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Photo-induced glycosylation using reusable organophotoacids†

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The glycosylation reactions of glycosyl trichloroacetimidates and several alcohols using an organophotoacid as an activator under photoirradiation proceeded smoothly to give the corresponding glycosides in high yields. The organophotoacid was recovered and reused without any loss of efficiency.

A large number of natural products containing mono- and oligosaccharides, such as proteoglycans, glycoproteins, glycolipids, and antibiotics, are important biological substances. Many biological studies of these glycomolecules at the molecular level have shed light on the biological significance of their carbohydrate moieties in molecular recognition for the transmission of biological information.[1] It is now recognized that carbohydrates are at the heart of a multitude of biological events, along with nucleic acids and proteins. In addition, several glycomolecules have been found to be useful as new functional materials.[2] For example, certain alkyl glycosides are expected to be biodegradable and environmentally benign next-generation surfactants. Therefore, glycomolecules continue to be the central focus of much research in chemistry, biology, and materials science. With this stimulating background, efficient synthesis of carbohydrate-containing products is of particular interest both in academia and in industry. In this context, glycosylation, which is a crucial organic synthetic method for attaching a sugar to other sugar moieties or other molecules, is becoming increasingly important in synthetic organic chemistry and carbohydrate chemistry, and considerable attention has been directed towards the efficiency of glycosylation methods.[3] From a synthetic standpoint, the efficiency of the glycosylation reaction is generally evaluated based on high chemical yield, regioselectivity, and α/β-stereoselectivity. However, little attention has been paid to the ecological efficiency of glycosylation. From an ecological point of view as well as that of energy considerations, reusable catalysts are greatly advantageous. The use of light as clean energy to promote the glycosylation reaction would also be beneficial. Several light-mediated *O*-[4] and *C*-[5]glycosylation reactions using a non-reusable redox catalyst have been reported previously. Herein we disclose a novel photo-induced glycosylation method using a reusable organocatalyst. To the best of our knowledge, this is the first demonstrated example of glycosylation with a reusable organophotoacid by light-switching.

Certain molecules show interesting properties in their excited states with respect to acidity. Although certain phenols and naphthols have been known as organophotoacids for decades,[6] the use of such organophotoacids in organic synthesis has been investigated only to a minor extent due to the very short lifetime of the excited state of organophotoacids. In this context, we previously demonstrated, for the first time, deprotection reactions using organophotoacids.[7] In this study, certain phenol and naphthol derivatives were found to work as efficient organophotoacids. Increased acidity in the excited state, induced by photoirradiation, was sufficient for the deprotection of several acid-sensitive protecting groups which are widely used in organic synthesis. From our continuing efforts in examining the use of organophotoacids in clean organic synthesis, we expected that the use of an organophotoacid would constitute a novel environmentally benign chemical glycosylation reaction.

To investigate our hypothesis, we selected glucosyl trichloroacetimidate **1**[8] and phenol and naphthol derivatives **2**–**5**[9,10] as a glycosyl donor and organophotoacids, respectively (Fig. 1). First, we investigated the glycosylation reaction of **1** with alcohol **8** using organophotoacid **2** with and without photoirradiation. We used a Blackray 100 W lamp irradiating at 365 nm,[11] as radiation at this long wavelength is not harmful to humans. The strength of the light, which was easily controlled by varying the power level of the lamp and the distance between the lamp and the reaction mixture, was measured using an actinometer.[12] The results of the glycosylation reactions carried out under various

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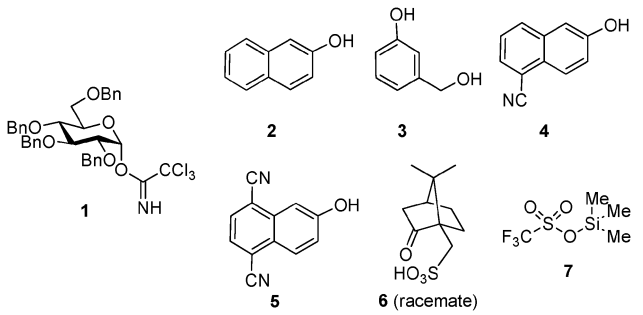


Fig. 1 Glycosyl donor **1**, organophotoacids **2–5**, Brønsted acid **6**, and Lewis acid **7**.

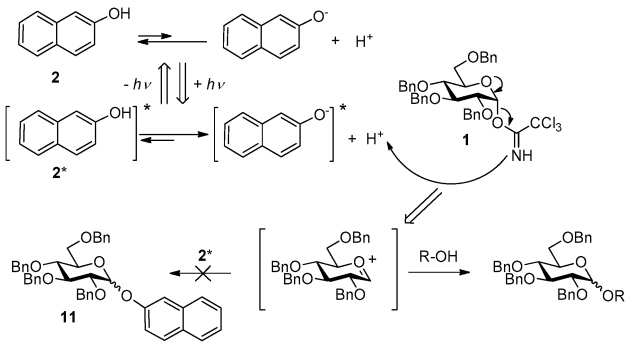


Fig. 2 Glycosylation reaction profile using organophotoacid **2** under photoirradiation.

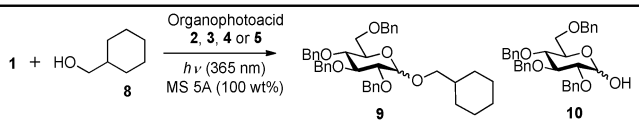
conditions are summarized in Table 1. First, it was found that the glycosylation reaction of **1** and alcohol **8** using organophotoacid **2** in Et_2O under photoirradiation proceeded to produce glycoside **9** in good yield (entry 2, Table 1). In the reaction without photoirradiation, we confirmed that glycosylation had not occurred, and a significant amount of glycosyl donor **1** was recovered (entry 1, Table 1). These results clearly demonstrate the usefulness of organophotoacid **2** together with photoirradiation for the glycosylation reaction. Also, these phenomena indicated that organophotoacid **2** was in the excited state, and the acidity significantly increased under photoirradiation, activating glycosyl donor **1**, as shown in Fig. 2. Furthermore, it is worthy of note that **2** in the excited state exhibited low nucleophilicity, and the naphthol glycoside **11** was not detected at all.

With these preliminary results in hand, we next examined the solvent effect on the glycosylation reaction of **1** and **8** using **2** in MeCN and i-Pr_2O, which were stable under the photoirradiation conditions. It was known that CH_2Cl_2 and THF, which are also widely used in glycosylation, were not suitable in this case due to their low stability toward light. It was found that when MeCN and i-Pr_2O were used, moderate yields of **9** were obtained along with a considerable amount of hydrolyzed product **10** (entries 3 and 4, Table 1). Interestingly, although weaker light was used for Et_2O due to its low boiling point compared to other solvents, MeCN and i-Pr_2O, it gave the highest yield of **9** (entry 2, Table 1). Based on these results, we next examined other organophotoacids **3–5** in the glycosylation reaction of **1** and **8** in Et_2O. It was found that when **5** was used, the result was similar to that obtained using **2** (entry 8, Table 1), while **3** and **4** were found to be less effective in the photo-induced glycosylation reaction (entries 6 and 7 in Table 1).

Next, we optimized the reaction conditions: concentration of **1**, amounts of **2** and **5**, and reaction time. These results are summarized in Table 2. It was found that the use of 0.5 M **1** gave the best results for organophotoacids **2** and **5** (entries 2 and 5 in Table 2). In addition, when 0.3 equiv. of **2** or 0.1 equiv. of **5** (compared to **1**) was used, the highest yield was obtained in each case (entries 2 and 10 in Table 2). Furthermore, we confirmed that a reaction time of 4 h was sufficient in both cases (entries 12 and 14, Table 2). Thus, we found that the use of 0.3 equiv. of **2** or 0.1 equiv. of **5** in the glycosylation of **1** and **8** at 35 °C for 4 h in Et_2O under photoirradiation (365 nm, 12 mW cm^{-2}) gave the best result with high reproducibility, producing glycoside **9** in high (~80%) yield.

Next, we performed mechanistic studies of the glycosylation reaction (Fig. 3). It was found that when the single α-glycoside **9α** was treated with only **2** or **5** without alcohol **8** under the conditions used for photo-induced glycosylation, no isomerization occurred, and **9α** was quantitatively recovered. This indicates that

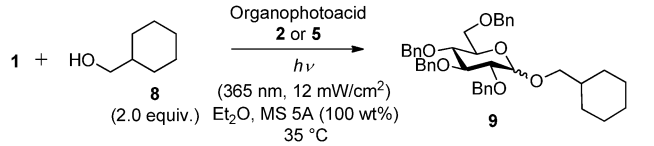
Table 1 Glycosylation reaction of donor **1** and alcohol **8** using organophotoacids **2–5** under various conditions



Entry	Organophotoacid (equiv.)	Light strength (mW cm^{-2})	Solvent	Temp. (°C)	Time (h)	Yield[a] (%) 9 (α : β)[b]	10	1
1[c]	**2** (0.3)	0	Et_2O	35	7	8	Trace	85
2[c]	**2** (0.3)	12	Et_2O	35	7	79 (54 : 46)	20	0
3[c]	**2** (0.3)	27	MeCN	50	2	56 (23 : 77)	37	0
4[c]	**2** (0.3)	27	i-Pr_2O	50	7	68 (54 : 46)	24	0
5[d]	**2** (0.3)	12	Et_2O	35	20	72 (61 : 39)	27	0
6[d]	**3** (0.3)	12	Et_2O	35	20	67 (49 : 51)	22	0
7[d]	**4** (0.3)	12	Et_2O	35	20	52 (61 : 39)	22	0
8[d]	**5** (0.3)	12	Et_2O	35	20	75 (59 : 41)	23	0

[a] Yield of the isolated product. [b] α : β Ratio was determined by ^{1}H-NMR analysis. [c] 3.0 equiv. of **8** was used. [d] 2.0 equiv. of **8** was used.

Table 2 Glycosylation of donor **1** and alcohol **8** using organophotoacid **2** or **5** under photoirradiation



Entry	Organophotoacid	Equiv. of **2** or **5**	Conc. of **1** (M)	Time (h)	Yield[a] (%) **9** ($\alpha:\beta$)[b]
1	**2**	0.3	0.1	20	72 (59 : 41)
2	**2**	0.3	0.5	20	83 (48 : 52)
3	**2**	0.3	1.0	20	81 (53 : 47)
4	**5**	0.3	0.1	20	75 (59 : 41)
5	**5**	0.3	0.5	20	79 (47 : 53)
6	**5**	0.3	1.0	20	72 (52 : 48)
7	**2**	0.1	0.5	20	74 (51 : 49)
8	**2**	0.5	0.5	20	76 (59 : 41)
9	**5**	0.05	0.5	20	71 (48 : 42)
10	**5**	0.1	0.5	20	81 (54 : 46)
11	**2**	0.3	0.5	2	60 (49 : 51)
12	**2**	0.3	0.5	4	83 (48 : 52)
13	**5**	0.1	0.5	2	44 (50 : 50)
14	**5**	0.1	0.5	4	80 (53 : 47)

[a] Yield of the isolated product. [b] $\alpha:\beta$ Ratio was determined by ^{1}H-NMR analysis.

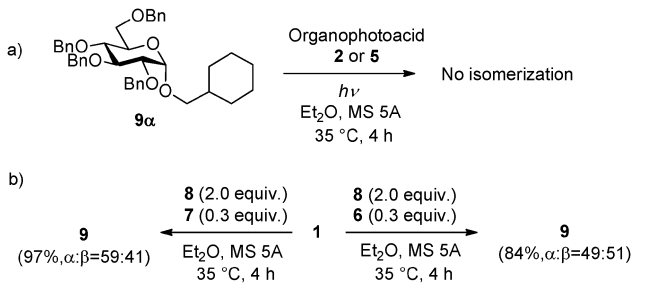
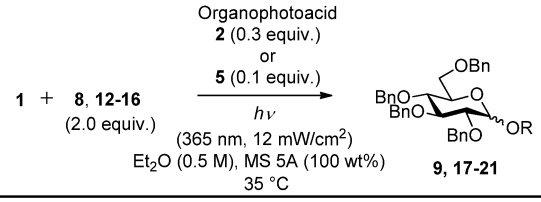


Fig. 3 Mechanistic study (a) of the glycosylation reaction of **1** and **8** using Brønsted acid **6** and Lewis acid **7** (b).

α/β-stereoselectivity was determined by kinetic control (Fig. 3a). In addition, when the Brønsted acid CSA (**6**) and the Lewis acid TMSOTf (**7**) (Fig. 1) were used as catalysts in the glycosylation of **1** and **8**, the results in terms of α/β-stereoselectivity were quite similar to those using **2** or **5** under photoirradiation (Fig. 3b). These results indicate that the relatively low α/β-stereoselectivity observed in the photo-induced glycosylation reaction under investigation was not due to the nature of the photoirradiation conditions, including the presence of an organophotocatalyst, and was dependent on the nature of the glycosyl donor **1**.[13]

With these favorable results in hand, we next examined the generality of the glycosylation method using several alcohols (**12–16**). As shown in Table 3, glycosylation of **12–16** as well as **8** with **1** using **2** under the photoirradiation conditions proceeded smoothly to give the corresponding glycosides **17–21** in high yields (entries 1–6, Table 3). Photo-induced glycosylation of **12–16** mediated by organophotoacid **5** using **1** also gave glycosides **17–21** in high yields (entries 7–12, Table 3). Next, we turned our attention to the type of glycosyl donor used (Table 4). When galactosyl and mannosyl trichloroimidates **22** and **23** were

Table 3 Glycosylation of donor **1** and alcohols **8** and **12–16** using organophotoacid **2** or **5**



Entry	Organophotoacid	Alcohol	Time (h)	Product	Yield[a] (%) ($\alpha:\beta$)[b]
1	**2**	**8**	4	**9**	83 (49 : 51)
2	**2**	**12**	4	**17**	78 (46 : 54)
3	**2**	**13**	8	**18**	73 (54 : 46)
4	**2**	**14**	8	**19**	72 (65 : 35)
5	**2**	**15**	4	**20**	83 (54 : 46)
6[c]	**2**	**16**	12	**21**	85 (48 : 52)
7	**5**	**8**	4	**9**	80 (53 : 47)
8	**5**	**12**	4	**17**	81 (45 : 55)
9	**5**	**13**	8	**18**	70 (50 : 50)
10	**5**	**14**	8	**19**	74 (70 : 30)
11	**5**	**15**	4	**20**	80 (46 : 54)
12[c]	**5**	**16**	12	**21**	87 (47 : 53)

[a] Yield of the isolated product. [b] $\alpha:\beta$ Ratio was determined by ^{1}H-NMR analysis. [c] 3.0 equiv. of **16** was used.

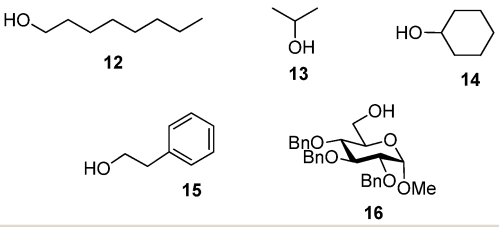
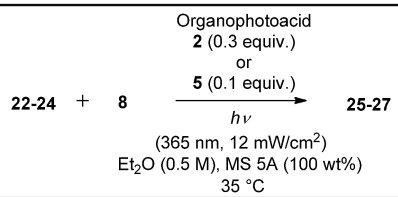
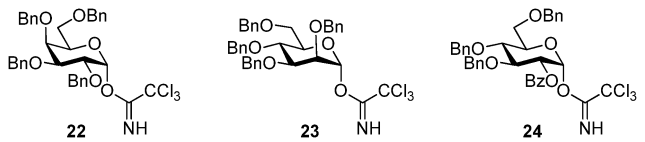


Table 4 Glycosylation of donors **22–24** and alcohol **8** using organophotoacid **2** or **5**



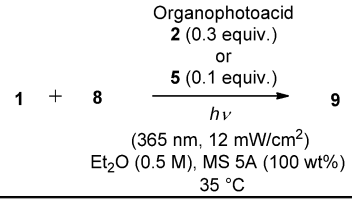
Entry	Donor	Organophotoacid	Time (h)	Product	Yield[a] (%) ($\alpha:\beta$)[b]
1	**22**	**2**	4	**25**	95 (80 : 20)
2	**22**	**5**	4	**25**	95 (90 : 10)
3	**23**	**2**	12	**26**	74 (55 : 45)
4	**23**	**5**	12	**26**	71 (52 : 48)
5	**24**	**2**	12	**27**	72 (0 : 100)
6	**24**	**5**	12	**27**	74 (0 : 100)

[a] Yield of the isolated product. [b] $\alpha:\beta$ Ratio was determined by ^{1}H-NMR analysis.



employed as glycosyl donors, the glycosylation of **8** using **2** or **5** proceeded to afford glycosides **25** and **26**, respectively, in high yields (entries 1–4, Table 4). In addition, to overcome the low α/β-stereoselectivity observed in the glycosylation reactions using

Table 5 Recovery and reuse of organophotoacids **2** and **5** in glycosylation of **1** and **8** under photoirradiation



Entry	Organophotoacid	Recovery yield[a] (%)	Reaction yield using recovered organophotoacid[a] (%) ($\alpha:\beta$)[b]
1	**2**	95	81 (51/49)
2	**5**	93	79 (54/46)

[a] Yield of the isolated product. [b] $\alpha:\beta$ Ratio was determined by ^{1}H-NMR analysis.

the glycosyl donors **1**, **22** and **23**, we carried out glycosylation of **8** using **24**, which possesses a benzoyl protecting group at the C2-position. In this case, high β-stereoselectivity was observed due to the participation effect of the C2-protecting group, and the β-glycoside **27** was selectively produced in high yield (entries 5 and 6 in Table 4).

Finally, we investigated the reusability of organophotoacids **2** and **5** (Table 5). It was found that after completion of the glycosylation reaction, both **2** and **5** were recovered in >90% yield *via* column chromatography and could be reused without any loss of efficiency. Furthermore, neither neutralization of the reaction mixture nor extraction of the product was required after completion of the reaction, because the removal of UV light rendered the reaction mixture almost neutral.[9,10] The work-up for the reaction involved only evaporation of the solvent, Et_2O, which was also found to be reusable.

Overall, the glycosylation reaction exhibited several environmentally benign features: (1) non-harmful UV light (365 nm) is used; (2) catalysts **2** and **5** are recoverable and reusable; (3) the work-up involves only evaporation of the solvent.

In summary, we have developed a novel glycosylation method, effective for several trichloroimidate glycosyl donors, using an organophotoacid under photoirradiation. The reaction is highly efficient and environmentally benign. As glycosylation is a very important step in the synthesis of carbohydrate-containing products, this useful method should find a wide range of applications in both academia and industry. The development of several different types of organophotocatalysts, including organophotoacids, and their application in environmentally benign organic synthesis is now under investigation in our laboratories.

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12 A radiometer sensor (UVX-36) purchased from UVP, Inc. was used. UV light at 12 mW cm^{-2} was obtained using one lamp placed at 5 cm from the reaction mixture. UV light at 27 mW cm^{-2} was obtained using two lamps placed at 3 cm from the reaction mixture.
13 It was confirmed that the other acid-sensitive glycosyl donors, such as the corresponding glycal or glycosyl diethyl phosphite, could not effectively be activated by the organophotoacids used.

