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Letter

Visible-Light-Mediated Oxidative Debenzylation Enables the Use of Benzyl Ethers as Temporary Protecting Groups

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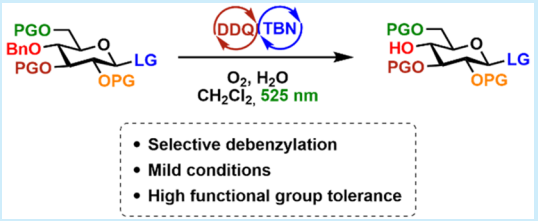
ABSTRACT: The cleavage of benzyl ethers by catalytic hydrogenolysis or Birch reduction suffers from poor functional group compatibility and limits their use as a protecting group. The visible-light-mediated debenzylation disclosed here renders benzyl ethers temporary protective groups, enabling new orthogonal protection strategies. Using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as a stoichiometric or catalytic photooxidant, benzyl ethers can be cleaved in the presence of azides, alkenes, and alkynes. The reaction time can be reduced from hours to minutes in continuous flow.

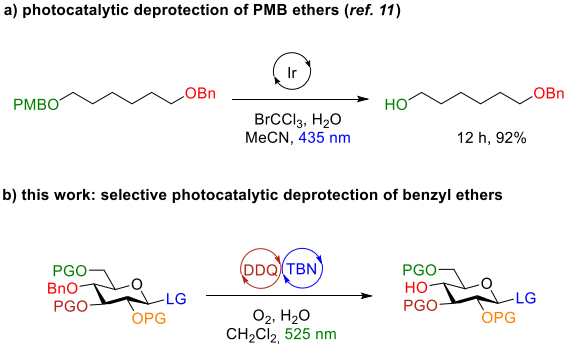


The synthesis of complex molecules such as biopolymers relies on protective groups to ensure chemo-, regio-, and stereoselectivity.[1] Protecting groups are of central importance to carbohydrate construction, where a host of hydroxyl groups have to be masked. Installation and selective removal are the basis for orthogonal protecting group strategies that are key to the synthesis of well-defined oligosaccharides.[2−4] Benzyl ethers are stable over a wide range of conditions, making them an ideal protecting group that is removed only at the very end of the synthesis.[1] For this very reason, however, benzyl ether cleavage requires harsh reduction/oxidation processes, such as catalytic hydrogenolysis, Birch reduction, or oxidation with ozone or BCl_3, which are incompatible with many functional groups[1,5] and are hazardous.[6,7] Methods for the mild and selective cleavage of benzyl ethers would render them attractive temporary protective groups that would conceptually change the strategic approach toward the synthesis of complex glycans.

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

A photocatalyst (PC) with a sufficiently strong oxidizing excited state could facilitate the oxidative cleavage of benzyl ethers with high functional group tolerance (Scheme 1b). To move this concept to practice, a suitable PC, H-atom acceptor, and terminal oxidant had to be identified using the debenzylation of C(3)-*O*-benzyl-tetraacetylglucoside (**1a**) as a model reaction. Initial efforts with common PCs were not successful. A combination of 4 mol % 9-mesityl-10-methylacridinium as the PC and 5.0 equiv of 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



Full conversion of the starting material and excellent selectivity toward the desired product (**1b**) were achieved using stoichiometric amounts of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) ($E^{3}_{DDQ^*/DDQ^{-\bullet}}$ = 3.18 V vs SCE[15]) and green-light irradiation (525 nm) in wet dichloromethane (Table 1, entry 1). In contrast with photochemical PMB deprotection,[11−13] an additional H-atom acceptor is not required, as the single electron transfer oxidation and the hydrogen abstraction are executed by DDQ upon irradiation.[16]

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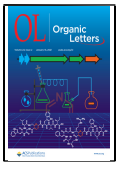
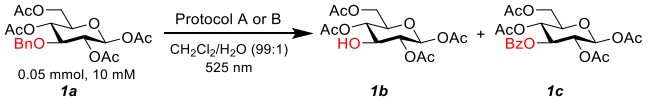


Table 1. Optimized Conditions and Control Experiments for the Visible-Light-Mediated Oxidative Debenzylation Using Catalytic and Stoichiometric Amounts of DDQ[a]



	entry	variation	time	1a [%][b]	1b [%][b]	1c [%][b]
DDQ, O_2-free, 1.5 equiv	1	none	30 min	n.d.[c]	96	<2
	2	440 nm	10 min	n.d.	78	16
	3	no light	24 h	99	n.d.	n.d.
DDQ, TBN, air, 25 mol% 25 mol%	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

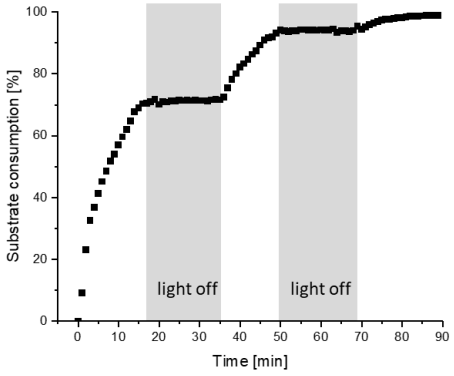
[a]Reaction conditions: **1a** (50 μmol), DDQ (Protocol A: 75 μmol, Protocol B: 12.5 μmol), TBN (Protocol B: 12.5 μmol), CH_2Cl_2 (5 mL), H_2O (50 μL), 525 nm irradiation at rt. [b]Determined by ^{1}H NMR using maleic acid as the internal standard. [c]Not detected.

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.[17]

To avoid the tedious separation of the stoichiometric byproduct 2,3-dichloro-5,6-dicyano-1,4-hydroquinone ($DDQH_2$), we ultimately developed a catalytic protocol using DDQ (25 mol %), *tert*-butyl nitrite (TBN, 25 mol %) as the cocatalyst, and air as the terminal oxidant (Table 1, entry 4).[18−25] The nitrite thermally or photochemically releases NO that is oxidized by O_2 to NO_2 and reoxidizes $DDQH_2$ to DDQ.[16] 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 (entries 3, 6, and 7). Monitoring the reaction using an LED-NMR setup supported the notion that the reaction ceases upon light source removal (Figure 1a).[26] When DDQ is used in catalytic amounts and no TBN is added, the reaction stops after one turnover (Table 1, entry 8). The late addition of TBN can restore DDQ, and the reaction smoothly proceeds until completion (Figure 1b). Under anaerobic conditions, the reaction did not go to completion, confirming that O_2 is required (Table 1, entry 9).

Both protocols were evaluated using carbohydrate substrates that carry multiple protecting groups (Scheme 2). The protocol using catalytic amounts of DDQ (protocol B) was slightly modified (2 equiv of TBN) to avoid long reaction times. Substrates containing acetyl, isopropylidine, and benzoyl protecting groups (**1a**−**4a**) were smoothly deprotected in <4 h using both protocols and were isolated in excellent yield (84−96%). Thioethers that could potentially poison palladium catalysts during hydrogenolysis were unproblematic using both

a) light on/off experiment



b) delayed TBN addition

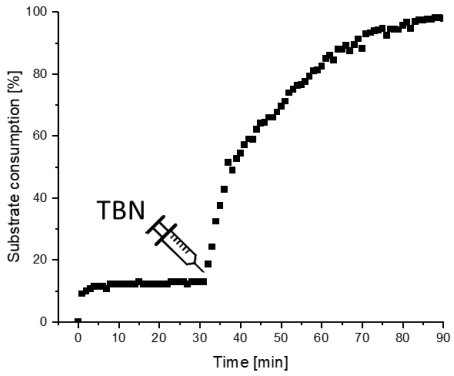


Figure 1. *In situ* NMR studies using an LED-NMR setup. For experimental details, see the Supporting Information.

photooxidative protocols, and no sulfoxide or sulfone side products were identified (**5a**−**11a**). Several common protecting groups that are not tolerated in hydrogenolysis or Birch reduction, such as fluorenylmethoxycarbonyl (**6a**, **7a**, **8a**), levulinic ester (**8a**), allyl carbonate (**9a**), propargyl carbonate (**10a**), and benzylidene (**12a**), were well tolerated. Azides (**11a**), which are essential for biorthogonal labeling, are stable to the 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 the desired product **13b**. Using the catalytic method (protocol B), longer reaction times resulted in significant cleavage of the Cbz group. (See the Supporting Information.) Phenylselenyl (**14a**) and *tert*-butyldimethylsilyl (TBS, **15a**)[27] groups are not stable under the conditions applied. Whereas the photocatalytic protocol enables the use of benzyl ethers as temporary protective groups, it is not the method of choice to globally deprotect carbohydrates. Full deprotection of perbenzylated glucose

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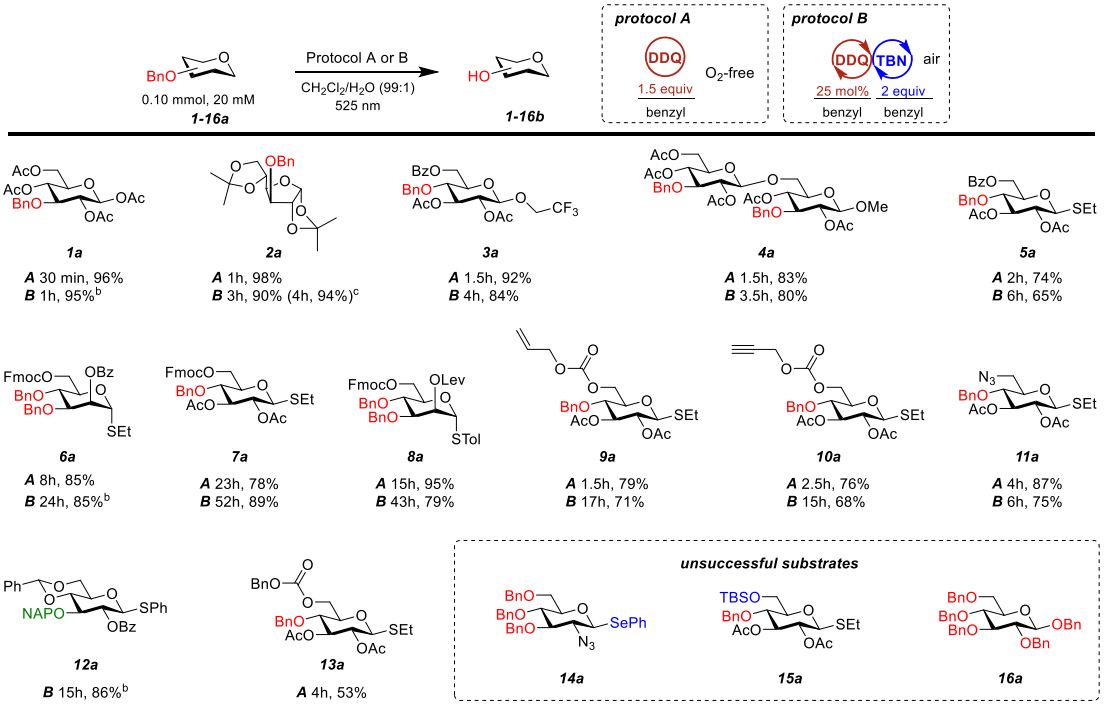
Scheme 2. Substrate Scope and Limitations for the Visible-Light-Mediated Oxidative Cleavage of Benzyl Ethers[a]



[a]Reaction conditions: benzyl ether (100 μmol), DDQ (protocol A: 150 μmol/benzyl, protocol B: 25 μmol/benzyl), TBN (protocol B, 200 μmol), CH_2Cl_2 (5 mL), H_2O (50 μL), 525 nm irradiation at rt. [b]Reaction on a 50 μmol scale. [c]Reaction on a 1.5 mmol scale. Isolated yields are reported.

(**16a**) was not feasible, and a complex mixture of partially deprotected 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 absorbs only 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 overoxidation and product degradation.

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 the reaction time and better irradiation.[28,29] A two-feed setup introduced the homogeneous reaction mixture and air into the reactor unit, which consisted of fluorinated ethylene propylene (FEP) tubing (0.8 mm i.d.) and a 440 nm light source. A short optimization study using C(3)-*O*-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 2c). The reaction time for the debenzylation of **10a** was significantly reduced to 3 min, whereas dibenzylated compounds **4a** and **6a** required 10 min.

In conclusion, we developed a mild, photocatalytic debenzylation protocol that is significantly more functional-group-tolerant than traditional methods. The proper choice of 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

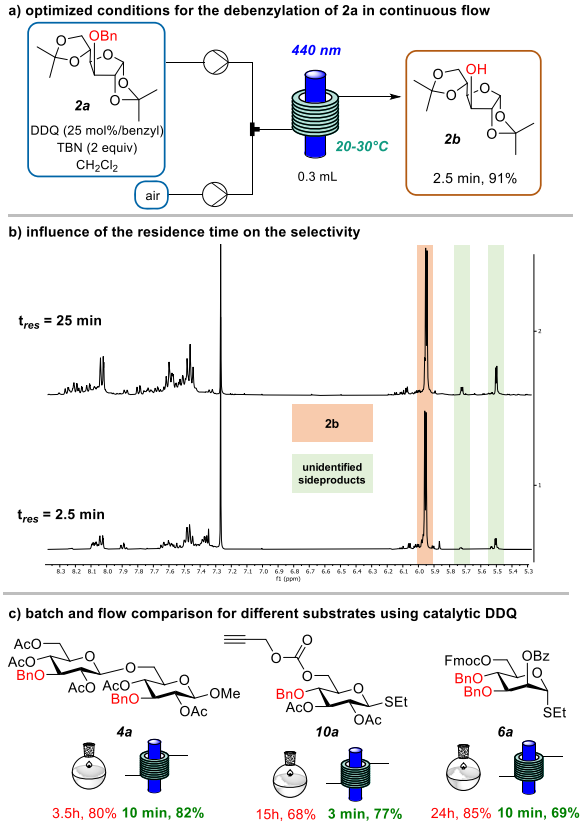


Figure 2. Visible-light-mediated oxidative cleavage of benzyl ethers using a continuous-flow system.

continuous-flow system helped to reduce the reaction times. Precise control of the reaction time and efficient irradiation in

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flow enabled the use of 440 nm to significantly reduce reaction times while maintaining high selectivities. The photooxidative debenzylation overcomes the current limitations of benzyl ethers as protecting groups that arise from the harsh conditions necessary for their cleavage. The methodology enables the use of benzyl ethers as a temporary protective group and is attractive for the development of new synthetic routes in glycan synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04026.

Detailed experimental procedures and characterization data for all compounds (PDF)

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Author Contributions

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

Notes

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The authors declare no competing financial interest.

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