Rational Design of Benzyl-Type Protecting Groups Allows Sequential Deprotection of Hydroxyl Groups by Catalytic Hydrogenolysis

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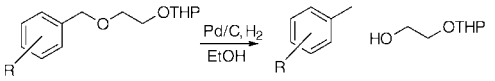
Benzyl protection of a hydroxyl group is one of the most frequently used procedures in synthesis because of the mild conditions involved in its removal by catalytic hydrogenolysis.[1−3] The synthesis of polyhydroxylated compounds often requires orthogonal protecting strategies to distinguish between hydroxyl groups. It would be highly desirable to develop a range of benzyl-type protecting groups with different reactivities that can be sequentially removed via catalytic hydrogenolysis. This requires a detailed understanding of the mechanism of the cleavage of the benzyl oxygen bond by the palladium hydrogen species. Recently, we have determined the amphipolar nature of the palladium hydrogen bond (modes **a**, $M^{\delta+} - H^{\delta-}$, or **b**, $M^{\delta-} - H^{\delta+}$) in both homogeneous[4] and heterogeneous[5] hydrogenation of alkenes. This has led us to test whether the electronic properties of the aromatic group can influence the rate of cleavage, which should in turn guide the development of hydroxyl protecting groups with different reactivities.

The results in Table 1 show that the rate of debenzylation can be dramatically affected by the electronic properties of the aromatic ring. The substitution of the electron-withdrawing trifluoromethyl group onto the aromatic ring severely retards debenzylation under 1 atm of hydrogen. In contrast, there is considerable acceleration by electron-donating substituents, which suggests that the benzylic carbon bears a partial positive charge in the transition state. The hydrogenolysis of benzyl alcohols carried out in acetic acid has shown that protonation of the hydroxyl group is essential for the cleavage of the carbon−oxygen bond.[6] Under the neutral conditions in our study, the reaction may occur by protonation of the benzyl oxygen atom, through the operation of mode **b**, $M^{\delta-} - H^{\delta+}$, to give a positively charged benzylic carbon. Alternativly, it is possible that palladium could act as a Lewis acid and coordinate to the benzyl oxygen atom to promote the same electron-deficient transition state (mode **a**, $M^{\delta+} - H^{\delta-}$).

The large difference in reactivity within this range of substituted benzyl groups suggests that they can be sequentially deprotected, therefore proving useful in multistep synthesis. To test the synthetic application of these groups, competition experiments were conducted on model systems with two differently substituted benzyl groups attached to ethanediol (Scheme 1a). Surprisingly, the benzyl group was cleaved first in competition with any of the substituted benzyl groups. This phenomenon has been observed with the 4-methoxybenzyl group (PMB); however, no explanation was proposed.[7,8] The results with the linker experiments (Scheme 1a) seem to contradict those obtained when only one benzyl group is involved (Table 1).

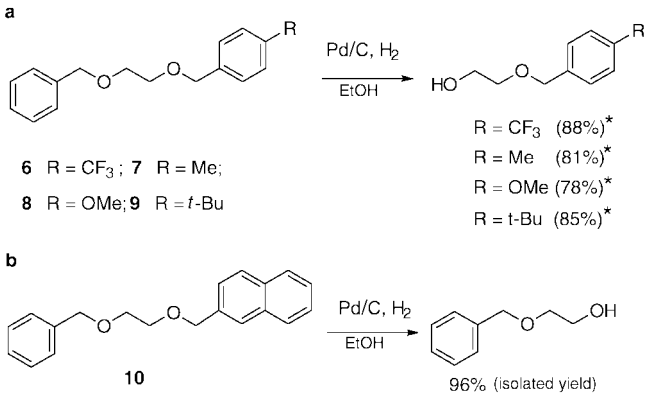
Table 1[a]



Substrate	k / (Ms^{-1}) x 10^{-6}	Relative Rate
1 R = 4-CF_3	0.080 ± 0.002	0.205
2 R = H	0.390 ± 0.008	1.00
3 R = 4-Me	3.07 ± 0.12	7.94
4 R = 3,5-Me	4.30 ± 0.22	11.01
5 R = 4-*t*-Bu	9.58 ± 0.78	24.78

[a] The reaction was monitored by ^1H NMR, and k was calculated from changes in concentration.

Scheme 1



* Yields are based on 75−85% conversion of starting materials.

Surface scientists have determined that the aromatic ring lies flat on the metal surface for optimal coordination.[9,10] It is possible that substitution on the aromatic ring could have an adverse steric effect that would interfere with the planar geometry required for effective binding and thus reduce its affinity for the metal surface. The linker experiments show that the limited number of active sites on the palladium surface could lead to a competition for adsorption sites between substituted and unsubstituted benzyl groups. This may explain why the least substituted benzyl group, although not electronically favored, can still be preferentially cleaved.

It is clear that for the rational design of selective benzyl type protecting groups both electronic factors and adsorption must be taken into account. For synthetic purposes, it would be desirable to find a more labile group than the benzyl group for protection of the hydroxyl functionality. We anticipated that the 2-naphthylmethyl (NAP) group would fulfill these criteria: it is electron rich and should have a

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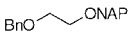
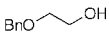
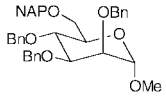
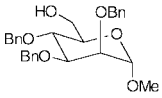
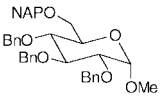
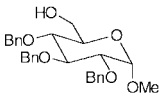
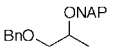
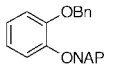
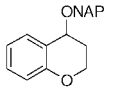
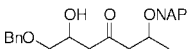
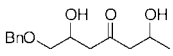
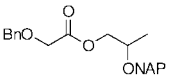
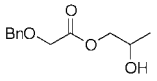
Table 2

	Substrate	Product[a]	Yield %[b]	Time / h
10			96	0.5
11			90	8.0
12			89	8.5
13			97	1.6
14			92	0.5
15			97	4.5
16			86	7.0
17			93[c]	8.0

[a] For the general procedure see ref 11. [b] Isolated yield. [c] Product underwent acyl migration to a mixture of esters in a ratio of 2.37:1 (the molecule shown is the major isomer).

high affinity to the palladium surface due to its flat extended aromatic system.[9] The hydrogenolysis of ether **10** shows that the NAP group can be selectively deprotected in the presence of a benzyl group (Scheme 1b). Interestingly, the deprotection of the benzyl group is strongly inhibited even after the NAP group has been completely removed. This is a desirable feature for clean sequential deprotection. It is possible that the 2-methylnaphthalene released during the reaction can compete with the benzyl group for the active sites on the palladium. This was confirmed in a control experiment where debenzylation of compound **2** (Table 1) was strongly inhibited by the addition of 1 equiv of 2-methylnaphthalene.

To investigate the synthetic utility of this new finding, the selective removal of NAP and benzyl groups was conducted on substrates **10**−**17** (Table 2). The results show that the NAP group can be cleanly removed from primary or secondary hydroxyl groups in the presence of single or multiple benzyl ethers.[11,12] In addition, the high-yielding hydrogenolysis of **14** provides a new approach to the differential debenzylation of phenolic molecules. Of particular interest are the hydrogenolysis reactions of ketone **16** and ester **17**. These are simple models that highlight an application in the synthesis of natural products on the basis of aldol and macrolactonization methodology.[13]

This study identifies that the two major factors controlling the removal sequence of different benzyl-protecting groups are the electronic properties of the aromatic ring and its affinity to the palladium surface. This understanding has led to the successful development of the NAP protecting group, which is more labile to catalytic hydrogenolysis than the benzyl group. Further tuning of the aromatic ring on the basis of this concept could provide a range of synthetically useful benzyl-type protecting groups that can be sequentially removed.

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Supporting Information Available: Experimental details and spectroscopic and analytical data for compounds **1**−**17** (13 pages).

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(11) Representative Procedure for Hydrogenolysis: **Methyl 2,3,4-Tri-*O*-benzyl-α-D-mannopyranoside.** A solution of ether **11** (0.185 g, 0.31 mmol) in ethanol (8 mL) was added to a stirred suspension of palladium on carbon (0.031 g, 10%) in ethanol (20 mL) that had been evacuated, purged with hydrogen, and stirred for 30 min under a hydrogen atmosphere. The reaction mixture was stirred for 7 h and then filtered through Florisil (ethyl acetate). The organic extracts were concentrated, and the resulting oil was purified by silica column chromatography (ethyl acetate/hexane, 1:3, R_f = 0.26) to afford methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside as a colorless oil (0.125 g, 90%).

(12) To assess the stability of the protecting group, ether **10** was subjected to a range of chemical conditions. The NAP group was stable in acidic and basic solutions and to organometallics such as methylmagnesium bromide and DIBAL-H. The ether shows partial decomposition in *n*-butyllithium at 30 °C.

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