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Regio- and Chemoselective Deprotection of Primary Acetates by Zirconium Hydrides

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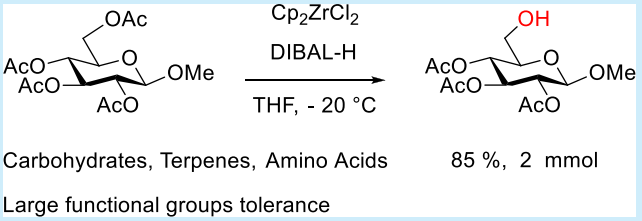
Supporting Information

ABSTRACT: A combination of DIBAL-H and Cp_2ZrCl_2 is shown to promote the regioselective cleavage of primary acetates on a broad scope of substrates, ranging from carbohydrates to terpene derivatives, with a high tolerance toward protecting groups and numerous functionalities found in natural products and bioactive compounds. Apart from providing highly valuable building blocks in only two steps from biosourced raw materials, this selective de-*O*-acetylation should also be strongly helpful to solve selectivity issues in organic synthesis.

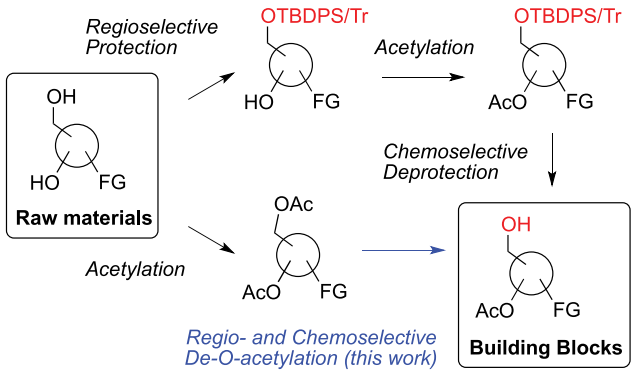


The development of selective methods for the modification of biosourced polyols into a large diversity of densely functionalized derivatives has been a matter of strong interest over the past decade.[1,2] In this context, efficient transformations giving rise to carbohydrates and terpenes with a polyacetylated framework, and a free primary alcohol available for further modifications, are highly desirable. Indeed, methods for the preparation of these key intermediates, massively involved in the synthesis of bioactive compounds, natural products, and biomaterials,[3] follow time-consuming synthetic routes relying on: (1) regioselective protection of the primary alcohol with a bulky electrophilic reagent, (2) acetylation of the secondary ones, and (3) chemoselective deprotection of the primary position thanks to orthogonality between protecting groups (Scheme 1).[4] Chemo- and regioselective deprotection of their peracetylated precursors has also been considered as an alternative approach to reduce the environmental impact and cost of their preparation, but these methods are suffering from several drawbacks. First, de-*O*-acetylation by esterases, which is commonly used to achieve selective deprotection of primary positions, is strongly specific, and the substrate scope for a given enzyme is thus quite narrow.[5] Moreover, advanced technologies, like immobilization on solid supports,[6] are needed to improve catalytic activity of esterases, but they are hard to implement for nonspecialists. On the other side, chemical methods leading to the selective removal of primary acetates are scarce. Tin-catalyzed methanolysis proves to be efficient on a broad-scope of substrate with a high tolerance toward functional groups,[7] but other esters like benzoates are also cleaved under those conditions.[8] Furthermore, this method is underused, presumably because of the difficult preparation of the hydroxy-tin catalyst. Iodine-catalyzed selective methanolysis of primary acetates has also been developed,[9] but some reports recently revealed that this transformation might be hard to handle.[10] By working on the development of new transformations for the modification of complex (bio)molecules,[11] we have recently identified bulky zirconium hydrides as promising candidates to promote the site-selective deprotection of polyfunctional peracetylated substrates (Scheme 1).

Indeed, zirconium hydrides, like Schwartz' reagent (Cp_2ZrHCl), are known to reduce carbonyl derivatives[12] and to induce hydrometalation of alkynes and alkenes with a high tolerance toward functional groups.[13] Their in situ generation from cheap, easy to handle, commercially available, and commonly used reagents for large scale industrial processes also opens the way to a convenient procedure where the manipulation of air and moisture sensitive organometallic species is not required.[14] In this context, we have investigated de-*O*-acetylation of peracetylated methyl-α-D-glucopyranoside **1** by mixtures of Cp_2ZrCl_2 and DIBAL-H.[15]

Peracetylated methyl-α-D-glucopyranoside **1** was first subjected to DIBAL-H (3 equiv) and Cp_2ZrCl_2 (3.5 equiv)

Scheme 1. Synthetic Approaches toward Polyacetylated Compounds with a Free Primary Alcohol



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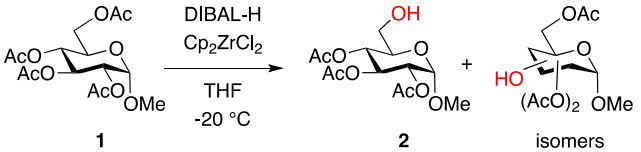
in toluene, dichloromethane, or diethyl ether at −20 °C, but de-*O*-acetylation remained random and conversion of the substrate low to moderate (entries 1−3) (Table 1).

Table 1. De-*O*-Acetylation of 1 by Cp_2ZrCl_2 and DIBAL-H



entry	solvent	Cp_2ZrCl_2 (equiv)	conv (%)[a]	selectivity (2: others)[a]
1[b]	$PhCH_3$	3.5	17	54:46
2[b]	CH_2Cl_2	3.5	32	72:28
3[b]	Et_2O	3.5	44	75:25
4[b]	THF	3.5	96[d]	97:3
5[c]	THF	1	100[e]	96:4
6[b]	THF		66	50:50

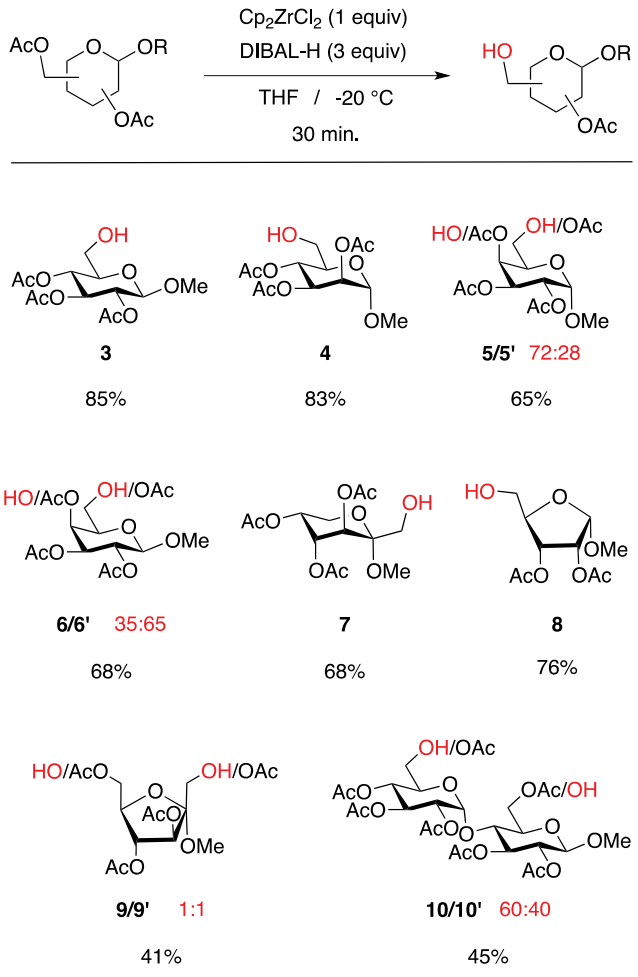
[a]Measured by ^1H NMR analysis of the crude. [b]Hydrolysis with 6 M HCl. [c]Hydrolysis with 3 M citric acid [d]78% isolated yield. [e]91% isolated yield.

Fortunately, compound **2** with a free primary alcohol was obtained in 78% isolated yield with a complete regioselectivity within 30 min in THF (entry 4). At this stage, it is worth noting that purification by silica gel flash chromatography was strongly hampered by large amounts of zirconium salts present in the crude product when hydrolysis of the reaction mixture was performed with a concentrated aqueous solution of hydrochloric acid. To improve efficiency of the purification step, the amount of Cp_2ZrCl_2 was diminished to 1 equiv and, most importantly, *hydrolysis was performed with a 3 M aqueous solution of citric acid*. Use of this triacid indeed delivered within minutes a crude product exempt of any Zr salt (SI, Figure S1). Purification by fast filtration over a small plug of silica then gave pure **2** in a 91% optimized isolated yield (entry 5). Finally, de-*O*-acetylation took place with a poor selectivity in absence of Cp_2ZrCl_2 (entry 6), thus confirming that zirconium hydrides are the active species responsible of this site-selective de-*O*-acetylation.

Deprotection of other peracetylated carbohydrates with Cp_2ZrCl_2 and DIBAL-H was next investigated in THF at −20 °C (Scheme 2). Selective de-*O*-acetylation at position 6 was achieved in the *β-gluco* and *α-manno* series to give **3** and **4** in 85 and 83% yield, respectively. However, competitive deprotection at position 4 occurred with *α*- and *β*-methyl galactopyranosides to give alcohols **5**/**5′** and **6**/**6′** as inseparable mixtures of regioisomers. Methyl-*α*-fructopyranoside and *α*-ribofuranoside delivered **7** and **8** in 68−76% yield, thus revealing that position of the primary acetate and ring size could be varied without affecting this transformation. However, competitive de-*O*-acetylation of the two primary positions of peracetylated methyl *α*-fructofuranoside and *β*-maltoside gave mixtures of alcohols **9**/**9′** and **10**/**10′** in moderate yields.

De-*O*-acetylation of carbohydrates bearing various functionalities was next considered (Scheme 3). Glycosyl donors, whose selective deprotection provides an expeditious access to highly relevant building blocks for bidirectional oligosaccharides synthesis, were first evaluated. Peracetylated phenyl *α*-thio-mannoside nicely delivered **11**, a suitable acceptor for iterative and one-pot glycosylation approaches,[16] in 65% yield. Anomeric acetates, which are usually readily removed,[17] were well tolerated as attested by the formation of **12** from glucose

Scheme 2. Site-Selective Deprotection of Peracetylated Carbohydrates: Scope and Limitations



pentaacetate in 72% yield. Hydrometalation of the electron-rich carbon−carbon double bond of peracetylated glucal did not occur either because **13**/**13′** were obtained in 71% yield. Regioselective de-*O*-acetylation of *N*-protected 2-deoxy 2-amino sugars was next investigated. First, the primary acetate of 2-azido glucose peracetate was easily removed to give **14** in 70% yield. Surprisingly, **15** was obtained in 81% yield by site-selective deprotection of peracetylated methyl *β*-*N*-acetyl glucosamine without affecting the acetamide moiety.[14b,18] *Reduction of carbonyl compounds by Cp_2ZrCl_2 and DIBAL-H in THF thus took place with a complete reversal of chemoselectivity compared to Cp_2ZrHCl.*[19]

Tolerance toward protecting groups commonly used in carbohydrate chemistry and deprotection of secondary acetates, were then evaluated. Under reaction conditions giving rise to site-selective deprotection of primary acetates (1 equiv Cp_2ZrCl_2, 3 equiv DIBAL-H, THF, −20 °C), benzylidene, isopropylidene, pivaloates, benzoates, as well as benzyl, *tert*-butyldimethylsilyl, and trityl ethers, remained intact.[20] Equatorial secondary acetates were cleaved in the absence of primary ones to give **16**/**16′** in 76% yield. However, axial secondary acetates showed a markedly reduced reactivity because alcohol **17** was only obtained in 45% yield despite the use of a large excess of Cp_2ZrCl_2 and DIBAL-H (9 equiv each).

Tolerance of functional groups toward this reductive de-*O*-acetylation was next investigated deeper on simple substrates.

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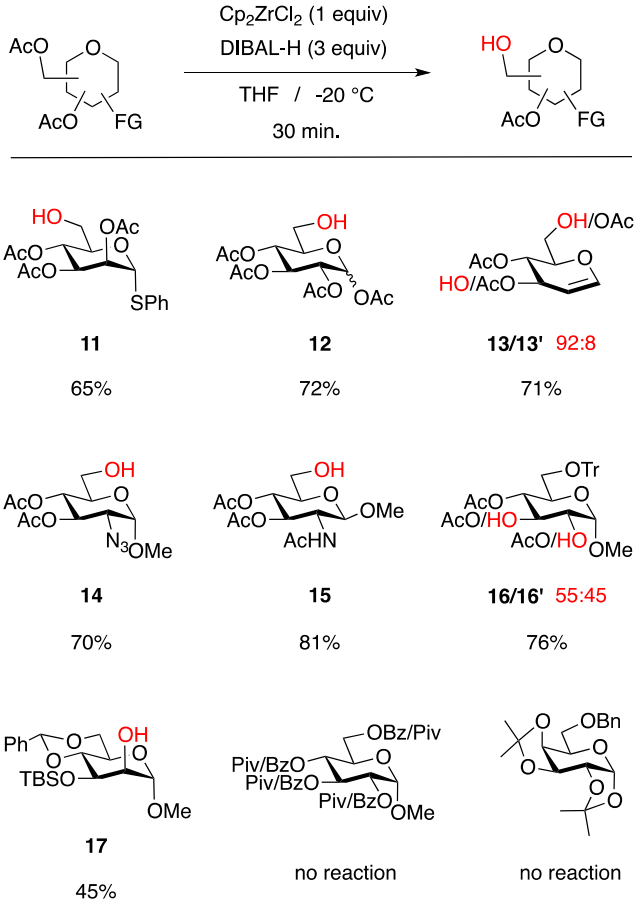
Scheme 3. Site-Selective Deprotection of Peracetylated Carbohydrates: Tolerance toward Functional Groups

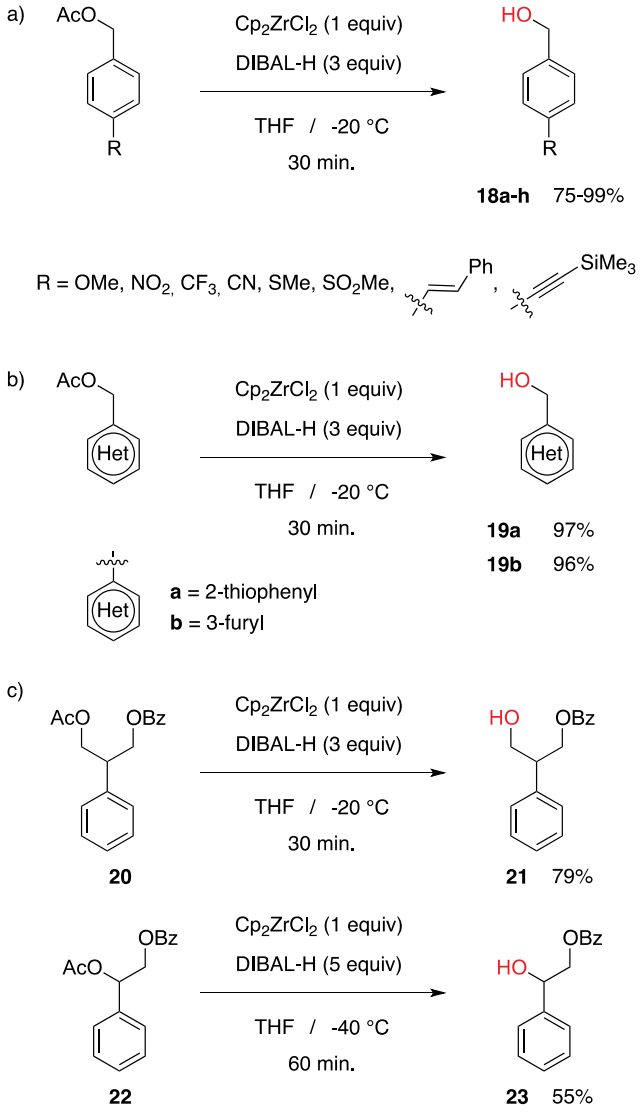


First, benzyl acetates having para methoxy, nitro, trifluoromethyl, nitrile, thioether, sulfone, alkyne, or alkene substituents were nicely transformed into the corresponding alcohols **18a−h** in 75−99% yields (Scheme 4a). The formation of thiophene and furan derivatives **19a,b**, in 97 and 96% yield, respectively, also showed that heteroaromatic compounds are compatible with this transformation (Scheme 4b). Selectivity between different esters was also evaluated, with substrates **20** and **22** bearing a primary benzoate and a primary or secondary acetate, respectively (Scheme 4c). At −20 °C in THF with 1 equiv of Cp_2ZrCl_2 and 3 equiv of DIBAL-H, **20** delivered **21** in 79% yield by selective removal of the acetate. However, under those standard reaction conditions, the deprotection of **22** also resulted in an additional de-*O*-benzoylation, giving rise to the diol. After careful optimization, **23** was finally obtained selectively, albeit in a moderate 55% yield because of a partial conversion of the substrate.

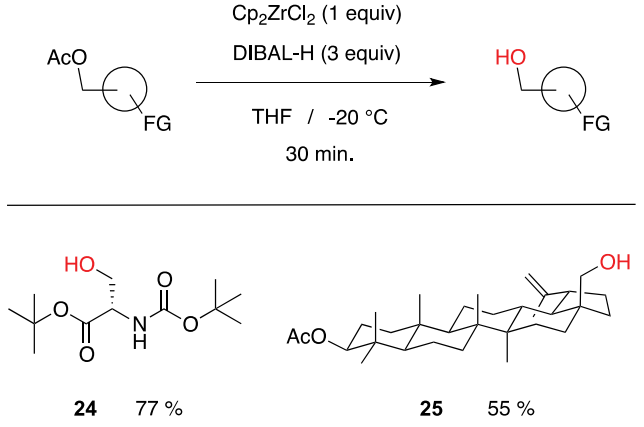
Site-selective and chemoselective deprotection of amino acids and terpenes was finally investigated to expand the scope of this transformation to noncarbohydrate scaffolds (Scheme 5). De-*O*-acetylation of *tert*-butyl Boc serine acetate into **24** in 77% yield also revealed that amino acid protecting groups were well tolerated. Finally, formation of **25** from peracetylated betulin took place without affecting either the equatorial secondary acetate or the electron-rich terminal olefin of this triterpene.

This new de-*O*-acetylation process was initially developed on the basis of in situ formation of Cp_2ZrHCl from DIBAL-H

Scheme 4. Chemoselective De-*O*-acetylation with Cp_2ZrCl_2 and DIBAL-H



Scheme 5. Chemo- and Site-Selective De-*O*-acetylation of Amino-Acid and Terpene Derivatives



and Cp_2ZrCl_2 mixtures in THF.[14b] However, this rationale was completely ruled out by site-selective de-*O*-acetylation of methyl *β*-*N*-acetyl glucosamine, which occurred without affecting the acetamide moiety. In this context, preliminary

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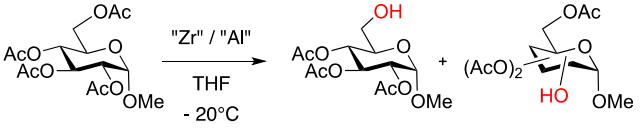
mechanistic studies were performed, with de-*O*-acetylation of peracetylated methyl-α-glucoside **1** being used as a probe to monitor the reactivity of reducing agents obtained from various mixtures of zirconium salts and metal hydrides (Table 2).

Table 2. Influence of the Zirconium Source and Reducing Agent



entry	zirconium (equiv)	hydride (equiv)	conv (%)[a]	selectivity (2: others)[a]
1	Cp_2ZrCl_2 (3.5)	DIBAL-H (3)	96	97:3
2	Cp_2ZrCl_2 (3.5)	$LiEt_3BH$ (3)	60	74:26
3	Cp_2ZrCl_2 (3.5)	$Al(OtBu)_3H$ (3)	88	63:37
4	Cp_2ZrHCl (3.5)		20	n/a
5	Cp_2ZrHCl (3.5)	DIBAL-H (3)	84	90:10

[a]Measured by ^1H NMR analysis of the crude.

We indeed made the assumption that the primary alcohol **2** should be nicely obtained when the proper reactive species would be present in the reaction media, otherwise low conversion and/or selectivity would be observed. Whereas in situ reduction of Cp_2ZrCl_2 by DIBAL-H[14b] gave **2** in high yield with a complete selectivity (entry 1), the use of $LiEt_3BH$ (entry 2)[14a] and $Al(OtBu)_3H$ (entry 3)[14c] delivered complex mixtures. Moreover, freshly prepared Schwartz' reagent[21] resulted in a very low conversion from which selectivity could not be determined (entry 4). Addition of DIBAL-H to Cp_2ZrHCl finally resulted in almost complete conversion and delivered **2** with a high level of selectivity (entry 5). Altogether, these results confirm that Schwartz' reagent is not the active species giving rise to the site-selective deprotection of primary acetates reported herein, and they strongly suggest that Zr/Al clusters might be involved in this transformation.[22]

In conclusion, a combination of DIBAL-H and Cp_2ZrCl_2 in THF was shown to selectively achieve the chemo- and regioselective reduction of primary acetates on substrates ranging from carbohydrates to terpenes and amino acids. Relying on the in situ formation of zirconium hydrides, this transformation proves to be compatible with the preactivated anomeric positions of some glycosyl donors, protecting groups commonly used in carbohydrate chemistry, and numerous functionalities found in bioactive compounds and natural products. This broad scope and highly tolerant site-selective deprotection of peracetylated substrates should provide new opportunities to solve selectivity issues in multistep organic synthesis. Deeper mechanistic studies are currently underway in our laboratory to identify the active reducing species leading to this transformation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03947.

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for compounds **2**−**25** (PDF)

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Notes

The authors declare no competing financial interest.

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