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p-Methylbenzyl Group: Oxidative Removal and Orthogonal Alcohol Deprotection

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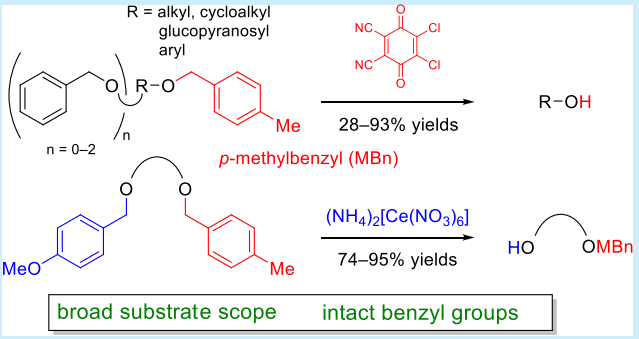
Supporting Information

ABSTRACT: We describe the practical removal of *p*-methylbenzyl (MBn) protections of alcohols by treatment with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone. When a molecule bears benzyl and MBn groups, the oxidant selectively removes the latter groups. Further, the MBn groups tolerate ceric ammonium nitrate, resulting in chemoselective removal of the *p*-methoxybenzyl group in the presence of the MBn groups. These orthogonal alcohol deprotections would provide novel synthetic strategies of organic compounds.



Hydroxy group protections are one of the most widely used strategies in organic synthesis.[1] Among multiple hydroxy groups, protection and deprotection of a selected one are necessary for conducting reactions at the specific site. Protecting groups of the hydroxy groups are generally classified into acetal, acyl, ethereal, and silyl ethereal types.[1] The benzyl (Bn) group is one of the most frequently used ethereal protecting group (Figure 1) because it survives under various

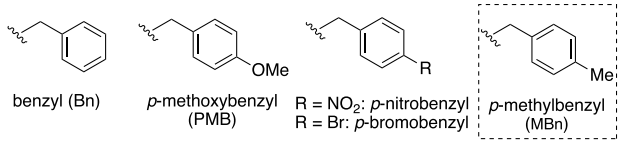


Figure 1. Benzyl-type protecting groups.

reaction conditions and cleaves specifically by hydrogenolysis.[1b,2] Analogues of the Bn group are also used to vary stability and to modulate their protection and deprotection conditions.[1a] Among these, the *p*-methoxybenzyl (PMB) group is a prominent protecting group due to its lability under oxidative conditions.[3] In the case of Bn-derived groups bearing electron-withdrawing substituents on the benzene ring, the deprotection protocol typically requires two steps. For example, cleavage of the *p*-nitrobenzyl group proceeds via reduction of the nitro group and subsequent oxidation of the produced *p*-aminobenzyl group.[4] Similarly, the removal of the *p*-bromobenzyl group proceeds in a two-step process via palladium-mediated amination followed by treatment with a protic or Lewis acid.[5] Differences in the reactivity for the removal of Bn protection analogues provides orthogonality[6] and enables the conversion of polyhydroxy-functionalized compounds.

The *p*-methylbenzyl (MBn) group is an uncommon analogue of the benzyl protecting group family. It has been used for the protection of phenols[7] and carbohydrates,[8] and its deprotection proceeds similar to that of the Bn group under hydrogenolysis[7a−c,8,9] and with the use of a Lewis acid.[7d,10] Additionally, a trifluoroacetic acid (TFA) cocktail (2% each of H_2O, ethanedithiol, and triisopropylsilane in TFA)[11] enables its removal, indicating that it is weaker than the Bn group (Scheme 1a). Further, results suggesting potential oxidative removal of the MBn group have been reported (Scheme 1b,c),[12−14] highlighting the possibilities for deprotection of this group using multiple approaches. As the PMB group also cleaves under acidic[15,16] and oxidative conditions,[3] variations in the reaction conditions for the removal of the Bn, MBn, and PMB groups would expand the orthogonality of their deprotection strategies. We report herein, practical oxidative cleavage conditions for the removal of the MBn protection and the chemoselective removal of the PMB group in the presence of the MBn group.

We explored the differences in the reactivity of the PMB and MBn groups under oxidative reaction conditions and exposed MBn ether **1**[17] to the typical oxidative conditions used for the removal of the PMB group (Scheme 2). The reactions were carried out with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) and ceric ammonium nitrate (CAN) as the oxidants.[18] While the reaction employing DDQ proceeded smoothly at ambient temperature to provide **2** in 93% yield, the reaction using CAN did not remove the MBn group effectively. The latter result suggests the possibility for the use of CAN for chemoselective deprotection of the PMB group in the presence

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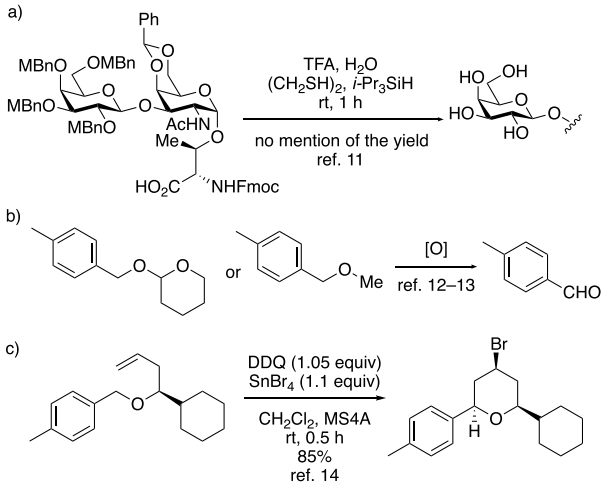
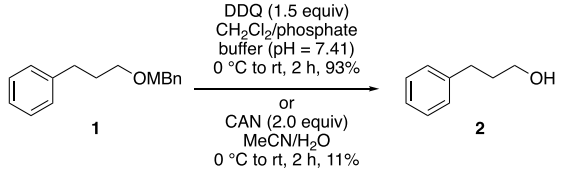
Scheme 1. (a) Known Acidic Cleavage of the MBn Group; (b) Results Suggesting Potential Oxidative Removal of the MBn Protection; (c) Oxidative Prins Cyclization



Scheme 2. Use of DDQ and CAN for the Oxidative Removal of the MBn Protecting Group

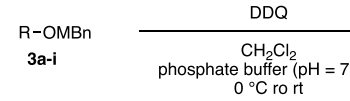


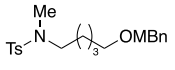
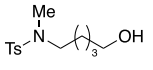
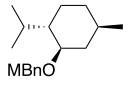
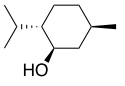
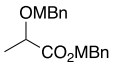
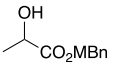
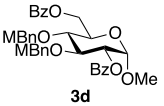
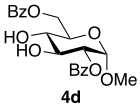
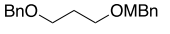
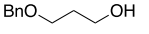
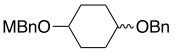
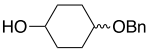
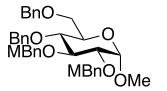
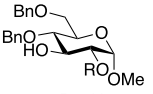
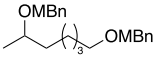
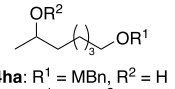
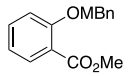
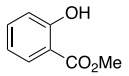
of MBn moieties in compounds bearing both of the protecting groups.

Having achieved MBn group deprotection using DDQ mediated oxidative reaction, we turned our attention to the study of the scope of this reaction with various reactants (**3a**–**i**, Table 1).[17] In the case of MBn protection for primary or secondary alcohols, the deprotection to corresponding alcohol proceeded in acceptable yield (entries 1–3). Notably, the MBn ester in **3c** survived under the deprotection conditions. We explored next the simultaneous cleavage of two vicinal MBn ethers in glucose derivative **3d**, which provided the 1,2-diol **4d** in 87% yield (entry 4). While DDQ-mediated deprotection of the Bn groups is reported,[19] the MBn group cleaved swiftly in the presence of the Bn group, showing chemoselectivity (entries 5–7). Deprotection of MBn ethers **3e** and **3f** carrying the Bn protection proceeded with the predominant formation of the alcohols **4e** and **4f** in 92 and 73% yield, respectively.[20] Furthermore, the reaction of **3g** with 2.1 equiv of DDQ gave a 64:19 mixture of **4ga** and **4gb**, indicating that the reactivity of the MBn group at O3 of glucose is greater than that at O2.[21] The result depicted in entry 8 was remarkable. Thus, the removal of the MBn group protecting the secondary alcohol prevailed to that protecting the primary alcohol to provide an 11:1 mixture of **4ha** and **4hb** in 66% yield with recovered **3h** in 20% yield.[22] The selectivity would be attributed to the difference in the electron density between the two MBn groups. The reaction of aryl MBn ether **3i** did not finish in 24 h, despite being conducted at 40 °C, and furnished the phenol **4i** in 28% yield with a recovery of **3i** in 51% yield (entry 9).

The MBn protections of ester **3c** and aryl ether **3i**, both of which hardly reacted with DDQ, were cleaved via hydrogenolysis (Scheme 3). The treatment of **3c** and **3i** with

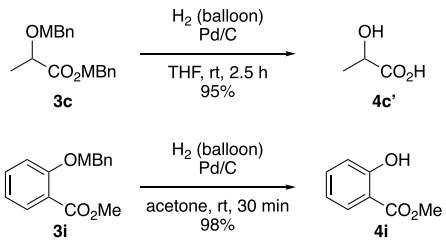
Table 1. Scope and Limitations of MBn Protections Using DDQ



entry	reactant	product	equiv of DDQ reaction time	isolated yield
1	 **3a**	 **4a**	1.3 3 h	91%
2	 **3b**	 **4b**	1.5 1 h	83%
3	 **3c**	 **4c**	1.3 15 h	86%
4	 **3d**	 **4d**	2.2 15.5 h	87%
5	 **3e**	 **4e**	1.5 3.3 h	92%
6	 **3f**	 **4f**	1.3 22 h	73% (22%)[b]
7	 **3g**	 **4ga**: R = H **4gb**: R = MBn	2.1 2 h	**4ga**: 64% **4gb**: 19%
8	 **3h**	 **4ha**: R^1 = MBn, R^2 = H **4hb**: R^1 = H, R^2 = MBn	1.1 13 h	66% (20%)[b] **4ha**/**4hb** = 11/1
9[a]	 **3i**	 **4i**	1.3 24 h	28% (51%)[b]

[a]At 40 °C. [b]The recovered yield of the reactant.

Scheme 3. Hydrogenolysis of the MBn Groups



hydrogen gas and palladium on carbon gave **4c′** and **4i** in both excellent yields, along with the removal of the MBn ether in the case of **3c**. Hydrogenolysis of MBn groups typically requires high pressures,[9,23] and it is noteworthy that the hydrogenolysis of **3c** and **3i** proceeded smoothly under an atmospheric pressure of hydrogen.

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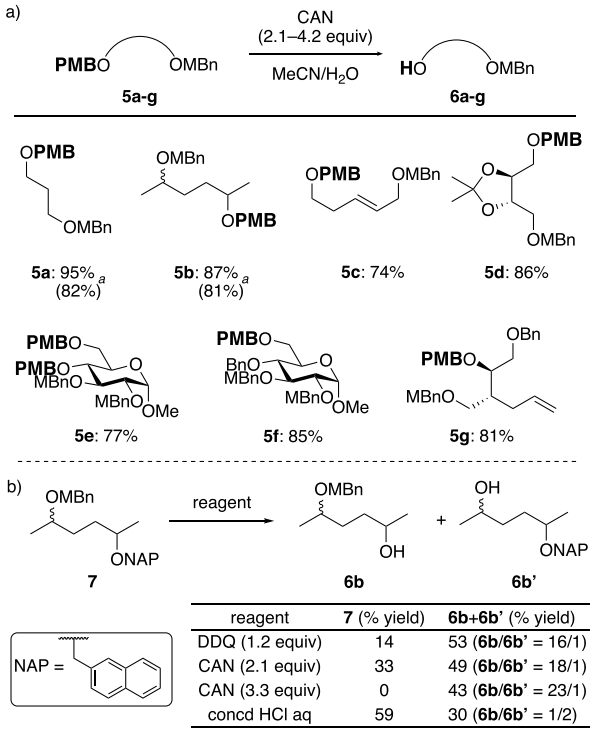
We next focused on chemoselective removal of the PMB group in the presence of the MBn group. As suggested in Scheme 2, the use of CAN as the oxidant allowed selective removal of the PMB group in the reactants **5a–g** (Scheme 4a).[17] The PMB protections for primary and secondary

Scheme 4. (a) Selective PMB Deprotection in the Presence of the MBn group(s). (b) Selective NAP Deprotection



reagent	**7** (% yield)	**6b**+**6b'** (% yield)
DDQ (1.2 equiv)	14	53 (**6b**/**6b'** = 16/1)
CAN (2.1 equiv)	33	49 (**6b**/**6b'** = 18/1)
CAN (3.3 equiv)	0	43 (**6b**/**6b'** = 23/1)
concd HCl aq	59	30 (**6b**/**6b'** = 1/2)

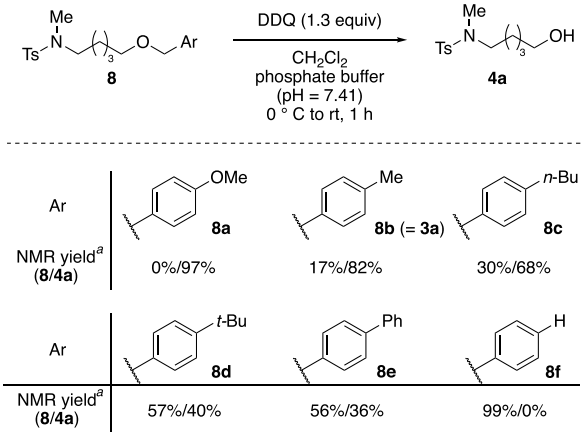
[a]Isolated yield with the use of concd HCl aq as the reagent.

alcohols (**5a** and **5b**) gave the corresponding alcohols **6a** and **6b**, respectively, in excellent yields by the treatment with CAN. The allylic MBn ether in the acyclic compound **5c** tolerated this condition to provide the primary alcohol **6c** in 74% yield. For **5d**, the PMB group was selectively removed to furnish **6d** in 85% yield despite a report of CAN-mediated acetonide removal.[24] Simultaneous cleavage of two PMB groups in **5e** also proceeded smoothly to give the diol **6e** in 77% yield. In addition, glucose derivative **5f** and acyclic alkene **5g** bearing the Bn, PMB, and MBn groups underwent selective removal of the PMB group, affording the corresponding alcohols **6f** and **6g** in 85% and 81% yield, respectively. We further confirmed that treatment of **5a** and **5b** with concd HCl aq induced chemoselective hydrolysis of the PMB group to afford alcohols **6a** and **6b**, respectively, in good yields, indicating that the MBn group tolerates the acidic conditions. Thus, when the instability of the PMB group under acidic conditions hinders intended transformation, the MBn group could serve as a useful alternative.

We further attempted the selective oxidative removal of 2-naphthylmethyl (NAP) group in **7** bearing the MBn group because the NAP group is also removable under oxidative conditions (Scheme 4b).[25] When 1.2 equiv of DDQ was used, the reaction was not completed to give a 16:1 mixture of **6b** and **6b′** in 53% yield with recovered **7** in 14% yield. Treatment with 2.1 equiv of CAN gave the similar result. Although the use of 3.3 equiv of CAN resulted in the disappearance of **7** and highly selective production of **6b**, the total yield of **6b** and **6b′** was reduced due to overreaction. *p*-Methylbenzaldehyde was detected in these crude ^{1}H NMR spectra (see the Supporting Information), indicating that the chemoselective removal of the NAP group is tricky under oxidative conditions. We also examined acidic hydrolysis of **7**; however, 59% of **7** was recovered along with 30% yield of **6b** and **6b′**, the latter being the major product.

The methyl group was determined as the most adequate *para*-substituent for the reaction with DDQ through evaluation of alkyl and aryl substituents as shown in Scheme 5. To probe

Scheme 5. Effect of the Substituent Group at the 4-Position on the Bn Group



[a]Pyrazine was used as the internal standard.

the substituent effect, we examined DDQ mediated deprotection of reactants **8a–f** using identical reaction conditions; where DDQ (1.3 equiv with respect to **8**), the pH of the phosphate buffer (7.4), the reaction temperature (room temperature), and the reaction time (1.0 h) were the same for all reactions. While the PMB group on **8a** was completely removed, the MBn group on **8b** was partly retained. On the other hand, the introduction of other alkyl groups led to a decrease in reactivity. A conversion yield was 68% with the use of the *p*-(*n*-butyl)benzyl group (**8c**), which was 14% lower than that obtained for **8b**. In addition, the reactivity of the *p*-(*tert*-butyl)benzyl group (**8d**) was inferior to that of **8c**. While the removal of the *p*-phenylbenzyl group (**8e**) proceeded similar to that described in a previous report,[26] the conversion yield was similar to that obtained with **8d**. Further, compound **8f** bearing the Bn protection remained intact in the presence of DDQ. These results suggest that hyperconjugation of alkyl or aryl substituents **8b–e** is essential for the reaction of the reactants with DDQ. Increase in electron density on the benzene ring through the inductive effect of the substituents allows the formation of a charge-transfer complex between the substituted benzyl group and DDQ. The different conversion yields obtained for **4a** from **8b–e** indicated that steric hindrance of the substituent group inhibits the deprotection reaction. The smaller size of the methyl group in comparison to other alkyl and aryl substituents facilitates the formation of the charge-transfer complex between the MBn group and DDQ, which induces the oxidation of the MBn group in the deprotection sequence.

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In summary, we revealed that the MBn groups installed on both primary and secondary alcohols smoothly cleave by the use of DDQ. The oxidation is believed to be promoted by the inductive effect of the methyl group. Additionally, the selective removal of the PMB group in the presence of the MBn group was achieved by the treatment of CAN. These results will accelerate the use of the MBn group in organic synthesis and will advance site-specific transformations in polyhydroxy systems.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02144.

Experimental procedures, analytical data, and copies of the ^{1}H and ^{13}C NMR spectra for all new products (PDF)

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Notes

The authors declare no competing financial interest.

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