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Regioselective removal of the anomeric *O*-benzyl from differentially protected carbohydrates

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ABSTRACT

A mild, regioselective deprotection of the anomeric *O*-benzyl from multi-functionally protected carbohydrates via catalytic transfer hydrogenation is described. The protocol is tolerant of *O*-benzyl and *O*-benzylidene protections at non-anomeric positions, groups which are normally labile under typical hydrogenolysis conditions.

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Carbohydrates are well known to have significant biological functions.[1] Owing to their polyfunctional (polyhydroxylated) nature, judicious choice of protecting group strategy is paramount at the undertaking of any complex oligosaccharide synthesis.[2]

One of the most critical positions in glycoside synthesis is the anomeric centre[3]; and consequently, a suitable protection is required for this position. At present, such groups fall into two broad categories: (1) those installed early in the synthetic scheme and which require deprotection prior to appending a suitable activating group to facilitate glycoside synthesis, such as *p*-methoxyphenyl,[4] *p*-nitrophenyl,[5] TMSEt,[6] allyl,[7] and most recently *N*,*O*-dimethylhydroxylamine;[8] or (2) those that are employed as latent activating groups facilitating eventual glycoside synthesis themselves, such as *n*-pentenyl glycosides,[9] thioglycosides,[10] and sulfoxides.[11] The traditional approaches may require preliminary multi-step manipulation of the molecule and/or may not be compatible particularly in complex oligosaccharide synthesis.

The *O*-benzyl ether is among the most popular groups used to protect the non-anomeric hydroxylic positions of carbohydrates for a variety of reasons:[12] (1) their ease of installation and removal, (2) they are very robust and stable, (3) not prone to migration unlike the commonly used esters and silyls, and (4) compared to most other protecting groups, their greater electron-donating nature allows the activation of both the glycosyl donor and acceptor for glycoside bond formation.[3,13] The *O*-Bn group may be introduced utilizing a variety of systems, the specific method dependent on the tolerance of the other protecting groups present toward acidic or basic conditions.[12] In addition, several methods have been developed for the selective removal of benzyl groups from non-anomeric positions in multi-benzylated substrates.[14] Despite these advantages, it has not been considered as a viable anomeric protecting group owing to the fact that its controlled regioselective removal has not been achieved in diversely-protected carbohydrates.[15] The most commonly used high-yielding deprotection conditions, hydrogenolysis employing $Pd/C/H_2$, will remove other benzyls as well as the popular and highly functional benzylidene groups,[16] while the less popular, strong Lewis acid methods,[12,17] will cleave glycoside bonds and other common protecting groups.[18]

Catalytic transfer hydrogenation (CTH)[19] has been widely employed in both carbohydrate-based and other benzyl deprotection strategies, utilizing a range of donors such as ammonium formate,[20] formic acid,[21] and cyclohexene.[22] CTH has advantages over conventional hydrogenation in that it is technically simpler and presents a reduced risk of explosion. Deprotection of a non-anomeric *O*-Bn has been achieved in the presence of a six-membered *O*-benzylidene ring; under conventional hydrogenolysis conditions utilizing a Raney nickel catalyst.[23] However, with substrates possessing five-membered benzylidene acetals, selective deprotection of a benzyl group was not possible.[23] Despite these advancements, minimal studies have been carried out for the regioselective removal of a benzyl group in multi-functional systems using CTH.[20a,24]

Bieg and Szeja described the regioselective hydrogenolysis of the anomeric *O*-Bn from a variety of per-*O*-benzylated monosaccharides

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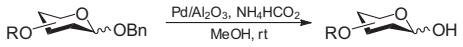
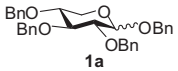
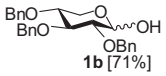
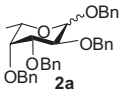
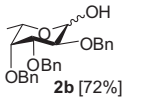
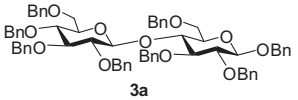
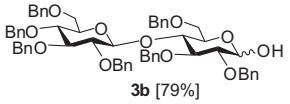
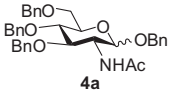
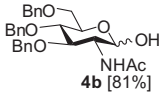
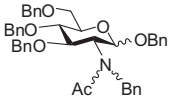
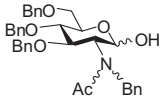
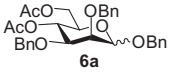
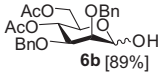
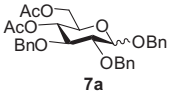
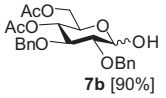
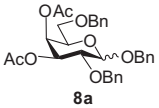
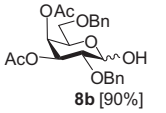
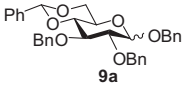
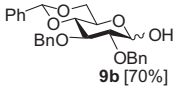
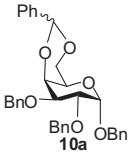
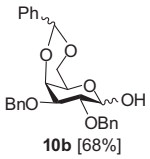
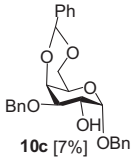
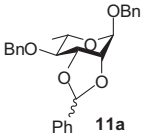
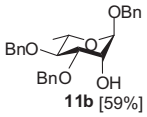
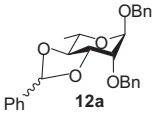
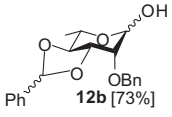
Table 1
Selective removal of the anomeric *O*-benzyl[27]



Entry	Substrate	Time (h)	Products[a] (yield%)
1	 **1a**	10	 **1b** [71%]
2	 **2a**	10	 **2b** [72%]
3	 **3a**	8	 **3b** [79%]
4	 **4a**	6	 **4b** [81%]
5	 **5a**	4	 **5b** [80%]
6	 **6a**	2	 **6b** [89%]
7	 **7a**	3	 **7b** [90%]
8	 **8a**	2	 **8b** [90%]
9	 **9a**	8	 **9b** [70%]
10	 **10a**	7	 **10b** [68%]  **10c** [7%]
11	 **11a**	3	 **11b** [59%]
12	 **12a**	0.5	 **12b** [73%]

[a] Isolated yields.

and disaccharides, utilizing Pd on the atypical solid support, Al_2O_3, with NH_4HCO_2 as the hydrogen source.[15b] To date, this valuable contribution remains the only report of the successful removal of the anomeric *O*-Bn of various substrates, in the presence of an interglycosidic bond as well as other *O*-benzyl groups. However, the development of this protocol, and the demonstration of its compatibility with other, typically hydrogenolysis-labile protecting groups, has not been explored. As a consequence, the anomeric *O*-Bn protection is not significantly employed in oligosaccharide syntheses. To the best of our knowledge, this Letter is the first to report findings that the $Pd/Al_2O_3/NH_4HCO_2$ system favors the regioselective removal of the anomeric *O*-benzyl group in the presence of other benzyl, acetate and most significantly, five-membered and six-membered benzylidene groups; in good yield.

The Pd/C system has been shown to result in greater rates of hydrogenolysis than that of Pd/Al_2O_3 albeit in non-carbohydrate systems.[25] This is presumably due to the lower surface area that exists with the alumina solid support.[26] This catalyst, as part of a

Table 2
^{13}C NMR comparison of reactant to products

Reactant	C-1 (ppm)	Product	C-1 (ppm)
1a	95.4 (α), 103.2 (β)	**1b**	91.4 (α), 97.7 (β)
2a	98.3 (α), 102.6 (β)	**2b**	91.8 (α), 97.7 (β)
3a	103.2 (β)	**3b**	91.3 (α), 97.3 (β)
4a	99.3 (α)	**4b**	92.1 (α)
5a	99.0 (α), 99.7 (α)	**5b**	92.7, 93.9, 94.1
6a	99.9 (β)	**6b**	93.2 (α), 93.5 (β)
7a	95.7 (α), 102.3 (β)	**7b**	91.3 (α), 97.5 (β)
8a	96.1 (α), 102.7 (β)	**8b**	91.7 (α), 97.6 (β)
9a	96.6 (α), 103.1 (β)	**9b**	92.2 (α), 97.8 (β)
10a	97.6 (α), 101.2 (α)	**10b**	92.5 (α), 96.5 (α)
		10c	98.7 (α)
11a	96.2 (α-*exo*), 96.1 (α-*endo*)	**11b**	98.2 (α)
12a	96.3 (α-*endo*), 96.8 (α-*exo*)	**12b**	92.1 (α-*endo*), 92.3 (β-*endo*), 92.1 (α-*exo*), 93.0 (β-*exo*)

controllable CTH system presented the most promising approach for the selective removal of an anomeric *O*-benzyl in multifunctional substrates. Ammonium formate was selected as the hydrogen donor due to its ease of handling, less toxic byproducts relative to cyclohexene and lower acidity relative to formic acid, an important factor when the substrate contained the acid-labile benzylidene. In order to establish the scope of this system, a set of diversely protected carbohydrate substrates was synthesized; with benzyl, acetate, and benzylidene groups in various positions and configurations (Table 1).

For the per-*O*-benzylated substrates (entries 1–3), the anomeric *O*-benzyl was selectively removed in good yield, as expected.[15b] Those derivatives which had combinations of *N*- and *O*-benzyls and acetates (entries 4–8) underwent faster selective anomeric *O*-benzyl removal than the per-*O*-benzylated substrates. Interestingly, those possessing *O*-acetates (entries 6–8) experienced the fastest average reaction times of all the types of substrates examined, suggesting a role for the electron-rich *O*-Ac groups in adsorbing to the alumina catalytic surface.

Most gratifyingly, results obtained with both the 1,3-dioxane and 1,3-dioxolane[28] benzylidene-protected derivatives indicated that regioselective removal of the anomeric *O*-Bn could be achieved. For entries 9, 10, and 12, the major product was that with only the anomeric hydroxyl free. With the 4,6-*O*-benzylidene galactopyranoside derivative, **10a**, minor amounts of the derivative bearing a free 2-OH was isolated, **10c**.[22c] Only the *S*-4,6-*O*-benzylidene derivative underwent deprotection of the 2-OBn; its *R* counterpart, with its phenyl ring in the sterically unfavored axial position, gave exclusively the product with a free anomeric hydroxyl.

The results obtained with the rhamnopyranoside derivatives, (entries 11 and 12) deserve special attention. A 1:1 diastereomeric mixture of *exo*- and *endo*-2,3-*O*-benzylidene rhamnopyranosides, **11a**, both underwent ring opening to yield exclusively the derivative bearing a 2-OH and 3-OBn. This appears to be the first example where: (1) a benzylidene ring is opened to yield a free OH on carbon and an *O*-Bn on the other, under palladium-catalyzed hydrogenolysis conditions[29] and (2) where both *exo*- and *endo*-isomers undergo the same exclusive stereoselective ring opening. They normally yield complementary ring-opened products.[30] In the latter case, Pastore and coworkers have also reported an occurrence of both the *exo*- and *endo*-2,3-*O*-benzylidene mannopyranosides yielding the 3-OH derivative when subjected to BH_3·THF/$Cu(OTf)_2$ mediated ring-opening.[31] With a diastereomeric mixture of *exo*- and *endo*-3,4-*O*-benzylidene derivatives, **12a**, the desired product bearing a free anomeric hydroxyl was obtained in good yield. The preservation of the *trans*-3,4-*O*-benzylidene rings was arguably the most significant result obtained: these *trans* fused five-membered bicyclic systems are among the most thermodynamically unstable of the *O*-benzylidene rings, due to the significant torsional strain that exists.[32] Their retention is an indication of the versatility and applicability of this regioselective CTH process.

Prolonged reaction times resulted in cleavage of the various *O*-benzylidene rings (whether five- or six-membered) as well as further debenzylations. Similarly, performing the reaction on the *O*-benzylidene protected substrates, but using the typical Pd/C catalyst instead, resulted in complex mixtures of debenzylated and benzylidene-deprotected products; the desired free-anomeric product being isolable only in minimal yield. This suggests that the role of the solid support is critical in allowing isolation of the product, with only the anomeric hydroxyl free, in practical yield. As reported in other non-carbohydrate systems,[25,26] it is likely that the lower surface area presented by the alumina facilitates a relatively slower, more controlled reaction, which allows the isolation of the desired product in good yield.

Of diagnostic interest, ^{13}C NMR analysis illustrated a useful relationship for suggesting the nature of the protecting group removed: deprotection of the anomeric *O*-Bn resulted in an average upfield shift of 5 ppm for C-1 (the anomeric carbon) for both anomers (Table 2). Where a 2-OH resulted (**10c** and **11b**), a downfield shift of around 2 ppm for C-1 was observed.

In summary, we have developed a mild method for the regioselective removal of an anomeric *O*-benzyl from an array of carbohydrate derivatives containing the commonly employed benzyl and benzylidene protecting groups in various configurations and conformations. Conventional wisdom dictates that the benzyl group is a permanent protecting group, only suitable for non-anomeric positions and to be removed generally at the end of a multi-step synthesis.[18b] These results, in conjunction with those for the various per-*O*-benzylated substrates,[15b] challenge that assumption. They suggest that the *O*-Bn be considered as a stable, easily introduced and robust anomeric protecting group, whose removal to generate a hemiacetal prior to glycosyl donor formation, is compatible with benzyl and benzylidene groups, which are known to be labile under typical hydrogenolysis conditions (Pd/C/H_2). This system utilizes a non-commonly used, but readily available solid support (Al_2O_3) for the Pd catalyst and has several benefits: (1) does not require an inert atmosphere, (2) minimizes hazards associated with an open, continuous source of H_2, (3) simple non-aqueous work-up, and (4) proceeds in good yield with relatively short reaction times at room temperature. It is envisioned that the utilization of an anomeric *O*-Bn-based protection strategy could significantly shorten reaction sequences and allow access to complex oligosaccharides via a facile route.

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Supplementary data

Supplementary data (NMR data and spectra data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.130.

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