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Chemoselective Oxidation of *p*-Methoxybenzyl Ethers by an Electronically Tuned Nitroxyl Radical Catalyst

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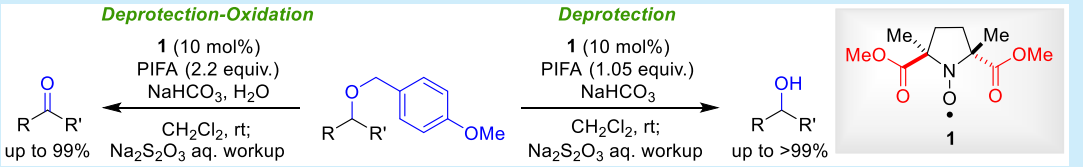


ABSTRACT: The oxidation of *p*-methoxy benzyl (PMB) ethers was achieved using nitroxyl radical catalyst **1**, which contains electron-withdrawing ester groups adjacent to the nitroxyl group. The oxidative deprotection of the PMB moieties on the hydroxy groups was observed upon treatment of **1** with 1 equiv of the co-oxidant phenyl iodonium bis(trifluoroacetate) (PIFA). The corresponding carbonyl compounds were obtained by treating the PMB-protected alcohols with **1** and an excess of PIFA.

Nitroxyl radicals such as 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO),[1] 2-azaadamantane *N*-oxyl (AZADO),[2] and their derivatives[3] have frequently been employed as organocatalysts for the oxidation of alcohols under safe and environmentally benign conditions. Generally, these catalysts selectively oxidize primary alcohols in the presence of secondary hydroxy groups by recognizing the steric environment of the substrates.[1,3e]

Most nitroxyl-radical-catalyzed alcohol oxidation reactions proceed via a nucleophilic addition of an oxygen atom of the hydroxy group to the oxoammonium cations (A), followed by proton abstraction (Figure 1).[1−3] We have previously

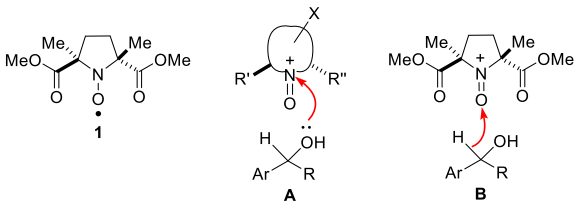
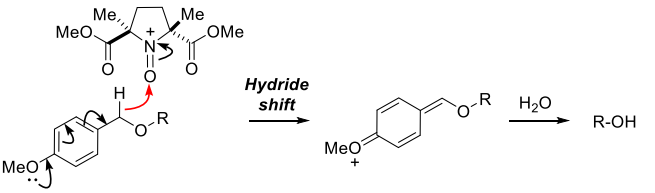


Figure 1. Nucleophilic addition of the oxygen atom (A) and hydride shift (B) as the key steps in the oxidation of benzylic alcohols with oxoammonium cations derived from the nitroxyl-type radical oxidation catalysts.

developed "electronically tuned" nitroxyl radical catalyst **1**, which contains electron-withdrawing ester groups adjacent to the nitroxyl group.[4] This catalyst oxidizes electron-rich benzylic alcohols much faster than electron-deficient ones, as the oxidation of benzylic alcohols by **1** proceeds via a rate-determining hydride transfer.[5] Owing to its unique oxidation mechanism as a nitroxyl radical catalyst, we envisaged that **1** might also be an effective oxidation catalyst for electron-rich benzylic ethers such as *p*-methoxybenzyl (PMB) ethers (Scheme 1).[6]

Scheme 1. Oxidation of PMB Ethers by Catalyst 1



The PMB group has been widely used as a protecting group for alcohols,[7] as it can be easily introduced via various methods[8] and removed using common oxidizing agents. For the oxidative deprotection of PMB ethers, stoichiometric amount of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[9] or more than 2 equiv of ceric ammonium nitrate (CAN)[10] are usually employed, although various other methods have been reported.[11] These common methods are not environmentally benign, as DDQ has the potential to liberate HCN and the deprotection by CAN requires more than 2 equiv of cerium, which is a rare-earth metal. Hence, the development of an environmentally benign and reliable method for the oxidative deprotection of PMB groups would be desirable.

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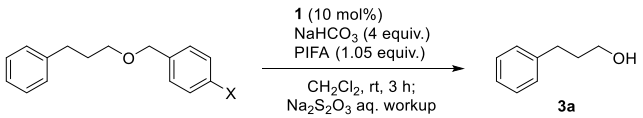
The direct oxidation of PMB-protected alcohols to carbonyl compounds is also a highly useful transformation, as it enables the one-step transformation of the protected alcohols into the corresponding aldehydes and ketones. So far, only a few reports regarding the direct transformation of PMB ethers into carbonyl compounds have been reported.[12] In addition, to the best of our knowledge, reports of the direct transformation of PMB-protected alcohols to carbonyl compounds at room temperature with good substrate generality remain elusive. Herein, we describe nitroxyl radical **1** catalyzed oxidative deprotection of PMB ethers, as well as the direct oxidation of PMB ethers into carbonyl compounds via alcohols (Scheme 1).

We first examined the properties of several nitroxyl radical catalysts for the oxidative deprotection of PMB-protected alcohols (Table 1). Treating *O*-(4-methoxyphenylmethyl)-3-phenylpropanol (**2a**) with 1.05 equiv of phenyl iodonium bis(trifluoroacetate) (PIFA) and 4 equiv of $NaHCO_3$ in the presence of 10 mol% of TEMPO, PROXYL, or Nor-AZADO[3b,c] in CH_2Cl_2 at room temperature for 3 h, followed by quenching with aqueous sodium thiosulfate, furnished 3-phenyl-1-propanol (**3a**) in low yield (15−27%; entries 1−3). Using 4-oxo-TEMPO, which contains an electron-withdrawing oxo group at the 4-position, also furnished **3a** in low yield (entry 4). On the other hand, racemic **4**, which contains an ester group next to the nitroxyl group, drastically increased the chemical yield (75%; entry 5). Racemic **1**, which contains two ester groups, was found to be the most suitable nitroxyl radical catalyst for this transformation (97%; entry 6). These results suggest that the electron-withdrawing ester groups adjacent to the catalytically active center play a pivotal role in improving the reactivity and selectivity of the oxidation of PMB ethers. Additionally, a nonsubstituted benzyl group (**5**) could also be deprotected by the **1**/PIFA system (entry 7). In contrast, the oxidation of electron-deficient CF_3-substituted **6** resulted in only moderate yield (entry 8).

To explore the scope of the oxidative deprotection of PMB groups, various PMB ethers were tested (Scheme 2). PMB-protected aliphatic primary (**2a** and **2b**), secondary (**2c**), and tertiary alcohols (**2d**) were efficiently deprotected to give the desired products (**3a**−**3d**) in high yield. PMB ethers derived from cyclic alcohols, including estradiol derivative **2g**, furnished the corresponding products (**3e**−**3g**) in high yield. PMB-protected diverse benzylic (**2h**−**2j**), allylic (**2k**), and

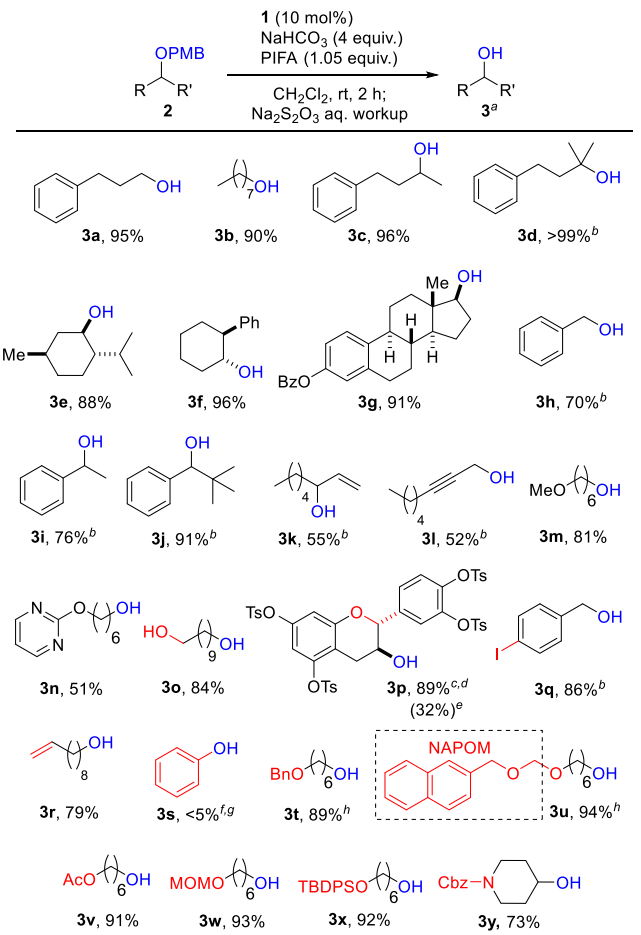
Table 1. Oxidative Deprotection of Benzylic Groups by Nitroxyl Radicals[a]



Entry	X	Catalyst	Conv. (%)[a]	Yield (%)[a]
1	OMe (**2a**)	TEMPO	24	17
2	OMe (**2a**)	PROXYL	18	15
3	OMe (**2a**)	Nor-AZADO	52	27
4	OMe (**2a**)	4-oxo-TEMPO	19	16
5	OMe (**2a**)	**4**	>99	75
6	OMe (**2a**)	**1**	>99	97
7	H (**5**)	**1**	>99	94
8	CF_3 (**6**)	**1**	95	51

[a]Conversions and yields were determined by ^{1}H NMR analysis of the crude reaction residue using 1,3,5-trimethoxybenzene as the internal standard.

Scheme 2. Oxidative Deprotection of PMB Groups by 1/PIFA[a]



[a]Isolated yields unless otherwise noted. [b]H_2O (2.0 equiv) was added. [c]1.3 equiv of PIFA was used. [d]The reaction was run for 3 h. [e]Yield obtained from a stoichiometric oxidation using DDQ; reaction conditions: DDQ (1.3 equiv), CH_2Cl_2/H_2O (50/1), rt, 3 h. [f]Yield was determined by ^{1}H NMR analysis of the crude reaction residue using 1,3,5-trimethoxybenzene as the internal standard. [g]PMB ether **2s** was recovered in 26% ^{1}H NMR yield. [h]1.1 equiv of PIFA was used.

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propargylic alcohols (**2l**) also provided the targeted products (**3h**−**3l**) in moderate to high yield. It is worth noting that using 2 equiv of H_2O in the case of **2d**, **2h**−**2l**, and **2q** is crucial to avoid the formation of 2,2,2-trifluoroacetic acid ester derived from alcohol **3** as a side product.[13] The **1**/PIFA system was also applicable to substrates that bear heteroatoms in, e.g., methyl ether (**2m**) and pyrimidine (**2n**) groups. Interestingly, the **1**/PIFA system deprotected the PMB groups, in a chemoselective fashion, without affecting the related oxidation-sensitive functional groups. For example, substrates bearing a primary aliphatic hydroxy group (**2o**), a cyclic benzylic ether group (**2p**), an iodoarene (**2q**), and an isolated alkene moiety (**2r**) were intact under the reaction conditions. However, a substrate with a phenol ether group (**2s**) did afford only very low amounts of the desired product, given that the produced phenol **3s** is oxidizable by PIFA.[14] Nevertheless, the **1**/PIFA system was used to remove PMB group from the substrates **2t** and **2u**, which contain additional oxidation sensitive benzyl and 2-naphthylmethoxymethyl (NAPOM)[15]-protected hydroxy groups, in chemoselective manners with 89% and 94% yield, respectively. Other selected protecting groups for alcohols (**2v**−**2x**) and amines (**2y**) also showed great resistance to **1**/PIFA system.

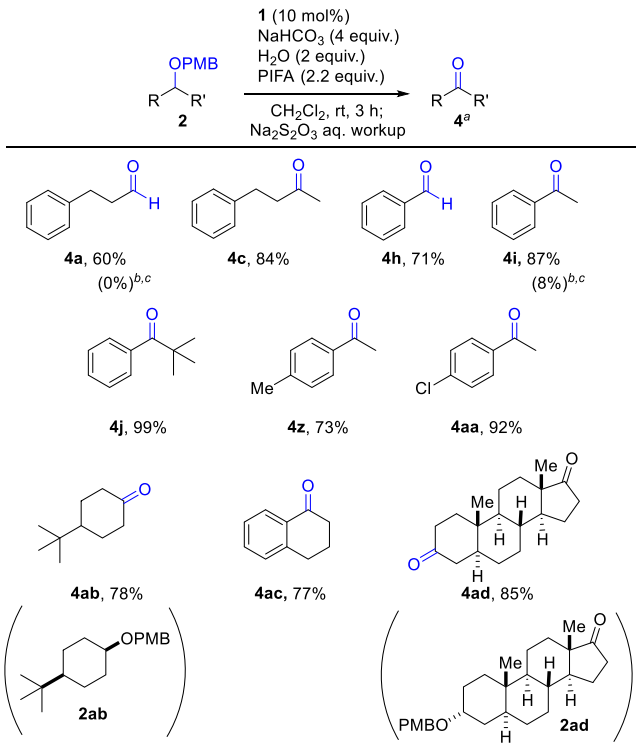
In addition to PMB-protected alcohols, the **1**/PIFA system was also applicable to several benzyl-protected alcohols (Scheme S1).

Subsequently, we investigated the direct oxidation of PMB-protected alcohols to carbonyl compounds via alcohols by treating PMB ethers **2** with 10 mol% of **1**, 4 equiv of $NaHCO_3$, 2 equiv of H_2O, and 2.2 equiv of PIFA in CH_2Cl_2 (Scheme 3). The direct oxidation of PMB-protected primary alcohol **2a** proceeded in only moderate yield due to the relatively low reactivity of the intermediate alcohols. On the other hand, PMB ethers derived from noncyclic aliphatic secondary (**2c**) and benzylic alcohols (**2h**−**2j**, **2z**, **2aa**) afforded the corresponding products in good to high yield. PMB-protected cyclic aliphatic and benzylic alcohols (**2ab** and **2ac**) also afforded the corresponding cyclic ketones (**4ab** and **4ac**) in good yield. Moreover, the androsterone derivative **2ad** with a steroid skeleton was converted into ketone **4ad** in 85% yield.

A plausible mechanism for the oxidation of PMB ethers by **1** is shown in Scheme 4. First, oxoammonium **A** is generated via the oxidation of nitroxyl radical **1** by PIFA. Since oxoammonium **A** is expected to be highly electron-deficient due to the adjacent ester groups, it should readily undergo a reductive transformation via hydride transfer from the PMB group to the oxygen of the oxoammonium to afford hydroxyamine **B** and oxocarbenium cation **C**. Then, the addition of water to **C** would give deprotected alcohol **3**. Oxidation of **3** could proceed via a hydride transfer in the case of benzylic alcohols, albeit it is unclear at present whether a similar process occurs in the case of aliphatic alcohols.[4a]

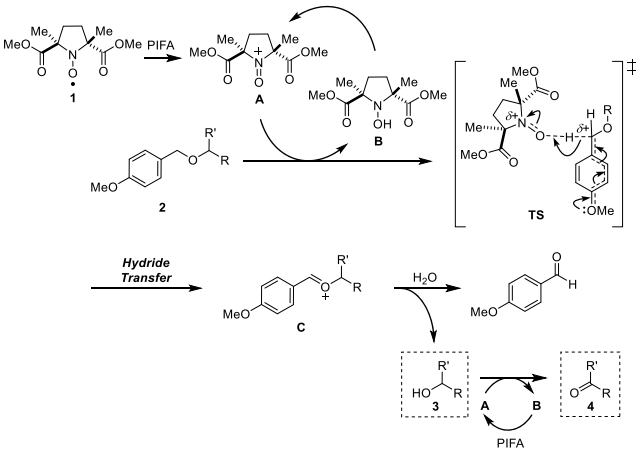
In conclusion, we have disclosed the utility of nitroxyl radical catalyst **1**, which contains electron-withdrawing ester groups adjacent to the nitroxyl group, for the oxidation of *p*-methoxy benzyl (PMB) ethers in the presence of an equivalent of phenyl iodonium bis(trifluoroacetate) (PIFA) to afford the corresponding alcohols. This system showed an excellent chemoselectivity profile for the deprotection of PMB ethers from a broad range of functional groups including diverse oxidation sensitive moieties. In addition, carbonyl compounds were obtained by treating PMB ethers with **1** in the presence of an excess of PIFA and water.

Scheme 3. Direct Synthesis of Ketones and Aldehydes from PMB-Protected Alcohols by 1/PIFA[a]



[a]Isolated yields unless otherwise noted. [b]The reaction was performed by using an excess of DDQ instead of **1** and PIFA; reaction conditions: DDQ (2.2 equiv), H_2O (2 equiv), CH_2Cl_2, rt, 3 h. [c]Yields were determined by ^1H NMR analysis of the crude reaction residue using 1,3,5-trimethoxybenzene as the internal standard.

Scheme 4. Plausible Mechanism for the Oxidative Deprotection of PMB Ethers Promoted by Nitroxyl Radical 1



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01839.

Example reactions for the deprotection of benzyl groups, mechanistic studies, experimental procedures, analytical data (^1H NMR, ^{13}C NMR, IR, HRMS) (PDF)

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Author Contributions

All authors contributed to writing this manuscript.

Notes

The authors declare no competing financial interest.

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