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Implementing the "Catch-and-Release" Concept into a Simple Method for Regioselective Cyclodextrin Modification

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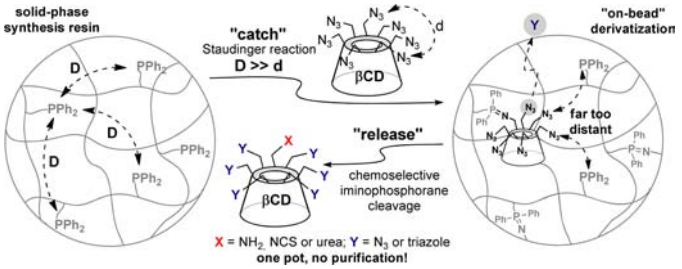
ABSTRACT



Differentiation of specific positions in axial-symmetrical cyclodextrins (CDs), exhibiting a dense display of identical functional groups, is challenging. A novel strategy toward this goal that exploits a solid matrix to display the complementary reagent functionalities sufficiently far from each other to prevent CDs from reacting through more than one site is reported. Using a "catch-and-release" process based on the Staudinger reaction, the utility of this concept to easily produce complex CD functionalization patterns in one pot and without any purification step is demonstrated.

The unique molecular inclusion capabilities of cyclodextrins (CDs) have been exhaustively exploited by the pharmaceutical, cosmetic, and food industries.[1] Chemical tailoring of native hexa-, hepta-, and octameric CDs (α-, β-, and γ-CD, respectively) has already benefited many current applications.[2] But the development of the myriad of potential applications envisioned for functionalized CDs[3] faces the enormous challenge of selectively manipulating the dense display of identical functional groups of CDs. Toward this end, only a handful of regioselective chemical manipulation schemes are available.[4] The most successful ones take advantage of the scaffolding or inclusion capabilities of the CD host to force a preferred approach and orientation of the CD-modifying reagent. In this way, the reaction outcome can be significantly restricted as compared to that statistically expected. The level of refinement achieved with this kind of approach is

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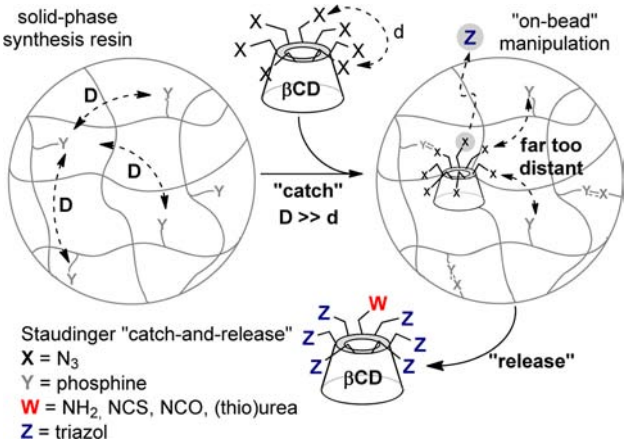
paradigmatically illustrated with a recent contribution from Sollogoub and co-workers,[4n] who showed how DIBAL-H can be used as a molecular scalpel to sequentially rip off selected benzyl protecting groups (among 18 similar ones!) to obtain a series of triply dissymmetrized αCD derivatives. These approaches have been mastered to furnish extraordinary selectivities, but their application is often limited to tight-matching CD-reagent pairs. Thus, development of tools to widen the accessible CD architectural scope would result in an excellent complement for the above strategies.

Orientating the CD-reagent pair and preventing a second reagent species to react the same CD molecule is crucial for the success of these strategies. We reasoned that, while executing this control is inherently difficult in solution, it might be easier with a reagent displayed on a solid support. Indeed, this has been shown to be successful to achieve monofunctionalization of 2-nm gold nanoparticles, only slightly larger than βCD.[5] More recently, Di Fabio and co-workers have demonstrated that solid-supported reagents can be used to graft a single label onto a series of CD scaffolds via phosphodiester linkages.[6] Only moderate yields were reported, probably due to either a suboptimal reagent display on the solid support or reaction conditions. Moreover, the precise functionalization site (primary or secondary rim) was not disclosed and final HPLC purification was required.

Herein, we have refined this concept into a flexible synthetic tool for site selective CD functionalization avoiding purification steps. For such a purpose, we have implemented an experimental setup permitting (i) the covalent capture of a fully symmetric CD derivative through a single position by a solid-supported reagent, (ii) eventual "on-bead" orthogonal elaboration of the remaining functional groups, and (iii) a final chemoselective release of the dissymmetric CD conjugate from the solid support in a sort of one-pot "catch-and-release"[7] process (Scheme 1).

The chemical reactivity for the catch-and-release process is not a trivial choice. In this case the versatility of the Staudinger reaction[8] between organic azides and phosphines has been considered. Staudinger reaction occurs in virtually any solvent to chemoselectively furnish iminophosphorane species in mild conditions and good yields. The "captured" iminophosphorane might be later released from the solid matrix chemoselectively in the form of e. g. an amine, iso(thio)cyanate or (thio)urea. In addition, iminophosphorane reactivity[9] is orthogonal to other azide-involving reactions, such as the Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC),[10] which would enable "on-bead" derivatization of the remaining functional groups.

Scheme 1. Schematic Representation of the Solid-Support-Assisted "Catch-and-Release" Protocol for Site Selective CD Functionalization



To optimize the experimental conditions, we first studied iminophosphorane formation in solution with the model monosaccharide azide **1**[11] (a surrogate of the βCD heptaazide **3**)[12] and a set of aromatic phosphines (Scheme 2). Reaction with triphenylphosphine (TPP) at rt indicated relatively fast kinetics ($t_{1/2}$ = 20–30 min, ^{31}P NMR-monitoring; Figure 1, ○ series) in all tested solvents (DCM, DMF, and 1,4-dioxane). The reaction with phosphine **4**,[13] with less electron-donating capabilities due to the presence of the carboxymethyl handle, was slower ($t_{1/2}$ = 80 min in 1,4-dioxane; Figure 1, △ series). Conversely, electron-rich phosphine **6**[13] fully recovered the performance of TPP, being the most appropriate choice to build on the solid support. Moreover, the reaction rate could be significantly increased at 40 °C ($t_{1/2}$ = 6 min in DMF; Figure 1, ◆ series) with negligible iminophosphorane hydrolysis after several hours provided anhydrous conditions were preserved. The optimal performance together with good resin swelling capabilities supported the choice of DMF for the assays on the solid support.

Coupling of carboxylic acid **5** onto glycine-loaded aminomethylated polystyrene (AM-PS, 0.39 mmol·g^{-1})[14] using conventional peptide coupling reagents furnished the resin-supported phosphine **7**, stable in the absence of moisture and oxygen. AM-PS is not a rigid matrix, but even at this relatively high loading, and assuming a swelling in the 5–10 mL·g^{-1} range, the average distance between reactive centers is estimated to be ca. 4 nm.[15] This is 3-fold larger than the maximum distance between the azido groups in βCD **3**.[16]

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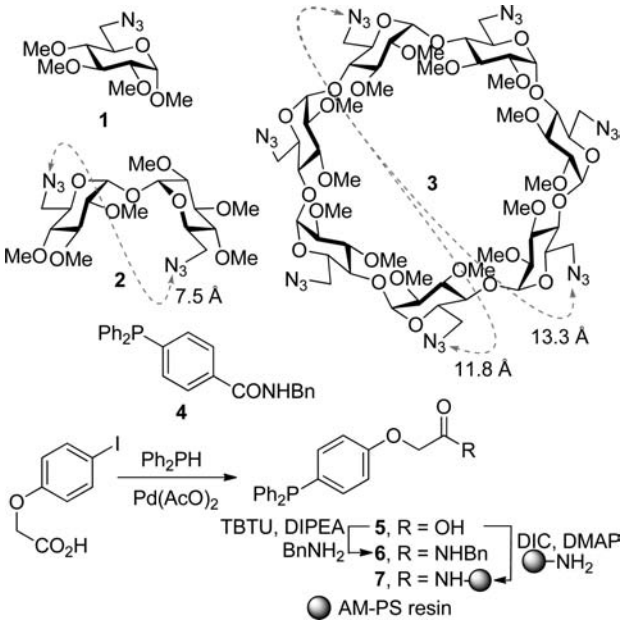
(13) See SI for synthetic details.

(14) Purchased from NovaBiochem.

(15) The interphosphine distance was estimated supposing an even distribution in fully swollen resins. From the total number of functional groups in a given resin volume, the volume per phosphine group, and therefore the average distance between them, was calculated.

Scheme 2. Structure of the Azides **1**–**3** and Phosphines **4**, **6**, and **7** Investigated To Optimize the Staudinger Reaction



The reaction of **1** with resin **7** in DMF is slow at rt ($t_{1/2}$ = 8 h), but practical rates were obtained at 40 °C (Figure 1, ■ series). Indeed, treating resin **7** with 2 equiv of azide **1** overnight at 40 °C in dry DMF under N_2 resulted in virtually complete consumption of the supported phosphine. Premature hydrolysis of the iminophosphorane (resin washings only contained the excess of azide) was not detected. Final hydrolysis with 9:1 DMF/water overnight at 40 °C afforded 6-aminoglucoside **8** in 89% yield (Scheme 3).[17]

α,α′-Trehalose diazide **2**[13] and βCD heptazide **3** appeared to be more demanding substrates. Only minute amounts were captured by resin **7** under the same conditions. Higher "catch" temperatures increased the reactivity but reduced the selectivity. Even diazide **2**, featuring a maximum interazide distance of 7.5 Å,[16] was doubly bound by two phosphine moieties, despite the much larger average resin interphosphine distance. Probably a temperature-induced increase in resin backbone mobility reduced the effective interphosphine distance. A similar effect was observed with more flexible supports (e.g., PEGA resin).[18]

Rewardingly, microwave (μw) irradiation revealed a completely different scenario. The catch efficiency increased up to 90% (estimated from the recovered azide) after irradiating resin **7** swollen in a DMF solution of either **2** or **3** at 60 °C (2 × 10 min, 40 W) under N_2. We hypothesize that the larger μw-absorption capability of DMF (as compared to nonpolar PS-resin) could selectively increase reagent diffusion and reactivity vs resin backbone mobility. Hydrolytic release of the supported iminophosphoranes

(16) Calculated by molecular modelling using ChemBio3D (ChemBioOffice package, CambridgeSoft).

(17) Analytical and spectroscopic data match with those of an authentic sample prepared in solution. See SI for details.

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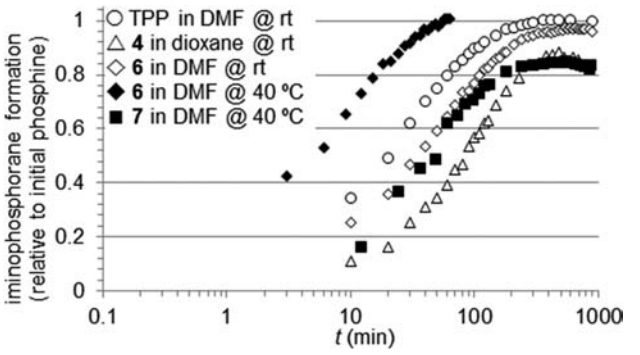
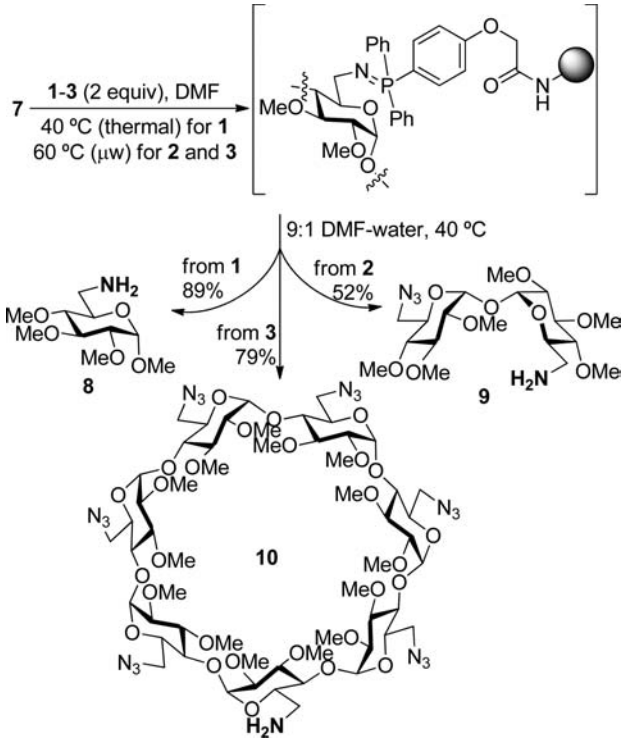


Figure 1. Iminophosphorane formation kinetics from azide **1** with different phosphines monitored by ^{31}P NMR. In a typical experiment, 50 μmol of phosphine in the indicated solvent were treated under N_2 with 2 equiv of **1** at either rt or 40 °C.

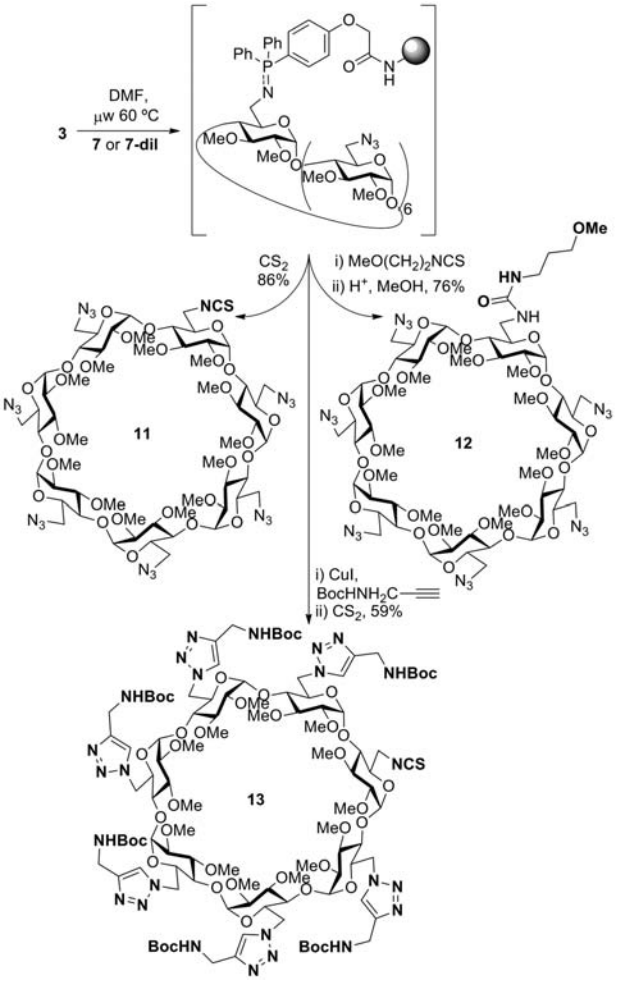
Scheme 3. Schematic Representation of the Solid-Support-Assisted Synthesis of Monoamines **8**–**10**



afforded the target monoreduced adducts (52 and 79% for **9** and **10**, respectively) virtually devoid of over-reduced adducts as denoted by ESI-MS and RP-HPLC (see Supporting Information (SI)).

The flexibility of iminophosphorane chemistry[9] was also exploited to produce alternative CD functionalization patterns (Scheme 4). Aza-Wittig-type reaction of the resin-bound CD iminophosphorane with CS_2 furnished the isothiocyanate **11** in 86% yield. Despite the fact that a clean HPLC trace is observed, a minor peak for diisothiocyanate conjugates was identified by ESI-MS (see SI).

Scheme 4. Selectively Functionalized βCD Derivatives **11**–**13** Obtained from Solid-Supported CD Iminophosphorane



Probably the interphosphine distance in the matrix is not sufficient to completely prevent doubly capturing a certain amount of CD **3**. Curiously, such over-reactivity was not observed in the case of amine **10**, despite the similar catch conditions. We reasoned that iminophosphorane hydrolysis may occur at a slower rate due to shrinking of the PS resin in the presence of water, thereby increasing the chance for doubly linked CD units to remain bound to the matrix. Conversely, the CS_2-DMF cocktail swells the PS resin much better, facilitating the release of all bound material (including mono- and bis-iminophosphoranes).

In order to minimize this drawback, we prepared a resin with a larger interphosphine distance. Thus, AM-PS resin was acylated with a 9:1 mixture of Boc- and Fmoc-protected glycine and the Boc groups were transformed into inert acetyl groups. Phosphine was then installed onto the remaining amino groups (see SI), resulting in a 10-fold diluted matrix (**7-dil**) with a ca. 40 μmol·g^{-1} loading and 7–9 nm interphosphine average distance.[15] To probe the performance of this support, CD **3** was sequentially loaded on and cleaved by 3-methoxypropylisothiocyanate to release a carbodiimide that in situ added water to furnish

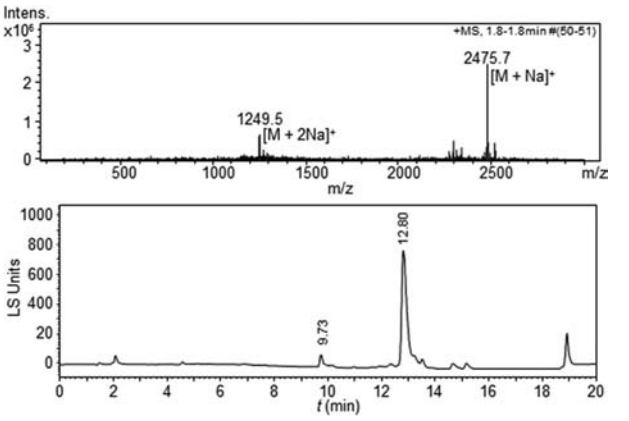


Figure 2. ESI-MS spectrum (top) and HPLC trace (bottom) of the crude bifunctional CD **13** obtained from **3**.

the corresponding urea **12** in 76% yield with undetectable traces of difunctionalized adducts (Scheme 4).

To push forward this strategy and take advantage of the greater selectivity of **7-dil**, on-bead manipulation of the solid-supported CD has been considered. The iminophosphorane tether should, in principle, remain unaffected by the conditions for CuAAC. Indeed, treating the supported CD iminophosphorane with an excess of a terminal alkyne (e.g., *N*-Boc propargylamine) in the presence of catalytic CuI, followed by CS_2-mediated release, afforded the bifunctional CD derivative **13** in 59% yield. The NMR spectrum of this conjugate is far too complex to assess purity and even identity, but the RP-HPLC trace and ESI-MS spectra confirmed both (Figure 2).

Production of such CD functionalization patterns, despite being feasible, is far from obvious using conventional solution phase techniques. Herein we demonstrate that the "catch-and-release" concept can be implemented with relative ease into a powerful tool for selective manipulation of macromolecular topology. Only βCD manipulation is described herein, but it is reasonable to suppose that this methodology would be suited for other cyclodextrins and macromolecular scaffolds. Room for improvement is still large, for example, considering more rigid solid supports. Work in this direction is currently in progress in our laboratories.

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Note Added after ASAP Publication. Scheme 4 was corrected on April 26, 2013.

Supporting Information Available. Spectroscopic and analytical data, and detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.