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ARTICLE

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Site-selective hexa-hetero-functionalization of α -cyclodextrin an archetypical C_6 -symmetric concave cycle

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Access to C_n ($n > 4$) symmetric cyclic concave molecules with a different function on each of their n subunits is an unmet challenge. The reason lies in the lack of a post-functionalization method whose site selectivity is sufficiently understood, predictable and modulable to access most functionalization patterns. Here we disclose a new site-directing rule for a debenzoylation reaction on cyclodextrins that solves this problem and allows the unprecedented access to penta- and ultimately hexa-differentiations of such C_6 concave cycles. This achievement opens the access to objects with very high-density information.

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The repartition of atoms in space through chemical bonding is the essence of synthetic chemistry. Chemists developed this ability over time allowing the conversion of small molecules into larger and ever more complex molecular architectures. The understanding and mastering of the rules of what could be once called a handcraft allowed its conversion into an art, the ‘art of total synthesis’ with so impressive achievements that they can be pointed out as master-pieces¹. This field induced the discovery of many new chemical transformations, the development of enantioselective synthesis being a striking example. Another approach consists in derivatizing pre-existing molecules in the diversity of structures offered by Nature. This approach also called semisynthesis has its own impressive realizations, the best illustration being certainly the famous story of taxol. This anti-cancer molecule is found in very low quantities in the bark of yews, so low, that its extraction could threaten the survival of the species. Its semisynthesis from an intermediate, 10-deacetyl baccatin III, abundantly found in the

leaves of the same trees allowed its industrial production². The key in this transformation is the selective reaction of each of the four free hydroxyl groups of 10-deacetyl baccatin III exploiting their innate reactivity differences. Central to this field is the ability to discriminate between functions and/or regions of the molecule, i.e., to achieve chemoselective and/or regioselective reactions, respectively. In other words, site-selectivity is the great challenge. This frontier area ultimately aims to transform any group on a given molecule based on their innate reactivity³ and the tuning of the reagent properties. Some steps towards this goal have been taken in particular with the regioselective C–H activations on complex molecules^{4–6}, but also the selective functionalization of reactive functions such as OH groups^{7–9}, or the regioselectivity in cyclization reactions^{10,11}.

Site-selective reactions occur because small differences in chemical environment, that is, electronic and/or steric properties pre-exist. But there are molecules, which are strictly symmetrical, for which it is thus necessary to create those differences. This is

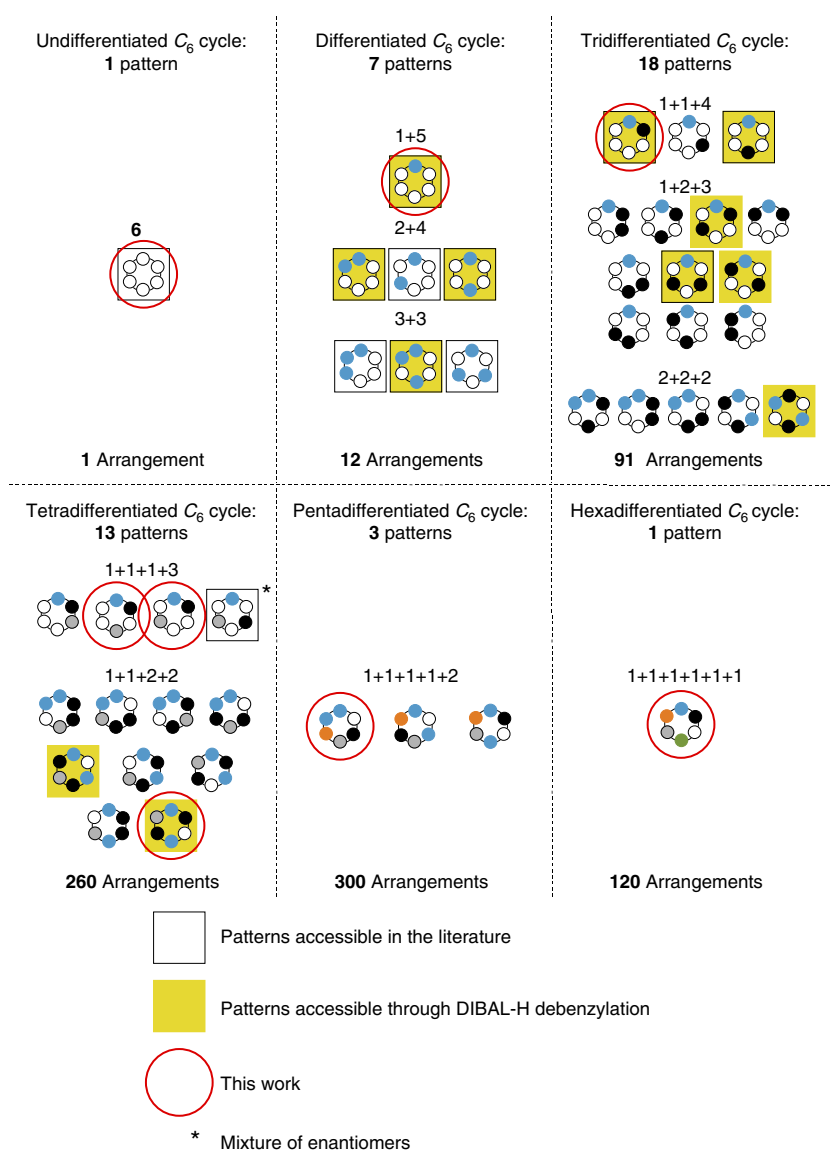


Figure 1 | Functionalization patterns. Schematic representation of all the possible functionalization patterns for C_6 concave cycles, each unit of the molecule is represented as a dot, if two units of the molecule bear two different functions, the dots have different colours. Below each collection of patterns the number of arrangements of the corresponding number of functions is indicated, for example, there are 300 arrangements of exactly five colours on six positions (see Supplementary Discussion).

the case of an important family of compounds: the cyclic concave molecules, which are at the root of supramolecular host-guest chemistry but also find applications in daily life and industry. These include naturally occurring cyclodextrins (CDs), but also synthetic compounds such as calixarenes, cucurbiturils, resorcinarenes, pillararenes, bambusurils, asararenes and so on. Those molecules built upon n identical subunits possess a C_n symmetry that hampers their selective functionalization because of the absence of innate reactivity difference between subunits. Furthermore, most of the time the individual units are isolated electronically from one another; therefore, the difference in reactivity has to rely solely on sterics and more generally on arrangement in space of the reactive sites. In fact, the very high majority of functionalizations of such molecules consists in the addition of one new function once^{12–19} or on all equivalent reactive sites. Even the addition of the same function twice has been the subject of intense research in the past 30 years or so^{20,21}. The extreme difficulty of the poly-hetero-functionalization of C_n symmetric molecules lies in the figures given by combinatorics: for a cycle of C_6 symmetry with six functionalizable sites there are 14 ways to arrange two functions, 130 ways to arrange three functions, 700 ways to arrange four functions, 2,635 ways to arrange five functions and 7,826 ways to arrange six functions. The arrangements of n beads of k colours can be generated on <http://www.jasondavies.com/necklaces/>, which corresponds to the well-known combinatorics problem of necklaces²². In practice, that means that reacting a C_6 functionalizable molecule with six different reagents of equal reactivity statistically leads to a mixture of 7,826 differently functionalized molecules, ranging from 6 molecules bearing six times the same substituent to 120 molecules with six different substituents.

Figure 1 shows the patterns of colour arrangements on a C_6 cycle that are classified according to the number of colours and translated in terms of differentiation of various reactive positions on a molecule. For sake of clarity, only the patterns are displayed and not all the arrangements. As an example, in the differentiated (2 different colours) section, we drew one blue ball plus five white ones, but not the one with five blue balls and one white, which is equivalent in terms of patterns, but which constitutes a totally different species if one thinks of a molecule with two different functions. Thus, the number of possible arrangements is given below each section. The patterns of functionalization that have

already been reported in the literature for all kinds of C_6 symmetric concave cycles are also indicated. It clearly appears that most differentiated cycles are now available. This relatively simple problem of regioselectivity, namely getting a single product out of 14, which could otherwise be separated²³, has been the prime challenge in this area for the past few decades. In the field of CDs, seminal work by Tabushi and Knowles paved the way to compounds with two²⁴ or three²⁵ identical functions in the 1970s and developed in the next 30 years^{20,21}, but heterofunctionalization of CDs was only accomplished after difficult separation of mixtures of regioisomers^{26,27}. It is only recently that strategies to get concave molecules with more than two different functions emerged. For instance a tridifferentiated C_4 resorcinarene, with three different groups, was synthesized en route to superbowl containers²⁸. Tridifferentiated calix(4)arenes were also synthesized as racemic mixtures because of their inherent asymmetry^{29–31}. In the realm of molecules of higher symmetry, C_6 calix(6)arenes with three^{32,33} or even four³⁴ functionalities (tetradifferentiated) have also been described albeit inherently as racemic mixtures. Regarding CDs, tridifferentiated compounds are accessible mainly through three methods: regioselective opening^{35–37} or formation³⁸ of bridged-CDs, imidazolyl-directed sulfonation³⁹ and regioselective debenzoylation^{40–42}. Tetradifferentiation has also been achieved using the last two methods^{39,43,44}.

This quick survey clearly shows a void in the literature: a method whose site directing effects are sufficiently understood, predictable and modulable to access most functionalization patterns, the ultimate challenge being the access to a hexadifferentiated C_6 concave cycle, a task out of sight with current available methodologies. Here we disclose a new site-directing rule for the debenzoylation reaction on CDs that allows the unprecedented construction of penta- and hexadifferentiated concave cycles. This achievement opens avenues to objects with very high-density information.

Results

Site-directing rules. To meet this challenge, it is necessary to delineate enough predictable directing effects for the functionalization of CDs. For some time now we have been developing methods to hetero-functionalize CDs based on the understanding of the mechanism of a deprotection reaction. This reaction is a

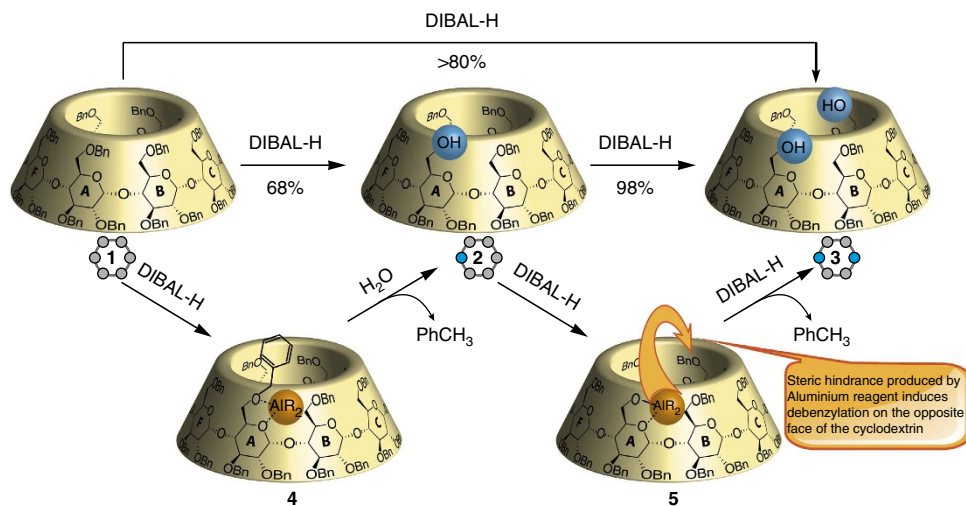


Figure 2 | Basic regioselective DIBAL-H deprotection of benzylated cyclodextrins. Per-benzylated CD 1 affords monol CD 2 or diol CD 3 depending on the reaction conditions. Under the action of DIBAL-H, monol CD 2 is converted into diol CD 3, indicating that the first deprotection orients the second one through steric hindrance induced by the aluminium reagent as shown on CD 5. Approach of DIBAL-H on sugar A is hampered by the presence of benzyloxy on position 6 of sugar B as shown on CD 4.

debenzylation reaction discovered serendipitously^{45,46} and operated by diisobutylaluminium hydride (DIBAL-H) leading to CD A,D-diol **3** from perbenzylated CD **1** (ref. 47). The mechanism of the reaction involves the chelation of the aluminium reagent between the primary and the endocyclic oxygen atoms of a glucopyranosidic unit as shown in CD **4** (Fig. 2). Furthermore, the double deprotection is a stepwise process, because it is possible to isolate monol CD **2** and react it to produce A,D-diol **3** again. Therefore, the first deprotection site-directs the second through steric hindrance of the aluminum oxide on intermediate **5** (Fig. 2).

This breakthrough allowed us to devise an easy and selective access to tridifferentiated CDs, and only recently did we report a route to tetradifferentiated ones. Hence, we have developed two different ways to site-direct a second debenzylation of functionalized CDs built on the reaction mechanism. In a first instance, we have shown that an azido group on sugar A of benzylated CD **6** was directing a debenzylation reaction mediated by DIBAL-H on the diametrically opposed sugar D to give CD **7** (ref. 40; Fig. 3a) This directing effect was attributed to the crowding induced by the attachment of the aluminium reagent to the nitrogen during the primary azide reduction in a similar way as in the conversion of **2** in **3**. In a second instance, we showed that steric decompression on the primary rim of the CD, caused by a vinyl group on sugar A of CD **8**, directed the deprotection reaction on the adjacent clockwise (viewed from the primary rim) sugar F to give CD **9**. This directing effect is the consequence of both the cyclic directionality of the CD, and the asymmetric effect of the substituents of neighbouring sugars on the approach of the aluminium reagent. This can be seen on CD **4** where the aluminium atom on unit A lies in the region of the benzyloxy group of the counterclockwise (view from top) sugar B (Fig. 2). Reversely, suppressing the benzyloxy group in sugar A as in **8** favoured approach of Al on its clockwise unit F to give **9**. This decompression could be accomplished in two ways either through replacement of the benzyloxy group in sugar A by less crowded methyl or vinyl groups as in **8** giving the clockwise F-monol **9** (Fig. 3b) or by bridging two diametrically opposed glucose units A and D as in CD **10** to give C,F-diol **11** (ref. 41; Fig. 3c). A higher degree of complexity was reached through combination of both methods, in a 'frustration' strategy, where a 6-vinyl sugar D was placed opposite to azido-derived sugar A in CD **12**, the action of DIBAL-H afforded an unexpected tetradifferentiated CD C,E-diol **13** (ref. 44; Fig. 3d). This combination of rules allowed the access to tetradifferentiated CDs in a very regioselective manner. However, this route is a dead-end towards hexadifferentiation of CDs, on the way of which we need to pass through a CD exhibiting three new functions added once each. The mono-functionalization of diol **13** would only lead to a statistical mixture of products. In fact, five site-directed mono-debenzylation are necessary to access the ultimate hexadifferentiated functionalization pattern.

Dissymmetrical bridge as a new site-directing tool. To reach that goal, we reasoned that we could combine our two rules in a different manner. Bridging A-amino,D-alcohol CD **7** could produce a dissymmetrical bridge with a sterically decompressed ether side D and a functionalizable secondary amine side A. Functionalization of the amine side A with a bulky group would prevent deprotection in its vicinity on sugar F and induce the desired third mono-deprotection only on sugar C. Hence, A-amino,D-alcohol CD **7** was methallyl-bridged to afford CD **14** in 55% yield. The amine in sugar A was further derivatized with a benzyl group to give **15** in 96% yield. Much to our disappointment, subsequent treatment with DIBAL-H only yielded either a mixture of

compounds or a C,F-diol **17** (65% yield) upon prolonged reaction time corresponding to a bis clockwise debenzylation. Use of a bulkier protecting group such as 3,5-di-tert-butylbenzyl did not induce any preferred deprotection affording C,F-diol **18** in 73% yield from CD **16**. Paradoxically, a regioselective mono-deprotection on sugar C was observed starting from unprotected A-amino,D-ether bridged CD **14** yielding CD **19** in 62% yield. The corresponding C,F-diol **20** could be obtained only under more forcing conditions ($T > 60^\circ\text{C}$, N_2 flux, longer reaction time), albeit in a rather moderate 42% yield (Fig. 4).

At first glance, this result violates the established directing rules mentioned above: the debenzylation occurs next to a bulky tertiary amine and not next to the secondary amine. We therefore hypothesized that DIBAL-H was complexing the secondary amine congesting the region surrounding the amine. The clockwise deprotection is then eased at the ether terminus of the bridge rather than next to the aluminium adduct. To sustain this proposal, we reacted the secondary A-amine **21** with DIBAL-H, and observed a clean formation of the expected diametrically opposed A-amino,D-hydroxy CD **22** in 65% yield. This regioselectivity derives from the directing effect of a first DIBAL-H molecule interacting with the secondary amine on sugar A producing **23**, and inducing the usual steric orientation of the second DIBAL-H on the diametrically opposed sugar unit D. (Fig. 5) The difference in bulk between a diisobutyl aluminium

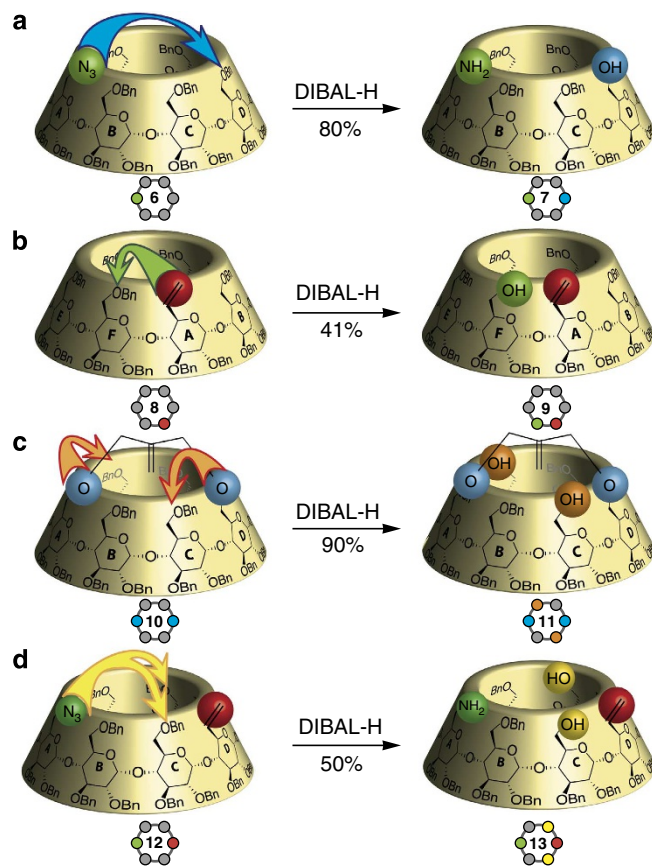


Figure 3 | Site-directing debenzylation effects on CDs. (a) A-azido CD **6** undergoes a tandem azide-reduction/O-debenzylation on the diametrically opposed sugar D to give CD **7**. (b) A vinyl group on sugar A of CD **8** induces a clockwise deprotection on sugar F to give CD **9**. (c) A,D-bridged CD **10** undergoes a double clockwise deprotection to afford C,F-diol CD **11**. (d) A frustrated A-azido, D-vinyl CD **12** undergoes a double deprotection on both sides of the vinyl group to give C,E-diol CD **13**.

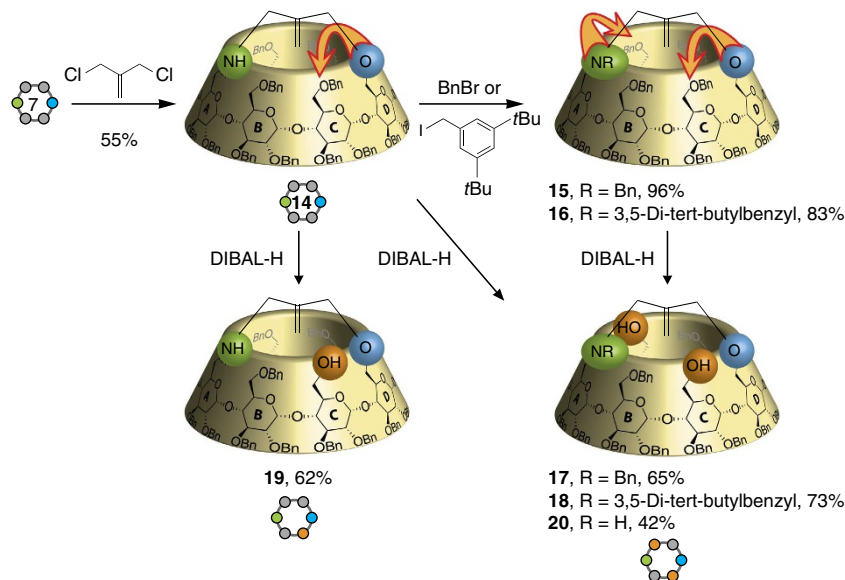


Figure 4 | Site-directing effect of an amino-ether bridge. A-amino,D-hydroxy CD **7** is methallyl bridged to give CD **14**. If the amine is protected as in CDs **15** and **16** DIBAL-H induces a double clockwise C,F-deprotection to give CDs **17** and **18**, respectively. If the amine of the bridge is not further protected as in CD **14**, DIBAL-H only induces a monodeprotection on sugar C clockwise to the ether moiety of the bridge on sugar D to give CD **19**. Complete experimental details and characterization are supplied in Supplementary Methods.

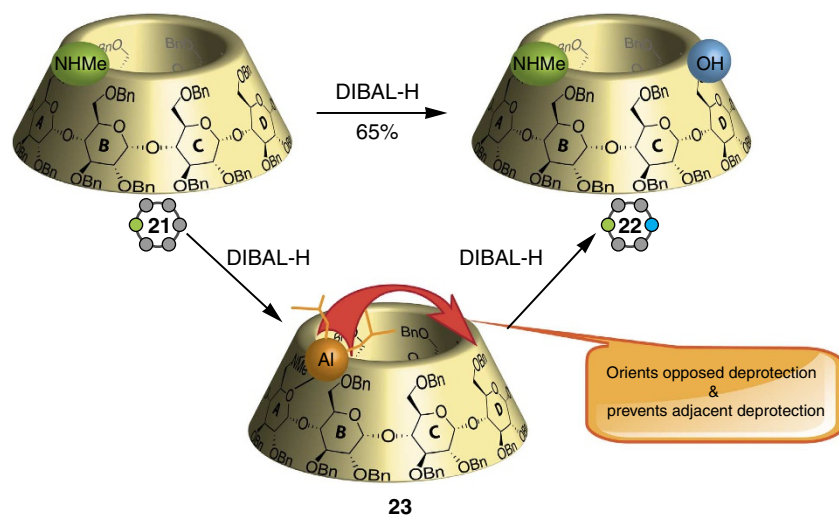


Figure 5 | Secondary amine site-directing effect through attachment of an aluminium reagent. When secondary amine-CD **21** is reacted with DIBAL-H, a diametrical deprotection occurs on ring opposite sugar D to give **22**. This indicates that the aluminium reagent attaches to the amine to give **23** to operate a site-direction through steric hindrance.

adduct and a benzyl group indeed accounts for the difference in reactivity between CDs **14** and **15**.

Synthesis of hexadifferentiated CDs. This breakthrough allowed us to plan the synthesis of the ultimately hexadifferentiated CD, displaying one unique functional group on each sugar unit. The first monodebenzylation was operated on perbenzylated CD **1**, to give monodifferentiated CD **2** in 64% yield⁴³. The free alcohol on sugar A was oxidized to the corresponding aldehyde and olefinated to afford the A-vinyl CD **8** in 90% yield. According to our previously established rules, sterically decompressed CD **8** underwent regioselective DIBAL-H-mediated debenzylation on sugar unit F adjacent to sugar A bearing the vinyl group to give CD **9** in 41% yield (64% based on recovering starting material)⁴³. The

hydroxyl group in tridifferentiated CD **9** was converted into an azido group using conventional procedures. The F-azido, A-vinyl CD **24** underwent a tandem azide-reduction/*O*-debenzylation reaction to afford the expected tetradifferentiated F-amino, C-hydroxy, A-vinyl CD **25** in 78% yield. Methallyl bridging of CD **25** gave the C,F-capped CD **26** (72%), which was monodebenzylated to give pentadifferentiated CD **27** in 56% yield, deprotection occurring on adjacent sugar B and clockwise to the ether moiety of the bridge following the new site-directing rule. The next step consisted in the duplication of the tandem reaction, that required amine protection in sugar F to avoid association with aluminium, which prevents efficient adjacent deprotections, as shown in the case of CD **14** (Fig. 4). In contrast, F-amino, B-azido CD **28** exclusively gave the diametrically opposed B-amino, E-hydroxy CD **29** in 70% yield, the first hexadifferentiated CD bearing six

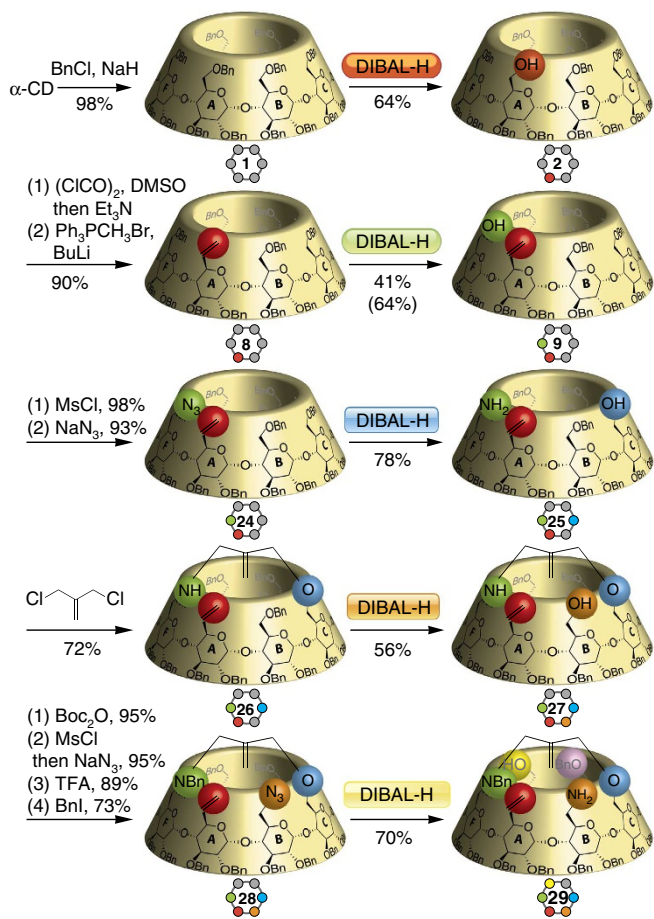


Figure 6 | Hexadifferentiation of α -CD through five successive site-directed DIBAL-H mono-debenzylations. Complete experimental details and characterization are supplied in Supplementary Methods.

different functional groups on its primary rim that is one different function on position 6 of each sugar units (Fig. 6).

Further chemical transformation of hexadifferentiated CD **29** allows the synthesis of CD **30** possessing six orthogonal functions: amine, alkene, azide, alcohol, ether and chloride. The reaction sequence consisted in the Boc-protection of the amine, chlorine substitution of the alcohol, deprotection of the bridge and azidation of the amine (Fig. 7). It is also possible to form another regioisomeric hexadifferentiated CD **32** using a different order of reactions starting from pentadifferentiated CD **28**. Hence, bridge-deprotection, azidation of the formed primary amine, methylation of the secondary amine and conversion of the hydroxyl group into a chloride affords pentadifferentiated CD **31** starting from CD **28**. CD **31** possesses five orthogonally functionalizable sites. Finally, action of DIBAL-H to operate a tandem azide reduction and diametrically opposed debenzylation affords hexadifferentiated CD **32** regioisomeric to CD **30** after azidation (Fig. 7).

Discussion

We now have in hand an ensemble of rules for the site-directed debenzylation of polybenzylated CDs that demonstrated its versatility in the accomplishment of the ultimate hexadifferentiation of this class of C_6 concave cycles. Incidentally, we also synthesized a pentadifferentiated CD, a level of complexity unreached before, and accessed two new tetradifferentiation patterns. We thus believe that our method is able to accomplish on-demand polyheterofunctionalization of CDs. Considering that monofunctionalization itself tremendously expanded the range of applications of CDs, it is easily foreseeable that increasing the degree of functionalization on molecules able to include guests and self-assemble will lead to objects with high-density information, which may find applications in areas as diverse as theragnostics, energy and smart materials.

Methods

Synthesis. Synthesis of all compounds are described in detail in Supplementary methods.

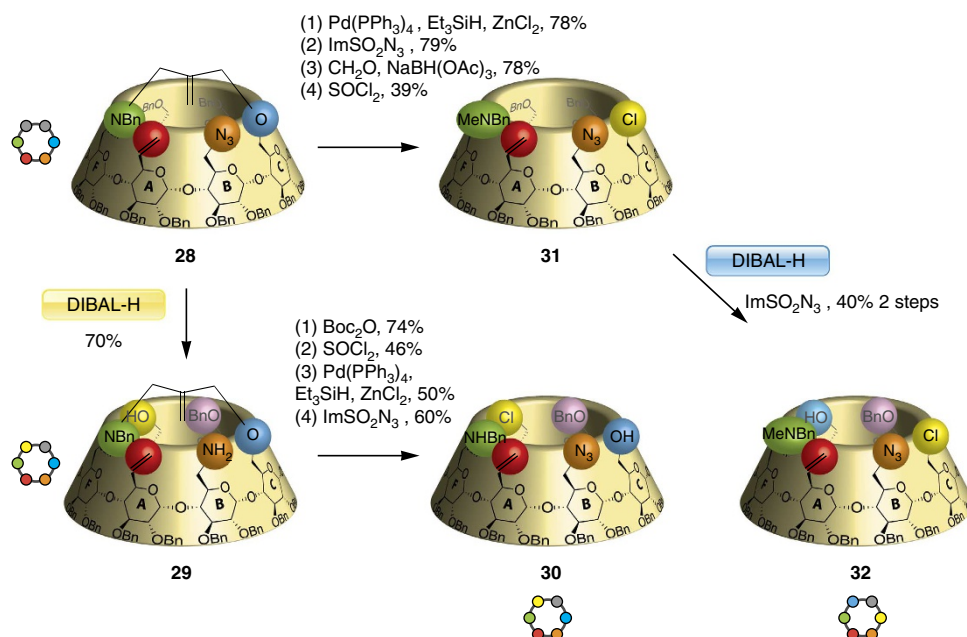


Figure 7 | Protecting group manipulation of penta- and hexadifferentiated α -CDs. Complete experimental details and characterization are supplied in Supplementary Methods.

Structure determination. All new compounds were thoroughly characterized by NMR spectroscopy, rigorously establishing the pattern of functionalization, see Supplementary Figs 1–26, Supplementary Tables 1–6 and Supplementary Methods. As a characteristic example, the detailed NMR analysis of hexadifferentiated CD 29 is given in the Supplementary Discussion.

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Author contributions

B.W., E.Z., S.G. and M.P. performed the syntheses; B.W., E.Z., S.G., M.P., M.G. and M.M., analysed the NMR data, M.M., Y.B., Y.Z. and M.S. analysed the data, M.S. designed the study and wrote the paper; all authors discussed the results and commented on the manuscript.

Additional information

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