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Stereocontrolled Photoinduced Glycosylation Using an Aryl Thiourea as an Organo photoacid

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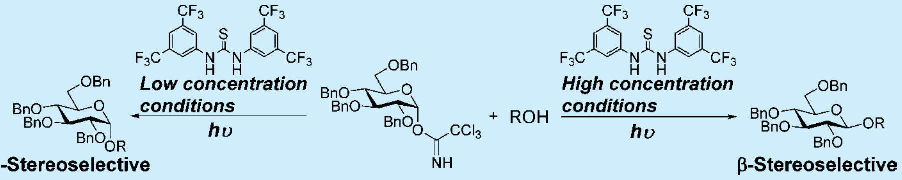
Supporting Information



ABSTRACT: Photoinduced glycosylation of alcohols with *α*-glucosyl trichloroacetimidates, using aryl urea and thioureas as organo photoacids, was examined under long wavelength UV (ultraviolet) irradiation. The results show, for the first time, that such glycosylations proceed effectively to give the corresponding glycosides in high yields. In addition, high *β*-stereoselectivity was obtained under high concentration conditions, whereas high *α*-stereoselectivity was realized under low concentration conditions.

Glycomolecules, which include a variety of mono-, oligo-, and polysaccharides such as proteoglycans, glycoproteins, glycolipids, and antibiotics, are important biologically active substances. A large number of recent molecular-level studies on these glycomolecules have provided insights into the biological significance of the carbohydrate (glycon) portion for molecular recognition during the transmission of biological information.[1] Carbohydrates, along with nucleic acids and proteins, play very important roles in many biological events. Additionally, some glycomolecules are being used as new functional materials.[2] For example, certain alkyl glycosides have potential as biodegradable surfactants. Therefore, glycomolecules are worth developing for applications in chemistry, biology, and materials science.

The efficient synthesis of carbohydrate-containing products is also of particular interest. Glycosylation, which involves the attachment of a sugar to other sugar moieties or other molecules (aglycons), is increasingly important in synthetic organic chemistry and carbohydrate chemistry, and efforts have been directed toward the development and efficiency of glycosylation methods.[3] The efficiency of a glycosylation reaction generally is evaluated using chemical yield, regioselectivity, and *α*/*β*-stereoselectivity. However, little attention has been paid to the ecological efficiency of glycosylation. In this context, several redox-type photoinduced glycosylation reactions have been reported.[4] The use of light as clean energy to promote glycosylation would be advantageous.[5] Previously, a type of photoinduced glycosylation, which uses certain naphthol derivatives as reusable organo photoacids, has been reported.[6] Organo photoacids possess an interesting property[7] in that their acidity increases in the photoexcited state. Therefore, organo photoacids can be used to control glycosylation by light-switching, and neutralization is not necessary for terminating the reaction. However, *α*/*β*-stereoselectivity cannot be controlled in photoinduced glycosylation using naphthol derivatives as organo photoacids. Therefore, this study has been focused on investigating aryl thioureas as organo photoacids for overcoming these limitations. Aryl thioureas have been used as hydrogen-bond-donating organocatalysts for many asymmetric syntheses,[8] as triplet sensitizers,[9] and in glycosylation reactions (for glycal),[10] but their usefulness is limited because of their moderate acidity[11] (e.g., compound **4** has a pK_a value of 8.5 in DMSO). Since a nitrogen anion can be stabilized through electron delocalization (resonance effect) over the sulfur atom and the aromatic rings, the acidity of aryl thioureas should increase significantly upon photoirradiation. Aryl thioureas in the excited state were expected to activate glucosyl trichloroacetimidate, which requires a pK_a value less than 5 for activation at room temperature (Figure 1).[12]

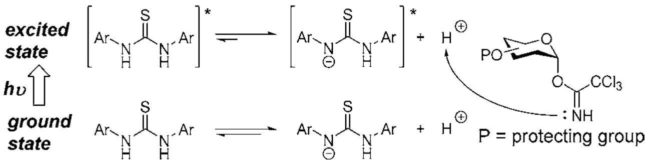


Figure 1. Photoinduced glycosylation using an aryl thiourea.

To investigate this hypothesis, the glucosyl trichloroacetimidate **1**, aryl urea **3**, and thioureas **2** and **4** were selected as glycosyl donor and candidates for organo photoacids, respectively (Figure 2). First, the glycosylation reaction of **1** with alcohol **5** (2.0 equiv) was examined using aryl urea **3** and thioureas **2** and **4** (0.3 equiv) in the presence of powdered 5 Å molecular sieves (MS) in Et_2O. A Blackray 100 W lamp at 365 nm[13] was used because irradiation

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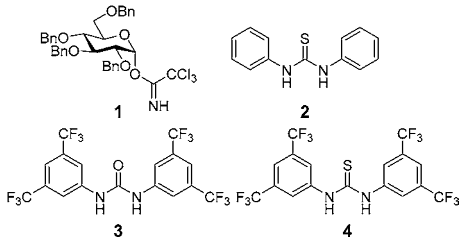
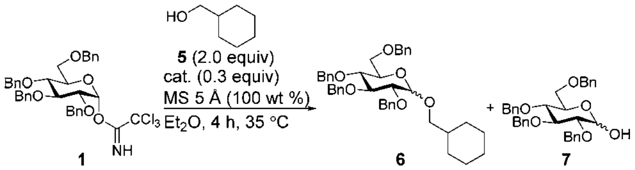


Figure 2. Chemical structures of glycosyl donor **1** and candidates of aryl urea **3** and thioureas **2** and **4** as organo photoacids.

at this wavelength is not harmful to humans. The strength of the light was measured using an actinometer.[14] The reaction mixture in an appropriate size of glassy vessel was stirred at ~360 rpm. The results, which are summarized in Table 1, showed that the use of aryl urea or thioureas **2**–**4** gave the corresponding glycoside **6**[6] in low to excellent yield (Table 1, entries 1–3) after photoirradiation. In particular, the corresponding glycoside **6** was obtained in excellent yield (92%, α/β = 35/65) when aryl thiourea **4** was used (Table 1, entry 3). In this experiment, donor **1** was not recovered and the hydrolyzed product **7** was also not produced. In contrast, glycosylation using thiourea **4** without photoirradiation did not occur, glucoside **6** was not produced, and a significant amount of **1** was recovered (Table 1, entry 4). In addition, it was confirmed that only MS 5 Å with photoirradiation did not promote the reaction, and **1** was recovered in quantitative yield (Table 1, entry 5). Furthermore, thiourea **4** had an absorption band near 365 nm (Figure S3). These results clearly indicate that aryl thiourea **4** promoted glycosylation as an organo photoacid. In addition, urea **3** was not effective (Table 1, entry 2 vs 3). In addition, the two trifluoromethyl groups of the benzene substituent, which are electron-withdrawing groups, were effective for increasing the acidity of the aryl thiourea, even in the photoexcited state (Table 1, entry 1 vs. 3). Interestingly, β-stereoselectivity was observed even when Et_2O was used as a solvent, which generally induces α-stereoselectivity.[15] Further results revealed that β-stereoselectivity improved with an increase in the concentration of **1** in Et_2O (Table 1, entries 6 and 7).

Table 1. Glycosylation Reactions of 1 and 5 Using Aryl Urea or Thiourea 2–4

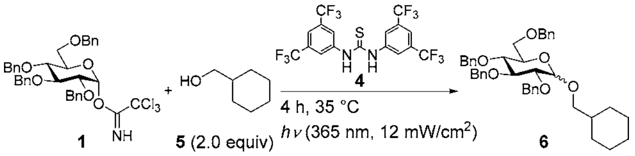


entry	cat.	concn of **1** (M)	$h\nu$[a]	**6** (α/β)[b]	yield (%) **1**	yield (%) **7**
1	**2**	0.5	+	19 (33:67)	54	0
2	**3**	0.5	+	62 (32:68)	30	0
3	**4**	0.5	+	92 (35:65)	0	0
4	**4**	0.5	–	0	84	9
5		0.5	+	0	92	0
6	**4**	0.8	+	87 (30:70)	0	0
7	**4**	1.0	+	85 (24:76)	0	5

[a] 365 nm, 12 mW/cm^2. [b] α/β ratios were determined by ^{1}H NMR analysis.

On the basis of these results, the reaction conditions were optimized. Results showed that glycosylation involving **1** and **5** using 0.5 equiv of thiourea **4** proceeded without photoirradiation, although the yield of **6** was low (Table 2, entry 1). In addition, when 0.1–0.5 equiv of **4** was used under photoirradiation, 0.3 equiv of **4** was sufficient and resulted in high reproducibility (Table 2, entries 2–4). Furthermore, when the concentration of **1** was greater than 1.0 M, the stirring efficiency was low with MS 5 Å. Therefore, glycosylaton reactions were performed using greater concentrations without 5 Å MS, which resulted in greater β-stereoselectivity (Table 2, entry 5, 2.0 M **1**). In addition, the solvent effect was examined using THF and MeCN in addition to Et_2O, which revealed that MeCN gave the best yield and β-stereoselectivity (Table 2, entries 6 and 7). However, this β-stereoselectivity did not result just from the effect of MeCN coordination with the generated oxionium intermediate[16] because a similar result was obtained when Et_2O was used as a solvent (Table 2, entry 3). The main reason for this high β-stereoselectivity is the S_N2 reaction mechanism of glycosylation involving **1** and an alcohol by photoactivated **4** using high concentrations (Scheme 1, path A). However, the effect of the MeCN may promote β-stereoselectivity.

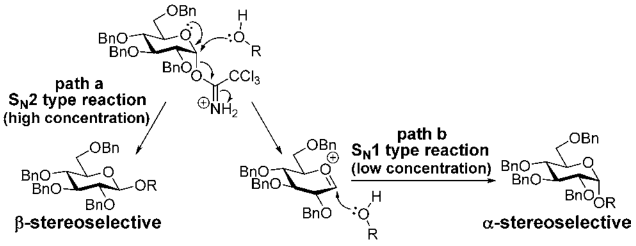
Table 2. Glycosylation of 1 and 5 Using Aryl Thiourea 4 at High Concentrations



entry	solv (M)	$h\nu$[a]	MS[b]	**4** (equiv)	yield (%) (α/β)[c]
1	Et_2O (1.0)	–	+	0.5	31 (22:78)
2	Et_2O (1.0)	+	+	0.1	82 (26:74)
3	Et_2O (1.0)	+	+	0.3	85 (24:76)
4	Et_2O (1.0)	+	+	0.5	87 (25:75)
5	Et_2O (2.0)	+	–	0.3	85 (16:84)
6	THF (2.0)	+	–	0.3	82 (19:81)
7	MeCN (2.0)	+	–	0.3	93 (8:92)

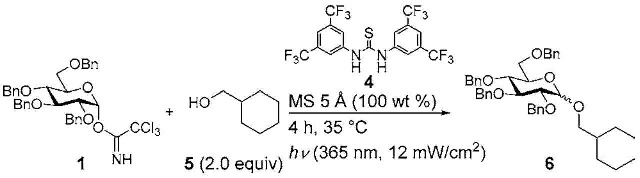
[a] 365 nm, 12 mW/cm^2. [b] MS 5 Å (100 wt % to donor) was used. [c] α/β ratios were determined by ^{1}H NMR analysis.

Scheme 1. Proposed Mechanism of Stereocontrolled Photoinduced Glycosylation Using Aryl Thiourea 4



Based on the reaction mechanism from the results in Table 2 and path A in Scheme 1, this photoinduced glycosylation reaction under low concentration conditions was expected to produce α-stereoselective glycosylation using catalyst **4** and Et_2O as the solvent. Therefore, glycosylation was conducted at 0.005 to 0.1 M **1** (Table 3, entries 1–5). The results indicated that the greatest α-stereoselectivity occurred at 0.01 M **1** in Et_2O (Table 3, entry 2). Furthermore, experiments were performed to optimize the reaction conditions using 0.1–1.0 equiv of **4** (Table 3, entries 6–

Table 3. Glycosylation Reaction of 1 and 5 Using Aryl Thioureas 4 Under Low Concentration Conditions



entry	solv (M)	**4** (equiv)	MS[a]	yield (%) (α/β)[b]
1	Et_2O (0.005)	0.3	+	73 (83:17)
2	Et_2O (0.01)	0.3	+	81 (83:17)
3	Et_2O (0.025)	0.3	+	88 (77:23)
4	Et_2O (0.05)	0.3	+	89 (67:33)
5	Et_2O (0.1)	0.3	+	84 (64:36)
6	Et_2O (0.01)	0.1	+	83 (81:19)
7	Et_2O (0.01)	0.5	+	78 (80:20)
8	Et_2O (0.01)	1.0	+	79 (82:18)
9	THF (0.01)	0.3	+	86 (81:19)
10	MeCN (0.01)	0.3	+	51 (41:59)
11	Et_2O (0.01)	0.3	−	74 (71:29)

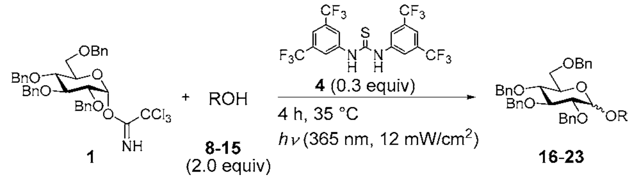
[a] MS 5 Å (100 wt % to donor) was used. [b] α/β Ratios were determined by ^1H NMR analysis.

8) and THF and MeCN as solvents (Table 3, entries 9−10) at a low concentration of 0.01 M **1**. However, no better result than that listed in Table 3, entry 3, was observed. The high α-stereoselectivity was due to the S_N1 reaction mechanism of glycosylation involving **1** and an alcohol by photoactivated **4** via the oxionium cation intermediate under low concentration conditions (Scheme 1, path B). Surprisingly, addition of 5 Å MS was very effective (Table 3, entry 11); the weak acidity of the 5 Å MS may assist path B, although the reason is not totally understood. Finally, glycosylation using 0.3 equiv of thiourea **4** (0.01 M in Et_2O) in the presence of 5 Å MS produced the best results with high α-stereoselectivity in high yield (Table 3, entry 2). When the single α-glycoside ***6α*** and β-glycoside ***6β*** were treated with only thiourea **4** without alcohol **5** under the same conditions used for photoinduced glycosylation, no isomerization occurred, and ***6α*** and ***6β*** were recovered quantitatively under both high and low concentration conditions. These results indicate that α/β-stereoselectivity was determined by the reaction kinetics.

Next, the scope and limitations of the glycosylation method were examined using the alcohols **8−15**. As shown in Table 4, the photoinduced glycosylation of alcohols **8−15** using thiourea **4** in Et_2O in the presence of 5 Å MS at low concentrations proceeded smoothly to give the corresponding glycosides **16−18**,[6] **19**,[17] **20**,[6] **21**,[18] **22**,[19] and **23**[20] in good to high yield with α-stereoselectivity (Table 4, entries 1−8). In contrast, high concentrations without 5 Å MS produced the corresponding glycosides **16−23** in high yield with β-stereoselectivity (Table 4, entries 9−16).

The generality of the glycosylation method was also investigated using alcohol **5** and the glycosyl donors galactosyl and mannosyl trichloroimidates **24** and **25**. The results are summarized in Table 5. Under low concentration conditions with 5 Å MS, glycosylation proceeded smoothly to give the corresponding glycosides **26**[6] and **27**[6] in high yields with complete α-stereoselectivity (Table 5, entries 1 and 2). In addition, high β-stereoselectivity was observed with high yields, even when galactosyl trichloroimidate **24** was used as the glycosyl donor under high concentration conditions without 5 Å MS

Table 4. Glycosylation Reaction of 1 and Alcohols 8−15 Using Aryl Thiourea 4



entry	solv (M)	ROH	product	yield (%) (α/β)[a]
1[b]	Et_2O (0.01)	**8**	**16**	84 (81:19)
2[b]	Et_2O (0.01)	**9**	**17**	90 (85:15)
3[b]	Et_2O (0.01)	**10**	**18**	85 (84:16)
4[b]	Et_2O (0.01)	**11**	**19**	83 (87:13)
5[b]	Et_2O (0.01)	**12**	**20**	78 (83:17)
6[b]	Et_2O (0.01)	**13**	**21**	75 (81:19)
7[b]	Et_2O (0.01)	**14**	**22**	68 (79:21)
8[b]	Et_2O (0.01)	**15**	**23**	56 (75:25)
9	MeCN (2.0)	**8**	**16**	90 (9:91)
10	MeCN (2.0)	**9**	**17**	87 (9:91)
11	MeCN (2.0)	**10**	**18**	87 (12:88)
12	MeCN (2.0)	**11**	**19**	88 (16:84)
13	MeCN (1.0)	**12**	**20**	89 (11:89)
14	MeCN (1.0)	**13**	**21**	85 (12:88)
15	MeCN (1.0)	**14**	**22**	83 (28:72)
16	MeCN (1.0)	**15**	**23**	84 (24:76)

[a] α/β ratios were determined by ^1H NMR analysis. [b] MS 5 Å (100 wt % to donor) was used.

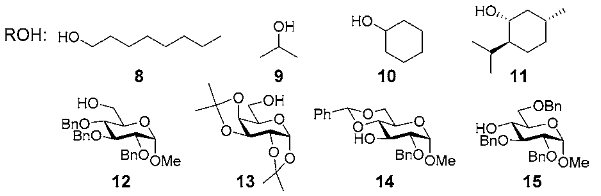
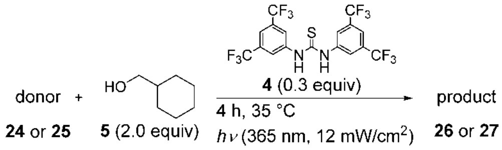
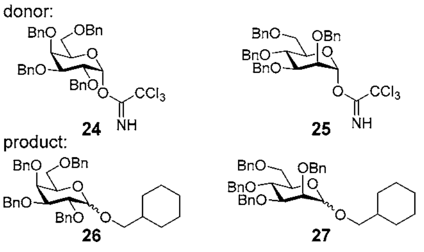


Table 5. Glycosylation Reaction of 24 or 25 and Alcohol 5 Using Aryl Thiourea 4



entry	donor	product	solv (M)	yield (%) (α/β)[a]
1[b]	**24**	**26**	Et_2O (0.01)	82 (α only)
2[b]	**25**	**27**	Et_2O (0.01)	81 (α only)
3	**24**	**26**	Et_2O (2.0)	94 (12:88)
4	**24**	**26**	MeCN (2.0)	90 (10:90)
5	**25**	**27**	Et_2O (2.0)	87 (49:51)
6	**25**	**27**	MeCN (2.0)	88 (48:52)

[a] α/β ratios were determined by ^1H NMR analysis. [b] MS 5 Å (100 wt % to donor) was used.



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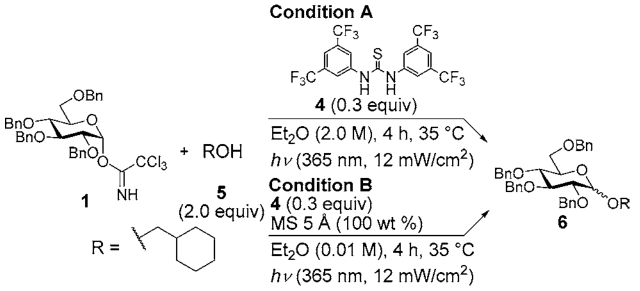
(Table 5, entries 3 and 4). However, this method was not applicable to mannosyl trichloroimidate **25** (Table 5, entries 5 and 6). This switch in α/β-stereoselectivity was not observed in photoinduced glycosylations using 2-naphtol and 5,8-dicyanonaphtol (Table S1).[6]

Finally, the reusability of organo photoacid **4** was investigated (Table 6). Glycosylation resulted in the recovery of ~90% **4** via SiO$_2$ column chromatography, which could be reused without any loss of efficiency. Further, neither neutralization of the reaction mixture nor extraction of the product was required after completion of the reaction because discontinuation of UV light irradiation rendered the reaction mixture almost neutral. Workup for the reaction involved only evaporation of the solvents (Et$_2$O and MeCN), which also could be reused.

Table 6. Recovery and Reuse of 4 in Glycosylation of 1 and 5



entry	condition	recovery of **4** (%)	reaction yield using recovered **4** (%) (α/β)[a]
1	**A**	89	84 (16:84)
2	**B**	91	83 (82:18)

[a] α/β ratios were determined by ^{1}H NMR analysis.

In conclusion, a novel glycosylation reaction method has been developed using thiourea **4** as an organo photoacid under photoirradiation. This reaction allows for α/β-stereoselectivity by adjusting the substrate concentration. This useful method should find a wide range of applications involving syntheses of carbohydrate-containing products and the development of organocatalysts for asymmetric organic reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01404.

Supporting figures, experimental procedures, syntheses, and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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(13) A Blak-ray (B-100A) purchased from UVP, Inc., was used.

(14) 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. Based on the optimized result in ref 5, we carried out the reaction for 4 h in this study.

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