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Development of a heterogeneous catalytic system using multiply charged cyclodextrins and proline-based organocatalysts

Vývoj heterogenního katalytického systému s využitím několikanásobně nabitých cyklodextrinů a prolinových organokatalyzátorů

Master's thesis

Supervisor: Assoc.Prof. RNDr. Jindřich Jindřich, CSc.

Prague, 2022

Declaration

Herewith I declare that I have written my master's thesis by myself and that all sources are listed in the bibliography. Neither this work, nor its significant part was used to obtain other academic titles. I agree that this work may be lent out or published.

Prague, 18.05.2022

Jan Zelený

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Abstract

Cyclodextrins are a class of organic molecules consisting of a cyclic system of α(1→4) linked glucose units. These compounds possess a range of interesting properties and can be derivatised to suit various industrial and scientific purposes. Among their derivatives are so-called multiply charged cyclodextrins, the development and application of which is an essential part of our group's research interest. These cyclodextrin derivatives are capable of binding electrostatically to different solid sorbents, such as silicagel or alumina. This electrostatic interaction is mediated by an array of permanently positively charged moieties which are covalently attached to the primary rim of a cyclodextrin unit. The free secondary rim then offers the possibility of further derivatisation and functionalisation of this system. The resultant cyclodextrin derivative represents a modular scaffold which can be used to immobilise different functional components.

This project focuses on the application of this system to the immobilisation of a Hayashi-Jørgensen-type catalyst for the purposes of heterogeneous catalysis. The work includes the assembly of the of the chosen catalytic system from its precursors and also the synthesis thereof. Furthermore, the resulting supramolecular system is tested for its catalytic properties using a conjugate addition of diethyl fluoromalonate to cinnamaldehyde as a model system. Lastly, sorption of the catalytic system onto three different sorbents is also attempted.

Keywords: supramolecular chemistry, cyclodextrins, heterogeneous catalysis, organocatalysis, Hayashi-Jørgensen catalyst

Abstrakt

Cyklodextriny jsou skupinou organických molekul, složených z cyklického uspořádání glukosových jednotek, propojených α(1→4) glykosidickými vazbami. Tyto sloučeniny vykazují řadu zajímavých vlastností a mohou být derivatizovány pro různé průmyslové i vědecké účely. Podskupinou těchto derivátů jsou tzv. několikanásobně nabité cycklodextriny, jejimž vývojem a využitím se naše výzkumná skupina do značné míry zabývá. Tyto deriváty cyklodextrinů jsou schopny vázat se na různé pevné nosiče, jakými jsou např. silikagel nebo alumina, prostřednictvím elektrostatické vazby. Tato interakce je zprostředkována seskupením permanentně kladně nabitých skupin, kovalentně vázaných na primární okraj cyklodextrinové jednotky. Volný sekundární okraj umožňuje další derivatizaci a funkcionalizaci tohoto systému. Výsledný cyklodextrinový derivát může sloužit jako supramolekulární nosič, který lze využít k imobilizaci různých funkčních komponentů.

Tato práce se zabývá využitím tohoto systému k imobilizaci organokatalyzátoru Hayashiho-Jørgensenova typu za účelem heterogenní katalýzy. Práce zahrnuje konstrukci vybraného katalytického systému z několika prekurzorů, jejichž syntéza je v práci rovněž obsažena. Katalytické schopnosti výsledného supramolekulárního systému jsou dále ověřeny s využitím konjugované adice diethyl fluoromalonátu na cinnamaldehyd, coby modelové reakce. Na závěr je rovněž otestována sorpce katalytického systému na tři různé sorbenty.

Klíčová slova: supramolekulární chemie, cyklodextriny, heterogenní katalýza, organokatalýza, Hayashiho-Jørgensenův katalyzátor

CONTENTS

SYMBOLS AND ABBREVIATIONS

Ar	aryl
CD	cyclodextrin
CGTase	cyclodextrin glycosyltransferase
CuAAC	Cu(I)-catalysed azide-alkyne cycloaddition
CV	column volume
DBTDL	dibutyltin dilaurate
DCM	dichloromethane
DEPT	distortionless enhancement by polarisation transfer
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dqf-COSY	double quantum filtered correlation spectroscopy
DRIFT	diffuse reflectance infrared Fourier transform
ee	enantiomeric excess
eq.	equivalent
ESI	electrospray ionisation
Et	ethyl group
exc.	excess
HMBC	heteronuclear multiple-bond correlation spectroscopy
HSQC	heteronuclear single-quantum correlation spectroscopy
*i*Pr	isopropyl
IR	infrared spectroscopy
JC	Jørgensen’s catalyst
MALDI	matrix-assisted laser desorption/ionisation
Me	methyl
MIM2	3,3'-(2-(λ^3-methyl)-2-methylpropane-1,3-diyl)bis(3-methylimidazolium)
MS	mass spectrometry
Ms	mesyl (methanesulfonyl)
MTZ	4-(λ^3-methyl)-1λ^2,2,3-triazole
NMR	nuclear magnetic resonance
NPrNIM	*N*-propyl-1,8-naphthalimide
Pg	propargyl (prop-2-yn-1-yl)
Ph	phenyl
r.t.	room temperature
TBAI	tetrabutylammonium iodide
*t*Bu	*tert*-butyl
TEG	tetraethylene glycol

Tf	triflate (trifluoromethanesulfonate)
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl(*p*-toluenesulfonyl)

1. INTRODUCTION

Our laboratory concerns itself mainly with supramolecular chemistry, particularly the chemistry and potential applications of cyclodextrin derivatives. As will be described in the following chapters, cyclodextrins are cyclic oligosaccharides, usually consisting of six to eight α(1→4) linked glucose units. Together, the free hydroxyl groups in positions 2, 3 and 6 of the individual glucose units form two distinct bands, commonly referred to as the primary (OH-groups in position 6) and secondary (OH-groups in positions 2 and 3) rim. These positions offer a range of possibilities for derivatisation of the native cyclodextrins. Combining specialised functions with the inherent properties of cyclodextrins, CD derivatives find application in a number of industrial sectors or research-oriented fields[1].

A special subgroup of these derivatives, so-called multiply charged cyclodextrins, have been developed in our laboratory[2]. These derivatives are formed by substituting one or several OH-groups on the cyclodextrin backbone by a positive charge-bearing moiety known as an anchor. Each anchor can carry up to three permanent charges. These cationic functionalities can bind electrostatically to solid supports, as long as their surface presents charges of the opposite sign[2]. For positively charged anchors (and by extension positively charged CDs), these can include silica gel, basic alumina, zeolites or cation-exchange resins. If one side (e.g. the primary rim) of the cyclodextrin is equipped with anchors, as is commonly the case, the other side remains free and can be decorated with various functional components. Thus, for instance, the primary rim of the cyclodextrin core can facilitate binding to a solid support, while the secondary rim acts as an attachment point for functionalities, such as catalysts, chiral selectors, chemosensors or other modifiers.

As mentioned above, cyclodextrin derivatives can be utilised as carriers for catalytically active species[3,4]. Immobilisation of the catalyst can simplify its recovery from the reaction mixture, thus increasing its recyclability. In an industrial setting, where flow chemistry is often employed, transfering a catalytic reaction from a homogeneous to a heterogeneous setup can make for a greener and more time- and cost-efficient process[5].

Organocatalysis is understood to be the acceleration of chemical reactions by substoichiometric amounts of an organic compound without the direct involvement of a metal atom in the catalytic cycle[6]. Some of the first molecules to be recognised as organocatalysts were naturally occuring amino acids, such as proline[7]. Based on this amino acid, a number of organocatalysts have subsequently been developed. A particular subgroup of these catalysts, namely diarylprolinol silyl ethers[8,9] – also known as Jørgensen- or Hayashi-Jørgensen catalysts, play an important role in this thesis, as will become evident in the following chapters.

2. AIM OF THE PROJECT

For the species of multiply charged cyclodextrins described in the introduction, several potential applications are currently being investigated by members of our research group. These include their use as reverse-phase modifiers, chiral selectors or water purification systems. In order to expand this array of functional derivatives, we decided to utilise a multiply charged cyclodextrin as the basis for a heterogeneous catalytic system. The idea being that such a conjugate might serve as a modifier for the simple conversion of a solid sorbent into a catalytically active stationary phase for catalytic batch and flow chemistry. Ultimately, the non-covalent mode of binding could even allow for the exchange of various modifiers, eventually providing the means of using one column or flow reactor for a variety of different purposes extending beyond catalysis alone.

It became, therefore, the aim of this project to devise a method for the immobiliation of a suitable organocatalyst onto a charged cyclodextrin carrier and, having constructed this supramolecular assembly, to test its electrostatic binding and catalytic capabilities.

To this end, the attachment of a suitable catalyst to the secondary rim of a β-cyclodextrin with seven bis(*N*-methylimidazolium) (MIM2) anchors on its primary rim (providing a total of 14 charges per molecule) became the principal subject of investigation. Lastly, a bifunctional tetraethyelene glycol linker was chosen to provide a flexible connection between the former components. This choice was prompted by the idea, that the relative length and flexibility of the TEG-linkers woud provide the tethered catalysts with enough freedom of movement as to imitate to some extent their behaviour in a homogeneous reaction mixture. A graphical layout of the key aims is presented in Figure 1.

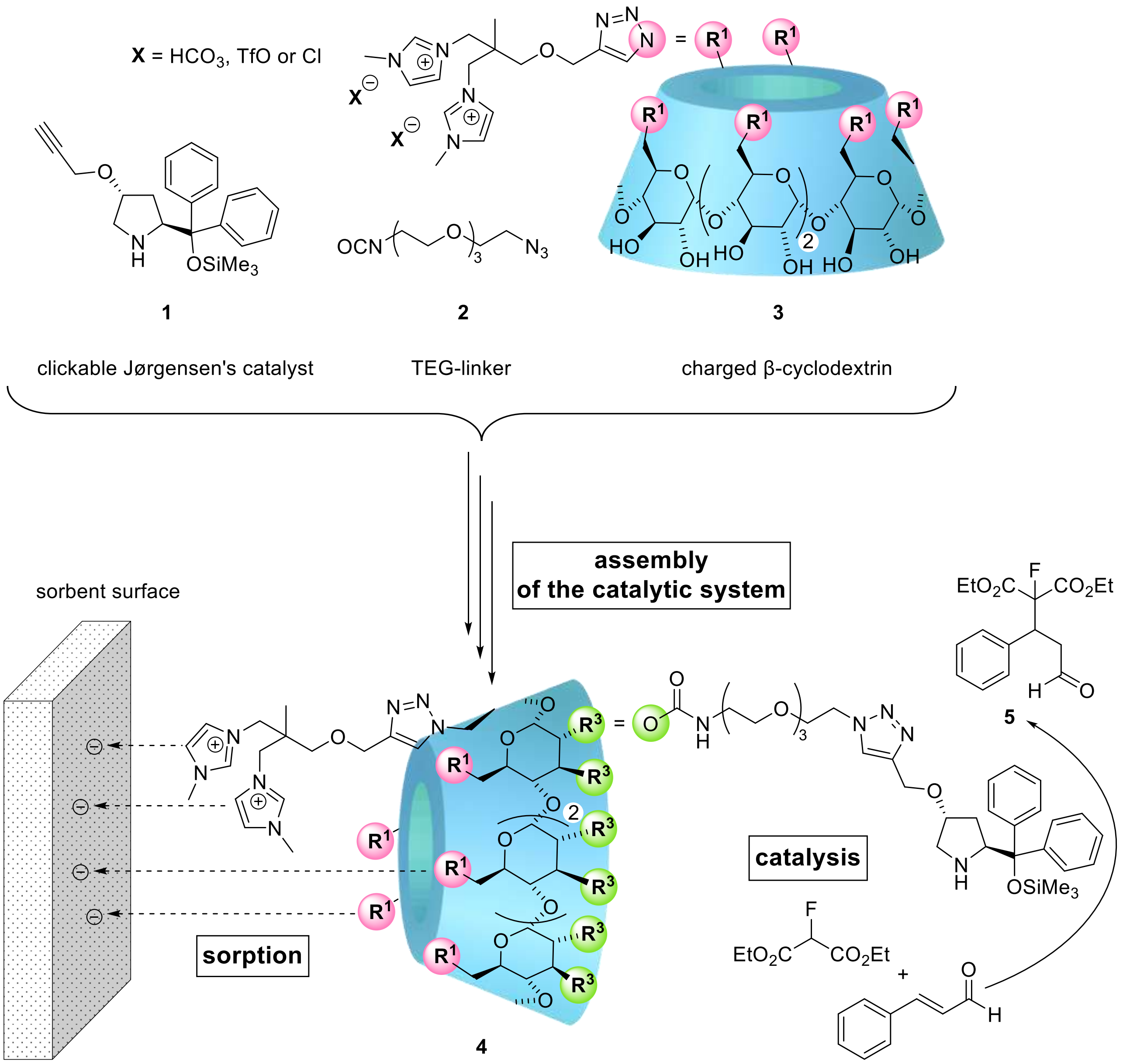


Figure 1: Assembly of the catalytic system **4** from its three main components and layout of further experimental proceedings.

3. OVERVIEW AND STATE OF THE ART

3.1 Supramolecular chemistry

According to Jean-Marie Lehn, one of its foremost proponents, supramolecular chemistry is “chemistry beyond the molecule”[10]. Just as other branches of chemistry deal with the covalent binding of chemical species, supramolecular chemistry studies the interaction between molecules, ions or radicals by non-covalent, intermolecular binding modes including electrostatic forces, hydrogen binding, van der Waals forces or donor-acceptor interactions[1,10]. Most of these interactions are of the host-guest type, leading to the formation of so-called host-guest complexes[1]. These include, for instance, complexes of crown ethers and alkali metal cations[11], complexes of calixarenes and various small organic molecules[12], or complexes of cucurbiturils and small organic cationic species[13]. Examples of common supramolecular hosts are shown in Figure 2. The same principles that govern host-guest interactions, are responsible for other supramolecular phenomena, such as molecular recognition or receptor-substrate interactions, all of which are essentially variations on the theme of molecular complementarity[14].

By definition, a supramolecular assembly (also called a supermolecule) consists of two or more interacting species. If, in addition to binding sites, these species possess reactive functions, a chemical transformation may occur as a result of their interaction. In such cases the interacting species can behave as supramolecular reactants or catalysts[14].

In other situations, the complex-forming partners can mutually increase each other’s solubility in solvents wherein the complexes are soluble. A good example of this phenomenon is the aforementioned complexation of alkali metal cations by cyclic polyethers, also known as crown ethers[11]. Similarly, a membrane-soluble receptor can bring about the translocation of a bound substrate through an environment in which the substrate by itself is insoluble. Hence, molecular recognition, transformation and translocation constitute the basic functions of supramolecular systems. Combinations of these functions in various settings can produce more advanced functions, eventually leading to what can be referred to as “molecular devices”[14].

Over the years, supramolecular chemistry, which lies at the intersection between chemistry, physics and biology, has developed into a broad discipline involving a vast palette of molecular structures and devices. Often inspired by biological features, supramolecular chemists have developed an array of systems, including for instance self-assembling structures[15], molecular devices facilitating drug delivery[16] or fragrance-release[17], catalytic assemblies or structures aimed at chemical sensing or separation[18].

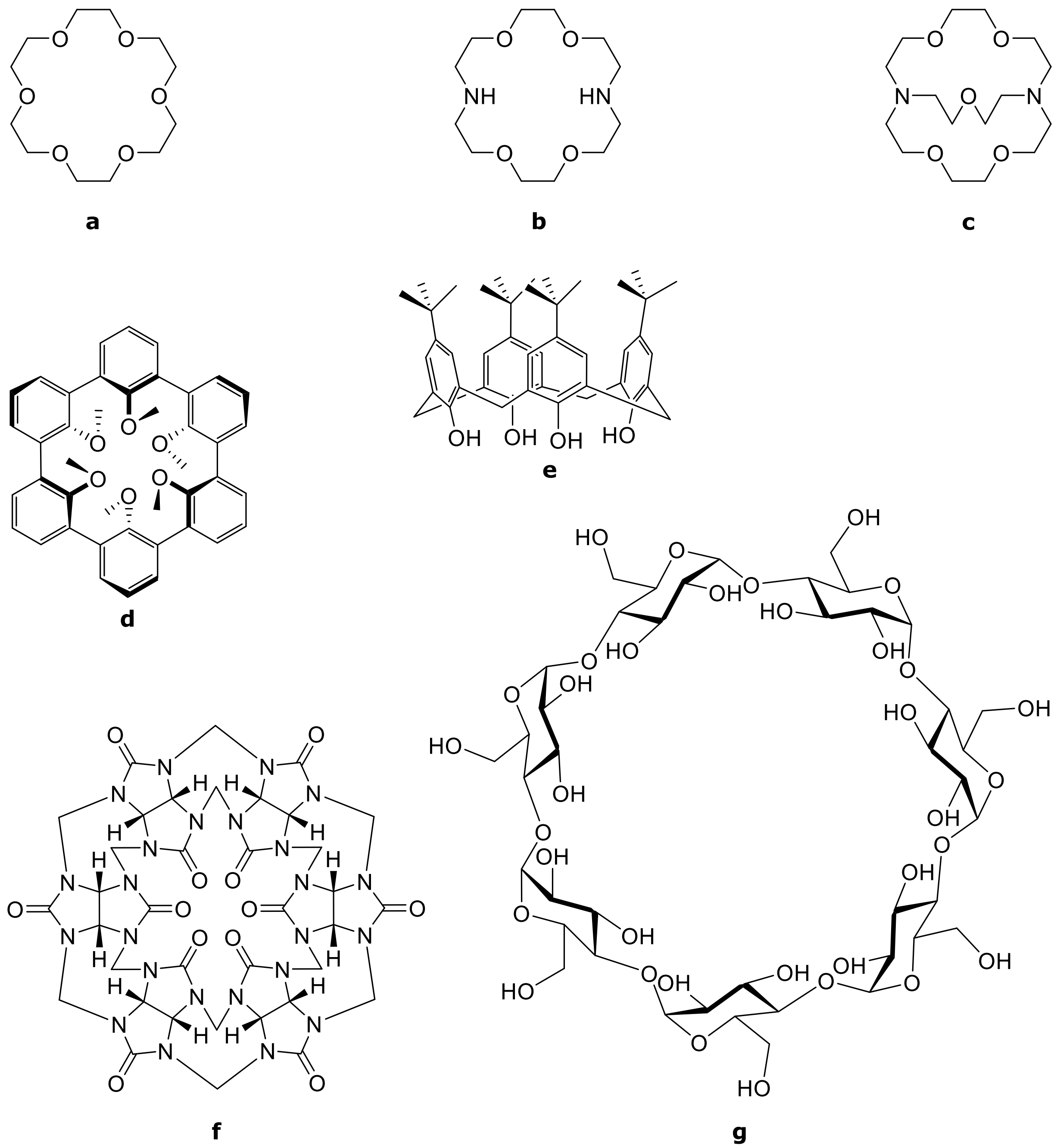


Figure 2: Common supramolecular hosts. a) crown ether (18-crown-6); b) azacrown (1,2-diaza-18-crown-6); c) cryptand ([2.2.2.]cryptand); d) spherand; e) calixarene; f) cucurbituril; g) β-cyclodextrin.

3.2 Cyclodextrins

One of the supramolecules shown in Figure 2 is a β-cyclodextrin (g), one of the most common representatives of this class of molecules. This compound plays a central role in this thesis. Therefore, prior to delving into the specifics of this work, it may be suitable to provide some basic information regarding cyclodextrins in general.

3.2.1 History

As early as 1891 the French chemist and pharmacist Antoine Villiers reported in the proceedings of the *Académie des Sciences* on the results he obtained after exposing potato starch to a so-called butyric ferment (a bacterial culture consisting most likely of *Bacillus amylobacter* and *Bacillus macerans*). In his account he states that under certain conditions, potato starch can be fermented to yield dextrins. The term "dextrins" was at the time used to denote the general decomposition products of starch. Among the by-products of this transformation were small amounts of highly crystalline materials, the properties of which were quite different to saccharides known at the time. After some investigation Villiers concluded that the composition of these novel crystalline carbohydrates, for which he coined the term "cellulosines", could be represented by multiples of the formula $[(C_6H_{10}O_5)_2 + 3H_2O]$. Of these cellulosines he obtained two distinct crystalline forms, which were most likely α- and β-cyclodextrin as they are known today.

After these seminal discoveries, Villiers abandoned his research of cellulosines in favour of alkaloids and it was not until the beginning of the 20th century that Austrian chemist and bacteriologist Franz Schardinger practically rediscovered Villiers's crystalline dextrins and revived their scientific investigation[19]. Schardinger is also credited with laying down the fundamentals of cyclodextrin chemistry[1]. It is for these reasons that cyclodextins are occasionally referred to as "Schardinger dextrins".

In the following years, several groups of scientists studied Schardinger's dextrins and together elucidated their structure and outlined their most notable properties. Freudenberg *et al.*, for example, concluded that the studied molecules consist of maltose units which are exclusively linked by $\alpha(1\rightarrow4)$ glycosidic bonds. They also correctly predicted a cyclic structure for the dextrins[20]. In the late 1940s, γ-cyclodextrin was discovered and characterised[1], thus completing the trio of the most common cyclodextrins[21,22] (Figure 3).

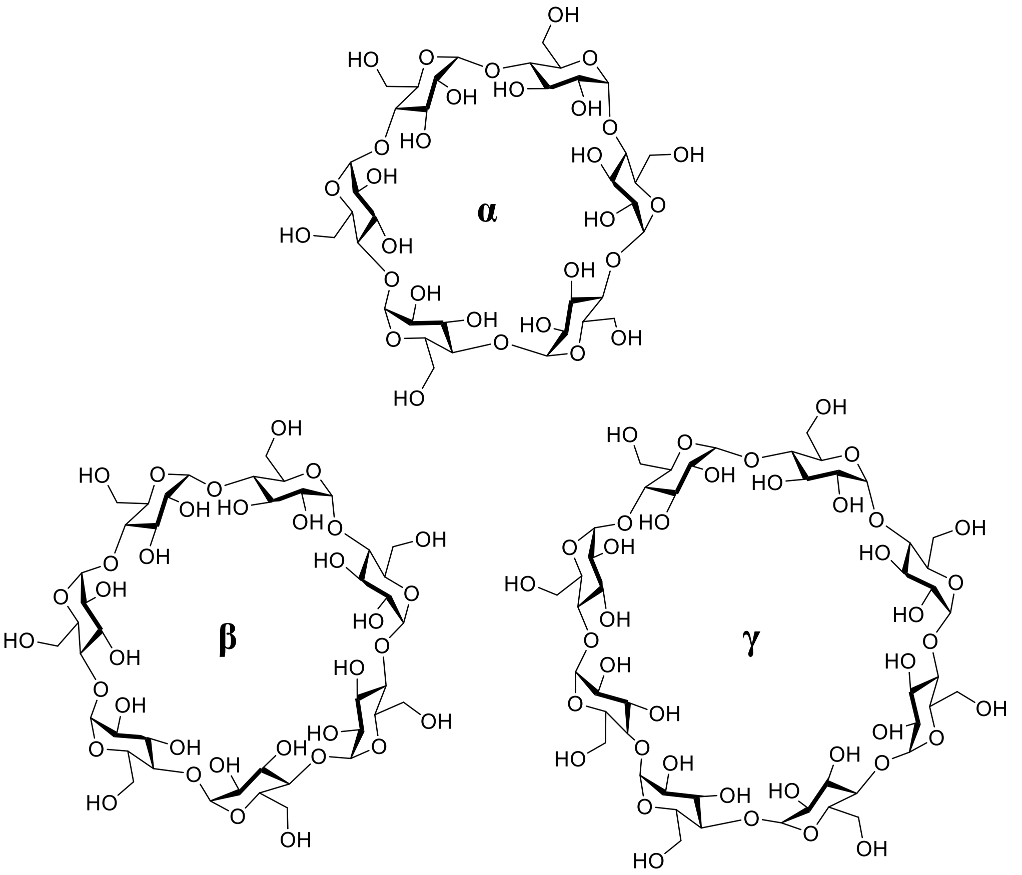


Figure 3: Structures of the most common cyclodextrins — α-CD, β-CD and γ-CD, consisting of 6, 7 and 8 glucose units, respectively.

These initial findigs represent the foundation of today’s understanding of cyclodextrin structure and chemistry. Since their time, many more pieces of information have been accumulated by numerous research groups, forming a more and more complete and high-resolution picture of the properties and potential applications of cyclodextrins.

3.2.2 Structure and properties

Today we know, that cyclodextrins *are* in fact cyclic oligosaccharides consisting most commonly of 6 to 8 α(1→4)-linked glucopyranose units. This cyclic system has a three-dimensional, cylindrical structure, which is often described as a conical cylinder or a hollow truncated cone, similar to a doughnut or a wreath[1]. For this reason, cyclodextrins are often drawn using the more descriptive conical representation (see Figure 4, a). Where necessary, a more simplified representation is used (Figure 4, b). The conical structure of cyclodextrins was demonstrated in the mid-1970s by the German biochemist and crystallographer Wolfram Saenger[19]. Since each of the glucopyranose units has a $^4C_1$ conformation, i.e. a chair conformation, in which carbon 4 is located above and carbon 1 below the reference plane of the chair (see Figure 4, c), all secondary hydroxyl groups are located on one edge of the cyclodextrin cone, while all primary hydroxyl groups occupy the other edge[1,23]. For this reason, the terms "primary rim" and "secondary rim" are used to describe the two sides of the cyclodextrin cone.

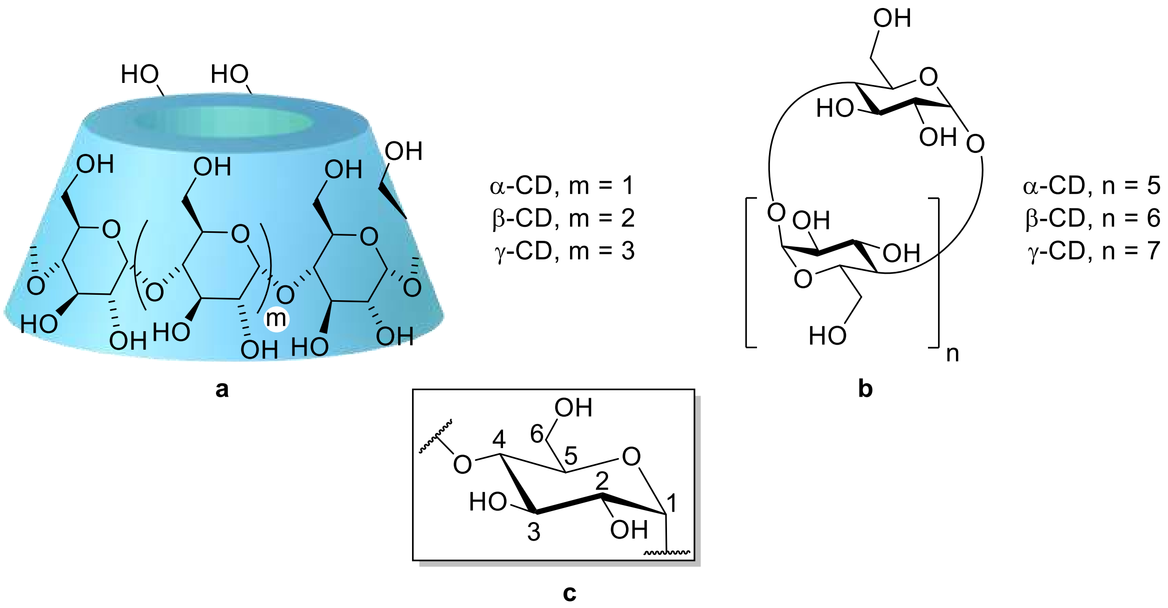


Figure 4: a) Conical 3D representation of cyclodextrin molecules; b) simplified skeletal structure; c) $^4C_1$ conformation and standard numbering of the glucopyranose unit.

On the secondary rim, the C2-OH group of one glucose unit can from a hydrogen bond with the C3-OH group of the neigbouring glucose unit, leading to the formation of a chain of intramolecular hydrogen bonds which stabilises the three-dimensional structure of the cyclodextrins[1,23]. This is especially the case with β-cyclodextrin, where a continuous band of hydrogen bonds is formed by the secondary hydroxyls, leading to a particularly rigid structure. The low water-solubility of β-cyclodextrin, as compared to other cyclodextrins – see Table 1, is thought to be a consequence of this strong intramolecular hydrogen bonding[1]. In α-cyclodextrin, on the other hand, the band of hydrogen bonds is weakened due to one of the glucose units occupying a distorted position, therefore, the solubility of α-CD is markedly higher compared to β-CD. Due to its higher flexibility, γ-cyclodextrin has the highest water solubility of the three major cyclodextrins.

Table 1: Properties of the three most common cyclodextrins[1].

	α-cyclodextrin	**β-cyclodextrin**	**γ-cyclodextrin**
other names	Schardinger's α-dextrin, cyclomaltohexaose, cyclohexaglucan, cyclohexaamylose, ACD, C6A	Schardinger's β-dextrin, cyclomaltoheptaose, cycloheptaglucan, cycloheptaamylose, BCD, C7A	Schardinger's γ-dextrin, cyclomaltooctaose, cyclooctaglucan, cyclooctaamylose, GCD, C8A
number of glucose units	6	7	8
molecular weight (g/mol)	972	1135	1297
solubility in water at r.t. (g/100 ml)	14.5	1.85	23.2

The water solubility of cyclodextrins arises from the presence of hydrophilic OH-groups on both sides of the molecule. However, the inside of the truncated cone is lined with the hydrogen atoms at C3, C5 and C6 and the glycosidic oxygen bridges, forming a hydrophobic cavity[1,23]. This is one of the most important features of cyclodextrins since it allows them to act as supramolecular hosts by including smaller molecules in their cavity – see chapter 3.2.4.

Although the most common cyclodextrins are those described and depicted above, other variants with larger and smaller rings have also been reported – see chapter 3.2.3.

3.2.3 Preparation and production

As mentioned above, cyclodextrins were first synthesised by Antoine Villiers through the action of *Bacillus amylobacter* and *Bacillus macerans* upon starch. The enzyme produced by these bacteria, which is responsible for the conversion of starch into cyclodextrins, is called cyclodextrin glucosyltransferase (also known as cycloamylose glucanotransferase, cyclodextrin glucanotransferase or CGTase)[1,19,23,24]. This enzyme is produced by a number of other microorganisms, including *Klebsiella oxytoca*, *Bacillus circulans*[1] or *Bacillus licheniformes*[21]. Enzymatic degradation of starch using isolated CGTase-type enzymes is still used for the production of cyclodextrins on an industrial scale[1,21]. In modern days, these enzymes are often genetically enhanced to increase yield and selectivity[21]. In the process of CD formation, one or several turns of the amylose helix are hydrolysed off by the CGTase and their ends are joined together forming a cyclic oligosaccharide[23]. There are two main industrial approaches to the synthesis of CDs – the "no-solvent process", where the action of CGTases produces a complicated mixture of CDs and other partially hydrolysed by-products; and the "solvent process" in which the reaction is driven towards the desired cyclodextrin by co-precipitation with a suitable organic complexing agent[1,21]. Most industrially produced CDs are formed in solvent processes[21].

A general procedure for cyclodextrin production *via* this process involves the following steps[1]:

- liquefaction of starch at an elevated temperature
- pre-hydrolysis of the viscous starch solution
- addition of CGTase and complexing agent to the cooled mixture
- complex formation with the nascent CDs and subsequent precipitation
- isolation of the complex by centrifugation or filtration
- washing of the filtrate
- recovery of excess complexing agent by distillation
- cleavage of the complex by heating in an aqueous suspension
- removal of the complexing agent by steam distillation or extraction
- purification of the crude CD by active charcoal, precipitation and filtration

The resulting type of cyclodextrin depends on the complexing agent of choice[1]. As mentioned above, the water solubility of β-CD is significantly lower compared to the other common cyclodextrins. Due to its lower solubility, β-CD precipitates from the reaction mixture more readily. This makes β-CD easier to separate and to purify compared its sibling CDs, leading, in turn, to a substantially lower price[21].

While larger cyclic oligosaccharides with 14, 26 or even beyond 100 glucose units have been prepared by enzymatic means, smaller CDs, on the other hand, cannot be prepared by CGTase enzymes due to their increased steric strain[23]. However, small cyclodextrins with three and four glucose units have been synthesised by Suzuki glycosylation of sterically modified glucose monomers[25]. A cyclodextrin with five glucose units, the so-called pre-α-CD, has also been synthesised[26].

3.2.4 Inclusion complexes

Thanks to their hydrophilic exterior and hydrophobic cavity, cyclodextrins lend themselves exceptionally well to the formation of host-guest complexes. In an aqueous solution, the cavity is occupied by water molecules. Obviously, the presence of water in a hydrophobic environment is energetically demanding due to polar-apolar interactions. The water molecules are therefore readily displaced by a more appropriate hydrophobic guest molecule[24]. Even so, the formation of inclusion complexes is rather nonspecific and only seems to be limited by the size of the guest molecule. Thus, a variety of molecules, ranging from salts and noble gasses to paraffins, alcohols, various aromatics, or drugs can form host-guest complexes with cyclodextrins[23,27,28]. Although the resulting inclusion complexes are usually formed in a 1:1 host:guest ratio, other modes of complexation are also possible, so that 2:1, 1:2, 2:2 or more complex associations often coexist[1]. Figure 5 shows some of these modes of association.

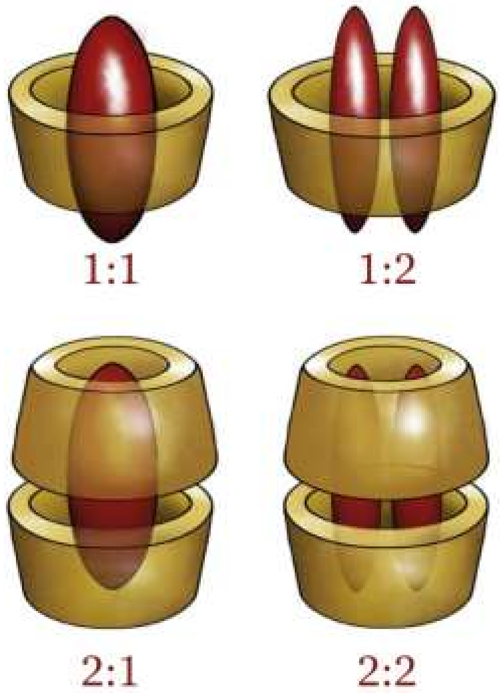


Figure 5: Basic modes of association showing four different host:guest ratios. Image adapted from Astray *et al.*[29]

Cyclodextrin inclusion complexes can be prepared by several methods including kneading, co-precipitation, freeze-drying or spray-drying. The choice of the method depends mainly on the properties of the guest molecule to be included in the desired complex[24].

For a number of reasons, cyclodextrins can be regarded as some of the most important supramolecular hosts. First, as pointed out above, they are produced in an environmentally friendly manner from a renewable natural material. Their annual production reaches thousands of tonnes, making cyclodextrins readily available and affordable. Cyclodextrins are also nontoxic and can therefore be consumed by humans as additives of pharmaceuticals, foods or cosmetics.

3.2.5 Applications

Many applications of cyclodextrin stem from their extensive complex-forming abilities. Since complexation leads to substantial changes in the physicochemical properties of the guest, encapsulation in a host-guest complex can be used to achieve desirable modifications of the guest's behaviour. These include, but are not limited to, solubility improvement, stabilisation or control of volatility. In the food industry, cyclodextrins are used to protect, preserve or (as is the case with certain alcoholic beverages) to enhance flavours[24]. The removal of undesired compounds from foodstuffs can also be achieved by inclusion complexation with cyclodextrins[30]. Toxic substances can be removed from industrial effluents in a similar manner[24]. Cheirsilp and Rakmai[24] have provided a comprehensive review describing the applications of CD inclusion complexes. Applications in cosmetics and toiletry include, for instance, the release of fragrances from perfumes or air fresheners or the suppression of unpleasant odours in hygienic items. β-cyclodextrin has been used to protect the components of essential oils against oxidation, heat- and light-induced degradation or evaporation. The ability of cyclodextrins to enhance the water solubility of nonpolar compounds has been exploited in the pharmaceutical industry. Increasing the solubility of a poorly soluble substance improves its bioavailability, which, in turn, allows for a reduction in the dose of the administered drug. Similarly to the aforementioned applications, CDs are used in pharmacological settings to mask unwanted flavours and odours or to release drugs in a controlled manner. Examples of drugs which have been released using CDs include the antibacterial and antifungal agent triclosan or the antibiotics ciprofloxacin and vancomycin. Furthermore, multicomponent complexation with *N*-acetylcysteine and β-CD has been used to reduce the toxicity of the antibiotic chloramphenicol against leukocytes[24,31].

Being composed of saccharide units, cyclodextrins are inherently chiral. This makes them useful as chiral selectors in various separation methods. Particularly in electrodriven separation techniques, such as capillary electrophoresis, CDs are among the most widespread chiral selectors[32,33]. When a mixture of enantiomers interacts with a cyclodextrin, inclusion complexes can form. However, one enantiomer will interact with the cavity in a different manner than its mirror image. This leads to differences in mobility and thus to the resolution of the mixture.

Cyclodextrins can be employed as mobile phase additives or as chiral stationary phases[34]. Of the chiral selectors applied in chromatographic practices, cyclodextrins have the broadest spectrum of selectivity, successfully separating enantiomers of amino acids, branched functionless hydrocarbons, molecules with planar or axial chirality and even compounds with chiral heteroatoms [32,33].

Aside from inclusion complexation, the use of cyclodextrins as supramolecular building blocks or carriers of catalysts has been investigated. The use of cyclodextrins as scaffolds and the immobilisation of catalysts using CDs will be discussed in the following chapters.

3.2.6 Derivatives

3.2.6.1 Nomenclature of cyclodextrin derivatives

As stated above, the three most common cyclodextrins with 6, 7 and 8 glucose units are called α-, β- and γ-cyclodextrin, respectively. The hydroxyl groups are referred to according to the number of their corresponding carbon atom. The carbon atoms in each glucose unit are numbered in the standard manner. If all hydroxyls in a given position are substituted for a different functional group, the prefix “per” is used to indicate full substitution (also known as persubstitution) in this position. Thus, per-6-azido-β-cyclodextrin, for example, is the term commonly used to describe a cyclodextrin with 7 glucose units in which all the hydroxyls in position 6 have been replaced by azide groups. The prefix “per” can also be replaced with a greek prefix indicating the exact number of functional groups or substitutions. In this case, per-6-azido-β-cyclodextrin would be referred to as heptakis(6-azido-6-deoxy)-β-cyclodextrin.

In the case of monosubstituted derivatives it is also necessary to differentiate between individual glucose units. To this end, glucose units are given capital letters A. B, C etc. in superscript. Alternatively, roman numerals can be used instead of letters. As an example, a β-cyclodextrin in which a hydroxyl group in position 2 of one glucose unit has been converted to an allyl ether and all the other hydroxyls are protected by methyl groups, would be called per-*O*-methyl-2^A-*O*-allyl-β-cyclodextrin[35].

The numbering conventions described above are summarised in Figure 6.

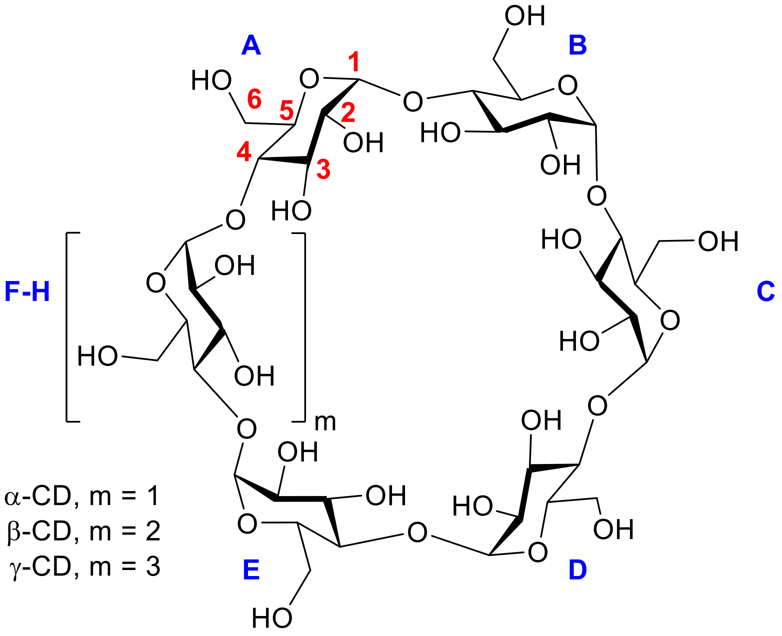


Figure 6: Numbering used for the description of cyclodextrin derivatives.

3.2.6.2 Functionalisation of cyclodextrins

Thanks to the abundance of hydroxyl groups present on both the primary and secondary rim of their molecules, cyclodextrins can be readily modified to fit specific purposes. Desirable features, such as increased solubility, improved complexation properties or surface-immobilisation, can be attained by an appropriate modification of the CD core[36]. Cyclodextrin derivatives can be divided into three categories, depending on the extent of modification and isomerism of the resulting compounds:

- **Randomly modified CDs**

  These cyclodextrin derivatives are prepared by swapping random hydroxy groups for other functionalities. This results in a mixture of differently substituted isomers, the relative proportion of which can vary from batch to batch. Randomly substituted CDs come into play when a modification of the broad physicochemical properties of the CD (e.g., solubility or charge distribution) is required[36]. Examples include randomly sulfated[37] or randomly methylated[38] CDs.

- **Single-isomer derivatives**

  In contrast to randomly modified CDs, single isomer derivatives are made up of molecules of one particular, well defined, isomer. The simplest and synthetically most attainable types of single-isomer derivatives are so-called persubstituted cyclodextrins. In these compounds, all of the available positions of a given type have been replaced by another functional group. Thus, per-2, per-3 or per-6 substituted derivatives are known. These substances find application in separation techniques, as supramolecular building blocks or in nanotechnology[36]. Examples from this work include per-6-iodo-β-cyclodextrin (**13**) or per-6-azido-β-cyclodextrin (**14**). A more complicated class of single-isomer derivatives is comprised of selectively multiply substituted cyclodextrins, which contain several different functional groups in precisely defined positions[36].

- **Monosubstituted derivatives**

  Monosubstituted CDs are a special case of single-isomer derivatives. Here, only one of the hydroxyl groups is converted to a different functionality. These derivatives are very versatile, as they find use in biomedical applications, separation techniques, nanotechnologies or catalysis (*vide infra*). Derivatives monosubstituted in position 6 are the most common since they are easiest to synthesise[39] – see below. A vast number of monosubstituted CDs is known, including cyclodextrins of various sizes monosubstituted with allyl, cinnamyl, propargyl, azido or amino groups. Propargyl and azido derivatives are of particular importance since they can undergo copper(I)-catalysed azide-alkyne cycloadditions (CuAAC)[36].

Due to the multitude of reactive groups present in a cyclodextrin molecule and due to their mutual competition, synthesising precisely defined (particularly monosubstituted) derivatives can prove a non-trivial matter. However, the hydroxyls in the three positions of each glucose unit do have somewhat differing properties that can synthetically be taken advantage of. The least acidic OH-group lies in position 6. Unlike the other two hydroxyls, the C6-OH is primary, making it also the most accessible. Therefore, upon deprotonation of the hydroxyls by excess base, a moderately reactive electrophile will react selectively with position 6. More reactive reagents, however, are less selective and can also react with the OH-groups on the secondary rim. In contrast to position 6, the C2-OH group is the most acidic (pKa = 12.2) and thus most readily deprotonated. When deprotonation is induced by a controlled amount of base, substitution occurs predominantly in this position[36]. Position 3 is the most difficult to functionalise selectively as it is the least accessible. Nevertheless, selective deprotection of perbenzylated CDs with a mixture of triethylsilane and iodine exposes this position in a good yield while leaving the other hydroxyls protected[35]. Other strategies for selective 3-functionalisation have also been explored. For example, alkylation of position 3 of β-CD with cinnamyl bromide provides satisfactory yields of the mono-3^A-*O*-alkylated product. This is due to the fact that β-CD and cinnamyl bromide form an inclusion complex, in which the alkylation agent is oriented in such a way that 3-alkylation is favoured[35,40].

As can be seen, the cavity of CDs also plays an important role in their functionalisation, as the outcome of the reaction can be profoundly affected by inclusion complexation of the reagent. This, in turn, can be influenced by the chosen solvents, which can alter the binding strength and the orientation of the host-guest system[36].

3.2.6.3 Multiply charged cyclodextrins

A special type of cyclodextrin derivatives, developed by members of our research group, are the so-called multiply charged cyclodextrins. These compounds are prepared by the attachment of charged "anchors" (see Figure 7) to a cyclodextrin core by virtue of a copper(I)-catalysed azide-alkyne cycloaddition, also known as a "click" reaction. These anchors are chemically stable compounds, containing in their molecule one to three spatially close permanent positive charges in the form of quaternary ammonium ions. The anchor is built around a neopentane core equipped with an unsaturated reactive group allowing for the aforementioned click reaction. The neopentane scaffold also prevents Hofmann elimination of the attached quaternary ammonium groups. Addition of these functionalities to a suitable cyclodextrin derivative yields a so-called modifier – a compound which is capable of binding non-covalently yet strongly to a negatively charged solid support, thus modifying the chemical properties thereof. So far, these modifiers have been used to convert Nafion® 117 membranes to chiral surfaces, usable for for the resolution of racemic mixtures of L- and D-tryptophan. In this case, the separation of enantiomers was caused by the immobilised cyclodextrins themselves, due to their inherent chirality – see above.

Figure 7 presents an overview of the 9 currently available cationic anchors with 1 to 3 trimethylammonium, *N*-methylimidazolium or pyridinium groups (top). In this project, the bis(*N*-methylimidazolium) anchor (MIM2) was used exclusively. Even though its synthesis was not part of this work, an overview is provided in the same figure (bottom).

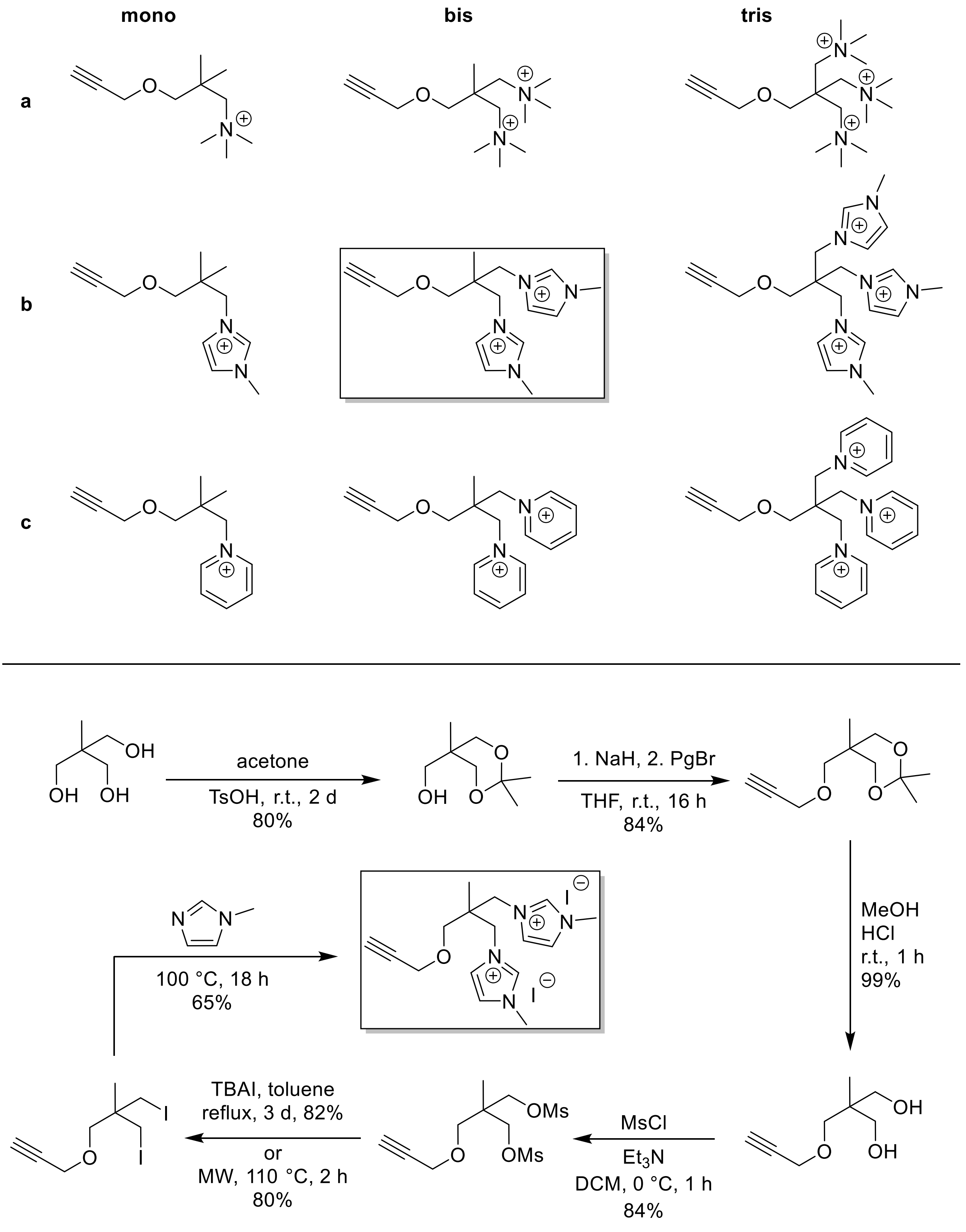


Figure 7: Top: propargyloxy (PgO-) derivatives of cationic anchors with 1 - 3 charges; a) trimethylammonium; b) *N*-methylimidazolium (MIM); c) pyridinium. Bottom: Synthesis of the PgOMIM2 anchor used in this work[2].

Apart from the charged cyclodextrins described above, other attempts to immobilise CDs by ionic interaction have been made. In 2008 a study was published describing the synthesis of cationic monocharged β-cyclodextrins and their use as chiral selectors. In this case, a β-cyclodextrin was monosubstituted with an *N*-alkylimidazolium group on the primary rim (the alkyl substituent being either a methyl or octyl group), while the remaining hydroxyls were converted to aryl (either phenyl or dimethylphenyl) carbamates – see Figure 8. The resulting monocharged modifier could be physically (i.e. electrostatically coated onto porous spherical silica gel to provide a chiral stationary phase for normal-phase HPLC[41]. A similar derivative was used earlier as a chiral stationary phase for HPLC and supercritical fluid chromatography[42]. Earlier still, charged cyclodextrins have been investigated as soluble mobile phase additives in capillary electrophoresis[43,44].

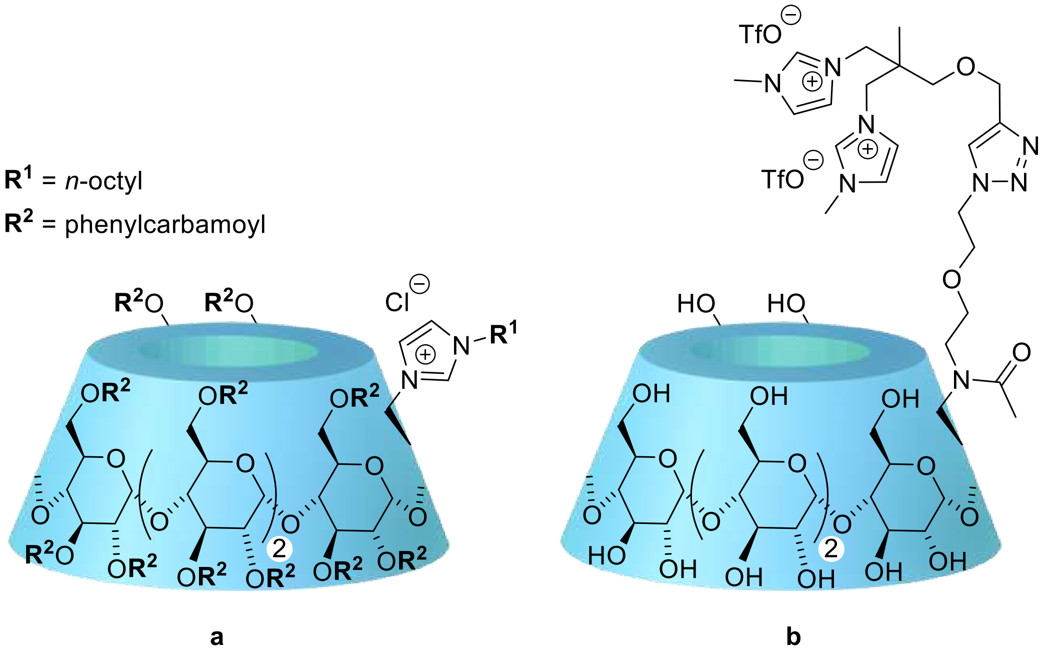


Figure 8: Comparison of cationic cyclodextrin-based modifiers used for chiral separation. a) monocharged β-cyclodextrin with *N*-alkylimidazolium group[42]; b) β-cyclodextrin monosubstituted with a MIM2 anchor bearing two charges[2].

3.2.7 Cyclodextrins as molecular scaffolds

Since cyclodextrins possess a large number of functionalizable hydroxyl groups, along with a six- to eightfold rotational symmetry and the additional function of host-guest chemistry, they are useful building blocks in the construction of various supramolecular scaffolds. For example, β-CD has been used as a scaffold in the preparation of specialised probes containing both MRI contrast agents in the form of gadolinium(III) complexes and fluorescein pendants to enable tracking of cell uptake. Due to the presence of several Gd^{III} centres in one molecule, an increased density of contrast agent was achieved, making this system useful in cell imaging techniques[45]. In another particularly interesting study, β-CD was used as a carrier for anthrax-inhibitory peptides, its sevenfold symmetry matching the heptameric subunit of the anthrax lethal toxin. The inhibitory activity of the resulting structure-based heptavalent inhibitor was more than 100 000 times greater than the activity of the monovalent inhibitory peptide[46].

3.2.8 Binding cyclodextrins to solid surfaces

As already touched upon, there are situations where attachment of cyclodextrins to a solid surface can prove beneficial. The modification of solid surfaces with supramolecular hosts can be used to provide materials with tailored interfacial properties and to confer chemical selectivity[47]. Examples include the aforementioned modification of stationary phases in separation techniques[2,42], binding of electrocatalysts to electrode surfaces[48], or even the modification of materials, such as textiles, to provide them with the ability to store and release fragrances over prolonged time spans[17]. Generally, immobilisation can be achieved in two distinct ways – either through the formation of a covalent bond between the CD and the solid surface, or *via* noncovalent interaction.

3.2.8.1 Covalent immobilisation

Even though many covalent immobilisation procedures involve multistep protocols[47], covalent binding is the method of choice when it comes to attaching cyclodextrins to solid surfaces. An online search for "cyclodextrin immobilisation" provides studies, most of which involve covalent binding of the cyclodextrin building blocks. To name a few examples, cyclodextrins have been attached to polymeric matrices *via* the Williamson ether synthesis. To this end, the primary hydroxyls of β-CD were converted to alkoxides and subsequently reacted with layers of poly(4-vinylbenzyl chloride). The resulting tethered CDs were used to store and release fragrances from the resulting material[17]. Similarly, the reaction between per-6-amino-β-CD and thin films of poly(glycidyl methacrylate) has been used to achieve cyclodextrin immobilisation *via* amine linkages with the immobilised CDs being used as hosts for *N,N*-dimethylformamide and cholic acid[49]. In a study aimed at the derivatisation of a graphene surface, an aniline-substituted β-CD was converted to its diazonium salt. Electrochemical dediazotisation provided an aromatic radical, which lead to the formation of a C-C bond between the graphene surface and the cyclodextrin derivative[47].

3.2.8.2 Noncovalent immobilisation

A different approach to the fixation of cyclodextrins (or any chemical species) to a solid surface involves the use of noncovalent interactions. With cyclodextrins, this usually involves electrostatic binding of an ionic CD derivative to a suitable charged carrier. Some of these cationic CDs that have been investigated in our research group include β-cyclodextrins monosubstituted with an exhaustively methylated ethylene- or propylenediamine group. The resulting doubly charged species can bind electrostatically to the anionic surface of a Nafion® 117 membrane[50]. Later, the more advanced multiply charged cyclodextrins were developed – see chapter 3.2.6.3.

Cyclodextrins have also been used as coatings of gold electrodes for applications, such as chemical sensing[51] and electrocatalysis[48]. In both cited cases, immobilisation was achieved *via* thiolate bonds. Although this type of bond is often regarded as a type of chemisorption or even covalent interaction, its true nature remains a subject of debate. A recent study, however, demonstrates that the majority of gold-sulfur bonds in self-assembled monolayers is of a physisorbed (or noncovalent) nature[52].

3.2.9 Cyclodextrins and catalysis

Because of their complex-forming abilities, cyclodextrins can also participate in the directing of chemical reactions. If, for instance, a reactant molecule forms an inclusion complex with a CD host, the parts of it protruding from the CD cavity will remain accessible to the reagent, while the rest of the molecule stays protected within the host-guest complex. This can lead to the preferential formation of some components of what would otherwise be a mixture of products. Cyclodextrins can also function as phase-transfer catalysts. By solubilizing hydrophobic molecules they enable the reaction to proceed in the bulk of the aqueous solution, rather than at the mere interface between water and an organic phase[30].

These, however, are not the only roles CDs can play in the catalysis of chemical reactions. Rather than acting as catalytic species themselves, they can serve as carriers for catalysts. In some cases, the CD can assist the catalytic process by pre-orienting the substrate within its cavity towards the attached catalytic centre[53]. This has, for instance, been exploited by Schlatter *et al.* in the enantioselective, ruthenium-catalysed reduction of aliphatic and aromatic ketones[54]. A good review of CDs in asymmetric and stereospecific synthesis, including their use in combination with transition metal catalysts, has been provided by Macaev and Boldescu[53]. The synergy between the cyclodextrin cavity and the attached catalytic species lead to the term "artificial enzymes" being used to describe such systems. Indeed, such systems have been used to imitate enzymatically catalysed processes in so-called biomimetic reactions. An engaging review of such CD-based catalytic systems has been compiled by Breslow and Dong[55].

What pertains more directly to this work, is the use of cyclodextrins as carriers of organocatalysts. In this regard, proline-cyclodextrin conjugates seem to be the most abundant catalytic assemblies in the literature[4] For example, .Liu and Zhang reported a β-CD derivative carrying a proline catalyst attached by a urea linkage[56]. This assembly was successfully used in the catalysis of asymmetric aldol reactions in aqueous environments. In a similar study, proline was connected to a β-CD carrier *via* several linkers. It was found, that the most flexible, linker provided the most efficient catalytic system for a model aldol reaction[3]. Self-inclusion behaviours of proline-modified cyclodextrins and their impacts on enantioselectivity were investigated by Shen and Ji[57]. An interesting approach to the CD-immobilisation of a proline catalyst was used by Liu *et al.* In this case, immobilisation was achieved not by covalent binding, but instead by the use of a proline derivative with a bulky adamantyl pendant which connected to the β-CD by inclusion complexation[58]. Overall, the immobilisation of proline-based catalysts onto CDs and the application of the resulting conjugates have been explored to an appreciable extent.

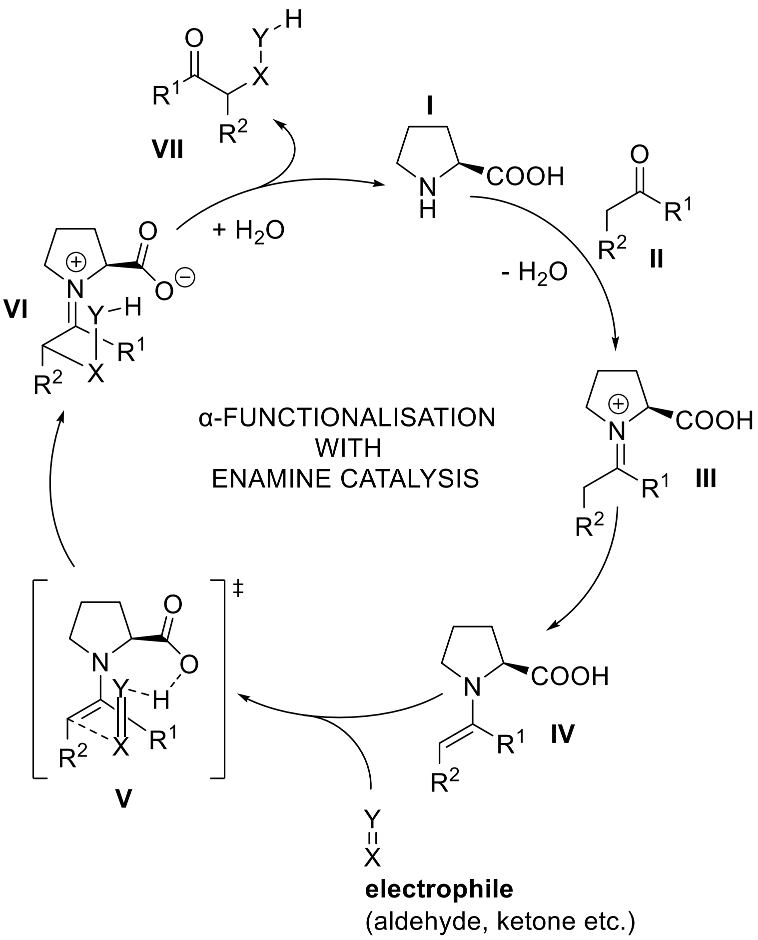
3.3 Proline-based organocatalysis

The term "organocatalysis" is associated with the acceleration of chemical transformations by the addition of catalytic amounts of an organic compound to the reaction mixture. Despite having been seemingly overlooked for some time, this subdiscipline of catalysis has seen tremendous expansion since the late 1990s[59]. This even lead some authors to use terms, such as "the golden age of organocatalysis" to describe the ensuing times of intense development in this field[6].

Most organocatalytic reactions are based on amine-containing molecules, such as amino acids, peptides or alkaloids[4,6]. Since amino acid catalysis is close related to enzyme catalysis, it can be regarded as a bridge between strictly synthetic and bioorganic chemistry[6]. Of the amino acids involved, proline is likely the most important. The 2021 Nobel Prize in Chemistry, awarded to Benjamin List and David W. C. MacMillan for their seminal work on proline-based organocatalysis[7,60], is sufficient proof.

Proline-catalysed reactions usually proceed through one of two main pathways involving either enamine or iminium species.

In the enamine pathway (Scheme 1), the secondary amine of the catalyst **I** attacks a carbonyl **II** resulting in the formation of iminium ion **III**. The iminium ion is converted to enamine **IV** by α-deprotonation. Addition of an electrophile proceeds through a highly organised transition state **V** towards another iminium ion, **VI**. Hydrolysis of this intermediate provides an α-functionalised product and regenerates the catalyst[6].

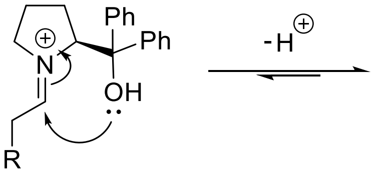


Scheme 1: Catalytic cycle of L-proline involving an enamine intermediate[6].

Enamine and iminium catalysis are often complementary processes, so that some transformations can occur through either one of these activation pathways[6]. An example of iminium catalysis is provided in the following chapter.

3.3.1 Hayashi-Jørgensen's catalysts

Due to the great catalytic potential of proline, many organocatalysts have been developed in its image. An array of such analogues is presented in a review by Dalko and Moisan[6]. A particular variant, so-called α,α-diarylprolinols, are some of the most successful aminocatalysts[61]. As the name implies, these catalysts contain a diphenylprolinol motif. This amino alcohol was synthesised in the 1930s and was used to some extent as a chiral auxiliary or as a ligand in reactions catalysed by Lewis acids. In enamine activation, however, this compound did not provide satisfactory results – particularly in terms of catalyst turnover[62,63]. Jørgensen and his colleagues attributed this behaviour to the formation of undesirable hemiaminal species which could inactivate significant amounts of the catalyst – see Scheme 2.



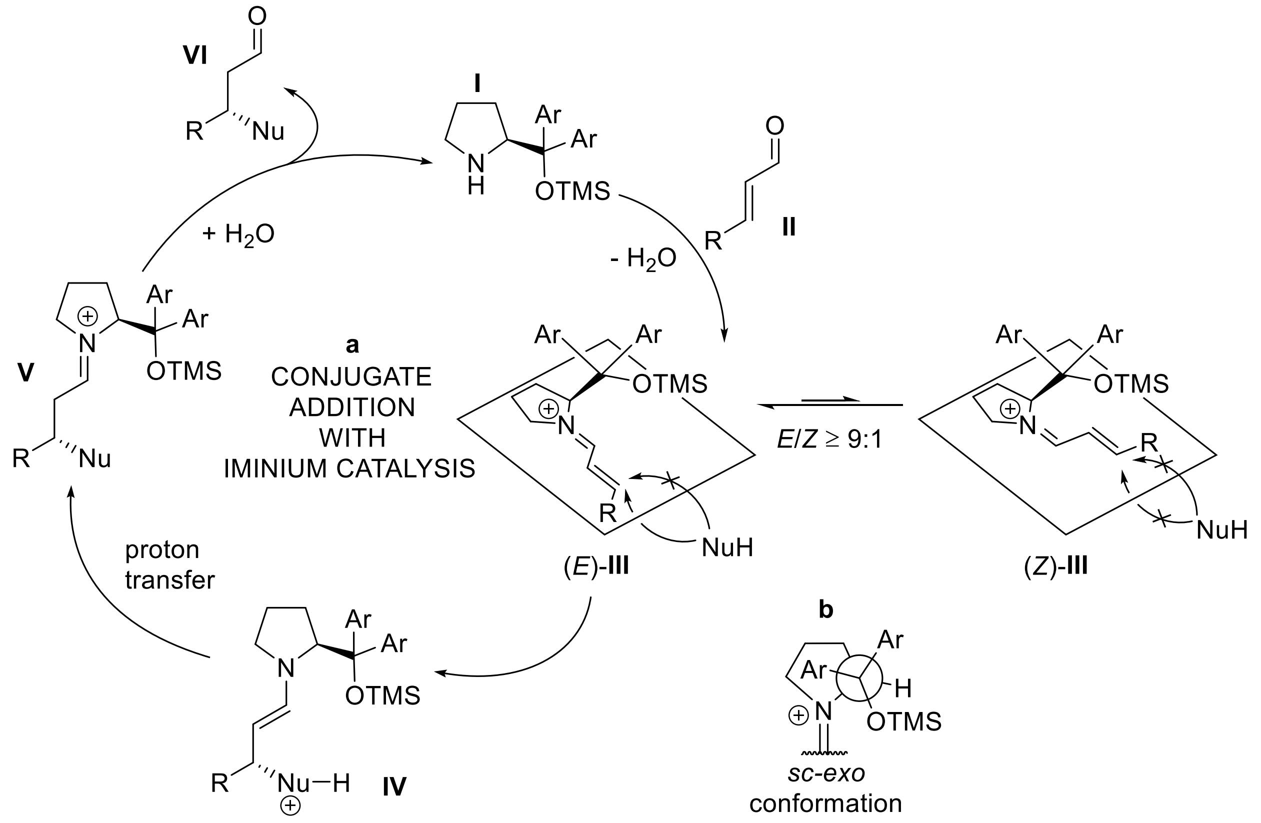
Scheme 2: Formation of an inactive, off-cycle hemiaminal.

Their solution to this issue was simple. Protection of the tertiary alcohol with a TMS group caused a dramatic improvement of the catalyst turnovers in α-functionalisation of aldehydes and provided the first of a novel class of diarylprolinol silyl ether catalysts suitable for a wide range of organic transformations[63]. The catalysts could be further improved and fine-tuned by modification of the geminal aryl groups[62,63].

Shortly afterwards, Hayashi *et al.* reported on the use of diarylprolinol silyl ethers with different silyl protecting groups in the catalysis of asymmetric Michael additions of aldehydes and nitroalkenes[8].

Due to these two authors' initial contributions, the class of diarylprolinol silyl ether catalysts if often referred to as Jørgensen-Hayashi or Hayashi-Jørgensen catalysts. For the sake of simplicity, the commonly used term "Jørgensen's catalyst" is applied throughout this work.

Scheme 3a presents one possible mechanism, by which Jørgensen-type catalysts can function. In tis case, a conjugate addition of a nucleophile to an α,β-unsaturated aldehyde is catalysed through an iminium activation pathway. As described by Nielsen *et al.*[64], the mechanism begins with the condensation of catalyst **I** and α,β-unsaturated substrate **II** forming iminium ion **III**. The most stable conformation of this iminium ion presents the nitrogen atom and the silyl group in a synclinal, exocyclic (*sc-exo*) relationship (Scheme 3b). As far as *E*/*Z*-isomerism is concerned, the *E*-isomer, (*E*)-**III**, is somewhat favoured. Nevertheless, under some conditions the *Z*-isomer, (*Z*-**III**), can be present in significant amounts. An s-*cis* conformation between the two double bonds is substantially more energetically demanding and is therefore not taken into consideration. The reason behind the high enantioselectivities achieved despite the presence of both *E*/*Z*-isomers in the chemical environment lies in the fact that nucleophilic attack on the *E*-isomer is less energetically demanding and therefore faster than attack on the *Z*-isomer. On the *E*-isomer, *Si*-facial attack is more favourable than attack from the *Re*-face hence the enantio- and diastereoselectivity of the catalyst. Thus, nucleophilic attack on the *Si*-face of (*E*)-**III** leads to the formation of enamine **IV** which, upon proton transfer, converts to iminium **V**. Hydrolysis of **V** liberates the β-functionalised product and regenerates the catalyst.



Scheme 3: Catalytic cycle of a Hayashi-Jørgensen-type catalyst providing iminium catalysis of a conjugate addition[64]. Nu = nucleophile.

3.4 Catalyst immobilisation

Despite their excellent activity, Jørgensen-Hayashi-type catalysts do have their drawbacks.

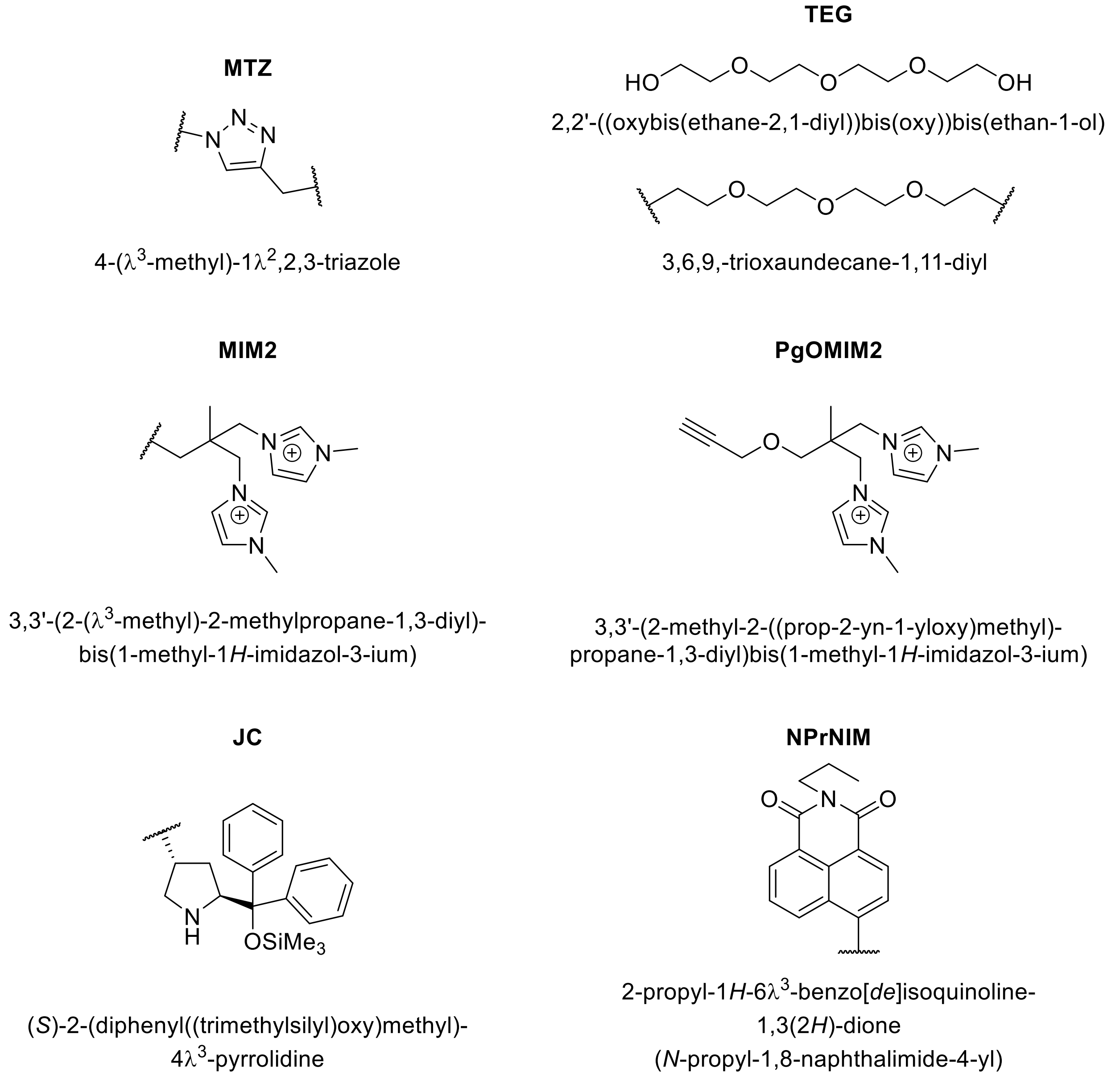
Proline is the only naturally occurring amino acid with a secondary amine functional group, making it more nucleophilic, than its sibling amino acids. This allows it to react with electrophilic molecules, such as carbonyls or Michael acceptors, leading to the formation of enamines and iminium ions. On the one hand, this is the basis for all its useful catalytic properties. On the other hand, however, its enhanced nucleophilicity can cause proline to react with miscellaneous electrophiles present in the reaction mixture, forming undesirable off-cycle species[6]. This can, however, be mitigated by the use of higher catalyst loadings[61]. Still, this does not eliminate another issue, namely the difficulty of separating the catalyst from the reaction mixture due to the occasional similarity of the products and the catalyst. In such cases, catalyst immobilisation is worth considering, as it can facilitate both product separation and catalyst recovery[65]. Mager and Zeitler, for instance, have examined a homogeneous, methoxypolyethylene glycol-linked Jørgensen's catalyst for the catalysis of conjugate additions of nitromethane to α,β-unsaturated aldehydes. Their immobilised catalyst could be separated from the reaction mixture by simple precipitation and the products were obtained in high yield with excellent enantioselectivities without the necessity for column chromatography[65]. In contrast, Lai et al. used an insoluble polystyrene resin as a solid support. Their covalently bound, solid-supported catalyst was used successfully in the enantioselective synthesis of 5-hydroxazolidines in both batch and flow assemblies[61].

As can be seen, catalyst immobilisation can provide both homogeneous and heterogeneous catalytic systems. In a heterogeneous arrangement, the advantages of heterogeneous over homogeneous catalysis can include, *inter alia*, increased efficiency and greater environmental friendliness. This is a key factor, especially now that environmental aspects of industrial processes are gradually being taken into consideration[5,66].

4. RESULTS AND DISCUSSION

4.1 A note on abbreviations and nomenclature

For the sake of simplicity, several abbreviations have been introduced throughout this work in order to replace the often unwieldy systematic nomenclature of some compounds or functional groups. Although they have been listed in the Symbols and abbreviations section, it may be helpful to revisit and clarify their usage. Figure 9 provides an overview of the abbreviations used in this text.



MTZ

4-(λ^3-methyl)-1λ^2,2,3-triazole

TEG

2,2'-((oxybis(ethane-2,1-diyl))bis(oxy))bis(ethan-1-ol)

3,6,9,-trioxaundecane-1,11-diyl

MIM2

3,3'-(2-(λ^3-methyl)-2-methylpropane-1,3-diyl)-bis(1-methyl-1*H*-imidazol-3-ium)

PgOMIM2

3,3'-(2-methyl-2-((prop-2-yn-1-yloxy)methyl)-propane-1,3-diyl)bis(1-methyl-1*H*-imidazol-3-ium)

JC

(*S*)-2-(diphenyl((trimethylsilyl)oxy)methyl)-4λ^3-pyrrolidine

NPrNIM

2-propyl-1*H*-6λ^3-benzo[*de*]isoquinoline-1,3(2*H*)-dione
(*N*-propyl-1,8-naphthalimide-4-yl)

Figure 9: Overview of specific abbreviations used in this work with the structures they represent and the corresponding systematic names.

Note that the abbreviation TEG is used both for tetraethylene glycol as a compound and for the 3,6,9,-trioxaundecane-1,11-diyl group that remains after its incorporation into the supramolecular structure. Also, contrary to conventional nomenclature, functionalities are listed starting from the cyclodextrin core and continuing outwards for greater clarity.

Figure 10 exemplifies the usage of the abbreviations shown in Figure 9 in naming the supramolecular assemblies discussed herein.

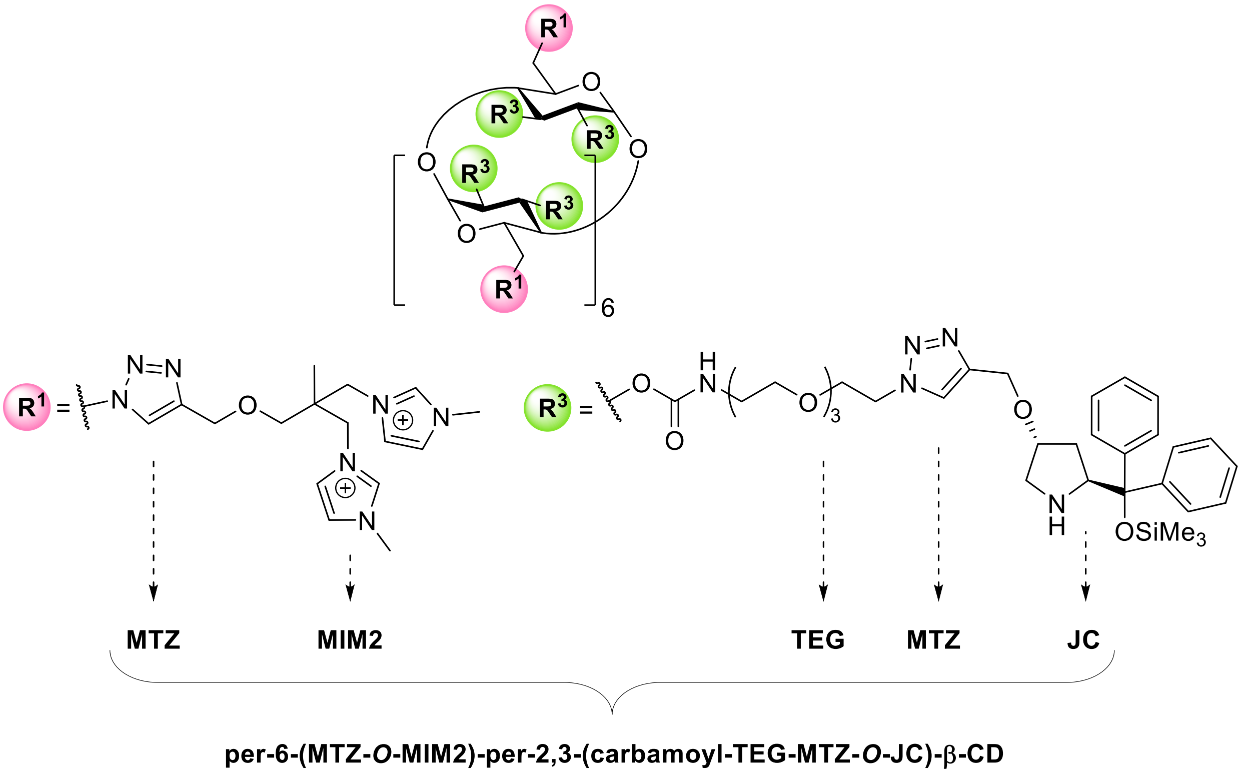


Figure 10: Example of simplified nomenclature.

4.2 Discussion of experimental procedures and results

The aim of this project was to investigate the possibility of using multiply charged cyclodextrins as carriers for catalysts. A model system, consisting of a 14× charged β-CD and an oligoethyleneglycol-tethered Jørgensen-Hayashi-type catalyst, was designed.

β-Cyclodextrin was chosen as the basis for this system because it is the most readily available. The choice of a tetraethylene glycol linker was prompted by the vision that its length and flexibility might enable the attached catalysts to move relatively freely in the surrounding solution. A diphenylprolinol silyl ether (Jørgensen-Hayashi) catalyst was chosen as a representative catalytic species since it is well studied and a straightforward method for its immobilisation was found in the literature[65]. The charges on the β-CD were provided by seven

MIM2 anchors attached to its primary rim *via* a 4-(λ^3-methyl)-1λ^2,2,3-triazole (MTZ) linkage. This connection is formed as a result of a "click" reaction between a per-6-azido-β-CD and a propargylic derivative of the MIM2 anchor (PgOMIM2, **15** – see Scheme 6). The synthesis of this precursor was not part of this project. Instead, the compound was taken from our reserves that had been provided earlier by other members of our group. The remaining components of the catalytic system (i.e., per-6-azido-β-CD, TEG linker and modified Jørgensen's catalyst) were synthesised from commercially available starting materials. These three building blocks were then assembled into the final catalytic system – see following chapters.

With the catalytic system **4** in hand, sorption and catalysis experiments were attempted. Silica gel, basic aluminium oxide and zeolite (powdered molecular sieves) were investigated as potential sorbents. The catalytic properties of the supramolecular assembly were tested using the Michael addition of diethyl fluoromalonate to cinnamaldehyde as a model reaction system. However, due to difficulties with characterisation of the target compound, not enough time could be devoted to optimisation of these experiments, so that the results thus obtained are only of a preliminary nature.

In an attempt to develop a more reproducible method for the sorption (and eventually desorption) experiments, a fluorescent analogue (**21**) of the original catalytic system was synthesised. This was achieved by a click reaction between a 4-propargylamino derivative of an *N*-propyl-1,8-naphthalimide (NPrNIM) fluorophore (**20**) and per-6-(MTZ-*O*-MIM2)-per-2,3-(oxy-TEG-azido)-β-CD (**17**). The fluorophore was synthesised from commercially available 4-bromo-naphthalic anhydride. Compound **17** is a variant of compound **16** with the TEG linkers attached to the CD core *via* an ether bond instead of a carbamate. This derivative was prepared as a potentially more stable precursor to the desired supramolecular assembly. Both compounds (**17** and **21**), however, were prepared too late to be thoroughly utilised.

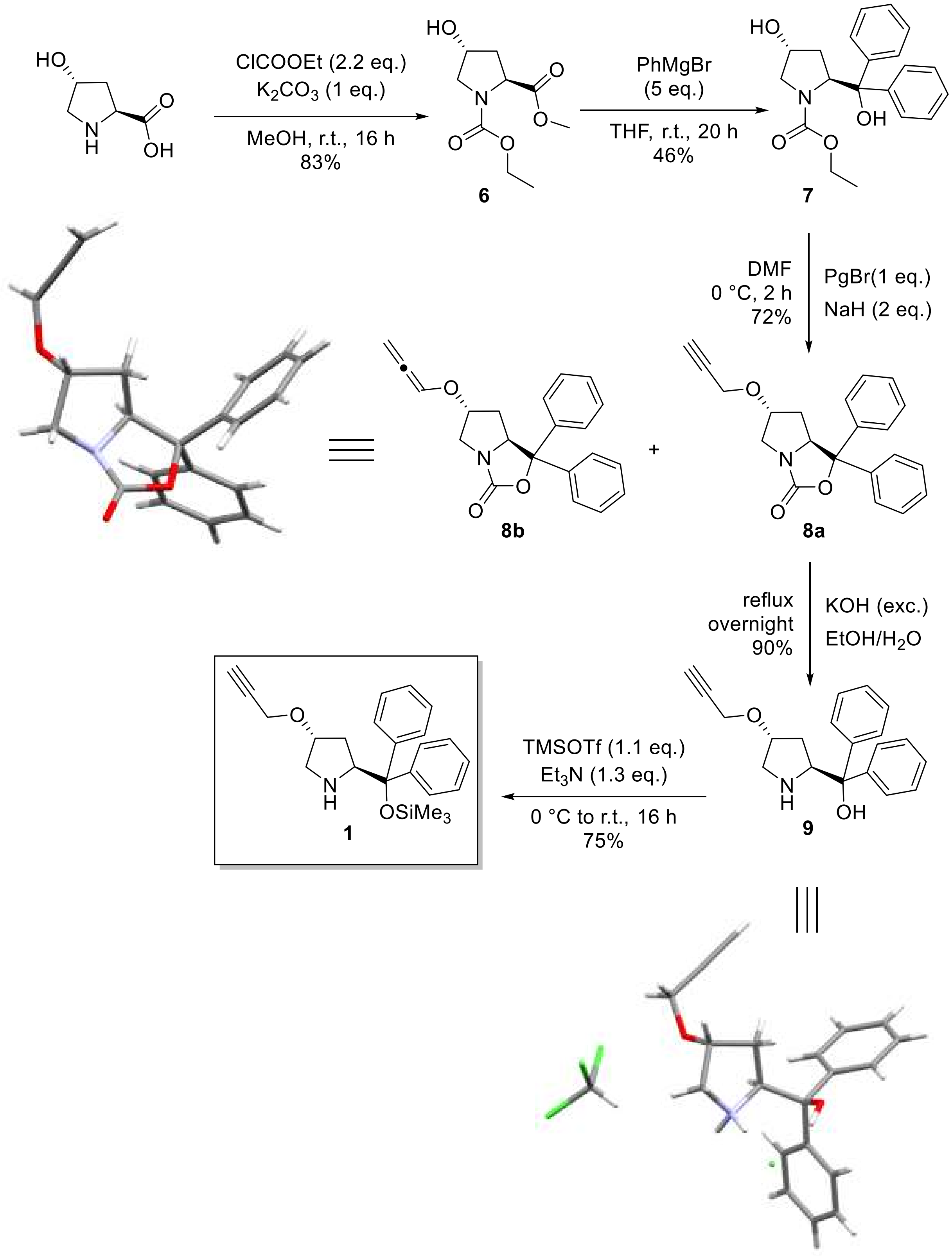
4.2.1 Synthesis of *O*-propargylic Jørgensen's catalyst

The synthesis of propargylic Jørgensen's catalyst **1** (Scheme 4) was carried out according to a published procedure[65] with slight modifications. First, commercial trans-4-hydroxy-L-proline was converted to its methyl ester **6** through base-catalysed esterification. The reaction was carried out in the presence of ethyl chloroformate, leading to the simultaneous introduction of an ethyloxycarbonyl group onto the nitrogen atom of the proline substrate. This reaction proceeded smoothly in good yields and did not require chromatographic purification.

The resulting methyl ester was then reacted with freshly prepared phenylmagnesium bromide resulting in the formation of the diphenylprolinol motif. Part of the product could be isolated by precipitation from the crude mixture of products, while the remainder had to be purified by column chromatography. Even though different procedures were attempted, the highest achieved yield was a moderate 46%.

The Grignard-product **7** was then subjected to an *O*-alkylation with propargyl bromide. The reaction was carried out under basic conditions, causing the formation of an intramolecular carbamate. During the purification of the crude product, a crystalline compound was observed. A sample was taken for X-ray crystallography with the expectation that this might be the desired product. The X-ray structure, however, showed that this compound (**8b**) is in fact the allene analogue of the required propargylic product **8a**. A search of the literature showed that the conversion of a propargyl into its allene analogue can occur in the presence of excess base[61]. This was taken into account during the subsequent runs of this reaction. Nevertheless, the obtained X-ray image provided a valuable insight into the structure and stereochemistry of the emerging catalyst. Interestingly, this side-product was not observed during the next step when excess base was used to hydrolyse intramolecular carbamate **8a** into propargylic diphenylprolinol **9**. The hydrolytic product was obtained in high yield and again a crystal structure could be obtained. The structure shows co-crystallisation with chloroform and a protonated secondary amine.

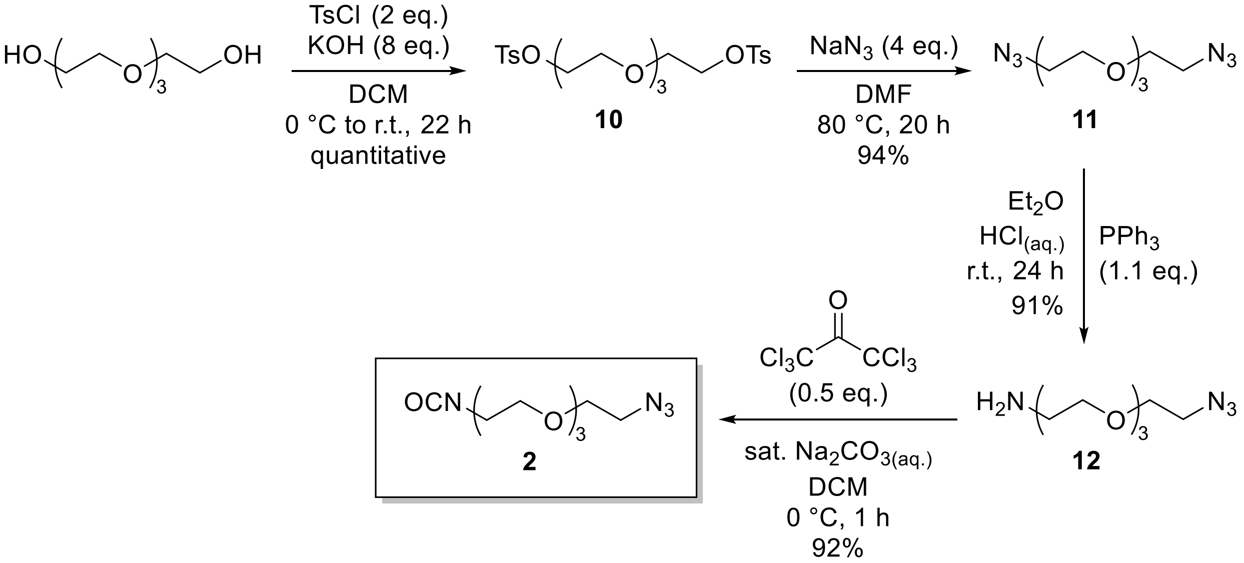
Finally, the tertiary hydroxyl in **9** was protected with a TMS ether providing 4-propargyloxy-diphenylprolinol silyl ether **1** in 19% overall yield.



Scheme 4: Synthesis of propargylic Jørgensen's catalyst **1** from trans-4-hydroxy-L-proline.

4.2.2 Synthesis of tetraethylene glycol linker

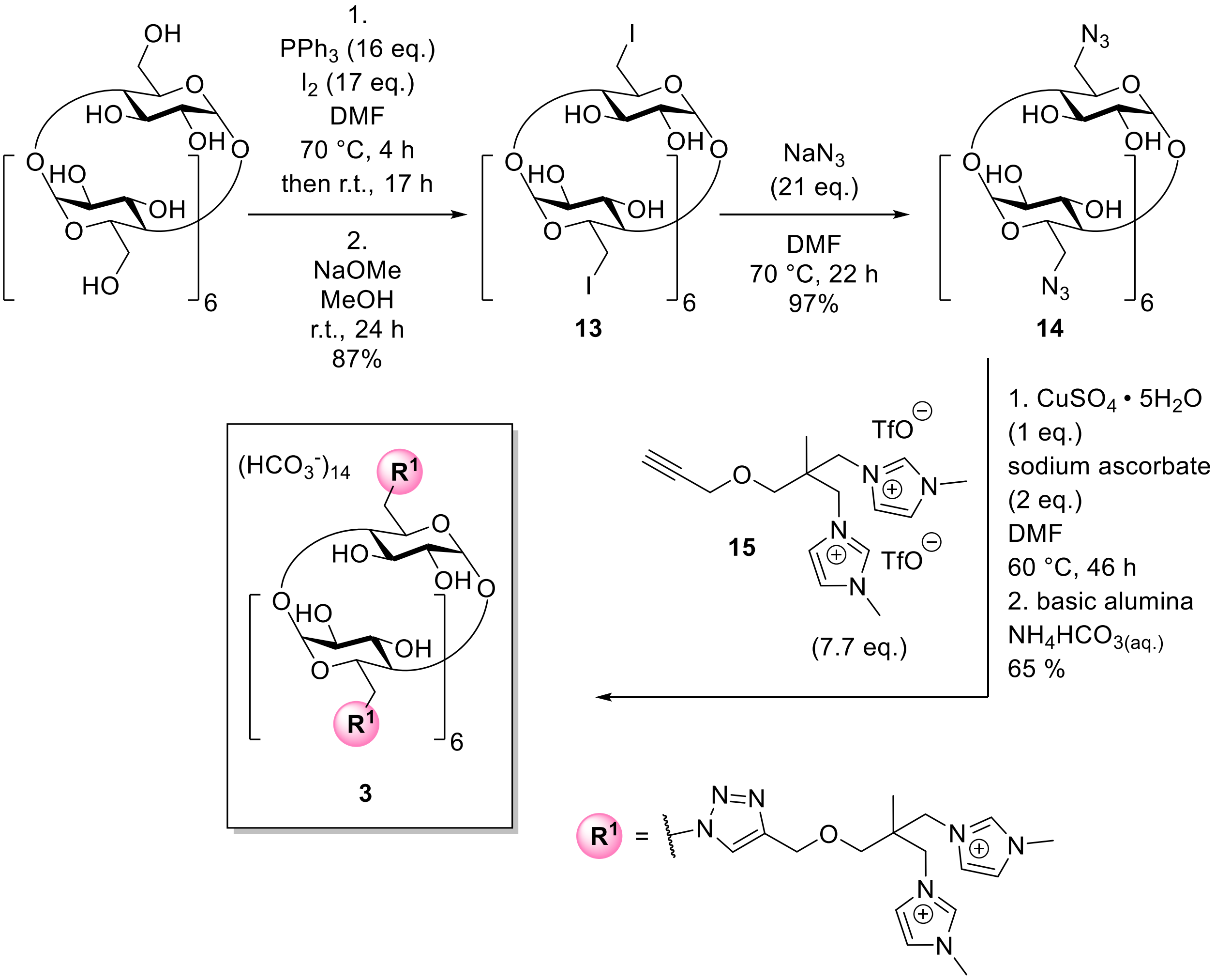
The TEG derivatives (Scheme 5) were synthesised according to an established procedure based on literature precedents[67]. Commercial tetraethylene glycol was first converted to its ditosylate **10** providing good leaving groups for the subsequent azidation. The reaction proceeded quantitatively and the product was used without purification in the next step. The tosylates were then substituted for azide groups providing TEG-diazide **11** in high yield. Mono-reduction of the diazide was achieved by a Staudinger reduction in a biphasic system. In this set-up, the reduction proceeds in the organic phase. When the monoamino product is formed and comes into contact with the acidic aqueous phase, it is protonated and thus migrates into the aqueous phase where it cannot undergo further reduction. The amino-azido derivative **12** was prepared od a 60 g scale and stored in this form until needed. The final isocyanate derivative **2** was synthesised only on a 1 g scale and always prepared freshly before use. Mostly, the intermediates were confirmed only by ^{1}H NMR as they are extensively used in our laboratory and their spectra are kown. The overall yield was 79%.



Scheme 5: Synthesis of azido-isocyanato-TEG-linker **2** from tetraethylene glycol.

4.2.3 Synthesis of multiply charged β-cyclodextrin

Per-6-iodo- and per-6-azido-β-cyclodextrins (Scheme 6) were prepared according to published procedures[68,69]. Both iodination and azidation proceeded in high yields on a 50 – 70 g scale. This can be attributed to the fact that per-6-substituted CD derivatives are most easily prepared thanks to the accessibility of the primary hydroxyl on C6[39]. Next, MIM2 anchors were attached through a CuAAC reaction in the presence of Cu(II) and sodium ascorbate as a reducing agent. The product was purified according to an optimised procedure on a column of basic alumina, separating first the the excess anchor and ascorbate and finally leaving behind any residual copper ions. The optimised procedure involved loading a 5% solution of the crude product in 0.01 M aqueous NH_4HCO_3 onto a column with a 70-fold amount of basic alumina and eluting first with 1 column volume (CV) of 0.01 M NH_4HCO_3, then with 1 CV of 0.1 M NH_4HCO_3 and lastly with 3 CV of 1 M NH_4HCO_3 to wash out the pure product. After equilibration of the column with 2 CV of 0.01 M NH_4HCO_3, the procedure could be repeated with another portion of the crude product. Thanks to this procedure, all of the crude product was purified using one column and a relatively high yield (65%) was achieved. The overall yield of charged β-CD **3** was 55%.



Scheme 6: Synthesis of per-6-(MTZ-*O*-MIM2)-β-CD **3** from native β-cyclodextrin.

4.2.4 Assembly of the catalytic system

When it came to assembling the individual components into the final catalytic system (Scheme 7), the difficulty substantially increased. This was due in part to the fact that from this point onwards, all compounds were highly charged organic salts with limited solubilities and troublesome purifications. Also, as soon as modifications of the secondary rim were introduced, NMR spectra became increasingly difficult to read and integrations provided highly inaccurate results.

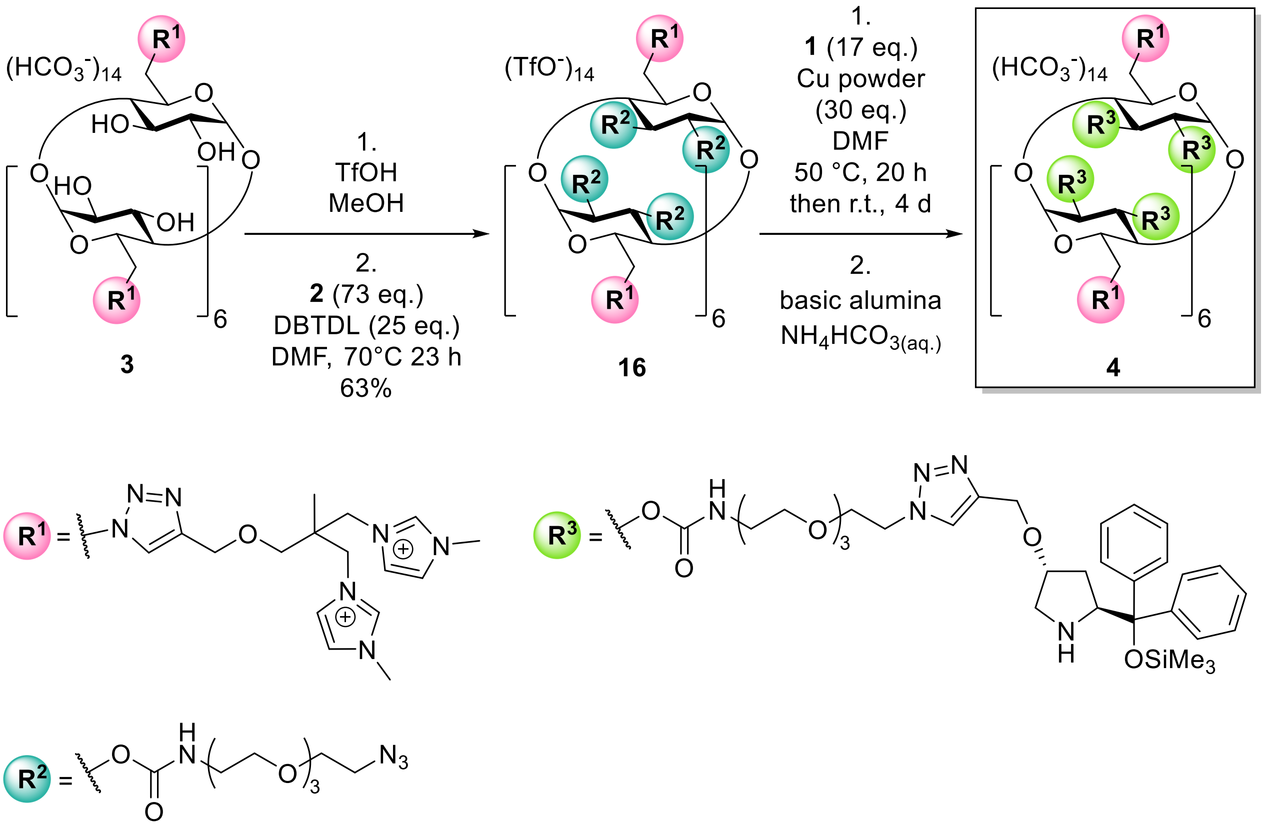
First, charged β-CD **3** was treated with an excess of TEG-isocyanate **2** in the presence of dibutyltin dilaurate (DBTDL) forming carbamate connections on the secondary rim.

Based on the ^{1}H NMR spectrum of compound **16**, an average substitution of 10 TEG linkers per β-CD was estimated. Increasing the reaction time, using a greater excess of isocyanate or heating the reaction mixture to higher temperatures failed to provide a higher average substitution. This is due to the increased steric crowding of the secondary rim with each new TEG-linker, making the subsequent connections more and more sterically demanding and therefore less and less favourable.

From there, a connection between charged CD derivative **16** and propargylic Jørgensen's catalyst **1** was formed *via* CuAAC, this time catalysed by elemental copper for a slightly easier purification. The reaction was monitored by IR spectroscopy which neatly showed the gradual disappearance of the azide signal at 2106 cm^{-1}. At the same time, the reaction was followed by TLC which showed the presence of a charged CD (immobile, carbonizable spot on the start line) which detected positively in ninhydrine indicating the presence of an amine functionality.

^{1}H NMR spectra, however, showed that the resulting substance deviated from the expected composition. Not only was the substitution significantly decreased but also, and perhaps more surprisingly, hardly any trimethylsilyl signals were detected. The average substitution with TEG-MTZ-*O*-JC groups per β-CD reached only six, five of which did not contain a $SiMe_3$ group. This clearly indicated that some form of decomposition had taken place. Another run of the reaction lead to no improvement. Mass spectrometry also failed to provide intelligible results.

In the time that was devoted to attempts at characterising compound **4**, preliminary catalysis and sorption experiments were performed – see chapters 4.2.7 and 4.2.6, respectively.

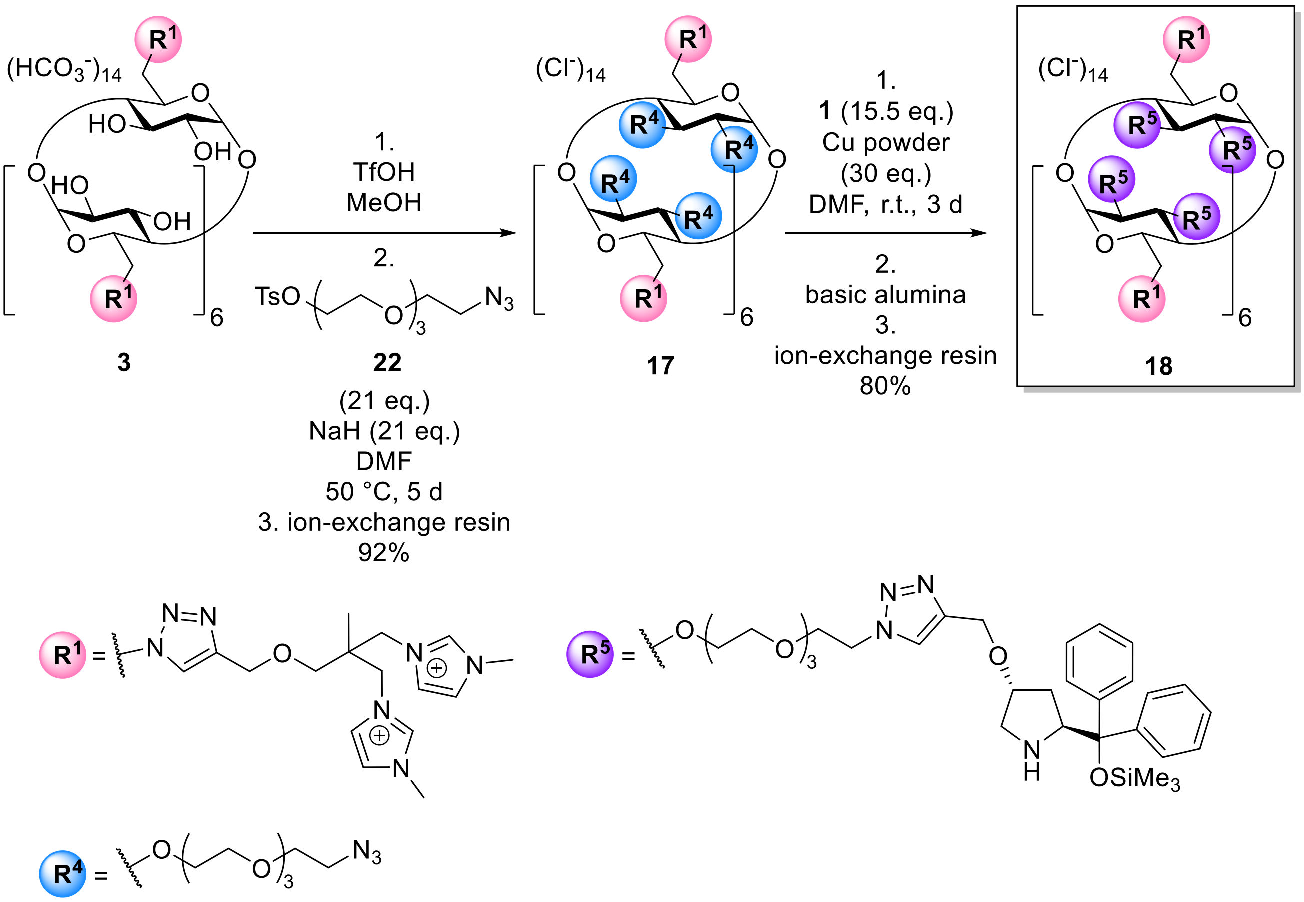


Scheme 7: Immobilisation of Jørgensen's catalyst onto per-6-(MTZ-*O*-MIM2)-β-CD *via* carbamate-TEG linkers leading to catalytic system **4**.

In an attempt to produce a more stable version of the catalytic system, an alternative strategy for the attachment of TEG linkers to the CD secondary rim was explored. Instead of forming a carbamate connection through the reaction of an isocyanate and a secondary hydroxyl, formation of an ether bond was suggested (Scheme 8).

To this end, charged β-CD **3** was treated with azido-tosyl-TEG **22** (the synthesis of this of which was not part of this project) under basic conditions, forming an ether linkage through S_N2 substitution. According to ^1H NMR spectra, the target compound **17** was obtained. However, the substitution was lower compared to its carbamoyl analogue with an average of only 6 substituents per β-CD.

Notwithstanding, the attachment of catalyst **1** *via* CuAAC was attempted. The reaction was set up analogously to the preparation of **4**. And the same results were observed by IR spectrometry and TLC as with compound **4**. ^1H NMR spectrum of the resulting conjugate revealed an approximate substitution of 10 TEG-MTZ-*O*-JC groups per β-CD almost all of which, however, were desilylated.



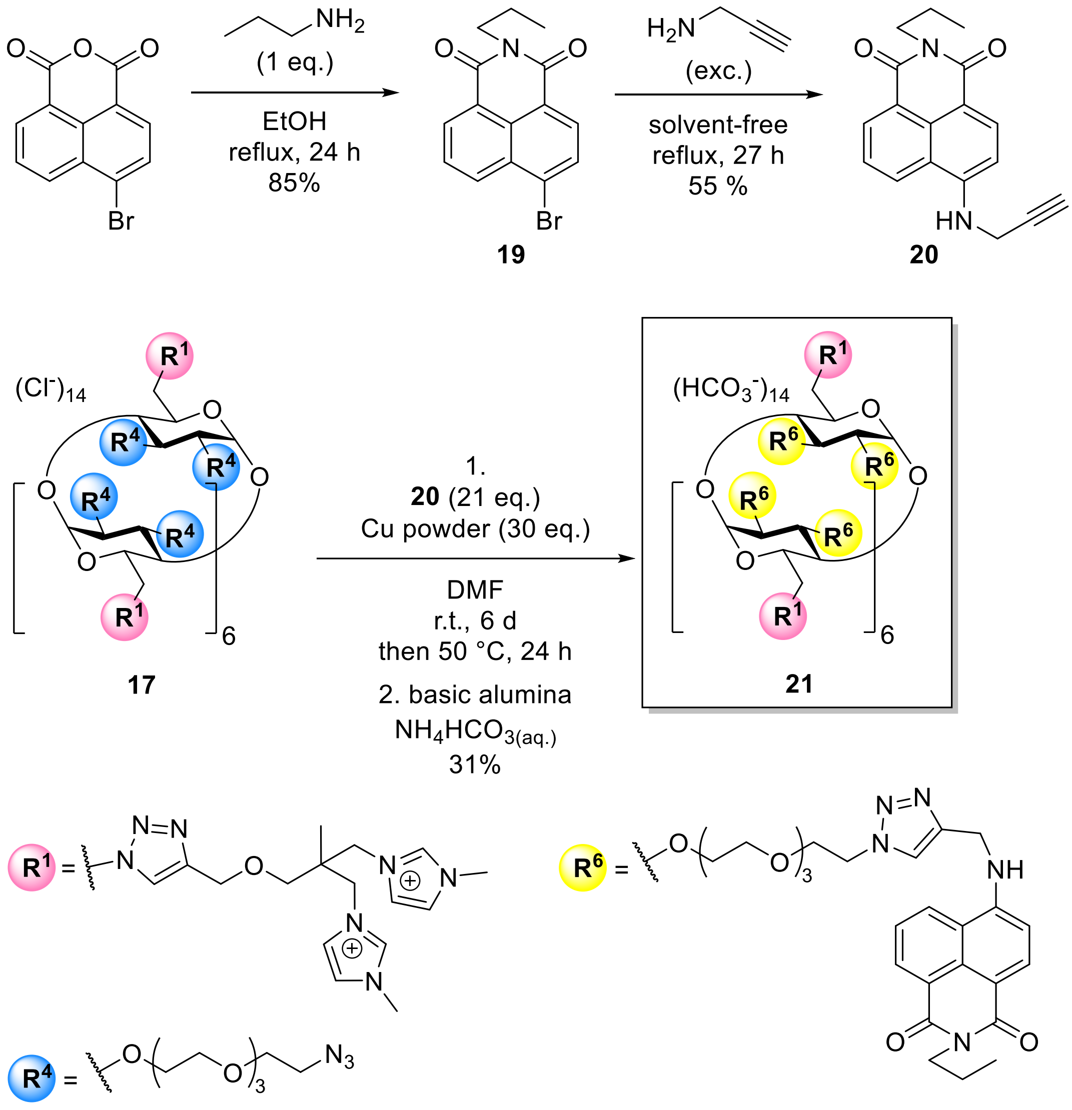
Scheme 8: Immobilisation of Jørgensen's catalyst onto per-6-(MTZ-*O*-MIM2)-β-CD *via* ether-TEG linkers leading to catalytic system **18**.

4.2.5 Synthesis of a fluorescent analogue of the catalytic system

When sorption experiments were performed, problems were encountered regarding the inconveniently situated absorption maximum of compound **4**. The maximum was located at 201 nm, a value close to the absorption cutoff of MeOH, potentially causing inaccurate readings. Since compound **4** showed no other absorption maximum, it was decided to synthesise a fluorescent analogue of the catalytic system. This was to be done by "clicking" a propargylic fluorophore onto a charged CD carrier bearing azido-TEG linkers. Compound **17** was chosen as, at the time, it was most abundantly available.

The fluorophore itself was synthesised in the following manner (Scheme 9)[70]:
First, commercial 4-bromo-1,8-naphthalic anhydride was refluxed with *n*-propylamine in EtOH and thus converted to 4-bromo-*N*-propyl-naphthalimide **19**. Bromide **19** was then refluxed in neat propargylamine leading to target compound **20** *via* nucleophilic aromatic substitution.

The propargylic fluorophore was then combined with charged β-CD **17** in a procedure analogous to the catalyst immobilisations described above. Completion of the reaction was again verified by tracking the IR signal of the azide group at 2106 cm^{-1}. TLC analysis also showed an immobile spot, characteristic of a charged CD, which exhibited fluorescence at 366 nm. From the ^1H NMR spectrum, a substitution of 10 TEG-MTZ-amino-NPrNIM pendants was estimated.



Scheme 9: Synthesis of 4-propargylamino-*N*-propyl-1,8-naphthalimide fluorophore **20** and its attachment to per-6-(MTZ-*O*-MIM2)-β-CD *via* ether-TEG linkers.

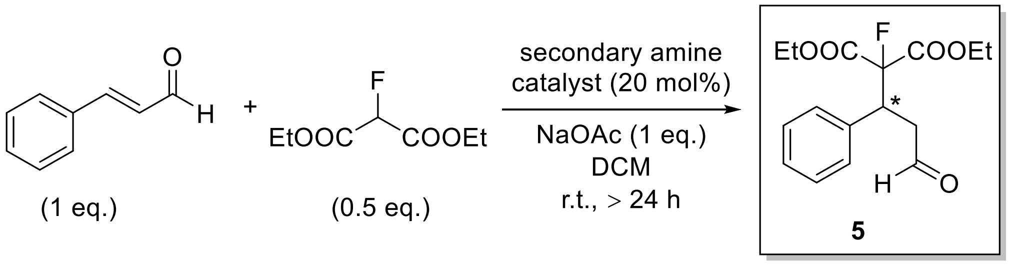
4.2.6 Model reaction and catalysis

Originally, the conjugate addition of nitromethane to cinnamaldehyde, also known as Henry reaction or nitro-Michael addition[65], was considered as a model system. Unfortunately, when this reaction was attempted under several different conditions with achiral catalysts (piperidine and racemic proline), only mixtures of products were obtained and the desired γ-nitroaldehyde could not be isolated.

Fortunately, a more feasible alternative was soon found in the literature[71]. The new reaction was still a conjugate addition with cinnamaldehyde serving as the representative α,β-unsaturated carbonyl but nitromethane was replaced by diethyl fluoromalonate as the nucleophile (Scheme 10).

Although complex reaction mixtures were obtained even in this set-up (likely due to the presence of cinnamaldehyde degradation products), samples of the desired Michael adduct could be isolated by column chromatography or preparative TLC. The presence of a fluorine atom in the nucleophile proved to be a great advantage since it allowed the reaction progress to be monitored by ^{19}F NMR and conversions to be determined even in cases where the product could not be isolated.

First, a racemic standard was successfully prepared using piperidine as an achiral catalyst. The reaction was then performed in a homogeneous set-up using propargylic Jørgensen's catalyst **1**. The product was obtained, although the isolated yield was only moderate due to difficulties with separating the product from the catalyst. In this case, traces of some persistent impurities remained even through chromatography and preparative TLC, substantially lowering the precision with which *ee* values could be determined. On a more positive note, however, this goes to show how useful catalyst immobilisation can be in the separation of reaction mixtures.



Scheme 10: General procedure for the conjugate addition of diethyl fluoromalonate to cinnamaldehyde providing Michael adduct **5**.

Later, the same reaction was attempted with supramolecular catalysts **4** and **18**. In both cases conversion was observed, with catalyst **4** providing a conversion of 90% after 7 days. Over the same time span, catalyst **18** brought about a conversion of approximately 60%. This may have been caused by the fact that catalyst **18** had seemingly undergone a more exhaustive desilylation, possibly leading to the formation of inactive species – see chapter 3.3.1., Scheme 2. When, for reference, the model reaction was performed without any catalyst, minor conversion was observed after a prolonged reaction time. This, however, did not lead to the target Michael adduct, of which no traces were detected. The results acquired from these preliminary catalytic experiments are summarised in Table 2.

Table 2: Summary of results from catalytic experiments

catalyst	**reaction time (d)**	**conversion (%)**	**isolated yield (%)**	***ee* (%)**
no catalyst (blank)	7	15*	—	—
piperidine	1	100	92	—
1	5	93	59	91
4	7	90	—	—
18	7	62	—	—

*Formation of target adduct **5** was not detected.

4.2.7 Sorption

Since the catalytic systems investigated in this work were designed to adsorb electrostatically onto solid supports, the ability of compound **4** to do so was tested. Three materials were chosen as solid sorbents, namely silica gel, basic aluminium oxide (activated, Brockmann I) and zeolite in form of powdered molecular sieves (UOP type 4A, Fluka).

Small amounts of these sorbents were added to solutions of **4** and absorbance values were monitored. A decrease in absorbance over time indicated migration of the charged analyte from the solution to the sorbent surface. From the difference between initial and final absorbance (and thus also concentration) the amount of adsorbed analyte and the sorbent capacity could be determined – see experimental section, chapter 6.2.7.

When sorption was carried out in neat methanol (Figure 11), only silica gel seemed to attract the analyte over time. In this case, a sorbent capacity of approximately 0.41 µmol of **4** per 1 g of silica gel was calculated. If the compound were fully substituted (i.e., with 14 TEG-tethered catalysts), this would amount to 5.7 µmol of catalytically active sites per 1 g of sorbent. In terms of mass, this capacity corresponds to approximately 5.3 mg/$g_{sorbent}$ (again supposing the theoretical M = 12910 g/mol).

With the other two sorbents no decrease in absorbance was observed. On the contrary, a slightly increased absorbance value was detected after completion of the experiment, making the determination of sorption capacity impossible. This unexpected result may have been caused by some impurities being leached from the sorbents.

The fact that compound **4** did not adsorb to two of the three sorbents was speculated to be caused by the formation of aggregates of the analyte with itself, making it less prone to adsorption. In an attempt to disperse these hypothetical aggregates, the same sorption experiments were carried out in a solution with increased ionic strength (0.15 M NaCl in 50% MeOH/water – Figure 12). In this case, a marked decrease in absorbance was observed with all three sorbents. Sorbent capacities of 0.46 µmol/$g_{sorbent}$ (5.9 mg/$g_{sorbent}$) and 0.65 µmol/$g_{sorbent}$ (8.4 mg/$g_{sorbent}$)were determined for alumina and zeolite, respectively. In the case of silica gel, the absorbance decreased below the calibrated range, making it impossible to calculate the sorbent capacity, however, indicating that the sorption capacity of silica gel was in this case greater than the amount of analyte in the sample. It is apparent from both sorption experiments that of the three investigated sorbents, compound **4** seems to have the highest affinity towards silica gel. Unfortunately, catalysis of the model reaction using the adsorbed catalyst was not attempted due to time constraints.

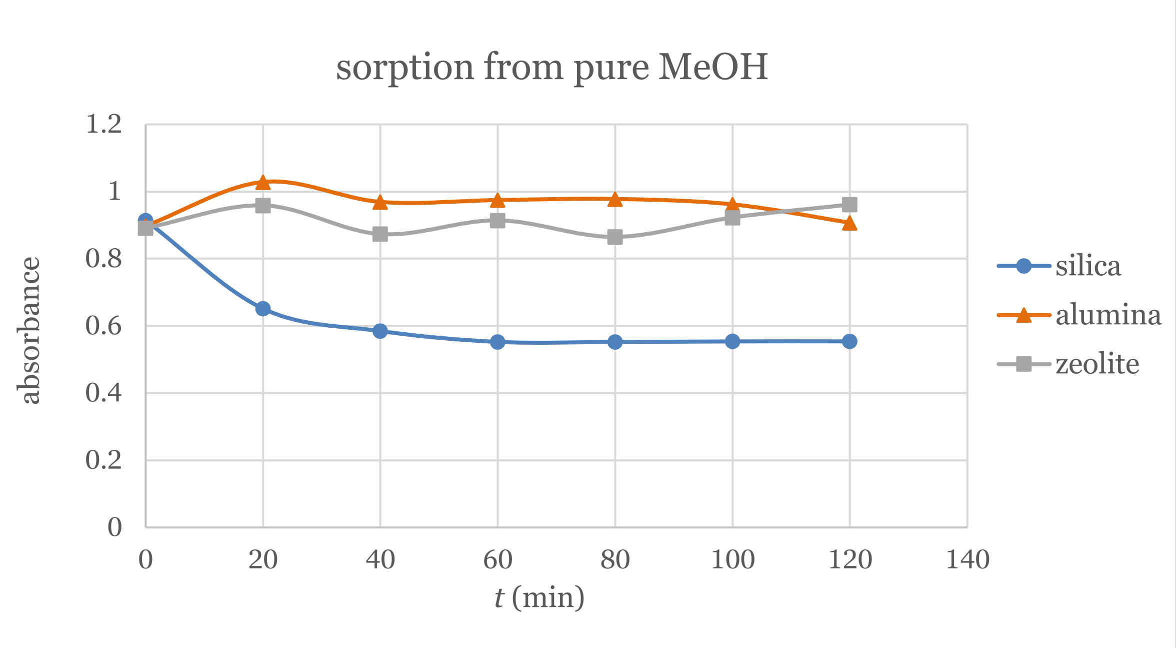


Figure 11: Absorbance time dependence of solutions of **4** in MeOH with different sorbents. The value at *t* = 0 represents the absorbance of the solutions prior to the addition of sorbents.

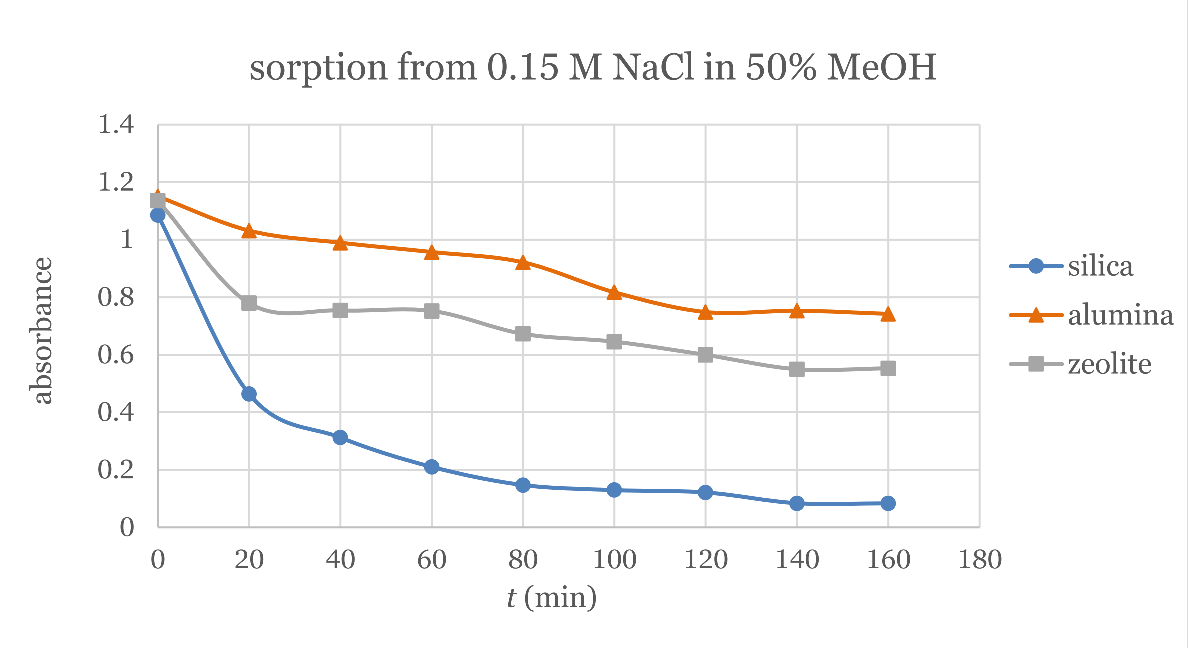


Figure 12: Absorbance time dependence of solutions of **4** in 0.15 M NaCl in 50% MeOH with different sorbents. The value at *t* = 0 represents the absorbance of the solutions prior to the addition of sorbents.

5. CONCLUSION

This thesis focused on the possibility of using multiply charged cyclodextrins as a means of immobilising organocatalysts onto solid sorbents using electrostatic interaction. To this end, a model catalytic assembly, namely per-6-(MTZ-*O*-MIM2)-per-2,3-(carbamoyl-TEG-MTZ-*O*-JC), was designed. The components of this supramolecular system were synthesised from commercial starting materials and assembled into the desired system. NMR spectra showed that the target compounds were not fully substituted and that partial decomposition of the tethered organocatalyst likely occurred. An alternative to the original catalytic system was prepared using ether bonds instead of carbamates to connect the TEG linkers to the CD core. In this case, full substitution was not achieved either and catalyst decomposition also took place.

It became apparent that NMR was not an ideal method to characterise this type of complicated, charged substances. Mass spectrometry using MALDI would likely have provided more conclusive results. Samples were sent to the Institute of Macromolecular Chemistry of the Czech Academy of Sciences and measurements were arranged. Regrettably, however, results were not received in time to be included in this thesis.

Nevertheless, the obtained compounds were tested for their electrostatic binding and catalytic abilities, providing encouraging results.

Most of the synthetic steps were carried out multiple times and could thus be optimised to some extent. However, with the benefit of hindsight, it would have been more efficient to rush towards the target compound in a "quick and dirty" manner first, and then optimise the synthetic procedures, rather than to spend precious time trying to optimise each step before continuing to the next. This strategy could potentially have freed up time to work on those experimental procedures where optimisation was indeed necessary.

Although the results reported herein are of a rather preliminary nature, they provide a valuable insight into the various intricacies of designing and constructing a heterogeneous, cyclodextrin-based catalytic system. This work could potentially function as a framework for further investigation into this class of supramolecular devices.

"It ain't much, but it's honest work."

6. EXPERIMENTAL SECTION

6.1 General methods, chemicals and instrumentation

(2*S*,4*R*)-4-Hydroxyproline was purchased from Fluorochem, UK. Other common chemicals were obtained from commercial sources and, unless stated otherwise, used without further purification.

Water was used in deionised form and all commercial organic solvents were distilled before use. Dry THF was obtained by refluxing with metallic sodium and benzophenone until a stable, deep blue coloration was obtained, followed by distillation into an oven-dried storage flask. Dry DMF was produced by stirring over calcium hydride overnight, followed by direct vacuum distillation into an oven-dried storage vessel. Dry solvents were stored over 3 Å molecular sieves (P-Lab, Czech Republic). The same molecular sieves were also added to reaction mixtures (10% by mass with respect to the given solvent), when rigorous dryness was required.

All reactions were carried out under an inert atmosphere of argon or nitrogen. The progress of each reaction was monitored by thin layer chromatography (TLC) using DC Alufolien Kieselgel 60 F254 (Merck, Germany) silica gel plates. The TLC plates were developed in closed chambers with mobile phase compositions specified in the respective experimental procedures as volume/volume ratios of the given solvents. Compounds on the developed TLC plates were visualised by the following methods:

a) UV lamp
    - λ = 254 or 366 nm
    - suitable for UV absorbing or fluorescent compounds

b) Basic permanganate
    - immersion in a basic solution of potassium permanganate (1.5 g $KMnO_4$, 10 g K_2CO_3 and 1.25 ml 10% NaOH in 200 ml water), followed by heating using a heat gun
    - general stain for oxidizable compounds

c) Ninhydrin
    - immersion in an alcoholic solution of ninhydrin (200 mg ninhydrin, 95 ml *n*-Butanol, 5 ml 10% acetic acid), followed by heating using a heat gun
    - specific stain for 1° and 2° amines

d) Carbonisation
    - immersion in 50% aqueous H_2SO_4 and heating by heat gun
    - detection of saccharides including cyclodextrins and their derivatives

e) Nitrobenzyl pyridine
  - immersion in a 1% ethanolic solution of 4-(4-nitrobenzyl) pyridine, followed by heating using a heat gun and immersion of the hot TLC plate in concentrated aqueous ammonia
  - detection of alkylating agents

f) AMC
  - immersion of the TLC plate in a solution prepared by combining phosphomolybdic acid (2.5 g), cerium sulfate hydrate (1 g) and sulfuric acid (1.2 M; 100 ml), followed by heating using a heat gun
  - general stain

Organic solutions obtained from extractions were dried over anhydrous magnesium sulfate. $MgSO_4$ was added to the organic solution in small portions until the salt ceased to form clumps and instead remained as a fine suspension.

Preparative column chromatography was carried out using silica gel (50 µm, 60 Å, SiliCycle) with a 30- to 50-fold excess of silica gel with respect to the crude mixture by mass. The composition of the mobile phases is indicated in the respective experimental procedures.

Solvents were evaporated on a rotary evaporator (Büchi, Switzerland) at temperatures between r.t. and 60 °C. This method of evaporation is herein referred to as evaporation under reduced pressure.

After evaporation under reduced pressure, synthetic products were dried to constant mass using a rotary oil pump at temperatures between r.t. and 70 °C. This procedure is herein referred to as drying *in vacuo*.

Counteranions were exchanged, where necessary, using a Dowex 1x8 strong anion exchange resin.

NMR spectra were acquired using a Bruker AVANCE III HD 400 spectrometer using the solvent peak as internal reference. Samples were dissolved in deuterated solvents ($CDCl_3$, DMSO-*d*6, CD_3OD and D_2O) procured from Armar, Germany. Chemical shift values, δ, are listed in ppm and coupling constants, J, in Hz. Where possible, assignments were made using DEPT and 2D spectra (DEPT, dqf-COSY, HSQC and HMBC). ^{19}F NMR spectra were acquired where necessary. Atom numberings for NMR assignments are provided in the experimental section. Cyclodextrin derivatives were numbered starting from the glucose skeleton (numbered in the standard manner) and continuing outwards to the substituent on the primary rim). Secondary rim substituents are not numbered, since no specific assignments could be made that would require such numbering.

Mass spectra were obtained using the LCMS 2020 spectrometer (Shimadzu, Japan) with electrospray-ionisation (ESI) or the microTOF-QIII (Bruker Daltonik, Germany) with ESI. In both cases nitrogen was used as a drying and nebulizer gas.

Diffuse reflectance infrared Fourier transform (DRIFT) spectroscopy was carried out using a Thermo Nicolet AVATAR 370 FT-IR spectrometer. Samples were mixed with KBr prior to measurement. The characteristic wavenumbers are listed in cm^{-1}.

UV-VIS spectroscopic spectra were measured with a Thermo Scientific Helios γ with thungsten and deuterium lamps and a wavelength range of 190-800 nm.

Chiral HPLC analysis was performed with a Shimadzu liquid chromatograph with a spectrophotometric detector (SPD-M20A). Chiral column Daicel Chiralpak IC was used for chiral separation of enantiomers.

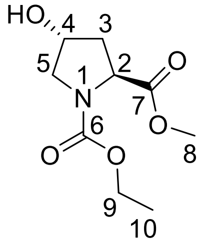
Specific optical rotation was measured, where necessary, at room temperature and 2 cm path length using an Autopol III (Rudolph research, USA) instrument.

6.2 Synthetic procedures

6.2.1 Synthesis of O-propargylic Jørgensen's catalyst

1-Ethyl-2-methyl-(2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (6)

(2*S*,4*R*)-4-Hydroxyproline (10 g; 76.3 mmol; 1 eq.) was suspended in methanol (120 ml). With stirring, K_2CO_3 (10.5 g; 76.0 mmol; 1 eq.) was added in small portions. A solution of ethyl chloroformate (16 ml; 108.5 mmol; 2.2 eq.) in methanol (32 ml) was then added dropwise. The mixture was stirred under an inert atmosphere for 16 h at ambient temperature. The solvent was subsequently evaporated under reduced pressure. The residue was suspended in chloroform (200 ml) and washed with distilled water (3 × 200 ml). The organic phase was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure, yielding the target compound as a colourless oil (13.6 g; 62.6 mmol; 82%).



6

$C_9H_{15}NO_5$
217.22 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 – 4.41 (m, 2H, H-2, H-4), 4.21 – 4.00 (m, 2H, H-9), 3.74 and 3.72 (s, 3H, H-8)*, 3.68 – 3.47 (m, 2H, H-5), 2.37 - 2.23 (m, 1H, H-3), 2.12 - 2.00 (m, 1H, H-3), 1.26 and 1.19 (t, 7.1 Hz, 3H, H-10)* ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.47 and 173.34 (C-7)*, 155.42 and 154.98 (C-6)*, 70.35 and 69.58 (C-4)*, 61.74 and 61.66 (C-9)*, 57.89 and 57.77 (C-2)*, 55.21 and 54.69 (C-5)*, 52.48 and 52.36 (C-8)*, 39.32 and 38.61 (C-3)*, 14.77 and 14.67 (C-10)* ppm.

NMR spectra are in accordance with the literature[65].

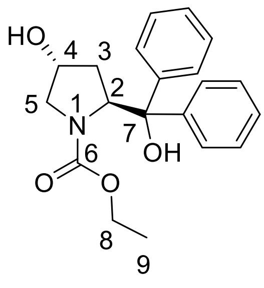
*Dual signals appear due to the presence of amide rotamers.

ESI–MS: calculated M = 217.22, found *m*/*z* = 217
IR (DRIFT, KBr): ν = 3431 (OH group), 2983, 2954, 2883, 1752 (C=O bond of ester), 1699, 1435, 1210 ,1172 cm^{-1}
$[\alpha]D^{25}$: - 70.9 (*c* = 1; $CHCl_3$)

Ethyl-(2*S*,4*R*)-4-hydroxy-2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate (7)

First, a solution of phenylmagnesium bromide was prepared in the following manner: Magnesium turnings (250 mg; 10.4 mmol; 0.9 eq.) were suspended in freshly distilled dry THF (6 ml), the mixture was cooled to 0 °C and a grain of iodine was added. Then, bromobenzene (1.2 ml; 11.5 mmol; 1 eq.) was added slowly with stirring under an inert atmosphere. After 2 h all the magnesium had dissolved and a solution of methyl ester **6** (500 mg; 2.3 mmol; 0.2 eq. with respect to the Grignard reagent) in THF (2.3 ml) was added dropwise. The mixture was stirred at ambient temperature overnight.

After 20 h the reaction was quenched by the addition of saturated aqueous NH_4Cl (5 ml), water (5 ml) and diethyl ether (10 ml). The phases were separated and the aqueous layer was extracted with ether (4 × 20 ml). The combined organic extracts were washed with brine (50 ml), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. At first, a yellow-orange oil was obtained. Upon addition of a small amount of chloroform, however, the product began to precipitate as a white solid. The precipitate was filtered off, yielding the desired product as a white, amorphous substance (168 mg; 0.57 mmol; 25%). The remaining filtrate was purified by column chromatography (hexane:EtOAc 1:1), which provided a further 196 mg of the product for a total yield of 364 mg; 1.07 mmol; 47%.



7

$C_{20}H_{23}NO_4$
341.41 g/mol

^{1}H NMR (600 MHz, DMSO-*d6*; 50 °C) δ 7.52 – 7.47 (m, 2H, H-Ar$_{ortho}$), 7.38 – 7.31 (m, 4H, H-Ar$_{ortho+meta}$), 7.27 – 7.22 (m, 1H, H-Ar$_{para}$), 7.21 – 7.17 (m, 2H, H-Ar$_{meta}$), 7.15 – 7.09 (m, 1H, H-Ar$_{para}$), 5.69 (s$_{br}$, 1H, OH-7), 5.04 (dd, *J* = 8.6, 4.4 Hz, 1H, H-2), 4.60 (d, *J* = 3.7 Hz, 1H, OH-4), 4.25 (s$_{br}$, 1H, H-4), 3.71 (s$_{br}$, 2H, H-8), 3.51 (d, *J* = 11.2 Hz, 1H, H-5), 3.43 (s, 1H, H-5), 2.02 (ddd, *J* = 13.5, 6.2, 4.5 Hz, 1H, H-3), 1.81 (t, *J* = 11.0 Hz, 1H, H-3), 0.89 (s$_{br}$, 3H, H-9) ppm.

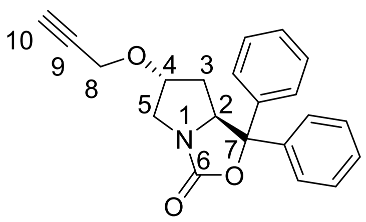
^{13}C NMR (151 MHz, DMSO-*d6*, 50 °C) δ 156.17 (C-6), 146.54 (C^q-Ar), 146.42 (C^q-Ar), 128.21 (C-Ar), 127.36 (C-Ar), 127.34 (C-Ar), 127.28 (C-Ar$_{ortho}$), 126.96 (C-Ar$_{para}$), 126.51 (C-Ar$_{para}$), 81.15 (C-7), 69.84 (C-4), 64.28 (C-2), 60.56 (C-8), 57.23 (C-5), 38.47 (C-3), 14.65 (C-9) ppm.

The ^{1}H NMR shifts differ from the literature due to the fact that DMSO-*d6* was used instead of $CDCl_3$. The ^{13}C NMR spectrum is in accordance with the literature[65].

ESI–MS: calculated M = 341.41, found *m/z* = 324 $[M-H_2O+H]^+$, 342 $[M+H]^+$
IR (DRIFT, KBr): ν = 3419 (OH group), 2999, 2951, 2912, 1687 (C=O bond of carbamate), 1417, 1200 cm^{-1}
$[\alpha]_D^{25}$: - 39.6 (*c* = 1; $CHCl_3$)

(6*R*,7a*S*)-1,1-Diphenyl-6-(prop-2-yn-1-yloxy)tetrahydro-1H,3H-pyrrolo[1,2-c]oxazol-3-one (8a)

Starting compound **7** (6.93 g; 20.3 mmol; 1 eq.) was dissolved in dry DMF (104 ml) and molecular sieves (3 Å) were added. The mixture was cooled to 0 °C and NaH (60% in mineral oil; 1.62 g; 40.5 mmol; 2 eq.) was added in small portions. Propargyl bromide (80% in toluene; 2.3 ml; 20.3 mmol; 1 eq.) was then added dropwise with continuous stirring. The mixture was then stirred under nitrogen for 2 hours at room temperature. Then, the reaction mixture was decanted into a 500 ml Erlenmeyer flask and quenched by the addition of saturated aqueous NH$_4$Cl (100 ml). The solution was extracted with DCM (3 × 150 ml). The combined organic extracts were dried over anhydrous MgSO$_4$ and evaporated under reduced pressure. As the resulting substance still contained a significant amount of DMF, it was dissolved in toluene (400 ml) and extracted with water (3 × 400 ml). The organic layer was again dried over MgSO$_4$ and evaporated. The crude product was purified by silica gel column chromatography (hexane:EtOAc 3:1; R$_f$ = 0.77) to yield the desired compound as a pale yellow, semicrystalline oil (2.9 g; 8.7 mmol; 43%).



8a

$C_{21}H_{19}NO_3$
333.39 g/mol

^{1}H NMR (400 MHz, CDCl$_3$) *δ* 7.54 – 7.50 (m, 2H, H-Ar), 7.39 – 7.27 (m, 8H, H-Ar), 4.84 (dd, *J* = 11.2, 5.0 Hz, 1H, H-2), 4.34 – 4.26 (m, 1H, H-4), 4.12 (d, *J* = 2.4 Hz, 2H, H-8), 4.05 (dd, *J* = 12.9, 5.9 Hz, 1H, H-5), 3.29 (dd, *J* = 13.0, 1.5 Hz, 1H, H-5), 2.43 (t, *J* = 2.4 Hz, 1H, H-10), 1.89 (dd, *J* = 14.0, 5.4 Hz, 1H, H-3), 1.24 – 1.15 (m, 1H, H-3) ppm.

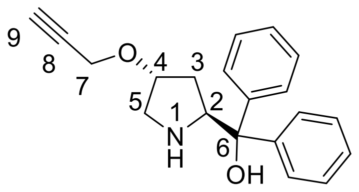
^{13}C NMR (101 MHz, CDCl$_3$) *δ* 160.51 (C-6), 143.00 (C-Ar), 140.22 (C-Ar), 128.76 (C-Ar), 128.63 (C-Ar), 128.57 (C-Ar), 127.96 (C-Ar), 126.19 (C-Ar), 125.52 (C-Ar), 85.89 (C-7), 79.23 (C-9), 78.25 (C-4), 75.01 (C-10), 67.40 (C-2), 56.77 (C-8), 53.76 (C-5), 36.09 (C-3) ppm.

The NMR spectra are in accordance with the literature[65].

ESI–MS: calculated M = 333.39, found *m/z* = 356 [M + Na]$^+$, 659 [2M + Na]$^+$
IR (DRIFT, KBr): ν = 3284 (C-H bond of alkyne), 2952, 2116 (triple bond of alkyne), 1755 (C=O bond of carbamate), 1092 cm^{-1}
[α]D^{25}: - 212.5 (*c* = 1; CHCl$_3$)

Diphenyl((2S,4R)-4-(prop-2-yn-1-yloxy)pyrrolidin-2-yl)methanol (9)

Carbamate **8a** (1.7 g; 5.1 mmol; 1 eq.) was dissolved in ethanol (170 ml) and an aqueous solution of potassium hydroxide (11.4 g; 203 mmol; 40 eq. in 204 ml H_2O) was added. The mixture was stirred at room temperature under N_2 overnight. Since the starting compound was not entirely consumed by the next day, the mixture was refluxed for a further 5 hours to drive the reaction to completion. Then, the reaction mixture was concentrated under reduced pressure to approximately half its initial volume and extracted with DCM (3 × 200 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, vacuum-filtered and evaporated under reduced pressure to provide 4-propargyloxy-diphenylprolinol **9** as a pale yellow oil (1.53 g; 4.98 mmol; 98%).



9

$C_{20}H_{21}NO_2$
307.39 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.59 (m, 2H, H-Ar), 7.46 – 7.42 (m, 2H, H-Ar), 7.37 – 7.30 (m, 3H, H-Ar), 7.23 – 7.13 (m, 3H, H-Ar), 4.64 (dd, J = 10.3, 6.5 Hz, 1H, H-2), 4.20 – 4.16 (m, 1H, H-4), 4.11 (d, J = 2.4 Hz, 2H, H-7), 3.10 – 2.97 (m, 2H, H-5), 2.42 (t, J = 2.4 Hz, 1H, H-9), 1.93 – 1.83 (m, 1H, H-3), 1.67 – 1.61 (m, 1H, H-3) ppm.

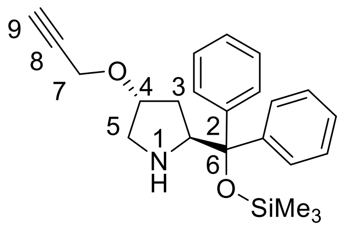
^{13}C NMR (101 MHz, $CDCl_3$) δ 146.68 (C^q–Ar), 144.55 (C^q–Ar), 128.66 (C-Ar), 128.28 (C-Ar), 127.14 (C-Ar), 126.82 (C-Ar), 126.24 (C-Ar), 125.42 (C-Ar), 79.69 (C^q–8), 78.36 (C-4), 77.06 (C-6), 74.65 (C-9), 63.84 (C-2), 56.08 (C-7), 51.69 (C-5), 32.96 (C-3) ppm.

The NMR spectra are in accordance with the literature[65].

ESI–MS: calculated M = 307.39, found m/z = 308.16 $[M+H]^+$, 290.14 $[M - H_2O + H]^+$
IR (DRIFT, KBr): ν = 3286 (C-H bond of alkyne), 3057, 2999, 2116 (triple bond of alkyne) cm^{-1}, no carbamate signal observed at 1755 cm^{-1}.
[α]D^{25}: - 100.0 (c = 1; $CHCl_3$)

(2S,4R)-2-(diphenyl((trimethylsilyl)oxy)methyl)-4-(prop-2-yn-1-yloxy)pyrrolidine (1)

Tertiary alcohol **9** (978 mg; 3.18 mmol; 1 eq.) was dissolved in dry DCM (12 ml) and triethyl amine (0.57 ml; 4.10 mmol; 1.3 eq.) was added dropwise through a septum. The mixture was cooled to 0 °C and trimethylsilyl triflate (0.65 ml; 3.50 mmol; 1.1 eq.) was slowly added. The reaction mixture was then stirred at room temperature under N_2 for 18 hours, after which it was poured into ice water (100 ml) and extracted with DCM (3 × 50 ml). The combined organic extracts were washed with brine (1 × 50 ml), dried over anhydrous $MgSO_4$, vacuum-filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane:EtOAc 8:1 → 2:1) providing diphenylprolinol silyl ether **1** as a yellow oil (909 mg; 2.39 mmol; 75%).



1

$C_{23}H_{29}NO_2Si$

379.58 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.48 – 7.44 (m, 2H, H-Ar), 7.35 – 7.31 (m, 3H, H-Ar), 7.30 – 7.27 (m, 3H, H-Ar), 7.25 – 7.21 (m, 2H, H-Ar), 4.43 (t, *J* = 8.0 Hz, 1H, H-2), 4.09 (d, *J* = 2.4 Hz, 2H, H-7), 4.0 – 3.96 (m, 1H, H-4), 3.03 (dd, *J* = 12.3, 2.4 Hz, 1H, H-5), 2.80 (dd, *J* = 12.0, 4.7 Hz, 1H, H-5), 2.38 (t, *J* = 2.4 Hz, 1H, H-9), 1.84 – 1.75 (m, 2H, H-3), -0.06 – -0.12 (m, 9H, H-Me$_3$Si) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) *δ* 145.49 (C^q–Ar), 144.60 (C^q–Ar), 128.57 (C-Ar), 128.04 (C-Ar), 127.94 (C-Ar), 127.83 (C-Ar), 127.49 (C-Ar), 127.42 (C-Ar), 82.70 (C^q–6), 79.92 (C^q–8), 78.18 (C-4), 74.44 (C-9), 64.16 ,(C-2), 56.13 (C-7), 51.96 (C-5), 34.37 (C-3), 2.28 (C-Me$_3$Si) ppm.

The NMR spectra are in accordance with the literature[65].

ESI–MS: calculated M = 379.58, found *m/z* = 380.20 $[M+H]^+$

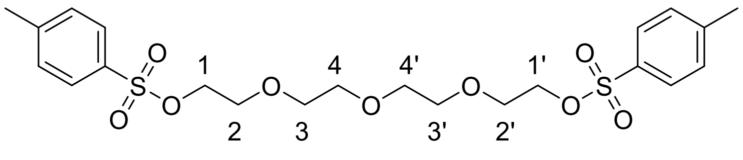
IR (DRIFT, KBr): ν =3303 (N-H bond), 3057, 2951, 2898, 2116 (triple bond of alkyne) cm^{-1}

[α]D^{25}: - 32.8 (c = 1; $CHCl_3$)

6.2.2 Synthesis of tetraethylene glycol isocyanate linker (2)

Tetraethylene glycol ditosylate (10)

Tetraethylene glycol (45 ml; 0.26 mol; 1 eq.) was dissolved in DCM (380 ml) in a 2 l flat bottom flask. The solution was cooled to 0 °C and tosyl chloride (99.5 g; 0.52 mol; 2 eq.) was added. Potassium hydroxide (116.7 g; 2.08 mol; 8 eq.) was added in small portions over the course of 1 hour. The mixture was stirred under argon at r.t. overnight. After 22 hours the reaction mixture was diluted with chloroform (300 ml) and washed with water (3 × 300 ml). The organic phase was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The product was obtained upon drying *in vacuo* at r.t. as a colourless oil (130.9 g). The mass was greater than the theoretical yield due to the presence of residual DCM and $CHCl_3$, as could be seen from the ^1H NMR spectrum. The bulk of the product was used without further purification or analysis in the next step.



10

$C_{22}H_{30}O_9S_2$

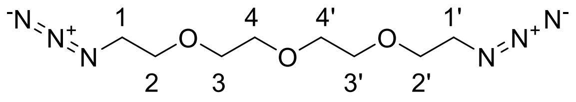
502.59 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.77 (m, 4H, H-Ar^{ortho}), 7.35 – 7.31 (m, 4H, H-Ar^{meta}), 7.26 (s, $CHCl_3$), 5.29 (s, DCM), 4.21 – 3.99 (m, 4H, H-1/1′), 3.69 – 3.65 (m, 4H, H-2/2′), 3.58 – 3.53 (m, 8H, H-3/3′/4/4′), 2.44 (s, 6H, H-CH_3Ar) ppm.

The NMR spectrum is in accordance with the literature[67].

1-Azido-2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethane
(TEG diazide, 11)

Ditosylate **10** (130.9 g; 0.26 mol; 1 eq.) was dissolved in DMF (570 ml). Sodium azide (67.5 g; 1.04 mol; 4 eq.) was added slowly with stirring under argon. The reaction mixture was heated to 80 °C and stirred overnight. After 20 hours the mixture was allowed to cool to r.t. and water (570 ml) was added. The mixture was equally divided into two 2 l separatory funnels and each half was extracted with toluene (2 × 700 ml). The organic phases were again divided evenly and washed with water (5 × 400 ml for either half). A proton NMR was taken to check for residual DMF. As no DMF was detected, the organic phases were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to afford the desired compound (59.5 g; 0.24 mol; 94%) as a pale-yellow oil.



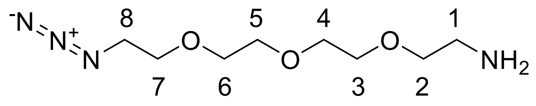
11
$C_8H_{16}N_6O_3$
244.26 g/mol

^{1}H NMR: (400 MHz, $CDCl_3$) δ 3.75 – 3.69 (m, 12H, H-2/2′/3/3′/4/4′), 3.29 (t, J = 5.1 Hz, 4H, H-1/1′) ppm.

The NMR spectrum is in accordance with the literature[67].

2-(2-(2-(2-Azidoethoxy)ethoxy)ethoxy)ethan-1-amine
(amino-azido-TEG, 2)

Diazide **11** (59.5 g; 0.24 mol; 1 eq.) was dissolved in diethyl ether (700 ml) and HCl (1 M; 700 ml) was added. Triphenyl phosphine (70.2 g; 0.27 mol; 1.1 eq.) was stirred in slowly. The resulting heterogeneous mixture was stirred under argon overnight using an overhead stirrer. After 24 hours the reaction mixture was vacuum-filtered to remove the precipitated triphenylphosphine oxide. The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 500 ml). The aqueous phase was then cooled to 0 °C and basified with potassium hydroxide (300 g). The basic solution was split into two 2 l separatory funnels and both halves were extracted with DCM (6 × 300 ml). The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to yield the mono-reduced product (48.3 g; 0.22 mol; 91%) as a yellow viscous oil.



12
$C_8H_{18}N_4O_3$
218.26 g/mol

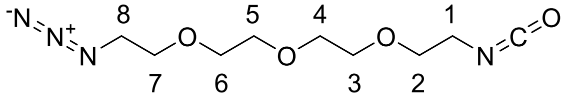
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 – 3.62 (m, 10H, H-2/3/4/5/6), 3.56 (t, J = 5.2 Hz , 2H, H-7), 3.40 (t, J = 5.1 Hz, 2H, H-1), 2.91 (t, J = 5.2 Hz, 2H, H-8), 2.80 (s_{br}, 2H, H-NH_2) ppm.

The NMR spectrum is in accordance with the literature[67].

^{13}C NMR (101 MHz, $CDCl_3$) δ 72.39 (C-7), 70.79, 70.75, 70.72, 70.37, 70.15, 50.84 (C-1), 41.54 (C-8).

1-Azido-2-(2-(2-(2-isocyanatoethoxy)ethoxy)ethoxy)ethane (azido-isocyanato-TEG, 2)

Azido-amino tetraethylene glycol (1.00 g; 4.6 mmol; 1 eq.) was dissolved in DCM (20 ml). A saturated aqueous solution of sodium carbonate (20 ml) was added and the biphasic mixture was stirred vigorously for 10 minutes. Then, the mixture was cooled to 0 °C and a solution of triphosgene (680 mg; 2.3 mmol; 0.5 eq.) in DCM (20 ml) was added. The mixture was stirred at 0 °C for 1 hour. Subsequently the reaction mixture was transferred to a separatory funnel and diluted with water (20 ml). The layers were separated and the organic phase was washed with HCl (1 M; 1 × 30 ml), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure yielding isocyanate **2** as a pale-yellow oil (1.01 g; 4.14 mmol; 92%).



2

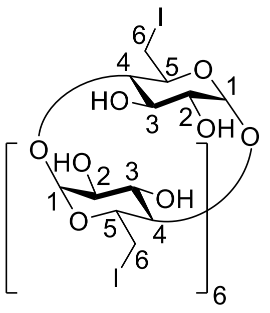
$C_9H_{16}N_4O_4$
244.25 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 – 3.65 (m, 10H), 3.64 – 3.62 (m, 2H), 3.43 – 3.56 (m, 4H) ppm.

6.2.3 Synthesis of multiply charged β-cyclodextrin (3)

Per-6-iodo-β-cyclodextrin (13)

In a 2 l three-necked round bottom flask fitted with a nitrogen inlet, a drying tube and a thermometer, triphenylphosphine (252 g; 0.96 mol; 16 eq.) was suspended in dry DMF (410 ml). The mixture was cooled to approximately 10 °C and elemental iodine (259 g; 1.02 mol; 17 eq.) was added slowly so that the temperature would not exceed 30 °C. Dry β-cyclodextrin (68.3 g; 0.06 mol; 1 eq.) was then added and the brown reaction mixture was heated to 70 °C and stirred at this temperature using an overhead stirrer. After 4 hours the heating was turned off and stirring continued at r.t. for another 17 hours. Then, the reaction mixture was diluted with MeOH (300 ml) and transferred to a 5 l Erlenmeyer flask with more MeOH (2700 ml). Then, a freshly prepared 12% solution of sodium methoxide in MeOH (550 ml) was added slowly, raising the pH to around 9 and causing a yellow precipitate to form. The basic mixture was stirred overnight at r.t. The precipitate was filtered off, washed with MeOH (4 × 500 ml), water (2 × 500 ml) and again with MeOH (4 × 500 ml). The washed precipitate was air dried and then dried for three days *in vacuo* at 70 °C to a constant weight. The product was obtained as an off-white, amorphous solid (98.9 g; 0.052 mol; 87%).



13
$C_{42}H_{63}I_7O_{28}$
1904.27 g/mol

^{1}H NMR (400 MHz, DMSO-*d6*) δ 6.03 (d, J = 6.8 Hz, 7H, OH-2), 5.92 (d, J = 2.2 Hz, 7H, OH-3), 4.99 (d, J = 3.6 Hz, 7H, H-1), 3.84 – 3.76 (m, 7H, H-6), 3.69 – 3.54 (m, 14H, H-3/H-5), 3.47 – 3.41 (m, 7H, H-6), 3.40 – 3.34 (m, 7H, H-2) 3.30 – 3.25 (m, 7H, H-4) ppm.

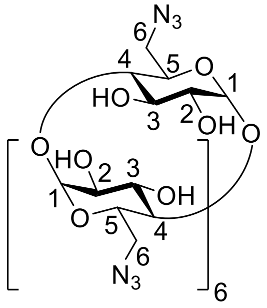
^{13}C NMR (101 MHz, DMSO-*d6*) δ 102.12 (C-1), 85.94 (C-4), 72.16 –71.90 (C-2/C-3), 70.92 (C-5), 9.47 (C-6) ppm.

The NMR spectra are in accordance with the literature[69].

MS-ESI: calculated M = 1904, found m/z = 1927 $[M+Na]^+$

Per-6-azido-β-cyclodextrin (14)

A 2 l three-necked round bottom flask fitted with a nitrogen inlet, a drying tube and a thermometer, was charged with DMF (500 ml) and per-6-iodo-β-cyclodextrin **13** (50 g; 26 mmol; 1 eq.). Sodium azide (36 g; 0.54 mol; 21 eq.) was added to the solution and the reaction mixture was heated to 70 °C and stirred under nitrogen overnight. After 22 hours heating was discontinued and excess NaN_3 was removed by vacuum filtration. DMF was evaporated from the filtrate *in vacuo* at 65 °C providing an orange-brown solid. Upon addition water (300 ml) a precipitate formed, which was collected by vacuum filtration, washed with water (3 × 200 ml) air dried and finally dried to constant mass *in vacuo* at 70 °C. The target compound was obtained as an orange powder (33 g; 25 mmol; 97%).



14
$C_{42}H_{63}N_{21}O_{28}$
1310.09 g/mol

^{1}H NMR (400 MHz, DMSO-*d6*) δ 5.81 (s_{br}, 14 H, OH-2/OH-3), 4.91 (d, *J* = 3.7 Hz, 7H, H-1), 3.82 – 3.68 (m, 14H, H-5/H-6), 3.65 – 3.51 (m, 14H, H-3/H-6), 3.41 – 3.31 (m, 14H, H-2/H-4) ppm.

The 1H NMR spectrum is in accordance with the literature[68].

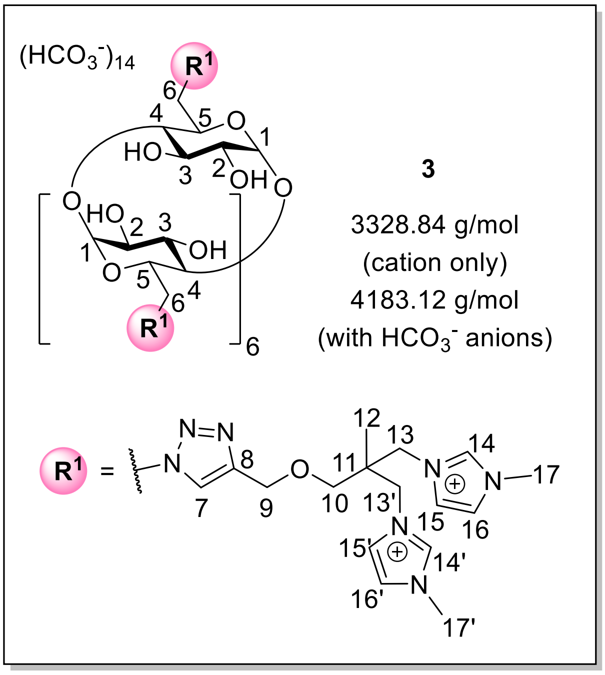
^{13}C NMR (101 MHz, DMSO-d*6*) δ 102.04 (C-1), 83.19 (C-4), 72.58 (C-3), 71.99 (C-2), 70.32 (C-5), 51.32 (C-6) ppm.

MS-ESI: calculated M = 1310, found *m*/*z* = 1333 $[M+Na]^+$

6.2.4 Assembly of the catalytic system

Per-6-(MTZ-*O*-MIM2)-β-cyclodextrin (3)

Per-6-azido-β-cyclodextrin **14** (5 g; 3.82 mmol; 1 eq.) was dissolved in DMF (250 ml) and PgOMIM2 anchor **15** (17.1 g; 29.2 mmol; 7.65 eq.) was added. The solution was bubbled with nitrogen for 40 minutes. Copper sulfate pentahydrate (954 mg; 3.82 mmol; 1 eq.) was added, followed by sodium ascorbate (1.51 g; 7.63 mmol; 2 eq.). The reaction mixture was heated to 60 °C and stirred under nitrogen for 46 h. DMF was then removed *in vacuo* at 60 °C. The crude product was loaded onto a column of basic alumina (250 g) and purified by gradient elution [aqueous NH_4HCO_3 0.01 M (1 CV) → 0.1 M (1 CV) → 1 M (3 CV)]. The purified product was dissolved in water (5% solution) and freeze-dried, providing the bicarbonate salt of the target compound **3** as a brown, amorphous solid (10.5 g; 2.51 mmol; 65%).



3

3328.84 g/mol
(cation only)
4183.12 g/mol
(with HCO_3^- anions)

^{1}H NMR (400 MHz, D_2O) δ 8.19 (s, 7H, H-7), 7.50 (dd, J = 10.4, 1.9 Hz, 14H, H-16/16'), 7.39 (dd, J = 18.8, 1.9 Hz, 14H, H-15/15'), 5.18 (d, J = 3.4 Hz, 7H, H-1), 4.72 (m, 7H), 4.60 – 4.48 (m, 21H), 4.35 (m, 21H), 4.19 (t, J = 14.5 Hz, 7H), 4.03 (t, J = 9.4 Hz, 7H, H-3), 3.92 and 3.90 (s, 42H, H-17/17') 3.44 (dd, J = 10.1, 3.2 Hz, 7H, H-2), 3.31 – 3.10 (m, 21H), 0.91 (s, 21H, H-12) ppm.

^{13}C NMR (101 MHz, D_2O, *t*BuOH) δ 144.24 (C-8), 138.24 – 136.86 (C-14), 128.05 (C-7), 124.54 – 124.05 (C-15/15', C-16/16'), 102.43 (C-1), 82.47 (C-4), 72.88 (C-3), 72.53 (C-2), 71.11 (C-10), 70.57 (C-5), 63.63 (C-9), 53.64 – 53.24 (C-13/13'), 50.79 (C-6), 40.49 (C-11), 36.55 (C-17/17'), 17.46 (C-12) ppm.

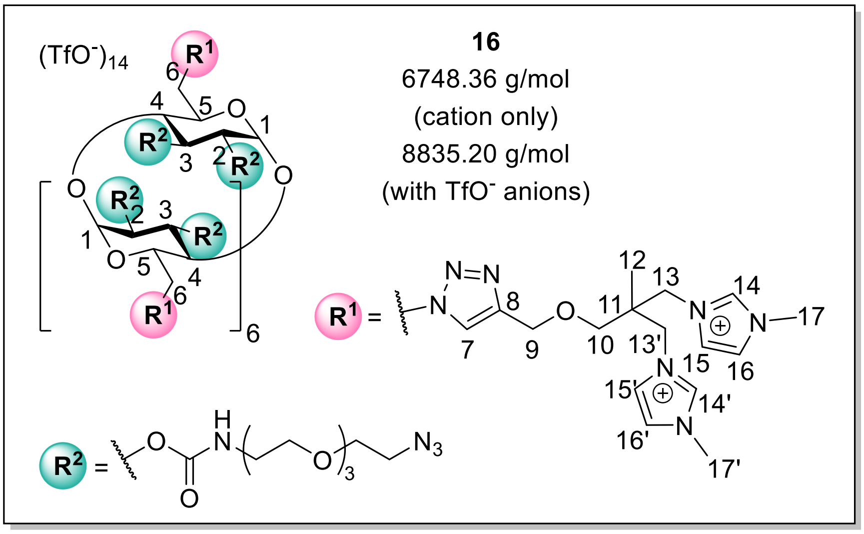
IR (DRIFT, KBr): ν = 3350, 3082, 2582, 1896, 1674, 1400, 1159, 1090, 1047 cm^{-1}, no azide signal observed at 2106 cm^{-1}.

Per-6-(MTZ-*O*-MIM2)-per-2,3-(carbamoyl-TEG-azido)-β-CD (16)

First, bicarbonate **3** (127 mg; 0.0303 mmol; 1 eq.) was dissolved in methanol (5 ml) and neutralised with TfOH (1 M in MeOH) to exchange the bicarbonate counterions for triflates. The neutral solution was evaporated under reduced pressure and the residue was dried *in vacuo* at 70 °C.

The dried triflate salt was dissolved in dry DMF (3.3 ml) and freshly prepared isocyanate **2** (537 mg; 2.2 mmol; 73 eq. ≈ 5 eq. per OH-group) was added, followed by DBTDL (450 µl; 0,76 mmol; 25 eq. ≈ 2 eq. per OH-group). The reaction mixture was heated to 70 °C and stirred at this temperature under nitrogen overnight. 23 hours later, the reaction mixture was poured into diethyl ether (120 ml). The resulting precipitate was isolated by vacuum filtration and washed with ether (3 × 50 ml). The sticky substance was then washed out of the filter with an excess of methanol (100 ml) and evaporated under reduced pressure. The brown oily residue was dissolved in water and freeze-dried.

The triflate salt of the target compound was obtained as a brown, amorphous solid (168 mg; 0.019 mmol; 63%).



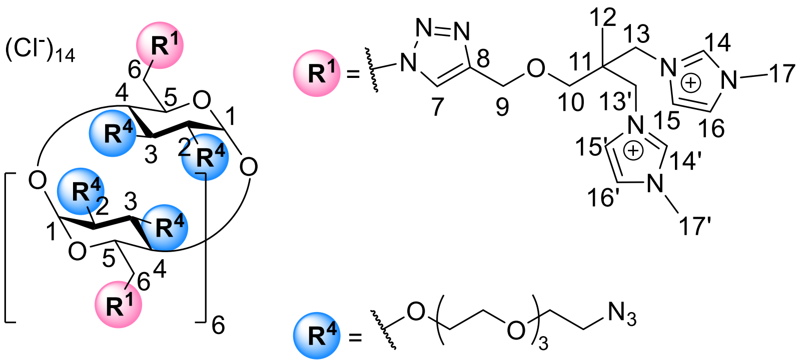
16
6748.36 g/mol
(cation only)
8835.20 g/mol
(with TfO⁻ anions)

¹H NMR (400 MHz, DMSO-*d6*) *δ* 9.40 – 9.07 (s, 14H, H-14/14’), 8.38 – 7.87 (m, 7H, H-7), 7.84 – 7.71 (m, 14H, H-16/16’), 7.70 – 7.54 (m, 14H, H-15/15’), 6.05 – 5.90 (s, 7H, NH-carbamate), 5.28 – 4.95 (m, 7H, H-1), 4.41 – 4.13 (m, 38H), 3.98 – 3.80 (m, 46H), 3.63 – 3.43 (m, 175H), 3.42 – 3.34 (m, 53H), 3.19 – 3.14 (m, 42H, H-17/17’), 1.34 – 1.17 (m, 16H), 0.94 – 0.70 (s, 21H, H-12) ppm.

IR (DRIFT, KBr): *ν* = 3336, 3089, 2871, 2532, 2108 (azide), 1732 (C=O bond of carbamate), 1549, 1261, 1120 cm⁻¹.

Per-6-(MTZ-*O*-MIM2)-per-2,3-(*O*-TEG-azido)-β-CD (17)

First, bicarbonate **3** (225 mg; 0.0533 mmol; 1 eq.) was dissolved in methanol (7 ml) and neutralised with TfOH (1 M in MeOH) to exchange the bicarbonate counterions for triflates. The neutral solution was evaporated under reduced pressure and the residue was dried *in vacuo* at 50 °C to provide a brown oily substance (292 mg; corresponding to 0.0539 mmol of **3** with triflate counterions). This compound was dissolved in DMF (3 ml) and azido-TEG tosylate **22** (423 mg; 1.13 mmol; 21 eq.) was added dropwise, followed by 60% sodium hydride in mineral oil (45 mg; 1.13 mmol; 21 eq.). The resulting mixture was heated to 50 °C under an inert atmosphere for 6 days. The reaction mixture was then precipitated into diethyl ether (20 ml). The precipitate was isolated by centrifugation and washed with ether (3 × 20 ml). The solid was then dissolved in water (100 ml) and passed through a strong anion-exchange resin in the chloride cycle, exchanging the tosylate counterions for chlorides. The aqueous solution was evaporated under reduced pressure at 45 °C and the resulting solid was dissolved in methanol. The insoluble NaCl by-product was removed by centrifugation and the desalinated solution was again evaporated. Finally, the product was obtained upon drying *in vacuo* at 50 °C as a brown, glassy solid (329 mg; 0.0425 mmol; 92%).



17
6146.01 g/mol
(cation only)
6642.31 g/mol
(with Cl⁻ anions)

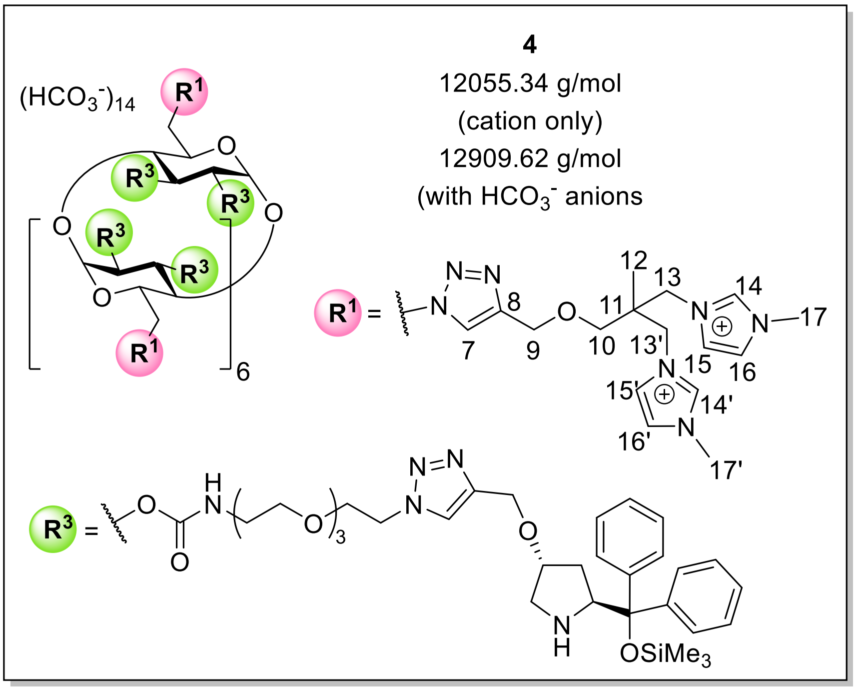
^{1}H NMR (400 MHz, DMSO-*d6*) *δ* 9.30 – 9.08 (m, 7H, H-7), 8.49 – 8.04 (m, 14H, H-14/14'), 7.86 – 7.30 (m, 28H, H-15/15', H-16/16'), 6.04 – 5.90 (m, 5H), 5.30 – 4.95 (m, 7H, H-1), 4.78 – 4.43 (m, 17 H), 4.41 – 4.26 (m, 16H), 4.25 – 4.13 (m, 14H), 4.12 – 4.06 (m, 10H), 3.96 – 3.80 (m, 34H), 3.62 – 3.56 (m, 24H), 3.56 – 3.43 (m, 99H), 3.42 – 3.34 (m, 39H), 3.18 – 3.08 (m, 45H), 1.67 – 1.17 (m, 19H), 0.93 – 0.65 (m, 21H, H-12) ppm.

IR (DRIFT, KBr): *ν* =3496, 3336, 2871, 2110 (azide), 1653, 1338, 1053 cm^{-1}.

Per-6-(MTZ-*O*-MIM2)-per-2,3-(carbamoyl-TEG-MTZ-*O*-JC)-β-CD (4)

Propargylic Jørgensen's catalyst **1** (364 mg; 0.96 mmol; 17 eq.) was dissolved in DMF (24 ml) and charged β-cyclodextrin with azido-TEG carbamate linkers **16** (500 mg; 0.057 mmol; 1 eq.) was added. The solution was bubbled with nitrogen for 30 minutes. Then, powdered copper metal (109 mg; 1.7 mmol; 30 eq.) was added. The mixture was stirred at 50 °C overnight. After 20 hours heating was turned off and the reaction mixture was stirred at r.t. for 4 days. Completion of the reaction was verified by DRIFT-IR (disappearance of the azide signal at 2106 cm^{-1}).

When the IR-signal of the azide had disappeared completely, the reaction mixture was precipitated into Et_2O (125 ml). Isolation of the precipitate failed, as it clogged the sintered funnel. The precipitate was therefore washed out of the filter with excess MeOH, leaving behind the metallic copper catalyst. The filtrate, now containing DMF, Et_2O and MeOH, was first evaporated on a rotary evaporator at 50 °C and then *in vacuo* at 60 °C. The residue was dissolved in MeOH (10 ml) and precipitated into Et_2O (80 ml). This time, the precipitate was isolated by centrifugation and washed with Et_2O (2 × 40 ml). The washed solids were dissolved in aqueous NH_4HCO_3 (1 M; 75 ml) and passed through a column of basic alumina (15 g) to remove any remaining Cu^{2+} ions. The resulting brown solution was evaporated under reduced pressure at 60 °C and the residue was dried *in vacuo* at 60 °C to constant mass. The supposed product was obtained as a brown solid (670 mg; 0.052 mmol; 91%).



4

12055.34 g/mol
(cation only)
12909.62 g/mol
(with HCO_3^- anions

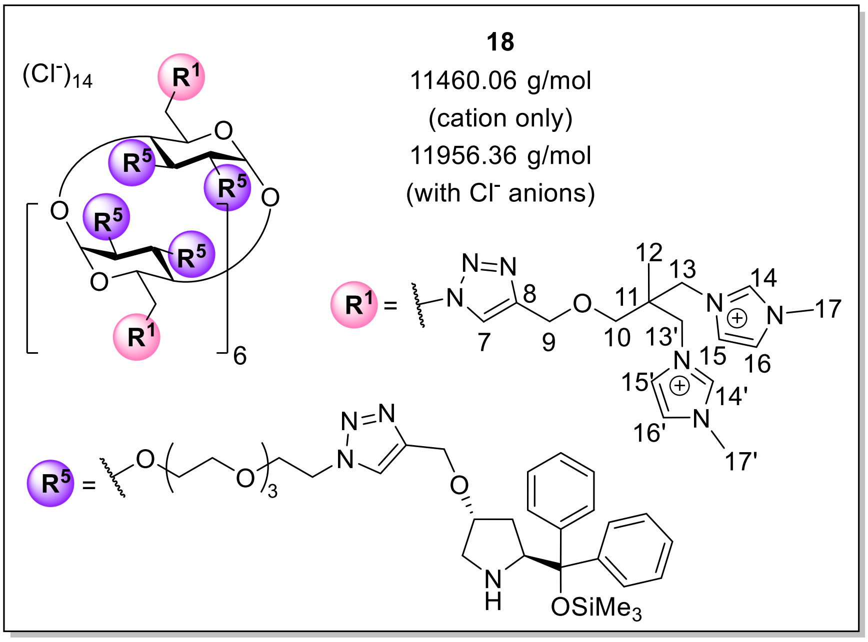
^{1}H NMR (400 MHz, MeOD) δ 8.19 – 7.97 (m, 14H), 7.96 – 9.78 (m, 14H), 7.55 – 6.81 (m, 70H), 6.46 – 6.17 (m, 14H), 5.60 – 4.95 (m, 7H, H-1), 4.65 – 4.56 (m, 14H), 4.55 – 4.22 (m, 42H), 4.19 – 3.92 (m, 21H), 3.90 – 3.65 (m, 42H, H-17/17'), 3.61 – 3.28 (m, 77H), 3.21 – 2.97 (m, 42H), 2.92 – 2.82 (m, 7H), 2.61 –2.52 (m, 7H), 2.10 – 1.48 (m, 28H) 0.92 – 0.56 (m, 21H, H-12), - 0.22 – - 0.49 (m, 21H, H-Me$_3$Si) ppm.

IR (DRIFT, KBr): ν = 3298, 2947, 2870 1722 (C=O bond of carbamate) cm^{-1}, no azide signal observed at 2106 cm^{-1}.

Per-6-(MTZ-*O*-MIM2)-per-2,3-(*O*-TEG-MTZ-*O*-JC)-β-CD (18)

Charged β-CD with azido-TEG ethers **17** (49 mg; 7.53 μmol; 1 eq.) and propargylic Jørgensen's catalyst **1** (44 mg; 0.117 mmol; 15.5 eq.) were dissolved in DMF (2 ml). The solution was bubbled with nitrogen for 30 min. Then, powdered copper metal (14 mg; 0.226 mmol; 30 eq.) was added and the reaction mixture was stirred under nitrogen at room temperature for 3 days. Completion of the reaction was verified by DRIFT-IR (disappearance of the azide signal at 2106 cm^{-1}).

The reaction mixture was then precipitated into diethyl ether (20 ml), the precipitate was separated by centrifugation and washed with ether (2 × 20 ml). The crude product was suspended in aqueous NH_4HCO_3 (1 M; 5 ml) and loaded onto a column of basic aluminium oxide (9 g). Elution was carried out with pure methanol due to the low solubility of the product in aqueous ammonium bicarbonate. The resulting solution was evaporated under reduced pressure at 40 °C. The residue was suspended in MeOH, filtered through cotton and passed through a strong anion-exchange resin in the chloride cycle, unifying the counterions to chlorides. The target compound was obtained upon evaporation of the methanolic solution as a brown, glassy solid (72 mg; 6.02 μmol; 80%).



18
11460.06 g/mol
(cation only)
11956.36 g/mol
(with Cl⁻ anions)

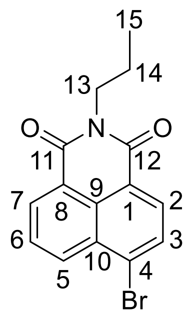
¹H NMR (400 MHz, MeOD) δ 8.31 – 7.83 (m, 21H), 7.69 – 7.41 (m, 28H), 7.40 – 7.08 (m, 42H), 6.59 – 6.34 (m, 7H), 5.59 – 5.14 (m, 21H), 4.75 – 3.45 (m, 245H), 3.29 – 3.14 (m, 21H), 3.11 – 2.95 (m, 14H), 2.83 – 2.58 (m, 7H), 2.43 – 1.93 (m, 14H), 1.90 – 1.71 (m, 7H), 1.66 – 1.45 (m, 7H), 1.42 – 1.21 (m, 7H), 0.93 – 0.66 (m, 21H, H-17/17'), -0.05 – - 0.16 (m, 4H, H-Me_3Si) ppm.

IR (DRIFT, KBr): ν = 3342 (secondary amine), 2877, 1668, 1092 cm^{-1}, no azide signal observed at 2106 cm^{-1}.

6.2.5 Synthesis of a fluorescent analogue of the catalytic system

4-Bromo-*N*-propyl-1,8-naphthalimide (19)

4-Bromo-1,8-naphthalic anhydride (300 mg; 1.08 mmol; 1 eq.) was suspended in ethanol (13 ml) and propylamine (89 µl; 1.08 mmol; 1 eq.) was added. The mixture was refluxed overnight. After 26 hours, the reaction mixture was evaporated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (hexane:EtOAc 20:1). The target compound was obtained as an off-white solid (293 mg; 0.921 mmol; 85%).



19
$C_{15}H_{12}BrNO_2$
318.17 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (dd, J = 7.3, 1.2 Hz, 1H, H-7), 8.58 (dd, J = 8.5, 1.2 Hz, 1H, H-5), 8.43 (d, J = 7.9 Hz, 1H, H-2), 8.05 (d, J = 7.8 Hz, 1H, H-3), 7.86 (dd, J = 8.5, 7.3 Hz, 1H, H-6), 4.20 – 4.12 (m, 2H, H-13), 1.76 (sext, J = 7.5 Hz, 2H, H-14), 1.01 (t, J = 7.4 Hz, 3H, H-15) ppm.

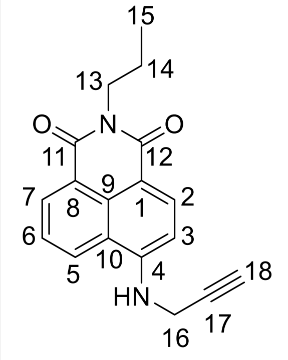
The ^{1}H NMR spectrum is in accordance with the literature[70]. Some assignments of aromatic protons differ.

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.65 (C-11), 163.63 (C-12), 133.21 (C-5), 132.02 (C-7), 131.21 (C-2), 131.09 (C-3), 130.64 (C-4), 130.18 (C-10), 129.03 (C-9), 128.07 (C-6), 123.17 (C-8), 122.31 (C-1), 42.07 (C-13), 21.37 (C-14), 11.51 (C-15) ppm.

MS-ESI: calculated M = 318.17, found m/z = 318

4-Propargylamino-*N*-propyl-1,8-naphthalimide (20)

Bromide **19** (97 mg; 318.2 mmol) was combined with neat propargylamine (2 ml) and the resulting mixture was heated to reflux overnight. After 28 hours, propargylamine was evaporated from the reaction mixture *in vacuo* at 40 °C. The crude product was purified by silica gel column chromatography (hexane:EtOAc 10:1 → 5:1 → 3:1 → 1:1) yielding the target compound as a bright yellow solid (49 mg; 0.154 mmol; 55%).



20

$C_{18}H_{16}N_2O_2$

292.34 g/mol

^{1}H NMR (400 MHz, DMSO-*d6*) *δ* 8.62 (dd, *J* = 8.6, 1.2 Hz, 1H, H-5), 8.45 (dd, *J* = 7.3, 1.0 Hz, 1H, H-7), 8.33 (d, *J* = 8.5 Hz, 1H, H-2), 8.14 (t, *J* = 5.8 Hz, 1H, NH), 7.72 (dd, *J* = 8.5, 7.3 Hz, 1H, H-6), 6.89 (d, *J* = 8.5 Hz, 1H, H-3), 4.24 (dd, *J* = 5.8, 2.5 Hz, 2H, H-16), 4.01 – 3.96 (m, 2H, H-13), 3.23 (t, *J* = 2.3 Hz, 1H, H-18), 1.63 (sext, *J* = 7.5 Hz, 2H, H14), 0.90 (t, *J* = 7.4 Hz, 3H, H-15) ppm.

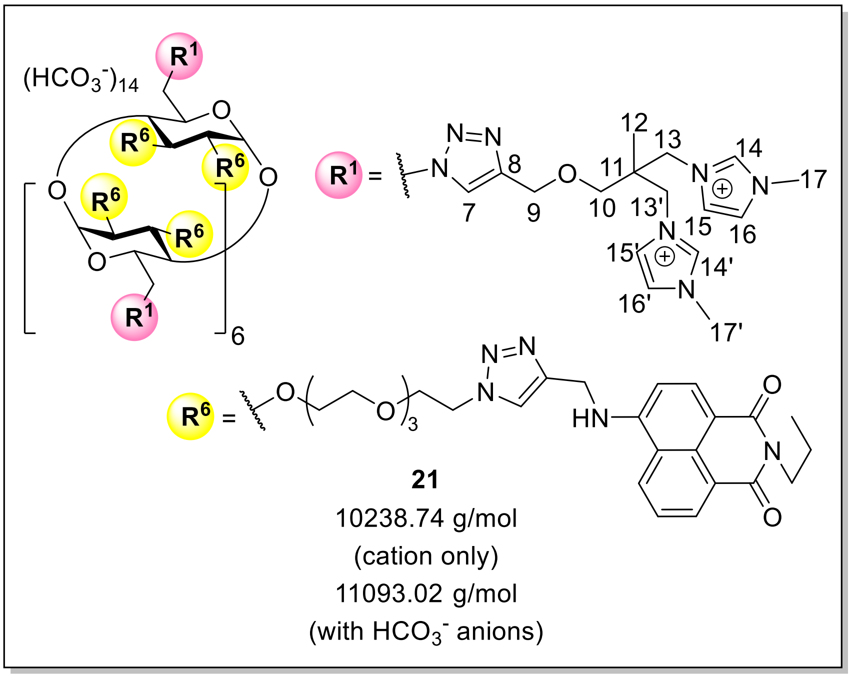
^{13}C NMR (101 MHz, DMSO-*d6*) *δ* 163.73 (C-11), 163.01 (C-12), 149.50 (C-4), 133.84 (C-2), 130.73 (C-7), 129.17 (C-9), 128.34 (C-5), 124.76 (C-6), 122.02 (C-8), 120.39 (C-10), 109.01 (C-1), 104.94 (C-3), 40.79 (C-13), 20.96 (C-14), 11.38 (C-15) ppm.

MS-ESI: calculated M = 292.34, found *m/z* = 293 $[M+H]^+$

Per-6-(MTZ-*O*-MIM2)-per-2,3-(*O*-TEG-MTZ-amino-NIM)-β-CD (21)

A 4 ml vial was charged with charged cyclodextrin chloride **17** (32 mg; 48.9 µmol; 1 eq.) and 4-propargylamino-1,8-phthalimide **20** (30 mg; 0.103 mmol; 21 eq.). The compounds were dissolved in DMF (2 ml) and the solution was bubbled with nitrogen for 30 min. Then, powdered copper metal (10 mg; 0.147 mmol; 30 eq.) was added and the mixture was stirred under nitrogen at room temperature for 6 days. Finally, the reaction was pushed to completion by heating to 50 °C for 24 h. Completion of the reaction was verified by DRIFT-IR (disappearance of the azide signal at 2106 cm^{-1}).

The reaction mixture was then poured into Et_2O (20 ml) and the resulting precipitate was separated by centrifugation. The solid was washed with Et_2O (2 × 20 ml), suspended in aqueous NH_4HCO_3 (1 M; 5 ml) and loaded onto a column of basic alumina (9 g). Elution was carried out with MeOH. The resulting solution was evaporated under reduced pressure at 40 °C to provide the bicarbonate of compound **21** as an orange, glassy solid (17 mg; 1.53 µmol; 31%).



21

10238.74 g/mol

(cation only)

11093.02 g/mol

(with HCO_3^- anions)

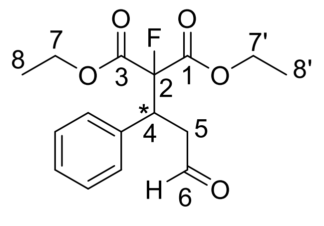
^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.3 – 9.91 (m, 1H), 9.51 – 9.16 (m, 2H), 9.0 – 8.59 (m, 10H), 8.56 – 8.27 (m, 14H), 8.24 – 7.88 (m, 21H), 7.85 – 6.96 (m, 28H), 6.90 – 6.66 (m, 7H), 6.57 – 6.02 (m, 14H), 5.44 – 5.00 (m, 7H), 4.94 – 4.56 (m, 14H), 4.50 – 4.33 (m, 21H), 4.24 – 4.07 (m, 154H), 3.94 – 3.82 (m, 35H), 3.78 – 3.60 (m, 49H), 3.57 – 3.42 (m, 70H), 1.68 – 1.40 (m, 28H), 0.89 – 0.79 (m, 21H, H-17/17’), 0.77 – 0.37 (m, 35H) ppm.

IR (DRIFT, KBr): ν = 3411, 3130, 2943, 2873, 1678, 1645, 1577, 1280, 1109 cm^{-1}, no azide signal observed at 2106 cm^{-1}.

6.2.6 Catalysis experiments

General procedure for the Michael addition of diethyl fluoromalonate to cinnamaldehyde

The addition of diethyl fluoromalonate to cinnamaldehyde catalysed by low-molecular secondary amine catalysts (i.e. propargylic Jørgensen's catalyst **1**, or piperidine) was performed according to a published procedure with minor modifications[72]. To a 4 ml vial were successively added DCM (2 ml/mmol of cinnamaldehyde), secondary amine catalyst (0.05 mmol; 0.2 eq.), cinnamaldehyde (1 eq.), diethyl fluoromalonate (0.5 eq.) and NaOAc (1 eq.). The resulting mixture was stirred in a sealed vial at room temperature overnight or longer if necessary. The reaction was monitored by ^{19}F NMR, where the signal of the reactant fluoromalonate at - 195 ppm gradually decreased in favour of a signal at - 174 ppm corresponding to the Michael adduct. When no further change was observed in the ^{19}F NMR spectra, the reaction mixtures were either evaporated under reduced pressure and purified by silica gel column chromatography (hexane:EtOAc 10:1 → 5:1) or a sample of the product was isolated by preparative TLC (hexane:EtOAc 2:1). A blank reaction without a catalyst was set up under the same conditions.



5

$C_{16}H_{19}FO_5$

310.32 g/mol

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.60 (q, J = 1.4 Hz, 1H, H-6), 7.36 – 7.23 (m, 5H, H-Ar), 4.38 – 4.26 (m, 1H, H-4), 4.33 (q, J = 7.2 Hz, 2H, H-7/7'), 4.29 – 4.26 (m, 2H, H7/7'), 3.06 (ddd, J = 17.6, 10.0, 1.8 Hz, 1H, H-5), 2.90 (ddd, J = 17.7, 3.9, 1.1 Hz, 1H, H-5), 1.33 (t, J = 7.1 Hz, 3H, H-8/8'), 1.01 (t, J = 7.1 Hz, 3H, H-8/8') ppm.

^{13}C NMR (101 MHz, CDCl$_3$) δ 198.92 (C-6), 165.69 – 165.28 and 164.99 – 164.60 (C-1, C-3)*, 136.57 (C^q-Ar), 129.48 (C-Ar), 128.74 (C-Ar), 128.27 (C-2), 63.31 – 62.72 (C-7/7'), 44.57 – 44.53 (C-4)*, 43.85 – 43.66 (C-5)*, 14.11 – 13.82 (C-8/8')* ppm.

*Dual signals appear due to hindered rotation around the C2–C4 bond.

^{19}F NMR (376 MHz, CDCl$_3$) δ -174.31 (d, J = 31.7 Hz) ppm.

HPLC (Chiralpak IC, 1 ml/min, heptane:*i*PrOH 80:20, 220 nm): t_R = 9.08 min (minor), 12.22 min (major).

Michael addition of diethyl fluoromalonate to cinnamaldehyde catalysed by compound 4

Supramolecular catalyst **4** (47 mg; 3.66 µmol; 0.0143 eq. ≈ 0.2 eq./14*) was suspended in DCM (1 ml). Diethyl fluoromalonate (20 µl; 0.128 mmol; 0.5 eq.), cinnamaldehyde (32 µl; 0.256 mmol; 1 eq.) and NaOAc (21 mg; 0.256 mmol; 1 eq.) were added successively. The mixture was stirred in a closed vial at room temperature for 1 week. The reaction was intermittently monitored by ^{19}F NMR.

Michael addition of diethyl fluoromalonate to cinnamaldehyde catalysed by compound 18

Supramolecular catalyst **18** (44 mg; 3.68 µmol; 0.0143 eq.*) was suspended in DCM (1 ml). Diethyl fluoromalonate (20 µl; 0.128 mmol; 0.5 eq.), cinnamaldehyde (32 µl; 0.256 mmol; 1 eq.) and NaOAc (21 mg; 0.256 mmol; 1 eq.) were added successively. The mixture was stirred in a closed vial at room temperature for 1 week. The reaction was intermittently monitored by ^{19}F NMR.

*Since the exact number of substituents in the catalytic systems **4** and **18** remained unknown, the compounds was treated as if they were fully substituted.

6.2.7 Sorption experiments

6.2.7.1 Calibration

First, a calibration curve had to be constructed in order to determine the dependence of UV-VIS absorbance on the concentration of compound **4** in solution. To this end, a stock solution of **4** (10^{-4} M in MeOH) was prepared. This solution was further diluted with MeOH to provide a series of five solutions ranging from 1 µM to 5 µM in concentration. This range of concentrations was used because higher concentrations exceeded the linearity of the absorbance-concentration dependence. Each of the five solutions was prepared in triplicate. Absorbance of the solutions was measured across a range of wavelengths between 190 and 400 nm. The maximum absorbance values (λ_{max} = 201 nm) were used to construct the following calibration curve.

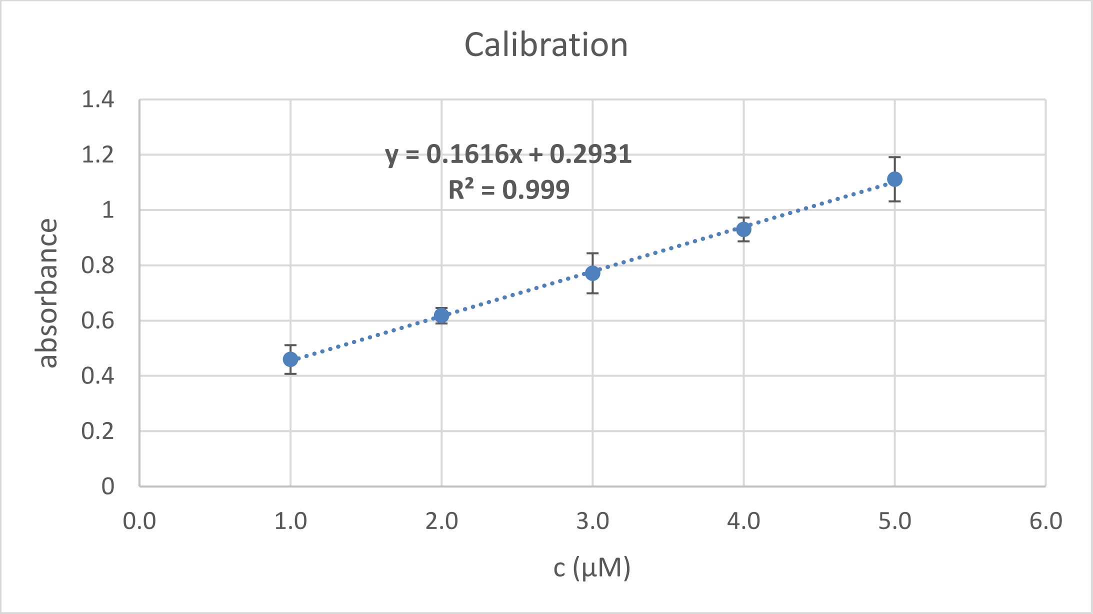


Figure 13: Absorbance concentration dependence for solutions of **4** in MeOH.

The resulting concentration dependence (equation (2) was further used to determine the sorption capacities of different sorbents.

$$A = 0.1616c + 0.2931 \tag{1}$$

$$c = \frac{A - 0.2931}{0.1616};\ [c] = \text{µM} \tag{2}$$

6.2.7.2 Sorption of compound 4 onto solid sorbents

Sorption experiments were performed according to the following procedure. First, a solution of **4** (≈ 4 µM in MeOH) was prepared using the same stock solution that had been used for calibration. After the initial absorbance of the solution had been measured, 2 ml of the solution were transferred into a 4 ml vial and a defined amount of sorbent was added (see Table 3). The mixture was stirred at room temperature for 5 min using a magnetic stir flea. Then, the sorbent was separated by centrifugation (10 min), the supernate was transferred to a quartz cuvette and the absorbance was measured. After the measurement, the supernate was returned to the same sorbent and the cycle of stirring, centrifugation and measurement was repeated until no changes in absorbance were observed. Before each set of measurements, a blank sample consisting of pure MeOH was measured. The acquired data were used to calculate sorbent capacities.

Table 3: Sorption of compound **4** from pure MeOH – summary of results.

		SORBENT		
		silica gel	**alumina**	**zeolite**
m (mg)		10.8	10.5	10.4
initial concentration of **4** (µM)		3.84	3.74	3.70
final concentration of **4** (µM)		1.61	**3.80***	**4.13***
concentration difference (µM)		2.23	–	–
amount of adsorbed (nmol)		4.46	–	–
SORBENT CAPACITY	$\text{nmol}_{\text{analyte}}/\text{g}_{\text{sorbent}}$	≥ 413	–	–
	$\mathbf{mg}_{\mathbf{analyte}}/\mathbf{g}_{\mathbf{sorbent}}$	**≥ 5.33**	**n.d.**	**n.d.**

*The final absorbance (and therefore also the calculated concentration) was greater than the initial, thus providing nonsensical results.

The same experiments as described above were carried out in a solution with increased ionic strength (0.15 M NaCl in 50% MeOH). Before each set of measurements 0.15 M NaCl in 50% MeOH was measured as a blank sample. The acquired data were evaluated using the same calibration dependence as before. The results are summarised in Table 4.

Table 4: Sorption of compound **4** from 0.15 M NaCl in 50% MeOH – summary of results.

		SORBENT		
		silica gel	**alumina**	**zeolite**
m (mg)		10.8	10.9	11.1
initial concentration of **4** (μM)		4.90	5.30	5.27
final concentration of **4** (μM)		**0.00***	2.78	1.60
concentration difference (μM)		4.90	2.52	3.60
amount of adsorbed (nmol)		9.80	5.04	7.20
SORBENT CAPACITY	$\text{nmol}_{\text{analyte}}/\text{g}_{\text{sorbent}}$	907	462	649
	$\mathbf{mg}_{\mathbf{analyte}}/\mathbf{g}_{\mathbf{sorbent}}$	**12**	**6.0**	**8.4**

*In the case of silica, the absorbance decreased below the calibrated range. The values shown here were calculated with the supposition that all of the analyte had been adsorbed.

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