Halobenzyl Ethers as Protecting Groups for Organic Synthesis

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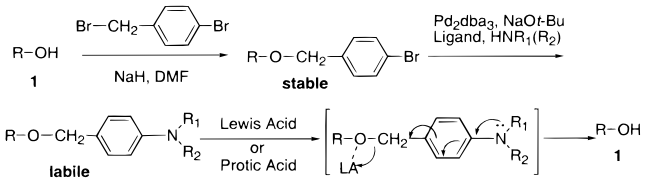
The differential protection of functional groups of similar reactivity is a major challenge for the synthesis of complex natural products. The task of distinguishing specific hydroxyl and amino groups becomes particularly daunting in oligosaccharide assembly when highly branched structures necessitate several selectively removable blocking groups. Over the years a host of protecting groups have been introduced, each making use of the unique reactivity of the particular masking moiety.[1] Traditionally, benzyl ethers have been employed for "permanent" protection and are removed during the late stages of a synthesis. Esters and silyl ethers, on the other hand, are used to "temporarily" protect hydroxyl groups to be unveiled during the synthesis. Orthogonality of protecting groups is a key issue for the planning and experimental execution of a given synthesis.

To increase the scope of available hydroxyl protecting groups, substituted benzyl ethers that can be selectively removed in the presence of unsubstituted benzyl ethers have been developed. These substituted benzyl ethers are generally less stable to different reaction conditions than unsubstituted benzyl ethers.[1] The 4-*O*-methoxy benzyl group (PMB) has found frequent application in natural product synthesis since it can be cleaved oxidatively in a selective manner.[1] The acid sensitivity of this group, while restricting its synthetic utility, has also been exploited for its removal.[2] More recently, other 4-*O*-substituted benzyl ethers containing acetate and trialkylsilyl substituents have been reported.[3] Although the removal of these benzyl ethers does not require catalytic hydrogenation, the necessity of treatment with base or fluoride, followed by oxidative cleavage renders them incompatible with ester, silyl, or PMB protecting groups.

A set of protecting groups that are equally or more stable than unsubstituted benzyl ethers and which may be removed selectively under mild conditions without affecting other commonly used protecting groups would be ideal. We anticipated that stable, readily accessible halogenated benzyl ethers[4] fulfill all of the aforementioned requirements and could be converted into labile arylamines by Pd-catalyzed amination.

The catalytic amination of aryl halides represents a mild alternative to the classical methods of aromatic C−N bond formation.[5] Here we describe the use of Pd-catalyzed aminations to convert stable halogenated benzyl ethers into substituted arylamines which can be cleaved by brief exposure to Lewis acids, protic acids, or oxidants (Scheme 1). Selective removal of substituted benzyl ethers in the presence of silyl ethers, alkyl and aryl esters, PMB ethers, acetals, or a glycal double bond was readily achieved.

Scheme 1



The introduction of halogenated benzyl ether protecting groups was accomplished in a straightforward manner by reaction of the hydroxyl group with the corresponding benzyl chloride or benzyl bromide in the presence of sodium hydride.[1,6] With a series of protected monosaccharides **2**−**5** in hand, Pd-catalyzed amination reactions employing different amines were explored (Table 1). Following recently developed protocols, the 4-bromobenzyl (PBB) protected galactose **2** was coupled with benzylamine or *N*-methyl aniline using $Pd_2(dba)_3$ (1 mol % Pd), and (*o*-biphenyl)P(*t*-Bu)$_2$ (2 mol %) as the catalyst system in the presence of sodium *tert*-butoxide.[7,8] The reactions were carried out at 80 °C for 5 h or alternatively at room temperature for 16 h. The 4-chlorobenzyl (PCB) moiety of galactose **3** could be efficiently *N*-arylated with *N*-methylaniline or morpholine. 2-Bromobenzyl ethers (OBB) could also be employed as demonstrated by the reaction of 2-bromobenzyl ether **5** with benzylamine to provide **9** in good yield. Additionally, amination of 4-iodobenzyl (PIB) functionalized galactoside **4** was accomplished in high yield (96%) at room temperature.

After protocols for the facile conversion of the stable halogenated benzyl ethers into a variety of arylamines had been established, conditions to facilitate the cleavage of these amines were explored (Table 2). Benzylamine **6** was quantitatively cleaved with strong Lewis acids ($TiCl_4$, $SnCl_4$) in only 5 min. Similarly, treatment of **6** with 1% dichloroacetic acid (DCA) gave deprotected product in a matter of minutes. Reaction with cerium(IV) ammonium nitrate yielded the free alcohol in modest yield after 30 min. Tertiary arylamine **7** was more labile to Lewis acids as it could be quantitatively cleaved by $ZnCl_2$. Aryl morpholino substrate **8** as well as ortho-substituted aryl benzylamine **9** required $TiCl_4$ for efficient cleavage.

With effective cleavage protocols in hand we exploited the differences in the rates of reaction between aryl chlorides, bromides, and iodides in Pd-catalyzed amination reactions.[7] A demonstration of our orthogonal protecting group strategy based on halogenated benzyl ethers is shown in the construction of a model trisaccharide (Scheme 2). Starting with differentially protected monosaccharide **10**,[9] the PIB group was selectively removed while no cleavage of the PBB and PCB groups occurred. Glycosylation employing mannosyl trichloroacetimidate **12** yielded 88% of the desired disaccharide **13.**[10] Removal of the PBB group proceeded smoothly in the presence of the C4 PCB group to fashion deprotected **14**. Alkylation with propyl iodide followed by cleavage of the PCB moiety gave **16** in 91% yield over 2 steps. Glycosylation with glucosyl phosphate **17** furnished trisac-

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999.
(2) Yan, L.; Kahne, D. E. *Synlett* **1995**, 523−524.
(3) Jobron, L.; Hindsgaul, O. *J. Am. Chem. Soc.* **1999**, *121*, 5835−5836.
(4) Initial studies with PBB, PCB in peptide synthesis: Yamashiro, D. *J. Org. Chem.* **1977**, *42*, 523−525. PCB in oligosaccharide synthesis: Pohl, N. L.; Kiessling, L. L. *Tetrahedron Lett.* **1997**, *38*, 6985−6988.
(5) (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067.
(6) Cost analysis of substituted benzyl halides: 4-chlorobenzyl chloride ($0.10/g), 4-bromobenzyl bromide ($0.70/g), 4-iodobenzyl bromide ($10/g).
(7) Wolfe, J. P.; Tomori, H.; Yin, J.; Sadighi, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−1174.
(8) The coupling with *n*-hexylamine resulted in the formation of a significant amount of the bis-arylation product.
(9) Please see Supporting Information for details of the preparation of **10** and **19**−**24**.
(10) Mayer, T. G.; Kratzer, B.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **1994**, *33*, 2177−2180.

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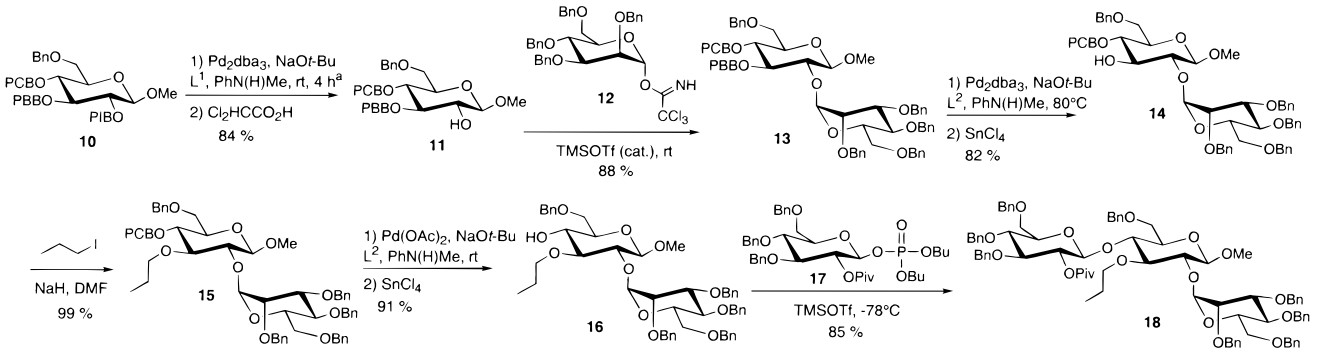
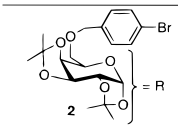
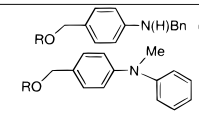
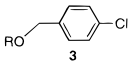
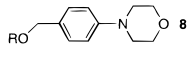
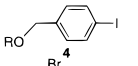
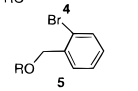
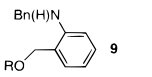
Scheme 2[a]



[a] Key: PCB = *p*-chlorobenzyl, PBB = *p*-bromobenzyl, PIB = *p*-iodobenzyl; L^1 = 1-(*N*,*N*-dimethylamino)-1′-(dicyclohexylphosphino)biphenyl, L^2 = (*o*-biphenyl)P(*t*Bu)$_2$.

Table 1. Pd-Catalyzed Amination of Halogenated Benzyl Ethers[a]

Halide	Amine	Product	Yield (%)
 **2**	H_2N-Bn	 **6**	91
			96
 **3**		**7**	89[b,c]
		 **8**	95[b]
 **4**		**7**	96[c,d]
 **5**	H_2N-Bn	 **9**	85

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.2 equiv of amine, 1.4 equiv of NaO*t*Bu, cat. Pd_2dba_3, (*o*-biphenyl)P(*t*Bu)$_2$ (2L/Pd), toluene (2 mL/mmol of halide), 80 °C. [b] $Pd(OAc)_2$ used in place of Pd_2dba_3. [c] The reaction was conducted at room temperature. [d] 1-(*N*,*N*-Dimethylamino)-1′-(dicyclohexylphosphino)biphenyl was used in place of (*o*-biphenyl)P(*t*Bu)$_2$ (1 L/Pd). 1.05 equiv of amine were used.

Table 2. Cleavage of Aminated Benzyl Ether Protecting Groups[a]

amine	reagent	time, min	yield	amine	reagent	time, min	yield
6	$SnCl_4$	5	>95	**7**	$ZnCl_2$	30	>95
6	1% DCA	5	>95	**8**	$TiCl_4$	5	>95
6	CAN	30	75[b]	**8**	1% TFA	5	>95
7	1% DCA	5	>95	**9**	$TiCl_4$	5	>95

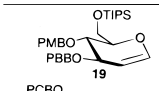
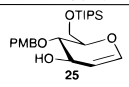
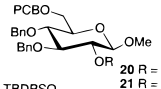
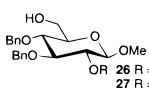
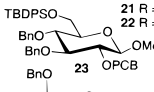
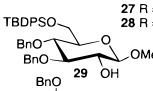
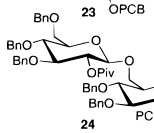
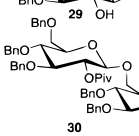
[a] The reactions were carried out in CH_2Cl_2 at room temperature. Yields are reported based on TLC analysis. [b] The reaction was carried out in 9:1 CH_3CN:H_2O.

charide **18** in 85% yield.[11] Differentially protected monosaccharides such as **10** are expected to provide facile entry into the construction of branched oligosaccharides and combinatorial carbohydrate libraries.

The compatibility of the novel benzyl ether protecting groups with other commonly used modes of protection was demonstrated using substrates **19**−**24**.[9] Removal of the PBB group from **19** was achieved in excellent yield (96%) while the silyl ether (TIPS), the PMB group, and the glycal double bond were not affected. PCB cleavage in the presence of acetyl and benzoyl groups was accomplished when K_3PO_4 was used in the amination step. Further orthogonality to secondary TBDMS and primary TBDPS groups allowed for the synthesis of **28** and **29** in good yield.

(11) Plante, O. J.; Andrade, R. B.; Seeberger, P. H. *Org. Lett.* **1999**, *1*, 211−214.

Table 3. Functional Group Compatability[d]

Substrate	Product	Method	Yield
 **19**	 **25**	A[a]	96
 **20** R = Ac **21** R = Bz **22** R = TBS	 **26** R = Ac **27** R = Bz **28** R = TBS	B[b] B[b] A[a]	87 79 70
 **23**	 **29**	A[b]	81
 **24**	 **30**	A[a,c]	89

[a] Cleaved with $ZnCl_2$. [b] Cleaved with $SnCl_4$. [c] $Pd(OAc)_2$ used in place of Pd_2dba_3. [d] A: 1.0 equiv of halide, 1.2 equiv of *N*-methylaniline, 1.4 equiv of NaO*t*Bu, cat. Pd_2dba_3, (*o*-biphenyl)P(*t*Bu)$_2$ (2L/Pd), toluene (2 mL/mol of halide). Room temperature, 12 h. B: 1.0 equiv of halide, 1.2 equiv of morpholine, 1.4 equiv of K_3PO_4, cat. $Pd(OAc)_2$, 1-(*N*,*N*-dimethylamino)- 1′-(dicyclohexylphosphino)biphenyl (1L/Pd), DME (2 mL/mmol of halide). 100 °C, 12 h.

In conclusion, a new concept for the protection of hydroxyl groups is reported. Halobenzyl ethers of comparable chemical inertness to unsubstituted benzyl ethers were efficiently differentiated in an iterative deprotection scheme by Pd-catalyzed amination followed by treatment with a Lewis or protic acid. The results disclosed here provide the basis for the design of a host of different halobenzyl ether protecting groups containing different substitution patterns. These halobenzyl ethers will be useful for the protection of hydroxyl as well as other functional groups. Furthermore, they should find wide application in the synthesis of natural products, complex carbohydrates, and the preparation of combinatorial carbohydrate libraries.

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Supporting Information Available: Detailed experimental procedures and compound characterization data, including ^1H and ^{13}C NMR spectral data for all described compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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