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Cap-Assisted Synthesis of Hetero-Trifunctional Cyclodextrins, from Flamingo Cap to Bascule Bridge

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This microreview focuses on the use of cyclodextrin-capping for the selective synthesis of cyclodextrins bearing three different functionalities. Three strategies have been employed and are discussed: dissymmetrical capping, regioselective opening of a symmetrical cap, and the more efficient cap-oriented regioselective deprotection.

Cyclodextrins (CDs) are naturally occurring water-soluble concave molecules possessing hydrophobic cavities. They are made up of six, seven or eight glucopyranosidic units linked in an α-1,4 fashion to form α-, β- or γ-CDs respectively (Figure 1).

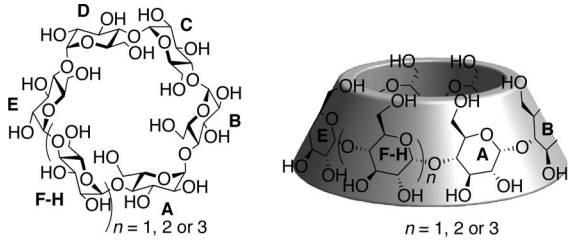

Figure 1. Structures of cyclodextrins.

Because of the high degrees of symmetry of those molecules and the similar reactivities of all their alcohol functions, selective functionalisation of CDs is a difficult task and has been very intensively studied. Out of all the possible patterns of functionalisation, only a small number are accessible in the literature.[1] Many of the published protocols for the preparation of CD derivatives also suffer from several limitations, such as low yields, poor regioselectivity and long reaction times; furthermore, products generally require time-consuming chromatographic purifications. Two major problems are encountered when one wants to functionalise a cyclic structure made up of identical subunits: control on the one hand of the number of similar functionalities introduced and, on the other hand, of the positions at which the modifications are introduced. Nonetheless, perfunctionalisation of all OH groups or access to all OH-2, OH-3 or OH-6 groups individually has been solved on the basis of small reactivity differences and is even used industrially. Monofunctionalisation in satisfactory yields can also be achieved by controlling the amounts of reagents used. A more complex task, which has been the cause of a lot of work for many years, consists of the functionalisation of two positions. With regard only to the primary rim, three strategies have been delineated to tackle this problem.

The first one is based on the use of sterically hindered reagents and for geometrical reasons has proved to be mainly efficient on α-CDs (Method A in Figure 2).[2] The second is also based on steric hindrance but in a reverse strategy. Our group developed a regioselective deprotection approach giving a very high-yielding route to A,D-functionalised CDs, the selectivity probably being enhanced by the hindrance of the rim as well as that of the reagent.[3] It is worth noting that this methodology is equally efficient on α- and β-CDs (Method B in Figure 2). The third func-

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tionalisation strategy consists of the selective capping of two positions on the rim, with certain positions on the rim being targeted selectively in a manner depending on the geometry of the cap;[4] it has mainly been developed on β-CD (Method C in Figure 2).

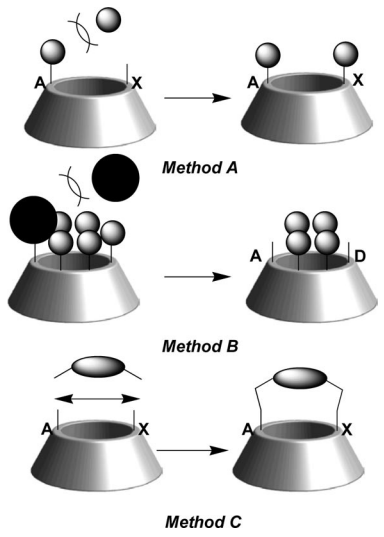


Figure 2. General methods for difunctionalisation of CDs.

The next challenge in this area is the introduction of two different functionalities, a process referred to as tridifferentiation of the rim, because three different functional groups (including hydroxy groups) are afterwards present on the rim. Excellent reviews on functionalisation of CDs[1] and more recently on CD-capping[4] have been written, but efficient access to tridifferentiated CDs is only a recent field of study and little has been written on this specific subject. The capping strategy is a powerful tool for difunctionalisation of CDs and is now finding use to achieve tridifferentiation of the primary rim. Introduction of two different functionalities onto CDs has been achieved through cyclodextrin dissymmetrical capping, by regioselective opening of a symmetrical cap, and more efficiently by cap-oriented regioselective deprotection, and this is the focus of this review.

Dissymmetrical Capping

The introduction of a dissymmetrical cap on the primary rim, proposed by Tabushi, was the first strategy for the introduction of two different functional groups onto β-CDs.[5] An *N*-benzyl-*N*-methylaniline-*p*,*p'*-disulfonate cap was introduced onto β-CD (Scheme 1) and was then oxidised with *m*CPBA to give the *N*-oxide derivatives **1**–**4** in 17% overall yield. The idea was to differentiate the two sides of the cap in terms of reactivity. Subsequent nucleophilic attack of sodium azide hence only takes place on the more electrophilic position; it is followed by the complete displacement of the cap by a thiophenol. The resulting product is therefore a tridifferentiated CD functionalised with an azido group and a thioether. In the original publication the regiochemical outcome of the reaction was rather unclear, although the authors converted their capped CD into a diiodide and compared it with a compound obtained through iodine displacement of a diphenylmethane-capped CD.[6] This, however, appeared to be a mixture of A–C and A–D regioisomers.[7] Furthermore, the cap can be oriented either in A–C or C–A manner, and in the end it seems that the final product is a mixture of the four products **5**–**8**. This is the result of the relative lack of regioselectivity of the cap, combined with its inability to differentiate the cyclic directionality of the CD. Tabushi called this strategy the "flamingo cap", because after the first reaction with sodium azide the cap is standing on one leg as flamingos do. (Scheme 1).

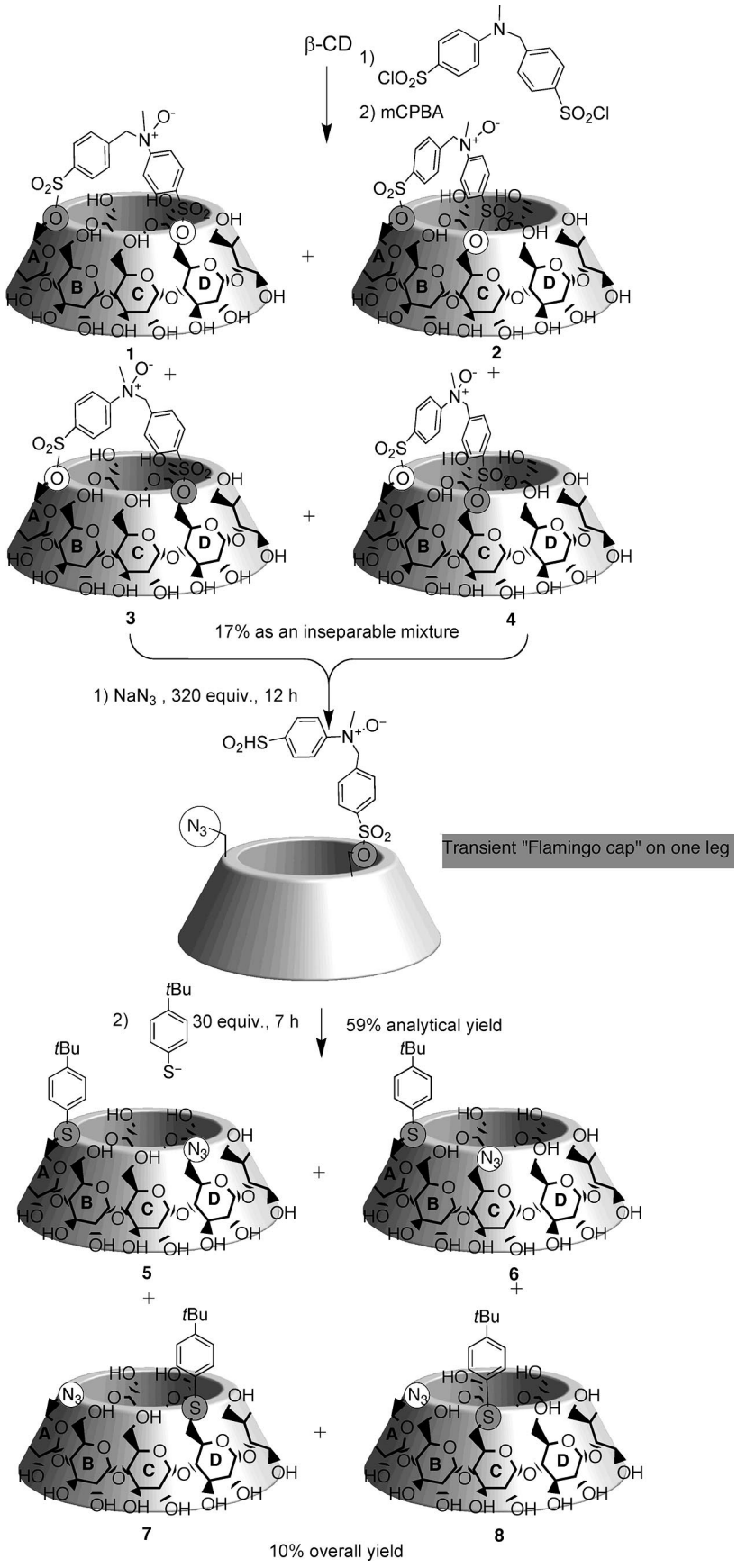
Breslow introduced an asymmetric cap at positions A and B via the diiodo-substituted CD **9** (Scheme 2), obtained through A,B-capping of β-CD. CD **9** was next treated with an asymmetric racemic dithiol to give a mixture of two pairs of regioisomeric diastereoisomers: **10** and **11**. Regioselectivity of the heterocapping was thus achieved, because only cycles A and B are functionalised, but the problem of the differentiation of the directionality was still unresolved because no discrimination between cycles A or B is exerted by the functional group.[8] (Scheme 2).

It is only very recently that a capping reaction that is both distance- and direction-selective was first described, by Fujita on γ-CD. The monotosylated γ-CD **12** (Scheme 3) was treated with L-cysteine, which reacted through its thiol group to afford the monofunctionalised CD **13**. The amino group was functionalised with a dansyl moiety, and the resulting acid CD **14** was subjected to esterification reaction conditions to afford the tridifferentiated CD **15** in 53% yield (estimated 7% from γ-CD).[9] To elucidate the structure of CD **15**, the authors independently prepared both regioisomers from precursors in which the regioisomery had been determined by a combination of amylase-promoted degradation and post-source decay mass spectrometry.[10] In a first approach the authors attributed this selectivity to a topological effect, through which the hindered dansyl group is preferentially located outside the cavity.

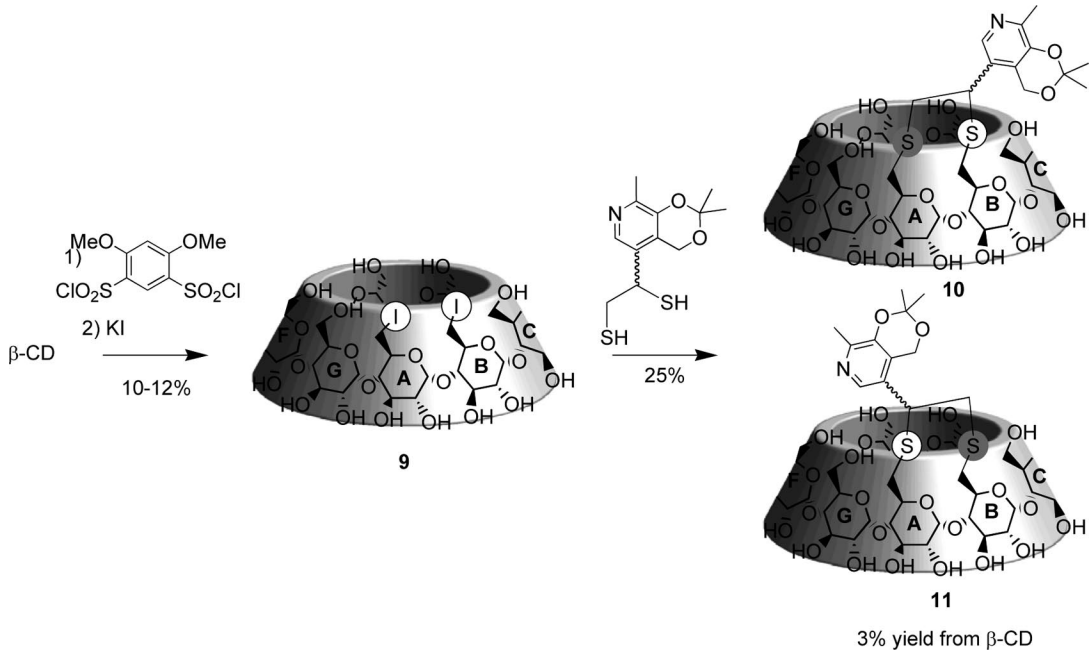
However, when they next turned their attention to β-CD, Fujita and Yuan found that the topology of the appended dansyl group had no influence on the reactivity. Indeed, with inversion of the stereogenic centre on the cysteine both *exo* and *endo* topologies were obtained in CDs **18** and **20** (Scheme 4), obtained from L- and D-cysteine, respectively, in 8–12% overall yields from β-CD by use of the same synthetic pathway as for γ-CD. Whatever the stereoisomery of the capping cysteine, it is the oxygen O-6^G that reacts. The orientational selectivity hence seems to originate in the directionality of the CD rather than in the topology of the formed cap.[11]

Regioselective Cap-Opening

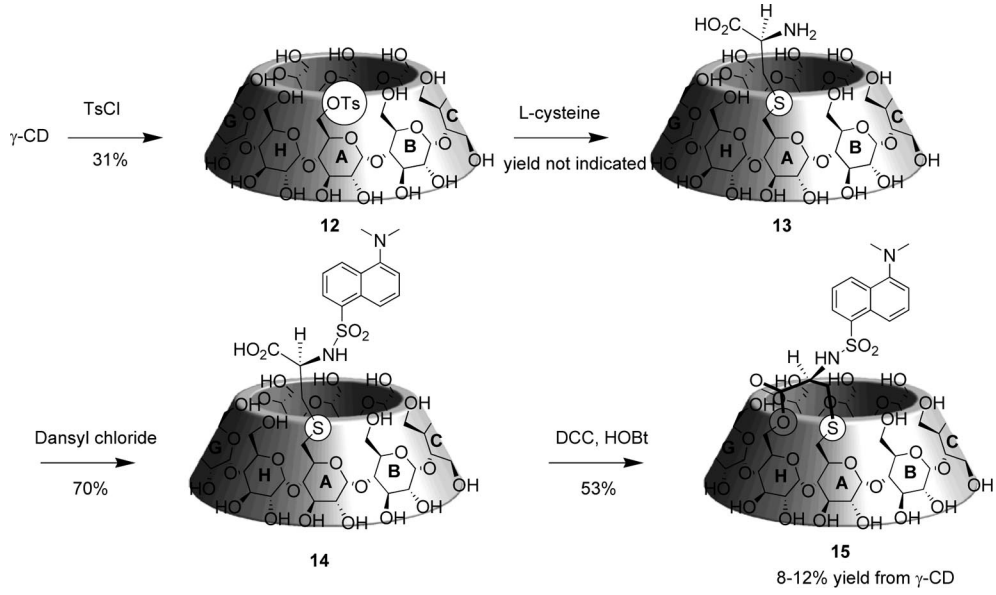
The reverse strategy, in which a cap is regioselectively opened, is also possible. Yuan and Fujita reported a very elegant regioselective attack of a symmetric disulfonated bridge (Scheme 5). The 6^A,6^B-mesitylenedisulfonyl-capped



Scheme 1. The flamingo cap.



Scheme 2. Breslow's A,B hetero-capping.



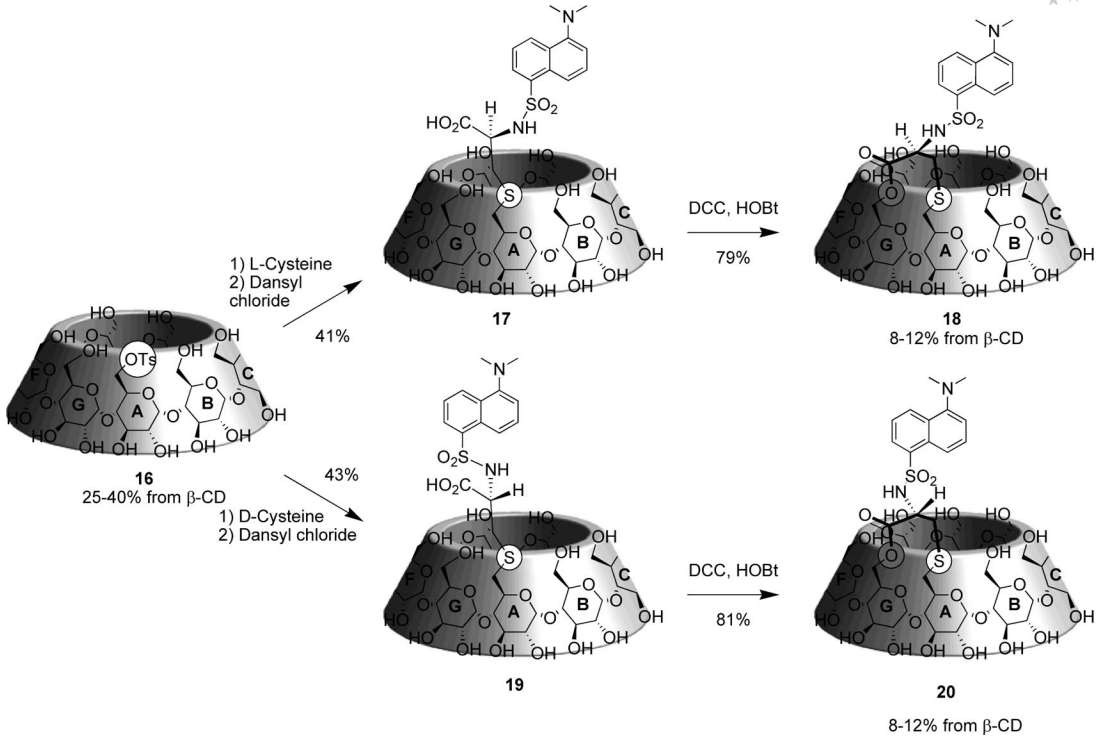
Scheme 3. Regioselective clockwise hetero-capping of γ-CD.

β-CD **21** was synthesised in 19% yield from β-CD and subjected to treatment with imidazole. This reaction resulted in the remarkable formation of the major product **22** (42%) together with traces of regioisomeric CD **23** (4%).[12]

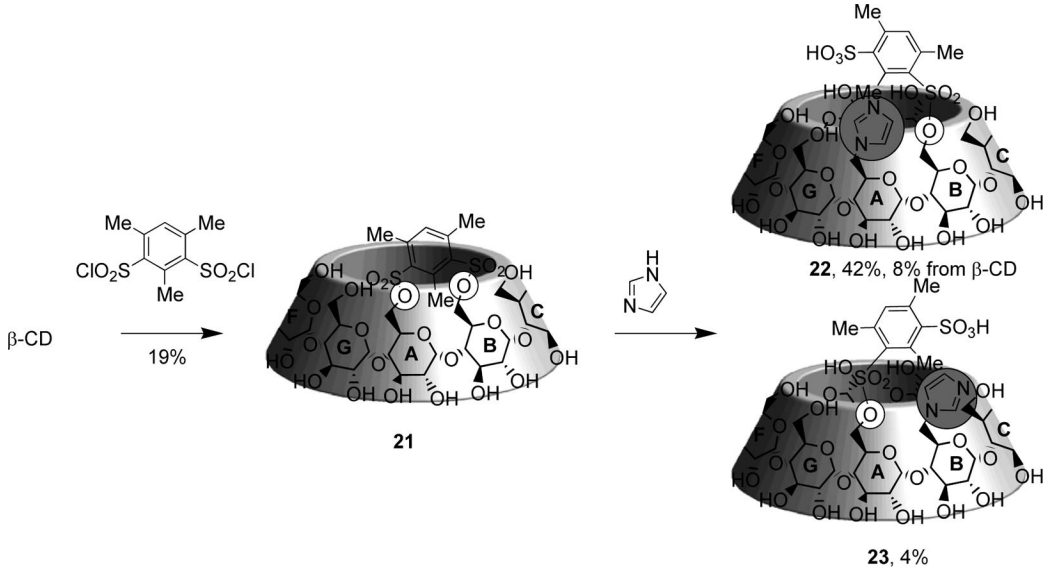
This reaction is to be compared with the nucleophilic substitution on 6^A,6^B-diiodo-CD by imidazole, which afforded a 3:2 mixture of the two regioisomeric mono-imidazolyl-mono-iodo-substituted CDs.[13] The capping is therefore clearly playing a role in the amplification of the reactivity difference between positions 6^A and 6^B in CD **21**. It seems that the cap is positioned so as to hinder position 6^B and therefore favours the approach to 6^A (Figure 3).

Cap-Oriented Reactivity

We have just outlined how capping of a CD could be dissymmetric in the cap formation or, more rarely, in its opening. A conceptually different approach was designed by our group when we showed that capping of CDs can



Scheme 4. Selectivity of hetero-capping on β-CD independent of topology.



Scheme 5. Regioselective cap-opening.

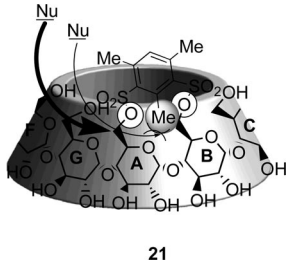
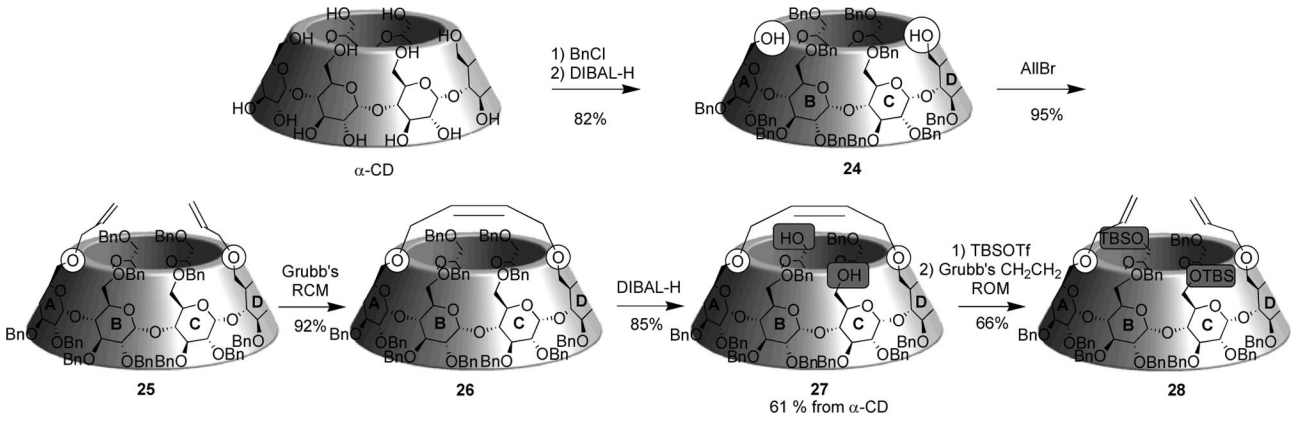
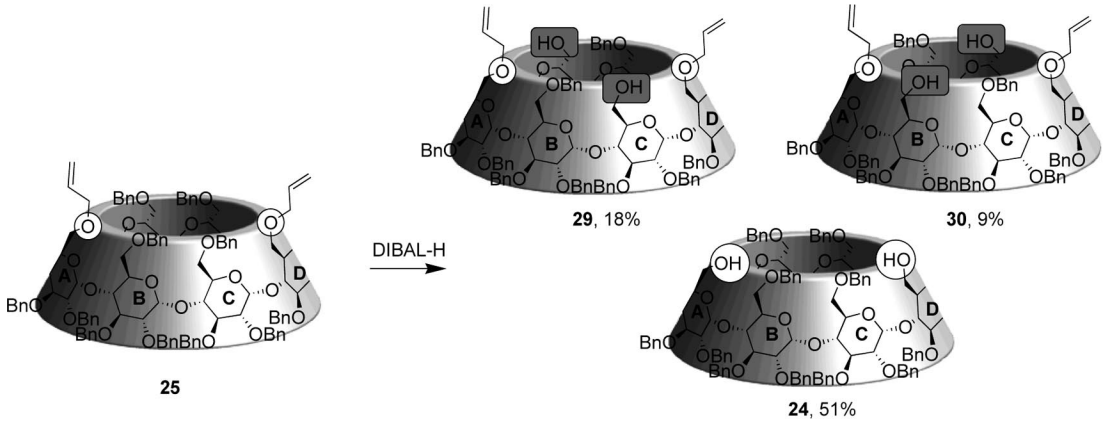


Figure 3. Steric hindrance of a methyl group of the cap accounts for the regioselectivity of the nucleophilic displacement.

induce changes in the reactivities of the neighbouring glucose units in a DIBAL-H-induced deprotection reaction.[3] A striking example of this strategy is shown in Schemes 6 and 7. The capped CD **26** is deprotected with DIBAL-H to give the single diol **27** in 85% yield, whereas the uncapped CD **25** under the same reaction conditions affords three diols – **24**, **29** and **30** – resulting from a deallylation and two debenzylation reactions, respectively, clearly underlining the critical importance of the capping of the CD for regioselectivity.[14] It is worth noting that the capped CD **26** was synthesised in 72% yield from α-CD by a classical perben-



Scheme 6. Bascule bridge strategy for the synthesis of tridifferentiated cDs.



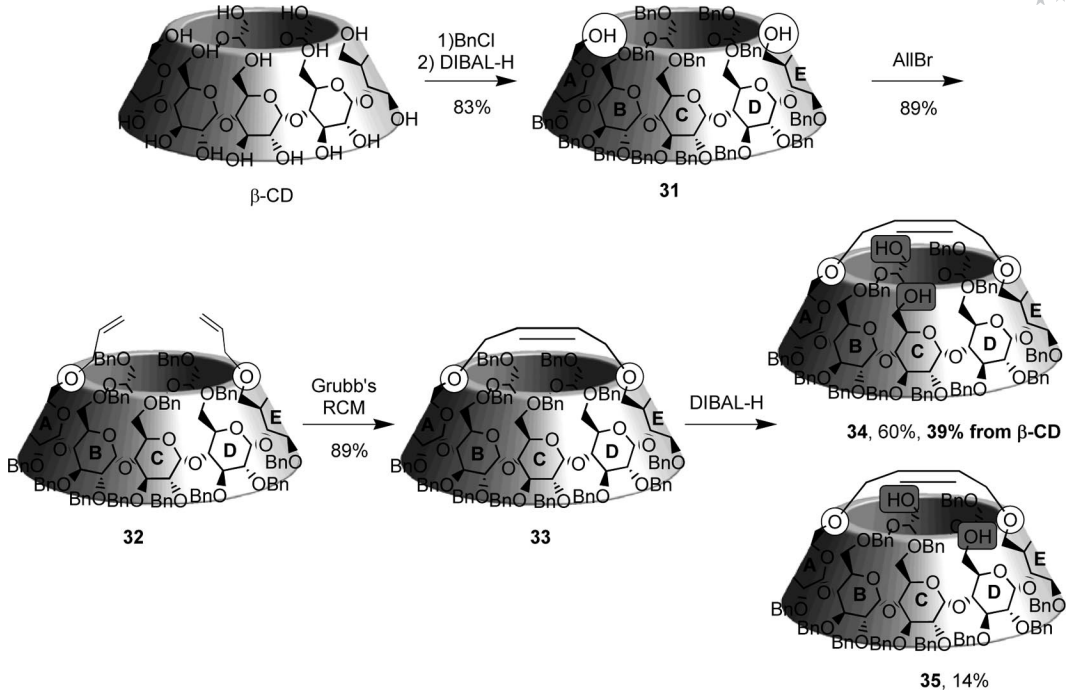
Scheme 7. Open bridge.

zylation/bisdebenzylation sequence, followed by allylation of the diol and ring-closing metathesis (RCM), such that the tridifferentiated CD **27** is produced in 61% overall yield from α-CD. Thanks to the reversibility of the metathesis reaction, it is possible to restore allyl protecting groups from the cap through ring opening metathesis (ROM), through which CD **28**, possessing three orthogonal protecting groups, is obtained. We called this iterative RCM-ROM process the bascule bridge strategy because it is reminiscent of the machinery of such a bridge (Scheme 6).

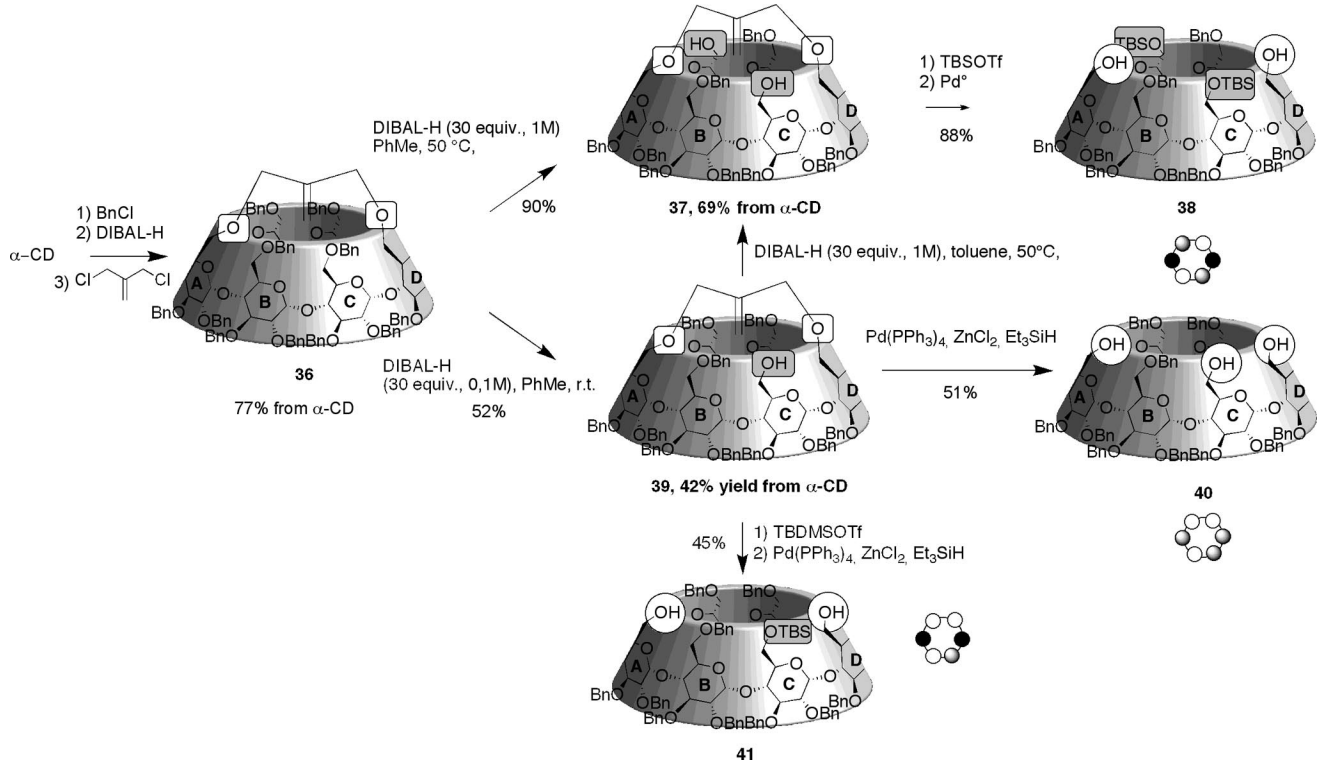
The same strategy was employed with β-CD, which was perbenzylated and 6^A,6^D-bis-debenzylated to provide **31** (Scheme 8) in 83% yield over two steps. Double allylation and RCM catalysed by the Grubbs catalyst afforded the bridged CD **33** in 79% yield. In this case, treatment of CD **33** with DIBAL-H afforded the major diol **34** together with the regioisomeric diol **35**, in 60% and 14% yields, respectively.[15] Tridifferentiated CD **34** was obtained in 39% yield from β-CD; it is worth noting that the bridge serves as a protecting group because it can be removed selectively through Pd^0-catalysed reaction.[16].

This strategy was optimised thanks to a direct method for capping of diol **24** introduced by Bols:[17] the capped CD **36** (Scheme 9) was produced in 77% yield from α-CD. DIBAL-H-induced deprotection on **36** afforded the tridifferentiated CD **37** in 90% yield (69% from α-CD). As in the case of the bascule bridge, it is possible to remove this cap in excellent yields by treatment with Pd^0 to afford the tridifferentiated uncapped CD **38**.[18] The DIBAL-H-induced deprotection reactions are very sensitive to its concentration, so it is therefore possible to delineate reaction conditions to produce mainly monodeprotected compounds. Applied to the capped CD **36**, the mono-debenzylation reaction afforded the alcohol **39** in 52% yield (42% from α-CD). This tridifferentiated CD **39** can be further transformed into the triol **40** or the diol **41** by use of the Pd^0-catalysed double deallylation reaction to remove the cap.[19].

A characteristic of this methodology is not only its extreme efficiency in terms of chemical yields but also its complete rationalisation and therefore predictability. Indeed, this strategy was rationally designed on the basis of the DI-

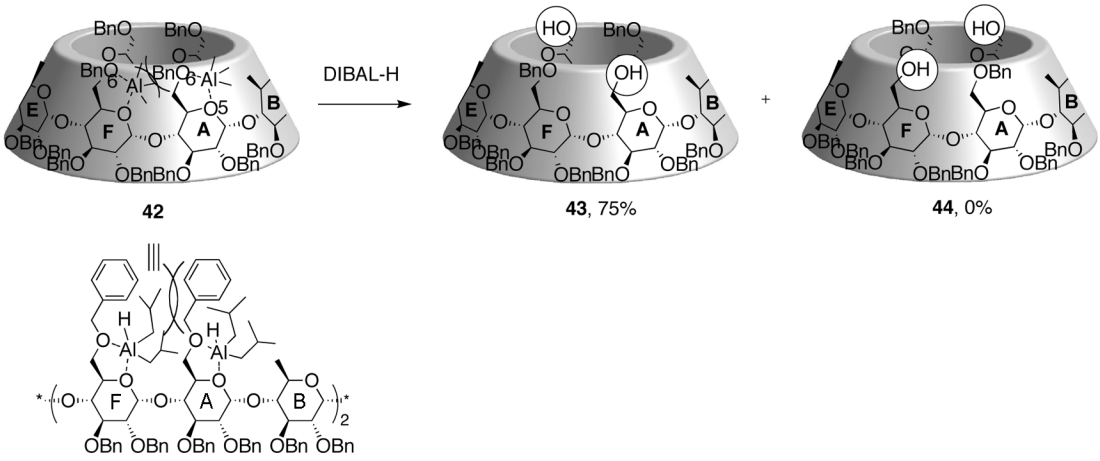


Scheme 8. Bascule bridge on β-CD.



Scheme 9. Optimised tridifferentiation of α-CD.

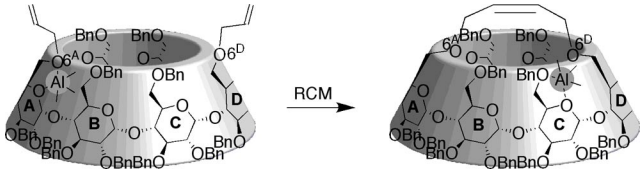
BAL-H-induced debenzylation reaction mechanism.[3] The approach of the aluminium reagent towards a glucopyranoside unit of the CD is highly sensitive to the steric hindrance exerted by the protecting group located on the primary position of the neighbouring counterclockwise sugar. As shown in Scheme 10, the approach of an aluminium reagent towards the O-5/O-6 pair of cycle **F** is hindered by the presence of a benzyl moiety on the 6-position of the counterclockwise sugar **A**. Because of the cyclic directionality of the CD, the reverse is not true: the 6-benzyloxy group of the clockwise sugar **F** seems to be too far away to interact with the aluminium reagents on sugar **A**. Therefore,



Scheme 10. The approach of the aluminium atom towards cycle **A** is hindered by BnO at the 6-position of cycle **B**, so the steric decompression on cycle **B** induces the kinetically favoured approach of aluminium towards cycle **A**.

when the benzyloxy group is removed, as in deoxy-CD **42**, cleavage of the benzyl group by DIBAL-H occurs only on cycle **A** as a result of the steric decompression at this position and no reaction is observed on cycle **F** because the approach of the aluminium reagent is still hindered by the presence of the benzyloxy group on sugar **A**[20] (Scheme 10).

It is also steric hindrance that accounts for the regioselective clockwise debenzylation reaction of the bascule-bridged CD **26** to afford the diol **27**. Indeed, we showed by molecular modelling that the tetramethylene-capping of the CD induces an orientation of O-6^A and O-6^D towards the inside of the cavity.[3] Very interestingly, this conformational change precludes the formation of chelates on these glucose moieties, making the cap DIBAL-H-resistant. Furthermore, the capping relieves steric hindrance on sugar units **C** and **F**. Therefore, cleavage of the benzyl groups can only occur on cycles **C** and **F**, where the approach of aluminium reagent is kinetically favoured in relation to cycles **E** and **B**, where it is hindered by the benzyloxy groups on **C** and **F**, and cycles **A** and **D**, where the O-6 oxygen atoms are inaccessible because they are inside the cavity (Scheme 11).



Scheme 11. Capping of the CD induces regioselectivity.

The capping strategy is a powerful tool for hetero-trifunctionalisation of cyclodextrins, provided that it is both distance- and direction-selective. It is worth noting that two other methods of tridifferentiation, published by Fujita and Yuan[21] and by ourselves,[22] based not on capping but on distance as well as directionality of the CD are available. In relation to all the possibilities, however, only a few patterns of heterofunctionalisation are accessible, and it will be a long time before we can selectively modify each glucose moiety individually, which constitutes the holy grail in this research (Figure 4).

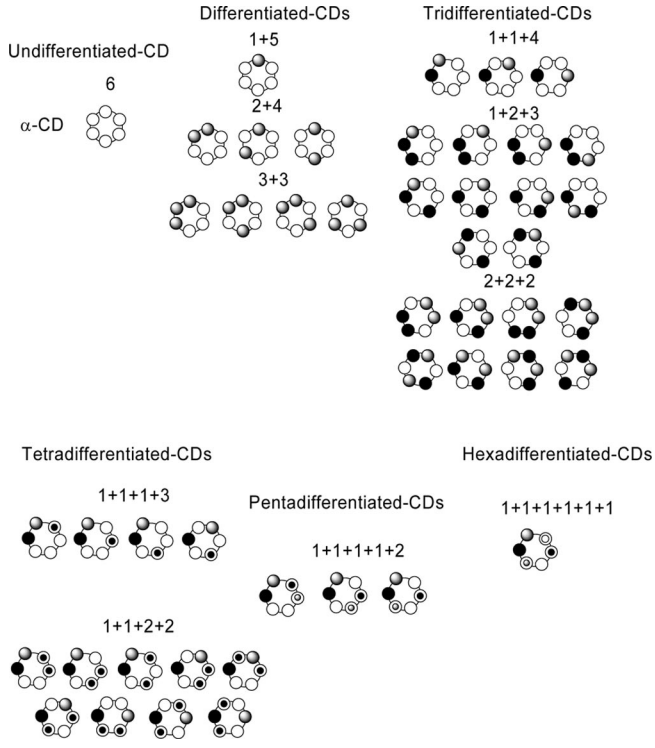


Figure 4. All patterns of functionalisation of the primary rim of α-CD.

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