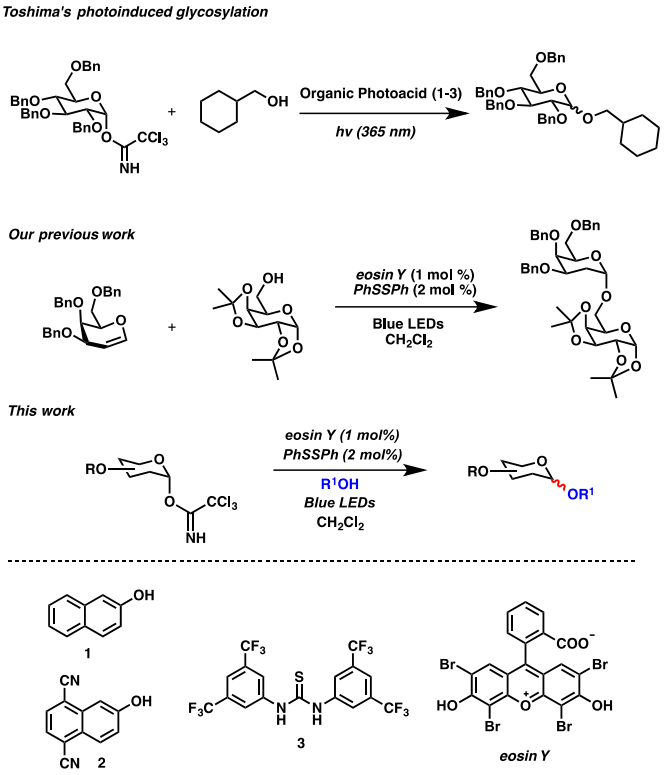
The development of visible-light-induced photoacid catalyzed glycosylation is reported. The eosin Y and PhSSPh catalysts system are applied to realize the glycosylation with different glycosyl donors upon light irradiation. The reaction shows a broad substrate scope, both glycosyl donors and acceptors, and highlights the mild nature of the reaction conditions.

Photoacids are molecules that become more acidic upon absorption of light.[1-3] These molecules have been applied in a variety of areas, including polymer synthesis,[4] proton-transfer processes,[5] molecular switches development,[6] and photodynamic therapy[7]. Moreover, photoacids have shown their unique activities in organic reactions, such as protonation, acetalization, esterification, Friedel-Crafts reaction, glycosylation, and other C-C/C-S bond formation reaction.[8] Phenolic derivatives, such as phenol and naphthol, have been proved to exhibit enhanced acidity (by several pKa units) upon on light irradiation.[1-3] Particularly, phenol, naphthol, and thiourea derivatives have been applied as photoacids to promote glycosylation reactions under light irradiation (365 nm) (Scheme 1). In 2014, Toshima reported a photo-induced glycosylation reaction, where phenol and naphthol derivatives were used photoacids catalyst (**1** and **2**, Scheme 1).[8e] The coupling between glycosyl trichloroacetimidates and alcohols has been effectively catalyzed by the organic photoacids, furnishing the corresponding disaccharides in excellent yields. The organic photoacid could be recovered and reused without loss of efficiency. More recently, Toshima reported another elegant photoacid promoted glycosylation, using thiourea derivative **3** as the photoacid catalyst (Scheme 1).[8f] These two unprecedented examples of photoacid promoted glycosylation reactions attracted our attention to the field of visible-light-induced photocatalytic glycosylation reactions. In 2018, our group reported a photocatalytic synthesis of 2-deoxyglycosides by using photocatalysts eosin Y and PhSSPh.[9] Eosin Y could serve as photoacid upon visible light irradiation[8a,m,10], activating the glycosyl donors. The co-catalyst PhSSPh[11] could successfully facilitate the regeneration process of the photocatalyst. A series of glycals could be converted to their corresponding 2-deoxyglycosides efficiently via the method. Continuing our studies on photoacid catalyzed glycosylation,[9,12] we herein reported its application to a more general glycosyl donor, the *O*-glycosyl trichloroacetimidates.[13]



Scheme 1. Photoacid catalyzed glycosylation.

[a] Department of Chemistry, University at Albany, State University of New York, 1400 Washington Avenue, Albany, New York 12222, USA. Email: twang3@albany.edu

[b]

† Current address: Department of Chemistry, SUNY Stony Brook 100 Nicolls Road, Stony Brook, New York 11790, USA

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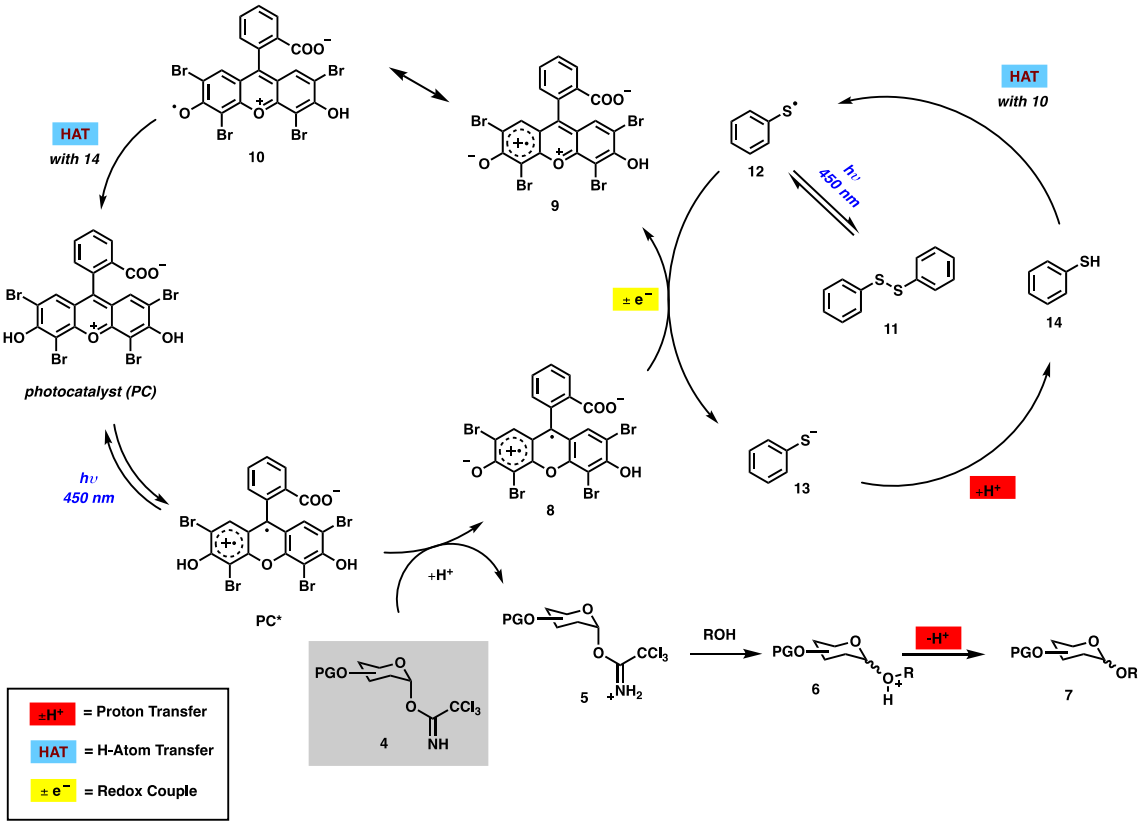
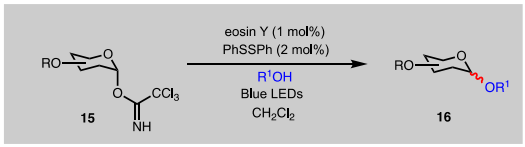


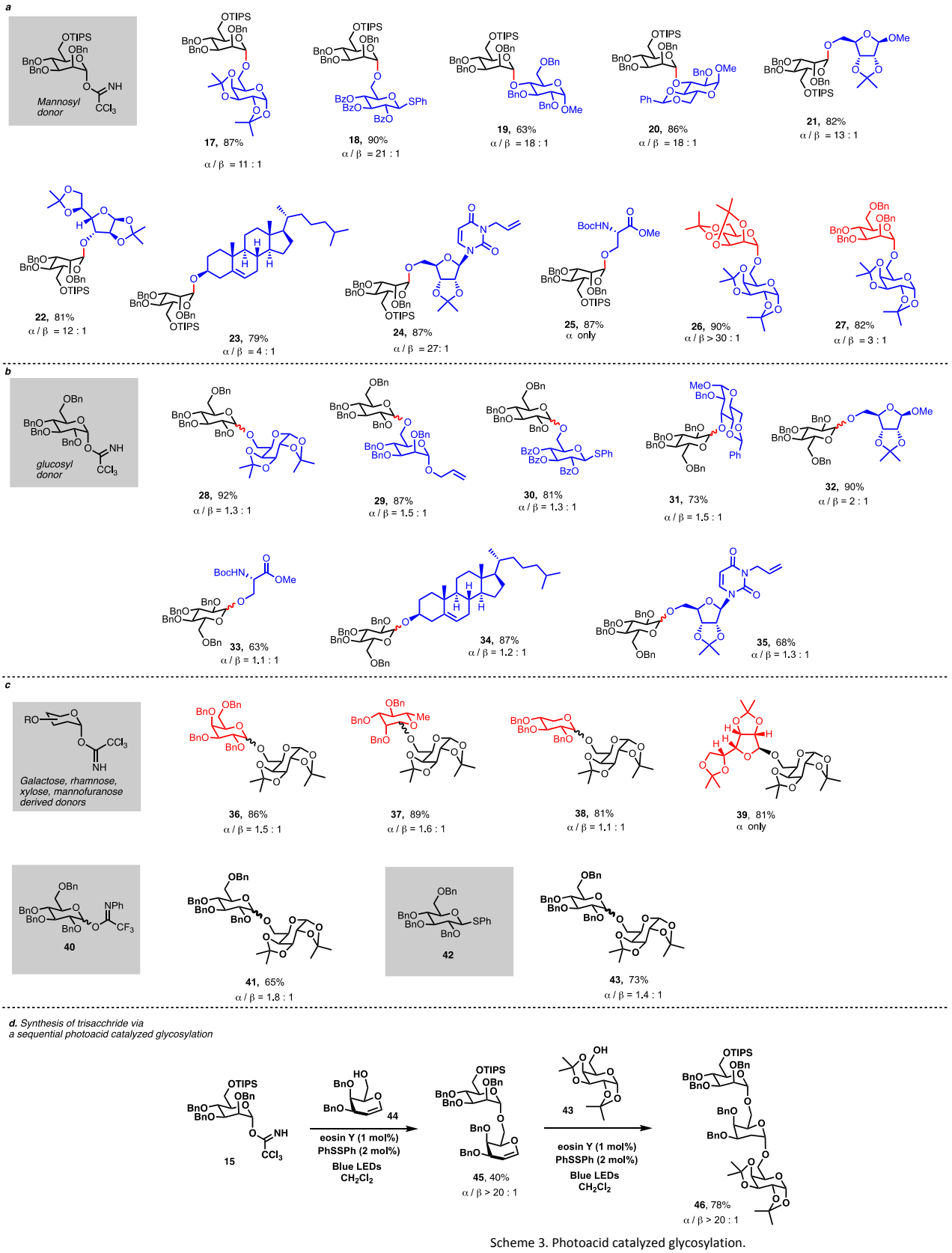
Scheme 2. Proposed mechanism.

Mechanistically, upon light irradiation, we anticipated the excited photocatalyst (**PC***) would perform as an acid, protonating the glycosyl trichloroacetimidates and generating the deprotonated photocatalyst (**8**)**.** The resulting intermediate **5** reacted with ROH to give intermediate 6, which would then be converted to the glycosylation product **7** through a proton transfer process (with **13**). A co-catalyst PhSSPh was used in this system, showing significant enhancement toward the reaction efficiency.[14] We proposed the PhSSPh could facilitate the photocatalyst regeneration process through a single single-electron transfer process between the deprotonated photocatalyst **8** and PhS• (**12**, generated from homolysis of S-S bond in PhSSPh). The resulting PhS^- (**13**) could act as a base to facilitate the proton transfer process with intermediate **6**, producing the glycosylation product **7** and a H-atom donor PhSH (**14**). Intermediate **10**, a resonance structure of **9**, would abstract a H-atom from the H-atom donor PhSH (**14**), regenerating the photocatalyst (**PC**) and PhS• (**12**). The proposed mechanism suggested that the photoacid catalyst is not only donating a proton (as typical Brønsted acid) to the substrate, but also showing its redox activity in the catalytic cycle.

With the proved concept in our previous report, we focused our attention on exploring the scope of the photocatalytic glycosylation reaction (Scheme 3).[15,16] Scheme 3a highlights the glycosylation products synthesized from 11 experiments probing 9 different alcohols (acceptors) and three mannose-derived *O*-glycosyl trichloroacetimidates (donors).[17] In all the cases between mannosyl donor (Scheme 3a) and nine different alcohols, the reaction proceeded smoothly in good to excellent yields (**17**-**25**, 63%-90%) and with moderate to excellent α-selectivity (**17**-**25**, 4:1 to α only). These examples demonstrated that the catalytic system is tolerant of common alcohol (acetals, ethers, esters) and amine (carbamate) protecting groups (**17**-**25**). The efficiency of the glycosylation is not affected by the hydroxyl position in acceptors. Different acceptors bearing primary alcohol (**17**, **18**, and **21**) or secondary hydroxyl at C3 or C4 (**19**, **20**, and **22**) coupled with mannosyl donor well to provide the resulting disaccharides efficiently. In addition, N-Boc-protected serine, cholesterol and a protected nucleotide could deliver the corresponding products (**23**-**25**) smoothly in 79%, 87%, and 87% yields. Moreover, the protecting group on the glycosyl donor is crucial for the stereoselectivity. Not surprisingly, a more locked conformation would favor the α-selectivity (**26**, α/β > 30:1, scheme 3); while changing the large silyl protecting group on C6 hydroxyl group to its corresponding benzyl ether significantly diminished the stereoselectivity (**27**, α/β = 3:1, Scheme 3a).[18]

Next, we evaluated the scope of the glycosyl donors. The process commenced with the glycosylation between perbenzyl glucosyl trichloroacetimidate and a series of alcohols (Scheme 3b).[16] Pleasingly, excellent yields were obtained in all examples despite the loss of stereoselectivity (**28**-**35**, 63%-92%). Additional glycosyl donors derived from galactose, rhamnose, xylose, mannofuranose could be successfully converted to the corresponding disaccharides in excellent yields, 85%, 89%, 81%, and 81% respectively (**36**-**39**). Particularly, the substrate with more rigid conformation would deliver a stereoselective result (**39**, α only). These results demonstrated that the catalyst system is suitable for different types of carbohydrate substrate.





d. Synthesis of trisacchride via a sequential photoacid catalyzed glycosylation

Scheme 3. Photoacid catalyzed glycosylation.

We then expanded the glycosyl donor to glucosyl trifluoroacetimidate **40** and thioglucoside **42.** Both of them could be promoted by the eosin Y/PhSSPh catalyst system, affording corresponding products **41** and **43** in the yield of 65% and 73% respectively. We further tested if there is any activation difference between glycal donor and glycosyl trichloroacetimidates donor, by subjecting glycosyl donor **15** and glycal **44** in the reaction condition. Although it is very hard to selectively activate the trichloroacetimidate **15** in presence of glycal donor, we were still able to isolate desired glycosylation product **45** in 40% yield. The disaccharide could be activated by the same catalyst system, coupling with another acceptor **43** to furnish trisaccharide **46** efficiently (78%). Happily, both steps have shown great stereoselectivities.

In summary, we have developed a visible-light-induced photoacid catalyzed glycosylation from O-glycosyl trichloroacetimidates. A range of functional groups are tolerated on the carbohydrate backbone, both on the donors and acceptors. A variety of glycosyl donors, derived from different sugars, are suitable for the glycosylation. The donors could be expanded to glycosyl trifluoroacetimidates and thioglycosyl substrates. A sequential synthesis of trisaccharide was realized and further application of the photoacid catalyzed glycosylation in complex carbohydrate synthesis are ongoing in our laboratory.

G.Z., J.L., and T.W. designed research; G.Z. and J.L. performed research; G.Z., J.L., and T.W. analyzed data; and G.Z., J.L., and T.W. wrote the paper. We are grateful to the University at Albany, State University of New York, for financial support. We thank National Science Foundation (MRI 1726724) for funding on NMR facility. We thank Prof. Alexander Shekhtman (SUNY-Albany) for NMR assistance.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1. L. M. Tolbert, J. E. Haubrich, *J. Am. Chem. Soc.* **1990**, *112*, 8163.
2. L. M. Tolbert, J. E. Haubrich, *J. Am. Chem. Soc.* **1994**, *116*, 10593.
3. L. M. Tolbert, K. M. Solntsev, *Acc. Chem. Res.* **2002**, *35*, 19.
4. (a) Y. Liao, *Acc. Chem. Res*. **2017**, *50*, 1956. (b) M. G. Ivan, J. C. Scaiano, Photoimaging and Lithographic Processes in Polymers. In *Photochemistry and Photophysics of Polymer Materials*; Allen, N. S., Ed., John Wiley & Sons: Hoboken, 2010.
5. H. Shizuka, *Acc. Chem. Res.* **1985**, *18*, 141.
6. L. A. Tatum, J. T. Foy, I. Aprahamian, *J. Am. Chem. Soc.* **2014**, *136*, 17438.
7. X. Yue, C. O. Yanez, S. Yao, K. D. Belfield, *J. Am. Chem. Soc.* **2013**, *135*, 2112.
8. (a) H. Yi, L. Niu, S. Wang, Y. Liu, A. K. Singh, A. Lei, *Org. Lett*. **2017**, *19*, 122. (b) R. P. Oates, P. B. Jones, *J. Org. Chem.* **2008**, *73*, 4743. (c) Z. Shi, P. Peng, D. Strohecker, Y. Liao, *J. Am. Chem. Soc.* **2011**, *133*, 14699. (d) P. J. Serafinowski, P. B. Garland, *J. Am. Chem. Soc.* **2003**, *125*, 962. (e) R. Iwata, K. Uda, D. Takahashi, K. Toshima, *Chem. Commun*. **2014**, *50*, 10695. (f) T. Kimura, T. Eto, D. Takahashi, K. Toshima, *Org. Lett.* **2016**, *18*, 3190. (g) L. A. Tatum, J. T. Foy, I. Aprahamian, *J. Am. Chem. Soc.* **2014**, *136*, 17438. (h) A. Das, T. Banerjee, K. Hanson, *Chem. Commun*. **2016**, *52*, 1350. (i) D. Das, S. Ayad, K. Hanson, *Org. Lett.* **2016**, *18*, 5416. (j) Z. M. Salem, J. Saway, J. J. Badillo, *Org. Lett.* **2019**, *21*, 8528. (k) A. Strada, M. Fredditor, G. Zanoni, S. Protti, *Molecules,* **2019**, *24*, 1318. (l) G. A. Bradshaw, A. C. Colgan, N. P. Allen, I. Pongener, M. B. Boland, Y. Ortin, E. M. McGarrigle, *Chem. Sci.* **2019**, *10*, 508. (m) J. Liu, S. Yin, H. Wang, H. Li, G. Ni, *Carbohydrate. Res.* **2020**, *490*, 107963.
9. G. Zhao, T. Wang, *Angew. Chem. Int. Ed*. **2018**, *57*, 6120.
10. D.-M. Yan, J.-R. Chen, W.-J. Xiao, *Angew. Chem. Int. Ed*. **2019**, *58*, 378.
11. D. J. Wilger, J. M. Grandjean, T. R. Lammert, D. A. Nicewicz, *Nat. Chem.* **2014**, *6*, 720.
12. J. Li, G. Zhao, T. Wang, *Synlett* **2020**, *31*, 823.
13. (a) R. R. Schmidt, J. Michel, *Angew. Chem. Int. Ed.* **1980**, *19*, 731. (b) X. M. Zhu, R. R. Schmidt, *Angew. Chem. Int. Ed.* **2009**, *48*, 1900.
14. In both our reported control experiments in reference 9 and Ni's report in reference 8m, the efficiency of the glycosylation was significantly dropped without the use of PhSSPh.
15. For reviews on photoinduced glycosylation, see: (a) R. Sangwan, P. K. Mandal, RSC Adv. 2017, 7, 26256. (b) H. Wang, P. Wu, X. Zhao, J. Zeng, Q. Wan. *Acta Chim. Sinica* **2019**, *77*, 231. For recent selective examples of visible-light-mediated glycosylations, see: (c) R.-Z. Mao, D.-C. Xiong, F. Guo, Q. Li, J. Duan, X.-S. Ye, *Org. Chem. Front*. **2016**, *3*, 737; (d) Y. Yu, D.-C. Xiong, R.-Z. Mao, X.-S. Ye, *J. Org. Chem.* **2016**, *81*, 7134; (e) R. S. Andrews, J. J. Becker, M. R. Gagne, *Angew. Chem. Int. Ed.* **2010**, *49*, 7274. (f) R. S. Andrews, J. J. Becker, M. R. Gagne, *Angew. Chem. Int. Ed.* **2012**, *51*, 4140. (g) M. L. Spell, K. Deveaux, C. G. Bresnahan, B. L. Bernard, W. Sheffield, R. Kumar, J. R. Ragains, *Angew. Chem. Int. Ed.* **2016**, *55*, 6515. (h) M. Spell, X. Wang, A. E. Wahba, E. Connor, J. Ragains, *Carbohydr. Res.* **2013**, *369*, 42. (i) P. Wen, D. Crich, *Org. Lett.* **2017**, *19*, 2402. (j) W. J. Wever, M. A. Cinelli, A. A. Bowers, *Org. Lett.* **2013**, *15*, 30. (k) H. Ye, C. Xiao, Q. Zhou, P. Wang, W.-J. Xiao, *J. Org. Chem.* **2018**, *83*, 13325.
16. Control experiment has demonstrated that light irradiation is essential for the success of the transformation.
17. (a) E. I. Balmond, D. M. Coe, M. C. Galan, E. M. McGarrigle, *Angew. Chem. Int. Ed.* **2012**, *51*, 9152. (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. (c) A. Gille, M. Hiersemann, *Org. Lett.* **2010**, *12*, 5258. (d) D. Indurugalla, A. J. Bennet, *J. Am. Chem. Soc.* **2001**, *123*, 10889. (e) K. Van derpoorten, M. E. Migaud, *Org. Lett*. **2004**, *6*, 3461. (f) S. Zhong, M. Mondon, S. Pilard, C. Len, *Tetrahedron Lett.* **2006**, *47*, 6221. (g) R. Babouri, L. Clarion, M. Rolland, A. Van der Lee, Z. Kabouche, J. N. Volle, D. Virieus, and J. L. Pirat, *Eur. J. Org. Chem*. **2017**, 5357. (h) C. F. Becker, X. Liu, D. Olschewski, R. Castelli, R. Seidel and P. H. Seeberger, *Angew. Chem. Int. Ed.* **2008**, *47*, 8215. (i) C. Bucher and R. Gilmour, *Angew. Chem. Int. Ed.* **2010**, *49*, 8724. (j) S. Chatterjee, S. Moon, F. Hentschel, K. Gilmore and P. H. Seeberger, *J. Am. Chem. Soc.*, **2018**, *140*, 11942. (k) P. B. Cranwell, A. T. Russell and C. D. J. S. Smith, *Synlett*, **2016**, *27*, 131. (l) P. Dallabernardina, F. Schuhmacher, P. H. Seeberger and F. Pfrengle, *Org. Biomol. Chem.* **2016**, *14*, 309. (m) S. Friedrich-Bochnitschek, H. Waldmann and H. Kunz, *J. Or.g Chem.* **1989**, *54*, 751. (n) K. Ikeuchi, K. Murasawa and H. J. S. Yamada, *Synlett*, **2019**, *30*, 1308. (o) M. Shaw and A. Kumar, *Org. Lett.* **2019**, ***21***, 3108. (p) J. Yang, C. Cooper-Vanosdell, E. A. Mensah and H. M. Nguyen, *J. Org. Chem.* **2008**, ***73***, 794.
18. S. Dharuman, D. Crich. *Chem. Eur. J.* **2016**, *22*, 4535.

