Organic & Biomolecular Chemistry

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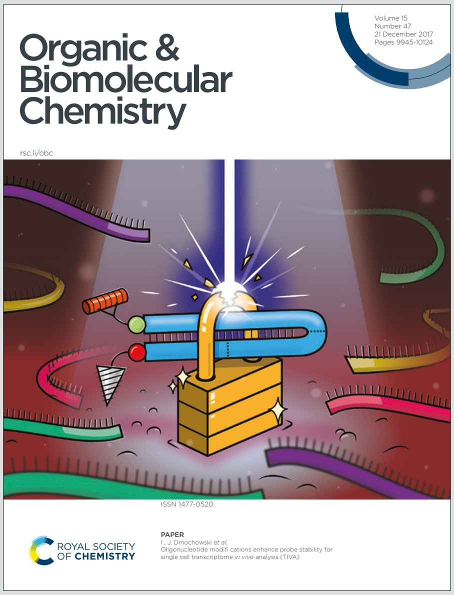

View Article Online
DOI: 10.1039/C9OB02674F

COMMUNICATION

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Photo-induced glycosylation using a diaryldisulfide as an organo-Lewis photoacid catalyst

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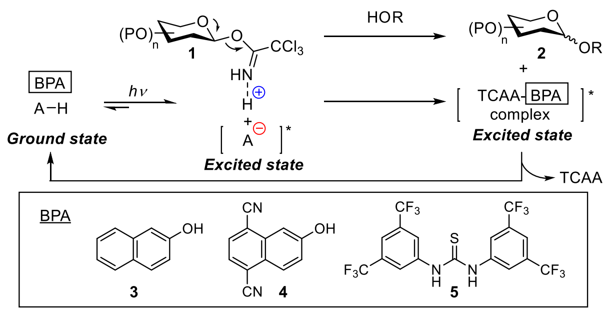
Photo-induced glycosylations of several acceptors with trichloroacetimidate donors using bis(2-naphtyl)disulfide as an organo-Lewis photoacid (LPA) catalyst proceeded effectively to give the corresponding glycosides in good to high yields. In addition, the grand and excited state absorption spectra of bis(2-naphtyl)disulfide with or without NEt_3 suggested the Lewis acidity of bis(2-naphtyl)disulfide upon photo-irradiation.

A wide variety of glycosides, such as glycoconjugates and oligosaccharides, are found in many biologically active natural products and highly functional molecules. To elucidate their precise biological and/or functional roles, homogeneous and structurally well-defined synthetic carbohydrates have been investigated. Thus, considerable effort has been devoted to developing an efficient glycosylation reaction, and several glycosylation methods have been reported.[1] However, in general, environmentally hazardous chemicals, such as strong acids and toxic metal reagents, are still used for most conventional glycosylation methods.[2] Therefore, greener methods[3] for glycosylation[4] and conversion[5] of carbohydrates that involve the use of environmentally benign solvents and catalysts are desired for environmental and energy reasons. In addition, the use of light as clean energy to promote glycosylation reactions also would be beneficial.[6] Previous reports have described photo-induced glycosylations[7] of glycosyl trichloroacetimidate donor **1** and several alcohols using several organo-Brønsted photoacid (BPA) catalysts, 2-naphthol (**3**),[7a] 5,8-dicyano-2-naphthol (**4**),[7a] and 1,3-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (**5**),[7b] which possess the interesting chemical property that their acidity increases in the photoexcited state. Results showed that glycosylations proceeded effectively to provide the corresponding glycoside **2** using only long-wavelength of UV light irradiation (Fig. 1A). In addition, after completion of the glycosylation reactions, a neutralization step for terminating the reaction was not necessary. Furthermore, **3**–**5** were recovered in high yields and could be reused. Recently, Wang and co-workers reported visible-light-induced glycosylations of several alcohols with glycals using eosin Y and diphenyldisulfide (PhSSPh) (**6a**) as a phenolic BPA catalyst and co-catalyst, respectively, for synthesis of 2-deoxy-α-glycosides.[6a] In this method, PhSSPh (**6a**) is proposed to act only as a redox-active catalyst for regeneration of the BPA catalyst, eosin Y, during the glycosylation reaction.

The present study focuses on diaryldisulfide **6** as a new type of organo-Lewis photoacid (LPA) catalyst[8] that would develop sufficient Lewis acidity to activate glycosyl donor **1** due to delocalization of the lone pair electrons on the sulfur atom into the aromatic ring upon photo-irradiation (Fig. 1B).

(A) Photoinduced glycosylations using organo-Brønsted photoacid (BPA) catalysts.



(B) Photoinduced glycosylation using an organo-Lewis photoacid (LPA) catalyst.

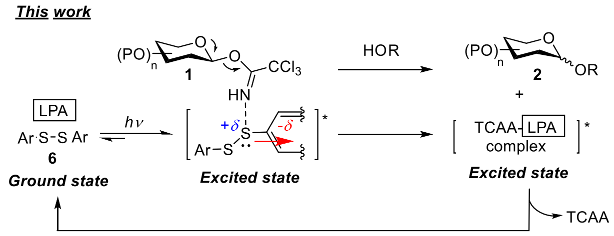


Fig. 1. Photo-induced glycosylation using (A) organo-Brønsted photoacid (BPA) catalysts and (B) an organo-Lewis photoacid (LPA) catalyst. TCAA = trichloroacetamide.

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Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x

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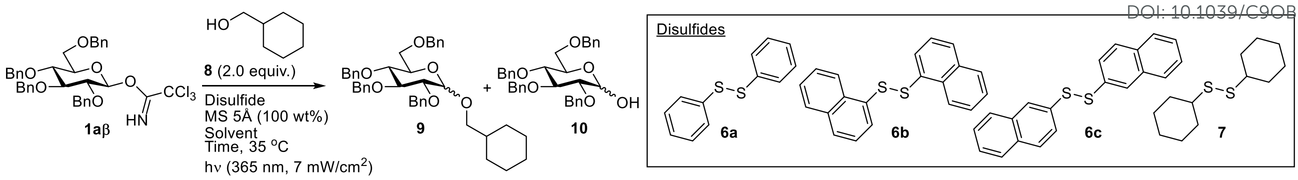
DOI: 10.1039/C9OB02674F

Table 1 Glycosylations of **1aβ** and **8** using a catalytic amount of disulfides.



Entry	Cat.	Equiv. of cat.	hν	Conc. of **1aβ** (M)	Solvent	Time (h)	Yield (%)		
							9 (α/β)[1]	**10**	**1aβ**
1	**6a**	0.05	+	0.8	Toluene	2	75 (79/21)	17	0
2	**6b**	0.05	+	0.8	Toluene	2	83 (71/29)	13	0
3	**6c**	0.05	+	0.8	Toluene	2	86 (70/30)	5	0
4	**7**	0.05	+	0.8	Toluene	2	25 (92/8)	6	65
5	–	–	+	0.8	Toluene	2	25 (95/5)	11	60
6	**6c**	0.05	–	0.8	Toluene	2	6 (α only)	0	92
7	**6c**	0.05	+	0.3	Toluene	2	80 (69/31)	15	0
8	**6c**	0.05	+	1.0	Toluene	2	82 (75/25)	11	0
9	**6c**	0.01	+	0.8	Toluene	2	78 (76/24)	15	0
10	**6c**	0.05	+	0.8	Et_2O	2	49 (82/18)	36	13
11	**6c**	0.05	+	0.8	THF	2	68 (81/19)	23	0
12	**6c**	0.05	+	0.8	MeCN	2	77 (77/23)	11	0
13	**6c**	0.05	+	0.8	CH_2Cl_2	2	83 (79/21)	12	0
14	**6c**	0.05	+	0.8	Toluene	1	23 (96/4)	22	48
15	**6c**	0.05	+	0.8	Toluene	4	84 (68/32)	5	0

[1] The α/β ratios were determined by ^1H-NMR analysis.

This present report demonstrates, for the first time, that certain diaryldisulfides can act as a reusable organo-LPA catalyst to effectively promote photo-induced glycosylation under mild reaction conditions.

To investigate this hypothesis, the glucosyl trichloroacetimidate **1aβ**, diaryldisulfides **6a-c**, and bis(cyclohexyl)disulfide (**7**) were selected as glycosyl donor, candidates for organo-LPA, and negative control, respectively. Initially, the glycosylation of cyclohexylmethanol (**8**) (2.0 equiv.) with **1aβ** was examined using a catalytic amount of disulfide in the presence of powdered molecular sieves (MS 5Å) in toluene with irradiation with non-harmful long-wavelength UV light (365 nm, 7 mW/cm^2) using a Black-ray 100 W lamp.[9] The strength of the light was measured using an actinometer, and controlled by the distance between the lamp and reaction mixture. Results are summarized in Table 1. Glycosylations of **1aβ** and **8** using diaryldisulfides **6a-c** (0.05 equiv.) under photo-irradiation provided, for the first time, the corresponding glycoside **9** in good to high yields with α stereoselectivity (entries 1-3). The bis(2-naphtyl)disulfide (**6c**) provided the highest yield (entry 3). In contrast, when dialkyldisulfide **7**, which did not have absorption bands near 365 nm, was used, the chemical yield of **9** decreased dramatically to 25%, and a significant amount of donor **1aβ** was recovered (entry 4). In addition, glycosylation was confirmed to proceed slightly, even in the absence of the disulfide catalyst with photo-irradiation, and gave **9** in the same yield (entry 4 vs. 5), indicating that **7** did not enhance reaction conversion. Furthermore, glycosylation using **6c** without photo-irradiation did not proceed, and **1aβ** was recovered in high yield (entry 6). These results suggested that **6c** significantly promoted glycosylation as an organo-photoacid. Next, the reaction conditions (concentration of **1aβ**, equiv. of **6c**, solvent, and reaction time) were optimized. Results showed that, although the α-stereoselectivity of **9** increased slightly with concentration, the use of 0.8 M of **1aβ** gave the best yield (entries 3, 7, and 8). When 0.01 equiv. of **6c** was used under photo-irradiation, the chemical yield of **9** decreased compared to that using 0.05 equiv. of **6c** (entry 3 vs. 9). In addition, the solvent effect was examined using Et_2O, THF, MeCN, and CH_2Cl_2, and indicated that toluene gave the best yield (entries 3 and 10–13). Furthermore, the reaction time of 2 h was confirmed to be sufficient for this glycosylation reaction (entries 3, 14, and 15). Therefore, 0.05 equiv. of **6c** used for glycosylation of **1aβ** and **8** at 35 °C in toluene under 2-hr photo-irradiation gave the best results, producing glycoside **9** in high yield.

Next, mechanistic studies of the present glycosylation were performed. When the single **9α** and **9β** were treated with **6c** without alcohol **8** under the same reaction conditions used for photo-induced glycosylation, no isomerization occurred, and **9α** and **9β** were recovered in high yields. These results indicate that α/β-stereoselectivity was determined by the reaction kinetics (Scheme 1A). Next, glycosylation of **1aα** and **8** was examined under the same reaction conditions to determine whether β-stereoselectivity occurred. Results showed that the reaction proceeded smoothly to provide **9** in 89% yield with β-stereoselectivity (α/β=27/73) (Scheme 1B). These results suggest that photo-induced glycosylation of **1a** and **8** proceeded mainly via an S_N2-like mechanism (Scheme 1C).

Next, the recovery and reusability of **6c** were examined. Results showed that 94% of **6c** could be recovered via column chromatography after glycosylation of **1aβ** and **8**, and could be reused without any loss of efficiency, producing **9** in 82% yield with the same α/β-stereoselectivity (α/β=70/30).

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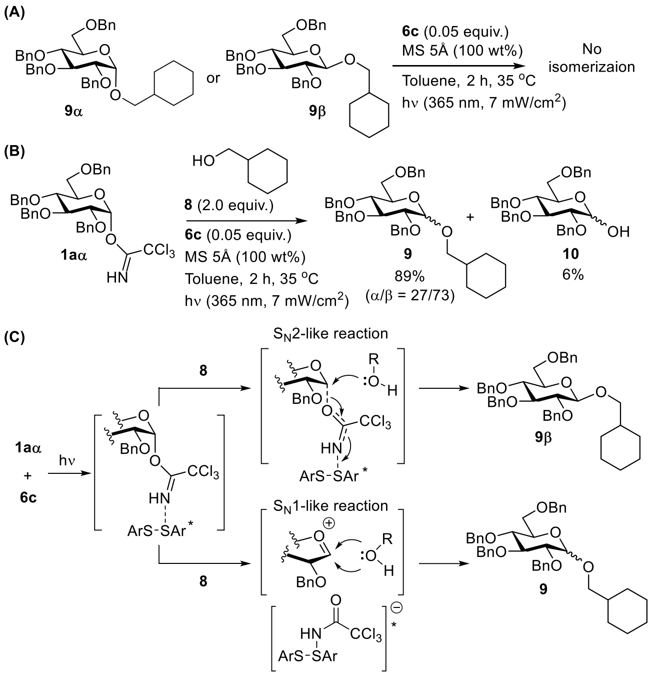


Scheme 1. (A) Mechanistic study of the glycosylation. (B) Photo-induced glycosylation of **1aα** and **8** using **6c**. (C) Proposed mechanism of photo-induced glycosylation of **1aα** and **8** using **6c**.

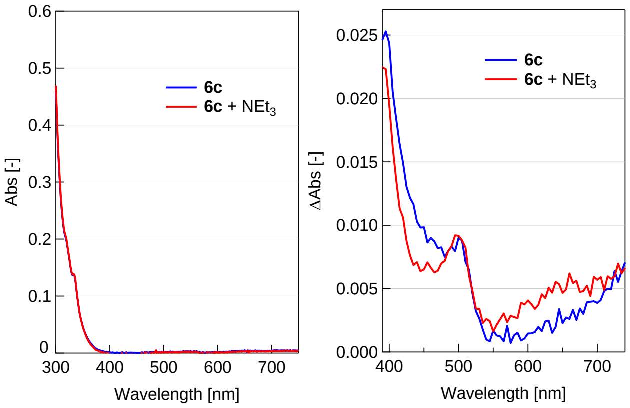
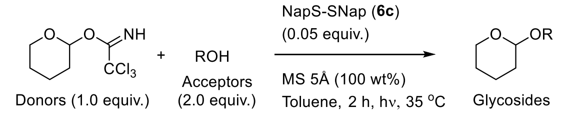
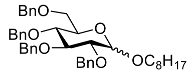
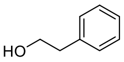
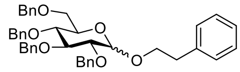
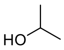
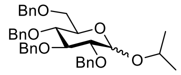
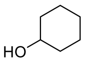
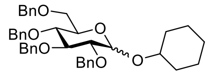
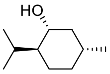
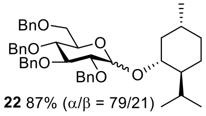
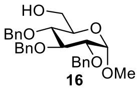
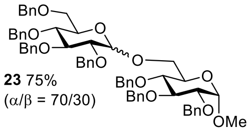
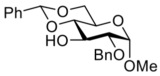
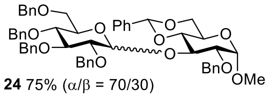
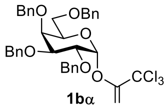
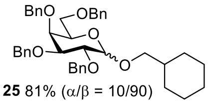
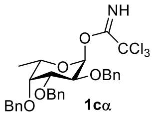
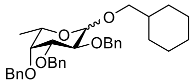
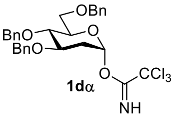
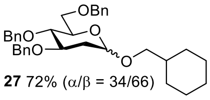
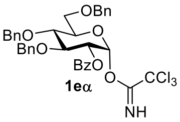
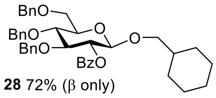
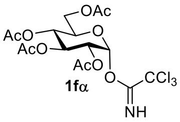
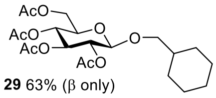


Fig. 2. (A) UV/Vis spectra of **6c** (500 μM) without and with NEt_3 (50 mM) in toluene. (B) The excited absorption spectra (355 nm, 3.1 mJ) of **6c** (500 μM) without and with NEt_3 (50 mM) in toluene at 14 μs.

These results indicated that **6c** did not decompose through radical or non-radical reactions under the photo-irradiation conditions used for the present glycosylation. Furthermore, the reaction mixture did not require neutralization or product extraction after reaction was complete, because turning off the UV light switch rendered the reaction mixture nearly neutral. Evaporation of the reaction solvent (toluene) was the only operation needed for work-up, and the solvent could be reused.

Table 2 Photo-induced glycosylations of several donors and acceptors using a catalytic amount of **6c**.



Entry	Donor	Acceptor	Glycoside (α/β)[1]
1	**1aβ**	HOC_8H_{17} **11**	 **18** 86% (α/β = 75/25)
2	**1aβ**	 **12**	 **19** 84% (α/β = 76/24)
3	**1aβ**	 **13**	 **20** 87% (α/β = 79/21)
4	**1aβ**	 **14**	 **21** 91% (α/β = 76/24)
5	**1aβ**	 **15**	 **22** 87% (α/β = 79/21)
6	**1aβ**	 **16**	 **23** 75% (α/β = 70/30)
7	**1aβ**	 **17**	 **24** 75% (α/β = 70/30)
8	 **1bα**	**8**	 **25** 81% (α/β = 10/90)
9	 **1cα**	**8**	 **26** 93% (α/β = 10/90)
10	 **1dα**	**8**	 **27** 72% (α/β = 34/66)
11	 **1eα**	**8**	 **28** 72% (β only)
12[2]	 **1fα**	**8**	 **29** 63% (β only)

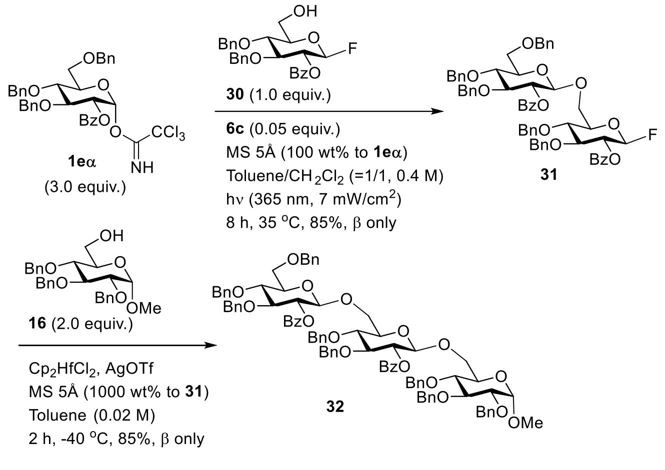
[1] The α/β ratios were determined by ^{1}H-NMR analysis.
[2] The reaction time was 6 h.

Next, to confirm the Lewis acidity of **6c** upon photo-irradiation, ground and excited state absorption measurements of **6c** in the absence and presence of NEt_3 in toluene were obtained. Results showed that the ground state absorption spectrum of **6c** in toluene was unaffected by addition of an excess of NEt_3 as shown in Fig. 2A, suggesting no additional structural formation derived from the dimeric units, (*i.e.*, charge-transfer complex). Next, to examine the excited-state dynamics, nanosecond transient absorption (nsTA) was measured for **6c** dissolved in toluene with and without NEt_3

upon excitation at 355 nm. The nsTA spectra in the absence of NEt_3 (*i.e.*, pristine **6c**) contained broad absorption bands in the range from *ca*. 390 to 500 nm containing the typical triplet-triplet absorption of naphthalene units.[10] In contrast, when NEt_3 (50 mM) was added to **6c**, the bands from 390 to 500 nm decreased, and new bands around 550 to 700 nm clearly appeared (Fig. 2B). These results suggest the Lewis acidity of **6c** under photo-irradiation, resulting in effective formation of complex **6c**-NEt_3.

Next, the generality of the glycosylation method was examined using alcohols **11–17** including secondary alcohols (Table 2). In all cases, glycosylation with **1aβ** using **6c** under photo-irradiation proceeded smoothly to give the corresponding glycosides **18–24** in good to high yields with moderate α-stereoselectivities (entries 1–7). Next, the effect of the type of glycosyl donor was investigated. When α-galactosyl and α-fucosyl trichloroacetimidates **1bα** and **1cα** were used, glycosylations of **8** using **6c** under photo-irradiation proceeded smoothly to give the corresponding glycosides **25** and **26** in high yields with high β-stereoselectivities (entries 8 and 9). In addition, β-stereoselectivity with good yield was observed, even when 2-deoxy-α-glucosyl trichloroacetimidate **1dα** was used (entry 10). Next, to overcome the moderate α/β-stereoselectivity, neighboring-group-assisted glycosylation using **1eα**, which possesses a Bz group at the C2-position, was examined. Results showed that the reaction also proceeded to provide the corresponding β-glycoside **28** in high yield with complete stereoselectivity (entry 11). In addition, when disarmed peracetylated glycosyl donor **1fα** was used, although longer reaction time was required, desired β-glycoside **29** was obtained in 63% yield with complete stereoselectivity (entry 12).

Finally, the present method was applied to the synthesis of trisaccharide **32**. Initially, photo-induced and chemoselective glycosylation of glycosyl fluoride **30** with **1eα** using **6c** with photo-irradiation proceeded effectively to provide **31** in 85% yield with complete β-stereoselectivity. In addition, a second glycosylation of **31** and **16** using Cp_2HfCl_2-AgOTf[11] provided **32** effectively in 85% yield as a single isomer.



Scheme 2. Synthesis of trisaccharide **32** using the present photo-induced glycosylation of **1eα** and **30**.

Conclusions

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DOI: 10.1039/C9OB02674F

In conclusion, a novel photo-induced glycosylation method using a trichloroacetimidate donor and diaryldisulfide **6c** as an organo-Lewis photoacid catalyst was developed. The photo-induced glycosylations of several trichloroacetimidate donors and alcohols in the presence of **6c** with photo-irradiation proceeded effectively under mild conditions to provide the corresponding glycosides in good to high yields. In addition, **6c** could be recovered and reused without any loss of efficiency. Furthermore, the ground and excited state absorption spectra of **6c** with or without NEt_3 in toluene suggested that **6c** possessed Lewis acidity and promoted formation of complex **6c**-NEt_3 upon photo-irradiation. This useful and environmentally benign glycosylation method should find various applications in the synthesis of not only biologically active compounds but also highly functional molecules.

Conflicts of interest

There are no conflicts to declare.

Notes and references

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