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Direct C−H Trifluoromethylation of Glycals by Photoredox Catalysis

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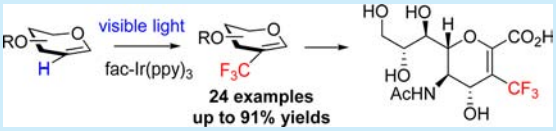
Supporting Information

ABSTRACT: A mild, efficient, and practical transformation for the direct C−H trifluoromethylation of glycals under visible light has been reported for the first time. This reaction employed fac-$Ir^{3+}(ppy)_3$ as the photocatalyst, Umemoto's reagent as the CF_3 source, and a household blue LED or sunlight as the light source. Glycals bearing both electron-withdrawing and -donating protective groups performed this reaction smoothly. This visible light-mediated trifluoromethylation reaction was highlighted by the trifluoromethylation of the biologically important Neu2en moiety.



Glycans play crucial roles in a variety of physiological and pathological processes.[1] Carbohydrate-based drug discovery is a subject of current interest and challenge. Some carbohydrate-based drugs and vaccines have been used to battle infectious diseases, diabetes, and other diseases.[2] Modifications are powerful strategies for reducing hydrophilicity and improving the affinity, oral bioavailability, and metabolic stability of native carbohydrates in the realm of carbohydrate-based drug discovery.[3] Due to the unique properties of the fluorine atom, the incorporation of fluorine into carbohydrates has become one of the most important modification approaches to address such issues.[3,4]

Trifluoromethyl (CF_3) is a useful structural motif in many bioactive molecules and a privileged group in medicinal chemistry, owing to the unique properties of CF_3 functionality on organic molecules, including lipophilicity, metabolic stability, high electronegativity, and bioavailability.[5] The development of new methodologies for the efficient introduction of a CF_3 group into organic compounds has been a hot topic in synthetic chemistry.[6] Especially, the photoredox-catalyzed[7] radical trifluoromethylation[8] has enabled many mild and efficient methods for trifluoromethylation of alkenes, (hetero)arenes, alkynes, phenol, and many other compounds.[9] Photoredox catalytic trifluoromethylation can be easily scaled-up using continuous flow technology, making the process more environmentally benign.[9b] Nonetheless, no general protocols for the modification of carbohydrates have emerged from those research efforts.[10]

In continuation of our interest in the area of carbohydrate synthesis and carbohydrate-based drug discovery,[11] we have now developed a method for the trifluoromethylation of glycals. Glycals are versatile building blocks for the construction of oligosaccharides and glycoconjugates, as well as other bioactive natural products or their derivatives.[12] Glycals or their derivatives have also been used as inhibitors or probes for glycosidases[13] such as the antiflu drugs Zanamivir,[14] Ianinamivir,[15] and Oseltamivir[16] (Figure 1). In fact, most glycals usually need to be modified to gain better biological functions. However, the modification of glycals has been a formidable challenge due to the structural complexity of carbohydrate substrates and the inactive electron-deficient double bond of glycals. Herein, we report a direct C−H trifluoromethylation of glycals using visible-light photoredox catalysis.

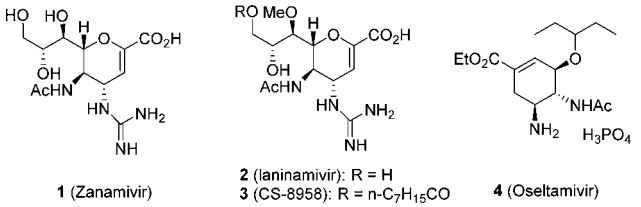


Figure 1. Glycal-derived drugs.

Our initial investigation of the reaction parameters was conducted using the less electron-deficient 6-*O*-benzyl-3,4-dideoxy-glycal **1a** as the substrate and a household blue LED as the light source (Table 1, and Table S1 in Supporting Information). We found that Togni reagent **2a**,[8f] Togni reagent **2b**, CF_3SO_2Na, CF_3SO_2Cl,[8j] or CF_3TMS was not an ideal CF_3 source (entries 1−5). However, the desired trifluoromethylated-3,4-dideoxy-glucal **3a** was obtained in good yield by the use of either Umemoto reagent **2c** (85%) or Umemoto reagent **2d** (80%) as the CF_3 source (entries 6−7). Different solvents were also tested (entries 8−12, Table S1), and anhydrous DMA was found to be the best choice (entry 13). Further screening of the ratio of reagents (entries 14−16), reaction time (Table S2), additives (Table S3), temperature (Table S4), and photocatalysts[7c] (entries 17−19) established the optimized conditions: fac-$Ir(ppy)_3$ (1.5 mol %) as catalyst and **2c** (1.5 equiv) as CF_3 source in DMA under the irradiation of visible light for 1.5 h at room temperature (entry 13, 91%). Control experiments showed that both light and the photocatalyst were essential for the reaction (entries 20−21).

Under the optimized reaction conditions, the scope of 3,4-dideoxy-glycal (**1b**−**e**) with different protective groups was

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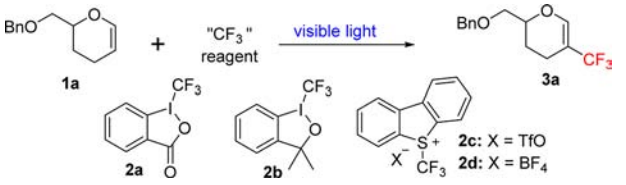
Table 1. Trifluoromethylation of 1a via Photoredox Catalysis[a]

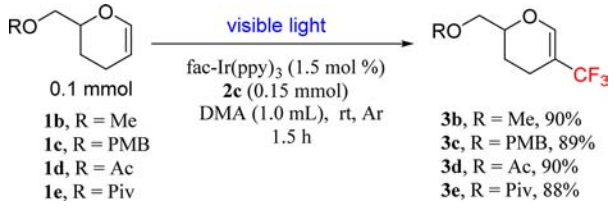


entry	"CF_3" reagent	solvent	catalyst	yield [%][b]
1	**2a**	DMF	fac-Ir(ppy)$_3$	trace
2	**2b**	DMF	fac-Ir(ppy)$_3$	trace
3	CF_3SO_2Na	DMF	fac-Ir(ppy)$_3$	0
4	CF_3SO_2Cl	DMF	fac-Ir(ppy)$_3$	0
5	CF_3TMS	DMF	fac-Ir(ppy)$_3$	0
6	**2c**	DMF	fac-Ir(ppy)$_3$	85
7	**2d**	DMF	fac-Ir(ppy)$_3$	80
8	**2c**	CH_3CN	fac-Ir(ppy)$_3$	0
9	**2c**	Et_2O	fac-Ir(ppy)$_3$	0
10	**2c**	DCM	fac-Ir(ppy)$_3$	0
11	**2c**	DMSO	fac-Ir(ppy)$_3$	71
12	**2c**	THF	fac-Ir(ppy)$_3$	0
13	**2c**	DMA	fac-Ir(ppy)$_3$	91
14	**2c** (1.2 equiv)	DMA	fac-Ir(ppy)$_3$	79
15	**2c** (2.0 equiv)	DMA	fac-Ir(ppy)$_3$	91
16	**2c** (5.0 equiv)	DMA	fac-Ir(ppy)$_3$	90
17	**2c**	DMA	Ru(bpy)$_3$Cl	79
18	**2c**	DMA	Ru(bpy)$_3$Cl·6H_2O	77
19	**2c**	DMA	Ru(bpy)$_3$(PF_6)$_2$	84
20	**2c**	DMA	–	0
21[c]	**2c**	DMA	fac-Ir(ppy)$_3$	0

[a]Reaction conditions: **1a** (0.10 mmol), "CF_3" reagent (0.15 mmol), photocatalyst (1.5 mol %), solvent (1.0 mL), under argon atmosphere, visible light, 1.5 h. [b]Yields determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. [c]In the dark.

surveyed, as shown in Scheme 1. To our delight, the reactions of the methylated (**1b**, 90%), *p*-methoxybenzylated (**1c**, 89%),

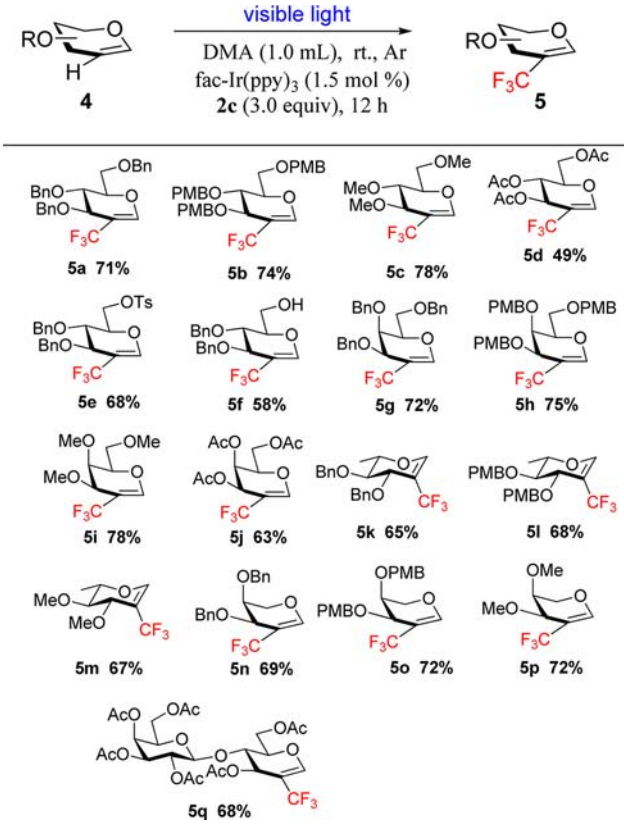
Scheme 1. Scope of Trifluoromethylation of Other Protected 3,4-Dideoxy-glucals



acetylated (**1d**, 90%), or pivaloylated (**1e**, 88%) 3,4-dideoxy-glycals were similar to that of **1a**. The desired products (**3b**–**e**) were obtained in high yields. The structures of the trifluoromethylated-3,4-dideoxy-glycals (**3b**–**e**) were unambiguously identified by ^1H, ^{13}C, and ^{19}F NMR analyses.

Subsequently, we proceeded to study the scope of the more electron-deficient and challenging hexose-derived glycals (Scheme 2). It was found that the most satisfactory yields were obtained by increasing **2c** to 3.0 equiv and the reaction time to 12 h (Table S5). Under the reoptimized conditions, the reactions of benzylated glucal/galactal/rhamnal/arabinal, and *p*-methoxybenzylated or methylated glucal/galactal/rhamnal/arabinal afforded the corresponding products in 65–78%

Scheme 2. Substrate Scope of Trifluoromethylation of Hexose-Derived Glycals[a]

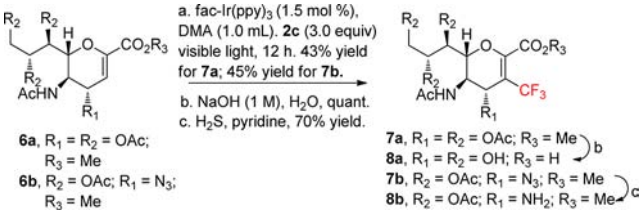


[a]Isolated yield.

yields. The tosyl-protected substrate (product **5e**, 68%) and the free hydroxyl-containing substrate (product **5f**, 58%) were tolerated under the standard conditions. Trifluoromethylation of the acetylated glucal (product **5d**, 49%) or acetylated galactal (product **5j**, 63%) gave the desired products in a lower yield, when compared with their benzylated, *p*-methoxybenzylated, methylated counterparts. This might result from the strong electron-withdrawing effect of the acetyl. An especially encouraging aspect of the chemistry was that the acetylated lactal could also be trifluoromethylated in good yield (product **5q**, 68%).

To further highlight the value of this transformation, the trifluoromethylation reactions of the most electron-deficient 2,3-unsaturated *N*-acetylneuraminic acid (Neu2en) derivatives were investigated (Scheme 3). Surprisingly, when the Neu5Ac2en substrate **6a** was treated under the standard conditions, the trifluoromethylated product **7a** was obtained in 43% isolated yield and the starting material **6a** was recovered in

Scheme 3. Photocatalytic C–H Trifluoromethylation of Neu2en Derivatives and Their Transformations



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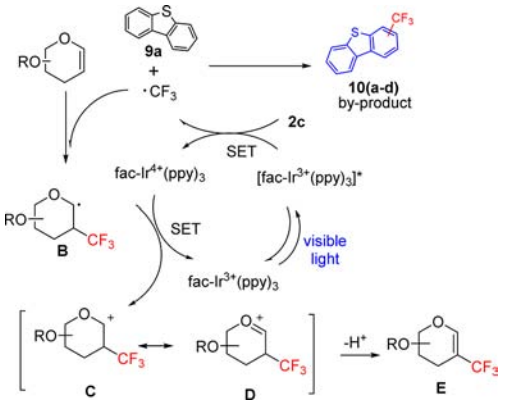
42% yield. Similarly, 2,3-unsaturated *N*-acetylneuraminic acid derivative **6b**, which is an important precursor of antiflu drug zanamivir, was successfully trifluoromethylated to give **7b** in 45% yield with 40% of **6b** recovered. Deprotection of **7a** and reduction of **7b** produced **8a** and **8b** in quantitative yield and 70% yield, respectively. These results showed that the trifluoromethyl group had little influence on functional group manipulations of the Neu2en moiety. Thus, it may have promising applications in the trifluoromethylation modification of Neu2en-derived drugs.

To gain insight into the reaction mechanism, a series of experiments were conducted under the standard conditions with **1a** and **2c** (see the Supporting Information for details). First, it was found that no reaction occurred in the absence of either light or photocatalyst, illustrating that light and the photocatalyst together triggered the trifluoromethylation reaction. Under the standard conditions, when **1a** was reacted with **2c**, product **3a**, trifluoromethylated dibenzothiophenes (**10**, comprising of four isomers **10a**–**d**), and dibenzothiophene (**9a**) were isolated in 91%, 11%, and 125% yield, respectively. The detection of **10a**–**d**, which is first reported in the trifluoromethylation reaction by the use of Umemoto's reagent as the CF_3 source, accounting for the excess of **2c**. The trifluoromethylation reaction of **1a** with **2c** was almost shut down by the addition of 2.0 equiv of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), a well-known radical scavenger, and TEMPO–CF_3[8n,17] was obtained in 120% yield based on ^{19}F NMR analysis, whereas the desired product **3a** was detected only in a trace amount (see the Supporting Information). This implied that a CF_3 radical intermediate was involved in the trifluoromethylation process. Moreover, the ethyl glycoside was isolated in 71% yield using ethyl alcohol as the cosolvent (Supporting Information), indicating a glycosylation process via a glycosyl oxocarbenium ion.

Based on these experimental results, a possible reaction mechanism is tentatively illustrated in Scheme 4. Initially, fac-

Scheme 4. Possible Reaction Mechanism



$Ir^{3+}(ppy)_3$ accepts a photon from the light source to form the excited state $[fac\text{-}Ir^{3+}(ppy)_3]^*$ via metal-to-ligand charge transfer (MLCT). This high-energy intermediate transfers a single electron to **2c** to generate the electron-deficient fac-$Ir^{4+}(ppy)_3$, CF_3 radical, and dibenzothiophene (**9a**). Addition of the CF_3 radical to the double bond of the glycal generates a glycosyl radical **B**, which would be oxidized by fac-$Ir^{4+}(ppy)_3$ to produce glycosyl oxocarbenium ion **C**, while returning fac-$Ir^{3+}(ppy)_3$ to the catalytic cycle. The subsequent deprotonation of **C** or **D** affords the desired product **E**. The formation of a small amount of trifluoromethylated dibenzothiophene might result from the free-radical aromatic substitution reaction of dibenzothiophene with the CF_3 radical.

In conclusion, a mild, efficient, and practical reaction for the direct C–H trifluoromethylation of glycals under visible light has been reported for the first time. This photocatalytic reaction employs fac-$Ir^{3+}(ppy)_3$ as the photocatalyst, Umemoto's reagent as the CF_3 source, and a household blue LED or sunlight (see the Supporting Information) as the light source. Glycals bearing both electron-withdrawing and -donating protective groups were shown to be suitable substrates for the reaction. This visible light-mediated trifluoromethylation transformation was further highlighted by the trifluoromethylation of the Neu2en moiety. The possible mechanism involves a CF_3 radical and a glycosyl oxocarbenium ion and was probed by a series of experiments. This novel protocol not only finds many applications in the synthesis of trifluoromethylated carbohydrates and carbohydrate-based drugs but also holds great potential in the trifluoromethylation of other electron-deficient compounds. Studies along this line are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03016.

Detailed experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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