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Blue Light Photocatalytic Glycosylation without Electrophilic Additives

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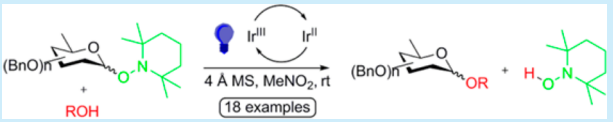
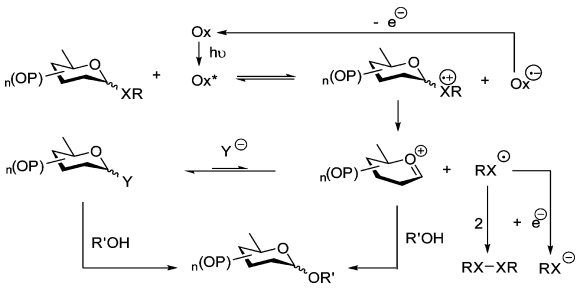
Supporting Information

ABSTRACT: Photocatalytic formation of glycosidic bonds employing stable and readily accessible *O*-glycosyl derivatives of 2,2,6,6-tetramethylpiperidin-1-ol is presented that employs an iridium-based photocatalyst and blue LEDs. The reaction proceeds at room temperature and in the absence of additives other than 4 Å molecular sieves. Stereoselectivities are modest but nevertheless dependent on the anomeric configuration of the donor, suggesting a substantial degree of concerted character.



Photostimulated glycosylation revolves around the notion of single electron transfer from a suitable electron-rich glycosyl donor to a photostimulated one-electron oxidant to give a radical cation−radical anion pair. In competition with back electron transfer, the radical cation expels a radical to give a glycosyl cation or oxocarbenium ion. The oxocarbenium ion is trapped directly either by the acceptor alcohol or by an anion present in the reaction mixture to form a reactive glycosylating species that undergoes reaction with the alcohol (Scheme 1), with the

Scheme 1. Photoglycosylation Concept



understanding that suitably protected systems may also engage in neighboring group participation. The expelled radical is typically considered to undergo degradation by radical−radical pathways such as dimerization. Alternatively, the expelled radical may suffer reduction by the radical anion resulting from the initial single electron transfer step, thereby rendering the process catalytic in the photostimulated oxidant, as envisaged by early workers in the field,[1] and now commonly called photocatalysis. A related concept is the homolytic scission of the anomeric C−S bond in thioglycosides on irradiation with UV light through quartz, followed by oxidation of the formed anomeric radical to the oxocarbenium ion with a stoichiometric oxidant.[2,3] Another approach is the use of photochemically stimulated strong acids with which to activate glycosyl donors through protonation and promote more conventional glycosylations.[4−6]

Noyori employed electron-rich aryl glycosides (Scheme 1, RX = ArO) and dicyanobenzene as the photostimulated oxidant by irradiation with a 200 W Hg lamp,[1] whereas subsequent work focused on the more readily oxidized thio- and selenoglycosides, with the use of charged photosensitizers to minimize back electron transfer,[7] irradiation in the visible range of wavelengths,[4,8] or both.[9] More recently, a number of photocatalytic methods employing visible-light-stimulated transition metal complex-based photo-oxidants and thio- or selenoglycosides have been described.[3,10−14] These latter processes employ readily available LEDs emitting visible light and offer broad functional group compatibility. Nevertheless, it is apparent that the simple photocatalytic mechanism envisaged by Noyori[1] is not operative in most of these cases and that potent electrophilic species, either generated in situ or added in stoichiometric fashion, contribute to the activation of the glycosyl donor.[3,10−14] Consequently, we were attracted by recent work on the photocatalytic generation of simple tertiary alkyl, allyl, and benzyl cations from sterically hindered *O*-alkyl hydroxylamines that proceeds in the absence of stoichiometric additives in which the photocatalytic cycle is closed by reduction of the expelled nitroxyl radical (Scheme 2, R = *t*-Alkyl).[15]

Encouraged by application of the process to *O*-tetrahydrofuranyl 2,2,6,6-tetramethylpiperidinoxide,[15] we considered that this process might be adapted to photocatalytic glycosylation through the use of *O*-glycosyl 2,2,6,6-tetramethylpiperidinoxides[16,17] as donors if the highly destabilizing effect of adjacent C−O bonds on cations[18] and oxocarbenium ions[19−23] could be overcome. Here, we report the successful reduction of this concept of LED-energized photocatalytic glycosylation in the absence of added electrophiles to practice employing *O*-glycosyl 2,2,6,6-tetramethylpiperidinoxides (Scheme 2, R = glycosyl).

Three α-glycopyranosyl fluorides **1**−**3** were prepared according to literature methods,[24−26] whereas **4** was accessed by hydrolysis of phenyl 2-azido-2-deoxy-3,4,6-tri-*O*-benzyl β-D-

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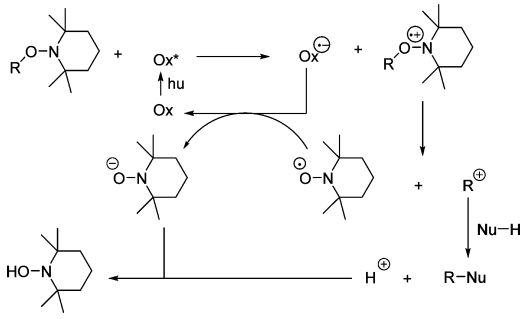
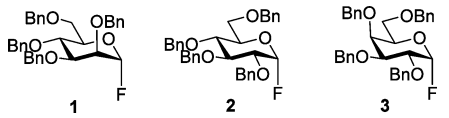
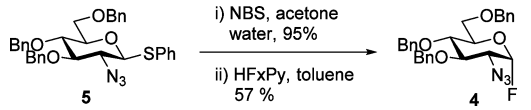
Scheme 2. Photocatalytic Cation Generation from Tempol Ethers and Tempol Glycosides





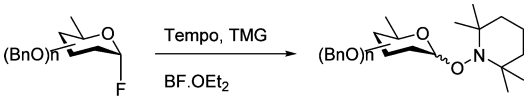
thioglucopyranoside **5** to the corresponding hemiacetal followed by treatment with HF·pyridine according to the method of Noyori et al. (Scheme 3).[27]

Scheme 3. Synthesis of Glycosyl Fluoride 4



Glycosyl fluorides **1**–**4** were then coupled to the persistent radical Tempo with activation by $BF_3{\cdot}OEt_2$ in acetonitrile at room temperature in the presence of tetramethylguanidine following the method of Sato.[17] Manno-configured donor **1** gave a single α-glycoside **6**, whereas gluco- and galacto-configured glycosyl fluorides **2**–**4** afforded separable α,β mixtures of the corresponding glycosides **7**–**9** (Table 1) by a reaction whose mechanism remains to be clarified.

Table 1. Synthesis of Tempol Glycosides



entry	glycosyl fluorides	tempol glycosides (yield, %)
1	**1**	**6α** (64) and **6β** (0)
2	**2**	**7α** (38) and **7β** (37)
3	**3**	**8α** (41) and **8β** (30)
4	**4**	**9α** (22) and **9β** (63)

Adapting the method of Knowles,[15] we photolyzed 0.1 M nitromethane solutions of the various Tempol glycosides with blue LEDs through Pyrex at room temperature in the presence of powdered 4 Å MS, 5 mol % of iridium photocatalyst **10**,[15] and the model acceptor alcohols **11**–**13**, monitoring with TLC or ESI MS.

Catalyst **10** was selected for this study as the optimum system in the Knowles work[15] on tertiary cation generation. Similarly, nitromethane was chosen as solvent by extrapolation from that study;[15] indeed, a brief investigation of acetonitrile as solvent revealed it to be far inferior. This preliminary investigation was limited to the use of Tempol derivatives following Knowles,[15] but it is recognized that other hydroxylamine derivatives may eventually prove advantageous. Blank reactions conducted in the dark or by photolysis in the absence of **10** did not proceed and indicated the need for **10** and its photolytic activation. Experiments conducted in the absence of molecular sieves were marred by formation of significant amounts of the hydrolyzed donor (hemiacetals) but also proceeded significantly more slowly, suggesting involvement of the sieves in the reaction mechanism.

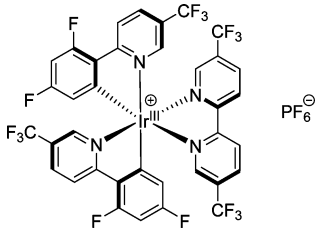


Table 2 reveals that good to excellent yields were obtained in all couplings conducted in this survey, with only modest differences in yield observed between the α- and β-anomers of a particular donor (compare Table 2, entries 4, 6, and 8 with 5, 7, and 9; and entries 10, 12, and 14 with 11, 13, and 15). Although the anomeric selectivity of the coupling reactions is modest, it is reproducibly a function of the anomeric configuration of the donor (compare Table 2, entries 4, 6, and 8 with 5, 7, and 9; and entries 10, 12, and 14 with 11, 13, and 15). Greater differences in selectivity between the two anomers of a given donor are observed with the more reactive cyclohexanol, which was additionally used in greater excess, and with the primary acceptor **12**, than with the less reactive secondary acceptor **13**. The implication is that glycosylation proceeds at least in part in a concerted manner in which displacement of the Tempo radical from the oxidatively activated donor is coupled with attack by the incoming acceptor. Such a concerted process can be interpreted as either a direct attack on the activated donor or an attack on the initially formed radical ion triplet before diffusive equilibration (Scheme 4). There is a steadily increasing body of kinetic evidence[28−37] that a variety of stereoselective glycosylation reactions proceed by associative reaction pathways rather than by dissociatively free glycosyl oxocarbenium ions that have only been observed in super acidic media.[22,23,38,39] In such classical glycosylation reactions, the associative pathways are more prevalent with more reactive acceptor alcohols,[40−43] consistent with the observed pattern in Table 2. The hexafluorophosphate counterion is not considered to intervene directly in the reaction mechanism except for providing charge stabilization consistent with studies on the influence of a variety of counterions on the stereoselectivity of glycosylation reactions.[38,44] The part of the reaction manifold that affords substitution with overall retention of configuration is best interpreted as taking place via solvent-separated ion triplets rather than via equilibration of the donor configuration followed by concerted displacement, as no evidence was found for donor anomerization in these reactions. The root cause of the observed acceleration of reaction rate by the 4 Å MS is presumably associated with their basic character[45] and the relative acidity[46] of the hydroxylamine Tempol.

In summary, a new photocatalytic glycosylation method is presented that functions under irradiation through Pyrex by blue LEDs and in the absence of additives other than **10** and 4 Å MS. The method uses stable and readily accessible Tempol glycosides as donors and neither requires nor generates in situ any strongly

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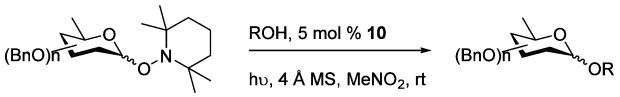
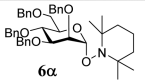
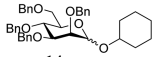
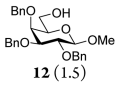
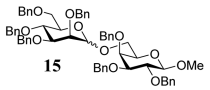
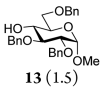
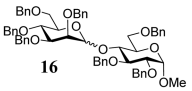
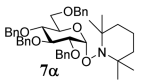
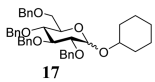
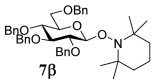
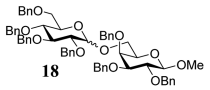
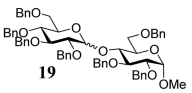
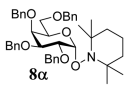
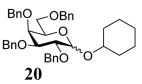
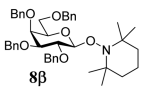
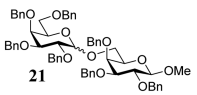
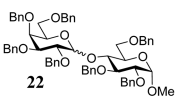
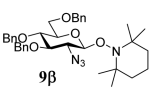
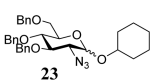
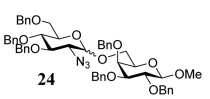
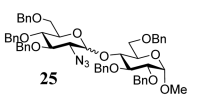
Table 2. Photoglycosylation of Alcohols with Donors 6–9 and Catalytic 10



6 - 9 **14 - 25**

entry	donor	acceptor (equiv)	photolysis time (h)	product	yield, %[a] α:β-ratio[b]
1	 **6α**	 **11** (3)	36	 **14**	80, 1.3:1
2	**6α**	 **12** (1.5)	48	 **15**	62, 1.5:1
3	**6α**	 **13** (1.5)	60	 **16**	64, 1:1
4	 **7α**	**11** (3)	36	 **17**	96, 1:2.5
5	 **7β**	**11** (5)	36	**17**	91, 1.2:1
6	**7α**	**12** (1.5)	48	 **18**	88, 1:1
7	**7β**	**12** (1.5)	48	**18**	79, 1.3:1
8	**7α**	**13** (1.5)	48	 **19**	69, 1.3:1
9	**7β**	**13** (1.5)	48	**19**	63, 1.6:1
10	 **8α**	**11** (3)	36	 **20**	95, 1:1.6
11	 **8β**	**11** (3)	36	**20**	87, 1.6:1
12	**8α**	**12** (1.5)	48	 **21**	82, 1.2:1
13	**8β**	**12** (1.5)	48	**21**	75, 1.4:1
14	**8α**	**13** (1.5)	48	 **22**	77, 1.6:1
15	**8β**	**13** (1.5)	48	**22**	59, 1.6:1
16	 **9β**	**11** (3)	36	 **23**	86, 1.8:1
17	**9β**	**12** (1.5)	72	 **24**	61, 1.4:1
18	**9β**	**13** (1.5)	60	 **25**	57, 2:1

[a]Combined yield of the isolated anomers. [b]Anomeric ratios were determined by integration of the ^{1}H NMR spectra of the crude photolysates before purification.

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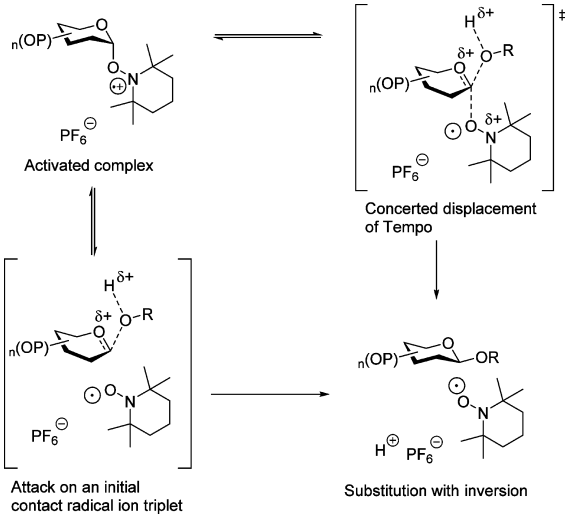
Scheme 4. Concerted and Radical Ion Triplet Mechanisms for Glycosylation



electrophilic agents. Further work expanding the scope and selectivity of this novel glycosylation is underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00932.

Full experimental details and ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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