

# Visible Light-Mediated Oxidative Debenzylation

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**ABSTRACT:** Protecting groups are key in the synthesis of complex molecules such as carbohydrates to distinguish functional groups of similar reactivity. The harsh conditions required to cleave stable benzyl ether protective groups are not compatible with many other protective and functional groups. The mild, visible light-mediated debenzylation disclosed here renders benzyl ethers orthogonal protective groups. Key to success is the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as stoichiometric or catalytic photooxidant such that benzyl ethers can be cleaved in the presence of azides, alkenes, and alkynes. The reaction time for this transformation can be reduced from hours to minutes in continuous flow.

The synthesis of complex molecules such as biopolymers relies on protective groups to ensure chemo-, regio- and stereoselectivity.<sup>1</sup> Protecting groups are of central importance to carbohydrate construction where a host of hydroxyl groups has to be masked. Installation and selective removal are the basis for orthogonal protecting group strategies that are key to the synthesis of well-defined oligosaccharides.<sup>2-4</sup> Benzyl ethers are stable to a wide range of conditions making them an ideal protecting group that is removed only at the very end of the synthesis.<sup>1</sup> For this very reason, however, benzyl ether cleavage requires harsh reduction/oxidation processes, such as catalytic hydrogenolysis, Birch reduction, or oxidation with ozone or  $\text{BCl}_3$  that are incompatible with many functional groups<sup>1,5</sup> and hazardous.<sup>6-7</sup> Methods for the mild and selective cleavage of benzyl ethers would render them attractive orthogonal protective groups that would conceptually change the strategic approach towards the synthesis of complex glycans.

Compared to benzyl ethers, PMB ethers can be cleaved selectively using mild stoichiometric oxidants<sup>1, 8-10</sup> Photoredox catalysis was used to selectively cleave PMB ethers (Scheme 1a).<sup>11-13</sup> Benzyl ethers ( $E_{\text{Bn-O-Me}} = 2.20 \text{ V vs SCE}$ )<sup>14</sup> have a significantly higher oxidation potential compared to PMB ethers ( $E_{\text{PMB-O-Me}} = 1.60 \text{ V vs SCE}$ )<sup>14</sup> and are stable during the photocatalytic PMB cleavage.<sup>11-13</sup>

A photocatalyst (PC) with a sufficiently strong oxidizing excited state could facilitate oxidative cleavage of benzyl ethers with high functional group tolerance (Scheme 1b). In order to reduce this concept to practice, a suitable PC, H-atom acceptor, and terminal oxidant had to be identified using the debenzylation of C(3)-benzyl-tetraacetylglucose (**1a**) as model reaction. Initial efforts with common photocatalysts were not successful. A combination of 4 mol% 9-mesityl-10-methylacridinium as PC and 5.0 equiv.  $\text{CBr}_4$ , for example, was capable of hydrolyzing the benzyl ether, but concomitant product degradation resulted in low yields (Table S2).

## Scheme 1. Visible light mediated oxidative deprotection strategies of PMB and benzyl ethers.

a) photocatalytic deprotection of PMB ethers (ref. 11)

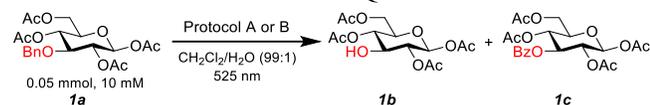


b) this work: selective photocatalytic deprotection of benzyl ethers



Full conversion of the starting material and excellent selectivity towards the desired product (**1b**) was achieved using stoichiometric amounts of DDQ ( $E_{\text{DDQ}^*/\text{DDQ}} = 3.18 \text{ V vs SCE}$ )<sup>15</sup> and green light irradiation (525 nm) in wet dichloromethane (Table 1, entry 1). In contrast to photochemical PMB deprotection,<sup>11-13</sup> an additional H-atom acceptor is not required, as the single electron transfer oxidation and the hydrogen abstraction are executed by DDQ upon irradiation.<sup>16</sup> The irradiation source is crucial for achieving high selectivity. Shorter wavelengths (440 nm) result in the formation of significant amounts of the corresponding benzoyl ester **1c** (Entry 2). The cleavage of benzyl ethers using simple substrates was previously reported using stoichiometric amounts of DDQ under UV irradiation, but suffered from low functional group compatibility.<sup>17</sup>

**Table 1.** Optimized conditions and control experiments for the visible light-mediated oxidative debenzoylation using catalytic and stoichiometric amounts of DDQ.<sup>a</sup>

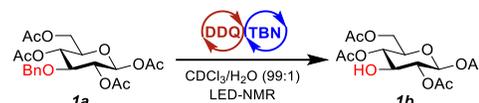


		entry	variation	time	1a [%] <sup>b</sup>	1b [%] <sup>b</sup>	1c [%] <sup>b</sup>
	O <sub>2</sub> -free	1	none	30 min	n.d. <sup>c</sup>	96	<2
		2	440 nm	10 min	n.d.	78	16
		3	no light	24 h	99	n.d.	n.d.
	air	4	none	2 h	n.d.	97	<2
		5	440 nm	30 min	n.d.	87	11
		6	no light	2 h	98	<2	n.d.
		7	no DDQ	2 h	100	n.d.	n.d.
		8	no TBN	2 h	77	23	n.d.
		9	degassed	2 h	57	40	<2

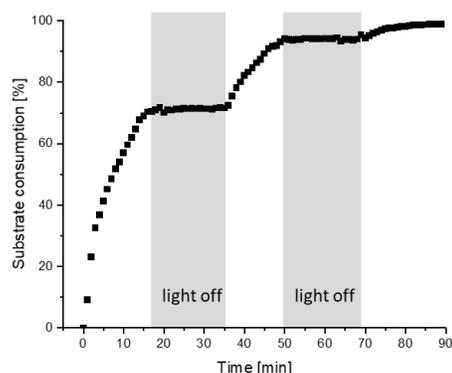
<sup>a</sup>Reaction conditions: **1a** (50 μmol), DDQ (Protocol A: 75 μmol, Protocol B: 12.5 μmol), TBN (Protocol B: 12.5 μmol), CH<sub>2</sub>Cl<sub>2</sub> (5 mL), H<sub>2</sub>O (50 μL), 525 nm irradiation at rt. <sup>b</sup>Determined by <sup>1</sup>H-NMR using maleic acid as internal standard. <sup>c</sup>not detected.

To avoid the tedious separation of the stoichiometric byproduct 2,3-dichloro-5,6-dicyano-1,4-hydroquinone (DDQH<sub>2</sub>), we ultimately developed a catalytic protocol using DDQ (25 mol%), *tert*-butyl nitrite (TBN, 25 mol%) as co-catalyst and air as terminal oxidant (Table 1, entry 4).<sup>18-25</sup> The nitrite thermally or photochemically releases NO that is oxidized by O<sub>2</sub> to NO<sub>2</sub> and re-oxidizes DDQH<sub>2</sub> to DDQ.<sup>16</sup> Similar to the protocol with stoichiometric amounts of DDQ, lower selectivities were observed at shorter wavelengths (entry 5). Control studies confirmed that photons and DDQ are necessary for productive catalysis (entry 3, 6 & 7). Monitoring the reaction using a LED-NMR setup supported that the reaction ceases upon light source removal (Figure 2, a).<sup>26</sup> When DDQ is used in catalytic amounts and no TBN is added, the reaction stops after one turnover (Table 1, entry 8). Late addition of TBN can restore DDQ and the reaction proceeds smoothly until completion (Figure 2, b). Under anaerobic conditions, the reaction did not go to completion, confirming that O<sub>2</sub> is required (Table 1, entry 9). Both protocols were evaluated using carbohydrate building blocks that carry multiple protecting groups (Table 2). The protocol using catalytic amounts of DDQ (protocol B) was slightly modified (2 equiv. TBN) to avoid long reaction times. Substrates containing acetyl, isopropylidene and benzoyl protecting groups (**1a-4a**) were smoothly deprotected in less than 4 h using both protocols and isolated in excellent yield (84 – 96%). Thioethers that could potentially poison palladium catalysts during hydrogenolysis were unproblematic using both photooxidative protocols and no sulfoxide or sulfone side products were identified (**5a-11a**). Several common protecting groups do not survive a hydrogenolysis or Birch reduction, such as fluorenylmethoxycarbonyl (**6a**, **7a**, **8a**), levulinic ester **8a**), allyl carbonate (**9a**), and propargyl carbonate (**10a**), and benzylidene (**12a**) were well tolerated. Azides (**11a**), that are essential for biorthogonal labeling, are stable to photooxidative benzyl ether cleavage. 2-Naphtylmethyl ether (NAP, **12a**) is routinely removed using stoichiometric amounts of DDQ in the

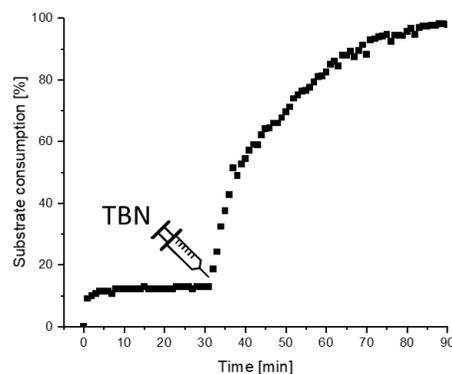
absence of light. The light mediated protocol using 25 mol% DDQ (protocol B) provides a valuable alternative to avoid stoichiometric amounts of organic oxidant. The benzyloxycarbonyl (Cbz) group was partially cleaved using stoichiometric amounts of DDQ (protocol A) resulting in a modest isolated yield of desired product **13b**. Using the catalytic method (protocol B), longer reaction times resulted in significant cleavage of the Cbz group (see the supporting information). Phenylselenenyl (**14a**) and *tert*-butyldimethylsilyl (TBS, **15a**)<sup>27</sup> groups are not stable under the conditions applied. Full deprotection of perbenzoylated glucose (**16a**) was not feasible and a complex mixture of partially protected derivatives precipitated during the reaction. The relatively long reaction times for some substrates are a major limitation, especially using the catalytic protocol. This is a result of the long wavelengths used, as DDQ only absorbs weakly above 450 nm (Figure S9). When a 440 nm irradiation source was applied, we observed significantly shorter reaction times but had severe selectivity issues due to over-oxidation and product degradation.



a) light on/off experiment

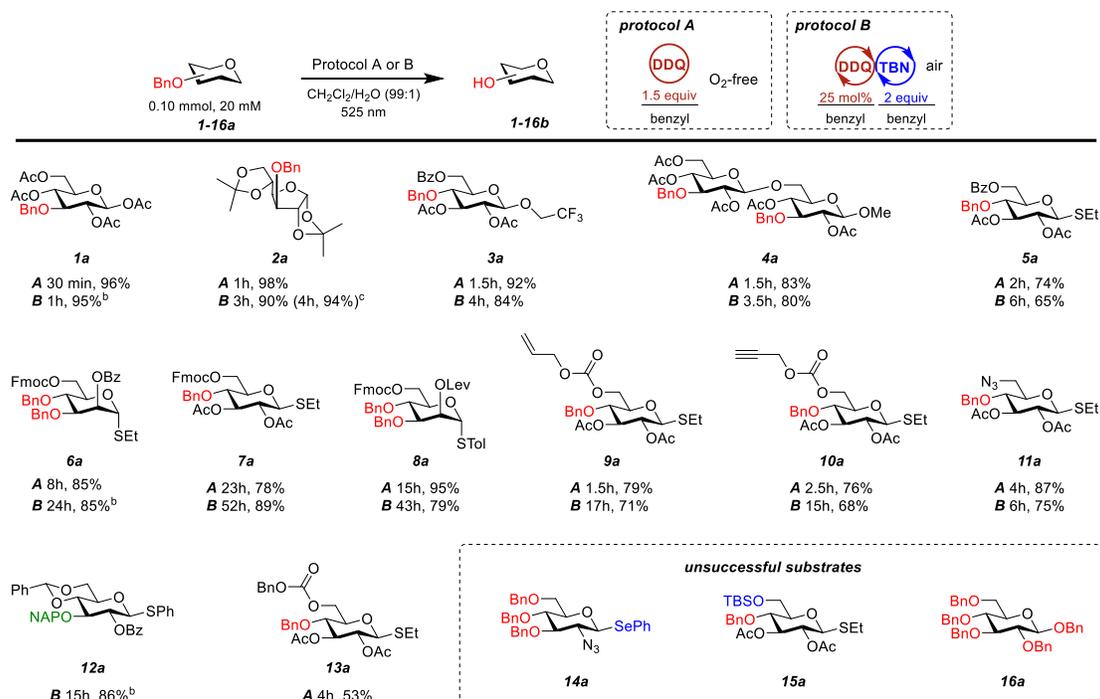


b) delayed TBN addition



**Figure 1.** *In situ* NMR studies using a LED-NMR setup. For experimental details, see the supporting information.

**Table 2.** Substrate scope and limitations for the visible light-mediated oxidative cleavage of benzyl ethers.<sup>a</sup>

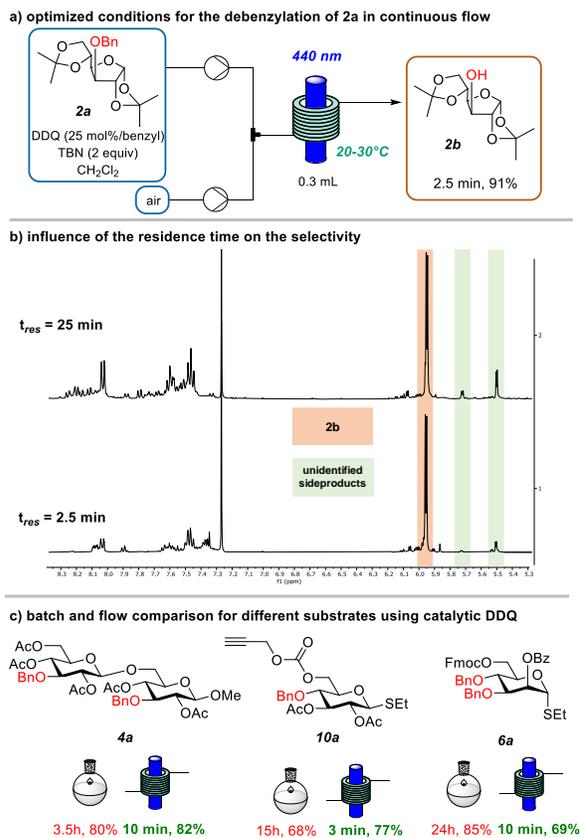


<sup>a</sup>Reaction conditions: benzyl ether (100 μmol), DDQ (protocol A: 150 μmol/benzyl, protocol B: 25 μmol/benzyl), TBN (protocol B, 200 μmol), CH<sub>2</sub>Cl<sub>2</sub> (5 mL), H<sub>2</sub>O (50 μL), 525nm irradiation at rt. <sup>b</sup>Reaction on 50 μmol scale. <sup>c</sup>Reaction on 1.5 mmol scale. Isolated yields are reported.

Slowing down a chemical reaction to avoid selectivity problems is a common strategy in batch. Continuous flow chemistry can help to overcome selectivity issues as it offers precise control over reaction time and better irradiation.<sup>28-29</sup> A two-feed setup introduced the homogeneous reaction mixture and air into the reactor unit, that consisted of FEP tubing (0.8 mm i.d.) and a 440 nm light source. A short optimization study using C(3)-benzyl-glucofuranose **2a** resulted in a significant reduction of the reaction time (2.5 min in flow at 440 nm versus 3 h in batch at 525 nm), while maintaining excellent selectivity (Figure 2a). An experiment using a longer residence time showed that selectivity issues indeed arise from prolonged reaction times at low wavelengths (Figure 2b)

The flow approach was subsequently tested for other substrates (Figure 2, c). The reaction time for the debenzilation of **2a** was significantly reduced to three minutes, while dibenzylated compounds **10a** and **6a** required ten minutes.

In conclusion, we developed a mild, photocatalytic debenzilation protocol that is significantly more functional group tolerant than traditional methods. The proper choice of the irradiation source is crucial for reaching high selectivities of benzyl ether cleavage in batch. Green light irradiation (525 nm) was superior over blue light (440 nm) in suppressing the formation of side products during batch reactions. A biphasic continuous flow system helped to reduce the reaction times. Precise control on the reaction time and efficient irradiation in flow enabled the use of 440 nm to significantly reduce reaction times while maintaining high selectivities. The photooxidative debenzilation overcomes current limitations of benzyl ethers as protecting group that arise from the harsh conditions necessary for their cleavage. The methodology enables the use of benzyl ethers as orthogonal protective group and is attractive for the development of new synthetic routes in glycan synthesis.



**Figure 2.** Visible light-mediated oxidative cleavage of benzyl ethers using a continuous flow system.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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