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μ-Waves avoid large excesses of diisobutylaluminium-hydride (DIBAL-H) in the debenzylation of perbenzylated α-cyclodextrin

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ABSTRACT

Regioselective double deprotection of cyclodextrins using diisobutylaluminium-hydride (DIBAL-H) has become an important tool in functional cyclodextrin synthesis. When conventionally heated a very large excess of reagent is necessary for the reaction to happen, when μ-waves irradiation is employed the quantity of DIBAL-H can be lowered down to 5 equiv. Reaction with a smaller quantity of DIBAL-H never achieved complete double debenzylation. These results also sustain the mechanistic hypothesis according to which a minimum of two aluminium atoms are necessary for each debenzylation to occur.

Cyclodextrins (CDs) are naturally occurring water-soluble concave molecules possessing a hydrophobic cavity, and made of six glucopyranosidic units linked in an α-1,4 fashion. Due to their high symmetry and to the close reactivity of all hydroxyl groups, selective functionalization of CDs is an intensively studied and challenging domain, but only a limited number of functionalization methods has been accessed so far. Functionalization of a cyclic structure formed of identical subunits must overcome two challenges: (1) the control of the number of identical functionalities introduced, (2) the control of the positions where the modifications are taking place. Functionalization of all OHs or all OH-2s, OH-3s, or OH-6s individually is feasible upon small reactivity differences, and monofunctionalization can be performed by controlling the amount of reagents. A more complex task consists in modifying two precise positions. Two strategies have been developed to tackle this problem: the first one is based on the use of sterically hindered reagents,[1] and the second one consists in capping the CD with bifunctional reagents.[2] Most of the available protocols describing the preparation of CD derivatives suffer many limitations, including low yields, poor regioselectivity, and long reaction times; furthermore the resulting CD derivatives generally require time-consuming chromatographic purifications. For some time now, we have developed an original strategy relying on an efficient regioselective deprotection reaction of perbenzylated CDs, giving access to CDs bearing two or three new functionalities on their primary rim.[3] This method is now classically employed for the synthesis of complex molecules such as, for example, artificial enzymes,[4] cyclic oligomers of CDs,[5] amphiphilic CDs,[6] or CD-vesicules.[7]

This CD deprotection reaction is based on a regioselective debenzylation reaction first discovered while working on mono- and disaccharides and which required a large excess of aluminium reagent,[8] relative to the number of oxygen atoms present in the starting material. For example, debenzylation of a monosaccharide required 5 equiv of aluminium reagent whereas 10 equiv were needed for a disaccharide, in both cases only a single debenzylation occurred (Scheme 1). Logically, when extended to CDs this reaction consumed an even larger excess of reagent, up to 120 equiv, which is a drawback for scale up. We rapidly experienced the importance of the concentration of reagent, and optimized the reaction conditions using 30 equiv of a 1 M solution of DIBAL-H allowing the conversion of perbenzylated CD **1** into diol **2** in 85% yield[3] (Scheme 1).

Attempts to further decrease the amount of reagent failed mainly due to reproducibility problems, which prompted us to explore μ-waves activation to overcome this limitation. According to our proposed reaction mechanism,[3] two DIBAL-H molecules are necessary to operate one debenzylation reaction. Four equivalents should be therefore sufficient to achieve the double debenzylation on perbenzylated cyclodextrins, however this assumption was difficult to sustain considering the large excess of reagent employed. (Scheme 2) Reaching the minimum DIBAL-H hence also becomes an important argument in support of the proposed mechanism.[3]

Hence, perbenzylated CD **1** was exposed to DIBAL-H in toluene and subjected to μ-waves irradiation, screening various temperatures, reagent concentrations and reaction times.[9] The kinetics of the reaction were monitored by NMR following specific signals of each product: a doublet at δ 5.13 ppm (6 × H-1) for starting perbenzylated CD **1**, a doublet at δ 5.77 ppm (2 × H-1) for diol **2**, and a

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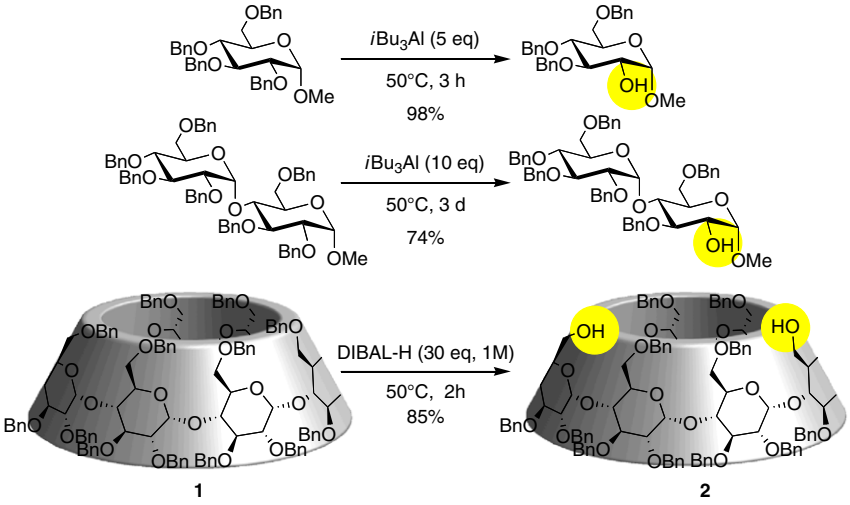
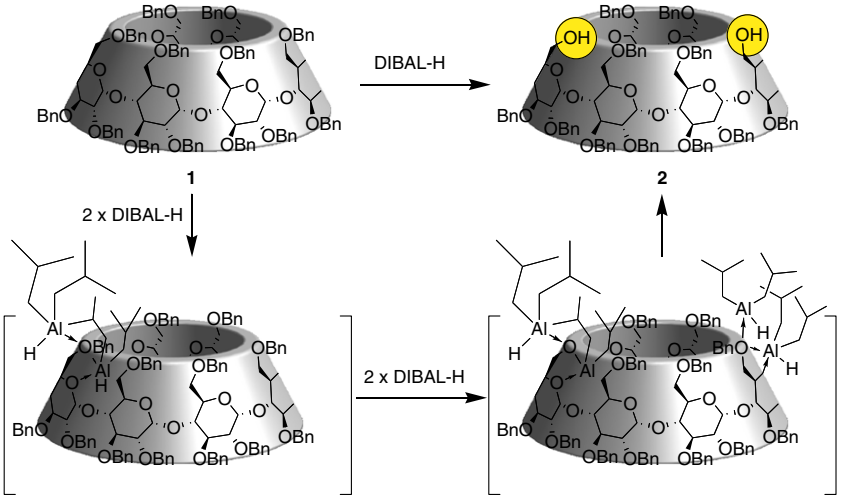


Scheme 1. Debenzylation reactions using isobutylaluminium reagents.



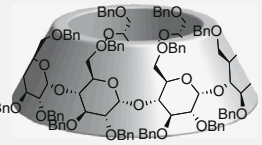
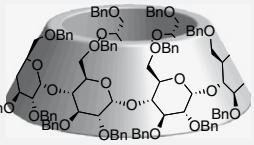
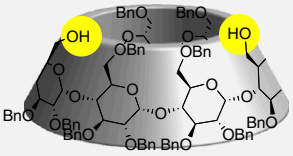
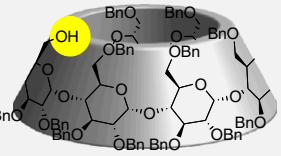
Scheme 2. Proposed debenzylation reaction mechanism involving two molecules of aluminium reagent.

doublet at δ 5.55 ppm (1×CHPh) for monol **3**, to assess the ratio of CD derivatives in the reaction mixture. The results are summarised in Table 1.

To reach the theoretical minimum amount of aluminium reagent, we used 5 equiv, keeping a slight excess, and observed that much higher temperatures than the ones attained with the oil bath were necessary to obtain decent conversions (Table 1, entries 1–6). The most efficient conditions were as follows: 5 equiv of a 1 M solution of DIBAL-H at 150 °C for 30 min gave a reproducible and complete conversion of perbenzylated CD **1** into diol **2** with neither traces of starting material nor monol intermediate **2**, but as in all cases accompanied by some overdebenzylation products detected by TLC (entry 6). These conditions were applied to convert 6 g of material and the CD diol was isolated in 64% yield.[10] We next reduced the quantities of aluminium reagent to 2.5 equiv, hoping that we could obtain monol **2** exclusively. However, these conditions resulted in a dramatic decrease of reaction kinetics, requiring an increase of the reagent concentration as well as longer reaction times to observe significant conversions (entries 7–12). Monol **3** was obtained in a satisfactory 65% yield, but was always contaminated with diol **2**, supporting a faster second debenzylation mechanism (entry 12). However, when comparing entries 6 and 12, even if the latter uses longer reaction times (60 min instead of 30 min) and more concentrated reagent (1.5 M instead of 1 M) only a small quantity of diol is formed probably because only 2.5 equiv of DIBAL-H are present. In order to reduce the proportion of **2** in the mixture, dilution of the aluminium reagent to a 0.5 M solution to slow down the second step was achieved but at least 5 equiv of DIBAL-H were needed to observe some conversion (see entries 7 and 8). Therefore upon treatment of CD **1** with 5 equiv of a 0.5 M solution of DIBAL-H at 130 °C (entries 13–15) or 150 °C (entries 16–20) the highest ratio in favour of monol **3** was reached after 30 min and 5 min respectively but always in the presence of diol **2**.

As a conclusion, we have an easy and fast access to a CD bearing two functionalities on its primary rim using a reduced amount of 5 equiv of DIBAL-H. Beside this practical optimization, which is crucial for further scaling up of the reaction, this work also provides an additional proof sustaining our mechanism proposal in which two aluminium atoms are involved and necessary for the reaction to occur.[3] Another advantage of our methodology is related to the relevant choice of benzyl protecting groups, which allows the use of modern efficient chemical reactions in apolar solvents and standard silica gel flash chromatography. Multistep syntheses of CD-based structures with a high degree of complexity are now possible in large scale using the DIBAL-H deprotection under μ-waves irradiation.

Table 1
Ratios of products **1**, **2** and **3** obtained in the μ-waves-assisted debenzylation reaction

Entry							
	Equiv	M	*T* (°C)	*t* (min)	**1**,%	**2**,%	**3**,%
1	5	1	60	60	51	11	38
2	5	1	80	60	7	48	45
3	5	1	100	60	0	72	28
4	5	1	150	15	0	84	16
5	5	1	150	20	0	91	9
6	5	1	150	30	0	100	0
7	2,5	0,5	150	30	95	0	5
8	2,5	0,5	150	60	94	0	6
9	2,5	1	150	30	88	0	12
10	2,5	1	150	60	86	0	14
11	2,5	1,5	150	30	82	0	18
12	2,5	1,5	150	60	22	13	65
13	5	0,5	130	5	21	20	59
14	5	0,5	130	15	15	24	61
15	5	0,5	130	30	13	29	58
16	5	0,5	150	0,5	30	10	60
17	5	0,5	150	1	26	12	62
18	5	0,5	150	5	18	18	65
19	5	0,5	150	15	13	24	63
20	5	0,5	150	30	12	27	61

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9. *General procedure for μ-waves-assisted debenzylation*: Perbenzylated α-cyclodextrine **1** was sealed in the μ-wave vial and purged with nitrogen. Then toluene and DIBAL-H were added at rt. The reaction mixture was heated under μ-waves, then poured on ice. HCl (1 mol L^{-1} in water) and EtOAc were added and the solution was stirred during one hour. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The ratio of perbenzylated cyclodextrine **1**, diol **2** and monol **3** was determined by ^1H NMR.
10. *Optimized procedure for diol* **3** *synthesis*: Perbenzylated α-cyclodextrine **1** (6.0 g, 2.3 mmol) was sealed in the μ-wave vial and purged with nitrogen. Then toluene (3.9 mL) and DIBAL-H (7.7 mL, 11.6 mmol) were added at rt. The reaction mixture was heated at 150 °C under μ-waves for 30 min, then poured on ice. HCl (15 mL, 1 mol L^{-1} in water) and EtOAc (20 mL) were added and the solution was stirred during 1 h. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. After purification by silica gel chromatography (Cy/EtOAc, 4:1), diol **2** (3.6 g, 64%) was obtained as a white foam.