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Cyclodextrines confinantes : synthèse, propriétés complexantes et utilisation en catalyse asymétrique

Confining Cyclodextrins: Synthesis, Coordination Properties and Applications in Asymmetric Catalysis

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A mon frère

"Success is not final, failure is not fatal:
it is the courage to continue that counts"

Winston Churchill (1874–1965)

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A vous tous, Merci.

Abbreviations

acac	acetylacetonate
ACNa	sodium 1-adamantanecarboxylate
CD	cyclodextrin
COD	1,5-cyclooctadiene
COSY	correlation spectroscopy
δ	chemical shift (ppm)
DABCO	1,4-diazabicyclo[2.2.2]octane
DIBAL	diisobutylaluminium hydride
DM-β-CD	2,6-permethylated β-CD
DMAP	4-dimethylaminopyridine
dmba	*o*-$C_6H_4CH_2NMe_2$
DMF	*N*,*N*'-dimethylformamide
ee	enantiomeric excess
ESI	electro-spray ionisation
GC	gas chromatography
HF	hydroformylation
HMBC	heteronuclear multiple bond correlation
HSQC	heteronuclear single quantum correlation
MALDI	matrix-assisted lase desorption/ionisation
MAO	methylaluminoxane
MeCN	acetonitrile
MS	mass spectrometry
NBD	norbornadiene, bicyclo[2,2,1]hepta-2,5-diene
NMR	nuclear magnetic resonance
ppm	parts per million
RAMEb-CD	randomly methylated β-cd
ROESY	rotating frame nuclear overhauser effect spectroscopy
SD	sodium dodecanoate
TBDMS	*tert*-butyldimethysilyl
THF	tetrahydrofurane
tht	tetrahydrothiophene
TOCSY	total correlation spectroscopy
TOF	turnover frequency
TON	turnover number
TPP	triphenylphosphine
TPPTS	sulfonated triphenylphosphine

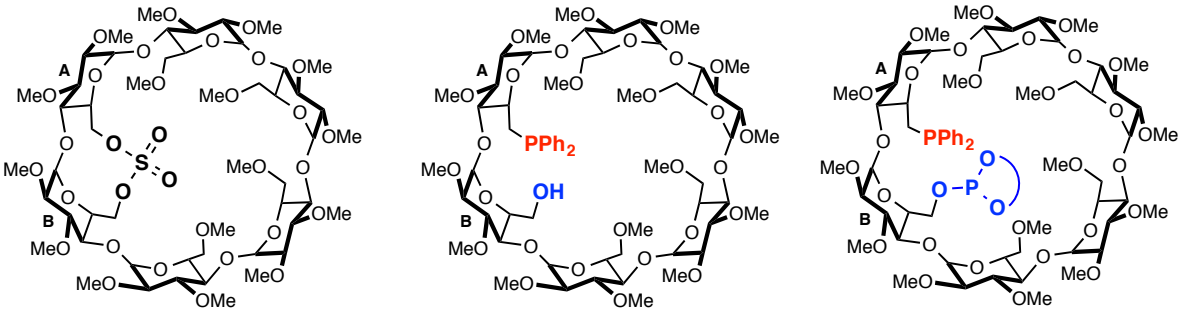
Contents

Synopsis

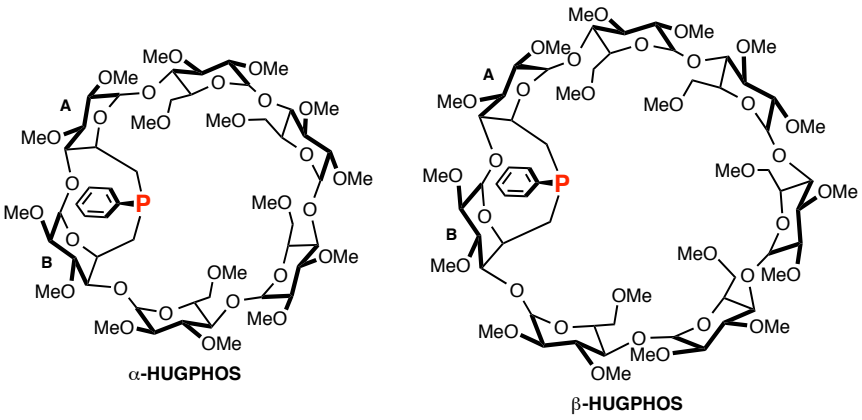
Ce mémoire de thèse est consacré à la synthèse de ligands phosphorés et azotés construits sur des plateformes cyclodextrine (CD) méthylée, ainsi qu'à l'étude de leurs propriétés complexantes et leur utilisation en catalyse homogène. Les CD sont des oligosaccharides cycliques ayant la forme d'un cône tronqué. Elles sont constitués d'unités D-(+)-glucopyranose reliées entre elles par des liaisons α-(1→4) et sont obtenues par dégradation enzymatique de l'amidon par la cyclodextrine-glycosyltransférase (CGT). Les plus étudiées d'entre elles, à savoir l'α-, la β- et la γ-CD, sont constituées respectivement de six, sept et huit unités glucose. Bien qu'hydrosolubles, les CD natives possèdent une cavité hydrophobe capable d'héberger de nombreuses molécules lipophiles en milieu aqueux. Associée à leur biocompatibilité, cette capacité à former des complexes d'inclusion dans l'eau est à l'origine de nombreuses applications industrielles, en particulier dans le domaine des industries pharmaceutique, cosmétique et agroalimentaire. La présence de nombreuses fonctions hydroxyle à la périphérie du cône en font également des plateformes de préorganisation performantes pour la construction de ligands mono- et multidentates, ces derniers pouvant être chélatants.

Le premier chapitre de ce mémoire de thèse est une mise au point de la littérature relative aux CD substituées par des groupements présentant un ou plusieurs atomes de phosphore trivalent. Il en décrit non seulement leurs synthèses, mais également leurs propriétés complexantes et catalytiques. La capacité de ces ligands hybrides P(III)/CD à se comporter comme première et deuxième sphère de coordination vis-à-vis de nombreux métaux de transition est illustrée par de multiples exemples. L'accent est également mis sur le rôle que joue la cavité CD de ces ligands dans la stabilisation d'espèces organométalliques inédites et son impact sur les propriétés catalytiques des complexes correspondants.

Les chapitres suivants sont consacrés à la conception de dérivés de CD principalement phosphorés mais également azotés et à leur utilisation en chimie de coordination et en catalyse homogène. Aussi, le deuxième chapitre porte sur le développement d'une nouvelle méthode d'hétérodifférenciation de la face primaire des CD méthylées par ouverture régiosélective d'un pont sulfate. Cette réaction permet le greffage de deux groupements différents sur deux unités glucose adjacentes de la CD. De tels dérivés constituent d'excellents produits de départ pour la préparation de plusieurs coordinats hybrides *phosphine-phosphite* dont la synthèse et les propriétés chélatantes et catalytiques sont décrites dans le troisième chapitre. Ces coordinats forment quantitativement des complexes de platine (II) et de rhodium (I) *cis*-chélatés. Malgré la flexibilité marquée du métallocycle à 12 chaînons, les complexes de rhodium(I) catalysent l'hydrogénation et l'hydroformylation d'oléfines prochirales avec des excès énantiomériques allant jusqu'à 92 %.

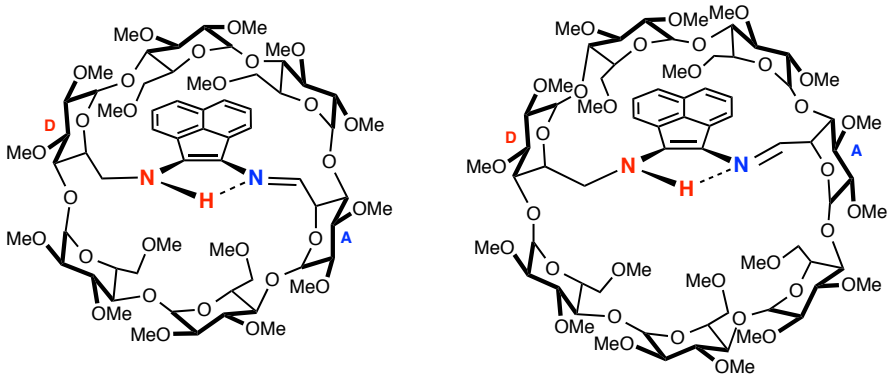


Le quatrième chapitre de ce mémoire concerne l'étude des propriétés complexantes et catalytiques de deux ligands confinants, à savoir l'α- et la β-HUGPHOS. Ces coordinats disposent d'un atome de phosphore ancré en deux points du macrocycle et dont le doublet libre du phosphore pointe vers l'intérieur de la cavité CD. Cet ancrage rigide permet de confiner le centre métallique au cœur du macrocycle, ce qui se traduit par la formation exclusive de complexes mono-ligandés en phosphore. Les complexes monophosphine de rhodium (I) ont été testés en hydroformylation asymétrique du styrène et ont fourni à la fois une très forte sélectivité en produit branché (98.3 %) et une énantiosélectivité très élevée (95 %). Une telle double performance n'avait encore jamais été observée en hydroformylation asymétrique du styrène.



Le dernier chapitre du manuscrit a trait au développement de coordinats confinants azotés. Des diaminoCD ont ainsi été pontées par l'acénaphtènequinone aussi bien en séries α- et que β-CD. Dans tous les cas, l'anse azotée de type *N*-(2-*N*'-alkylaminoacenaphthenyl)alkylimine qui se forme est dissymétrique et son installation sur la face primaire de cyclodextrines de symétrie C_1 se fait de manière régiospécifique. Les doublets libres des deux atomes d'azote sont systématiquement orientés vers le centre de la cavité.

L'oxydation du pont par voie chimique ou électrochimique conduit à une anse imidazole 1,2-disubstituée très courte qui provoque une forte déformation du squelette cyclodextrine.



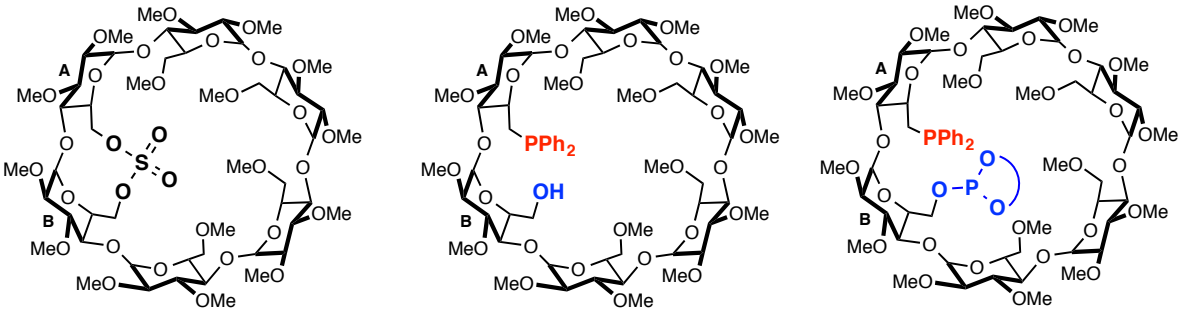
Mots-clés: cyclodextrine • phosphore (III) • ligand azoté • confinement • catalyse homogène • hydroformylation asymétrique • hydrogénation asymétrique • rhodium • palladium • platine • ruthénium

Synopsis

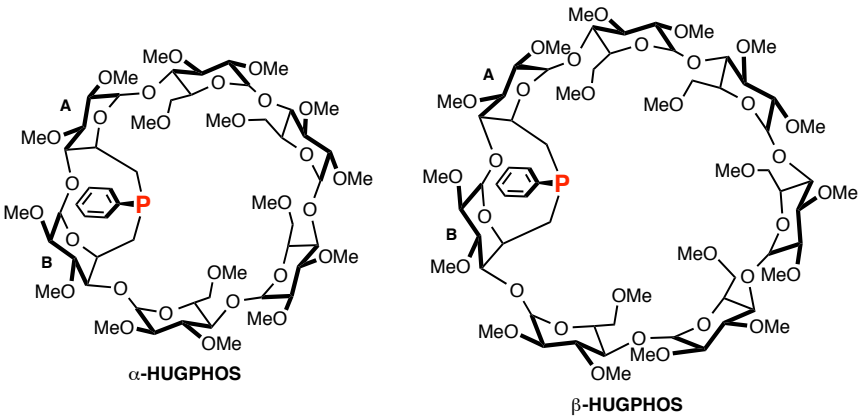
This thesis describes the synthesis, coordinating properties and catalytic properties of phosphorus- and nitrogen-containing ligands built on methylated cyclodextrin (CD) scaffolds. CDs are naturally occurring, bucket-shaped cyclooligosaccharides. The most common ones, named α-, β- and γ-CD, are respectively made up of 6, 7 and 8 D-(+)-glucopyranose units linked together via α-(1→4) bonds. They are produced on an industrial scale via the enzymatic degradation of starch by the CGT enzyme (cyclodextrin-glycosyltransferase). Despite the presence of numerous hydroxyl groups on their surface, which makes them water-soluble, their cavities are hydrophobic and can host a wide range of hydrophobic compounds in aqueous media. These host-guest properties combined with their biocompatibility have been extensively exploited in fields as diverse as cosmetic and pharmaceutical formulation as well as food industry. CDs are also perfect preorganisation platforms for the preparation of mono– and multidentate ligands, notably chelating ones, provided the many hydroxyl groups that decorate their surface can be discriminated.

The first chapter of this manuscript is a review dealing with CDs substituted with coordinating groups bearing at least one phosphorus (III) atom. It focuses not only on their synthesis, but also on their coordination properties and the use of their metal complexes in homogeneous catalysis. The ability of these P(III)/CD hybrids to operate as first and second coordination sphere ligands towards various transition metals is highlighted with a large number of examples. Special emphasis is put on the role played by the macrocycle in the stabilisation of novel organometallic species and on its impact on the catalytic properties of metallic complexes.

The next chapters are devoted to the design and synthesis of phosphorus- and nitrogen-containing CD ligands as well as their use in coordination chemistry and catalysis. Thus, the second chapter is concerned with a novel method of heterodifferenciation of the CD primary face by regioselective opening of a sulfate bridge. This methodology allows the regioselective introduction of two different coordinating groups on two adjacent glucose units of the CD. Such derivatives are key starting materials for the preparation of hybrid ligands such as *phosphine–phosphite* ones, the synthesis of which as well as their coordinating and catalytic properties are described in the third chapter. These *P*,*P′* ligands produce quantitatively *cis*-chelate complexes with platinum (II) and rhodium (I) precursors. Despite the marked flexibility of the 12-membered chelate rings of the resulting rhodium complexes, these catalyse the asymmetric hydroformylation and hydrogenation of prochiral olefins with enantiomeric excesses as high as 92 %.

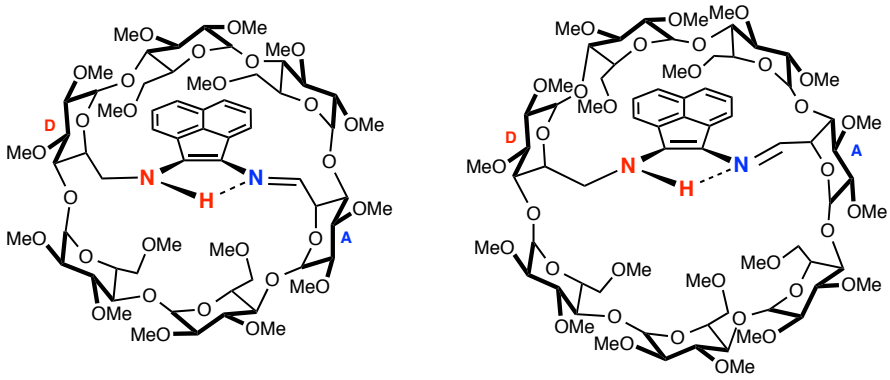


The fourth chapter deals with the coordination and catalytic properties of two confining ligands, namely α- and β-HUGPHOS. These ligands have their P(III) atom grafted to the CD core, with the P lone pair pointing toward the centre of the cavity. This rigid anchoring forces the confinement of a metal centre inside the CD upon complexation, thereby allowing the stabilisation of unprecedented singly phosphorus-ligated complexes. Rhodium (I) monophosphine complexes derived from HUGPHOS ligands were assessed in asymmetric hydroformylation of styrene and produced very high isoselectivity (98.3 %) *together* with very high enantioselectivity (95 %).



The last part of this thesis is concerned with the development of new confining ligands in which the main donor atom is nitrogen instead of phosphorus. Thus, capping of α- or β-diamino-CD derivatives with acenaphtenequinone (a symmetrical diketone) resulted in both cases in the formation of a CD capped by a non-symmetric *N*-(2-*N*'-alkylaminoacenaphthenyl)alkylimine handle. Its installation on the primary face of C_1 CD derivatives was found to be regiospecific. These compounds possess intra-annular nitrogen donor atoms having their lone pairs oriented toward the centre of the cavity.

Chemical or electrochemical oxidation of the bridge leads to a very short 1,2-disubstituted imidazole handle, which induces a strong deformation of the CD scaffold.

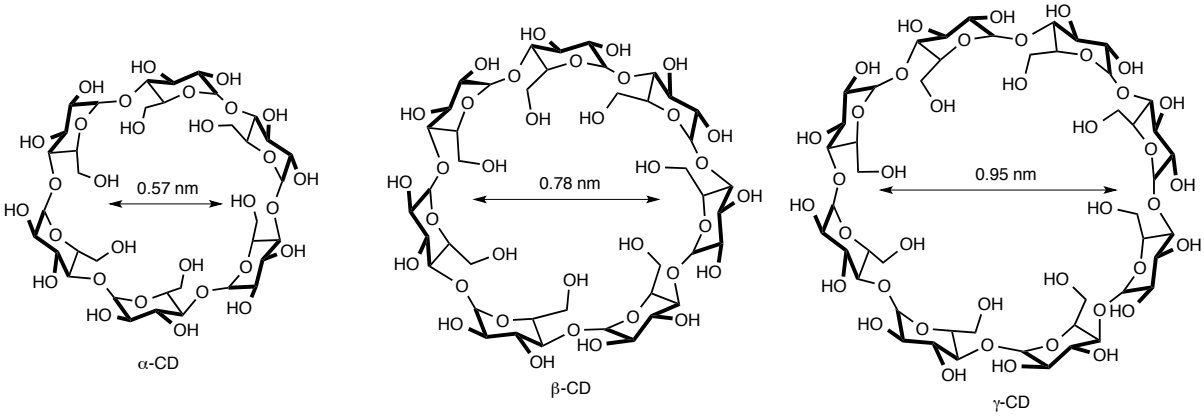


Keywords: cyclodextrin • phosphorus (III) • nitrogen ligands • confinement • homogeneous catalysis • asymmetric hydroformylation • asymmetric hydrogenation • rhodium • palladium • platinum • ruthenium

Introduction générale et objectifs

Introduction générale et objectifs

Les glucides sont une famille de molécules naturelles optiquement actives très prisées en synthèse organique en raison de la présence de nombreux centres stéréogéniques qui en font des produits de départ de choix pour la synthèse de molécules organiques à haute valeur ajoutées. De par leur structure hautement asymétrique et la présence de nombreux groupements fonctionnels modifiables, les glucides constituent également des plateformes modulables pour la construction de coordinats chiraux utilisables en catalyse asymétrique.[1] Formant une classe à part de sucres non réducteurs, les cyclodextrines (CD) sont particulièrement adaptées au greffage de groupements coordinants en raison de la robustesse que leur confère leur structure macrocyclique.[2] Ayant une forme de cône tronqué, ces oligosaccharides cycliques qui proviennent de la dégradation enzymatique de l'amidon, ont été découverts par Villiers à la fin du 19ème siècle.[3] Dotés de fonctions hydroxyle primaires sur le bord le plus étroit du cône appelé face primaire et d'hydroxyles secondaires sur le bord le plus évasé ou face secondaire, ils sont constitués d'unités D-(+)-glucopyranose reliées entre elles par des liaisons α-(1→4).[4] Contrairement à la plupart des cavitands génériques, les CD sont chirales et énantiomériquement pures. Solubles dans l'eau, elles possèdent néanmoins une cavité hydrophobe capable d'héberger un grand nombre de substances hydrophobes en milieu aqueux. Cette capacité à former des complexes d'inclusion relativement stables et biocompatibles est à l'origine de nombreuses applications industrielles.[5]



Cyclodextrines commerciales

Aussi, les CD ont fait l'objet de plus de 72000 publications à ce jour, et ce dans des domaines extrêmement variés allant de la chimie analytique[6] à l'industrie agro-alimentaire[7] et pharmaceutique[8] en passant par la chimie biomimétique,[9] la chimie des polymères,[10] la chimie inorganique[11] et la catalyse.[12] Bien que la majorité de ces études porte sur l'utilisation de CD natives, un regain d'intérêt pour les cyclodextrines modifiées a été suscité par le développement récent de méthodes très efficaces de fonctionnalisation régiosélective. Ces avancées ont permis, dans une certaine mesure, de différencier les nombreux groupements hydroxyle identiques présents sur le macrocycle, notamment ceux de la face

primaire, ce qui a rendu possible le greffage de groupements coordinants de manière non aléatoire. En raison de la très grande stabilité conformationnelle de la plateforme cyclodextrine, de tels ligands se sont avérés particulièrement utiles pour la synthèse de complexes d'intérêt catalytique dans lesquels le centre métallique est piégé dans la cavité chirale. Le confinement du site actif est de nature à modifier considérablement les propriétés des catalyseurs, tant du point de vue de leur activité que de leurs sélectivités, notamment de l'énantiosélectivité.[13]

Ce mémoire de thèse est consacré au développement de nouveaux systèmes catalytiques dérivés de métallocyclodextrines. De nature plurisdisciplinaire, les travaux qui y sont décrits ont trait à la mise au point de nouvelles méthodes de fonctionnalisation régiosélective des cyclodextrines donnant accès à des ligands hétérodentés à chiralité inhérente, à la synthèse de ligands phosphorés et azotés susceptibles d'induire le confinement d'un centre métallique et à l'étude des propriétés catalytiques des complexes métalliques correspondants, notamment en hydrogénation et en hydroformylation asymétriques d'oléfines prochirales.

Le manuscrit se compose des cinq chapitres suivants :

Chapitre I. *Cyclodextrin and phosphorus (III): a versatile combination for coordination chemistry and catalysis.* Ce chapitre est une mise au point portant sur les CD substituées par des groupements comprenant un ou plusieurs atomes de phosphore trivalent. On y trouvera un descriptif détaillé de leur synthèse ainsi que de leurs applications en complexation et catalyse. La mise au point est subdivisée en deux parties, l'une traitant de CD phosphorées comportant un seul substituant (monosubstitution de la CD), l'autre de CD polysubstituées.

Chapitre II. *Regioselective opening of sulfato-capped cyclodextrins.* Le deuxième chapitre de ce mémoire a trait au développement d'une nouvelle méthode d'hétérodifférenciation régiospécifique de la face primaire des CD. Des α- et des β-CD méthylées portant 2 ou 4 fonctions hydroxyle situées sur la face primaire du macrocycle ont été pontées respectivement par une ou deux anses sulfato. Une fois formés, les ponts sulfato peuvent être ouverts par substitution avec différents nucléophiles. En raison de la chiralité des CD, l'ouverture se fait de manière régiosélective, voire régiospécifique lorsqu'un nucléophile suffisamment encombré est employé.

Chapitre III. *Heterobidentate ligands built on a cyclodextrin platform: application in rhodium catalysed asymmetric reactions.* Dans le troisième chapitre du manuscrit est décrite la synthèse de quatre ligands *phosphine-phosphite* obtenus à partir d'une α-CD méthylée comportant une fonction hydroxyle résiduelle et un groupement diphénylphosphinyle (voir chapitre II). Ces ligands hybrides forment quantitativement des complexes *cis*-chélate

flexibles à 12 chaînons avec des cations métalliques d^8 (Pt(II), Rh(I)). Les complexes de rhodium correspondants ont été testés en hydrogénation asymétrique d'esters de déhydroaminoacides N-substitués ainsi qu'en hydroformylation asymétrique du styrène.

Chapitre IV. *Phosphinocyclodextrins as confining units for catalytic centres. Applications to carbon-carbon bond forming reactions.* Le chapitre IV est consacré à l'étude des propriétés complexantes et catalytiques des ligands α- et β-HUGPHOS, deux cyclodextrines équipées chacune d'un atome de phosphore dont le doublet pointe vers le cœur de la cavité CD. Le confinement du centre métallique restreint la complexation à la coordination d'une seule phosphine. Il a été établi pour la première fois qu'avec une phosphine tertiaire, l'hydroformylation du styrène pouvait conduire à la fois à une haute sélectivité en produit branché (98.3 %) et à une énantiosélectivité élevée (95 %).

Chapitre V. *Regiospecific installation of unsymmetrical imine-enamine and imidazole caps over cyclodextrins using a symmetrical diketone reagent.* Le dernier chapitre du manuscrit porte sur l'installation régiospécifique d'une anse *N*-(2-*N*'-alkylaminoacenaphthenyl)alkylimine dissymétrique sur des α- et β-CD méthylées. L'oxydation du pont par voie chimique ou électrochimique conduit à une anse imidazole 1,2-disubstitué très courte qui provoque une forte déformation du squelette cyclodextrine. L'imidazole ainsi formé a permis de synthétiser un complexe du cuivre homoleptique de formule $[CuL_2]BF_4$.

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Chapter I

Cyclodextrin and phosphorus (III): a versatile combination for coordination chemistry and catalysis

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Cyclodextrin and phosphorus (III): a versatile combination for coordination chemistry and catalysis

I. 1. Introduction

Since their discovery by Villiers at the end of 19th century,[1] cyclodextrins (CDs) have gathered huge interest among the scientific community.[2] The considerable number of publications related to CDs (no less than 72000 since their discovery) reflect the many applications these naturally-occurring and non toxic cyclic oligosaccharides have found in fields as diverse as drug formulation,[3] analytical chemistry,[4] biomimetic chemistry,[5] inorganic chemistry,[6] catalysis,[7] polymers,[8] artificial sensors,[9] and food industry.[10] The commercially available CDs, which are the only ones with well-defined and rigid cavities, are made of six, seven or eight glucopyranose units (α-, β- and γ-CD, respectively).[11] With their α-1,4-linked D-(+)-glucopyranose units rigidly held in the ubiquitous $^4C_1$ chair conformation, these CDs, whether native or chemically modified, adopt a stable conical shape.[12] Native CDs comprise primary hydroxyl groups located at the narrow end of the cone called primary hydroxyl face or primary face, and secondary hydroxyl groups at the wider rim called secondary hydroxyl face or secondary face (Figure 1). Unlike most synthetic cavitands, native CDs are water-soluble chiral host molecules for many lipophilic compounds in aqueous media.[13]

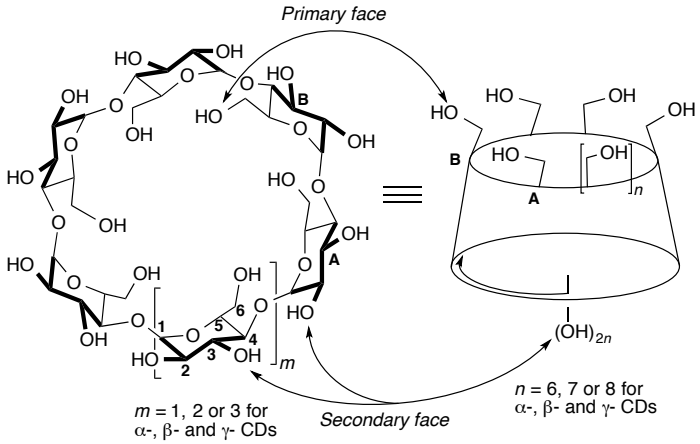
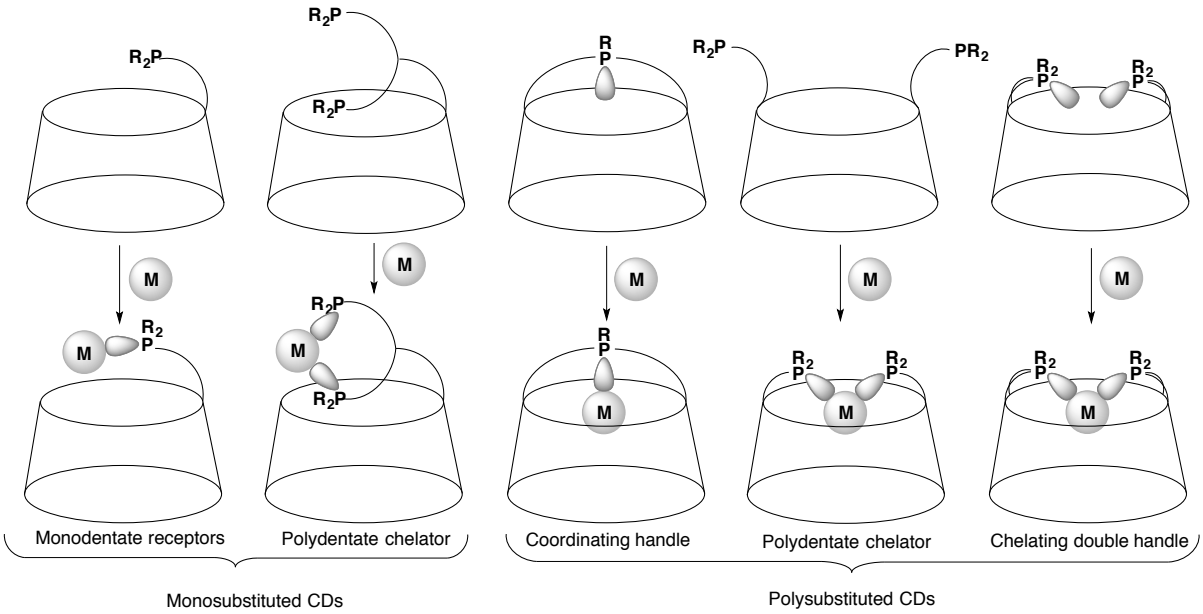


Figure 1. Native CDs and two representations.

Because of the possibility of introducing various donor groups at given locations on the macrocyclic structure, the CD skeleton (native or chemically modified) constitutes a versatile preorganisation platform for the synthesis of ligands that can act both as first and second coordination spheres for transition metals. This particular feature is of prime importance when the stabilization of unusual metal organic species, notably catalytic ones, is sought.[14] Among all coordinating atoms that have been anchored to a CD, phosphorus (III) is certainly the one that attracted the most interest because of its widespread use in catalysis.[15]

In recent years, numerous CD derivatives bearing appended P(III) ligands have been designed to combine the exceptional host-guest properties of the chiral CDs with the versatile coordination and catalytic properties of the P(III) atom. This review article will focus on their synthesis and applications, most notably their coordination and catalytic ones. Aqueous

organometallic catalysis as well as supramolecular assemblies involving non-covalently bonded CDs and P(III) ligands will not be discussed here as it has already been recently reviewed by Monflier.[16] The first part of the present review will cover CDs having a single pending arm that contains one or several P(III) donor atoms. The second part deals with CD derivatives substituted by two P(III) containing moieties as well as CDs in which a phosphine unit is covalently attached to the CD torus via two anchoring points (Scheme 1). Special emphasis will be put on the ability of the CD-P(III) hybrids to stabilize unusual organometallic species, to behave as encapsulating units and to act as supramolecular catalysts. Where possible, comparison between different systems will be made in order to clarify the influence of the CD cavity on the coordination properties of the P(III) atom and the catalytic outcome of reactions performed in non-aqueous media. Also, a rapid overview of the various functionalisation methods enabling introduction of the phosphorus moiety on the torus will be given.



Scheme 1. CD receptors with covalently bonded phosphorus(III) units and their metal complexes.

Figures derived from crystal structures are indicated by fat arrows (when needed) and all necessary data have been recovered from the Cambridge Crystallographic Data Centre (CCDC). For clarity, they do not include counter-ions and solvents nor hydrogen atoms. Carbon atoms are depicted in grey, whilst oxygen, nitrogen, phosphorus, sulfur and halogen atoms are in red, blue, orange, yellow and green, respectively. Metal centres of complexes are represented in space-filling form.

I. 2. Monosubstituted CDs

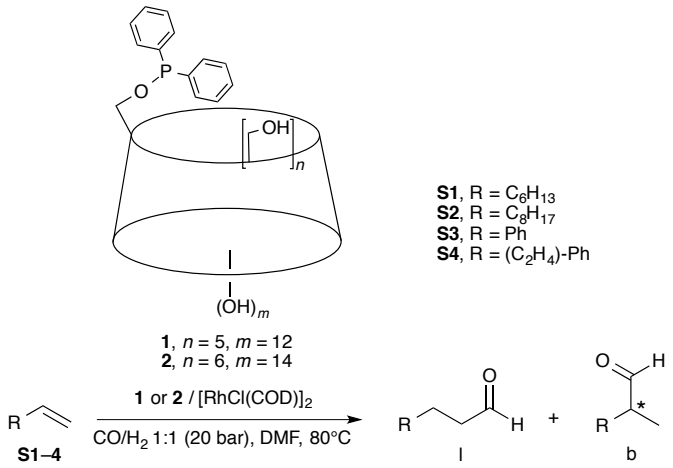
Several CD platforms have been equipped with coordinating atoms in order to take advantage of the remarkable host-guest properties of CDs for stabilizing unusual transition metal complexes or delivering a substrate with a given shape and size to a catalytic centre. Both features could lead to the development of new transition metal catalysts with improved selectivities and activities. Because of the ease with which they can be obtained, both native and modified CDs substituted with a single coordinating fragment, whether monodentate or polydentate, have been studied in the first place.

I. 2. 1. CD monofunctionalisation

Access to CDs monosubstituted either on the primary or secondary face have become available since the 90's and most of these derivatives are now commercially available.[17] Actually, CD monofunctionalisation has been covered as far back as 1998 by D'Souza in a special issue of Chemical Reviews dedicated to CDs.[12b] The method of choice for performing mono-modifications consists in performing S_N2 reactions on 6-monotosyl-CDs with various nucleophiles (*vide infra*). Being compatible with strongly basic conditions and easy to purify, less hydrophilic 6-monotosyl-permethylated-CDs offer more possibilities than their polyhydroxylated counterparts for the introduction of phosphane groups. For example, 6-monotosyl-permethylated-β-CD can be obtained simply by methylating 6-monotosyl-β-CD with sodium hydride and methyl iodide in DMF.[18]

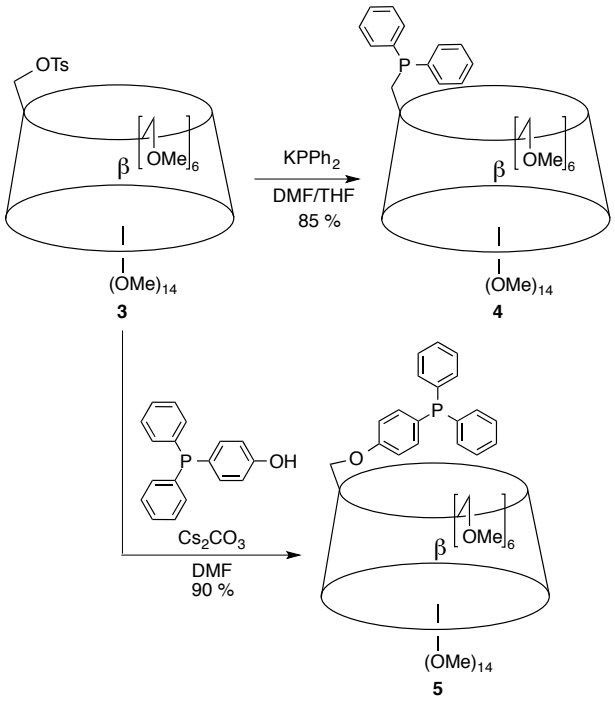
I. 2. 2. Monodentate ligands

Phosphinites **1** and **2** have been synthesised by Ichikawa et al. by reacting respectively α- and β-CD with chlorodiphenylphosphine in pyridine. Both ligands were tested for substrate discrimination in rhodium catalysed hydroformylation (Scheme 2).[19] Hydroformylation of oct-1-ene, dec-1-ene, styrene and 4-phenylbut-1-ene (**S1–4**) had to be carried out in DMF, since the rhodium (I) complex obtained in situ from **2** and $[RhCl(COD)]_2$, is not soluble in water, but only in strongly polar organic solvents. Activities were moderate while regioselectivities are typical of those observed with conventional Wilkinson-type catalysts (l/b = 2.8, 2.8, 0.4 and 1.8 for the four above substrates, respectively).[20] Competitive hydroformylation experiments carried out with **2**/$[RhCl(COD)]_2$ indicated that significantly lower substrate selectivity was obtained in this case compared to that displayed by the related diphosphine **18**/$[Rh(COD)_2]BF_4$ combination. Indeed, **S4** is converted up to 6.7 times faster than **S2** with **18**, but only 1.6 times faster with **2**. The analogous α-CD-based catalytic system **1**/$[RhCl(COD)]_2$ showed no significant selectivity change with respect to the control experiment. According to several authors, the observed selectivity enhancement is unlikely the result of an inclusion complex between the substrate and the CD, because organic solvents such as DMF are known to prevent such non covalent interactions.[16b]



Scheme 2. Ichikawa's phosphinite **1** and **2** ligands.

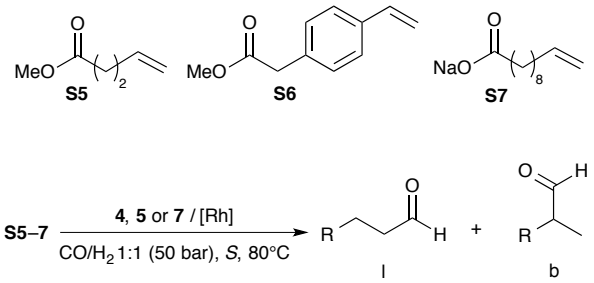
From 2010 onwards, Monflier et al. developed a series of phosphines in which the P(III) coordinating unit is covalently bonded to a fully methylated β-CD (**4**, **5**) or to the more water-soluble randomly methylated β-CD (RAMEb-CD) platforms (**7**). All of them were tested in metal catalysed reactions such as hydrogenation and/or hydroformylation of olefins. Phosphines **4** and **5** were synthesised by nucleophilic substitution of the tosyl group of **3** with diphenylphosphide and 4-(diphenylphosphino)phenate, respectively (Scheme 3). Extensive NMR experiments in D_2O proved that one of the phenyl rings of the PPh_2 unit of **4** is included in the β-CD cavity as for Reetz's non methylated diphosphine analogue **11** (*vide infra*).[21] This self-inclusion is strong enough to prevent the formation of stable inclusion complexes in water both with 1-adamantanecarboxylate (ACNa) and sodium dodecanoate (SD), which are known for being excellent guest molecules for CDs. Such a strong supramolecular interaction proved to be detrimental to both the molecular recognition and catalytic properties of **4**. It is to note that its α-CD analogue was already reported, but no study about the inclusion of a phenyl ring in water was made.[22] This ligand was tested in the rhodium-catalysed hydrogenation of the water-soluble olefin 2-methyl-3-buten-2-ol. Virtually quantitative conversion was observed after only 4 h reaction time under 1 bar of H_2. Ligand **4** was also used for the HF of methyl 4-pentenoate (**S5**). Good activities were observed in water, but both chemoselectivity and regioselectivity were in the same range as those observed in heptane (Table 1, entries 1-3 then 4-6). These results are nearly identical to the those obtained under the same conditions with the related TPPTS/water and TPP/heptane systems indicating that the CD cavity has a limited impact on the catalytic outcome (Table 1, entries 17 and 20).



Scheme 3. Synthesis of phosphines **4** and **5**. Ts = Toluenesulfonyl.

In order to prevent self-inclusion, the methylated CD platform was equipped with a rigid and longer coordinating arm.[23] Indeed, through-space correlations between aryl and inner cavity protons could no longer be detected in the ROESY spectrum of **5**. Furthermore, **5** forms stable inclusion complexes with several guest molecules such as ACNa, SD or **S7**, as revealed again by ROESY experiments. With $[Rh(COD)_2]BF_4$, **5** afforded *cis*-bis(phosphine) complex $[Rh(\mathbf{5})_2(COD)]$, while reaction of **5** with $[Rh(acac)(CO)_2]$ under H_2/CO atmosphere afforded the tris-phosphine complex $[RhH(\mathbf{5})_3(CO)]$ as revealed by both $^{31}P\{^1H\}$ and ^1H NMR spectroscopy. None of these complexes have been isolated. Interestingly, unlike **4**, ligand **5** is poorly soluble in water, probably because the hydrophobic PPh_3 unit is here fully exposed to the aqueous outside environment. As previously noticed for palladium complex $[PdCl_2(\mathbf{10})]$ (*vide infra*),[24] rhodium complexes of **5** are noticeably more water-soluble than the free ligand.

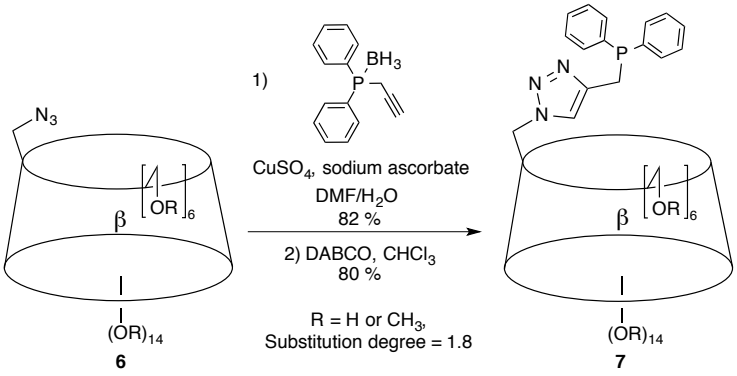
Table 1. Rhodium-catalysed hydroformylation of **S5-7** using **4**,**5** or **7**.[a]



Entry	L	Substrate	Solvent	Competitive Guest (equiv.)[b]	*t* [h]	Conv[c] [%]	l/b[d]	Ref
1	**4**	**S5**	Water	-	2	96	1.8	[21]
2[e]				-		97	1.8	
3[f]				-		89	1.7	
4			Heptane	-	2	83	1.2	
5[e]				-		82	1.2	
6[f]				-		88	1.2	
7	**5**	**S5**	Water	-	2	82	1.1	[23]
8				ACNa (0.3)		82	1.1	
9		**S6**	Water	-	2	87	0.1	
10				ACNa (0.3)		70	0.1	
11		**S7**	Water	-	0.25	99	2.8	
12				ACNa (1)		80	3.3	
13				ACNa (9)		32	3.2	
14	**7**	**S5**	Water	-	6	99	0.7	[25]
15				ACNa (0.3)		99	1.8	
16				SD (0.3)		98	1.9	
17	**TPPTS**	**S5**	Water	-	2	98	1.8	[21]
18				ACNa (0.3)		98	1.8	[25]
19				SD (0.3)		98	1.8	[25]
20	**TPP**	**S5**	Heptane	-	2	98	1.8	[21]

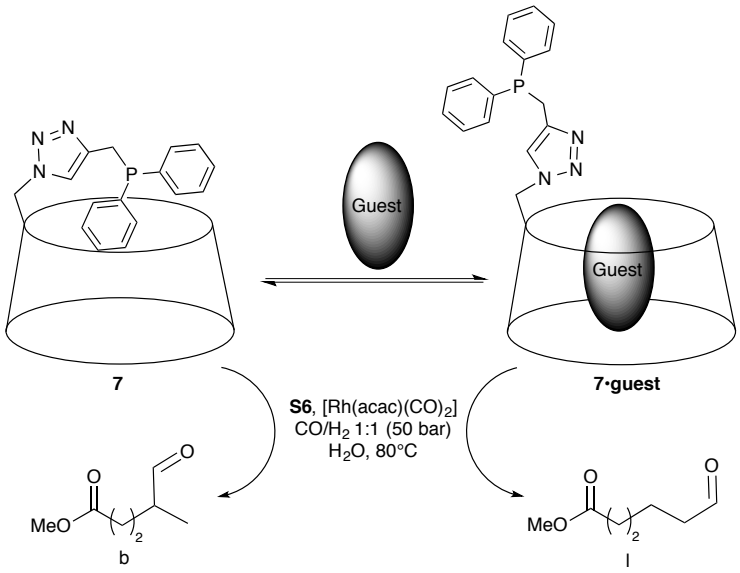
[a] Substrat/Rhodium = 500, Ligand/Rhodium = 4, $P(CO/H_2)$ = 50 bar, (CO/H_2) = 1/1, T = 80 °C. [b] Equivalent of competitive guest added with respect to substrate. [c] Determined by GC using decane as internal standard. [d] l/b aldehyde ratio. [e] Run carried out with Ligand/Rhodium = 8. [f] Run carried out with $P(CO/H_2)$ = 25 bar.

Olefin **S7**, which forms an inclusion complex with **5** was tested in rhodium-catalysed hydroformylation together with two olefins that have no affinity for the CD cavity (**S5** and **S6**) (Table 1, entries 7-13). The presence of a competitive CD guest molecule did not alter the way both **S5** and **S6** are hydroformylated and more or less the same l/b ratio and conversion as with **4** or TPPTS were observed (Table 1, entries 1 and 17, respectively). Conversely, substrate **S7** displayed a remarkable activity (TOF up to 1980 h^{-1}) and noticeably higher l/b ratio (2.8 instead of 1.1). In keeping with a CD cavity playing an active role in the catalytic process, addition of a competitive guest such as ACNa reduced dramatically the activity but had no real impact on selectivity (Table 1, entries 12-13).



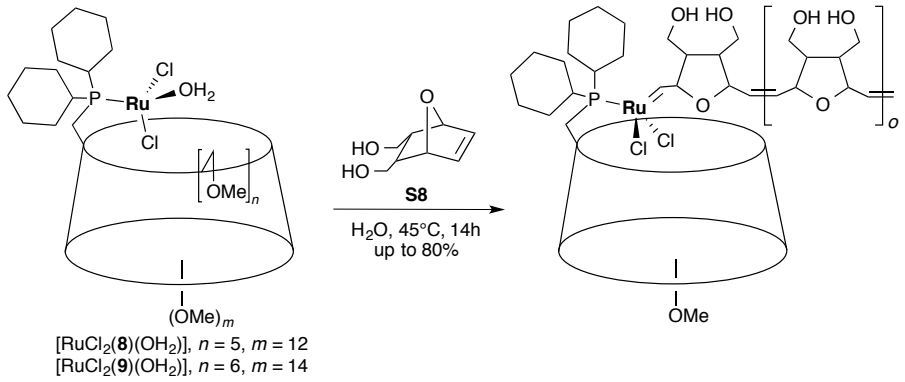
Scheme 4. Synthesis of **7**.

While one of the phenyl rings is firmly held in the CD cavity of **4** and cannot be displaced by a competitive guest in water, this is not the case for **7** the buried phenyl group of which can be expelled from the cavity by ACNa. Phosphine **7** was obtained by copper catalysed azide-alkyne cycloaddition between borane-protected diphenylpropynylphosphine and 6-azido-RAMEb-CD **6**, followed by phosphine deprotection using DABCO (Scheme 4). The influence of these conformational changes on the catalytic performance of **7** was assessed by carrying out rhodium-catalysed hydrofomylation reactions in water with olefin **S5** – which does not form inclusion complexes with β-CDs – and CD guest molecules ACNa and SD, the latter preventing self-inclusion. In the presence of competitive guests, standard l/b ratios of around 2 were observed (Table 1, entries 15-16 and 17-19) whereas without, the branched product became the major product (Table 1, entry 14). The authors suggest that with an included a guest molecule, **7** is bulkier than on its own, a feature which may favor the formation of the linear regioisomer (Scheme 5).[20c] However, with a phosphorus atom closer to the CD unit, steric crowding around the phosphorus atom is probably more severe in the self-included species than in the guest-occupied one. Such a steric crowding is known to be a key factor for promoting the formation of monophosphine complexes at the expense of bis(phosphine) ones. Because singly phosphorus-ligated complexes are known to promote the formation of branched aldehydes, the unusual regioselectivity observed here is probably a direct consequence of a higher than usual proportion of P-monoligated complexes under hydroformylation conditions.



Scheme 5. Guest tuneable conformation of **7** and main hydroformylation products for each case.

Recently, the group of Harada has described the use of two dicyclohexylphosphine derived from methylated α– and β-CD (**8** and **9**, respectively) in ring-opening metathesis polymerisation (ROMP).[26] Their syntheses are nearly identical to that of **4** as they were obtained by the treatment of the corresponding 6-monotosyl-permethylated-CD (**3** in the case of β-CD derivative **9**) with deprotonated borane-dicyclohexylphosphine complex, followed by deprotection of the resulting phosphine-borane adduct with refluxing morpholine. Surprisingly, **9** was obtained with an overall yield (18 %) much lower than that reported by Monflier for **4**. When reacted with ruthenium trichloride in refluxing ethanol, these ligands form unprecedented air stable 14-valence electrons complexes [$RuCl_2$(**8**)(OH_2)] and [$RuCl_2$(**9**)(OH_2)], both having seemingly tetrahedral geometry (Scheme 6). Both complexes catalyse the ring-opening metathesis polymerization (ROMP) of the water-soluble substrate **S8** in water. The CD cavity was shown to play an active role in the catalytic reaction as conversions with the CD-based systems (31 and 80 % conversion for [$RuCl_2$(**8**)(OH_2)] and [$RuCl_2$(**9**)(OH_2)] respectively within 14 h at 45°C) were much higher than with CD-free water-soluble analogues. Moreover, CD-guest molecules such as 3-chlorophenol or adamantane inhibit the catalytic reaction to a certain extent, proof that supramolecular catalysis is at work in this system. As expected, the best host-molecule for **S8**, namely [$RuCl_2$(**9**)(OH_2)] was more active than its smaller analogue [$RuCl_2$(**8**)(OH_2)]. Note that possible inclusion of a cyclohexyl ring into the macrocycle, in a manner similar to that observed with **11** (*vide infra*), was not discussed.



Scheme 6. ROMP of olefin **S8** using [$RuCl_2$(**8**)(OH_2)] and [$RuCl_2$(**9**)(OH_2)].

I. 2. 3. Polydentate ligands

The very first CDs bearing appended P(III) ligands were reported independently by the groups of Ito and Reetz in 1993. The group of Ito managed to attach a chiral ferrocenyldiphosphine to the secondary face of a 2,6-permethylated-β-CD (DM-β-CD) by reacting a mesylated derivative of hydroxyethoxy-substituted 1,1'-bis(diphenylphosphino)ferrocene with the fully deprotonated DM-β-CD.[24] Although the resulting ligand (**10**) is almost insoluble in water, the corresponding [$PdCl_2$(**10**)] complex displays high solubility in this medium (Figure 2). It was shown by means of conductivity measurements that [$PdCl_2$(**10**)] assembled in micelle-like aggregates above a given concentration. So far, no catalytic studies involving this ligand have been reported.

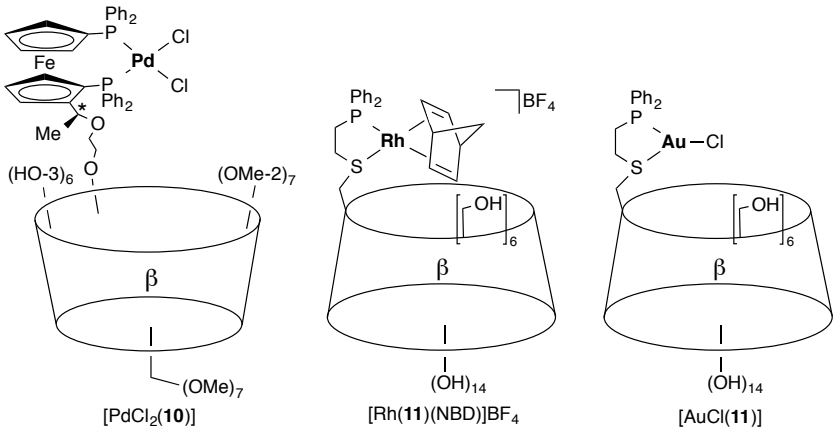


Figure 2. First examples of phosphine-functionalised CD complexes derived from **10** and **11**.

Around the same time, Reetz et al. reported the heterobidentate phosphine/thioether ligand **11**, which was synthesised by nucleophilic substitution of a 6-monotosyl-CD by 2-(diphenylphosphino)ethanethiol. Phosphine **11** readily forms the complexes [Rh(**11**)(NBD)]BF_4[27] and [AuCl(**11**)][28] (Figure 2). Surprisingly, unlike the related cavity-free [Rh($Ph_2PCH_2CH_2SMe$)(NBD)]BF_4 complex, [Rh(**11**)(NBD)]BF_4 turned out to be rather ineffective as a hydrogenation catalyst, but no explanation was given for this lack of reactivity.[29] A crystal structure reported eight years later showed that the cavity of **11** is able

to entrap specifically one of the two phenyl group by forming a self-inclusion complex in the solid state as for previously mentioned phosphines **4** and **7** (Figure 3). However, there is no evidence for such inclusion in solution as no 2D NMR experiments have ever been performed.[30]

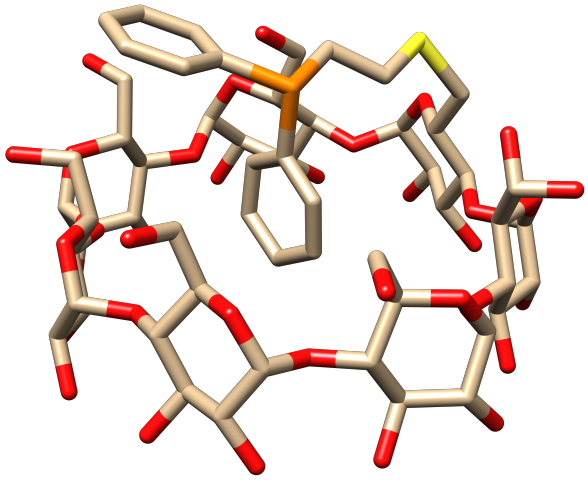
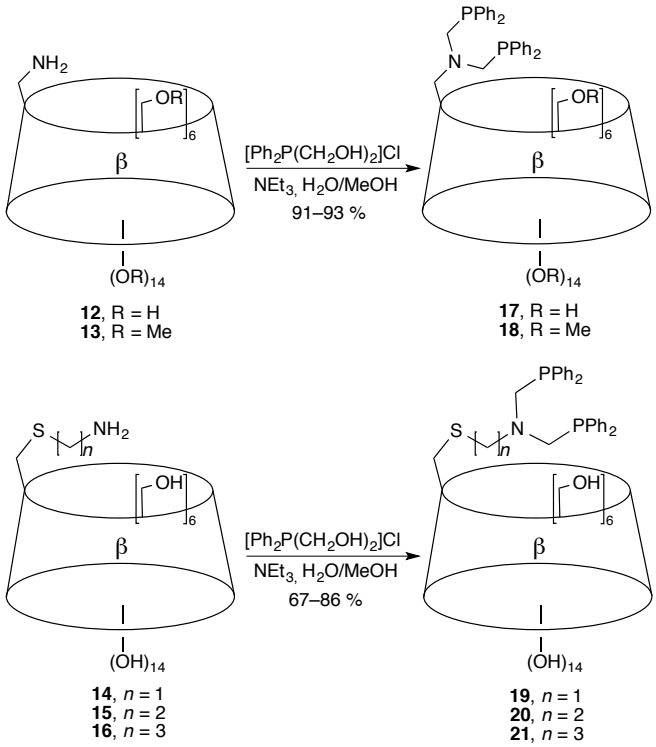


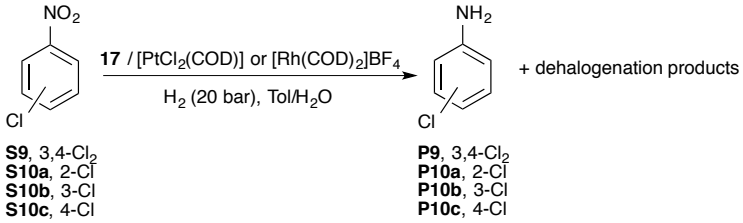
Figure 3. Molecular structure of **11** showing one of the two phenyl groups included in the CD cavity (side view).

The first chelating ligands (**17**-**21**) associating a P(III) donor atom with a CD cavity were reported by Reetz et al. He was able to prove that supramolecular catalysis operates in these hybrid systems since the CD unit acts here as a receptor towards various hydrophobic substrates in water and is able to discriminate between them during catalysis.[31] Ligands **17**-**21** were obtained in good yields from 6-deoxy-6-amino-CDs **12**-**16** respectively, in a Mannich-like reaction with $[Ph_2P(CH_2OH)_2]Cl$ (Scheme 7). Competitive hydrogenation experiments were carried with catalysts prepared *in situ* from **17**-**21** and $[Rh(COD)_2]BF_4$.[32] For solubility reasons, the reactions were performed in a 30 % DMF-water mixture. The lipophilic olefin 4-phenylbut-1-ene (**S4**) was converted up to 6.7 times faster than dec-1-ene (**S2**) when using **18**, whereas the same reaction with a related CD-free catalyst led to no substrate selectivity. For comparison, a substrate selectivity of only 55:45 was observed with the standard Wilkinson catalyst (**S4** reacts only 1.2 times faster than **S2**). Preferential substrate inclusion by the CD cavity, as demonstrated by the decrease in selectivity upon addition of the competitive guest *p*-xylene to the reaction mixture, was invoked for this remarkable product distribution.



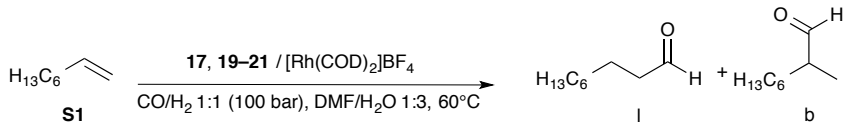
Scheme 7. Synthesis of diphosphines **17**-**21**.

The CD cavity in diphosphine **17** is also responsible for the high chemoselectivity observed in the rhodium (I)- and platinum (II)-catalysed reductions of halo-nitro aromatic compounds under organic solvent-free biphasic conditions (Scheme 8).[33] The complexes resulting from the reaction of **17** with either **[**$PtCl_2(COD)$] or $[Rh(COD)_2]BF_4$ act as both phase transfer and transition metal catalysts in the reduction of 3,4-dichloronitrobenzene **S9** to amine **P9** (chemoselectivity: 99.5%). The same catalysts afforded **P10** in 99.5% selectivity upon reduction of chloronitrobenzene **S10**. In both cases, hardly any dehalogenation products were detected. Clearly, chemoselectivities are significantly improved when using ligand **17** instead of the water-soluble, but cavity-free TPPTS ligand (99.5 % *vs.* 90 % selectivity respectively, for the transformation of **S10c**). It seems that the formation of an inclusion complex between the substrate and the CD is essential for achieving such catalyst performances.



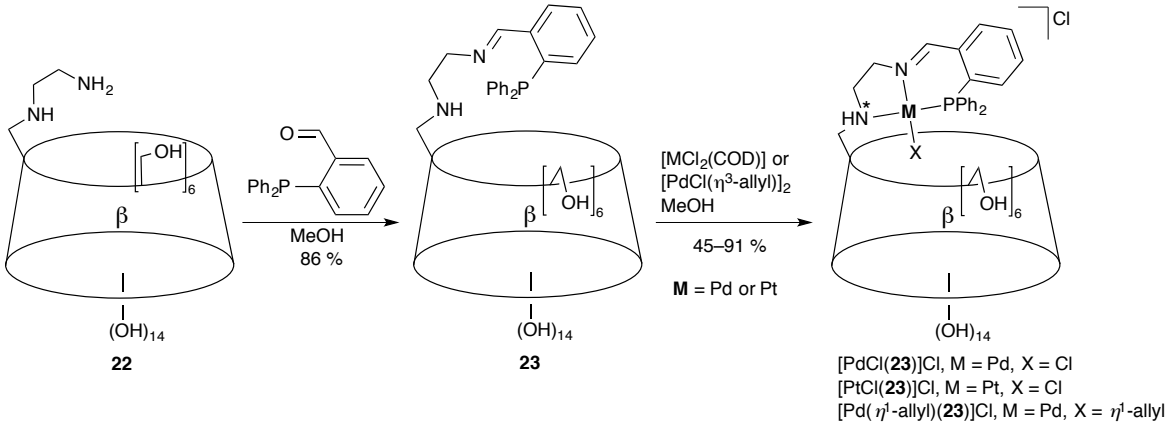
Scheme 8. Chemoselective metal catalysed reduction of 3,4-dichloronitrobenzene **S9** and chloronitrobenzene **S10**.

Diphosphines **17** and **19**–**21** were also used in the hydroformylation of oct-1-ene (**S1**) and other unreactive olefins again under biphasic conditions (Scheme 9). Although very robust and chemoselective (up to 99 % aldehydes with TON up to 3200), the highest l/b ratio was comparable to that observed with the standard Wilkinson catalyst (l/b = 3.2 vs. 2.8, respectivelly).[20a] The presence of a flexible coordinating arm probably prevents the cavity from having any significant impact on selectivity.



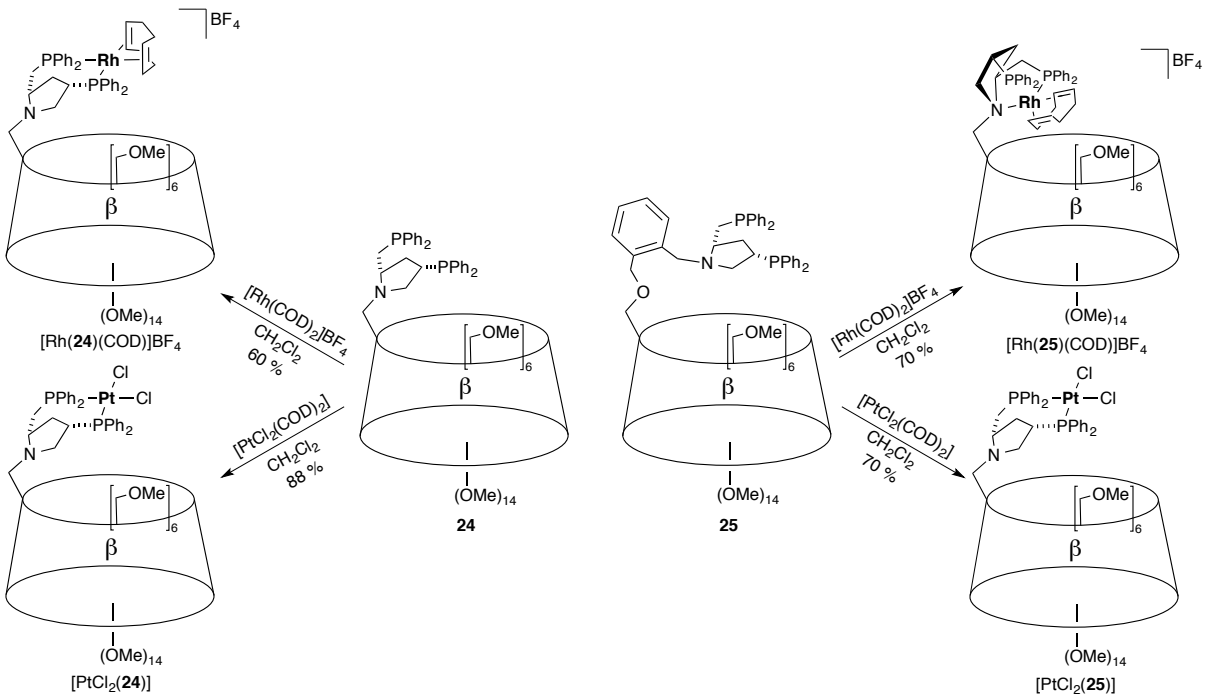
Scheme 9. Rhodium-catalysed hydroformylation of **S1**.

In 2001, Jia et al. reported the synthesis of the *P,N,N* tridentate ligand **23**, which was obtained by condensation of the diamino-β-CD **22** with 2-(diphenylphosphino)benzaldehyde (Scheme 10). This ligand was used for the preparation of the Pd(II) and Pt(II) complexes [PdCl(**23**)]Cl, [PtCl(**23**)]Cl and [Pd(η^1-allyl)(**23**)]Cl.[34] In all chelate complexes, the *N*H nitrogen becomes stereogenic upon complexation, which resulted in the formation of a 1:1 mixture of two diastereomers, as revealed by the presence of two close singlets in the corresponding $^{31}P\{^1H\}$ NMR spectrum.



Scheme 10. Synthesis of *P,N,N* tridentate ligand **23** and his complexes.

The chiral (2*S*,4*S*)-(−)-4-(diphenylphosphino)-2-(diphenylphosphinomethyl) pyrrolidine fragment could be successfully attached to a methylated β-CD derivative, leading to diphosphines in which the pyrrolidine is either directly connected to the CD C-6 carbon (**24**) or separated from the CD unit by an *o*-xylyl spacer (**25**) (Scheme 11). The two phosphines were used for the preparation of chelate complexes [Rh(**24**)(COD)]BF_4, [$PtCl_2$(**24**)] and [Rh(**25**)(COD)]BF_4, [$PtCl_2$(**25**)].[35] Note that ligand **25** behaves as a tridentate *P,N,N* ligand in the five-coordinate [Rh(**25**)(COD)]BF_4 complex unlike analogous **24**, which behaves as a chelating diphosphine in [Rh(**24**)(COD)]BF_4, probably because of steric congestion between the CD platform and the coordinating unit. Despite the potential both rhodium complexes may have in asymmetric hydrogenation, no catalytic experiments have ever been reported.



Scheme 11. Diphosphines **24** and **25** and their rhodium and platinum complexes.

I. 3. Polysubstituted CDs

Exact positioning of the metal as close as possible to the CD interior appears to be essential for forcing the metal centre to interact with the CD chiral wall, so as to fully exploit the potential CD cavities have in terms of metal protection, chiral induction and hemilabile behaviour. Such a goal can be achieved by creating two or more anchor points on the macrocyclic structure, which can then be used for grafting either pendant or capping P(III) handles. In the former, close proximity between the metal centre and the CD interior is ensured by the propensity of the polydentate ligands to form large chelate rings directly above the cavity, whereas in the latter, it is the inward-pointing nature of the donor atoms that forces the metal centre to stay in close proximity to the CD cavity upon complexation.

I. 3. 1. CD multifunctionalisation

Differentiating hydroxyl groups in CDs, which is needed for the selective introduction of various P(III) units onto the macrocycle, has been thoroughly investigated over the last 20 years. Whereas D'Souza reported only a handful of moderate yielding methods for accessing multisusbtituted CD derivatives in his review of 1998,[12b] many different approaches have been developed since to get hold of gram-scale quantities of CD derivatives, most of them dealing with the introduction of two, three and four identical groups onto the CD primary face. However, some of these more modern methods, which have been recently reviewed,[36] have allowed to go a step further since access to tri and tetradifferenciated CDs (*i.e.* CD derivatives bearing three and four different substituents respectively) have also become

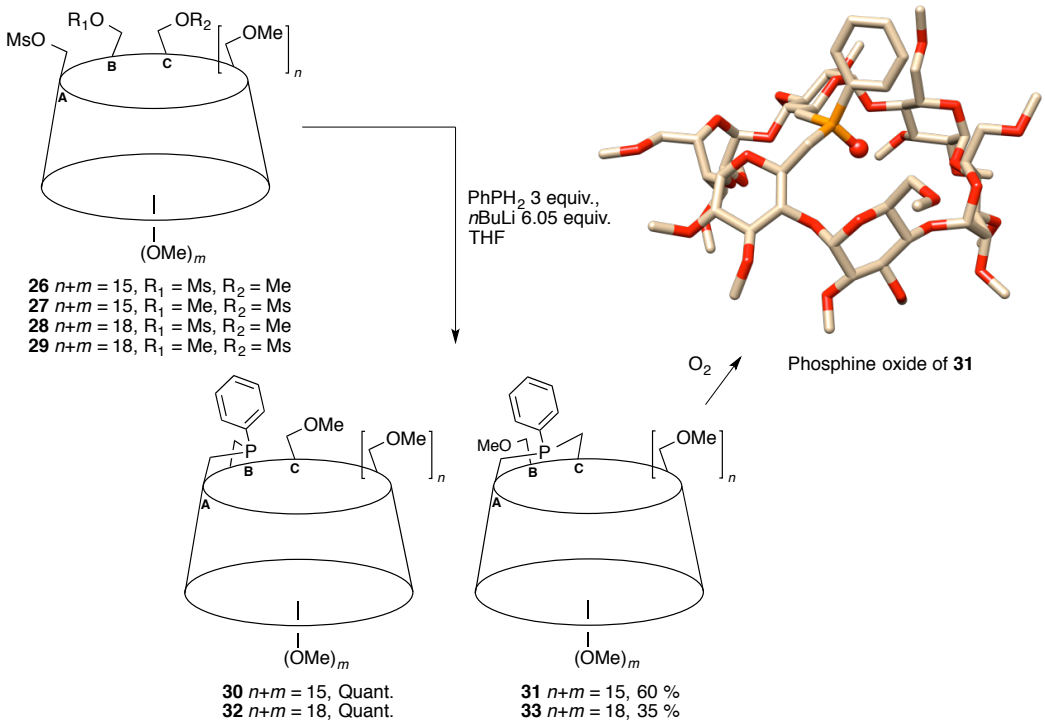
possible. Since no phosphorus-containing CDs multisubstituted at the secondary face have been so far prepared, only primary face derivatisation will be mentioned in the following. Since 1998, two main strategies have been implemented for achieving effective regioselective difunctionalisation:

i) The first one is based on the use of sterically hindered protecting groups (trityl and supertrityl), including bridging ones (bis(supertrityl)) groups, for promoting the formation of given multisubstituted species. Upon alkylation of the remaining hydroxyl groups, chromatographic separation of the various alkylated species can be achieved.[37] This reaction pathway, dubbed the "long" method, is classical in glycochemistry and allows the synthesis of most multisubstituted CDs, including challenging γ-CD derivatives;

ii) The second strategy also relies on steric hindrance but in a reverse sense. Starting from perbenzylated CDs, benzyl groups are surgically removed by adding precise amounts of DIBAL.[38] The observed high regioselectivity results from very specific steric interactions between the benzylated primary face and the bulky hydride reagent. Compared to the first one, this method is equally efficient for the α- and β-CD series and affords higher yields of a given regioisomer. However, it does not allow the synthesis of all isomers, notably A,B-difunctionalised CD derivatives. Noticeably, this strategy is also effective in the case of persilylated CD derivatives.[39]

I. 3. 2. Monodentate ligands

CD derivatives rigidly capped with a coordinating handle have found many applications in various fields of chemistry and particularly enzyme mimicry.[6, 40] This type of CDs are expected to maintain the metal centre as close as possible to the cavity entrance for optimal metal confinement. This is only possible if the lone pair of the coordinating atom is oriented toward the cavity centre. In this respect, the length of the capping binding unit as well as its rigidity are crucial for the metal centre to be ideally positioned with respect to the cavity.[41] In the case of phosphine ligands, Armspach and Matt achieved this goal by bridging two CD glucose units with a single P(III) atom. The first derivatives with a phosphorus lone pair pointing towards the cavity interior (**30**–**33**), were obtained by reaction of dilithium phenylphosphide (Li_2PPh) in THF with dimesylates **26**–**29**, respectively (Scheme 12).[37d, 42, 43a] Remarkably, the ring-closure reaction, which does not require high dilution, is stereospecific.



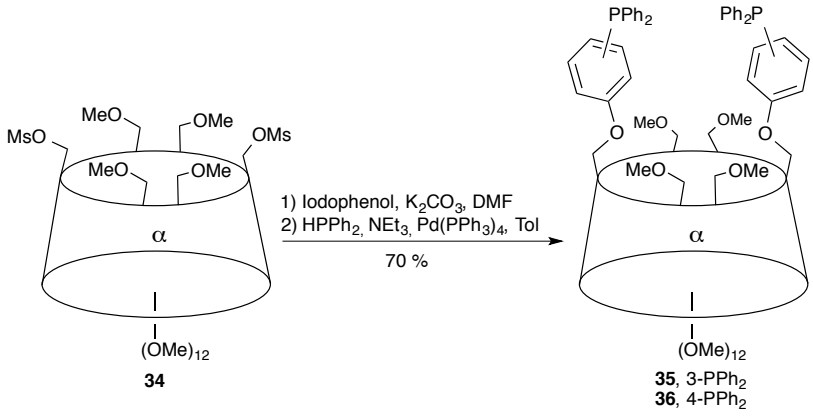
Scheme 12. Synthesis of capped CDs **30**–**33**. Ms = methanesulfonyl

Unsurprisingly, ligands **32** and **33** and the respective α-CD counterparts **30** and **31** form monophosphine complexes when opposed to metal complexes such as $[(PdCl(dmba)]_2$ or [AuCl(tht)].[22, 42-43] The "*endo*" orientation of the phosphorus atom was unambiguously established thanks to a 2D NMR ROESY experiment carried out on complex [PdCl(dmba)(**30**)], which showed strong through-space correlations between the two diastereotopic N*Me* groups and all primary methoxy protons. Further, the significant downfield shift experienced by the H-5^A proton is fully consistent with an encapsulation of the chloride atom within the CD.[14b] Although not as efficient as for **30** and **32**, the ring closure leading to **31** and **33** remains stereospecific. In the case of **31** and **33**, the presence of a very short "PPh" bridging unit between two *non*-neighbouring glucose moieties induces a strong deformation of the CD torus. This was revealed by the unusually wide chemical shift range in which the anomeric protons resonate and later confirmed by the molecular structure of oxidized **31**, which shows clearly that one of the glucose units (unit B) has undergone a dramatic conformational change upon capping from the standard $^4C_1$ chair conformation to a higher energy $^5S_1$ skew boat one. Despite the potential of the afforementioned ligands, neither coordination study nor catalytic experiments have, to this date, ever been reported.

I. 3. 3. Polydentate ligands

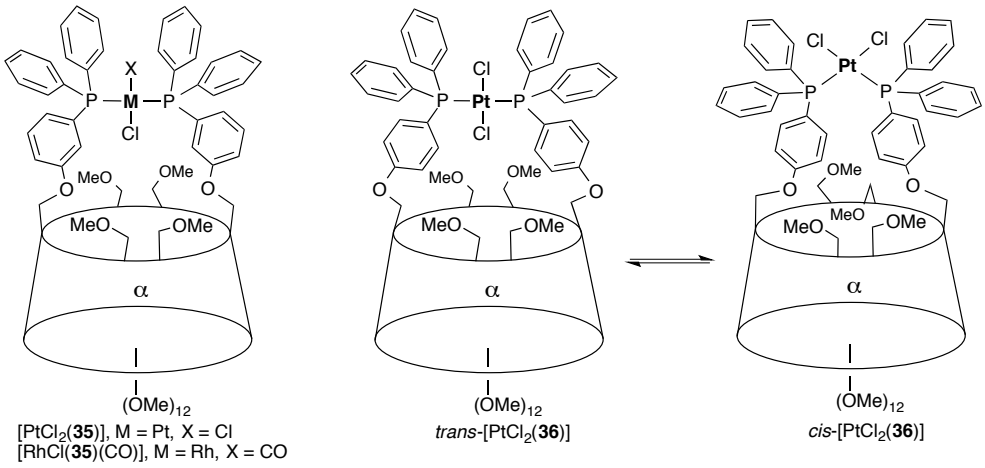
i) Phosphine ligands

The simplest way of bringing a metal centre as close as possible to the CD interior consists in using CDs equipped with two rigid coordinating arms. Upon metal complexation, these podands form large chelate rings in which the metal centre sits above the cavity entrance.[40] Bidentate triarylphosphines **35** and **36** were the first diphosphines of this type to be synthesised. Both were obtained from α-CD using a regioselective difunctionalisation procedure[37a], which allows the convenient introduction of two mesylate leaving groups onto diametrically opposed (A and D) glucose units.[44] Reacting the C_2-symmetric dimesylate **34** with either 3- or 4-iodophenol (Scheme 13) afforded iodoaryl ether compounds that produced respectively **35** and **36** in 70 % overall yields following a palladium-catalysed carbon–phosphorus cross coupling developed by Stelzer.[45]



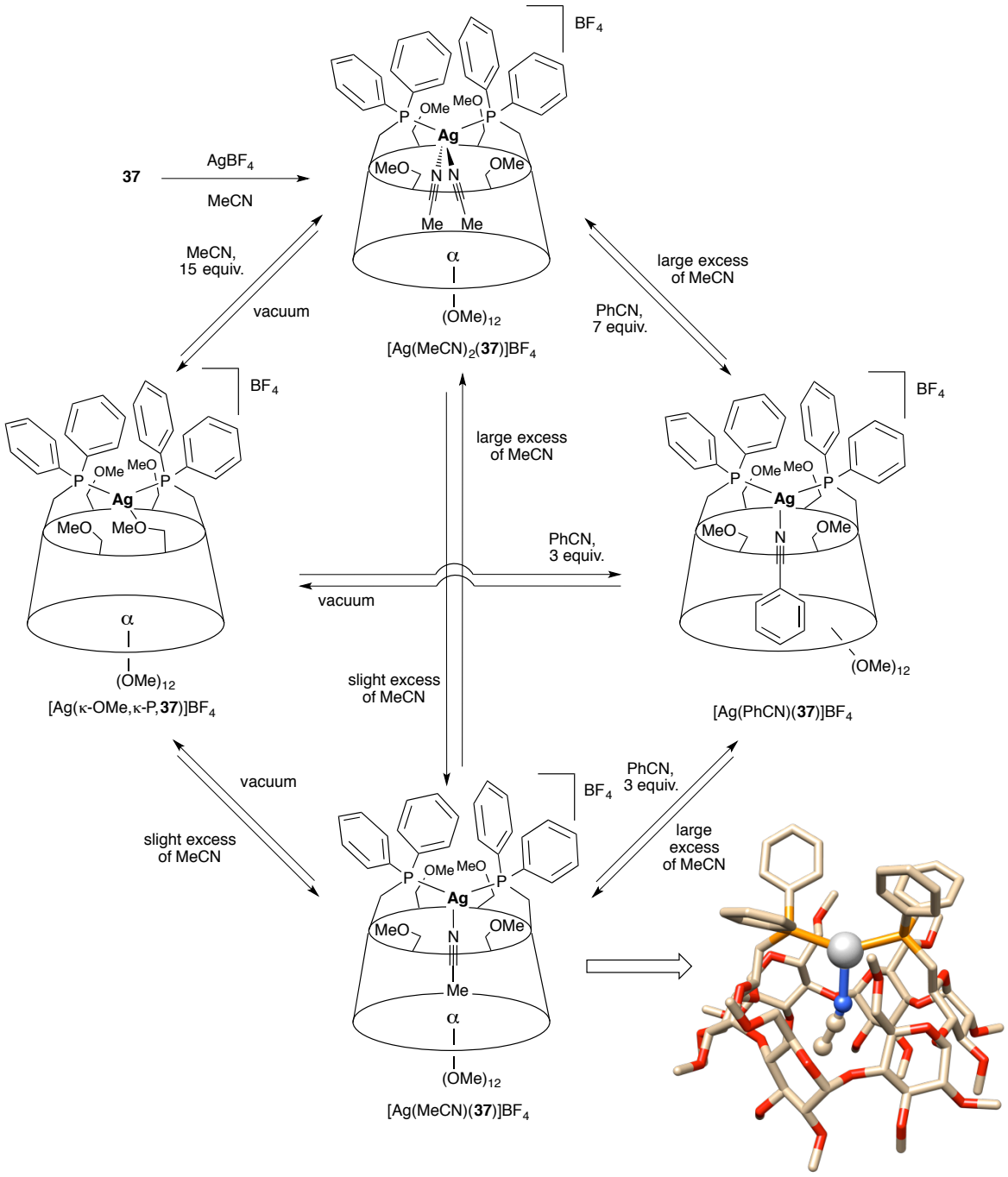
Scheme 13. Synthesis of bidentate ligands **35** and **36**. Ms = methanesulfonyl

Despite the 27-bond separation between the two donor atoms, **35** and **36** form quantitatively chelate complexes when opposed to a number of d^6, d^8 and d^{10} cations, even in the absence of high-dilution conditions. **35** appears to strongly favour *trans* chelation as exemplified by the exclusive formation of complexes *trans*-[RhCl(**35**)(CO)] and *trans*-[$PtCl_2$(**35**)] (Scheme 14). This is less true for **36**, which gives a rapidly interconverting mixture of both *trans*-[$PtCl_2$(**36**)] and *cis*-[$PtCl_2$(**36**)] chelate complexes, meaning that isolation of the individual isomers was not possible. Similarly, cationic chelate complexes [Au(**35**)]BF_4 and [Ag(**35**)]BF_4, which both display a linear geometry, were the only species formed after metal complexation. The difference of coordination properties between **35** and **36**, which differ from each other only by the aromatic substitution pattern, clearly underlines the fact that small structural changes in the CD ligand can have a major impact on its coordination mode.



Scheme 14. Coordination chemistry of **35** and **36**.

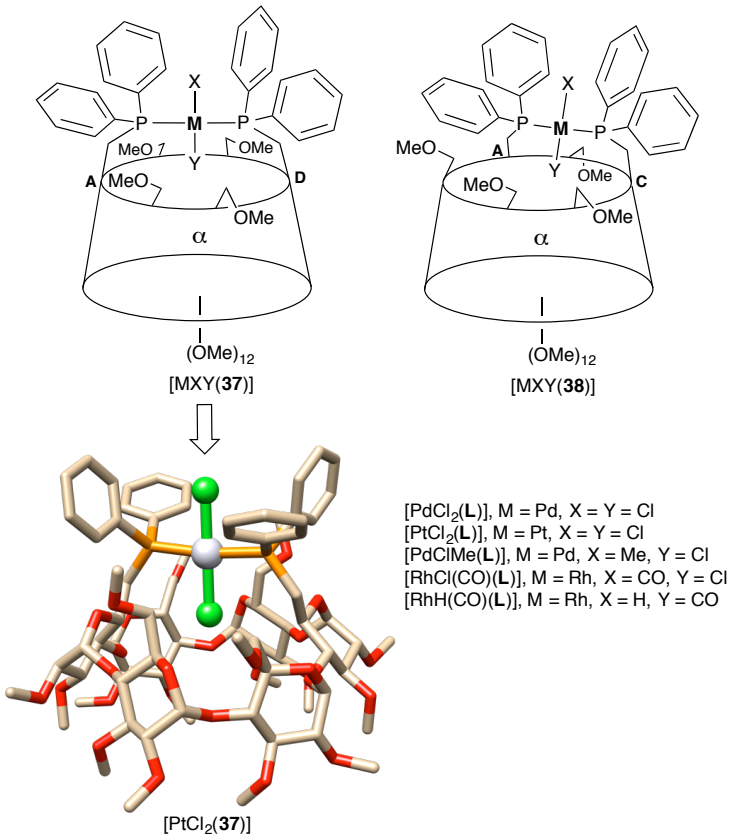
The complex *trans*-[RhCl(**35**)(CO)] catalyses the hydroformylation of oct-1-ene (**S1**) in a 6:4 mixture of H_2O and MeOH. The use of methanol is necessary because the complex is not soluble in pure water, but this solvent probably precludes the formation of a strong inclusion complex between the olefin and the CD host. This is reflected by the observed linear / branched aldehyde selectivity (l/b = 2.3), which is typical of hydroformylation tests carried out in organic media with Rh complexes of TPP.



Scheme 15. Diphosphine **37** as probe for nitrile ligand-exchange process.

In order to maximize the chances of interaction between the first coordination sphere of the metal and the CD walls, very short pendant phosphine groups were grafted onto the CD macrocycle. This was achieved by reacting either the C_2 symmetric dimesylate $6^A,6^D$-dimesylate-α-CD **34** or its regioisomeric counterpart $6^A,6^C$-dimesylate-α-CD **27** with an excess of "in situ" prepared $LiPPh_2$ at – 78° in THF.[46] When engaged in a chelate complex, the resulting diphosphines (**37** and **38**, respectively) are perfect for studying ligand-exchange processes taking place within the cyclodextrin core by NMR, the cavity interior being lined with many protons (H-3 and H-5).[47] Indeed, reaction of **37** with 1 equivalent of $AgBF_4$ in MeCN leads quantitatively to the unusual complex [Ag(**37**)$(MeCN)_2$]BF_4, which comprises

two MeCN ligands coordinated to the metal centre (Scheme 15). The presence of MeCN inside the cavity was inferred from ROESY cross-peaks between protons of coordinated MeCN and inner cavity H-3 and H-5 protons. On the other hand, only one molecule of the larger benzonitrile ligand fits in the cavity resulting in the exclusive formation of the trigonal complex [Ag(**37**)(PhCN)]BF_4, even in the presence of excess benzonitrile. Formation of the MeCN-free complex [Ag(κ-OMe,κ-P,**37**)]BF_4 was achieved by adding acetone, which is known to promote ligand-substitution reactions, prior to evaporation.



Scheme 16. *trans*-spanning behaviour of **37** and **38**.

With all four primary face methoxy groups behaving as hemilabile ligands, this complex shows fluxional behaviour at the ^{1}H NMR time scale. Each of them is involved in turn in the coordination of the silver cation. Unlike its AD counterpart, [Ag(κ-OMe, κ-P-**38**)]BF_4 displays a sharp ^{1}H NMR spectrum, suggesting non-fluxional ligand behaviour, probably because the methoxy group of glucose unit B is ideally positioned for coordination. It is noteworthy that all ligand exchange processes operating for **37** stand for **38**, except those involving the bis acetonitrile complex [Ag(**37**)$(MeCN)_2$]BF_4 which is not formed in the latter case.[46] Diphosphines **37** and **38** are perfectly suited for forming *trans*-chelate square-planar complexes with d^8 cations according to molecular models. In stark contrast with **36**, the only chelate complexes that are formed upon complexation have a trans geometry (*trans*-[$PdCl_2$(**37**)], [$PtCl_2$(**37**)], [$PdCl_2$(**38**)], and *trans*-[$PtCl_2$(**38**)]), although the formation of small amounts of oligomeric material was also detected (Scheme 16). With their short coordinating arms that force the metal centre to stay close to the CD mouth, diphosphines **37** and **38**

behave both as first and second coordination sphere ligands. Indeed, weak C-H•••Cl-M interactions force the M-Cl bond to stay inside the CD cavity in all chlorido complexes derived from **37** and **38**, including those having exogenous ligands different from chloride. Interestingly, chloride substitution with hydride in *trans*-[RhCl(CO)(**37**)] and *trans*-[RhCl(CO)(**38**)] causes the {X–Rh–CO} rod (with X = Cl or H) to rotate about its P•••P axle and leads to the confinement of the exogenous ligand of highest affinity for the cavity, in this case the CO ligand.

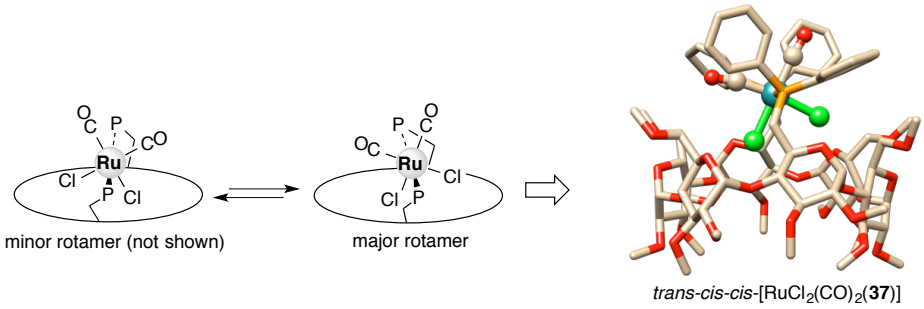
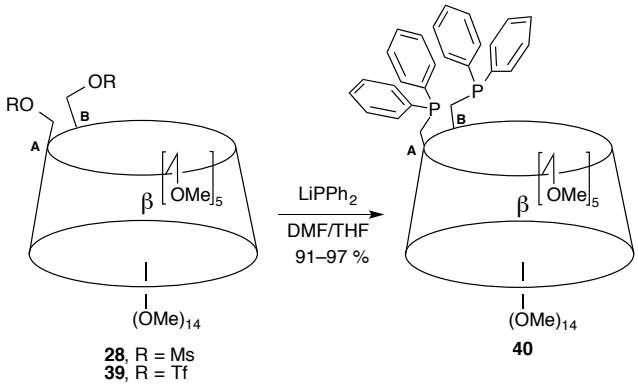


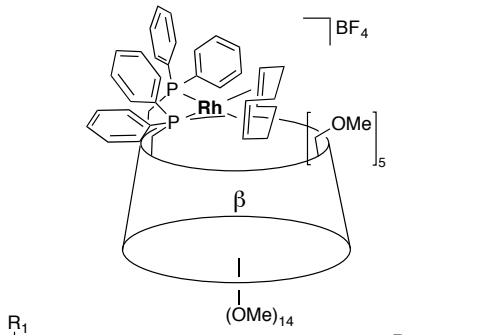
Figure 4. Rotamers of *trans-cis-cis*-[$RuCl_2(CO)_2$(**37**)].

In the case of the octahedral complex *trans-cis-cis*-[$RuCl_2(CO)_2$(**37**)], the cavity captures both chlorido ligands, each competing for the CD central position. This generates an exchange between two rotamers, each corresponding to a different orientation of the {$Ru(CO)_2Cl_2$} cross as revealed in the solid state by X-ray diffraction studies. In solution, this movement is fast at room temperature since both IR and ^{1}H NMR spectra of the complex reflect an apparent C_2-symmetry (Figure 4).



Scheme 17. Synthesis of diphosphine **40** built upon β-CD. Ms = methanesulfonyl, Tf = trifluoromethanesulfonate

Whereas **37** and **38** give rise solely to *trans*-chelate complexes, the analogous $6^A,6^B$-bis(diphenylphosphine) reported by Jia (**40**) behaves as an exclusive cis chelator when opposed to $[PtCl_2(COD)]$ or $[Rh(COD)_2]BF_4$.[48] Harsher reaction conditions or the use of a better leaving group than mesylate such as triflate are required to introduce two PPh_2 units on adjacent glucose units, probably because steric hindrance is more severe in **40** than in **37** and **38** (Scheme 17). Because of their spatial proximity, the two phosphorus atoms give rise to a strong through-space ^{31}P–^{31}P NMR coupling as revealed by a $^{31}P\{^1H\}$–$^{31}P\{^1H\}$ COSY experiment. Complex $[Rh(\mathbf{40})(COD)]BF_4$ was used in the rhodium-catalysed asymmetric hydrogenation of prochiral substrates (**S11**-**16**) and afforded up to 92 % *ee*. It is noteworthy that the best *ee* was obtained with dicarboxylic acid **S15**, which is capable of forming hydrogen bonds with some of the CD oxygen atoms (Scheme 18). This remarkable study constitutes the first example of metallocyclodextrins that give rise to high chiral induction without the presence of an additional auxiliary chiral group on the CD. However, the precise location of the metal centre with respect to the CD torus was not determined.

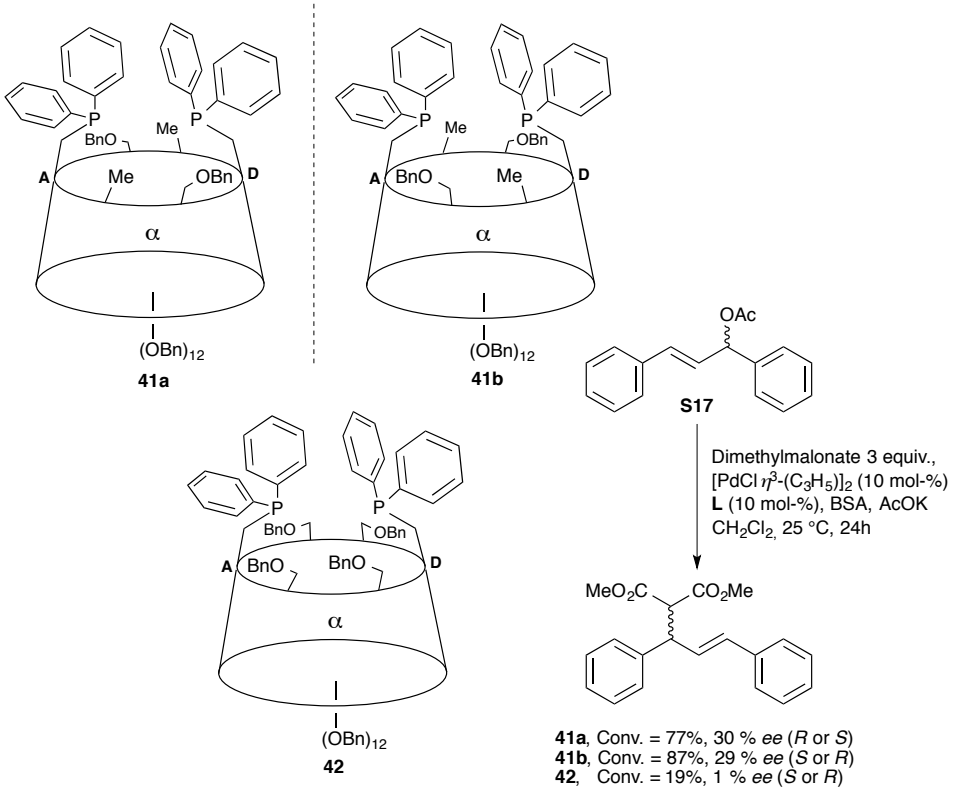


S11, R1 = Ph, R2 = COOH, R3 = NHCOOMe, *ee* 64 %
S12, R1 = Ph, R2 = COOMe, R3 = NHCOOMe, *ee* 61 %
S13, R1 = H, R2 = COOH, R3 = NHCOMe, *ee* 60 %
S14, R1 = H, R2 = COOMe, R3 = NHCOMe, *ee* 78 %
S15, **R1 = H, R2 = COOH, R3 = CH_2COOH, *ee* 92 %**
S16, R1 = H, R2 = COOMe, R3 = CH_2COOMe, *ee* 62 %

Scheme 18. Rhodium-catalysed hydrogenation using chiral $[Rh(\mathbf{40})(COD)]BF_4$ complex.

Introduction of two different substituents on an achiral conical cavitand will lower its symmetry point group and generate inherent chirality. This term was used for the first time by Böhmer to describe calixarenes with a non-symmetrical substitution pattern.[49] Strictly speaking, this definition cannot apply to CDs because their numerous stereogenic centres make them chiral molecules as such. However, CDs displaying opposed substitution patterns have been coined "pseudo" enantiomers, because each has a shape that is the mirror image of the other. Sollogoub et al. put this concept on trial by synthesising $6^A,6^D$-bis(diphenylphosphines) **41a**, **41b** and **42** from the corresponding benzylated dimesylates according to the method used for the preparation of methylated analogue **37**. In order to prove the pseudo-enantiomeric relationship between **41a** and **41b** (Scheme 19),[50] the two diphosphines as well as their "inherently achiral" analogue **42** were assessed in the palladium-catalysed asymmetric allylic alkylation of **S17** using dimethylmalonate as nucleophile. As

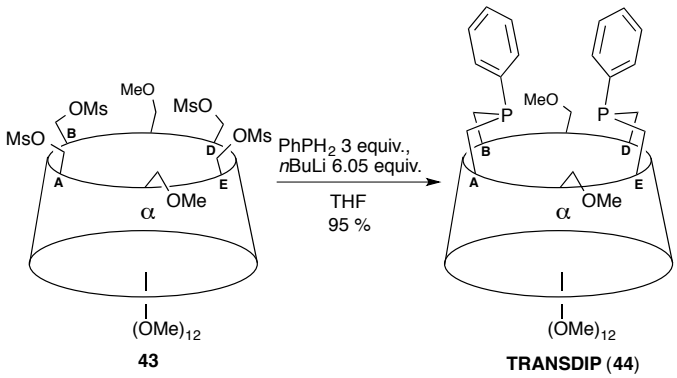
expected for a pair of "pseudo" enantiomers, **41a** and **41b** produced modest, but opposite enantioselectivities (*ee* = 30 %) whereas **42** did not induce any selectivity.[51] The "pseudo" enantiomeric complexes [(η^3-PhCH-CH-CHPh)Pd(**41a**/**41b**)]$^+$ were also assessed by circular dichroïsm and gave rise to opposite cotton effects in the region above 350 nm in keeping with enantiomeric environments around the metal.



Scheme 19. Diphosphines **41a**, **41b** and **42** tested in asymmetric Tsuji-Trost allylic alkylations.

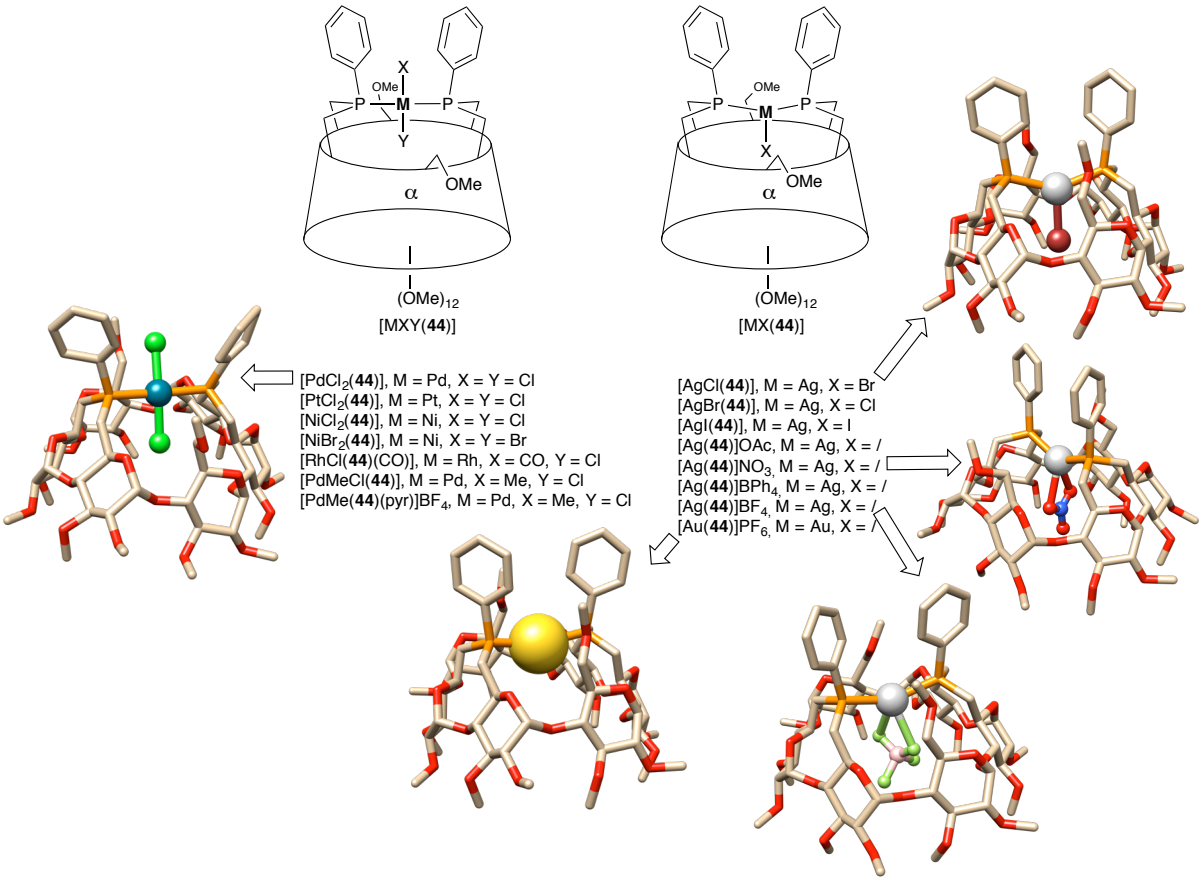
A much more rigid and preorganised diphosphine was prepared by introducing two short phenyl phosphinidene caps on the primary face of an α-CD derivative. Thus, tetramesylate **43**, which can be prepared in gram-scale quantities following a tetrafunctionalisation method devised by Armspach and Matt,[37b] reacts with dilithium phenylphosphide (Li_2PPh) in THF to give diphosphine **44**.[42] As for phosphines **30**-**33**, the ring-closure reaction is next to quantitative as well as being diastereospecific (Scheme 20). It is also regiospecific as only adjacent glucose units are being bridged. Unlike phosphines **30**-**33** that readily oxidize in air, **44** is much less prone to oxidation because the two lone pairs which are spatially quite close to each other within the CD cavity are shielded from the outside environment.[41a] Clear evidence for the inwardly pointing character of the phosphine units came from the existence of through space coupling between the equivalent phosphorus atoms and C-6^{C,F} atoms of non bridged glucose units. Diphosphine **44** was found to be the first authentic *trans*-spanning diphosphine since it forms neither bimetallic complexes nor polynuclear oligomers, but only *trans* chelate complexes when opposed to d^8 and d^{10}cations, unlike many diphosphines that have been sold as such.[52] For example, the 6^A,6^D-diphosphinated CD **37** cannot be considered as a genuine trans chelating ligand as it gives rise

to significant amount of polynuclear oligomeric material in addition to a *trans* chelate complex.



Scheme 20. Synthesis of TRANSDIP (**44**).

The exclusive *trans*-spanning character of **44** does not only originate from its rigid CD backbone combined with an ideal P,P separation but also from the inability of the small α-CD cavity to host more than one small exogenous ligand such as chlorido at a time.[53] For example, when reacted with $[PdCl_2(PhCN)_2]$, a trans chelate complex (*trans*-[$PdCl_2$(**44**)]) with a P-M-P angle of about 173° is being formed. When engaged in unsymmetrical halido complexes, **44** behaves in the same way as **37** and **38** since a halido ligand is always located inside the cavity and free rotation about the P–M–P axle occurs (Scheme 21).[41a] For example, *trans*-[PdMe(**44**)pyridine]BF_4 undergoes major conformational changes upon substituting pyridine with chloride, since the methyl group originally nested in the cavity is clearly located outside in the resulting complex ([PdMeCl(**44**)]). Even if **44** is perfect for forming trans chelate square planar complexes, it is flexible enough to form silver complexes [Ag(**44**)]X (X = Cl, Br, I, OAc, NO_3, BF_4 or BPh_4) with deformed trigonal and tetrahedral geometries.[14d, 54] In the solid state, all silver complexes adopt a usually large P-M-P angle ranging from 139° for [Ag(**44**)]NO_3 to 152° for [Ag(**44**)]BF_4. Anions that are compatible with the cavity size-wise such as Cl^-, Br^-, NO_3^- and BF_4^- form weak, non covalent bonds with inner-cavity H-5 protons, in addition to coordination bonds with silver. For those that have low affinity for silver such as BF_4^-, the metallocyclodextrin behaves as a true ditopic receptor since here, anion encapsulation is a direct result of the synergistic binding of the anion to both metal and cavity inner-wall. Remarkably, the $^{31}P\{^1H\}$ NMR chemical shifts of the P(III) atoms are very sensitive to the nature of the included anion.



Scheme 21. Coordination properties of **44** towards late transition metals.

The natural bite angle of diphosphine **44** is likely to be somewhat smaller than 180°, since for complex [Au(**44**)]PF_6,[55] which lacks cavity-interacting exogenous ligands, a slight deviation from linearity was observed in the solid state (P-M-P : 164°). Note that in this complex the two P-Au vectors are directed toward the cavity centre. The important variations in terms of P–M–P angles may originate from the ability or not of the CD torus to serve as a second coordination sphere. Depending on the strength of the weak interactions at work,[47] the metal centre sits more or less deeply in the cavity, which in turn affects the P-M-P angle (Figure 5).[14d, 54]

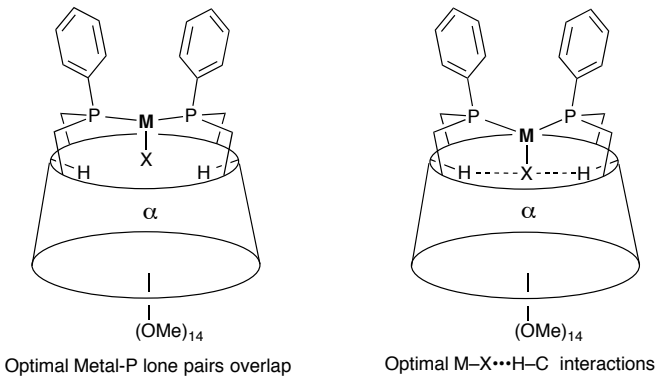
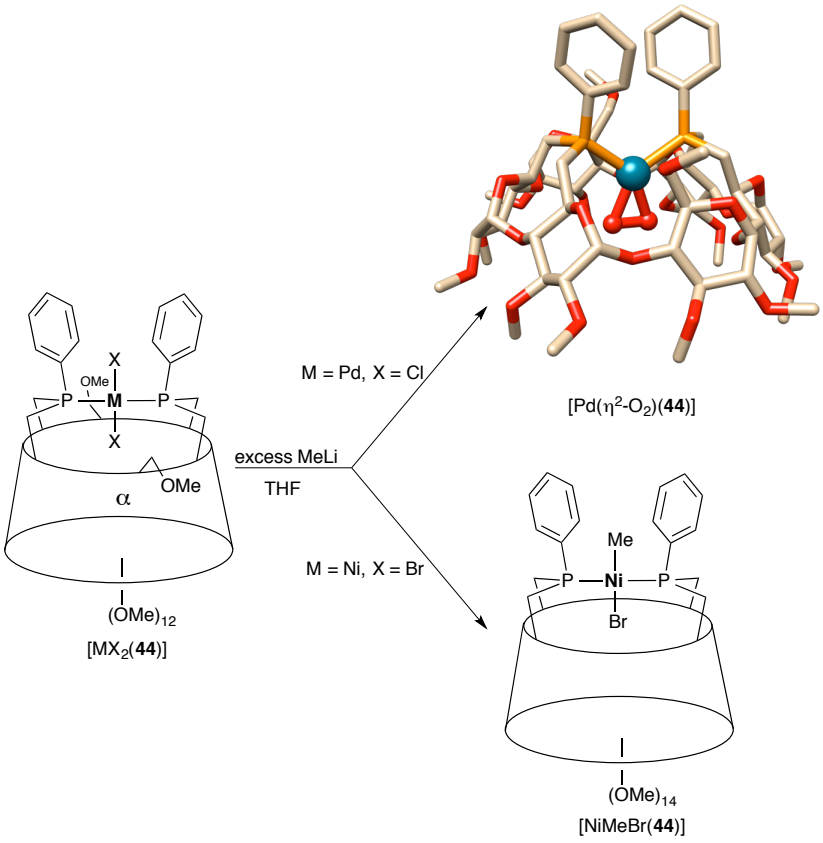


Figure 5. Back and forth movement of the metal into the CD, affecting the P-M-P angle.

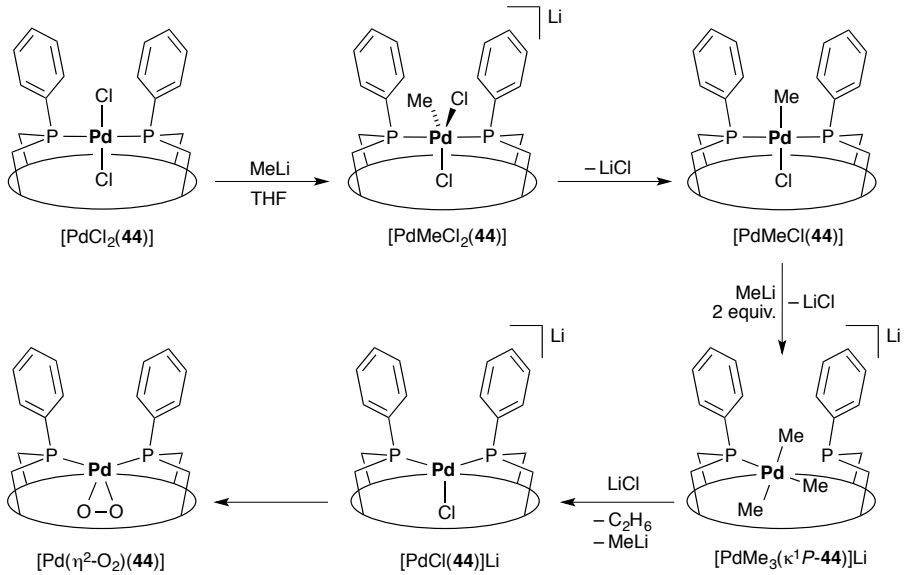
Being a trans spanning ligand, **44** should not be able to form organometallic complexes capable of mediating the formation of a carbon-carbon bond, since *cis*-coordination of the groups that are being coupled is required.[56] To test this hypothesis, which has been confirmed with other *trans*-spanning diphosphines,[52b] a number of Ni and Pd complexes known to catalyse such transformations have been prepared. Reaction of [$NiBr_2$(**44**)] with MeLi, even in excess, leads quantitatively to the exceptionally stable monomethylated complex [NiMeBr(**44**)], but not to the expected dimethyl species[41a], probably because the CD provides adequate steric protection against nucleophilic attack by MeLi. In the same vein, reaction of [$PdCl_2$(**44**)] with one equivalent of MeLi results quantitatively in the formation of the expected monomethylated complex ([PdMeCl(**44**)]). However, when [$PdCl_2$(**44**)] is reacted with *excess* MeLi (3 equiv. or more), a cascade of transformations leading to the production of ethane occurs (Scheme 22)[57] in stark contrast with other *trans*-spanning diphosphines, which give very stable trans chelate dimethylpalladium complexes.[56a, 58]



Scheme 22. Alkylation of [$NiBr_2$(**44**)] and [$PdCl_2$(**44**)] with excess MeLi.

Once again, the inner-cavity protons were used as NMR probes for exploring the different organometallic processes at work.[47] Thanks to a series of low temperature 2D NMR experiments, the mechanisms of the whole set of reactions could be established (Scheme 23). First, addition of 1 equivalent of MeLi to [$PdCl_2$(**44**)] leads quantitatively to [PdMeCl(**44**)] via a five coordinate trigonal bipyramidal intermediate [$PdMeCl_2$(**44**)] which precipitates out of C_6D_6, allowing its purification and spectroscopic characterization. Complex [PdMeCl(**44**)]

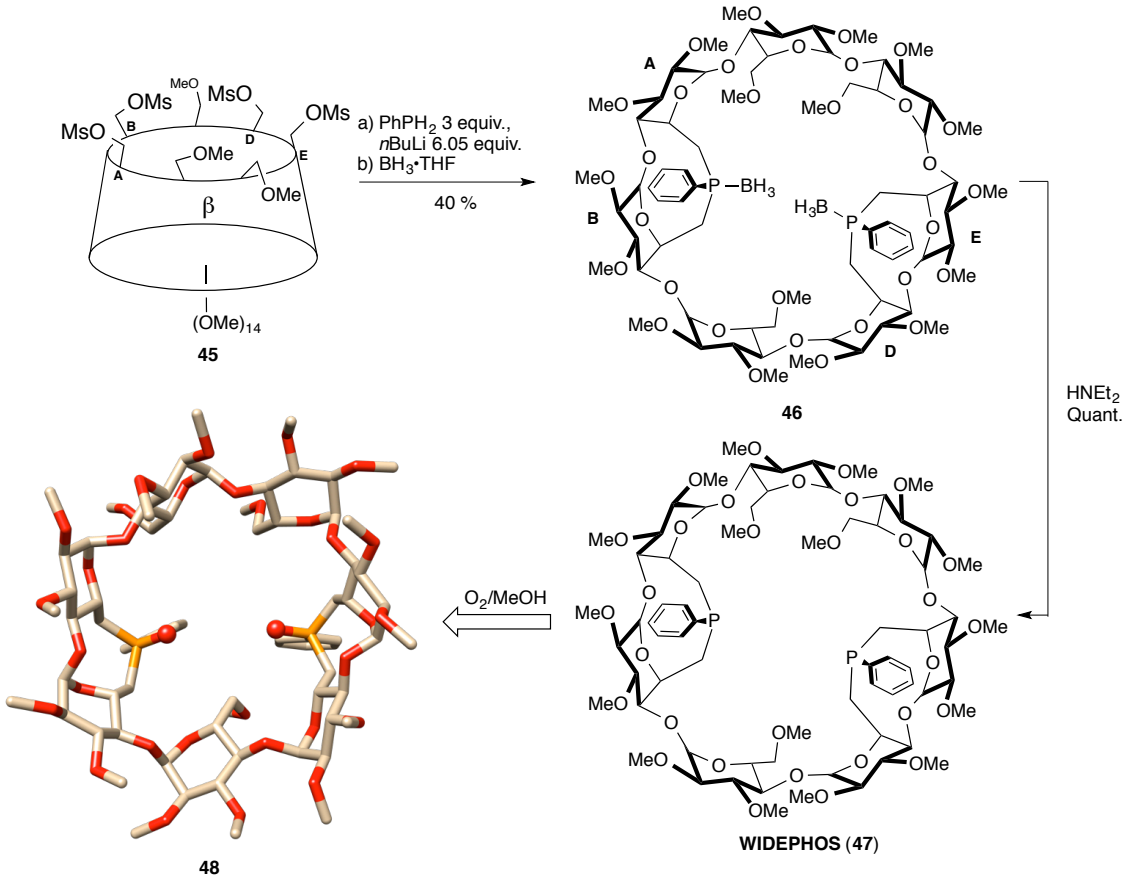
reacts with two extra equivalents of MeLi at –40 °C, to give [$PdMe_3(\kappa^1P$-**44**)]Li, in which one phosphorus atom is dissociated. Because this transient species have methyl groups that are disposed *cis* to each other, reductive elimination is allowed in this case and takes place at room temperature to afford ethane, together with the Amatore-Jutand-type[59] Pd^0 complex [PdCl(**44**)]Li.[60] The latter is easily oxidized by air, affording peroxo complex [Pd(η-O_2)(**44**)],[61] the molecular structure of which constitutes the first example of a structurally-characterized metallo-cavitand containing a {M(η^2-O_2)} unit. The P-M-P angle is the smallest (111.5°) for a complex derived from *trans* chelating **44**. It is however more in line with a trigonal geometry rather than a square planar one and is significantly larger than that of the only other reported [Pd(η^2-O_2)(PP)] chelate complex (104.5°).[62]



Scheme 23. Reaction pathway leading to the production of ethane from [$PdCl_2$(**44**)] and the formation of peroxo complex [Pd(η^2-O_2)(**44**)].

Despite being trans chelates, nickel complexes such as [$NiCl_2$(**44**)], [$NiBr_2$(**44**)], [NiMeBr(**44**)] and were found to be highly active in α-olefin oligomerisation[41a] after activation with methylaluminoxane (MAO). In the case of ethylene and for all catalysts, activity and selectivity to C-4 (dimerization) lie in the range found for [$NiBr_2(Ph_2PCH_2CH_2PPh_2)$]/MAO. This means that the catalytic reaction is not affected by steric crowding, probably because it takes place outside the CD hollow. The major difference between the TRANSDIP-based catalyst and other diphosphane systems is the high stability of the former. Unlike other diphosphine nickel catalysts, which undergo rapid desactivation, the TRANSDIP-based catalyst was found to be active over a prolonged period with a TOF reaching its maximum value after an hour, whereupon it decreases very slowly. As far as propylene is concerned, the observed activity was about eightfold lower than that of the reference system, probably because of greater crowding about the nickel centre.[63] Since the formation of a C-C bond requires a *cis* arrangement of the metal-bonded groups undergoing migratory insertion,[56] it is likely that one of the two phosphorus atoms dissociates during the

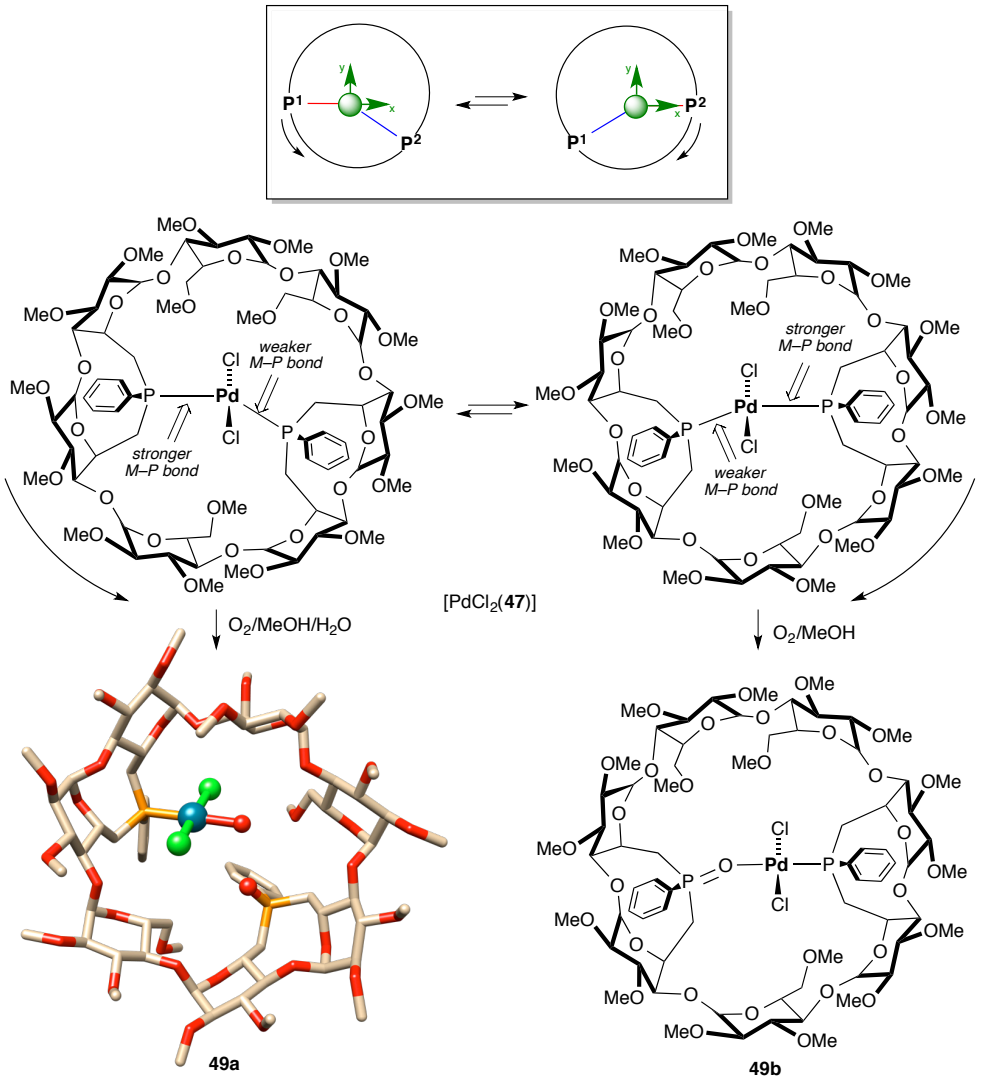
course of the catalytic cycle as previously described for the formation of [$PdMe_3(\eta^1$-**44**)]Li.[57] This is in stark contrast with the initially proposed mechanism.[41a]



Scheme 24. Synthesis of **WIDEPHOS** (**47**), starting from tetramesylate **45**.

A larger analogue of TRANSDIP, coined WIDEPHOS (**47**), was recently synthesised from β-CD.[37d] Similarly to HUGPHOS and TRANSDIP ligands, the synthesis of **47** relies on the regio- and stereospecific bridging of adjacent mesylated glucose units of $6^A,6^B,6^D,6^E$-tetramesylate β-CD **45** with excess Li_2PPh in THF. In contrast with TRANSDIP, the double-capping reaction is far from being quantitative (40 %) as significant amounts of elimination products are being formed. For purification purposes, **47** had to be protected with BH_3•THF to afford the non-oxidable phosphine-borane adduct **46,** which after purification could be deprotected with $HNEt_2$ (Scheme 24). Proof that the double-capping reaction had occurred was inferred from an X-ray diffraction study on the oxidised ligand **48**. Unlike TRANSDIP, **47** behaves as an imperfect trans-chelator because the P•••P separation is rather large (6.91Å) and the two phosphorus lone pairs do not face each other but are at an angle much lower than 180° (151.8° according to the molecular structure of **48**).[14e] This means that in all *trans*-chelate complexes of WIDEPHOS, whether *trans* square planar ([$PtCl_2$(**47**)], [$PdCl_2$(**47**)] and [RhCl(**47**)(CO)]), or linear ([Au(**47**)]PF_6), overlapping between metal and phosphorus orbitals is not optimal. Such constraints on the metal first coordination sphere manifests itself by a balance wheel-like oscillation of the macrocyclic ligand around the coordinated metal during which the two P lone pairs alternately maximize their overlap with the metal $d_{x^2-y^2}$ orbital.

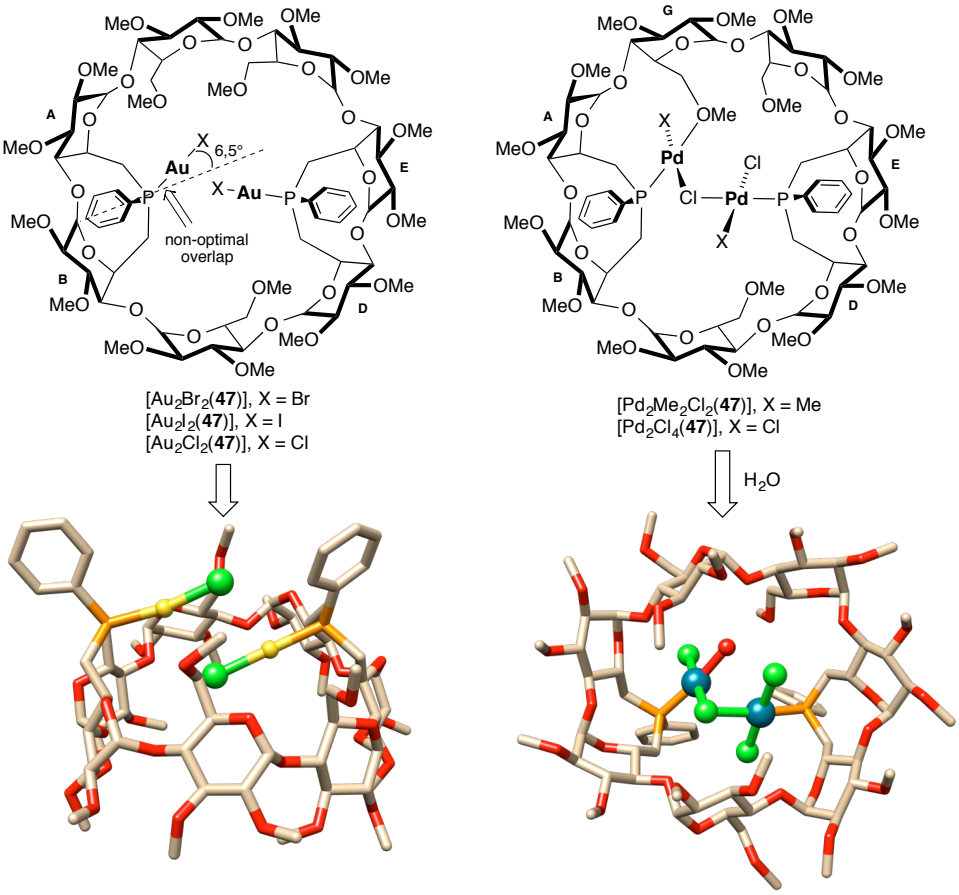
This motion, christened oschelation, does not involve any M-P bond dissociation (Scheme 25).[64] Not surprisingly, the complexes are rather unstable and sensitive to oxidation. For example, [$PdCl_2$(**47**)] gets partially oxidized by air in methanol to afford an equimolar mixture of **49a** and **49b**. In each compound, one of the two P-metal bonds has been cleaved and one phosphorus atom oxidized.



Scheme 25. Balance wheel movement of WIDEPHOS in [$PdCl_2$(**47**)] (view along the CD axis) and mono-oxidised complexes **49a** and **49b**. The green arrows in the top drawing indicate the orientation of the $d_{x^2-y^2}$ metal orbital involved in the two M–P bonds.

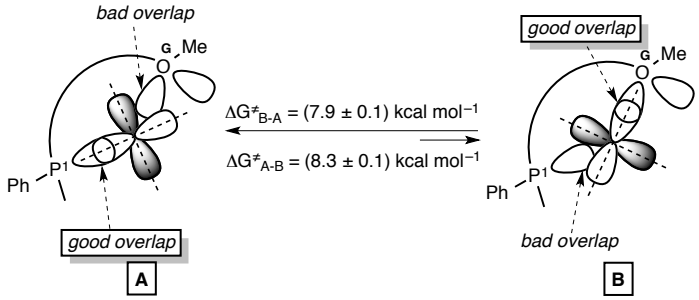
While a genuine *trans*-chelator like TRANSDIP only binds one metal centre at a time, WIDEPHOS is capable of accommodating up to two metal centres.[43b] Bimetallic complexes are ubiquitous in catalysis and molecular recognition[65], but the confinement of two metal centres within a molecular cavity,[66] as much as diphosphines designed to bring two metal centres close together are a rare occurrence.[52b, 67] Because of the unique location of the two P(III) donor atoms within the rigid macrocyclic framework, the binding of one metal centre strongly influences the coordination behaviour of the second donor atom in dinuclear complexes of WIDEPHOS. For example, one of the two {P-Au-Cl} fragments in

[Au_2Cl_2(**47**)] is coordinated in the same way as in the unconstrained monophosphine complex [AuCl(**32**)] while the coordination sphere of the second one is significantly disturbed by the presence of the first metal centre. The same holds true for other halido complexes such as [Au_2Br_2(**47**)] and [Au_2I_2(**47**)] (Scheme 26). The molecular structure of [Au_2Cl_2(**47**)] clearly shows non-optimal coordination of one {AuCl} unit to the P(1) atom (bridging the A and B glucose units).



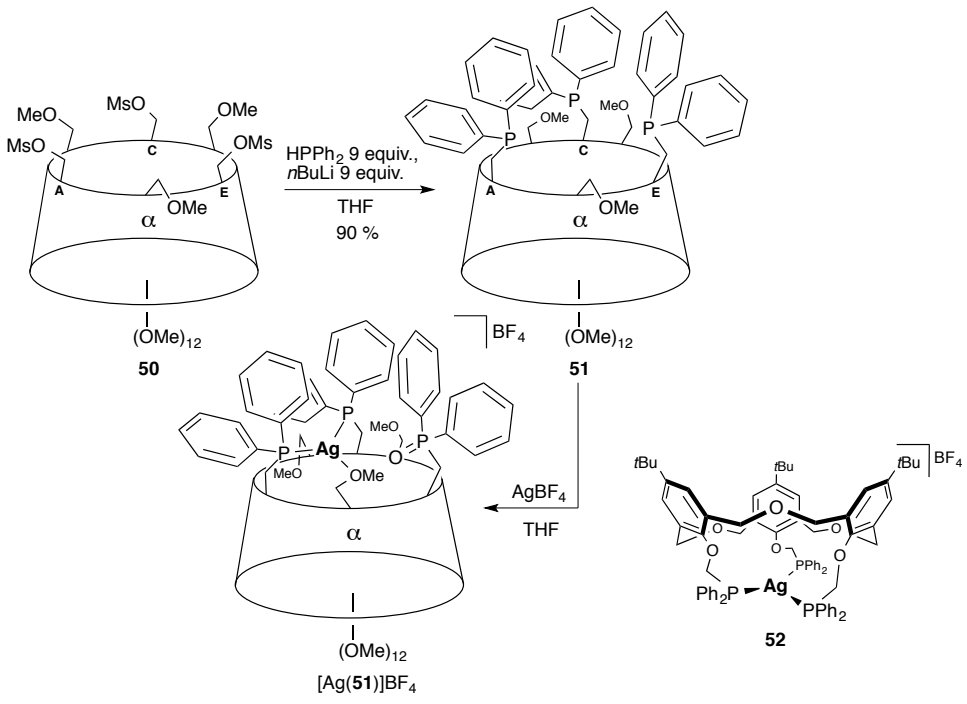
Scheme 26. Dinuclear complexes [Au_2X_2(**47**)] and [$Pd_2X_2Cl_2$(**47**)].

Ligand **47** affords quantitatively bridged dinuclear palladium(II) complexes ([Pd_2Cl_4(**47**)] and [$Pd_2Me_2Cl_2$(**47**)], respectively) when reacted with two equivalents of [$PdCl_2(PhCN)_2$] or [PdMeCl(COD)] (Scheme 28).[43b] Because of its rigidity and the steric crowding generated by the cavity, WIDEPHOS cannot adapt to the flat- or roof-like structures usually expected for a {$Pd_2X_2Cl_2$} motive and instead, affords complexes in which two square planar palladium metal centres are linked by a single μ-chlorido bridge. These complexes also display fluxional behaviour as a result of oschelation, but in this case, two different types of donor atoms are involved in the dynamic process, namely the 6^A,6^B-P(III) and the 6-MeO^G atoms. Unlike the mononuclear oschelate complexes mentioned previously, the two equilibrating species associated with [Pd_2Cl_4(**47**)] are not present in equal amounts (Scheme 27). No catalytic reactions involving **47** have been reported to date.



Scheme 27. Equilibrium between species **A** and **B** taking place in the dinuclear complex [Pd_2Cl_4(**47**)].

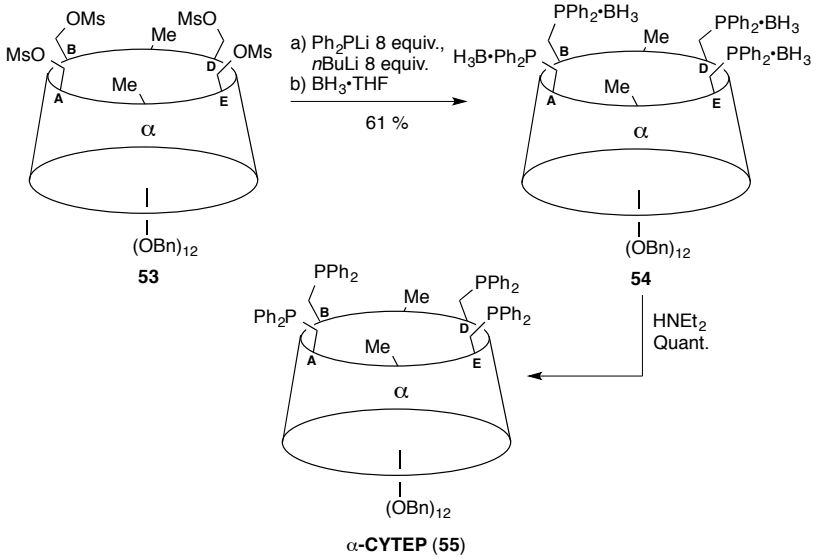
Triphosphine **51** was synthesised from **50** in the same way as **37** and **38** (Scheme 28).[22] This ligand constitutes the first example of a C_3 symmetric triphosphine built on a macrocyclic platform. Unlike the related (C_{3v}-symmetrical) hexahomotrioxacalix[3]arene-based triphosphine **52**,[68] the three phosphorus atoms of which can bind an Ag(I) metal centre simultaneously, **51** act as a bidentate chelator toward $AgBF_4$, the non coordinated sidearm being readily oxidized in air. Such coordination mode is probably imposed by the rigid α-CD backbone, which is not flexible enough for the third donor atom to bind the metal centre. **51** was assessed in the rhodium-catalysed hydroformylation of oct-1-ene (**S1**). Catalyst activity turned out to be low (TOF = 10) and the l/b ratio (2.0) unexceptional.



Scheme 28. Synthesis and coordination properties of triphosphines **51**.

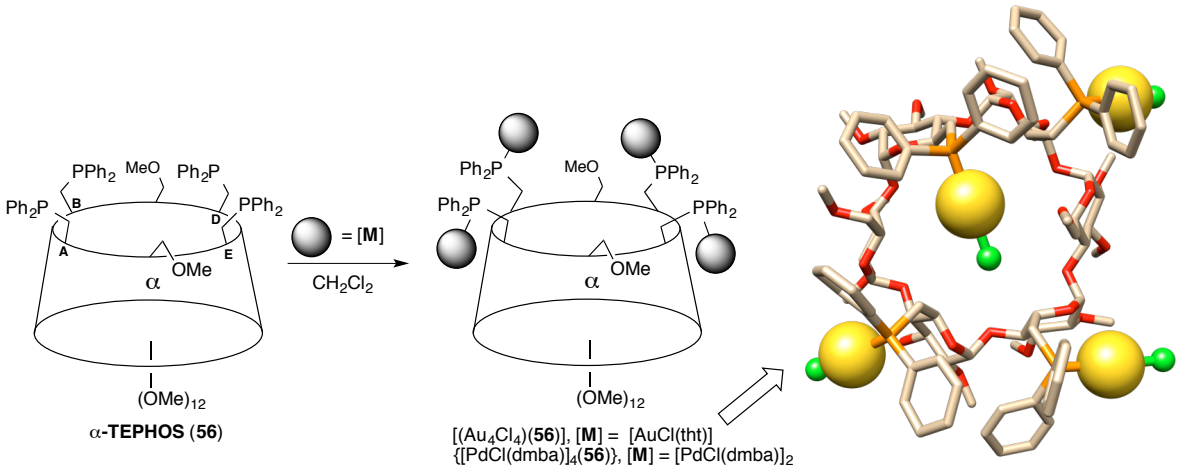
While the use of ligands that promote the formation of singly phosphane ligated complexes are highly beneficial in carbon-carbon bond forming reactions (*vide supra*),[69] polyphosphines such as Doucet's and Santelli's TEDICYP, are also known to exhibit exceptional turn-over numbers (TONs) in the same type of reactions, notably in Suzuki-

Miyaura coupling.[70] This discovery prompted Sollogoub et al. to design an analogous tetraphosphine (**55**), but built on a benzylated CD platform (Scheme 29).[38d, 71] This ligand, coined α-CYTEP,[72] was prepared from tetramesylate **53** in the same way as **37**, **38**, and **50**, but required a borane protection/deprotection sequence for purification purposes.[37b] Upon reaction with 0.5 equivalent of $[PdCl(\eta^3\text{-allyl})]_2$, **55** afforded a fluxional complex, in which all P(III) atoms compete for Pd coordination. The catalytic system $[Pd(\eta^3\text{-allyl})(\alpha\text{-CYTEP})]BF_4$ displayed modest activity in the coupling of phenyl boronic acid (**S19**) with activated *para*-bromoacetophenone (**S20**) at standard Pd/substrate ratios (TOF = 6, TON = 1000, 1 day, Pd/S = 1.10^{-3} or 0.1 mol %). However, the catalytic system led to exceptionally high TOF and TON values at very low Pd/substrate ratio and for prolonged reaction times (TOF = 3.4×10^{11}, TON = 1.0×10^{9}, 14 days, Pd/S = 1.10^{-12}). Compared to free $[PdCl(\eta^3\text{-allyl})]_2$, the $[Pd(\eta^3\text{-allyl})(\alpha\text{-CYTEP})]$ complex led to a 3.4 fold increase of both TOF and TON. This study exemplifies the fact that both metal confinement and multiple dynamic binding of the metal by P(III) donor atoms can act together to stabilize the catalytic active species.



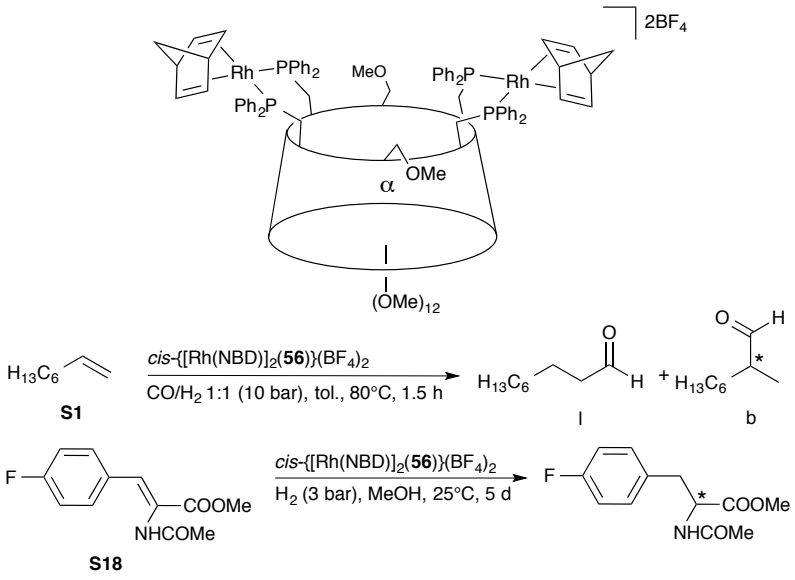
Scheme 29. Synthesis of **α-CYTEP** (**55**).

A few years earlier, the analogous C_2 symmetric tetraphosphine **56** (α-TEPHOS) was synthesised from tetramesylate **43** in the same way as **55**. It forms tetranuclear complexes {[PdCl(dmba)]$_4$(**56**)} and [(AuCl)$_4$(**56**)] when respectively opposed to 2 equivalents of [(PdCl(dmba)]$_2$ and 4 equivalents of [AuCl(tht)] (Scheme 30).[73] Interestingly, [(AuCl)$_4$(**56**)] has C_1 symmetry in the solid state, one of the P-Au-Cl rod being included in the CD cavity while the three others are clearly located outside. Because this complex has an average C_2 symmetry on the NMR time scale at a temperature as low as –80 °C, a fast motion in which all four P-Au-Cl units occupy alternatively the centre of the macrocycle occurs.



Scheme 30. Coordination chemistry of **α-TEPHOS** (**56**).

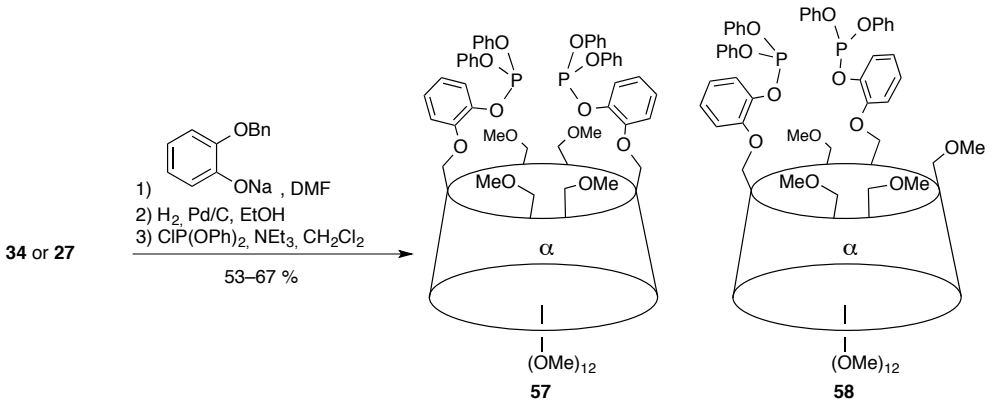
Reaction of **56** with neutral $[PtCl_2(COD)]$ afforded a mixture of chelate and oligomeric complexes that could not be separated. However, when opposed to cationic $[Rh(NBD)(THF)_2]BF_4$, α-TEPHOS formed the dinuclear complex *cis*-$\{[Rh(NBD)]_2$(**56**)$\}(BF_4)_2$ in 66 % yield. The double chelation is regiospecific since only adjacent phosphinated glucose units are being bridged (Scheme 31). *cis*-$\{[Rh(NBD)]_2$(**56**)$\}(BF_4)_2$ was assessed in both hydroformylation of oct-1-ene (**S1**) (l/b = 3.2) and asymmetric hydrogenation of prochiral olefins (**S18**) (up to 25 % *ee)* but the observed selectivities are modest and catalyst activity low as a result of severe steric crowding around the metal centres.[74]



Scheme 31. Asymmetric hydrogenation of dimethyl itaconate and asymmetric hydroformylation of oct-1-ene with *cis*-$\{[Rh(NBD)]_2$(**56**)$\}(BF_4)_2$.

ii) Other P(III) ligands

Like diphosphines **35** and **36**, diphosphites **57** and **58** have their P(III) donor atoms well away from the cavity. They constitute the first phosphite-type ligand derived from a CD.[75] Their synthesis involved nucleophilic substitution of dimesylates **34** or **27** with sodium 2-(benzyloxy)phenate, followed by hydrogenolysis of the resulting benzyl ethers (H_2, Pd/C) and reaction with chlorodiphenylphosphite (Scheme 32).



Scheme 32. Synthesis of diphosphite **57** and **58**.

Unlike diphosphines **35** and **36**, diphosphites **57** and **58** form chelate complexes only with highly reactive cationic metal precursors such as $AgBF_4$ or $[Rh(NBD)(THF)_2]BF_4$ and not neutral ones. The former are known to undergo fast coordination by P(III) donor atoms, favouring thereby chelation. Since the chelate rings that are being formed are rather large, they are also fairly flexible as confirmed by the fluxional behaviour observed for both complexes [Rh(NBD)(**57**/**58**)]BF_4. Such a phenomenon has been detected whenever there is a significant degree of flexibility in the coordinating arms (See also chelate complexes derived from ligands **35** and **36**). [Rh(NBD)(**57**/**58**)]BF_4 were assessed in the metal-catalysed asymmetric hydrogenation of dimethyl itaconate (**S16**). Surprisingly, only [Rh(NBD)(**58**)]BF_4 is an active hydrogenation catalyst. Despite the flexibility of its large chelate ring, [Rh(NBD)(**58**)]BF_4 gave rise to a remarkable enantioselectivity for a catalyst having a CD unit as the only source of chirality (83.6 % *ee*). However, very low activities were measured (17 % conversion after 24 h under 1 bar of H_2), reflecting severe steric crowding around the metal. Ligands **57** and **58** were also assessed in rhodium-catalysed hydroformylation of oct-1-ene (**S1**). Both rates and regioselectivities are comparable to those observed for the corresponding CD free bulky diphosphite, indicating that no supramolecular interactions are at work during this catalytic reaction.

I. 4. Conclusion

With their well-defined chiral cavity, CDs decorated with P(III) donor atoms possess a rich coordination chemistry that has led to many applications in transition metal catalysis, notably in asymmetric reactions. The development of modern methods of CD functionalisation has played a pivotal role in the synthesis of phosphano-CDs capable of maintaining the metal centre within or at least close to their hollow, where the second coordination sphere properties of the sugar macrocycle can be fully expressed and metal confinement achieved. These two features have proved essential for stabilizing highly reactive intermediates, thereby altering significantly the selectivities of catalytic reactions and improving the stability of the catalysts. In this respect, the NMR study of transient catalytic processes taking place within the cavity, in particular by means of 2D NMR experiments such as ROESY, has been facilitated by the proton-rich CD inner-wall. When associated with P(III) donor atoms, CDs also constitute effective chiral inductors in metal-catalysed asymmetric reactions, provided their phosphorus atom(s) is(are) rigidly held close to the cavity. Reflecting on the work that has already been achieved, a delicate balance has to be found in the degree of metal confinement, so that maximum selectivity can been achieved without compromising activity. Ways of combining P(III) atoms with other donor atoms such as nitrogen and sulfur on a CD platform will have to be found in the future to fully exploit the potential cyclodextrins have to offer in homogeneous catalysis.

I. 5. References

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Chapter II

Regioselective opening of sulfato-capped cyclodextrins

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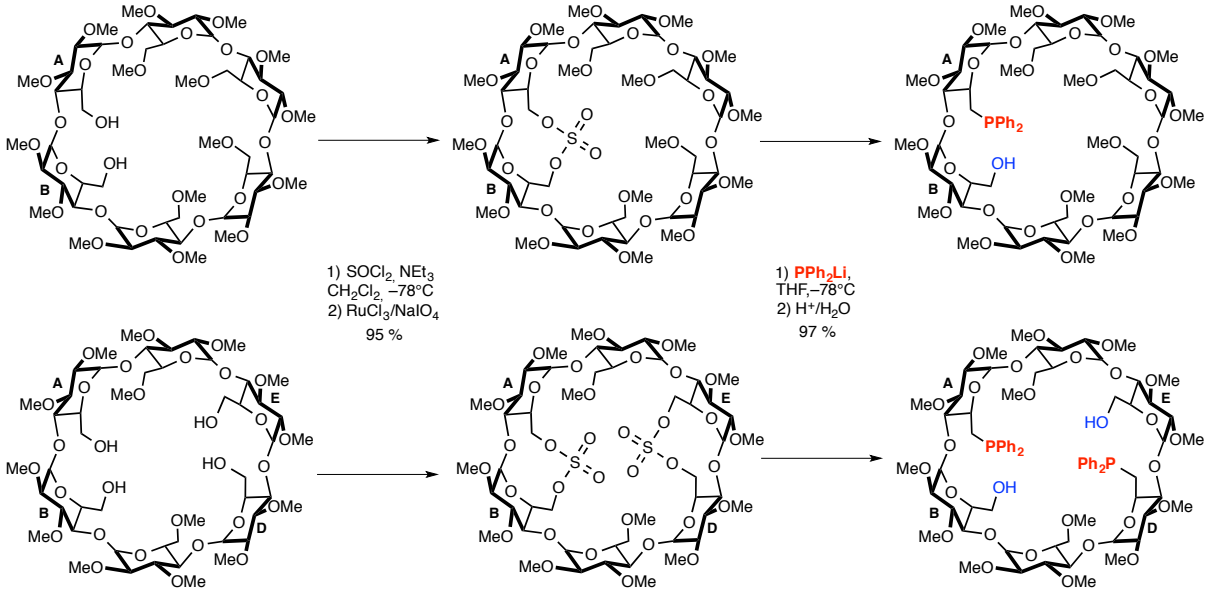
Summary – Chapter II

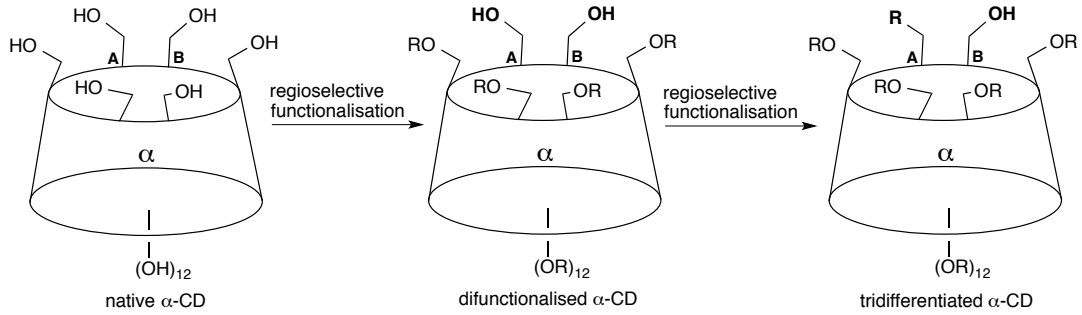
Methylated α- and β-cyclodextrins (CDs) comprising 2 or 4 primary hydroxyl groups were capped with one or two sulfato handle(s), respectively. Each capping step was highly efficient and involved only adjacent glucose units. The resulting cyclic sulfates were found to undergo regioselective opening with various nucleophiles. With sufficiently bulky nucleophiles, such as lithium diphenylphosphide, nucleophilic attack occurred *regiospecifically*. The resulting tridifferentiated CD derivatives constitute valuable starting materials for the preparation of heteropolydendate, chiral CD ligands.

Une ou deux anses sulfato ont été installées sur des cyclodextrines méthylées comprenant respectivement 2 et 4 fonctions hydroxyle primaire et ce en séries α- et β-CD. Seul le pontage d'unités glucose adjacentes a été observé. Les sulfates cycliques correspondants ont ensuite été ouverts avec des nucléophiles de nature et de taille différentes. L'utilisation de nucléophiles stériquement encombrés tels que le diphenylphosphure de lithium permet de réaliser cette ouverture de manière régiospécifique. Les CD tridifférenciées ainsi obtenues constituent d'excellents produits de départ pour la préparation de ligands hétéropolydentés chiraux dérivés de CD.



II. 1. Introduction

Chemical modification of CDs continues to attract a great deal of attention because access to tailor-made CDs responding to specific requirements is only possible if some of the hydroxyl groups that decorate the CD torus can be substituted at given positions.[1] However, because of the highly symmetrical nature of the native CDs, differentiating their numerous identical hydroxyl groups remains a challenge that has been met with success only recently as detailed briefly in chapter I.



Scheme 1. Native, difunctionalised and tridifferentiated α-CD.

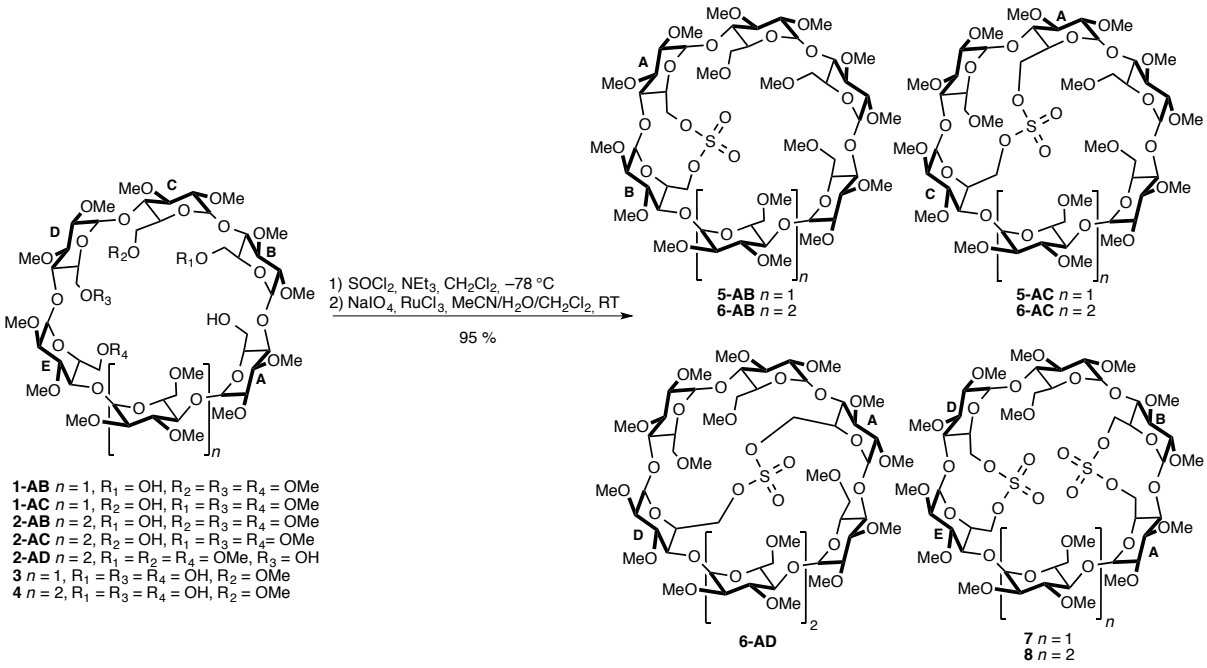
Such a differentiation can be carried out stepwise as shown in Scheme 1. Difunctionalized CD are nowadays easily accessible, but further regioselective or better regiospecific differentiation, which leads to given tridifferentiated CDs, is much more difficult. Sollogoub and co-workers have demonstrated that the partial and regiospecific removal of bulky benzyl protecting groups from the narrow end of perbenzylated CDs by DIBAL can be used for this particular transformation.[2] Alternately, regiospecific opening via nucleophilic attack of a sulfato group capping the A,D units of a benzylated β-CD has also proved effective.[3] In this chapter we show that the cyclic sulfates **5**–**8**,‡ all derived from methylated CDs, can be used effectively for the synthesis of tridifferentiated CDs.

‡ *Compounds 7 and 8, prepared during a MSc internship, as well as the solid state structure of 7 have already been described in the PhD dissertation of R. Gramage-Doria.*[4]

II. 2. Results and discussion

II. 2. 1. Synthesis of proximally, sulfato-capped CD derivatives

Bols et al. have recently achieved the synthesis of cyclic sulfates built on benzylated α- and β-CD scaffolds. Such cyclisations can also be carried out on methylated analogues provided Bols's reaction conditions are modified.[5] While A and D glucose units are bridged in sulfato-capped benzylated CDs, proximal capping can be carried out on both diols (**1**, **2**) and tetrols (**3**, **4**), resulting respectively in single (**5**, **6**) and double capped species (**7**, **8**). Typical reaction conditions for the formation of sulfates **5**–**8** involved reaction of the polyols with thionyl chloride in CH_2Cl_2 and NEt_3 at low temperature (–78°C) followed by oxidation of the resulting mixture of diastereomeric cyclic disulfites with $RuCl_3/NaIO_4$ (Scheme 2). Remarkably, the overall yields of both single and double cyclization/oxidation sequences were virtually quantitative (95%) for both α- and β-CD series. Only the use of a mild base, with the reaction mixture kept at low temperature, allowed these cyclisations to reach this level of regioselectivity.



Scheme 2. Synthesis of cyclic sulfates **5**–**6** and disulfates **7**–**8** from the corresponding diols **1**–**2** and tetrols **3**–**4**.

Proximal capping in **7**–**8** was unambiguously established by means of extensive NMR studies and a single-crystal X-ray diffraction study carried out on disulfate **7** (Figure 1, left).[5]

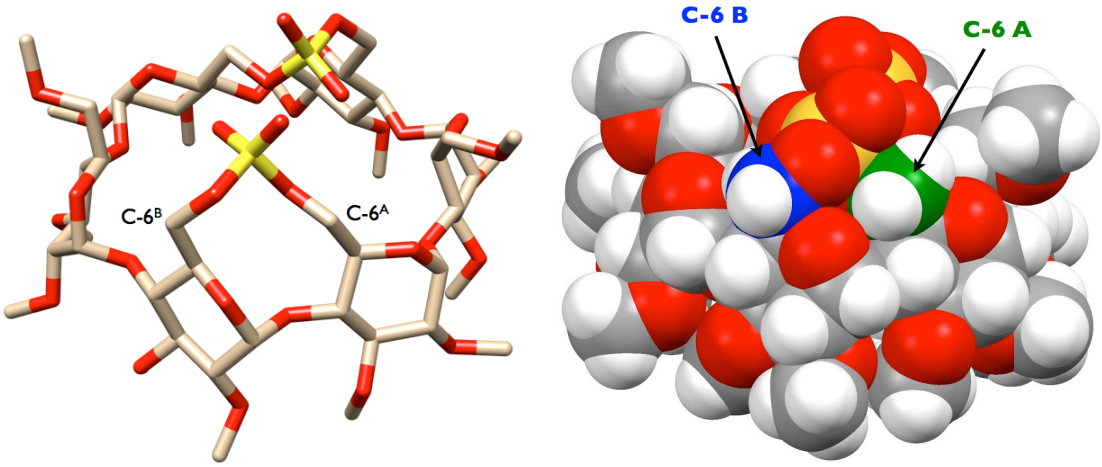
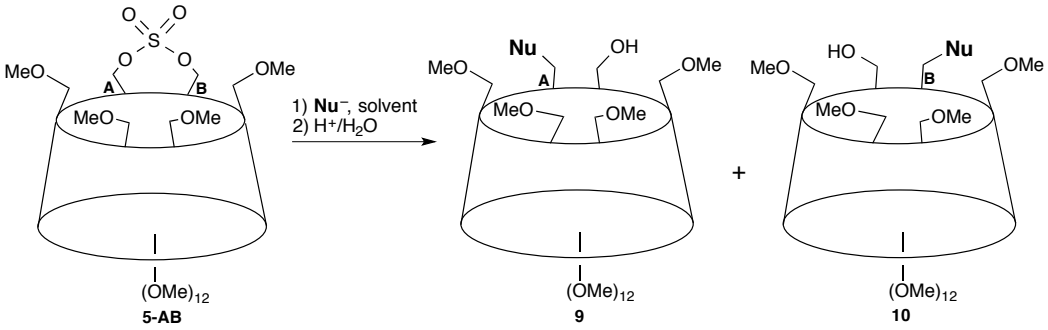


Figure 1. X-Ray structure of the C_2–symmetric, doubly sulfato-capped derivative **7** (side-view of the CD scaffold). The spacefill view on the right shows that the C-6^A atom (in green) is perfectly positioned for nucleophilic backside attack compared to its C-6^B counterpart (in blue). The solvent molecules are not shown.

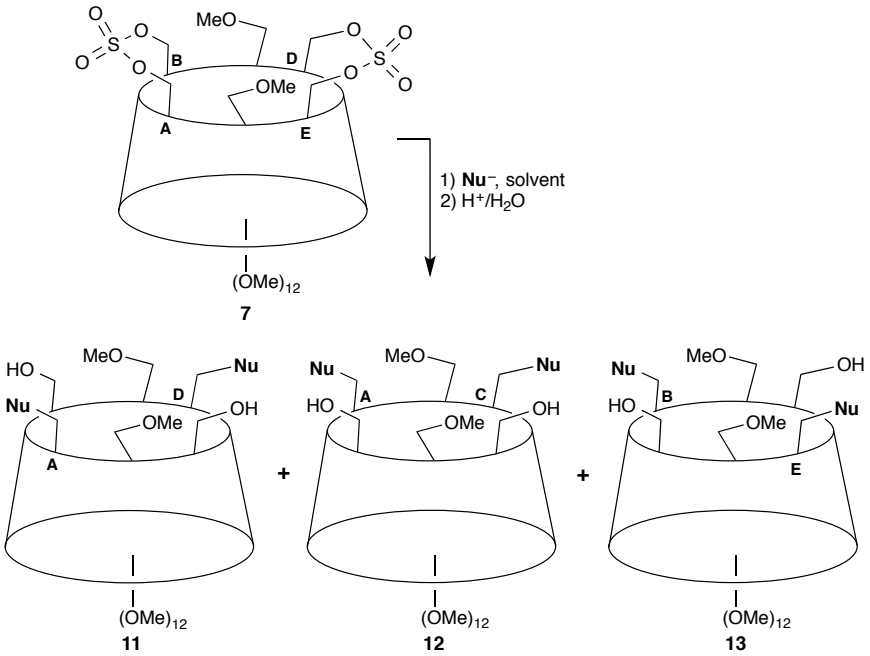
II. 2. 2. Regioselective openings of sulfate 5-AB and disulfate 7

Careful examination of the molecular structure of **7** gives a strong indication of the carbon atoms that are more susceptible to nucleophilic substitution (Figure 1, right).[5] The C-6^A is clearly available for backside attack, whereas the approach of the nucleophile on C-6^B is partially blocked by neighbouring glucose unit C (the same comment holds for their symmetric counterparts, C-6^D and C-6^E, respectively). Unlike Bols's case,[3] achieving a highly regioselective nucleophilic attack on the sulfato bridges is here much more of a challenge as no bulky benzyl groups, which might facilitate discrimination of the attack position, are present.



Scheme 3. Reactivity of sulfate **5-AB**.

We were delighted to observe that *regiospecific* opening of sulfato groups took place both in the singly and doubly proximally capped α-CDs (**5-AB** and **7** respectively) provided the nucleophile is not only bulky, but also strong enough for the reaction to occur at low temperature.[6] Thus, treatment of **5-AB** with lithium diphenylphosphide at –78°C and subsequent phosphorus protection with BH_3 followed by hydrolysis of the remaining sulfate anion afforded cavitand **9a** in 97 % overall yield (Scheme 3; Table 1, entry 1).



Scheme 4. Reactivity of disulfate **7**.

C_2-Symmetric, diphosphine-borane **11a** (Scheme 4; Table 1, entry 6) was obtained from **7** according to the same procedure in 60 % yield, as a *single* regioisomer. Both **9a** and **11a** bear three different, pro-coordinating groups at precise locations on the CD scaffold. Full NMR assignment of phosphine-borane **9a** using 2D COSY, TOCSY, HMQC and ROESY NMR experiments confirmed glucose unit A as being the only one having undergone nucleophilic attack. In the case of doubly capped species **11a**, full NMR assignment of oxidized diphosphine **14** (Scheme 5) as well as a single-crystal X-ray diffraction study (Figure 2) carried out on **11a** confirmed phosphination of the A and D glucose units.

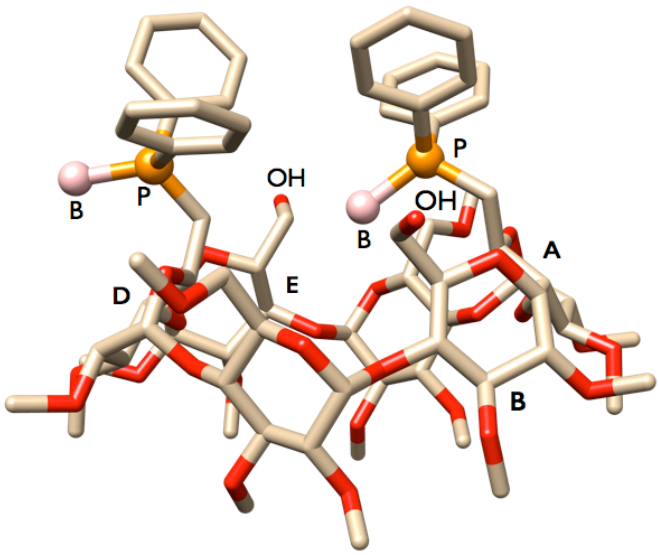
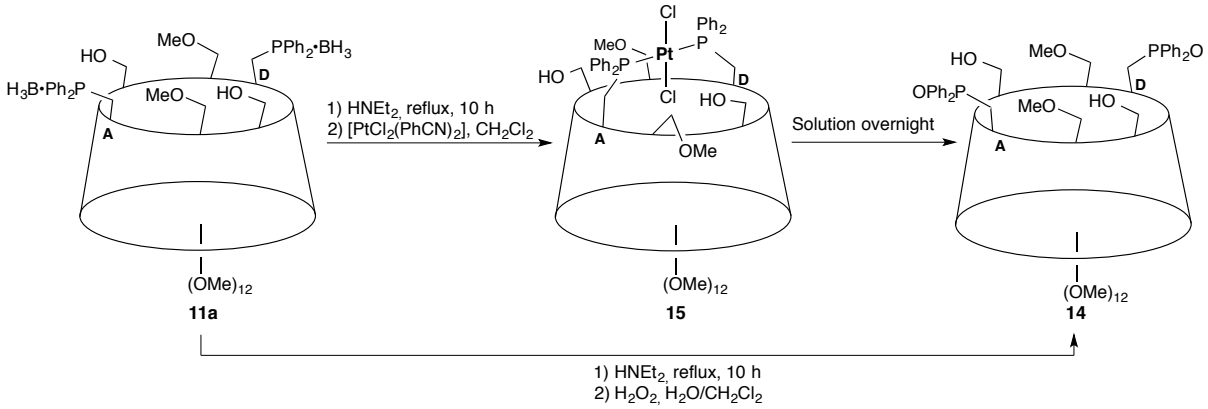


Figure 2. X-ray structure of the diphosphine borane adduct **11a** (side-view). This structure shows one of the P-BH_3 entities plunging into the cavity. The solvent molecules are not shown.

Interestingly, in the solid state, a BH_3 moiety is nested at the cavity entrance, its upper part being protected by the four Ph rings, so as to lead to full encapsulation of this borane unit, whereas the second BH_3 unit is pushed away from the CD torus. Phosphine-boranes can be easily deprotected in refluxing diethylamine, leading quantitatively to the corresponding phosphines. In the case of **11a**, the corresponding free diphosphine was not characterized since it undergoes partial oxidation very easily. Full oxidation was carried out with H_2O_2 to give **14** (Scheme 5). The free diphosphine reacts with $[PtCl_2(PhCN)_2]$ to give *trans* chelate complex **15** as revealed by a $^1J_{P,Pt}$ coupling constant of 2644 Hz, which is typical for platinum complexes with *trans* stereochemistry.[7] Note that this complex is unusually unstable in solution, most probably because of the presence of the two close together hydroxyl moieties, which can displace the P(III) atoms. This results in the rapid air oxidation of the ligand followed by demetallation.



Scheme 5. Diphosphine dioxide **14** and platinum complex **15**.

In stark contrast with the results obtained by Bols,[3b] moderate regioselectivities were observed with the small azide and thioacetate nucleophilic anions (Scheme 3; Table 1, entries 3-5). Not surprisingly, the opening reaction with sodium azide is temperature sensitive as cooling the same reaction mixture from 50°C to 0°C increased the regioisomeric excess by 8 % (Scheme 3; Table 1, entry 4), confirming that the reaction operates under kinetic control. The regioselectivity was further improved by using the medium-sized phthalimide anion instead of azide (Scheme 3; Table 1, entry 2). Thus, tridifferentiated CD **9b**, which could be separated from its regioisomer **10b** by standard column chromatography, was recovered in 87% isolated yield vs. 5 % yield for **10b**. An X-ray crystal structure of **9b** proved that the nucleophilic attack had once again taken place mainly on the A glucose unit of cyclic sulfate **5-AB** (Figure 3). Similarly to the X-ray crystal structure of **11a**, the bulky grafted group, in this case phthalamide, closes the primary face without penetrating the cavity.

Table 1. Experimental conditions for the opening of sulfates **5–6** and disulfates **7–8**.

Entry	CD	Nu^- [a]	n[b]	Solvent	T (°C)	Product	Yield (%)	*re* (%)[c]
1	**5-AB**	Diphenylphosphide	2.2	THF	−78	**9a**	97[e]	100
2		Phthalimide	4	DMF	0	**9b** + **10b**	92[d]	87
3		Azide	5	DMF	50	**9c** + **10c**	98[d]	59
4		Azide	4	DMF	0	**9c** + **10c**	94[d]	67
5		Thioacetate	4	DMF	0	**9d** + **10d**	91[d]	50
6	**7**	Diphenylphosphide	3.5	THF	−78	**11a**	60[e]	100
7		Phthalimide	8	DMF	0	**11b** + **12b**	82[d]	33
8	**5-AC**	Diphenylphosphide	2.2	THF	−78	**16** + **17**	95[e]	40
9	**6-AB**	Diphenylphosphide	2.2	THF	−78	**18a** + **19a**	95[e]	22
10	**6-AB**	Phthalimide	12	DMF	0	**18b** + **19b**	76[d]	23
11	**6-AC**	Diphenylphosphide	2.2	THF	−78	**20** + **21**	94[e]	18
12	**6-AD**	Diphenylphosphide	2.2	THF	−78	**22** + **23**	97[e]	15

[a] Nucleophile. [b] Equivalents of nucleophile. [c] Regioisomeric excess determined by ^{1}H NMR and/or HPLC, *re* = (|[**A**]−[**B**]|)/([**A**]+[**B**]). [d] Yield of regioisomers mixture after acidic work-up. [e] Yield of regioisomers mixture after borane protection and acidic work-up.

Performing the same reaction with the doubly capped CD **7** (Scheme 4; Table 1, entry 7) gave C_2-symmetric **11b** as the major regioisomer (isolated yield 50%). The only possible C_1-symmetric regioisomer (**12b**) was isolated in 28 % yield, but the presence of the second conceivable C_2-symmetric species (**13b**) was not detected. This is hardly surprising as the formation of the latter is strongly disfavoured considering the outcome of the reaction between **5-AB** and potassium phthalimide. Again, full assignment by NMR spectroscopy confirmed the same substitution pattern in N-containing **11b** as in P-containing **11a**. Note that tridifferentiated CD **11b** constitutes a key intermediate for accessing C_2-symmetric nitrogen ligands as the phthalimide groups may easily be converted into primary amino groups.

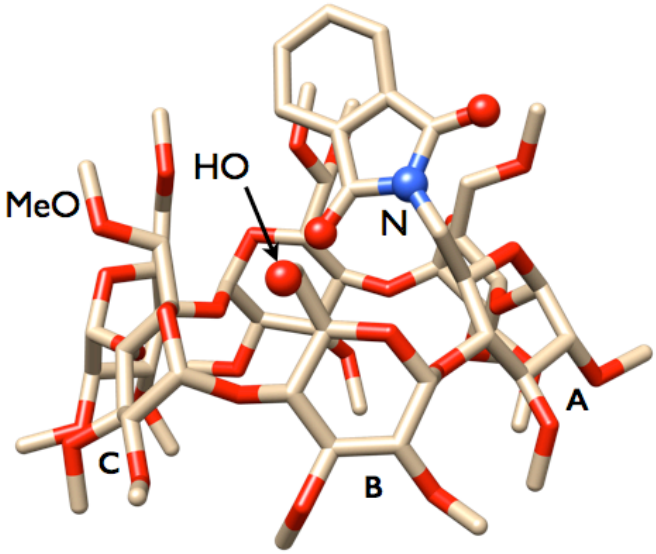
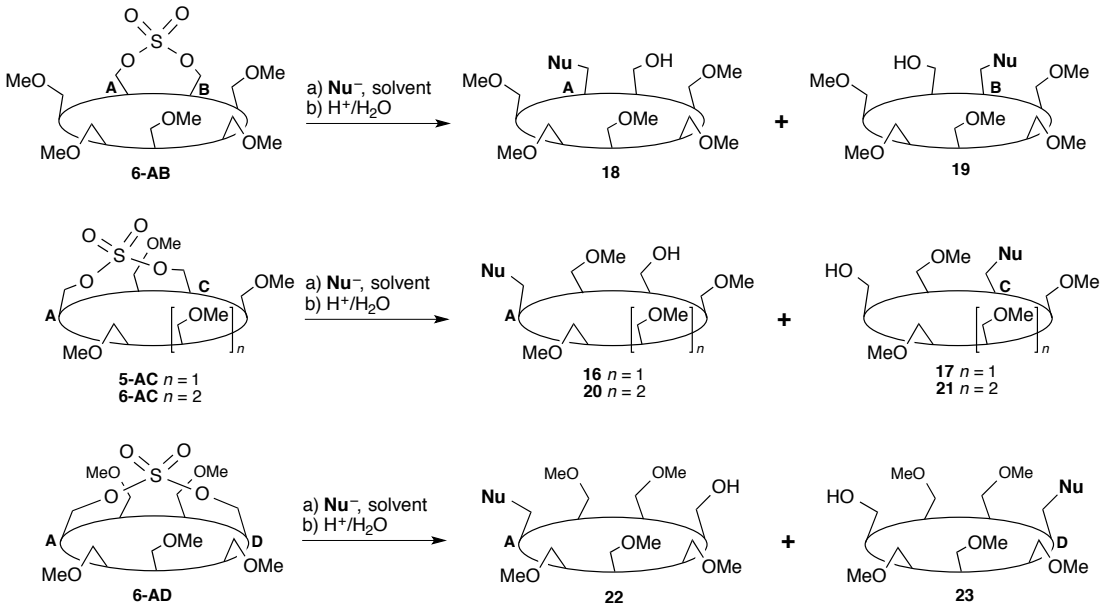


Figure 3. X-ray structure of the major regioisomer of phthalimide **9b** (side-view). The solvent molecules are not shown.

II. 2. 3. Reactivity of other sulfato-capped CDs

Similar sulfate openings were also carried out on other sulfato-capped CDs including β-CDs (**6-AB**, **5/6-AC**, **6-AD**), but much lower regioselectivities than previously were observed (Scheme 6; Table 1, entries 8–12), even in the presence of lithium diphenylphosphide at –78°C. It seems that the CD distortion created by AC-caps and the higher flexibility of the methylated β-CD scaffold result in a poorer differentiation between the two CD C-6 carbon atoms involved in the cyclic sulfate opening. Furthermore, the different regioisomers could not be separated by column chromatography.



Scheme 6. Reactivity of sulfates **5-AC** and **6**.

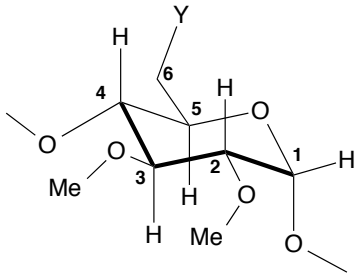
II. 3. Conclusion

We have shown that methylated CDs bearing 2 or 4 hydroxyl groups could be converted straightforwardly into cyclic sulfates in high yield. These capped CDs undergo regioselective opening with various nucleophiles, this occurring preferentially on the less sterically hindered C-6 atoms of the sulfato bridge(s) (C-6^{A} for **5**–**AB** and C-$6^{A,D}$ for **7**). The nucleophilic attack, which is highly sensitive to steric bulk, could be made *regiospecific* with highly sterically hindered nucleophiles such as lithium diphenylphosphide. The effective synthesis of tridifferentiated methylated CDs opens the way to the constitution of a library of heteropolydendate CD ligands that may find applications in asymmetric catalysis and molecular recognition.

II. 4. Experimental section

II. 4. 1. General procedures

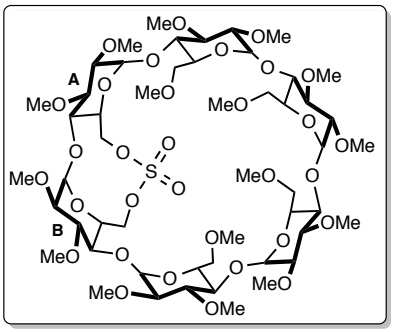
All commercial reagents were used as supplied. All manipulations were performed in Schlenk-type flasks under N_2 with degassed solvent. Solvents were dried by conventional methods and distilled immediately prior to use. Column chromatography was performed on silica gel 60 (particle size 40-63 μm, 230-240 mesh). $CDCl_3$ was passed down a 5-cm-thick alumina column and stored under N_2 over molecular sieves (3 Å). Routine ^1H, $^{31}P\{^1H\}$ and $^{13}C\{^1H\}$ NMR spectra were recorded with Bruker FT instruments (AVANCE 300, 400, 500, 600 spectrometers). ^1H NMR spectral data were referenced to residual protiated solvents (δ = 7.26 ppm for $CDCl_3$), ^{13}C chemical shifts are reported relative to deuterated solvents (δ = 77.00 ppm for $CDCl_3$), and the ^{31}P NMR data are given relative to external H_3PO_4. Mass spectra were recorded with a Bruker MicroTOF spectrometer (ESI) using CH_2Cl_2, MeCN or MeOH as solvent. Elemental analyses were performed by the Service de Microanalyse, Institut de Chimie UMR 7177, Strasbourg. Melting points were determined with a Büchi 535 capillary melting point apparatus. High pressure liquid chromatography were performed on a Varian Prostar instrument (Prostar 230 solvent delivery module, Prostar 355 differential refractor and Prostar 335 UV detector with reverse-phase column Pursuit C18). Compounds **1**–**AB** and **2**–**AB**,[8] **1**–**AC**,[9] **2**–**AC** and **2**–**AD**,[10] **3**,[11] **4**,[5] **7** and **8**,[4] and $[PtCl_2(PhCN)_2]$[12] were synthesised according to literature procedures. In this chapter, the cyclodextrins are depicted as seen from the secondary face, the glucose units being ranged counterclocwise in the following order: A, B, C, D, E, F, G. The numbering of the atoms within a glucose unit is as follows:



II. 4. 2. Procedure for determining the glucose units linked by a given capping unit

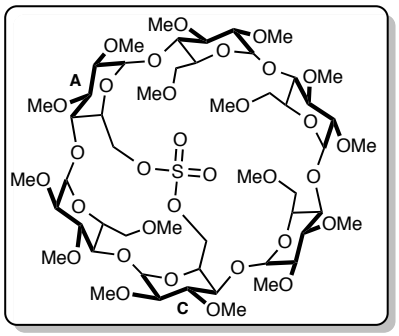
Our strategy for full structural assignment began with the differentiation between capped and non-capped C-6 carbon atoms by DEPT 135. These appear as two distinct sets of signals. The H-6 protons could then be identified using ^1H-^{13}C HMQC (Heteronuclear Multiple Quantum Coherence spectroscopy) or edited HSQC (Heteronuclear Single Quantum Coherence spectroscopy). By using TOCSY (TOtal Correlation SpectroscopY) and COSY (COrrelated SpectroscopY), each H-6 proton was correlated to the set of protons belonging to the same glucose residue. The connectivity between individual glucose units was then established via a ROESY (Rotating frame Overhause Effect SpectroscopY) experiment showing the proximity between H-4_N and H-1_{N+1} protons (N and N+1 standing for neighbouring glucose moieties labeled in the alphabetical order). [13]

II. 4. 3. Synthesis and characterisation

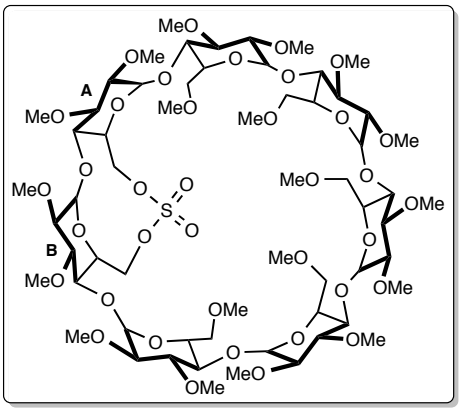


6^A,6^B-Dideoxy-6^A,6^B-sulfato-2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^C,6^D,6^E,6^F-hexadeca-*O*-methyl-α-cyclodextrin (5–AB): A solution of freshly distilled thionyl chloride (0.112 g, 69 μL, 0.94 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of **1–AB** (0.500 g, 0.42 mmol) and NEt_3 (0.106 g, 145 μL, 1.05 mmol) in CH_2Cl_2 (100 mL) at –78°C. The reaction mixture was[3] stirred for 1 h at –78°C whereupon it was allowed to reach room temperature for an additional 1 h, quenched with saturated aqueous $NaHCO_3$ (80 mL), and extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) before being evaporated to dryness to afford a colourless residue, which was dissolved in a mixture of CH_2Cl_2 (6 mL), MeCN (6 mL) and water (12 mL). Ruthenium trichloride (0.005 g, 30×10^{-3} mmol) and sodium periodate (0.225 g, 1.05 mmol) were then added and the reaction mixture was stirred for 12 h at room temperature before adding saturated aqueous $NaHCO_3$ (200 mL). Subsequent extraction with $CHCl_3$ (3 × 50 mL) was followed by drying of the organic extracts ($MgSO_4$). Removal of the solvent in vacuo gave a colourless residue, which was subjected to column chromatography (SiO_2; CH_2Cl_2/MeOH, 97:3 to 95:5, *v*/*v*) to afford **5–AB** (0.498 g, 96%) as a colourless solid. R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.63; m.p. 147°C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by COSY) = 3.08 (t, 1 H, $^3J_{H4\text{-}H3} = {}^3J_{H4\text{-}H2}$ = 9.3 Hz, H-$4^{A\text{ or }B}$), 3.12–3.21 (6 H, H-2), 3.26 (t, 1 H, $^3J_{H4\text{-}H3} = {}^3J_{H4\text{-}H5}$ = 9.5 Hz, H-$4^{B\text{ or }A}$), 3.37 (s, 6 H, OMe), 3.38 (s, 3 H, OMe), 3.39 (s, 3 H, OMe), 3.47 (s, 6 H, OMe), 3.49 (s, 6 H, OMe), 3.50 (s, 3 H, OMe), 3.53 (s, 3 H, OMe), 3.61 (s, 3 H, OMe), 3.62 (s, 3 H, OMe), 3.63 (s, 3 H, OMe), 3.64 (s, 3 H, OMe), 3.65 (s, 3 H, OMe), 3.66 (s, 3 H, OMe), 3.45–3.67 (12 H, H-3, H-6), 3.72–3.85 (8 H, H-4, H-5, H-6a or H-6b), 3.89–3.96 (2 H, H-5, H-6a or H-6b), 4.11 (t, 1 H, $^2J_{H6a\text{-}H6b} = {}^3J_{H6a\text{-}H5}$ = 11.3 Hz, H-$6a^{A\text{ or }B}$), 4.15 (dd, 1 H, $^3J_{H5\text{-}H6b}$ = 3.5 Hz, $^3J_{H5\text{-}H\text{-}4}$ = 9.5 Hz, H-$5^{B\text{ or }A}$), 4.30 (d, 1 H, $^2J_{H6a\text{-}H6b}$ = 10.0 Hz, H-$6a^{B\text{ or }A}$), 4.43 (ddd, 1 H, $^3J_{H5\text{-}H6a}$ = 11.3 Hz, $^3J_{H5\text{-}H4}$ = 8.2 Hz, $^3J_{H5\text{-}H6b}$ = 1.8 Hz , H-$5^{A\text{ or }B}$), 4.90 (d, 1 H, $^3J_{H1\text{-}H2}$ = 2.7 Hz, H-1), 4.91 (dd, 1 H, $^2J_{H6b\text{-}H6a}$ = 10.0 Hz, $^3J_{H6b\text{-}H5}$ = 3.5 Hz, H-$6b^{B\text{ or }A}$), 5.03 (d, 1 H, $^3J_{H1\text{-}H2}$ = 3.3 Hz, H-1), 5.06 (d, 1 H, $^3J_{H1\text{-}H2}$ = 3.4 Hz, H-1), 5.07–5.10 (3 H, H-1), 5.11 (dd, 1 H, $^2J_{H6b\text{-}H6a}$ = 11.3, $^3J_{H6b\text{-}H5}$ = 1.8, H-$6b^{A\text{ or }B}$) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 25ºC): δ (assignment by HMQC) = 57.85, 58.05, 58.17, 58.28, 58.41, 58.60, 59.06, 59.15, 59.24, 59.32, 61.85, 61.92 [×2], 62.07, 62.14, 62.32 (OMe), 67.57, 70.07 (C-5), 70.44, 70.82 (C-6), 70.90, 71.25, 71.29 (C-5), 71.41 [×2] (C-6), 71.86 (C-5), 73.94 (C-$6^{A\text{ or }B}$), 75.76 (C-$6^{B\text{ or }A}$), 81.44, 81.54, 81.63, 81.72 [×3], 81.81 [×2], 81.91, 81.96, 82.07 [×2], 82.28, 82.31, 82.35, 82.47 (C-2, C-3, C-4), 83.98 (C-$4^{A\text{ or }B}$), 86.63 (C-$4^{B\text{ or }A}$), 98.81, 99.89, 100.04, 100.09, 100.26, 101.12 (C-1)

ppm; elemental analysis (%) calcd for $C_{52}H_{90}O_{32}S{\cdot}C_7H_8$ (1281.50 + 92): C 52.43, H 7.31, found: C 52.25, H 7.53; MS (ESI-TOF): *m/z* (%): 1281.50 (100) $[M + Na]^+$.

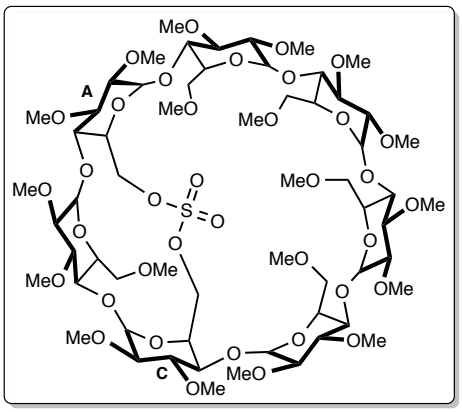


$6^A,6^C$-Dideoxy-$6^A,6^C$-sulfato-$2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^B,6^D,6^E,6^F$-hexadeca-*O*-methyl-$\alpha$-cyclodextrin (5–AC): This compound was prepared from **1–AC** (0.200 g, 0.17 mmol) according to the above procedure (0.107 g, 50 %). R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.65; m.p. 147°C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by COSY) = 3.05–4.02 (76 H, H-2, H-3, H-4, H-5, H-6, OMe), 4.12–4.33 (5 H, H-5, H-6), 4.42 (t, 1 H, $^3J_{H5\text{-}H6a} = {}^3J_{H5\text{-}H6b} = 10.2$ Hz, H-5), 4.68–4.73 (2 H, H-6), 4.97–5.06 (5 H, H-1), 5.26 (d, 1 H, $^3J_{H1\text{-}H2} = 3.4$ Hz, H-1) ppm; $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25ºC): δ (assignment by HMQC) = 59.80–64.72 (16 C, OMe), 71.27–77.16 (12 C, C-5, C-6), 79.56–85.35 (18 C, C-2, C-3, C-4), 96.35–103.39 (6 C, H-1) ppm; elemental analysis (%) calcd for $C_{52}H_{90}O_{32}S$ (1281.50): C 49.60, H 7.20, found: C 49.66, H 7.27; MS (ESI-TOF): *m/z* (%): 1281.50 (100) $[M + Na]^+$.

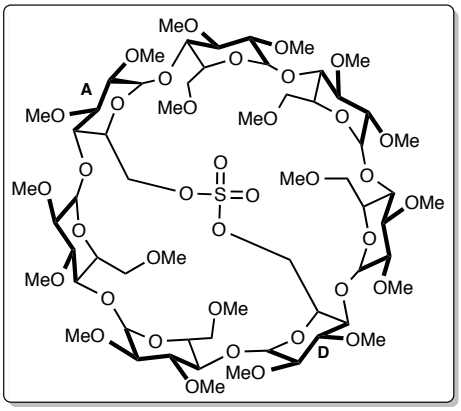


$6^A,6^B$-Dideoxy-$6^A,6^B$-sulfato-$2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^C,6^D,6^E,6^F,6^G$-nonadeca-*O*-methyl-$\beta$-cyclodextrin (6–AB): This compound was prepared from **2–AB** (0.530 g, 0.38 mmol) according to the above procedure (0.420 g, 76 %). R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.56; m.p. 150°C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by COSY) = 3.04–3.18 (8 H, H-2, H-$4^{B\text{ or }A}$), 3.30 (s, 3 H, OMe), 3.31 (s, 9 H, OMe), 3.31 (1 H, H-$4^{A\text{ or }B}$), 3.32 (s, 3 H, OMe), 3.41 (s, 3 H, OMe), 3.42 (s, 9 H, OMe), 3.43 (s, 3 H, OMe), 3.45 (s, 3 H, OMe), 3.49 (s, 3 H, OMe), 3.55 (s, 9 H, OMe), 3.56 (s, 3 H, OMe), 3.57 (s, 3 H, OMe), 3.58 (s, 3 H, OMe), 3.59 (s, 3 H, OMe), 3.28–3.68 (16 H, H-3, H-4, H-6), 3.69–3.80 (8 H, H-5, H-6), 3.81–3.87 (2 H, H-5, H-6), 3.90 (m, 1 H, H-5), 4.05 (ddd, 1 H, $^3J_{H5\text{-}H6a} = 1.2$ Hz, $^3J_{H5\text{-}H6b} = 3.5$ Hz, $^3J_{H5\text{-}H\text{-}4} = 9.8$ Hz, H-$5^{A\text{ or }B}$), 4.13 (dd, 1 H, $^2J_{H6a\text{-}H6b} =$

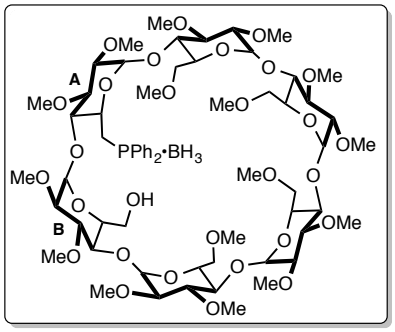
10.5 Hz, $^{3}J_{H6a\text{-}H5}$ = 12.3 Hz, H-6a$^{B\text{ or }A}$), 4.28 (ddd, 1 H, $^{3}J_{H5\text{-}H6a}$ =12.3 Hz, $^{3}J_{H5\text{-}H6b}$ =2.4 Hz, $^{3}J_{H5\text{-}H\text{-}4}$ = 7.6 Hz, H-5$^{B\text{ or }A}$), 4.33 (dd, 1 H, $^{2}J_{H6a\text{-}H6b}$ = 10.0 Hz, $^{3}J_{H6a\text{-}H5}$ = 1.2 Hz, H-6a$^{A\text{ or }B}$), 4.60 (dd, 1 H, $^{2}J_{H6b\text{-}H6a}$ = 10.0 Hz, $^{3}J_{H6b\text{-}H5}$ = 3.5 Hz, H-6b$^{A\text{ or }B}$), 4.82 (d, 1 H, $^{3}J_{H1\text{-}H2}$ = 3.7 Hz, H-1), 4.96 (dd, 1 H, $^{2}J_{H6b\text{-}H6a}$ = 10.5 Hz, $^{3}J_{H6\text{-}H5}$ = 2.4 Hz, H-6b$^{B\text{ or }A}$), 4.98 (d, 1 H, $^{3}J_{H1\text{-}H2}$ = 3.6 Hz, H-1), 5.02 (d, 1 H, $^{3}J_{H1\text{-}H2}$ =3.7 Hz, H-1), 5.04 (d, 1 H, $^{3}J_{H1\text{-}H2}$ = 3.6 Hz, H-1), 5.05 (d, 1 H, $^{3}J_{H1\text{-}H2}$ = 4.3 Hz, H-1), 5.09 (d, 1 H, $^{3}J_{H1\text{-}H2}$ = 3.9 Hz, H-1), 5.19 (d, 1 H, $^{3}J_{H1\text{-}H2}$ = 4.2 Hz, H-1) ppm; $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$, 25ºC): δ (assignment by HMQC) = 57.97, 58.04, 58.17, 58.27, 58.56, 58.76, 58.81[×3], 58.87, 58.96, 59.02, 60.73, 61.13, 61.16, 61.34, 61.40, 61.52 [×2] (OMe), 68.06 (C-5$^{B\text{ or }A}$), 68.68 (C-5$^{A\text{ or }B}$), 70.23 (C-6), 70.31, 70.62, 70.70 (C-5), 70.85 (C-6), 70.88 (C-5), 71.00 [×2] (C-6), 71.26 (C-5), 71.30 (C-6), 73.93 (C-6$^{B\text{ or }A}$), 74.26 (C-6$^{A\text{ or }B}$), 77.96, 79.49, 80.01, 80.28, 80.80, 81.25, 81.30, 81.35 [×2], 81.37 [×2], 81.45, 81.55, 81.60, 81.69, 81.77, 81.80, 81.87, 82.06, 82.28, 82.48 (C-2, C-3, C-4), 98.22, 98.41, 98.46, 98.55, 98.63, 99.82, 100.39 (C-1) ppm; elemental analysis (%) calcd for $C_{61}H_{106}O_{37}S{\cdot}CH_2Cl_2$ (1463.54 + 84.93): C 48.09, H 7.03, found: C 48.22, H 7.22; MS (ESI-TOF): *m/z* (%): 1485.60 (100) $[M + Na]^{+}$.



6^{A},6^{C}-Dideoxy-6^{A},6^{C}-sulfato-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},2^{G},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},3^{G},6^{B},6^{D},6^{E},6^{F},6^{G}-nonadeca-*O*-methyl-β-cyclodextrin (6–AC): This compound was prepared from **2–AC** (0.200 g, 0.14 mmol) according to the above procedure (0.092 g, 44 %). R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.57; m.p. 150°C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by COSY) = 3.11–4.27 (97 H, H-2, H-3, H-4, H-5, H-6, OMe), 4.59 (d, 1 H, $^{2}J_{H6b\text{-}H6a}$ = 13.4 Hz, H-6), 4.88 (d, 1 H, $^{3}J_{H1\text{-}H2}$ = 3.2 Hz, H-1), 5.01–5.05 (3 H, H-1), 5.09 (d, 1 H, $^{3}J_{H1\text{-}H2}$ = 3.4 Hz, H-1), 5.16 (d, 1 H, $^{2}J_{H6b\text{-}H6a}$ = 12.0 Hz, H-6), 5.49–5.53 (2 H, H-1) ppm; $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$, 25ºC): δ (assignment by HMQC) = 55.44–59.59 (19 C, OMe), 67.02–71.29 (14 C, C-5, C-6), 75.95–80.50 (21 C, C-2, C-3, C-4), 91.45–97.71 (7 C, H-1) ppm; elemental analysis (%) calcd for $C_{61}H_{106}O_{37}S{\bullet}2H_2O$ (1463.54 + 36.02): C 48.86, H 7.39, found: C 48.98, H 7.57; MS (ESI-TOF): *m/z* (%): 1485.60 (100) $[M + Na]^{+}$.

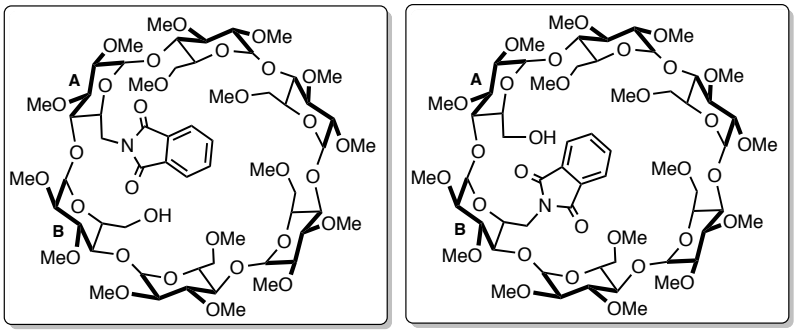


$6^{A},6^{D}$-Dideoxy-$6^{A},6^{D}$-sulfato-$2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},2^{G},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},3^{G},6^{B},6^{C},6^{E},6^{F},6^{G}$-nonadeca-*O*-methyl-$\beta$-cyclodextrin (6–AD): This compound was prepared from **2–AD** (0.200 g, 0.14 mmol) according to the above procedure (0.075 g, 35 %). R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.57; m.p. 150°C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by COSY) = 3.15–4.57 (96 H, H-2, H-3, H-4, H-5, H-6, OMe), 4.42 (t, 1 H, $^3J_{H5\text{-}H6a} = {}^3J_{H5\text{-}H6b}$ = 10.2 Hz, H-5), 4.51 (d, 1 H, $^2J_{H6b\text{-}H6a}$ = 12.0 Hz, H-6), 4.54 (d, 1 H, $^2J_{H6b\text{-}H6a}$ = 12.0 Hz, H-6), 4.97–5.00 (2 H, H-1), 5.02–5.05 (2 H, H-1), 5.07 (d, 1 H, $^3J_{H1\text{-}H2}$ = 3.1 Hz, H-1), 5.58 (d, 1 H, $^3J_{H1\text{-}H2}$ = 3.4 Hz, H-1), 5.67 (d, 1 H, $^3J_{H1\text{-}H2}$ = 3.2 Hz, H-1) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 25ºC): δ (assignment by HMQC) = 55.48–60.08 (19 C, OMe), 65.91–72.23 (14 C, C-5, C-6), 76.52–81.86 (21 C, C-2, C-3, C-4), 92.60–98.01 (7 C, H-1) ppm; elemental analysis (%) calcd for $C_{61}H_{106}O_{37}S{\bullet}2H_2O$ (1463.54 + 36.02): C 48.86, H 7.39, found: C 49.06, H 7.67; MS (ESI-TOF): *m*/*z* (%): 1485.60 (100) $[M + Na]^+$.



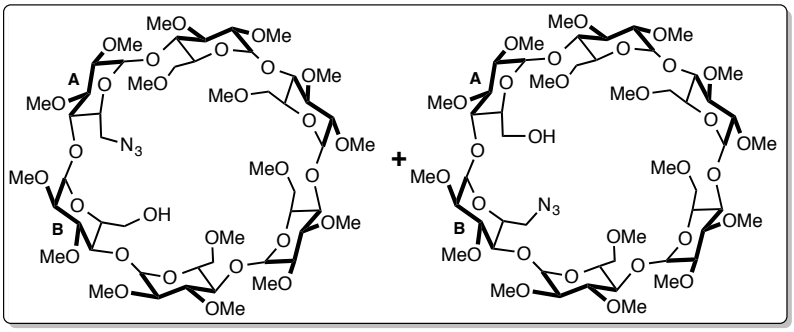
***P*-{6^{A}-Deoxy-6^{A}-diphenylphosphinyl-$2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},6^{C},6^{D},6^{E},6^{F}$-hexadeca-*O*-methyl-$\alpha$-cyclodextrin} borane (9a):** *n*-BuLi (1.60 M in hexane, 1.20 mL, 1.94 mmol) was added dropwise at –78°C to a stirred solution of diphenylphosphine (0.347 g, 485 µL of 20.3% *wt/wt* in hexane, 0.37 mmol) in THF (10 mL). After 30 min, the dark red diphenylphosphide solution was transferred via a cannula to a stirred solution of **5**–**AB** (0.200 g, 0.16 mmol) in THF (10 mL) kept at –78°C. The solution was further stirred at –78°C for 1 h before being allowed to reach 0°C over 1 h. $BH_3{\cdot}$THF (1.00 M in THF, 10 mL, 10 mmol) was then added dropwise at 0°C, and the reaction mixture allowed to reach room temperature before being stirred for a further 12 h. Once the solvent was removed *in vacuo*, the solid was taken in THF (8 mL) and H_2SO_4 (0.20 mL, 50% *wt/wt* solution in water) was added. The reaction mixture was stirred for 1 h at room temperature before adding saturated aqueous $NaHCO_3$ (50 mL). Subsequent extraction with $CHCl_3$ (3 × 50 mL) was followed by drying of the organic extracts ($MgSO_4$). Removal of the solvent under vacuum gave a colourless

residue, which was subjected to column chromatography (SiO_2; CH_2Cl_2/MeOH, 97:3, *v/v*) to afford **9a** (0.215 g, 97%) as a colourless solid. R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v/v*) = 0.43; Retention time (reverse-phase column Pursuit C18, isocratic elution with MeCN:H_2O, 1:1, with a flow rate of 1mL.min^{-1}) = 10.79 min; m.p. 210–212°C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY, TOCSY, HMQC, and ROESY) = 0.86 (br s, 3 H, P-BH_3), 2.39 (d, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 11.8 Hz, H-6a^B), 2.52 (dd, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 11.5 Hz, $^3J_{H\text{-}6a,H\text{-}5}$ = 2.8 Hz, H-6a^A), 2.54 (d, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 11.0 Hz, H-6a^F), 2.76 (s, 3 H, OMe-6^F), 2.82 (d, $^2J_{H\text{-}6b,H\text{-}6a}$ =11.4 Hz, H-6b^B), 2.89 (m, 1 H, H-6b^A), 2.99 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}3}$ = 9.5 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 3.4 Hz, H-2^B), 3.03 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}3}$ = 9.9 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 3.4 Hz, H-2^F), 3.11 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}3}$ = 9.8 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 2.9 Hz, H-2^A), 3.13 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}3}$ = 9.3 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 2.9 Hz, H-2^C), 3.17 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}3}$ = 9.5 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 3.1 Hz, H-2^E), 3.18 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}3}$ = 9.5 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 2.7 Hz, H-2^D), 3.20 (dd, 1 H, $^3J_{H\text{-}4,H\text{-}3}$ = $^3J_{H\text{-}4,H\text{-}5}$ = 9.0 Hz, H-4^A), 3.39 (s, 3 H, OMe-2), 3.42 (s, 3 H, OMe-6^D), 3.43 (s, 6 H, OMe-2), 3.44 (s, 3 H, OMe-2), 3.45 (s, 6 H, OMe-6^{C,E}), 3.46 (1 H, H-6a^C), 3.47 (s, 6 H, OMe-2), 3.53 (1 H, H-3^A), 3.54 (1 H, H-3^C), 3.55 (1 H, H-6a^D), 3.56 (1 H, H-3^D), 3.58 (s, 3 H, OMe-3), 3.58 (1 H, H-3^E), 3.59 (1 H, H-5^B), 3.60 (s, 3 H, OMe-3), 3.61 (s, 3 H, OMe-3), 3.61 (1 H, H-3^F), 3.62 (1 H, H-3^B), 3.63 (s, 3 H, OMe-3), 3.63 (1 H, H-4^B), 3.67 (s, 3 H, OMe-3), 3.67 (1 H, H-4^E), 3.68 (s, 3 H, OMe-3), 3.68 (2 H, H-4^C, H-6b^B), 3.69 (1 H, H-4^D), 3.70 (2 H, H-4^F, H-6b^D), 3.75 (d, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 10.3 Hz, H-6a^E), 3.85 (d, 2 H, $^3J_{H\text{-}5,H\text{-}4}$ = 9.7 Hz, H-5^{C,F}), 3.93 (d, 1 H, $^3J_{H\text{-}5,H\text{-}4}$ = 13.8 Hz, H-5^D), 3.94 (d, 1 H, $^3J_{H\text{-}5,H\text{-}4}$ = 12.4 Hz, H-5^E), 3.99 (dd, 1 H, $^2J_{H\text{-}6b,H\text{-}6a}$ = 10.6 Hz, $^3J_{H\text{-}6b,H\text{-}5}$ = 2.8 Hz, H-6b^E), 4.05 (dd, 1 H, $^2J_{H\text{-}6b,H\text{-}6a}$ = 10.3 Hz, $^3J_{H\text{-}6b,H\text{-}5}$ = 2.1 Hz, H-6b^C), 4.45 (td, 1 H, $^3J_{H\text{-}5,H\text{-}6a}$ = $^3J_{H\text{-}5,P}$ = 9.6 Hz, $^3J_{H\text{-}5,H\text{-}4}$ = 9.0 Hz, H-5^A), 4.63 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 2.9 Hz, H-1^A), 4.96 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 2.9 Hz, H-1^C), 4.99 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.4 Hz, H-1^B), 5.01 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.4 Hz, H-1^F), 5.09 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 2.7 Hz, H-1^D), 5.10 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.1 Hz, H-1^E), 7.36–7.45 (6 H, *m*-H, *p*-H), 7.64 (td, 2 H, $^3J_{o\text{-}H,m\text{-}H}$ = $^3J_{o\text{-}H,P}$ = 8.8, $^4J_{o\text{-}H,p\text{-}H}$ = 2.1 Hz, *o*-H), 7.83–7.86 (2 H, *o*-H) ppm, OH^B not assigned; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 25ºC): δ (assignment by HMQC) = 27.53 (d, $^1J_{C,P}$ = 41.3 Hz, C-6^A), 57.63 [×2], 57.70, 58.25, 58.26, 58.88, 58.90, 59.14, 59.25 [×2] (OMe), 60.43 (C-6), 61.34, 61.52, 61.86, 61.90, 61.93, 62.01 (OMe), 68.02 (C-6), 68.68 (C-5), 69.79 (C-6^B), 70.74 [×2] (C-5), 70.98 (C-6), 71.15 [×2] (C-5), 71.28, 71.34 (C-6), 72.00 (C-5), 79.85, 80.74, 80.82, 81.11, 81.23, 81.28, 81.35, 81.40, 81.56, 81.72, 81.82, 81.92, 82.08, 82.27, 82.37, 82.79, 82.82 (C-2, C-3, C-4), 87.75 (d, $^3J_{C,P}$ = 41.3 Hz, C-4^A), 97.16, 99.40, 100.14, 100.37, 100.46, 100.84 (C-1), 128.92 (d, $^3J_{C,P}$ = 10.0, C$_{meta}$), 128.99 (d, $^3J_{C,P}$ = 10.0, C$_{meta}$), 130.51 (d, $^1J_{C,P}$ = 53.4 , C$_{ipso}$), 131.27 (d, $^2J_{C,P}$ = 8.3 Hz, C$_{ortho}$), 131.29 (s, C$_{para}$), 131.41 (s, C$_{para}$), 131.69 (d, $^2J_{C,P}$ = 9.9 Hz, C$_{ortho}$), 132.24 (d, $^1J_{C,P}$ = 56.7 , C$_{ipso}$) ppm; ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$, 25ºC): δ = 12.1 (br s) ppm; elemental analysis (%) calcd for $C_{64}H_{104}BO_{29}P$·2MeOH (1401.63 + 64): C 54.62, H 8.11, found: C 54.92, H 7.83; MS (ESI-TOF): *m/z* (%): 1401.63 (100) [M + Na]$^+$.

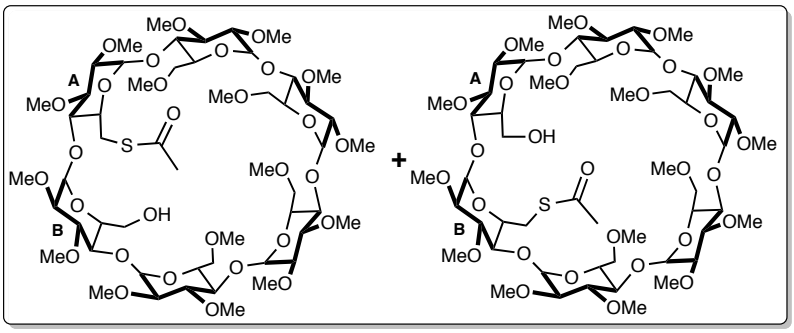


6^{A}-Deoxy-6^{A}-(1,3-dioxoisoindolin-2-yl)-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},6^{C},6^{D},6^{E},6^{F}-hexadeca-*O*-methyl-α-cyclodextrin (9b) and 6^{B}-deoxy-6^{B}-(1,3-dioxoisoindolin-2-yl)-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},6^{C},6^{D},6^{E},6^{F}-hexadeca-*O*-methyl-α-cyclodextrin (10b): Powdered potassium phthalimide (0.135 g, 0.64 mmol) was added to a stirred solution of **5**–**AB** at 0°C (0.200 g, 0.16 mmol) in DMF (0.80 mL). After 1 h, the reaction mixture was allowed to reach room temperature and then kept at this temperature for 12 h under stirring. It was then evaporated to dryness and the residue was retaken in THF (8 mL). H_2SO_4 (0.20 mL, 50% *wt/wt* solution in water) was added and the reaction mixture was stirred for 1 h at room temperature before adding saturated aqueous $NaHCO_3$ (50 mL). Subsequent extraction with $CHCl_3$ (3 × 50 mL) was followed by drying of the organic extracts ($MgSO_4$). Removal of the solvent in vacuo gave a colourless residue, which was subjected to column chromatography (SiO_2; CH_2Cl_2/MeOH, 97:3, v/v) to afford 2 colourless solids, **9b** (0.180 g, 87%) and **10b** (0.006 g, 5 %). **9b** R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.58; m.p. 228–230°C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY, TOCSY, HMQC, and ROESY) = 2.24 (br s, 1 H, OH), 2.70 (dd, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 10.3 Hz, $^3J_{H\text{-}6a,H\text{-}5}$ = 1.5 Hz, H-6a), 2.99 (s, 3 H, OMe), 3.06 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}3}$ = 9.8 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 3.5 Hz, H-2), 3.16 (m, 1 H, H-2^{A}), 3.17 (m, 1 H, H-2^{B}), 3.18 (s, 3 H, OMe), 3.12–3.21 (3 H, H-2), 3.31 (t, 1 H, $^3J_{H\text{-}4,H\text{-}3}$ = $^3J_{H\text{-}4,H\text{-}5}$ = 9.3 Hz, H-4^{A}), 3.37 (s, 3 H, OMe), 3.34–3.38 (m, 1 H, H-5), 3.43 (s, 3 H, OMe), 3.44 (s, 3 H, OMe), 3.46 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 3.48 (s, 3 H, OMe), 3.49 (s, 3 H, OMe), 3.51 (s, 3 H, OMe), 3.52 (m, 1 H, H-3^{A}), 3.59 (s, 3 H, OMe), 3.60 (s, 3 H, OMe), 3.61 (s, 3 H, OMe), 3.61 (m, 1 H, H-4^{B}), 3.62 (s, 3 H, OMe), 3.64 (m, 1 H, H-3^{B}), 3.65 (s, 3 H, OMe), 3.67 (s, 3 H, OMe), 3.41–3.70 (12 H, H-3, H-4, H-6), 3.73–3.76 (m, 1 H, H-5), 3.79–3.86 (2 H, H-6a), 3.86–3.91 (2 H, H-6a or H-6b, H-$6a^{B}$), 3.92–4.03 (4 H, H-5, H-$6a^{A}$, H-$6b^{B}$), 4.12 (ddd, 1 H, $^3J_{H\text{-}5,H\text{-}6a}$ = $^3J_{H\text{-}5,H\text{-}4}$ = 9.0 Hz, $^3J_{H\text{-}5,H\text{-}6b}$ = 2.6 Hz, H-5^{A}), 4.15–4.19 (m, 1 H, H-5^{B}), 4.34 (dd, 1 H, $^2J_{H\text{-}6b,H\text{-}6a}$ = 14.2, Hz, $^3J_{H\text{-}6b,H\text{-}5}$ = 2.5 Hz, H-$6b^{A}$), 4.91 (d, 1 H, $^3J_{H1\text{-}H2}$ = 2.8 Hz, H-1^{A}), 4.95 (d, 1 H, $^3J_{H1\text{-}H2}$ = 3.1 Hz, H-1), 5.03 (d, 1 H, $^3J_{H1\text{-}H2}$ = 3.1 Hz, H-1), 5.07 (d, 1 H, $^3J_{H1\text{-}H2}$ = 3.1 Hz, H-1), 5.09 (d, 1 H, $^3J_{H1\text{-}H2}$ = 3.4 Hz, H-1), 5.18 (d, 1 H, $^3J_{H1\text{-}H2}$ = 3.3 Hz, H-1^{B}), 7.73–7.75 (2 H, *m*-H), 7.81–7.83 (2 H, *o*-H) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 25ºC): δ (assignment by HMQC) = 39.78 (C-6^{A}), 57.83 [×3], 58.02 [×2], 58.13, 58.65, 58.96, 59.00, 59.14, 61.65, 61.80 [×3], 61.88, 61.98 (OMe), 62.14 (C-6^{B}), 69.44 (C-5), 69.68 (C-6), 70.92 (C-6), 70.94 (C-5), 70.98 (C-6), 71.23, 71.27, 71.34 (C-5), 71.66 (C-6), 72.25 (C-5), 80.92, 81.06, 81.17, 81.29, 81.30, 81.47, 81.60, 81.78, 81.87, 81.97, 82.19 [×2], 82.23 [×3], 82.37, 82.60, 85.43 (C-2, C-3, C-4), 99.15, 99.83, 99.88, 100.06, 100.11, 100.47 (C-1), 123.11 (C_{meta}), 132.17 (C_{ipso}), 134.06 (C_{ortho}), 168.08 (CO) ppm; elemental analysis (%) calcd for $C_{60}H_{95}NO_{31}\cdot CH_2Cl_2$ (1326.38 + 84.93): C 51.91, H 6.93, N 0.99, found: C 51.83, H 6.92,

N 0.98; MS (ESI-TOF): *m/z* (%): 1348.58 (100) $[M + Na]^+$. **10b** R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.54; m.p. 228–230°C; ^1H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ = 3.24 (s, 3 H, OMe), 3.32 (s, 3 H, OMe), 3.41 (s, 3 H, OMe), 3.45 (s, 3 H, OMe), 3.46 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 3.49 (s, 3 H, OMe), 3.50 (s, 3 H, OMe), 3.51 (s, 3 H, OMe), 3.53 (s, 3 H, OMe), 3.62 (s, 3 H, OMe), 3.63 (s, 3 H, OMe), 3.64 (s, 3 H, OMe), 3.65 (s, 3 H, OMe), 3.66 (s, 3 H, OMe), 3.68 (s, 3 H, OMe), 3.05–4.22 (36 H, H-2, H-3, H-4, H-5, H-6), 4.98 (d, 1 H, $^3J_{H1\text{-}H2}$ = 3.2 Hz, H-1), 4.99 (d, 1 H, $^3J_{H1\text{-}H2}$ = 3.3 Hz, H-1), 5.06 (d, 1 H, $^3J_{H1\text{-}H2}$ = 2.9 Hz, H-1), 5.09 (d, 1 H, $^3J_{H1\text{-}H2}$ = 3.3 Hz, H-1), 5.11 (d, 1 H, $^3J_{H1\text{-}H2}$ = 3.5 Hz, H-1), 5.37 (d, 1 H, $^3J_{H1\text{-}H2}$ = 3.6 Hz, H-1), 7.73–7.75 (2 H, *m*-H), 7.83–7.87 (2 H, *o*-H) ppm; elemental analysis (%) calcd for $C_{60}H_{95}NO_{31}\cdot H_2O$ (1326.38 + 18.02): C 53.60, H 7.27, N 1.04, found: C 53.67, H 7.26, N 0.98; MS (ESI-TOF): *m/z* (%): 1348.58 (100) $[M + Na]^+$.

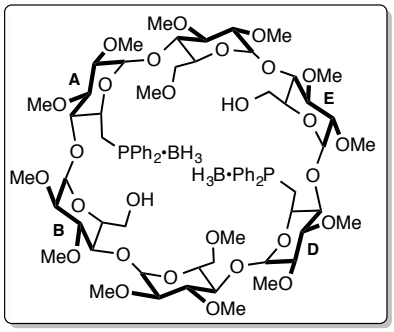


6^A-Deoxy-6^A-azido-2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^C,6^D,6^E,6^F-hexadeca-*O*-methyl-α-cyclodextrin (9c) and 6^B-deoxy-6^B-azido-2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^C,6^D,6^E,6^F-hexadeca-*O*-methyl-α-cyclodextrin (10c): Powdered sodium azide (0.042 g, 0.64 mmol) was added to a stirred solution of **5**–**AB** at 0°C (0.200 g, 0.16 mmol) in DMF (0.80 mL) according to the above procedure. Reaction led to an inseparable mixture of regioisomeres **9c** and **10c** (0.180 g, 94 %). R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.70; Retention time (reverse-phase column Pursuit C18, isocratic elution with MeCN:H_2O, 1:1, with a flow rate of 1mL.min^{-1}) = 17.49 and 18.16 min; elemental analysis (%) calcd for $C_{52}H_{91}N_3O_{29}\cdot H_2O$ (1221.55 + 18.02): C 50.36, H 7.56, N 3.39, found: C 50.33, H 7.50, N 3.18; MS (ESI-TOF): *m/z* (%): 1244.55 (100) $[M + Na]^+$.



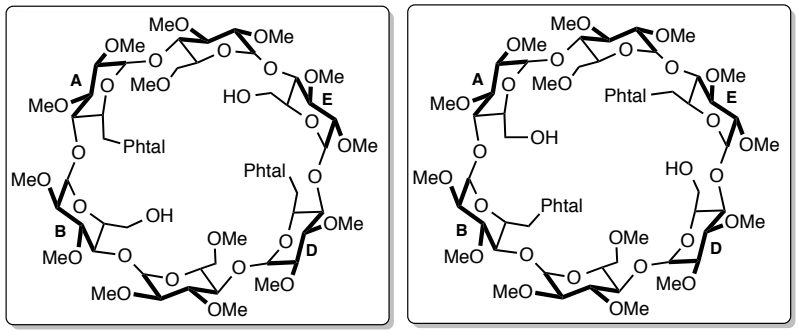
6^A-Deoxy-6^A-(S-thioacetylmethyl)-2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^C,6^D,6^E,6^F-hexadeca-*O*-methyl-α-cyclodextrin (9d) and 6^B-deoxy-6^B-(S-thioacetylmethyl)-2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^C,6^D,6^E,6^F-hexadeca-*O*-methyl-α-cyclodextrin (10d):

Powdered potassium thioacetate (0.073 g, 0.64 mmol) was added to a stirred solution of **5**–**AB** at 0°C (0.200 g, 0.16 mmol) in DMF (0.80 mL) according to the above procedure. Reaction led to an inseparable mixture of regioisomeres **9d** and **10d** (0.180 g, 91 %). R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.55; Retention time (reverse-phase column Pursuit C18, elution with MeCN:H_2O 1:1 over 40 min with a flow rate of 1mL.min^{-1}) = 14.82 and 16.32 min; Selected ^{1}H NMR signals (400.1 MHz, $CDCl_3$, 25ºC): δ = 2.30 (s, 0.87 H, $CH_3C(O)S$) and 2.33 (s, 3 H, $CH_3C(O)S$) ppm; elemental analysis (%) calcd for $C_{54}H_{94}O_{30}S{\cdot}0.5H_2O$ (1255.37 + 9.01): C 51.30, H 7.57, found: C 51.37, H 7.69; MS (ESI-TOF): *m/z* (%): 1277.54 (100) [*M* + Na]$^+$.



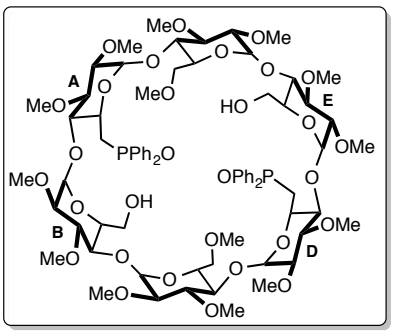
***P*,*P*'-{6^A,6^D-Dideoxy-6^A,6^D-di(diphenylphosphinyl)-2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^C,6^F-tetradeca-*O*-methyl-α-cyclodextrin} diborane (11a):** *n*-BuLi (1.60 M in hexane, 1.83 mL, 2.87 mmol) was added dropwise at –78°C to a stirred solution of diphenylphosphine (0.520 g, 725 µL of a 20.3% *wt/wt* solution in hexane, 0.57 mmol) in THF (10 mL). After 30 min, the dark red diphenylphosphide solution was transferred via a cannula to a stirred solution of **7** (0.200 g, 0.16 mmol) in THF (10 mL) kept at –78°C. The solution was further stirred at –78°C for 1 h before being allowed to reach 0°C over 1 h. BH_3·THF (1.00 M in THF, 10 mL, 10 mmol) was then added dropwise at 0°C, and the reaction mixture allowed to reach room temperature before being stirred for an additional 12 h. Once the solvent was removed *in vacuo*, the solid was taken in THF (8 mL) and H_2SO_4 (0.20 mL, 50% *wt/wt* solution in water) was added. The reaction mixture was stirred for 1 h at room temperature before adding saturated aqueous $NaHCO_3$ (50 mL). Subsequent extraction with $CHCl_3$ (3 × 50 mL) was followed by drying of the organic extracts ($MgSO_4$). Removal of the solvent in vacuo gave a colourless residue, which was subjected to column chromatography (SiO_2; CH_2Cl_2/MeOH, 97:3, v/v) to afford **11a** (0.140 g, 59%) as a colourless solid. R_f (SiO_2, CH_2Cl_2/MeOH, 92:8, *v*/*v*) = 0.38; Retention time (reverse-phase column Pursuit C18, isocratic elution with MeCN:H_2O, 1:1, with a flow rate of 1mL.min^{-1}) = 18.27 min; m.p. 142-145 °C.; ^{1}H NMR (300.1 MHz, $CDCl_3$, 25ºC): δ (assignment by COSY) = 1.10 (br s, 6 H, P-BH_3), 2.77 (s, 6 H, OMe-6), 2.85 (d, 2 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 11.2 Hz, H-6a^{C,F}), 3.02 (d, 4 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = $^2J_{H\text{-}6b,H\text{-}6a}$ = 11.9 Hz, H-6^{B,E}), 3.07–3.13 (8 H, H-2^{B,C,E,F}, H-6^{A,D}), 3.18 (d, 2 H, $^1J_{H\text{-}6b,H\text{-}6a}$ = 11.2 Hz, H-6b^{C,F}), 3.23 (dd, 2 H, $^3J_{H\text{-}2,H\text{-}3}$ = 9.9 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 2.8 Hz, H-2^{A,D}), 3.46 (s, 6 H, OMe), 3.47 (s, 6 H, OMe), 3.49 (s, 6 H, OMe), 3.59 (s, 6 H, OMe), 3.64 (s, 6 H, OMe), 3.69 (s, 6 H, OMe), 3.43–3.85 (18 H, H-3, H-4, H-5^{B,C,E,F}, OH), 4.39 (m, 2 H, H-5^{A,D}), 4.67 (d, 2 H, $^3J_{H\text{-}1,H\text{-}2}$ = 2.8 Hz, H-1^{A,D}), 5.01 (d, 2 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.1 Hz, H-1^{C,F}), 5.17 (d, 2 H, $^3J_{H\text{-}1,H\text{-}2}$ = 2.9 Hz, H-1^{B,E}), 7.36–7.50 (12 H, *m*-H, *p*-H), 7.73–7.86 (8 H, *o*-H) ppm; ^{13}C{^{1}H} NMR (75.5

MHz, $CDCl_3$, 25ºC): δ (assignment by HMQC) = 26.91 (d, $^1J_{C,P}$ = 37 Hz, C-$6^{A,D}$), 58.09 [×2], 58.76, 61.29, 61.38, 61.47, 61.76 (OMe), 61.29 (C-$6^{B,E}$), 69.23, 71.22, 71.49 (C-5), 69.93 (C-$6^{C,F}$), 79.63, 80.76, 80.84, 81.15, 81.28, 81.41, 82.03, 82.55 (C-2, C-3, C-4), 86.26 (d, $^1J_{C,P}$ = 5.7 Hz, C-$4^{A,D}$), 97.60, 100.00, 100.23 (C-1), 128.66 (d, $^3J_{C,P}$ = 10.5, C_{meta}), 128.80 (d, $^3J_{C,P}$ = 10.5, C_{meta}), 130.94 (s, C_{para}), 131.03 (s, C_{para}), 130.83 (d, $^1J_{C,P}$ = 16.0 Hz, C_{ipso}), 131.32 (d, $^1J_{C,P}$ = 21.0 Hz, C_{ipso}), 131.78 (d, $^2J_{C,P}$ = 9.0 Hz, C_{ortho}), 131.87 (d, $^2J_{C,P}$ = 9.0 Hz, C_{ortho}) ppm; $^{31}P\{^1H\}$ NMR (121.5 MHz, $CDCl_3$, 25ºC): δ = 12.5 (br s) ppm; elemental analysis (%) calcd for $C_{74}H_{112}B_2O_{28}P_2 \cdot 0.5MeOH$ (1532.70 + 16): C 57.76, H 7.42, found: C 57.97, H 7.36; MS (ESI-TOF): *m/z* (%): 1555.70 (100) $[M + Na]^+$.



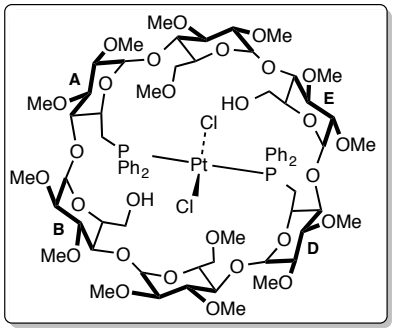
6^A,6^D-Dideoxy-6^A,6^D-di(1,3-dioxoisoindolin-2-yl)-2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^C,6^F-tetradeca-*O*-methyl-α-cyclodextrin (11b) and 6^A,6^C-dideoxy-6^A,6^C-di(1,3-dioxoisoindolin-2-yl)-2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^B,6^E-tetradeca-*O*-methyl-α-cyclodextrin (12b): Powdered potassium phthalimide (0.230 g, 1.24 mmol) was added to a stirred solution of **7** at 0°C (0.200 g, 0.16 mmol) in DMF (1.60 mL). The reaction mixture was allowed to reach room temperature in an ice bath for 12 h under stirring. The reaction mixture was then evaporated to dryness and the residue was retaken in THF (8 mL). H_2SO_4 (0.20 mL, 50% *wt/wt* solution in water) was added and the reaction mixture was stirred for 1 h at room temperature before adding saturated aqueous $NaHCO_3$ (50 mL). Subsequent extraction with $CHCl_3$ (3 × 50 mL) was followed by drying of the organic extracts ($MgSO_4$). Removal of the solvent in vacuo gave a colourless residue, which was subjected to column chromatography (SiO_2; CH_2Cl_2/MeOH, 97:3, v/v) to afford 2 colourless solids, **11b** (0.110 g, 50%) and **12b** (0.071 g, 28 %). **11b** R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.50; m.p. 164°C; ^1H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY, TOCSY, HMQC, and ROESY) = 2.71 (d, 2 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 11.1 Hz, H-$6a^{C,F}$), 2.72 (s, 3 H, OMe-$6^{C,F}$), 3.08 (dd, 2 H, $^3J_{H\text{-}2,H\text{-}3}$ = 9.7 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 3.8 Hz, H-$2^{C,F}$), 3.20 (dd, 2 H, $^3J_{H\text{-}2,H\text{-}3}$ = 9.9 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 2.7 Hz, H-$2^{A,D}$), 3.23 (dd, 2 H, $^3J_{H\text{-}2,H\text{-}3}$ = 5.1, $^3J_{H\text{-}2,H\text{-}1}$ = 3.3 Hz, H-$2^{B,E}$), 3.25 (t, 2 H, $^3J_{H\text{-}4,H\text{-}3}$ = $^3J_{H\text{-}4,H\text{-}5}$ = 10.1 Hz, H-$4^{B,E}$), 3.35 (t, 2 H, $^3J_{H\text{-}4,H\text{-}3}$ = $^3J_{H\text{-}4,H\text{-}5}$ = 9.0 Hz, H-$4^{A,D}$), 3.46 (s, 6 H, OMe-2), 3.50 (s, 6 H, OMe-2), 3.51 (s, 6 H, OMe-2), 3.52 (m, 2 H, H-$6b^{C,F}$), 3.58 (m, 2 H, H-$3^{C,F}$), 3.59 (m, 2 H, H-$3^{A,D}$), 3.60 (m, 2 H, H-$6a^{B,E}$), 3.61 (m, 2 H, H-$3^{B,E}$), 3.62 (s, 6 H, OMe-3), 3.63 (s, 6 H, OMe-3), 3.66 (m, 4 H, H-$4^{C,F}$, H-$5^{C,F}$), 3.67 (m, 2 H, H-$3^{C,F}$), 3.70 (s, 6 H, OMe-3), 3.99 (t, 2 H, $^2J_{H\text{-}6b,H\text{-}6a}$ = $^3J_{H\text{-}6b,H\text{-}5}$ = 12.8 Hz, H-$6b^{B,E}$), 4.03 (d, 2 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 13.9 Hz, H-$6a^{A,D}$), 4.30 (dd, 2 H, $^3J_{H\text{-}5,H\text{-}6b}$ = 12.8 Hz, $^3J_{H\text{-}5,H\text{-}4}$ = 10.1 Hz, H-$5^{B,E}$), 4.45 (ddd, 2 H, $^3J_{H\text{-}5,H\text{-}6a}$ = 3.2 Hz, $^3J_{H\text{-}5,H\text{-}6b}$ = 17.4 Hz, $^3J_{H\text{-}5,H\text{-}4}$ = 9.0 Hz, H-$5^{A,D}$), 4.87 (dd, 2 H, $^2J_{H\text{-}6b,H\text{-}6a}$ = 13.9 Hz, $^3J_{H\text{-}6b,H\text{-}5}$ = 3.2 Hz, H-$6b^{A,D}$), 4.88 (d, 2 H, $^3J_{H\text{-}1,H\text{-}2}$ = 2.7 Hz, H-$1^{A,D}$), 5.03 (d, 2 H,

$^{3}J_{H\text{-}1,H\text{-}2}$ = 3.8 Hz, H-1^{C,F}), 5.15 (d, 2 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1^{B,E}), 7.62–7.65 (4 H, *m*-H), 7.93–7.96 (4 H, *o*-H) ppm; $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$, 25ºC): δ (assignment by HMQC) = 40.11 (C-6^{A,D}), 57.49, 57.83, 58.45, 59.19, 61.33, 62.03, 62.18 (OMe), 62.69 (C-6^{B,E}), 68.05 (C-5), 70.03 (C-6^{C,F}), 71.18, 72.54 (C-5), 81.34, 81.39, 81.45, 81.52, 81.71, 81.78, 81.84, 82.90, 86.99 (C-2, C-3, C-4), 98.61, 99.42, 100.72 (C-1), 123.70 (C_{meta}^{A,D}), 132.19 (C_{ipso}^{A,D}), 134.21 (C_{ortho}^{A,D}), 168.93 (CO) ppm; elemental analysis (%) calcd for $C_{66}H_{94}N_2O_{32}\cdot 0.5CHCl_3$ (1427.45 + 58.96): C 53.71, H 6.40, N 1.58, found: C 53.71, H 6.68, N 1.58; MS (ESI-TOF): *m/z* (%): 1449.57 (100) [*M* + Na]$^{+}$. **12b** R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.53; m.p. 164°C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by COSY) = 2.98 (s, 3 H, OMe), 3.28 (s, 3 H, OMe), 3.43 (s, 3 H, OMe), 3.45 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 3.51 (s, 3 H, OMe), 3.52 (s, 3 H, OMe), 3.55 (s, 3 H, OMe), 3.60 (s, 3 H, OMe), 3.63 (s, 3 H, OMe), 3.65 (s, 3 H, OMe), 3.68 (s, 9 H, OMe), 3.05–4.40 (36 H, H-2, H-3, H-4, H-5, H-6), 4.94 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 2.7 Hz, H-1), 4.98 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.1 Hz, H-1), 5.00 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1), 5.13 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.1 Hz, H-1), 5.31 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 2.9 Hz, H-1), 5.42 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1), 7.64–7.91 (8 H, aromatic-H); $^{13}C\{^{1}H\}$ NMR (100.6 MHz, CDCl3, 25ºC): δ (assignment by HMQC) = 37.72 (C-6$^{A\text{ or }D}$), 38.82 (C-6$^{D\text{ or }A}$), 57.78 [×2], 58.03 [×2], 58.31, 58.38, 58.61, 59.09, 61.61, 61.66, 61.76, 61.82, 61.86, 62.05 (OMe), 61.35, 62.31, 71.31, 71.54 (C-6), 69.31, 69.40, 71.17, 71.46, 72.19, 72.24 (C-5), 81.08, 81.25 [×2], 81.43, 81.50, 81.59 [×2], 81.68, 81.70 [×2], 81.80, 81.88 [×2], 82.09 [×2], 82.43, 84.73, 85.21 (C-2, C-3, C-4), 98.97, 99.15, 99.33, 99.55, 99.91 [×2] (C-1), 123.17, 123.47 (C_{meta}), 132.11 [×2] (C_{ipso}), 134.09 [×2] (C_{ortho}), 168.51, 168.70 (CO) ppm; elemental analysis (%) calcd for $C_{66}H_{94}N_2O_{32}\cdot CH_2Cl_2$ (1427.45 + 84.93): C 53.21, H 6.40, N 1.85, found: C 53.01, H 6.64, N 1.61; MS (ESI-TOF): *m/z* (%): 1449.57 (100) [*M* + Na]$^{+}$.

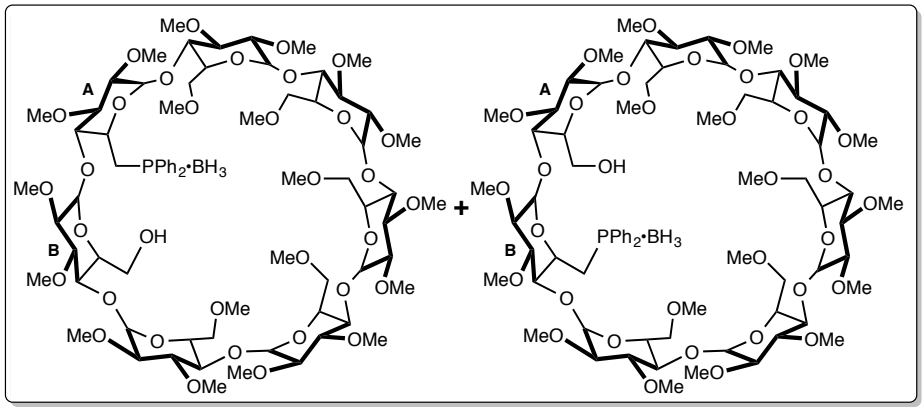


6^{A},6^{D}-Dideoxy-6^{A},6^{D}-di(diphenyloxophosphinyl)-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},6^{C},6^{F}-tetradeca-*O*-methyl-α-cyclodextrin (14): *n*-BuLi (1.20 mL of a 1.60 M solution in hexane, 1.94 mmol) was added dropwise at –78°C to a stirred solution of diphenylphosphine (0.520 g, 725 µL of a 20.3% *wt/wt* solution in hexane, 0.57 mmol) in THF (10 mL). After 30 min, the dark red diphenylphosphide solution was transferred via a cannula to a stirred solution of **3** (0.200 g, 0.16 mmol) in THF (10 mL) kept at –78°C. The solution was stirred at –78°C for a further 1 h. The reaction mixture was quenched at –78°C with distilled water (0.50 mL) and the colourless precipitate was filtered over Celite and the filtrate was evaporated to dryness. The dried filtrate was taken in THF (8 mL) and H_2SO_4 (0.20 mL, 50% *wt/wt* solution in water) was added. The reaction mixture was stirred for 1 h at room temperature before adding

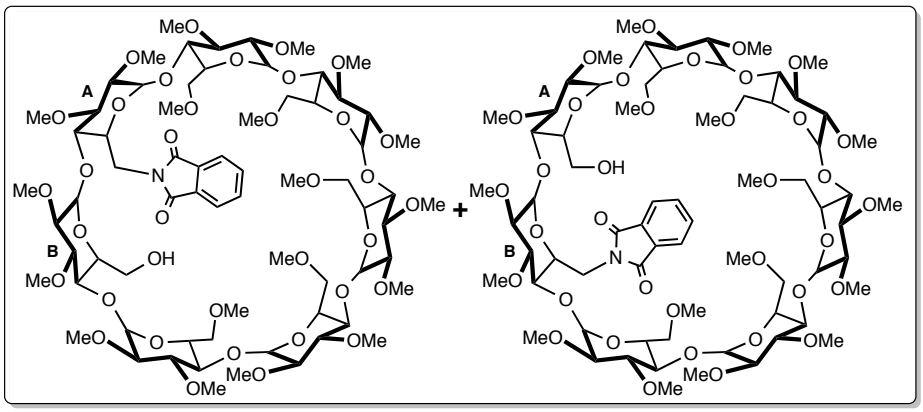
saturated aqueous $NaHCO_3$ (50 mL). Subsequent extraction with $CHCl_3$ (3 × 50 mL) was followed by drying of the organic extracts ($MgSO_4$). Removal of the solvent in vacuo gave a colourless residue which was dissolved in CH_2Cl_2 (20 mL) and then aqueous H_2O_2 (58 μL, 35% *wt/wt* solution in water, 0.56 mmol) was added. The mixture was stirred for 2 h at room temperature whereupon it was quenched with saturated aqueous $NaHCO_3$ (50 mL) then extracted with $CHCl_3$ (3 × 30 mL) and dried ($MgSO_4$). Evaporation of the solvents gave a colourless powder, which was subjected to column chromatography (SiO_2; CH_2Cl_2/MeOH, 97:3, v/v) to afford **14** (0.120 g, 50%) as a colourless solid. R_f (SiO_2, CH_2Cl_2/MeOH, 92:8, *v*/*v*) = 0.42; m.p. 135-137 °C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY, TOCSY, HMQC, and ROESY) = 2.53 (ddd, 2 H, $^2J_{H\text{-}6a,P}$ = 15.3 Hz, $^2J_{H\text{-}6a,H\text{-}6b}$ = 11.1 Hz, $^2J_{H\text{-}6a,H\text{-}5}$ = 3.2 Hz, H-6a^{A,D}), 2.63 (s, 6 H, OMe-6^{C,F}), 3.13 (dd, 2 H, $^3J_{H\text{-}2,H\text{-}3}$ = 9.8 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 2.7 Hz, H-2^{A,D}), 3.16 (dd, 2 H, $^3J_{H\text{-}2,H\text{-}3}$ = 10.1 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 3.8 Hz, H-2^{C,F}), 3.17 (m, 2 H, H-6a^{C,F}), 3.29 (dd, 2 H, $^3J_{H\text{-}2,H\text{-}3}$ = 9.5 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 3.9 Hz, H-2^{B,E}), 3.39 (s, 6 H, OMe-3), 3.43–3.48 (4 H, H-6b^{C,F}, H-4^{A,D}), 3.51 (s, 6 H, OMe-2), 3.54 (s, 6 H, OMe-2), 3.57 (s, 6 H, OMe-2), 3.64 (m, 2 H, H-6b^{A,D}), 3.66 (m, 2 H, H-3^{A,D}), 3.68 (s, 6 H, OMe-3), 3.72 (dd, 2 H, $^3J_{H\text{-}3,H\text{-}2}$ = 10.1 Hz, $^3J_{H\text{-}3,H\text{-}4}$ = 18.1 Hz, H-3^{C,F}), 3.73 (dd, 2 H, $^3J_{H\text{-}3,H\text{-}2}$ = 9.5 Hz, $^3J_{H\text{-}3,H\text{-}4}$ = 18.1 Hz, H-3^{B,E}), 3.82 (dd, 2 H, $^3J_{H\text{-}4,H\text{-}3}$ = 18.0 Hz, $^3J_{H\text{-}4,H\text{-}5}$ = 8.8 Hz, H-4^{C,F}), 3.85 (s, 6 H, OMe-3), 3.89 (d, 2 H, $^3J_{H\text{-}5,H\text{-}4}$ = 8.8 Hz, H-5^{C,F}), 3.95–4.03 (4 H, H-5^{B,E}, H-6a^{B,E}), 4.02 (dd, 2 H, $^3J_{H\text{-}4,H\text{-}3}$ = 18.1 Hz, $^3J_{H\text{-}4,H\text{-}5}$ = 10.3 Hz, H-4^{B,E}), 4.42 (d, 2 H, $^2J_{H\text{-}6b,H\text{-}6a}$ = 11.1 Hz, H-6b^{B,E}), 4.48 (ddd, 2 H, $^3J_{H\text{-}5,H\text{-}6a}$ = 3.2 Hz, $^3J_{H\text{-}5,H\text{-}6b}$ = 17.4 Hz, $^3J_{H\text{-}5,H\text{-}4}$ = 8.8 Hz, H-5^{A,D}), 4.69 (d, 2 H, $^3J_{H\text{-}1,H\text{-}2}$ = 2.7 Hz, H-1^{A,D}), 4.94 (d, 2 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.9 Hz, H-1^{B,E}), 5.58 (d, 2 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.8 Hz, H-1^{C,F}), 6.03 (br s, 2 H, OH^{B,E}), 7.12 (td, 4 H, $^3J_{o\text{-}H,m\text{-}H}$ = $^3J_{o\text{-}H,P}$ = 7.6, $^4J_{o\text{-}H,p\text{-}H}$ = 3.0 Hz, *o*-H), 7.23 (td, 2 H, $^3J_{m\text{-}H,o\text{-}H}$ = $^3J_{m\text{-}H,p\text{-}H}$ = 7.6, $^4J_{m\text{-}H,P}$ = 1.3 Hz, *m*-H), 7.47–7.57 (10H, *o*-H, *m*-H, *p*-H), 7.78–7.84 (4H, *m*-H) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 25ºC): δ (assignment by HMQC) = 32.26 (d, $^1J_{C,P}$ = 73.4 Hz, C-6^{A,D}), 56.98, 58.18, 58.32, 59.60, 59.65 (OMe), 60.08 (C-6^{B,E}), 61.82, 62.14 (OMe), 68.23 (d, $^2J_{C,P}$ = 7.3 Hz, C-5^{A,D}), 70.43 (C-5), 70.88 [×2] (C-4, C-5), 71.54 (C-6^{C,F}), 80.40, 80.98, 81.16, 81.78 [×2], 81.88, 84.15, 88.08 (C-2, C-3, C-4), 96.81, 96.95, 97.01(C-1), 128.46 (d, $^3J_{C,P}$ = 11.7, C$_{meta}$), 128.53 (d, $^3J_{C,P}$ = 11.7, C$_{meta}$), 130.34 (s, C$_{para}$), 130.44 (s, C$_{para}$), 131.28 (d, $^2J_{C,P}$ = 18.6 Hz, C$_{ortho}$), 131.41 (d, $^2J_{C,P}$ = 26.1 Hz, C$_{ortho}$), 133.57 (d, $^1J_{C,P}$ = 100.8 , C$_{ipso}$), 135.40 (d, $^1J_{C,P}$ = 102.8 , C$_{ipso}$) ppm; ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$, 25ºC): δ = 32.66 (s) ppm; elemental analysis (%) calcd for $C_{74}H_{106}O_{30}P_2 \cdot 0.5CH_2Cl_2$ (1537.56 + 42.5): C 56.63, H 6.83, found: C 56.81, H 7.10; MS (ESI-TOF): *m/z* (%): 1559.62 (100) $[M + Na]^+$.



6^{A},6^{D}-Dideoxy-6^{A},6^{D}-di(diphenylphosphinyl)-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},6^{C},6^{F}-tetradeca-*O*-methyl-α-cyclodextrin (15). 11a (80 mg, 0.053 mmol) was dissolved in diethylamine (8 mL) and the resulting solution was heated at reflux for 10 h. The precipitate was filtered off over Celite and filtrate was evaporated under vacuum. A solution of $[PtCl_2(PhCN)_2]$ (0.031 g, 0.0656 mmol) in CH_2Cl_2 (50 mL) was then added to the solid in CH_2Cl_2 (200 mL), under vigorous stirring. After 20 min the reaction mixture was evaporated to dryness, and subsequent solid was subjected to column chromatography (SiO_2; CH_2Cl_2/MeOH, 98:2, v/v) to afford **15** (0.052 g, 44 %) as a pale yellow solid. R_f (SiO_2, CH_2Cl_2/MeOH, 92:8, *v*/*v*) = 0.44; m.p. dec.; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by COSY) = 2.82 (t, 2 H, $^2J_{H\text{-}6a,H\text{-}6b} = {}^3J_{H\text{-}6a,H\text{-}5}$ = 13.1 Hz, H-6a^{A,D}), 2.93 (s, 6 H, OMe-6^{C,F}), 3.00 – 3.08 (6 H, H-2$^{A,D\text{ and }C,F\text{ or }B,E}$, H-4^{A}), 3.11 – 3.18 (4 H, H-2, H-6a^{B,E}), 3.28 (br d, 2 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 13.1 Hz, H-6b^{A,D}), 3.38 (d, 2 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 12.8 Hz, H-6a^{C,F}), 3.46 (s, 6 H, OMe), 3.48 (s, 6 H, OMe), 3.53 (s, 6 H, OMe), 3.60 (s, 6 H, OMe), 3.65 (s, 6 H, OMe), 3.77 (s, 6 H, OMe), 3.45 – 3.83 (14 H, H-3, H-4^{B,C,E,F}, H-6b^{B,C,E,F}), 3.95 – 4.03 (6 H, H-5^{B,C,E,F}, OH^{B,E}), 4.70 (d, 2 H, $^3J_{H\text{-}1,H\text{-}2}$ = 2.2 Hz, H-1^{A,D}), 5.06 (d, 2 H, $^3J_{H\text{-}1,H\text{-}2}$ = 2.9 Hz, H-1), 5.10 (d, 2 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.0 Hz, H-1), 5.16 (t, 2 H, ^3J = 9.4 Hz, H-5^{A,D}), 7.31 – 7.43 (12 H, *m*-H, *p*-H), 7.49 – 7.56 (4 H, *o*-H), 8.05 – 8.12 (4 H, *o*-H) ppm; ^{13}C{^{1}H} NMR (150.9 MHz, $CDCl_3$, 25ºC): δ (assignment by HMQC) = 34.61 (C-6^{A,D}), 58.19, 58.43 (OMe-2), 59.77 (OMe-6), 59.87 (OMe-2), 61.77, 62.05, (OMe-3), 62.10 (C-6^{B,E}) 62.32 (OMe-3), 70.60 (C-5^{A,D}), 71.16 (C-6^{C,F}), 72.12, 72.86 (C-5^{B,C,E,F}), 80.53, 81.24, 81.39, 81.65, 81.68, 82.06, 82.48, 83.89 (C-2, C-3, C-4^{B,C,E,F}), 90.16 (C-4^{A,D}), 98.48 (C-1^{A,D}), 98.94, 101.24 (C-1^{B,C,E,F}), 128.08 (virtual t, $^3J_{C,P} = {}^5J_{C,P'}$ = 4.7 Hz, *m*-C), 128.54 (virtual t, $^3J_{C,P} = {}^5J_{C,P'}$ = 4.7 Hz, *m*-C), 130.62 (s, *p*-C), 131.24 (s, *p*-C), 133.65 (virtual t, $^2J_{C,P} = {}^4J_{C,P'}$ = 5.6 Hz, *o*-C), 136.35 (virtual t, $^2J_{C,P} = {}^4J_{C,P'}$ = 5.6 Hz, *o*-C) ppm, *ipso*-C not detected; ^{31}P{^{1}H} NMR (161.9 MHz, $CDCl_3$, 25ºC): δ = 7.37 (s with Pt satellites, $^1J_{P,Pt}$ = 2644 Hz) ppm; elemental analysis (%) calcd for $C_{74}H_{106}Cl_2O_{28}P_2Pt{\cdot}2MeOH{\cdot}CH_2Cl_2$ (1793.52 + 64 + 85): C 47.94, H 6.20, found: C 48.15, H 6.12; MS (ESI-TOF): *m*/*z* (%): 1793.52 (67) $[M + Na]^+$, 1809.50 (33) $[M + K]^+$.

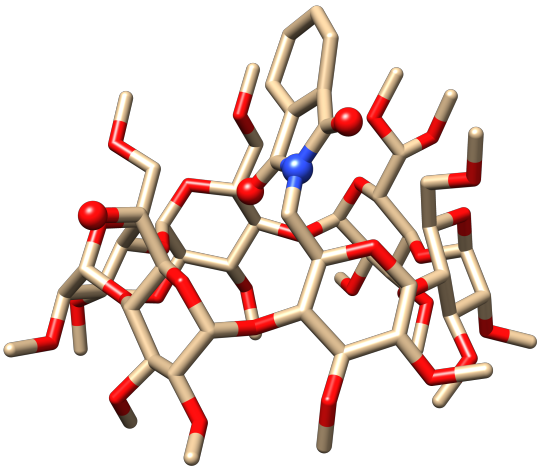


***P*-{6^{A}-Deoxy-6^{A}-diphenylphosphinyl-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},2^{G},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},3^{G}, 6^{C},6^{D},6^{E},6^{F},6^{G}-nonadeca-*O*-methyl-*β*-cyclodextrin} borane (18a) and *P*-{6^{B}-deoxy-6^{B}-diphenylphosphinyl-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},2^{G},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},3^{G},6^{C},6^{D},6^{E},6^{F},6^{G}-nonadeca-*O*-methyl-*β*-cyclodextrin} borane (19a):** Prepared from **6**–**AB** (0.200 g, 0.14 mmol) according to **5a** procedure. Reaction led to an inseparable mixture of regioisomeres **18a** and **19a** (0.204 g, 96 %). R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.51; Selected $^{31}P\{^{1}H\}$ NMR signals (121.5 MHz, $CDCl_3$, 25ºC): δ = 13.43 and 14.25 ppm; elemental analysis (%) calcd for $C_{73}H_{120}BO_{34}P{\cdot}2CH_2Cl_2$ (1583.50 + 169.87): C 51.38, H 7.13, found: C 51.45, H 7.10; MS (ESI-TOF): *m/z* (%): 1605.74 (100) $[M + Na]^+$.

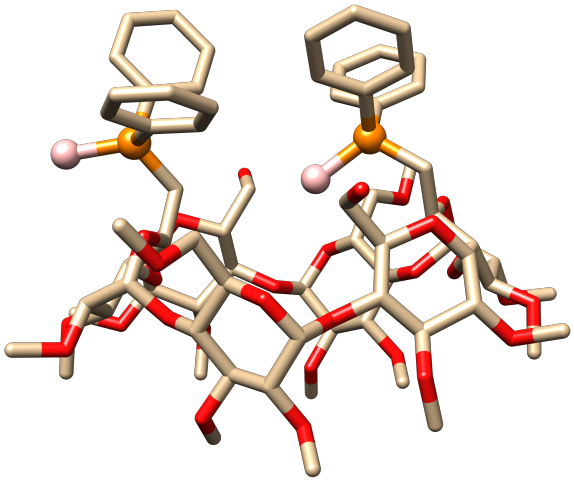


6^{A}-Deoxy-6^{A}-(1,3-dioxoisoindolin-2-yl)-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},2^{G},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},3^{G}, 6^{C},6^{D},6^{E},6^{F},6^{G}-nonadeca-*O*-methyl-*β*-cyclodextrin (18b) and 6^{B}-deoxy-6^{B}-(1,3-dioxoisoindolin-2-yl)-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},2^{G},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},3^{G},6^{C},6^{D},6^{E},6^{F},6^{G}-nonadeca-*O*-methyl-*β*-cyclodextrin (19b): Prepared from **6**–**AB** (0.200 g, 0.14 mmol) according to **5b** procedure. Reaction led to an inseparable mixture of regioisomeres **18b** and **19b** (0.160 g, 76 %). R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.46; elemental analysis (%) calcd for $C_{69}H_{111}NO_{36}{\cdot}CH_3C(O)OC_2H_5$ (1530.60 + 88.11): C 54.17, H 7.41, N 0.87 found: C 54.23, H 7.39, N 0.89; MS (ESI-TOF): *m/z* (%): 1552.68 (100) $[M + Na]^+$.

II. 4. 4. Crystal structure analyses



X-ray crystallographic data of 9b: Single crystals of **9b** were obtained by slow diffusion of pentane into a dichloromethane solution of the compound. Crystal data for $C_{60}H_{95}NO_{31}\cdot 0.5CH_2Cl_2\cdot H_2O\cdot 1.5C_5H_{12}$ (**9b**$\cdot 0.5CH_2Cl_2\cdot H_2O\cdot 1.5C_5H_{12}$), M_r = 1495.07, monoclinic, space group $P2_1$, a = 15.2970(10), b = 15.7262(8), c = 16.6710(10) Å, β = 90.778(6)°, V = 4010.1(4) Å^3, Z = 2, ρ_{calcd} = 1.238 g cm^{-3}, $\lambda(Mo_{K\alpha})$ = 0.71073 Å, μ = 0.129 mm^{-1}, $F(000)$ = 1608, T = 120 K. The sample (0.26 × 0.16 × 0.08 mm) was studied with an Oxford Diffraction Xcalibur Saphir 3 CCD with graphite monochromatised $Mo_{K\alpha}$ radiation. The structure was solved with SIR-97,[14] which revealed the non-hydrogen atoms of the molecule. After anisotropic refinement, many hydrogen atoms were found with a Fourier difference analysis. The whole structure was refined with SHELX-97[15] and full-matrix least-square techniques. Use of F^2 magnitude; x, y, z, β_{ij} for C, O, S atoms, x, y, z, in riding mode for H atoms, 917 variables and 7789 observations with [$I > 2.0\sigma(I)$], R = 0.0680, R_W = 0.1911, and S_w = 0.830, $\Delta\rho$ < 0.929 e Å^{-3}. The compound is rather poor diffracting. It crystallizes with half a molecule of pentane inside the cavity and one molecule of pentane, half a molecule of CH_2Cl_2 and one water molecule outside. It must be emphasised that the O46-C49 O-methyl and C62....C67 aromatic groups are disordered. The disordered aromatic group was refined in isotropical mode due to correlations in anisotropical mode. The A-level alerts in the checkcif are mainly due to the external pentane molecule, which is difficult to refine. CCDC 826891.



X-ray crystallographic data of 11a: Single crystals of **11a** were obtained by slow diffusion of pentane into a dichloromethane solution of the compound. Crystal data for $C_{74}H_{112}B_2O_{28}P_2 \cdot 3CH_2Cl_2 \cdot 1.5C_5H_{12}$ (**11a**$\cdot 3CH_2Cl_2 \cdot 1.5C_5H_{12}$), M_r = 1896.19, orthorhombic, space group $P2_12_12_1$, a = 16.0969(4), b = 22.4367(5), c = 27.7517(7) Å, V = 10022.8(4) Å^3, Z = 4, ρ_{calcd} = 1.257 g cm^{-3}, $\lambda(Mo_{K\alpha})$ = 0.71073 Å, μ = 0.274 mm^{-1}, $F(000)$ = 4036, T = 120 K. The sample (0.22 × 0.12 × 0.10 mm) was studied with an Oxford Diffraction Xcalibur Saphir 3 CCD with graphite monochromatised $Mo_{K\alpha}$ radiation. The structure was solved with SIR-97,[14] which revealed the non-hydrogen atoms of the molecule. After anisotropic refinement, many hydrogen atoms were found with a Fourier difference analysis. The whole structure was refined with SHELX-97[15] and full-matrix least-square techniques. Use of F^2 magnitude; x, y, z, β_{ij} for C, O, S atoms, x, y, z, in riding mode for H atoms, 1029 variables and 8413 observations with [$I > 2.0\sigma(I)$], R = 0.0935, R_W = 0.2645, and S_w = 0.932, $\Delta\rho$ < 0.658 e Å^{-3}. CCDC 822184.

II. 5. References

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Chapter III

Heterobidentate ligands built on a cyclodextrin platform: application in rhodium catalysed asymmetric reactions

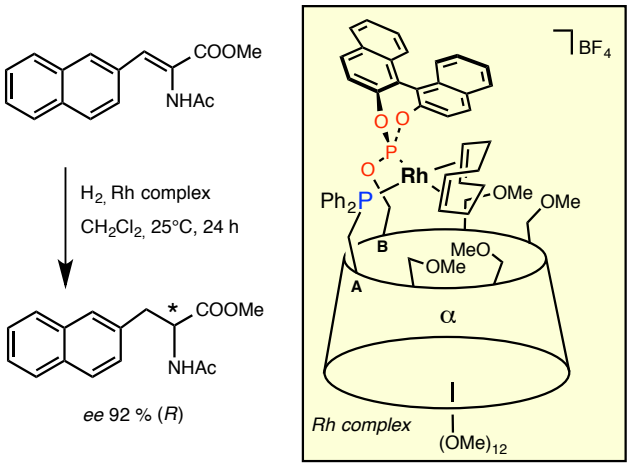
Chapter III

Heterobidentate ligands built on a cyclodextrin platform: application in rhodium catalysed asymmetric reactions

Summary – Chapter III

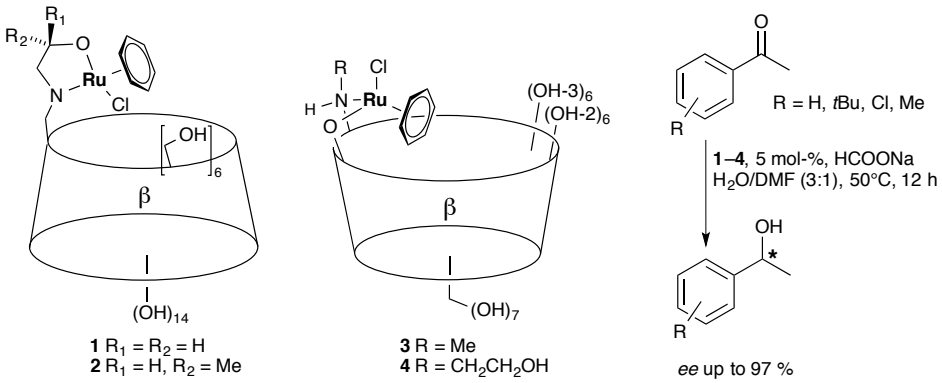
Four hybrid *phosphine-phosphite* ligands were synthesised by regioselective A,B-functionalisation of a methylated α-cyclodextrin (α-CD) scaffold (See chapter II). In all these ligands the phosphite part comprises a 2,2'-bis(aryloxy)phosphinoxy group. The ligands, which display inherent chirality (as defined by Böhmer), readily form 12-membered chelate rings with d^8-metal ions. In the most flexible chelates (those with an unsubstituted 2,2'-bisphenoxy group), the metal plane describes a fan-like motion about the P···P' axis, this occurring with concomitant fast atropisomerisation of the biaryl unit. When the latter is blocked, as in the 2,2'-binapthyloxyphosphites, the fanning motion no longer takes place. Rhodium complexes of the CDs were assessed in asymmetric hydrogenation of α-dehydroamino acid esters and hydroformylation of styrene. Poor enantiodiscrimination was observed for the highly mobile chelate complexes, while the more rigid ones all resulted in significant *ee*'s. The best performing hydrogenation catalyst is the one in which both chiral components – CD and (*S*)-binapthyl – may act in a synergistical way. An α-CD amino alcohol was also synthesised using the regioselective A,B functionalization described in chapter II. It was used for the attempted synthesis of hybrid *P,N* ligands.

Quatre coordinats mixtes phosphine-phosphite ont été synthétisés à partir d'une α-cyclodextrine (CD) méthylée, préfonctionnalisée au niveau de deux unités glucose adjacentes (Voir chapitre II). Les parties phosphite des ligands sont soit du type 2,2'-bis(phenoxy)phosphinoxy, soit du type 2,2'-binapthyloxyphosphinoxy. Ces coordinats ont deux caractéristiques principales: a) ils présentent une chiralité inhérente telle que définie par Böhmer; b) ils forment facilement des chélates à 12 chainons avec les ions métalliques d^8. En solution, le plan métallique des complexes comportant l'entité 2,2'-bis(phenoxy)phosphinoxy décrit un mouvement d'éventail autour de l'axe virtuel P···P', concomitamment à une atropoisomérisation rapide du groupement biaryle. Dans les complexes comportant l'entité 2,2'-binaphthyloxyphosphinoxy, l'atropoisomérisation est empêchée et le mouvement d'éventail n'est plus observé. Les quatre ligands, associés à du rhodium, ont été évalués en hydrogénation asymétrique d'esters de déhydroaminoacides N-substitués ainsi qu'en hydroformylation du styrène (rhodium). L'énantiodiscrimination observée peut atteindre 92% avec les chélates présentant une forte rigidité, mais elle est beaucoup plus faible pour les chélates ayant une grande flexibilité. Le catalyseur qui conduit aux meilleurs résultats en hydrogénation est celui dans lequel les deux composantes chirales – CD et (S)-binaphthyle – peuvent agir en synergie. Un aminoalcool dérivé d'α-CD a également été synthétisé en utilisant la méthode de fonctionnalisation régiosélective décrite dans le chapitre II. Le potentiel de ce dernier pour la synthèse d'hybrides P,N a été évalué.



III. 1. Introduction

Despite the presence of numerous stereogenic centres embedded in their rigid skeleton, to date only few CD derived ligands have been used in asymmetric catalysis. In the corresponding metal catalysts the reaction usually takes place outside the cavity that is far from the centres of chirality where efficient asymmetric induction could occur. Nevertheless, when the catalytic centre of these complexes is maintained in a rigid manner with respect to the CD backbone, significant *ee*'s can be obtained. Such a feature has been observed, for example, in metallo-CDs capable of forming transient inclusion complexes in a water/DMF mixture with the prochiral substrates to be transformed (Scheme 1).[1] With these supramolecular catalysts, which consist in CD derivatives bearing an appended chiral amino alcohol on either side of the CD torus, ketones were enantioselectively reduced with ruthenium (up to 97% *ee*).



Scheme 1. Enantioselective reduction of ketones using supramolecular catalysts **1**–**4**.

Chirality transfer from the glucose units to the metal first sphere of coordination could be also often very effective when *rigid* chelate complexes can be obtained from CDs bearing two close pendant arms (Figure 1). However, only few report dealing with asymmetric catalysis using CD based ligands in organic media have been reported today.[2]

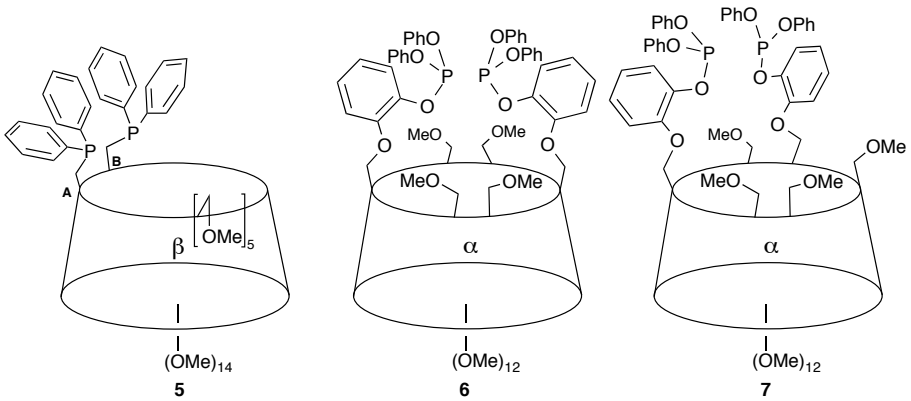


Figure 1. CD derivatives used for asymmetric hydrogenation.

A potential strategy for enhancing the chiral induction of a conical cavitand consists in making its shape *inherently chiral* by anchoring regiospecifically a set of distinct groups on its conical backbone, so as to produce a macrocycle with a substitution pattern non superimposable with its mirror image (Figure 2).[3] Note, the term inherent chirality was first introduced by Böhmer and co-workers, namely for calixarenes having a non-symmetrical substitution pattern.[4] It was recently extended to CDs by Sollogoub as exposed in the first chapter of this thesis (See Chapter I, **41a**, **41b** and **42**).[5] However, whether the effects of inherent chirality will synergistically add to those induced by the asymmetric centres of the backbone is difficult to predict. It is worth mentioning here that diphosphine based on other inherently chiral macrocycles have already been reported.[6]

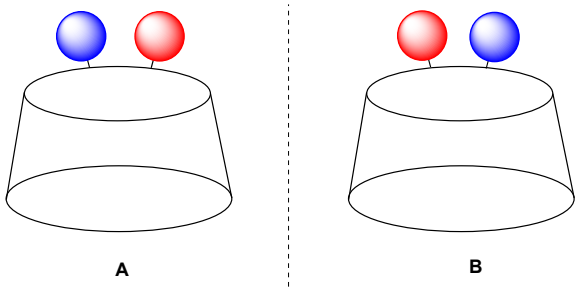


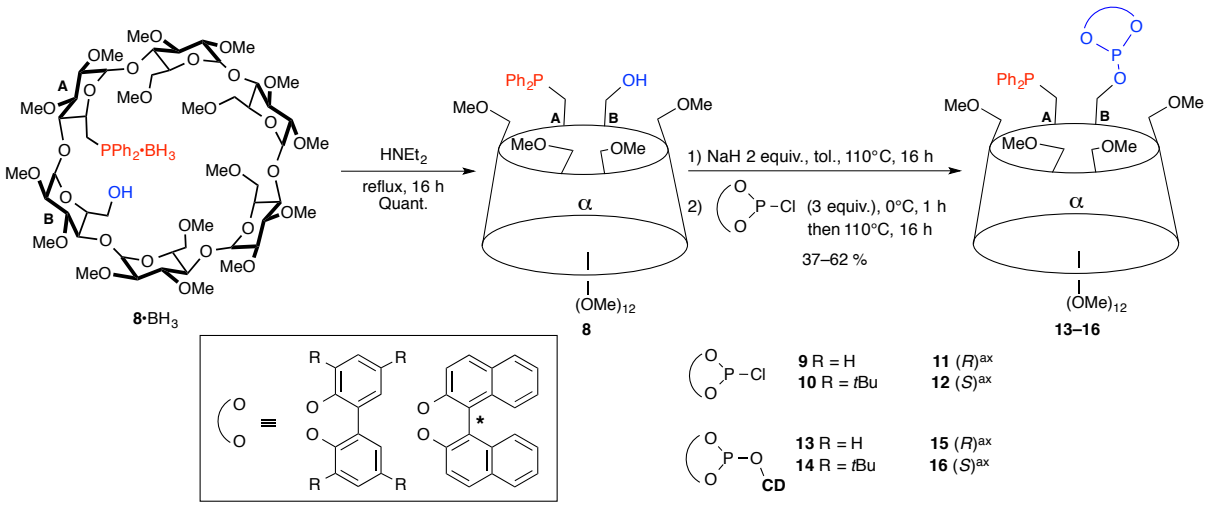
Figure 2. Principe of inherently chirality of conical cavitands.

In this chapter we describe the first *inherently chiral* CDs bearing two distinct coordinating groups, namely a phosphine unit and a phosphite one. This type of hybrid ligand has been chosen because *i*) chiral *phosphine-phosphites* constitute a class of ligands that have found many applications in asymmetric catalytic transformations,[7] notably hydrogenation[8] and hydroformylation[9] of prochiral olefins; *ii*) of the easy access of the starting hybrid cavitand using the regioselective sulfate opening described in chapter II, namely phosphine-borane adduct **8•BH$_3$** (called **9a** in chapter II). The resulting CD derivatives are ideal for chelate formation and have been assessed in the rhodium-catalysed hydrogenation of α-dehydroamino acid esters and hydroformylation of styrene. Also, taking advantage of the tridifferentiation methodology described in chapter II, we describe the synthesis of the α-CD amino alcohol **28**, which was used for the attempted preparation of hybrid phosphite-phosphoramidite ligands.

III. 2. Results and discussion

III. 2. 1. Synthesis of phosphine-phosphite hybrid ligands

The phosphine borane adduct **8•BH$_3$** described in chapter II, was the starting material for the synthesis of the heterobidendate ligands. Its deprotection was carried out with boiling diethylamine (Scheme 2).[10] Surprisingly, phosphorochloridites **9-12** did not react with the CD primary hydroxyl group of **8** in the presence of a tertiary amine such as NEt_3, which are reaction conditions generally used for the formation of phosphites from secondary and tertiary alcohols. Only the CD alkoxide obtained by reacting **8** with NaH in hot toluene (110 °C), was nucleophilic enough to give the corresponding *phosphine-phosphite* ligands **13-16** with isolated yields ranging from 37 to 62 %.



Scheme 2. Synthesis of *phosphine-phosphite* ligands **13-16**.

The chemical shifts for the two phosphorus donor atoms are typical of phosphite ($146.6 \leq \delta \leq 150.7$ ppm) and diarylalkylphosphine ($-21.4 \leq \delta \leq -20.3$ ppm) functionalities. All NMR spectra displayed sharp signals at room temperature except for biphenyl derivative **14**, the $^{31}P\{^{1}H\}$ NMR spectrum of which, recorded at 60°C, showed a broad singlet for the phosphite phosphorus atom, while the phosphine signal was sharp. This is likely due to a fluxional behaviour involving the *t*Bu–substituted biphenyl unit, which is congested enough to interact sterically with the CD platform so that slow interconversion of biphenyl occurs at the NMR time scale as previously noticed for similar bulky bis(phosphites).[11] This is obviously not the case with the less sterically demanding ligand **13** in which the same process is much faster, neither so in the binaphthyl derivatives **15** and **16** where free rotation about the aryl-aryl bond is prevented. None of our ligands displayed ^{31}P–^{31}P through-space coupling, unlike other sugar-based *phosphine-phosphite* ligands.[12]

III. 2. 2. Chelating properties

Despite the 10-bond separation between the two donor atoms, we were delighted to find out that all CD ligands form readily chelate complexes, as could easily be deduced from a combination of ESI-MS and NMR spectroscopy. Thus, the neutral Pt(II) complex **17** (Figure 3) was obtained quantitatively by reacting a stoichiometric amount of the *phosphine-phosphite* ligand **13** with $[PtCl_2(PhCN)_2]$ in CH_2Cl_2 (mass spectrum showing a peak corresponding to the $[M + Na]^+$ cation). It is noteworthy that chelate formation did not require high dilution conditions. Cationic complexes could also be obtained, again without oligomeric material being formed, by simply mixing the ligand with a metal precursor. For example, the Rh complexes **18**–**21** were obtained by reacting $[Rh(COD)_2]BF_4$ with the appropriate heterobidentate ligand (**13**–**16**) in CH_2Cl_2. The NMR spectra of the platinum complex **17**, and the rhodium complexes **19** and **20**, are broad at room temperature. Upon raising the temperature to 60°C, all NMR spectra became sharp. The ^{31}P–^{31}P coupling constants for all five complexes are typical of *cis* stereochemistry (23 Hz $\leq {}^2J_{P,P'} \leq$ 42 Hz).[8a] As expected for C_1-symmetric compounds, four distinct signals were detected for the vinylic protons of the coordinated cyclooctadiene in all rhodium complexes.

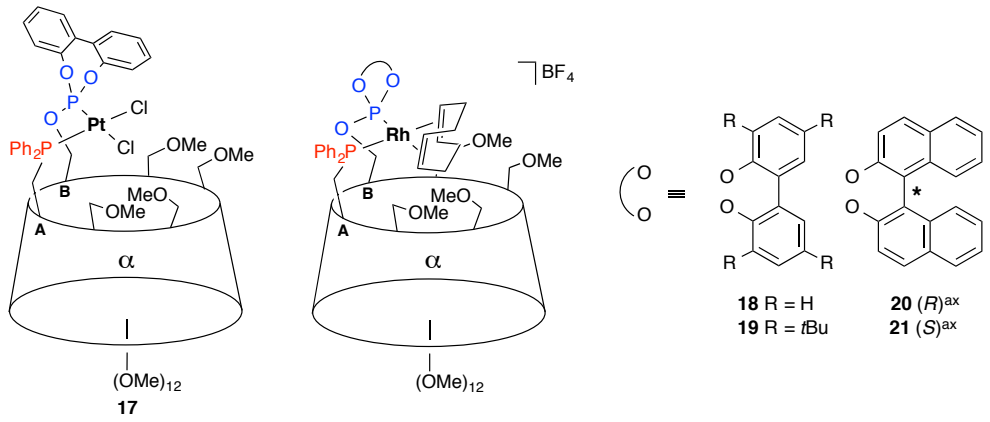


Figure 3. *cis*–Chelate complexes obtained from hybrid ligands **13**-**16**.

As revealed by a variable-temperature (VT) NMR study, complex **17** displayed fluxional behaviour in solution. The $^{31}P\{^1H\}$ NMR spectrum recorded in $CDCl_3$ at –60°C (CD_2Cl_2 was not used for the VT NMR studies because of poor solubility of **17** in this solvent at low temperature) revealed the presence of four species, two of them having broad signals at this temperature while the other two, present in a 60:40 ratio, displayed sharp ones (Figure 4, bottom). Each of the latter are characterized by an ABX pattern ($^2J_{PA,PB}$ = 23 Hz, $^1J_{PA,Pt}$ = 3343 Hz and $^1J_{PB,Pt}$ = 5878 Hz (major species, *open squares*) and $^2J_{PA,PB}$ = 23 Hz, $^1J_{PA,Pt}$ = 3364 Hz and $^1J_{PB,Pt}$ = 5965 Hz (minor species, *filled squares*)) indicative of *cis* complexes. Upon raising the temperature (Figure 4, top), the signals first broadened, then coalesced near –30°C, and finally merged at +60°C into a single ABX spectrum ($^2J_{PA,PB}$ = 23 Hz, $^1J_{PA,Pt}$ = 3408 Hz and $^1J_{PB,Pt}$ = 6136 Hz).

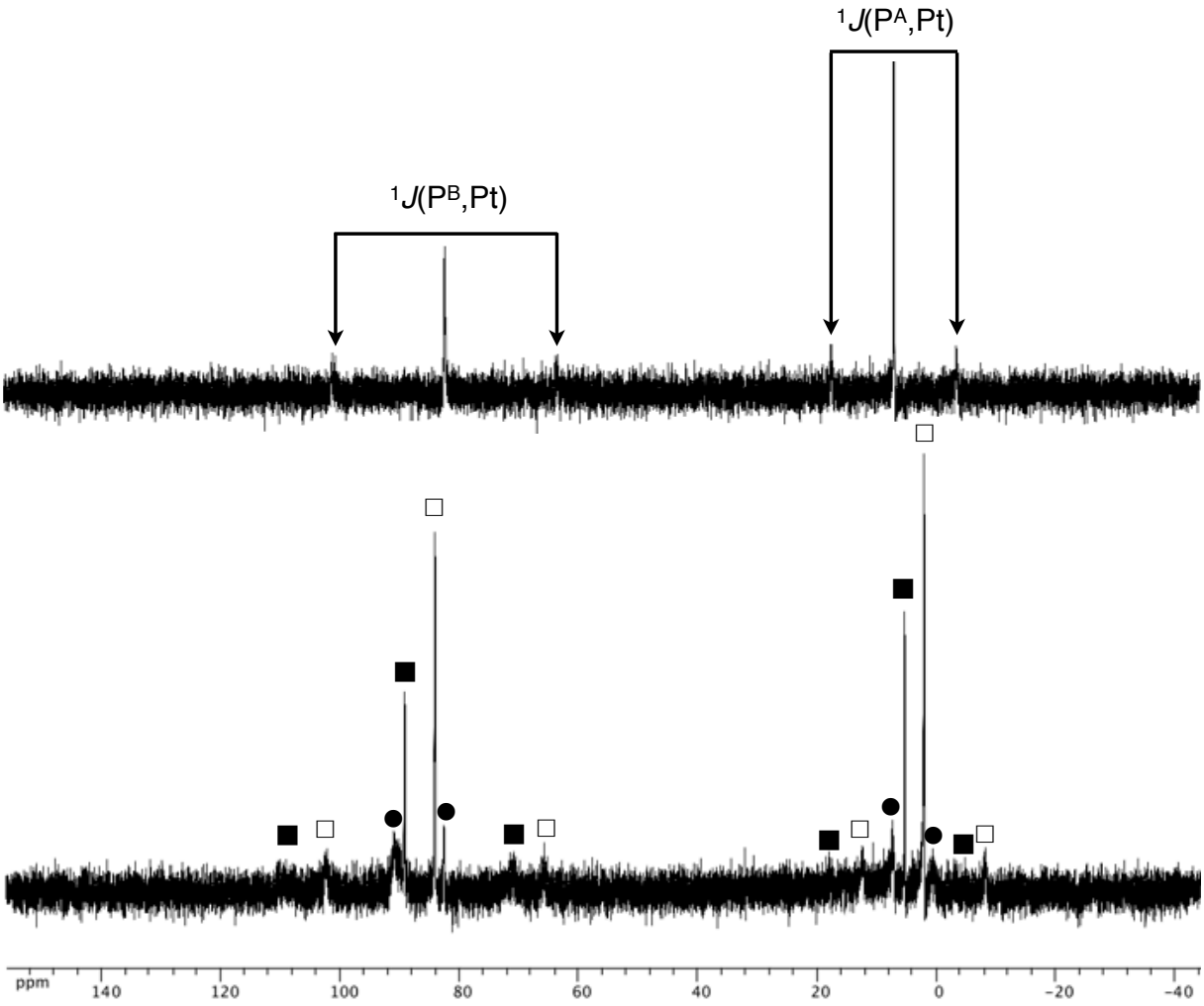


Figure 4. $^{31}P\{^1H\}$ NMR spectra of platinum complex **17**, recorded in $CDCl_3$ at 121.5 MHz +60°C (top) and at –60°C (bottom). The ABX patterns of the two sharp species are represented by filled and open squares whereas the two broad species are represented by dots.

The best way to rationalise the observed data is to consider two different motions. One of them involves interconversion of the sterically unhindered biphenyl unit, while the second one is related to a fan-like movement of the $\{P_2PtCl_2\}$ plane about the $P^A\cdots P^B$ axis with a free energy of activation $\Delta G^{\neq} = (10.7 \pm 0.2)$ kcal mol^{-1}). Confirmation of the flexibility of the rather large chelate ring came from a ROESY experiment at 60°C, which showed that **10** gave rise to cross-peaks originating from through-space correlations between the outer-cavity H-4^A proton and ortho–aromatic protons of *both* phenyl rings of the PPh_2 unit. SPARTAN calculations produced two energy-minimized conformers, one of them having its $\{P_2PtCl_2\}$ unit oriented towards the centre of the cavity, the other being clearly located outside (Figure 5). In keeping with the observed NMR data, the phenyl ring that comes close to the CD is different in each conformer. The calculations also revealed that in the "in" and "out" forms the bis-aryl moieties have opposite configurations.

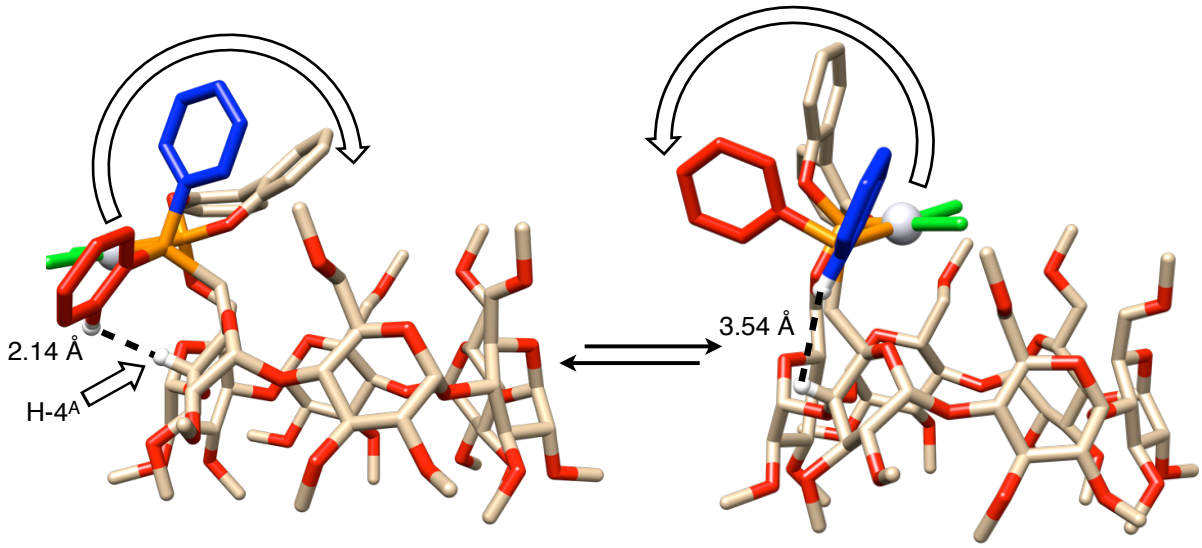


Figure 5. Two energy-minimized conformers of **17** (Spartan) that are consistent with its ROESY spectrum, which revealed cross-peaks between ortho aromatic protons of *both* phenyl rings of the PPh_2 unit and the same H-4^A proton (distances given).

Variable temperature $^{31}P\{^1H\}$ NMR studies were also performed for the rhodium complexes **20** and **21**. In these binaphthyl containing complexes atropisomerisation is blocked, so that the only possible motion is the fanning motion of the chelate ring. Both $^{31}P\{^1H\}$ NMR spectra recorded in $CDCl_3$ remained sharp upon cooling the samples to –60 °C suggesting that a single conformer was present in both cases. It is to note that CD_2Cl_2 was not used for the VT NMR studies because of poor solubility of **20** and **21** in this solvent at low temperature. Careful analysis of the 2D ROESY spectrum of **21** revealed that here the H-4^A atom correlates with the ortho protons of only one P-*phenyl* ring unlike that of **17** for which two cross-peaks were observed. This is a confirmation that only one conformer of **21** is present in solution, however its identification ("in" or "out" form) was not achieved. Indeed, ROESY spectra performed on both complexes **20** and **21** did not provide any useful information about the location of the metal unit with respect to the CD cavity. Clearly, the nature of the biaryl unit has a deep impact on the mobility of the chelate ring.

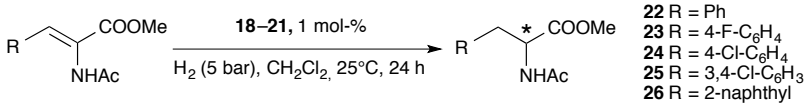
III. 2. 3. Catalytic studies

Five different α-dehydroamino esters (**22**–**26**) were used to assess the performance of complexes **18**–**21** in asymmetric catalysis. As shown by Table 1, all *phosphine-phosphite* Rh complexes promoted olefin hydrogenation with reasonable reaction rates under 5 bar of H_2 at room temperature. Not surprisingly the presence of bulky *t*Bu groups in **14** slowed down the reaction to a certain extent (Table 1, entries 6-10). However, as noticed previously by van Leeuwen[13] and Ruiz,[12] these substituents are extremely beneficial for efficient asymmetric induction. Ligand **14** is no exception as it led to significantly higher *ee*'s than those obtained with the much more flexible **13** (4.5 fold increase on average depending on the substrate

used).

The fact that modification of this particular unit produced dramatic changes in the enantioselectivity indicates that the phosphite unit is predominantly responsible for enantiodiscrimination. Without the presence of stereogenic biaryl units, the formation of the (*R*) enantiomer was always favoured whatever the substrate used. It is clear that the chirality of the cyclodextrin platform is somehow transferred to the chelate ring, but the question whether enantiodiscrimination is caused by the inherent chirality of the CD platform and/or by a particular conformation of the metallocycle remains open. Interestingly, a permethylated $6^A,6^B$-diphosphino-β-CD reported by Jia,[2b] which is not inherently chiral, produced enantioselectivities very close to those obtained with catalyst **19** in the asymmetric hydrogenation of **22** (entry 6).

Table 1. Rhodium catalysed asymmetric hydrogenation of α-dehydroamino esters with phosphine/phosphite complexes **18**–**21**.[a]



Entry	Complex	R	Conv (%)[b]	*ee* (%)[c]	Config
1	**18**	Ph	100	8	*S*
2		4-F-C_6H_4	100	14	*R*
3		4-Cl-C_6H_4	100	8	*R*
4		3,4-Cl-C_6H_3	100	12	*R*
5		2-naphthyl	100	10	*R*
6	**19**	Ph	73	60	*R*
7		4-F-C_6H_4	95	48	*R*
8		4-Cl-C_6H_4	62	56	*R*
9		3,4-Cl-C_6H_3	97	34	*R*
10		2-naphthyl	16	52	*R*
11	**20**	Ph	100	24	*S*
12		4-F-C_6H_4	100	46	*S*
13		4-Cl-C_6H_4	100	34	*S*
14		3,4-Cl-C_6H_3	100	24	*S*
15		2-naphthyl	100	70	*S*
16	**21**	Ph	100	58	*R*
17		4-F-C_6H_4	100	58	*R*
18		4-Cl-C_6H_4	100	62	*R*
19		3,4-Cl-C_6H_3	100	52	*R*
20		2-naphthyl	100	92	*R*

[a] General conditions: $P(H_2)$ = 5 bar; T = 25°C, 24 h; [substrate/Complex = 100:1]. [b] Conversions were determined by means of ^{1}H NMR analysis. [c] Enantioselectivities were determined by chiral GC analysis using a CHROMPAK chiral fused silica 25m x 0.25mm. Coating Chirasil-L-Val column.

A clear match/mismatch relationship was observed upon introducing a stereogenic binaphthyl unit into the phosphite-coordinating unit. While the (*S*)-binaphthyl-based catalyst **21** led to a significant increase in the amount of (*R*)-enantiomer being produced, reaching 92 % for the bulky naphthyl-containing substrate **26** (Table 1, entry 20), the presence of its (*R*)-binaphthyl counterpart (**20**) reversed the sense of enantiodiscrimination (formation of the (*S*)-product), and led to significantly lower *ee*'s (Table 1, entries 11-15). Clearly, the introduction of a (*S*)-binaphthyl moiety is enhances the enantiodiscrimination brought about by the CD skeleton. We further observed a significant *ee* increase upon lowering the H_2 pressure to 1 bar (Table 2, entry 3).

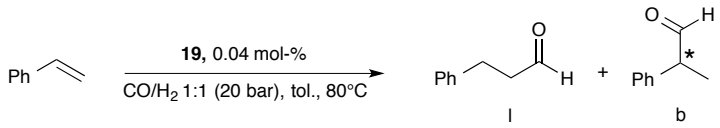
Table 2. Optimisation of the catalytic hydrogenation of **24** with best-performing complex **21**.

Entry	*T* (°C)	*P*(H_2)	Time (h)	Charge (mol%)	Conv (%)[a]	*ee* (%)[b]	Config
1	25	5	24	1	100	62	*R*
2	0	5	4	1	63	60	*R*
3	25	1	24	1	100	75	*R*
4	25	5	24	0.25	75	71	*R*

[a] Conversions were determined by means of ^{1}H NMR analysis. [b] Enantioselectivities were determined by chiral GC analysis using a CHROMPAK chiral fused silica 25m x 0.25mm. Coating Chirasil-L-Val column.

Complex **19** was also assessed in the asymmetric hydroformylation of styrene (Table 3). The linear and branched aldehydes were formed in a standard l/b ratio for styrene. Compared to other *phosphine-phosphite* ligands[9,14] the activity of the catalyst is above average and the observed enantioselectivities, despite being moderate (up to 50 % *ee* in favour of the (*R*) product), are comparable to those obtained with the best performing analogues.

Table 3. Hydroformylation of Styrene with inherently chiral precatalyst **19**.[a]

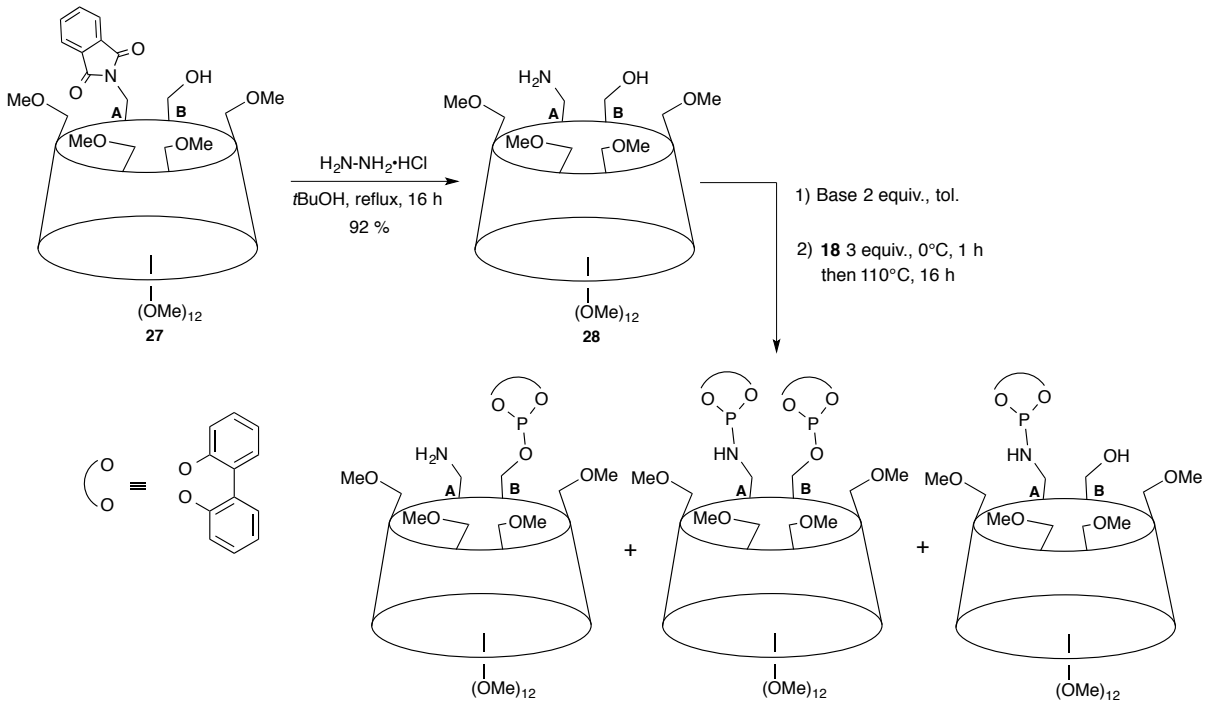


Entry	Conv[b] (Time)	TOF[c]	Aldehydes[b] l (%)	b(%)	l/b[d]	*ee* (%)[e]
1	59.8 (4)	374	24.2	75.8	0.3	50
2	>99 (7)	104	23.8	76.2	0.3	50

[a] Styrene (5 mmol), styrene/**19** = 2500, *T* = 80°C, toluene/*n*-decane (15mL/0.5mL), incubation overnight at 80°C under *P*(CO/H_2) = 20 bar (CO/H_2 1:1 v/v). [b] Determined by GC using decane as internal standard. [c] mol(converted styrene) mol(Rh)$^{-1}$h^{-1}. [d] l/b aldehyde ratio. [e] Determined by chiral-phase GC after reduction with $LiAlH_4$.

III. 2. 4. Attempts to synthesise other hybrid ligands

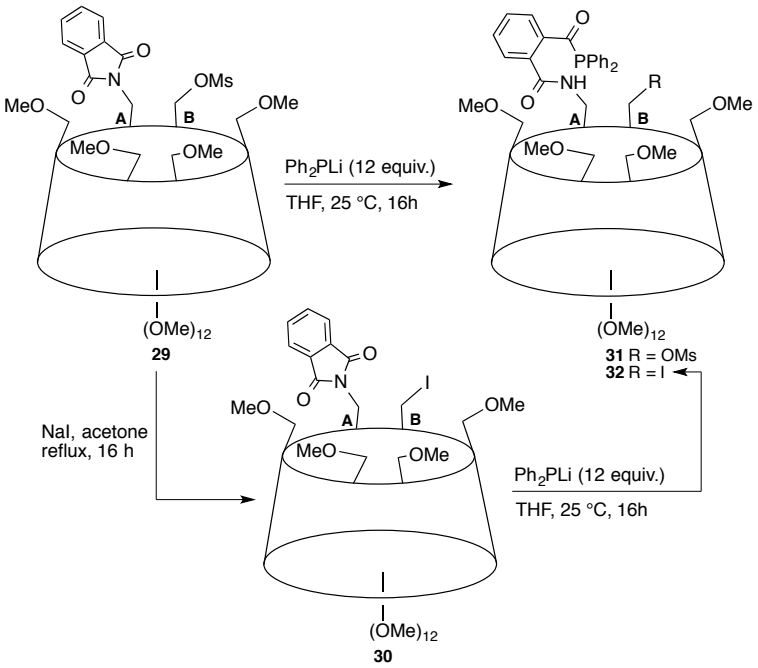
As outlined in the second chapter, CD-derived cyclic sulfates readily undergo regioselective opening with very high regioselectivity not only in the presence of bulky nucleophiles such as lithium diphenylphosphide but also with smaller ones like potassium phthalimide to afford **27.** (See chapter II, Scheme 3; Table 1, entry 2). Hydrazinolysis of **27** with excess hydrazine in *tert*-butanol afforded **28** in high yield (Scheme 3). Like **8**, this amino alcohol constitutes a potential starting material for the synthesis of hybrid *P,N* ligands as well as *P,P'* ligands such as *phosphite-phosphoramidite* ones. The latter have already proven very efficient in various metallo-catalysed reactions[15] such as allylic alkylation[16] or the asymmetric hydrogenation of α-dehydroamino esters.[17] Unfortunately, phosphorochloridite **18** did not react, neither with the CD primary hydroxyl group nor with the primary amine group of **28** in the presence of a tertiary amine such as pyridine or NEt_3, even after 4 days in refluxing toluene. However, treatment of amino alcohol **28** with excess base (NaH, LDA or *n*BuLi) in toluene followed by the addition of stoichiometric amounts of **9** afforded the expected hybrid ligand but only as part of an unseparable mixture containing also compounds with a single P(III) unit (Scheme 3). All of them were identified by ESI-MS and $^{31}P\{^{1}H\}$ NMR spectroscopy (*vide supra*). Finally, the formation of a *N,P,O*-capped CD was not observed upon reacting **28** with dichlorophenylphosphine.



Scheme 3. Synthesis of amino alcohol **28** and its reaction with **18**.

27 can also be regarded as a precursor of P,N hybrid ligands. Therefore, mesylation of the primary hydroxyl group of **27** with mesyl chloride in pyridine in the presence of DMAP (4-dimethylaminopyridine) was undertaken to give **29** almost quantitatively (Scheme 4). Attempts to substitute the mesylate group of **29** failed even in the presence of a large excess of lithium diphenylphosphide, and gave instead **31**, which was not isolated because of its

rapid decomposition over silica. No improvement was observed when the iodo derivative **30**, which was obtained by treating **29** with sodium iodide in refluxing acetone, was used instead. It seems that nucleophilic addition of diphenylphosphide to the phthalimide unit of **29** or **30** is more favourable than nucleophilic substitution of the mesyl or iodo groups of **29** and **30**, respectively.



Scheme 4. Reactivity of **29** and **30** toward lithium diphenylphosphide.

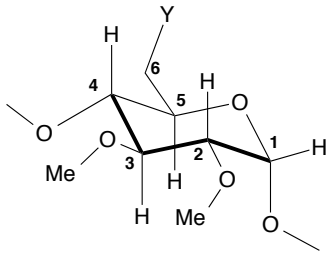
III. 3. Conclusion

Access to the first C_1-symmetric heterobidentate ligands built on a cavity-shaped molecule was made possible by proximally substituting a methylated α-CD with two different coordinating groups. Despite the large separation between the two donor atoms, all the *phosphine-phosphite* ligands proved to be preorganised enough to form quantitatively both neutral Pt(II) and cationic Rh(I) chelate complexes. As shown by extensive NMR studies, chelate complex **17** undergoes two motions in solution, one being associated with atropisomerisation of the biphenyl unit, the other being a fan-like movement of the metallocyclic unit about the P•••P' axle, which displaces the metal centre from above the cavity to its exterior. Such motions are impeded in the binapthyl complexes **20** and **21**. Poor enantiodiscrimination was observed when using **18** in the asymmetric hydrogenation of α-dehydroamino acid esters. On the contrary, the more rigid complexes **19**–**21** all resulted in significant *ee*'s, the best performing system (**21**) being the one in which both chiral components – CD and (*S*)-binaphthyl – may behave in a synergistical way. Even better chiral induction is expected with analogues having bulkier biaryl units that should enhance the inherently chiral properties of the C_1-symmetric CD platform.

III. 4. Experimental section

III. 4. 1. General procedures

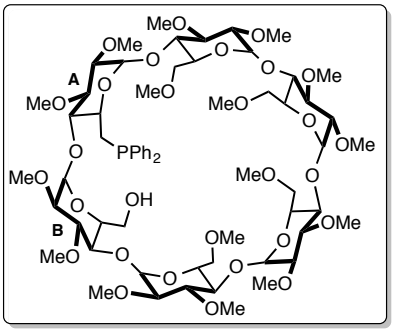
All commercial reagents were used as supplied. All manipulations were performed in Schlenk-type flasks under N_2 with degassed solvent. Solvents were dried by conventional methods and distilled immediately prior to use. Column chromatography was performed on silica gel 60 (particle size 40-63 μm, 230-240 mesh), beforehand dried overnight at 150°C. $CDCl_3$ was passed down a 5-cm-thick alumina column and stored under N_2 over molecular sieves (3 Å). Routine ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded with Bruker FT instruments (AVANCE 400, 500, 600 spectrometers). ^1H NMR spectral data were referenced to residual protiated solvents (δ = 7.26 ppm for $CDCl_3$) and ^{13}C chemical shifts are reported relative to deuterated solvents (δ = 77.16 ppm for $CDCl_3$). Mass spectra were recorded with a Bruker MicroTOF spectrometer (ESI) using CH_2Cl_2, MeCN or MeOH as solvent. Elemental analyses were performed by the Service de Microanalyse, Institut de Chimie UMR 7177, Strasbourg. Melting points were determined with a Büchi 535 capillary melting point apparatus. Optical rotations were measured on a Perkin-Elmer 341 digital polarimeter with a path length of 1 dm. The catalytic solutions were analysed by using a Varian 3900 gas chromatograph equipped with a WCOT fused-silica column (25m × 0.25mm) or with a Chirasil-DEX CB column (25 m × 0.25 mm). **8•BH$_3$** and **27**,[10] **9** and **10**,[18] **11** and **12**[19] and $[PtCl_2(PhCN)_2]$[20] were synthesised according to literature procedures. In this chapter, the cyclodextrins are depicted as seen from the secondary face, the glucose units being ranged counterclocwise in the following order: A, B, C, D, E, F. The numbering of the atoms within a glucose unit is as follows:



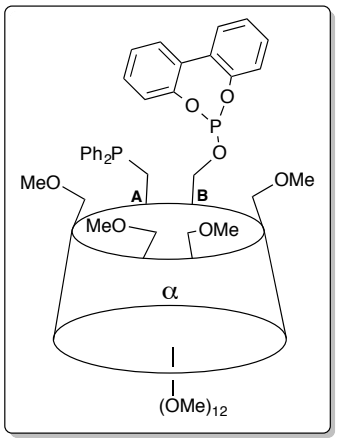
III. 4. 2. Procedure for determining the glucose units linked by a given capping unit

Our strategy for full structural assignment began with the differentiation between capped and non-capped C-6 carbon atoms by DEPT 135. These appear as two distinct sets of signals. The H-6 protons could then be identified using ^1H-^{13}C HMQC (Heteronuclear Multiple Quantum Coherence spectroscopy) or edited HSQC (Heteronuclear Single Quantum Coherence spectroscopy). By using TOCSY (TOtal Correlation SpectroscopY) and COSY (COrrelated SpectroscopY), each H-6 proton was correlated to the set of protons belonging to the same glucose residue. The connectivity between individual glucose units was then established via a ROESY (Rotating frame Overhause Effect SpectroscopY) experiment showing the proximity between H-4$_N$ and H-1$_{N+1}$ protons (N and N+1 standing for neighbouring glucose moieties labeled in the alphabetical order).[21]

III. 4. 3. Synthesis and characterisation

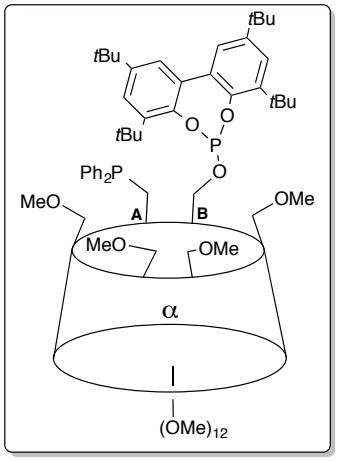


6^A-Deoxy-6^A-diphenylphosphinyl-2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^C,6^D,6^E,6^F-hexadeca-*O*-methyl-α-cyclodextrin (8): A solution of **8•BH_3** (1.258 g, 0.91 mmol) in degassed $HNEt_2$ (20 mL) was refluxed for 12 h. After cooling down to room temperature, the reaction mixture was evaporated to dryness. The residue was treated with toluene and the resulting suspension filtered through a pad of Celite. Removal of the solvent *in vacuo* afforded analytically pure **8** (1.241 g, 99 %) as a colourless solid. R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.64; m.p. dec.; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY and HSQC) = 1.49 (m, 1 H, OH^B), 2.60 (ddd, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 15.6 Hz, $^2J_{H\text{-}6b,P}$ = 2.6 Hz, $^3J_{H\text{-}6a,H\text{-}5}$ = 5.9 Hz, H-$6a^A$), 2.70 (td, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 15.6 Hz, $^2J_{H\text{-}6b,P}$ = $^3J_{H\text{-}6b,H\text{-}5}$ = 3.9 Hz, H-$6b^A$), 3.06 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}3}$ = 9.2 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 3.0 Hz, H-2), 3.08 (s, 3 H, OMe), 3.12–3.20 (5 H, H-2), 3.21 (m, 1 H, H-6), 3.39 (s, 3 H, OMe), 3.40 (s, 3 H, OMe), 3.43 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 3.48 (s, 9 H, OMe), 3.49 (s, 3 H, OMe), 3.50 (s, 3 H, OMe), 3.62 (s, 3 H, OMe), 3.63 (s, 9 H, OMe), 3.64 (s, 3 H, OMe), 3.66 (s, 3 H, OMe), 3.37–3.92 (26 H, H-3, H-4, H-5, H-6), 4.18 (m, 1 H, H-5^A), 4.91 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1), 5.00–5.03 (2 H, H-1), 5.04–5.07 (3 H, H-1), 7.14–7.19 (2 H, *p*-H), 7.22–7.33 (4 H, *m*-H), 7.39–7.48 (4 H, *o*-H) ppm; $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 31.83 (d, $^1J_{C,P}$ = 18.3 Hz, C-6^A), 57.77, 57.91, 57.93, 58.16, 58.89, 59.12 [×5] (OMe), 61.41 (C-6^B), 61.66, 61.76, 61.86, 61.91 [×3] (OMe), 70.79, 70.92, 71.05 (C-5), 71.09, 71.19 (C-6), 71.35, 71.45 (C-5), 71.52 [×2] (C-6), 72.14 (C-5), 81.11, 81.21, 81.24, 81.28, 81.33 [×2], 81.78, 81.97, 82.06, 82.14, 82.17 [×2], 82.31 [×2], 82.36, 82.48 [×2] (C-2, C-3, C-4), 87.14 (d, $^3J_{C,P}$ = 11.6 Hz, C-4^A), 99.32, 99.85, 99.93, 100.07, 100.22, 100.48 (C-1), 128.15–128.70 [×6], 132.79–133.20 [×4] (C-*arom*), 137.94 (d, $^1J_{C,P}$ = 14.1 Hz, C-*ipso*^{A}), 140.34 (d, $^1J_{C,P}$ = 12.3 Hz, C-ipso'^{A}) ppm; $^{31}P\{^1H\}$ NMR (161.9 MHz, $CDCl_3$, 25ºC): δ = –22.8 (s) ppm; elemental analysis (%) calcd for $C_{64}H_{101}O_{29}P$•$2H_2O$ (1365.44 + 36.03): C 54.85, H 7.55, found: C 55.15, H 7.53; MS (ESI-TOF): *m/z* (%): 1387.61 (100) $[M + Na]^+$.



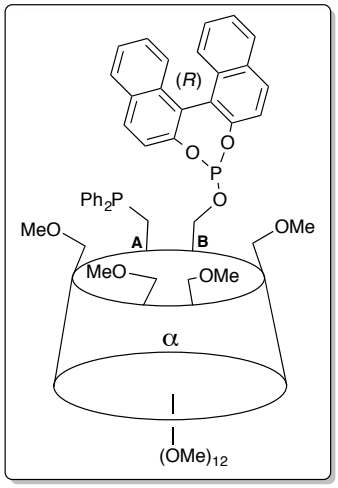
6^A,6^B-Dideoxy-6^A-diphenylphosphinyl-6^B-(2,2'-bisphenoxyphosphinoxy)-2^A,2^B,2^C,2^D,2^E, 2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^C,6^D,6^E,6^F-hexadeca-*O*-methyl-α-cyclodextrin (13): Powdered sodium hydride (60 % dispersion in oil) (0.019 g, 0.47 mmol) was added to a solution of anhydrous **8** (0.255 g, 0.19 mmol) in toluene (7.0 mL). The suspension was stirred at 100°C for 16 h before being cooled to 0°C. A solution of (1,1'-biphenyl-2,2'-diyl)chlorophosphite (**9**) (0.187 g, 0.75 mmol) in toluene (7.5 mL) was then added at 0°C and the resulting reaction mixture stirred at 0°C for 1 h. The temperature was subsequently raised to 100°C and the slurry stirred at this temperature for an additional 16 h. After cooling down, it was evaporated to dryness *in vacuo*. The residue was subjected to column chromatography (short pad of Al_2O_3, CH_2Cl_2, followed by CH_2Cl_2/THF (50:50, *v/v*)). If necessary, the resulting colourless solid was further purified by column chromatography (SiO_2; CH_2Cl_2/THF, 90:10 to 85:15, *v/v*) to afford analytically pure **13** (0.145 g, 49 %). R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v/v*) = 0.72; m.p. dec.; $[\alpha]_D^{20}$ = +105° (CH_2Cl_2, *c* = 4.0); ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY and HMQC) = 2.55 (dt, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 14.7 Hz, $^2J_{H\text{-}6b,P}$ = $^3J_{H\text{-}6b,H\text{-}5}$ = 3.2 Hz, H-6b^A), 2.60 (ddd, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 14.7 Hz, $^2J_{H\text{-}6a,P}$ = 2.9 Hz, $^3J_{H\text{-}6a,H\text{-}5}$ = 8.3 Hz, H-6a^A), 3.01 (s, 3 H, OMe), 3.07 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}3}$ = 9.9 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 3.4 Hz, H-2), 3.09 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}3}$ = 10.6 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 3.3 Hz, H-2), 3.14–3.20 (3 H, H-2), 3.22 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}3}$ = 9.4 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 2.9 Hz, H-2), 3.32 (dd, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 11.9 Hz, $^3J_{H\text{-}6b,H\text{-}5}$ = 2.2 Hz, H-6b), 3.37 (s, 6 H, OMe), 3.38 (s, 3 H, OMe), 3.44 (s, 3 H, OMe), 3.45 (s, 3 H, OMe), 3.48 (s, 9 H, OMe), 3.51 (s, 3 H, OMe), 3.61 (s, 3 H, OMe), 3.62 (s, 3 H, OMe), 3.63 (s, 6 H, OMe), 3.64 (s, 3 H, OMe), 3.67 (s, 3 H, OMe), 3.33–3.96 (25 H, H-3, H-4, H-5, H-6), 4.14 (ddd, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 11.8 Hz, $^2J_{H\text{-}6a,P}$ = 2.5 Hz, $^3J_{H\text{-}6a,H\text{-}5}$ = 9.4 Hz, H-6a^B), 4.22 (ddd, 1 H, $^3J_{H\text{-}5,H\text{-}6b}$ = 3.2 Hz, $^3J_{H\text{-}5,H\text{-}6a}$ = 8.3 Hz, $^3J_{H\text{-}5,H\text{-}4}$ = 17.7 Hz, H-5^A), 4.89 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1), 4.93 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 2.9 Hz, H-1), 4.95 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1), 5.05 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1), 5.06 (d, 1 H, $^3J_{H\text{-}1,H,2}$ = 3.6 Hz, H-1), 5.08 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.4 Hz, H-1), 7.09 (d, 1 H, *J* = 7.8 Hz, H-*arom*), 7.12 (d, 1 H, *J* = 7.9 Hz, H-*arom*), 7.17–7.50 (16 H, H-*arom*) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 25ºC): δ (assignment by HMQC) = 31.57 (d, $^1J_{C,P}$ = 14.0 Hz, C-6^A), 57.74, 57.78, 57.81, 57.97, 58.11, 58.18, 58.72, 59.05, 59.11 [×2], 61.69, 61.78 [×2], 61.87, 61.90 [×2] (OMe), 63.37 (d, $^2J_{C,P}$ = 9.5 Hz, C-6^B), 70.89 (C-5^A), 71.04 (C-6), 71.09 [×2] (C-5), 71.19, 71.24 (C-6), 71.33, 71.45 [×2] (C-5), 71.54 (C-6), 80.89, 81.20, 81.31 [×2], 81.40, 81.59, 81.68, 81.96, 82.02 [×2], 82.06 [×2], 82.15, 82.41, 82.45, 82.55 [×2] (C-2, C-3, C-4), 87.66 (C-4^A), 99.20, 99.55, 100.04, 100.06, 100.09, 100.47 (C-1), 124.96, 125.08 (C-*arom*), 128.02 (d, $^1J_{C,P}$ = 10.1 Hz, C-*ipso*^{A}), 128.28, 128.36, 128.42,

128.51, 128.57, 128.70, 128.77, 128.87, 129.01 [×2], 129.86, 129.92, 130.59, 132.59 (C-*arom*), 131.50 (d, $^{1}J_{C,P}$ = 12.5 Hz, C-*ipso*'^{A}), 132.76, 133.04, 133.24, 133.52, 136.14, 138.97 (C-*arom*) ppm; $^{31}P\{^{1}H\}$ NMR (161.9 MHz, $CDCl_3$, 25ºC): δ = –21.4 (s, P^A), 146.6 (s, P^B) ppm; elemental analysis (%) calcd for $C_{76}H_{108}O_{31}P_2 \bullet CH_2Cl_2$ (1579.60 + 84.93): C 55.56, H 6.66, found: C 55.86, H 6.61; MS (ESI-TOF): *m/z* (%): 1601.60 (100) $[M + Na]^+$.



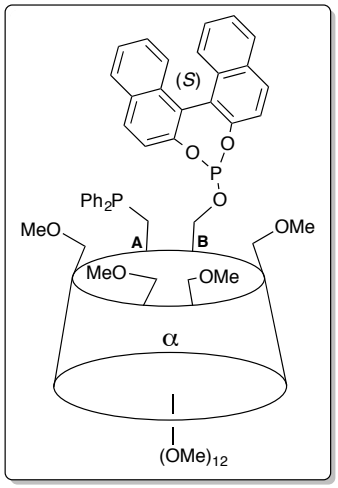
6^{A},6^{B}-Dideoxy-6^{A}-diphenylphosphinyl-6^{B}-(4,4',6,6'-tetra-*tert*-butyl-2,2'-bisphenoxyphosphinoxy)-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},6^{C},6^{D},6^{E},6^{F}-hexadeca-*O*-methyl-α-cyclodextrin (14): This compound was prepared according to the procedure used for the synthesis of **13** , by reacting **8** (0.200 g, 0.15 mmol) with (4,4',6,6'-tetra-*tert*-butyl-1,1'-biphenyl-2,2'-diyl)chlorophosphite (**10**) (0.278 g, 0.58 mmol). The crude was subjected to column chromatography (SiO_2; CH_2Cl_2/MeOH, 97:3, *v/v*) to afford **14** (0.164 g, 62 %) as a colourless solid. R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v/v*) = 0.72; m.p. dec.; $[\alpha]_D^{20}$ = +140° (CH_2Cl_2, *c* = 5.0); ^{1}H NMR (500.1 MHz, $CDCl_3$, 25ºC): δ (assignment by COSY) = 1.34 (s, 9 H, *t*Bu), 1.35 (s, 9 H, *t*Bu), 144 (s, 9 H, *t*Bu), 1.46 (s, 9 H, *t*Bu), 2.37 (ddd, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 14.9 Hz, $^{2}J_{H\text{-}6a,P}$ = 2.9 Hz, $^{3}J_{H\text{-}6a,H\text{-}5}$ = 10.7 Hz, H-6a^{A}), 2.67 (dt, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 14.9 Hz, $^{2}J_{H\text{-}6b,P}$ = $^{3}J_{H\text{-}6b,H\text{-}5}$ = 2.8 Hz, H-6b^{A}), 3.05 (s, 3 H, OMe), 3.08 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}3}$ = 10.1 Hz, $^{3}J_{H\text{-}2,H\text{-}1}$ = 2.9 Hz, H-2), 3.09 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}3}$ = 10.1 Hz, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.1 Hz, H-2), 3.15 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}3}$ = 10.1 Hz, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.2 Hz, H-2), 3.20 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.7 Hz, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.3 Hz, H-2), 3.21 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.2 Hz, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.7 Hz, H-2), 3.22 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}3}$ = 10.1 Hz, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.2 Hz, H-2), 3.36 (s, 3 H, OMe), 3.37 (s, 3 H, OMe), 3.46 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 3.48 (s, 3 H, OMe), 3.49 (s, 3 H, OMe), 3.50 (s, 3 H, OMe), 3.51 (s, 3 H, OMe), 3.52 (s, 3 H, OMe), 3.58 (s, 3 H, OMe), 3.62 (s, 3 H, OMe), 3.63 (s, 3 H, OMe), 3.64 (s, 6 H, OMe), 3.65 (s, 3 H, OMe), 3.33–3.96 (27 H, H-3, H-4, H-5, H-6), 4.24 (m, 1 H, H-5^{A}), 4.85 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.7 Hz, H-1), 4.95 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.1 Hz, H-1), 5.02 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1), 5.07 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1), 5.08 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1), 5.12 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 2.9 Hz, H-1), 7.14 (d, 1 H, ^{4}J = 2.4 Hz, H-*arom*^{B}), 7.15 (d, 1 H, ^{4}J = 2.3 Hz, H-*arom*^{B}), 7.19–7.33 (8 H, H-*arom*^{A}), 7.40 (d, 1 H, ^{4}J = 2.4 Hz, H-*arom*^{B}), 7.41 (d, 1 H, ^{4}J = 2.3 Hz, H-*arom*^{B}), 7.43–7.47 (2 H, H-*arom*^{A}) ppm; $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$, 25ºC): δ = 31.09, 31.12, 31.35, 31.53 [×9] (CH_3-^{t}Bu), 32.54 (d, $^{1}J_{C,P}$ = 13.8 Hz, C-6^{A}), 34.58, 34.53, 35.29, 35.33 (C-^{t}Bu), 57.57, 57.59, 57.68, 57.95, 58.20 [×2], 58.64, 58.80, 59.08 [×2], 61.55, 61.66, 61.73, 61.87, 61.89, 61.92 (OMe), 62.77 (d, $^{2}J_{C,P}$ = 23.3 Hz, C-6^{B}), 70.85 (C-6), 70.99, 71.07,

71.10 (C-5), 71.16 (C-6), 71.18 (C-5), 71.23 (C-6), 71.45, 71.53 (C-5), 71.59 (C-6), 80.82, 81.16, 81.28 [×2], 81.32, 81.42, 81.54, 81.59, 81.73, 81.93, 81.96 [×2], 82.08, 82.41, 82.56, 82.69, 82.74 (C-2, C-3, C-4), 89.15 (d, $^{3}J_{C,P}$ = 11.6 Hz, C-4^{A}), 98.96, 99.48, 99.97, 100.01, 100.58, 100.89 (C-1), 123.77, 124.08, 126.24, 126.51, 128.18, 128.24, 128.29, 128.58, 128.64, 128.85, 132.41, 132.56, 132.97, 133.13, 133.35 (C-*arom*), 139.22 (d, $^{1}J_{C,P}$ = 11.6 Hz, C-*ipso*^{A}), 139.77, 140.07 (C-*arom*), 141.24 (d, $^{1}J_{C,P}$ = 11.6 Hz, C-*ipso*'^{A}), 145.44, 145.74, 145.80, 145.85, 146.32 (C-*arom*) ppm; $^{31}P\{^{1}H\}$ NMR (161.9 MHz, $CDCl_3$, 60ºC): δ = –20.6 (s, P^{A}), 149.2 (br. s, P^{B}) ppm; elemental analysis (%) calcd for $C_{92}H_{140}O_{31}P_2 \bullet 2H_2O$ (1802.89 + 36.02): C 60.05, H 7.89, found: C 59.75, H 7.94; MS (ESI-TOF): *m/z* (%): 1826.88 (100) [*M* + Na]$^{+}$.



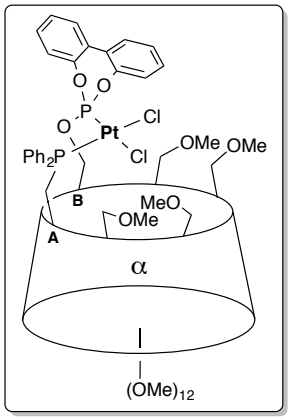
6^{A},6^{B}-Dideoxy-6^{A}-diphenylphosphinyl-6^{B}-(*R*)-(1,1'-binaphthyl-2,2'-bisoxyphosphinoxy)-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},6^{C},6^{D},6^{E},6^{F}-hexadeca-*O*-methyl-α-cyclodextrin (15): This compound was prepared in 49 % (0.128 g) according to the procedure used for the synthesis of **13**, by reacting **8** (0.216 g, 0.16 mmol) with [(*R*)-1,1'-binaphthyl-2,2'-diyl]chlorophosphite (**11**) (0.222 g, 0.63 mmol). R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.72; m.p. dec.; $[\alpha]_D^{20}$ = +20° (CH_2Cl_2, *c* = 5.0); ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY and HSQC) = 2.51 (dt, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 14.9 Hz, $^{2}J_{H\text{-}6b,P}$ = $^{3}J_{H\text{-}6b,H\text{-}5}$ = 3.4 Hz, H-6b^{A}), 2.61 (ddd, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 14.9 Hz, $^{2}J_{H\text{-}6a,P}$ = 3.1 Hz, $^{3}J_{H\text{-}6a,H\text{-}5}$ = 8.4 Hz, H-6a^{A}), 3.00 (s, 3 H, OMe), 3.06 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.0 Hz, $^{3}J_{H\text{-}2,H\text{-}1}$ = 2.9 Hz, H-2), 3.07 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.7 Hz, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.3 Hz, H-2), 3.15 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.9 Hz, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.3 Hz, H-2), 3.18 (s, 3 H, OMe), 3.16–3.22 (2 H, H-2), 3.24 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.8 Hz, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.2 Hz, H-2), 3.29 (dd, 1 H, $^{2}J_{H\text{-}6b,H\text{-}6a}$= 10.9 Hz, $^{3}J_{H\text{-}6b,H\text{-}5}$ = 1.5 Hz, H-6b), 3.37 (s, 3 H, OMe), 3.42 (m, 1 H, H-6b^{B}), 3.45 (s, 6 H, OMe), 3.47 (s, 3 H, OMe), 3.49 (s, 6 H, OMe), 3.50 (s, 3 H, OMe), 3.52 (s, 3 H, OMe), 3.57 (s, 3 H, OMe), 3.61 (s, 3 H, OMe), 3.63 (s, 3 H, OMe), 3.64 (s, 3 H, OMe), 3.65 (s, 3 H, OMe), 3.67 (s, 3 H, OMe), 3.44–3.99 (24 H, H-3, H-4, H-5, H-6), 4.17 (t, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = $^{3}J_{H\text{-}6a,H\text{-}5}$ = 10.5 Hz, H-6a^{B}), 4.22 (ddd, 1 H, $^{3}J_{H\text{-}5,H\text{-}6b}$ = 3.4 Hz, $^{3}J_{H\text{-}5,H\text{-}6a}$ = 8.4 Hz, $^{3}J_{H\text{-}5,H\text{-}4}$ = 17.7 Hz, H-5^{A}), 4.77 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1), 4.93 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1), 4.99 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 2.9 Hz, H-1), 5.05 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.1 Hz, H-1), 5.07 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.1 Hz, H-1), 5.11 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1), 7.14–7.49 (17 H, H-*arom*), 7.77–7.99 (5 H, H-*arom*) ppm; $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 32.15 (d, $^{1}J_{C,P}$ = 14.3 Hz, C-6^{A}), 57.48, 57.78,

57.82, 57.95, 58.13, 58.26, 58.67, 59.12 [×2], 59.18, 61.69, 61.70, 61.73, 61.86, 61.89, 61.92 (OMe), 63.34 (d, $^{2}J_{C,P}$ = 16.6 Hz, C-6^{B}), 71.06 [×2], 71.11 (C-5), 71.17, 71.22 (C-6), 71.32 (C-5), 71.40 (C-6), 71.45 [×2] (C-5), 71.53 (C-6), 80.79, 81.18, 81.33 [×4], 81.40, 81.60, 81.74, 81.99 [×2], 82.17, 82.23, 82.43, 82.45, 82.61, 82.62 (C-2, C-3, C-4), 88.00 (d, $^{3}J_{C,P}$ = 11.2 Hz, C-4^{A}), 99.09, 99.20, 100.03, 100.11, 100.35, 100.48 (C-1), 121.86, 122.52, 124.03, 124.28, 124.80, 125.06, 125.33, 126.04, 126.26, 127.00, 127.11, 127.47, 128.16, 128.34, 128.39, 128.43, 128.60, 128.67, 128.86, 129.06, 129.44, 130.23, 131.02, 131.40, 131.50, 132.36, 132.54, 133.07, 133.28, 139.69, 140.65, 141.44 (C-*arom*) ppm; $^{31}P\{^{1}H\}$ NMR (161.9 MHz, $CDCl_3$, 25ºC): δ = –20.3 (s, P^{A}), 148.9 (s, P^{B}) ppm; elemental analysis (%) calcd for $C_{84}H_{112}O_{31}P_2 \bullet H_2O$ (1679.72 + 18.01): C 59.43, H 6.77, found: C 59.72, H 6.99.; MS (ESI-TOF): *m/z* (%): 1701.66 (100) $[M + Na]^{+}$.



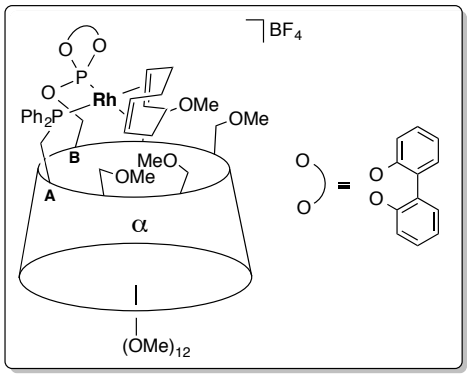
6^{A},6^{B}-Dideoxy-6^{A}-diphenylphosphinyl-6^{B}-(*S*)-(1,1'-binaphthyl-2,2'-bisoxyphosphinoxy)-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},6^{C},6^{D},6^{E},6^{F}-hexadeca-*O*-methyl-α-cyclodextrin (16): This compound was prepared in 37 % (0.110 g) according to the procedure used for the synthesis of **13**, by reacting **8** (0.245 g, 0.18 mmol) with [(*S*)-1,1'-binaphthyl-2,2'-diyl]chlorophosphite (**12**) (0.252 g, 0.72 mmol). R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.72; m.p. dec.; $[\alpha]_D^{20}$ = +224° (CH_2Cl_2, *c* = 5.0); ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY and HSQC) = 2.64 (dt, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 14.6 Hz, $^{2}J_{H\text{-}6b,P}$ = $^{3}J_{H\text{-}6b,H\text{-}5}$ = 3.2 Hz, H-6b^{A}), 2.71 (ddd, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 14.8 Hz, $^{2}J_{H\text{-}6a,P}$ = 2.6 Hz, $^{3}J_{H\text{-}6a,H\text{-}5}$ = 7.4 Hz, H-6a^{A}), 3.02 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.0 Hz, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.1 Hz, H-2), 3.04 (s, 3 H, OMe), 3.12–3.19 (4 H, H-2), 3.22 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}3}$ = 10.1 Hz, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.1 Hz, H-2), 3.34 (s, 3 H, OMe), 3.35 (s, 3 H, OMe), 3.37 (s, 3 H, OMe), 3.43 (s, 3 H, OMe), 3.48 (s, 9 H, OMe), 3.49 (s, 3 H, OMe), 3.52 (s, 3 H, OMe), 3.61 (s, 3 H, OMe), 3.63 (s, 9 H, OMe), 3.64 (s, 3 H, OMe), 3.67 (s, 3 H, OMe), 3.31–3.93 (26 H, H-3, H-4, H-5, H-6), 4.14 (t, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = $^{3}J_{H\text{-}6a,H\text{-}5}$ = 10.8 Hz, H-6a^{B}), 4.23 (ddd, 1 H, $^{3}J_{H\text{-}5,H\text{-}6b}$ = 3.2 Hz, $^{3}J_{H\text{-}5,H\text{-}6a}$ = 7.4 Hz, $^{3}J_{H\text{-}5,H\text{-}4}$ = 17.0 Hz, H-5^{A}), 4.82 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1), 4.94 (d, 2 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.1 Hz, H-1), 5.04–5.07 (3 H, H-1), 7.18–7.54 (18 H, H-*arom*), 7.82 (d, 1 H, *J* = 8.7 Hz, H-*arom*), 7.85 (d, 1 H, *J* = 8.2 Hz, H-*arom*), 7.90–7.97 (2 H, H-*arom*) ppm; $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 32.15 (d, $^{1}J_{C,P}$ = 14.2 Hz, C-6^{A}), 57.65, 57.77, 57.85, 58.00, 58.08, 58.14, 58.76, 59.11 [×3], 61.66, 61.80 [×2], 61.83, 61.89 [×2] (OMe), 63.46 (d, $^{2}J_{C,P}$ = 15.2 Hz, C-6^{B}), 71.10 [×2] (C-5), 71.18, 71.24 (C-6), 71.33, 71.39, 71.41, 71.46 (C-5),

71.56 [×2] (C-6), 80.91, 81.21, 81.24, 81.27, 81.38, 81.45, 81.75, 81.93, 82.06, 82.15 [×2], 82.20, 82.29, 82.33, 82.47, 82.50, 82.56 (C-2, C-3, C-4), 87.89 (d, $^{3}J_{C,P}$ = 10.5 Hz, C-4^{A}), 99.35, 99.58, 100.0, 100.02, 100.04, 100.43 (C-1), 120.57 (d, $^{2}J_{C,P}$ = 6.5 Hz, C-*ipso*^{B}), 121.84, 122.12, 122.92 (C-*arom*),, 124.36 (d, $^{2}J_{C,P}$ = 5.2 Hz, C-*ipso*'^{B}), 124.86, 125.02, 126.13, 126.22, 127.03, 127.05, 128.15, 128.27, 128.34, 128.41 [×2], 128.47, 128.50, 128.56, 128.73, 129.36, 130.22, 131.02, 131.49, 132.74, 132.89 [×2], 132.96, 133.11 (C-*arom*), 139.41 (d, $^{1}J_{C,P}$ = 11.8 Hz, C-*ipso*^{A}), 140.82 (d, $^{1}J_{C,P}$ = 12.0 Hz, C-*ipso*'^{A}), 147.47 (C-*arom*) ppm; $^{31}P\{^{1}H\}$ NMR (161.9 MHz, $CDCl_3$, 25ºC): δ = –20.9 (s, P^{A}), 150.7 (s, P^{B}) ppm; elemental analysis (%) calcd for $C_{84}H_{112}O_{31}P_2$•$CHCl_3$ (1679.72 + 119.38): C 56.75, H 6.33, found: C 56.75, H 6.65; MS (ESI-TOF): *m/z* (%): 1701.66 (100) $[M + Na]^+$.

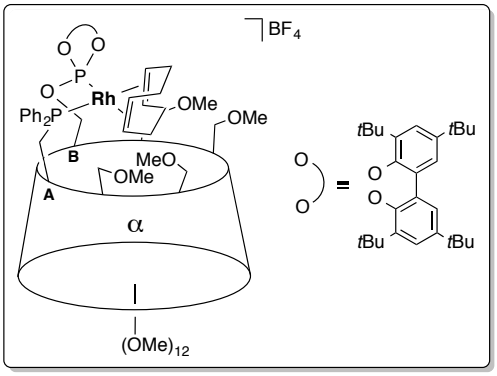


***cis*-*P,P'*-Dichloro-{6^{A},6^{B}-dideoxy-6^{A}-diphenylphosphinyl-6^{B}-(2,2'-bisphenoxyphosphinoxy)-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},6^{C},6^{D},6^{E},6^{F}-hexadeca-*O*-methyl-α-cyclodextrin} platinum (II) (17):** A solution of $[PtCl_2(PhCN)_2]$ (0.009 g, 0.02 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a solution of **13** (0.030 g, 0.02 mmol) in CH_2Cl_2 (2 mL) under vigorous stirring. After 5 min, the reaction mixture was evaporated to dryness *in vacuo* to afford analytically pure **17** (0.035 g, 99 %) as a pale yellow solid. R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.74; m.p. dec.; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY and HSQC) = 1.70 (m, 1 H, H-6^{B}), 3.01 (s, 3 H, OMe), 3.09 (s, 3 H, OMe), 3.10–3.21 (6 H, H-2, H-6^{A}), 3.27 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.2 Hz, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.1 Hz, H-2), 3.36 (s, 3 H, OMe), 3.43 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 3.48 (s, 3 H, OMe), 3.50 (s, 6 H, OMe), 3.51 (s, 3 H OMe), 3.52 (s, 6 H, OMe), 3.61 (s, 3 H, OMe), 3.63 (s, 9 H, OMe), 3.64 (s, 3 H OMe), 3.45–3.71 (15 H, H-3, H-4, H-6), 3.71–3.85 (5 H, H-6), 3.86–4.08 (5 H, H-4, H-5), 4.30 (m, 1 H, H-5^{A}), 4.45 (br. m, 1 H, H-5^{B}), 4.78 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1), 4.84 (br m, 1 H, H-6^{A}), 4.86 (m, 1 H, H-1), 5.05 (m, 2 H, H-1), 5.12 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.4 Hz, H-1), 5.25 (br. m, 1 H, H-1), 7.20–7.46 (10 H, H-*arom*), 7.56–7.62 (4 H, H-*arom*), 7.84–7.93 (4 H, H-*arom*) ppm; $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$, 50ºC): δ (assignment by HSQC) = 24.90 (dd, $^{1}J_{C,PA}$ = 10.5 Hz, $^{3}J_{C,PB}$ = 8.0 Hz, C-6^{A}), 57.66 [×2], 57.82 [×2], 58.02, 58.29 [×2], 58.85, 59.09, 59.22, 59.67, 61.30, 61.56 [×2], 61.86 [×2] (OMe), 70.01 (virtual t, $^{2}J_{C,PB}$ = $^{4}J_{C,PA}$ = 16.0 Hz, C-6^{B}), 70.54, 71.12 (C-6), 71.24, 71.52 [×2] (C-5), 71.59 (C-6), 71.72 [×3] (C-5), 72.01 (C-6), 80.42 [×2], 80.67 [×2], 81.16 [×2], 81.28, 81.37, 81.82, 81.87, 82.08 [×3], 82.15, 82.30, 82.44, 82.56 (C-2, C-3, C-4), 83.76 (d, $^{3}J_{C,P}$ = 9.8 Hz, C-4^{A}), 98.30, 99.45, 99.77, 100.31, 100.38, 100.62 (C-1), 126.26, 126.43 [×2], 127.63, 127.76, 127.86, 127.94, 128.03, 128.55,

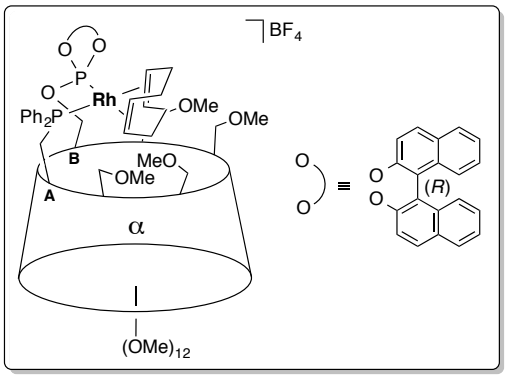
128.85, 129.21, 129.52, 129.65, 129.74 [×2], 130.26 [×2], 130.86, 130.92, 132.34, 134.06 [×2] (C-*arom*), 148.13 (dd, $^{1}J_{C,PA}$ = 9.1 Hz, $^{3}J_{C,PB}$ = 3.0 Hz, C-*ipso*^{A}), 148.50 (dd, $^{1}J_{C,PA}$ = 10.1 Hz, $^{3}J_{C,PB}$ = 3.1 Hz, C-*ipso*'^{A}) ppm; $^{31}P\{^{1}H\}$ NMR (161.9 MHz, $CDCl_3$, 60ºC): δ = 6.7 (d with Pt satellites, $^{2}J_{PA,PB}$ = 22.7 Hz, $^{1}J_{PA,Pt}$ = 3407.9 Hz, P^{A}), 82.1 (d with Pt satellites, $^{2}J_{PB,PA}$ = 22.7 Hz, $^{1}J_{PB,Pt}$ = 6136.4 Hz, P^{B}) ppm; elemental analysis (%) calcd for $C_{76}H_{108}Cl_2O_{31}P_2Pt$ (1845.45): C 49.46, H 5.90, found: C 49.23, H 6.08; MS (ESI-TOF): *m/z* (%): 1826.60 (100) $[M - Cl + H_2O]^+$, 1867.63 (48) $[M + Na]^+$.



***cis-P,P'*-(Cycloocta-1,5-diene)-{6^{A},6^{B}-dideoxy-6^{A}-diphenylphosphinyl-6^{B}-(2,2'-bisphenoxyphosphinoxy)-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},6^{C},6^{D},6^{E},6^{F}-hexadeca-*O*-methyl-α-cyclodextrin}rhodium (I) (18):** A solution of $[Rh(COD)_2]BF_4$ (0.031 g, 0.08 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a solution of **13** (0.120 g, 0.08 mmol) in CH_2Cl_2 (4 mL) under vigorous stirring. After 5 min, the volume of the reaction mixture was reduced to 1 mL and pentane (20 mL) was added to precipitate **18**, which was collected by filtration to afford a bright yellow powder (0.141 g, 99 %). R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.30; m.p. dec.; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by COSY) = 1.55–1.66 (br. m, 1 H, allylic protons of COD), 1.73–1.82 (br. m, 1 H, allylic protons of COD), 1.98–2.33 (6 H, allylic protons of COD), 2.35 (s, 3 H, OMe), 2.97 (s, 3 H, OMe), 3.25 (s, 3 H, OMe), 3.35 (s, 3 H, OMe), 3.41 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 3.48 (s, 3 H, OMe), 3.49 (s, 3 H, OMe), 3.51 (s, 3 H, OMe), 3.53 (s, 3 H, OMe), 3.55 (s, 3 H, OMe), 3.57 (s, 3 H, OMe), 3.58 (s, 3 H, OMe), 3.59 (s, 3 H, OMe), 3.62 (s, 6 H, OMe), 2.65–4.31 (37 H, H-1, H-2, H-3, H-4, H-5, H-6), 4.33 (m, 1 H, vinylic protons of COD), 4.40 (m, 1 H, H-1), 4.93 (m, 1 H, vinylic protons of COD), 5.00 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.1 Hz, H-1), 5.08 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 2.9 Hz, H-1), 5.09 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1), 5.10 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.0 Hz, H-1), 5.35 (m, 1 H, vinylic protons of COD), 5.92 (m, 1 H, vinylic protons of COD), 7.01–7.59 (12 H, H-*arom*), 7.64–7.97 (4 H, H-*arom*), 8.30 (m, 2 H, H-*arom*) ppm; $^{31}P\{^{1}H\}$ NMR (161.9 MHz, $CDCl_3$, 25ºC): δ = 21.7 (dd, $^{1}J_{PA,Rh}$ = 142.0 Hz, $^{2}J_{PA,PB}$ = 40.9 Hz, P^{A}), 121.2 (dd, $^{1}J_{PB,Rh}$ = 269.2 Hz, $^{2}J_{PB,PA}$ = 40.9 Hz, P^{B}) ppm; elemental analysis (%) calcd for $C_{84}H_{120}BF_4O_{31}P_2Rh{\bullet}CH_2Cl_2$ (1877.49 + 84.93): C 52.02, H 6.27, found: C 52.00, H 6.50; MS (ESI-TOF): *m/z* (%): 1681.54 (100) $[M - COD - BF_4]^+$.

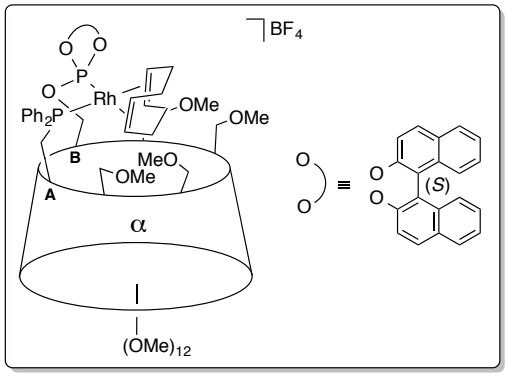


***cis*-*P,P'*-(Cycloocta-1,5-diene)-{6^{A},6^{B}-dideoxy-6^{A}-diphenylphosphinyl-6^{B}-(4,4',6,6'-tetra-*tert*-butyl-2,2'-bisphenoxyphosphinoxy)-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},6^{C},6^{D},6^{E},6^{F}-hexadeca-*O*-methyl-α-cyclodextrin}rhodium (I) (19):** This compound was prepared in 99% yield (0.155 g) according to the procedure used for **18**, by reacting **14** (0.134 g, 0.07 mmol) with $[Rh(COD)_2]BF_4$ (0.030 g, 0.07 mmol). R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.30; m.p. dec.; ^{1}H NMR (400.1 MHz, $CDCl_3$, 60ºC): δ (assignment by COSY) = 1.33 (s, 9 H, *t*Bu), 1.40 (s, 9 H, *t*Bu), 1.59 (s, 9 H, *t*Bu), 1.88 (s, 9 H, *t*Bu), 1.98–2.08 (br. m, 1 H, allylic protons of COD), 2.18–2.31 (br. m, 1 H, allylic protons of COD), 2.32–2.56 (6 H, allylic protons of COD), 2.41 (t, 1 H, $^3J_{H\text{-}4,H\text{-}3} = {}^3J_{H\text{-}4,H\text{-}5} = 8.4$ Hz, H-4), 2.80–2.87 (2 H, H-2, H-6), 2.97–3.03 (2 H, H-2), 3.10 (s, 3 H, OMe), 3.29 (s, 3 H, OMe), 3.32 (s, 3 H, OMe), 3.40 (s, 3 H, OMe), 3.46 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 3.49 (s, 3 H, OMe), 3.52 (s, 3 H, OMe), 3.53 (s, 3 H, OMe), 3.54 (s, 3 H, OMe), 3.56 (s, 6 H, OMe), 3.57 (s, 3 H, OMe), 3.58 (s, 3 H, OMe), 3.61 (s, 6 H, OMe), 3.05–3.97 (29 H, H-2, H-3, H-4, H-5, H-6), 3.99–4.08 (3 H, H-1, H-5, vinylic protons of COD), 4.13 (m, 1 H, vinylic protons of COD), 4.28 (m, 1 H, H-5), 4.35 (m, 1 H, H-1), 4.76 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2} = 2.8$ Hz, H-1), 4.83 (m, 1 H, vinylic protons of COD), 5.05–5.10 (3 H, H-1), 5.83 (m, 1 H, vinylic protons of COD), 7.12–7.19 (3 H, H-*arom*), 7.35–7.45 (4 H, H-*arom*), 7.52 (s, 1 H, H-*arom*), 7.53–7.59 (2 H, H-*arom*), 7.62 (s, 1 H, H-*arom*), 7.83 (m, 1 H, H-*arom*), 8.30–8.38 (2 H, H-*arom*) ppm; $^{31}P\{^1H\}$ NMR (161.9 MHz, $CDCl_3$, 60ºC): δ = 19.6 (dd, $^1J_{PA,Rh}$ = 142.9 Hz, $^2J_{PA,PB}$ = 37.4 Hz, P^A), 121.1 (dd, $^1J_{PB,Rh}$ = 266.7 Hz, $^2J_{PB,PA}$ = 37.4 Hz, P^B) ppm; elemental analysis (%) calcd for $C_{100}H_{152}BF_4O_{31}P_2Rh{\bullet}2CH_2Cl_2$ (2101.92 + 169.87): C 53.93, H 6.92, found: C 54.02, H 7.18; MS (ESI-TOF): *m/z* (%): 1905.80 (100) [*M* – COD – BF_4]$^+$, 2014.90 (6) [*M* – BF_4]$^+$.



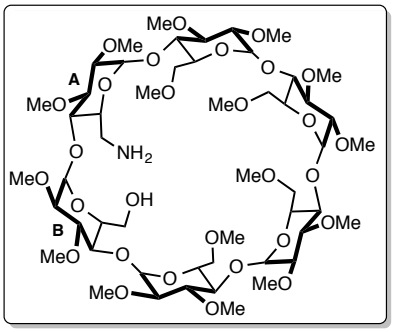
***cis-P,P'*-(Cycloocta-1,5-diene)-{6^{A},6^{B}-dideoxy-6^{A}-diphenylphosphinyl-6^{B}-(*R*)-(1,1'-binaphthyl-2,2'-bisoxyphosphinoxy)-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},6^{C},6^{D},6^{E},6^{F}-hexadeca-*O*-methyl-α-cyclodextrin}rhodium (I) (20):** This compound was prepared in 99 % yield (0.126 g) according to the procedure used for the synthesis of **18**, by reacting **15** (0.108 g, 0.06 mmol) with $[Rh(COD)_2]BF_4$ (0.026 g, 0.06 mmol). R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.30; m.p. dec.; ^{1}H NMR (400.1 MHz, $CDCl_3$, 60ºC): δ (assignment by COSY) = 1.68–1.84 (br. m, 1 H, allylic protons of COD), 1.94–2.05 (br. m, 1 H, allylic protons of COD), 2.07–2.17 (4 H, allylic protons of COD), 2.40 (t, 1 H, $^3J_{H\text{-}4,H\text{-}3} = {}^3J_{H\text{-}4,H\text{-}5} = 9.6$ Hz, H-4^B), 2.34–2.46 (2 H, allylic protons of COD), 2.84 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}3} = 9.9$ Hz, $^3J_{H\text{-}2,H\text{-}1} = 3.5$ Hz, H-2), 2.90 (dd, 1 H, $^2J_{H\text{-}6a,H\text{-}6b} = 11.7$ Hz, $^3J_{H\text{-}6b,H\text{-}5} = 2.5$ Hz, H-6b^A), 3.01 (s, 3 H, OMe), 3.01–3.03 (m, 1 H, H-6a^A), 3.05 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}3} = 9.7$ Hz, $^3J_{H\text{-}2,H\text{-}1} = 3.3$ Hz, H-2), 3.26 (s, 3 H, OMe), 3.29 (s, 3 H, OMe), 3.38 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 3.48 (s, 3 H, OMe), 3.50 (s, 3 H, OMe), 3.51 (s, 3 H, OMe), 3.52 (s, 3 H, OMe), 3.56 (s, 3 H, OMe), 3.57 (s, 3 H, OMe), 3.59 (s, 3 H, OMe), 3.60 (s, 3 H, OMe), 3.63 (s, 3 H, OMe), 3.64 (s, 3 H, OMe), 3.65 (s, 3 H, OMe), 3.14–3.87 (25 H, H-2, H-3, H-4, H-5, H-6), 3.91–3.96 (m, 1 H, H-5), 3.99–4.10 (4 H, H-5, H-6), 4.15 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2} = 3.3$ Hz, H-1), 4.19 (m, 1 H, vinylic protons of COD), 4.33 (m, 1 H, H-5), 4.41 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2} = 2.6$ Hz, H-1), 4.45 (m, 1 H, vinylic protons of COD), 5.04 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2} = 3.2$ Hz, H-1), 5.07 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2} = 3.1$ Hz, H-1), 5.08 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2} = 3.1$ Hz, H-1), 5.10 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2} = 3.5$ Hz, H-1), 5.25 (m, 1 H, vinylic protons of COD), 5.58 (m, 1 H, vinylic protons of COD), 7.14–7.60 (14 H, H-*arom*), 7.80 (t, 1 H, *J* = 7.3 Hz, H-*arom*), 7.88–8.07 (4 H, H-*arom*), 8.33–8.41 (3 H, H-*arom*) ppm; $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 28.58–28.80 (4 C, allylic C of COD), 31.0 (d, $^1J_{C,P} = 20.6$ Hz, C-6^A), 56.44, 56.56, 56.59, 56.69, 56.83, 56.90, 57.18, 57.33, 57.96, 58.06, 58.12, 60.60, 60.78, 60.80, 60.90, 60.92, (OMe), 65.62 (d, $^3J_{C,P} = 6.3$ Hz, C-5^B), 66.81 (C-6), 69.05, 69.16 (C-5), 69.54 (d, $^2J_{C,P} = 14.1$ Hz, C-6^B), 69.65 (C-5), 69.97, 70.15 (C-6), 70.29 (d, $^2J_{C,P} = 19.2$ Hz, C-5^A), 71.24 (C-5),71.41 (C-6), 77.69, 77.82, 80.84, 81.21, 81.32, 81.38, 81.47, 81.58, 81.79 [×2], 82.40, 82.54, 82.60, 82.63, 82.91, 82.96, 83.07 (C-2, C-3, C-4), 87.03 (d, $^3J_{C,P} = 13.5$ Hz, C-4^A), 94.84 (vinylic C of COD), 97.21, 97.48, 99.09, 99.39, 99.71, 100.27 (C-1), 100.45, 106.02, 111.49, (vinylic C of COD), 116.74, 119.37, 119.74, 123.05, 123.29, 124.29, 124.73, 124.83, 125.72, 125.80, 126.11, 126.29, 126.44, 127.22, 127.40, 127.44, 128.03, 128.38, 128.49, 128.82, 128.93, 129.02, 129.70, 129.79, 129.95, 130.37, 130.63, 130.78, 132.42, 132.67, 145.21 (d, $^1J_{C,P} = 9.1$ Hz, C-*ipso*^{A}), 146.36 (d, $^1J_{C,P} = 11.9$ Hz, C-*ipso*^{A}) ppm; $^{31}P\{^1H\}$ NMR (161.9 MHz, $CDCl_3$, 60ºC): δ = 21.9 (dd, $^1J_{PA,Rh} = 142.0$ Hz, $^2J_{PA,PB} = 42.0$ Hz, P^A), 122.1 (dd, $^1J_{PB,Rh} = 270.0$ Hz, $^2J_{PB,PA} = 42.0$ Hz, P^B) ppm;

elemental analysis (%) calcd for $C_{92}H_{124}BF_4O_{31}P_2Rh$ (1977.62): C 55.87, H 6.32, found: C 55.68, H 6.57; MS (ESI-TOF): *m/z* (%): 1781.55 (100) $[M - COD - BF_4]^+$.

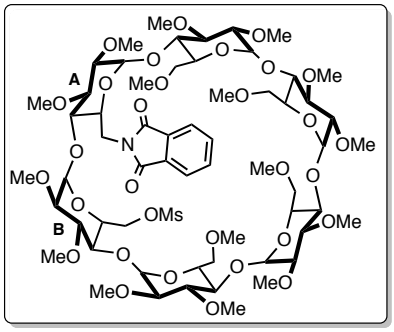


***cis-P,P'*-(Cycloocta-1,5-diene)-{6^A,6^B-dideoxy-6^A-diphenylphosphinyl-6^B-(*S*)-(1,1'-binaphthyl-2,2'-bisoxyphosphinoxy)-2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^C,6^D,6^E,6^F-hexadeca-*O*-methyl-α-cyclodextrin}rhodium (I) (21):** This compound was prepared in 99 % yield (0.110 g) according to the procedure used for the synthesis of **18**, by reacting **16** (0.095 g, 0.06 mmol) with $[Rh(COD)_2]BF_4$ (0.023 g, 0.06 mmol). R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.30; m.p. dec.; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY and HSQC) = 1.71 (br. m, 1 H, allylic protons of COD), 1.91 (br. m, 1 H, allylic protons of COD), 2.00–2.29 (6 H, allylic protons of COD), 2.38 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}3}$ = 9.6 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 3.1 Hz, H-2^A), 2.81 (br. d, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 9.6 Hz, H-6), 2.84 (t, 1 H, $^3J_{H\text{-}4,H\text{-}3}$ = $^3J_{H\text{-}4,H\text{-}5}$ = 8.7 Hz, H-4^B), 2.88 (s, 3 H, OMe), 2.91 (dd, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 11.7 Hz, $^3J_{H\text{-}6b,H\text{-}5}$ = 2.3 Hz, H-6b), 3.00 (dd, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 11.7 Hz, $^3J_{H\text{-}6b,H\text{-}5}$ = 2.9 Hz, H-6b), 3.02 (s, 3 H, OMe), 3.04–3.10 (3 H, H-2), 3.11 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}3}$ = 10.2 Hz, $^3J_{H\text{-}2,H\text{-}1}$ = 3.9 Hz, H-2^B), 3.15–3.22 (3 H, H-2, H-3, H-6), 3.23 (dd, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 9.7 Hz, $^3J_{H\text{-}6b,H\text{-}5}$ = 2.0 Hz, H-6b), 3.28 (s, 3 H, OMe), 3.33 (s, 3 H, OMe), 3.40 (s, 3 H, OMe), 3.44 (s, 3 H, OMe), 3.45 (s, 3 H, OMe), 3.46 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 3.48 (s, 3 H, OMe), 3.51 (s, 3 H, OMe), 3.55 (s, 3 H, OMe), 3.58 (s, 3 H, OMe), 3.59 (s, 3 H, OMe), 3.61 (s, 3 H, OMe), 3.62 (s, 3 H, OMe), 3.27–3.68 (17 H, H-1, H-3, H-4, H-5, H-6), 3.72–3.77 (2 H, H-5, vinylic protons of COD), 3.79 (d, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 10.2 Hz, H-6), 3.86 (m, 1 H, H-5), 3.88–3.95 (2 H, H-6, H-6B), 4.30 (m, 1 H, H-6A), 4.40 (m, 1 H, H-5^A), 4.50 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 2.5 Hz, H-1), 4.56 (m, 1 H, vinylic protons of COD), 4.67 (m, 1 H, vinylic protons of COD), 4.90 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1), 4.92 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1), 5.02 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1), 5.04 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.1 Hz, H-1), 5.40 (m, 1 H, vinylic protons of COD), 7.23–7.54 (10 H, H-*arom*), 7.62–7.67 (3 H, H-*arom*), 7.72–7.78 (2 H, H-*arom*), 7.83 (d, 1 H, *J* = 9.5 Hz, H-*arom*), 7.89 (d, 1 H, *J* = 9.8 Hz, H-*arom*), 7.99 (d, 1 H, *J* = 9.6 Hz, H-*arom*), 8.02 (d, 1 H, *J* = 10.1 Hz, H-*arom*), 8.05–8.10 (2 H, H-*arom*), 8.31 (d, 1 H, *J* = 10.2 Hz, H-*arom*) ppm; ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 28.85 (d, $^1J_{C,P}$ = 18.9 Hz, C-6^A), 29.64–29.94 (4 C, allylic C of COD), 57.53, 58.10, 58.15 [×2], 58.23, 58.29, 58.84, 59.11, 59.16, 59.88, 61.04, 61.18, 61.36, 61.44, 61.69, 61.92 (OMe), 68.47 (d, $^3J_{C,P}$ = 4.9 Hz, C-5^B), 69.14 (d, $^2J_{C,P}$ = 14.0 Hz, C-6^B), 70.00, 70.59 (C-6), 71.26 (d, $^2J_{C,P}$ = 23.3 Hz, C-5^A), 71.34, 71.38 (C-5), 71.43 [×2] (C-6), 71.76, 72.32 (C-5), 79.96, 80.21, 80.83, 80.91, 81.03, 81.10, 81.27, 81.52, 81.70, 81.88, 82.02, 82.28, 82.42, 82.47 [×2], 82.72, 83.64 (C-2, C-3, C-4),

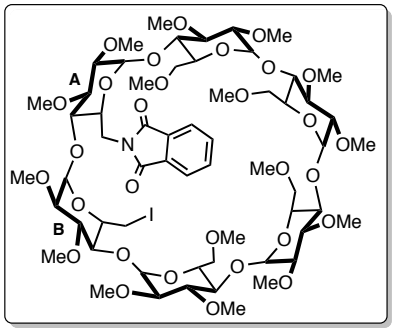
88.19 (d, $^{3}J_{C,P}$ = 7.1 Hz, C-4^{A}), 94.40 (vinylic C of COD), 98.53, 98.71, 99.44, 99.85, 100.37 [×2] (C-1), 100.16, 108.48, 112.75 (vinylic C of COD), 120.27, 121.47, 122.52, 122.43, 126.08, 126.21, 126.79, 127.04, 127.07, 127.80, 128.19, 128.27, 128.28, 128.41, 128.89, 128.96, 129.04, 129.62, 129.97, 130.84, 130.98, 131.20, 131.92, 132.17, 132.45, 132.80, 133.51, 133.60, 133.65, 133.74, 146.64 (d, $^{1}J_{C,P}$ = 6.6 Hz, C-*ipso*^{A}), 148.75 (d, $^{1}J_{C,P}$ = 13.8 Hz, C-*ipso*^{A}) ppm; $^{31}P\{^{1}H\}$ NMR (161.9 MHz, $CDCl_3$, 25ºC): δ = 20.7 (dd, $^{1}J_{PA,Rh}$ = 139.7 Hz, $^{2}J_{PA,PB}$ = 41.3 Hz, P^{A}), 122.6 (dd, $^{1}J_{PB,Rh}$ = 2708 Hz, $^{2}J_{PB,PA}$ = 41.3 Hz, P^{B}) ppm; elemental analysis (%) calcd for $C_{92}H_{124}BF_4O_{31}P_2Rh{\bullet}2CH_2Cl_2$ (1977.62 + 169.87): C 52.57, H 6.01, found: C 52.59, H 6.30; MS (ESI-TOF): *m/z* (%): 1781.62 (100) $[M - COD - BF_4]^+$.



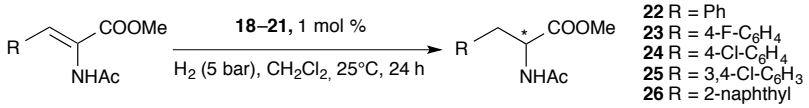
6^{A}-Deoxy-6^{A}-amino-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},6^{C},6^{D},6^{E},6^{F}-hexadeca-*O*-methyl-α-cyclodextrin (28): Hydrazine monohydrochloride (0.502 g, 492 μL, 15.68 mmol) was added to a solution of **27** (1.040 g, 0.78 mmol) in *tert*-butanol (12 mL) and refluxed for 4h. The resulting white suspension was evaporated in vacuo and retaken in 2M NaOH solution (50 mL). Subsequent extraction with $CHCl_3$ (3 × 50 mL) was followed by drying of the organic extracts ($MgSO_4$). Removal of the solvent in vacuo gave a colourless residue, which was subjected to column chromatography (SiO_2; CH_2Cl_2/MeOH/NH_4OH, 91:8:1, *v/v*) to afford **28** (0.870 g, 93%) as a colourless solid. R_f (SiO_2, CH_2Cl_2/MeOH/NH_4OH, 89:10:1, *v/v*) = 0.36; m.p. 115°C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by COSY) = 1.93–2.15 (3 H, NH_2, OH), 3.03–3.21 (8 H, H-2, H-6^{A}), 3.35–3.38 (12 H, OMe), 3.46 (s, 3 H, OMe), 3.47 (s, 6 H, OMe), 3.48 (s, 6 H, OMe), 3.49 (s, 3 H, OMe), 3.61 (s, 3 H, OMe), 3.62 (s, 12 H, OMe), 3.63 (s, 3 H, OMe), 3.43–3.81 (28 H, H-3, H-4, H-5, H-6), 3.82–3.97 (2 H, H-6^{B}), 4.99–5.05 (6 H, H-1) ppm; $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 42.64 (C-6^{A}), 57.82, 57.89 [×2], 57.94 [×2], 58.00, 59.00 [×2], 59.05, 59.18, 61.74, 61.77 [×3], 61.84, 61.88 (OMe), 62.30 (C-6^{B}), 71.14, 71.22, 71.32 [×2] (C-5), 71.39, 71.45 [×3] (C-6), 72.44, 72.67 (C-5), 81.17–83.21 (C-2, C-3, C-4), 99.77 [×2], 99.89, 100.04 [×2], 100.09 (C-1) ppm; elemental analysis (%) calcd for $C_{52}H_{93}NO_{29}$ (1196,28): C 52.21, H 7.84, N 1.17, found: C 49.92, H 7.54, N 1.13; MS (ESI-TOF): *m/z* (%): 1196.60 (100) $[M + H]^+$.



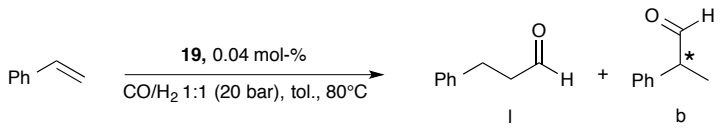
$6^A,6^B$-Dideoxy-6^A-(1,3-dioxoisoindolin-2-yl)-6^B-*O*-methylsulfonyl-$2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^C,6^D,6^E,6^F$-hexadeca-*O*-methyl-$\alpha$-cyclodextrin (29): Methylsulfonyl chloride (0.036 g, 24 μL, 0.31 mmol) was added to a solution of azeotropicaly dried **27** (0.375 g, 0.28 mmol) and *N*,*N*- dimethylpyridine (0.035 g, 0.28 mmol) in anhydrous pyridine (5 mL). The reaction mixture was stirred at room temperature for 14 h, whereupon water (30 mL) was added. The solution was then extracted with ethyl acetate (3 × 30 mL), and the organic phase was washed respectively with 2 M HCl (2 × 30 mL), 2 M NaOH (30 mL), and sat. $NaHCO_3$ (30 mL) before being dried ($MgSO_4$). Removal of the solvent in vacuo gave a colourless residue, which was subjected to column chromatography (SiO_2; CH_2Cl_2/MeOH, 96:4, *v*/*v*) to afford **29** (0.385 g, 85%) as a colourless solid. R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.63; m.p. 149°C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by COSY) = 2.74 (dd, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 2.0 Hz, $^3J_{H\text{-}6a,H\text{-}5}$ = 11.0 Hz, H-6a^A), 2.95 (s, 3 H, SO_2Me), 3.10 (s, 3 H, OMe), 3.15 (s, 3 H, OMe), 3.38 (s, 3 H, OMe), 3.43 (s, 3 H, OMe), 3.44 (s, 3 H, OMe), 3.46 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 3.48 (s, 3 H, OMe), 3.49 (s, 3 H, OMe), 3.50 (s, 3 H, OMe), 3.60 (s, 3 H, OMe), 3.61 (s, 3 H, OMe), 3.62 (s, 6 H, OMe), 3.65 (s, 3 H, OMe), 3.68 (s, 3 H, OMe), 3.02–4.14 (31 H, H-2, H-3, H-4, H-5, H-6), 4.22 (dd, 1 H, $^2J_{H\text{-}6b,H\text{-}6a}$ = 2.0 Hz, $^3J_{H\text{-}6b,H\text{-}5}$ = 13.9 Hz, H-6b^A), 4.40–4.45 (m, 1 H, H-5^A), 4.55–4.63 (2 H, H-6^B), 4.94 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1), 4.95 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1), 5.03 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1), 5.04 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.4 Hz, H-1), 5.07 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1), 5.26 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1), 7.73–7.77 (2 H, *m*-H), 7.81–7.84 (*o*-H) ppm; $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$, 25ºC): δ = 39.60 (C-6^A), 57.76, 57.79, 57.98, 57.85, 58.06, 58.22, 58.73, 58.91 [×2], 59.23, 61.68, 61.80, 61.88, 61.95, 62.01, 62.03 (OMe), 69.60 (C-6), 69.66, 69.86 (C-5), 70.18, 70.87, 70.93 (C-6), 70.96, 71.25, 71.38, 71.43 (C-5), 71.61 (C-6), 80.89, 80.95, 80.99, 81.15, 81.20, 81.35, 81.77 [×2], 81.91, 81.94, 81.98, 82.14, 82.27, 82.32, 82.52 [×2], 82.56, 85.29 (C-2, C-3, C-4), 99.21, 99.96, 100.05, 100.10, 100.18, 100.52 (C-1), 123.07 (C_{meta}), 132.27 (C_{ipso}), 134.03 (C_{ortho}), 168.13 (CO) ppm; elemental analysis (%) calcd for $C_{61}H_{97}NO_{33}S•2CH_2Cl_2$ (1404,48 + 169.85): C 48.06, H 6.47, N 0.89, found: C 47.73, H 6.32, N 0.73; MS (ESI-TOF): *m/z* (%): 1426.56 (100) $[M + Na]^+$.



$6^A,6^B$-Dideoxy-6^A-(1,3-dioxoisoindolin-2-yl)-6^B-iodido-$2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^C,6^D,6^E,6^F$-hexadeca-*O*-methyl-$\alpha$-cyclodextrin (30): To a stirred solution of **29** (0.300 g, 0.22 mmol) in an acetone/toluene mixture (30 mL, 1:1, *v*/*v*) was added NaI (0.096 g, 0.64 mmol). After 16 h at reflux, the reaction mixture was cooled to room temperature and filtered over celite. Removal of the solvent in vacuo gave a yellowish residue, which was subjected to column chromatography (SiO_2; CH_2Cl_2/MeOH, 96:4, *v*/*v*) to afford **30** (0.252 g, 82%) as a colourless solid. R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.66; m.p. > 250°C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by COSY) =2.67 (dd, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 10.2 Hz, $^3J_{H\text{-}6a,H\text{-}5}$ = 1.6 Hz, H-6a), 3.05 (s, 3 H, OMe), 3.12 (s, 3 H, OMe), 3.38 (s, 3 H, OMe), 3.42 (s, 3 H, OMe), 3.43 (s, 3 H, OMe), 3.45 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 3.48 (s, 3 H, OMe), 3.49 (s, 3 H, OMe), 3.52 (s, 3 H, OMe), 3.59 (s, 3 H, OMe), 3.60 (s, 6 H, OMe), 3.61 (s, 3 H, OMe), 3.63 (s, 3 H, OMe), 3.68 (s, 3 H, OMe), 3.04–4.22 (), 4.92 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1), 4.93 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1), 5.03 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1), 5.09 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.1 Hz, H-1), 5.16 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1), 5.20 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.4 Hz, H-1), 7.74–7.77 (2 H, *m*-H), 7.82–7.85 (*o*-H) ppm; ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 25ºC): δ = 10.47 (C-6^B), 39.05 (C-6^A), 56.78, 56.84, 56.86, 56.93 [×2], 57.28, 57.68, 57.89, 58.04, 58.20, 60.68, 60.75, 60.84, 60.87, 60.95, 61.01 (OMe), 67.99 (C-5), 68.58 (C-6), 68.80 (C-5), 69.72, 69.79 (C-6), 69.94, 70.25, 70.40, 70.37 (C-5), 70.70 (C-6), 79.52, 79.87, 79.95, 80.16 [×2], 80.44, 80.67, 80.72, 80.80, 80.93, 81.00, 81.16 [×3], 81.25, 81.61, 84.14, 85.39 (C-2, C-3, C-4), 98.22, 98.42, 98.66, 99.03, 99.15, 99.25, 99.38 (C-1), 122.14 (C_{meta}), 131.16 (C_{ipso}), 133.17 (C_{ortho}), 167.06 (CO) ppm; elemental analysis (%) calcd for $C_{60}H_{94}INO_{30}$•CH_2Cl_2 (1436,29 + 84.93): C 48.16, H 6.36, N 0.92, found: C 47.99, H 6.33, N 0.88; MS (ESI-TOF): *m/z* (%): 1458.48 (100) $[M + Na]^+$.



General procedure for the hydrogenation experiments: The hydrogenation experiments were carried out in a glass-lined, 100 mL stainless steel autoclave containing a magnetic stirring bar. In a typical run, the autoclave was charged with preformed rhodium complexes **18-21** (0.01 mmol) and substrate **22-26** (1.0 mmol), then closed and flushed with nitrogen. CH_2Cl_2 (5 mL) was added and the autoclave flushed with H_2. The solution was stirred under H_2 (5 atm) at 25°C. After completion of the reaction, the solution was subjected to filtration through a short silica gel column. Conversion was determined by ^{1}H NMR. *Ee*'s were determined by GC using CHROMPAK chiral fused silica 25m x 0.25mm. Coating Chirasil-L-Val column.



General procedure for the hydroformylation experiments: The hydroformylation experiments were carried out in a glass-lined, 100 mL stainless steel autoclave containing a magnetic stirring bar. In a typical run, the autoclave was charged under nitrogen with a solution of preformed rhodium complex (**19**, 0.002 mmol) in toluene (1 mL) and toluene (14 mL). Once closed, the autoclave was flushed twice with syngas (CO/H_2 1:1 v/v), pressurised with 20 bar of a CO/H_2 mixture and heated at 80°C. After 16 h, the autoclave was depressurised then styrene (0.57 mL, 0.521 g, 5.0 mmol) and decane (0.50 mL) were added to the reaction mixture. The autoclave was then heated (80°C) and pressurised (5 bar). Progress of the reaction was monitored by sampling the reaction mixture and analysing it by gas chromatography using a WCOT fused-silica column (25m × 0.25mm). This also allowed to determine the l/b ratio. In order to determine the enantiomeric excess, a sample of the reaction mixture (toluene) was treated with $LiAlH_4$ for 0.2 h. After filtration, the solution containing enantiomeric alcohols was analysed by GC with a Chirasil-DEX CB column (25 m × 0.25 mm).

III. 5. References

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Chapter IV

Phosphinocyclodextrins as confining units for catalytic centres. Applications to carbon-carbon bond forming reactions

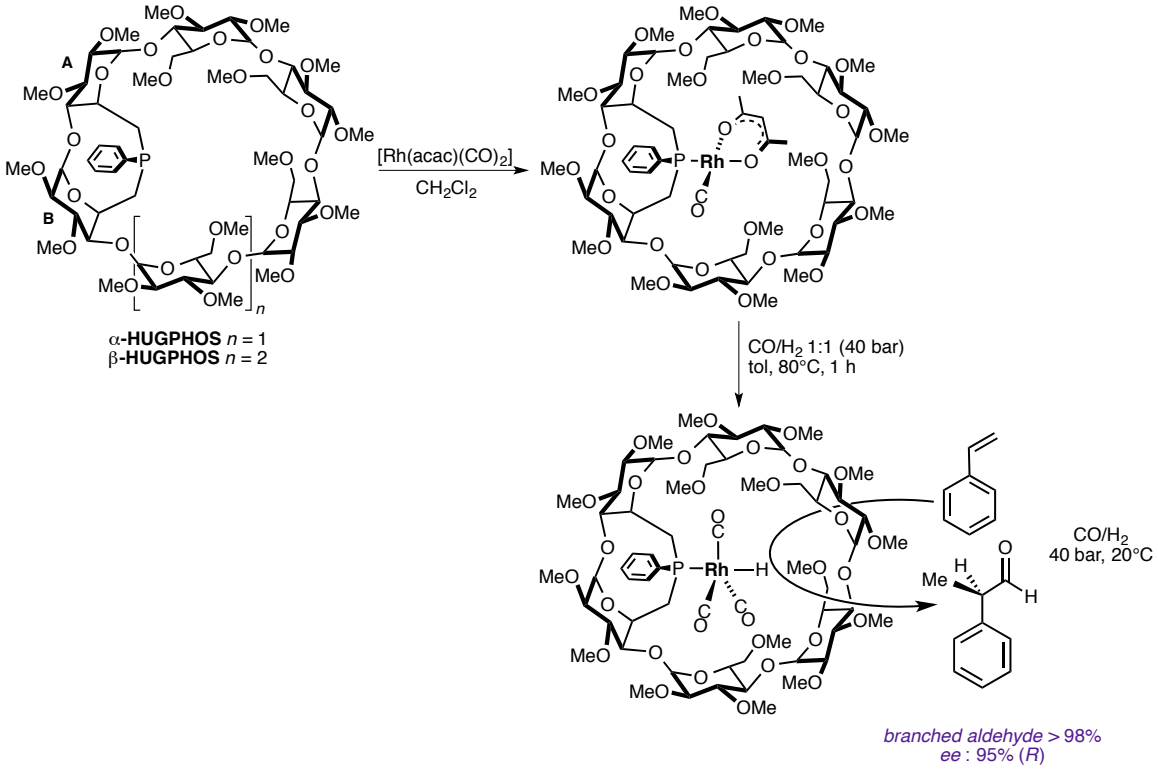
Chapter IV

Phosphinocyclodextrins as confining units for catalytic centres. Applications to carbon-carbon bond forming reactions

Summary – Chapter IV

The capacity of two cavity-shaped ligands, α-HUGPHOS and β-HUGPHOS, to generate exclusively singly phosphorus-ligated complexes, in which the cyclodextrin cavity tightly wraps around the metal centre, was explored with a number of late transition metal cations. Both cyclodextrin-derived ligands were assessed in palladium-catalysed Mizoroki-Heck coupling reactions between aryl bromides and styrene on one hand, and the rhodium-catalysed asymmetric hydroformylation of styrene on the other hand. The *inability* of both chiral ligands to form standard bis(phosphine) complexes under catalytic conditions was established by high-pressure NMR studies and shown to have a deep impact on the two carbon-carbon bond forming reactions both in terms of activity and selectivity. Indeed, when used as ligands in the rhodium-catalysed hydroformylation of styrene, they lead to *both* high isoselectivity *and* enantioselectivity.

La propension des phosphino-cyclodextrines α- et β-HUGPHOS à former avec des ions transitionnels exclusivement des complexes monophosphine a été vérifiée avec des centres Pd(II), Pt(II), Rh(I) et Ru(II). Dans les complexes correspondants, le centre métallique est maintenu de manière rigide au cœur de l'entité cyclodextrine. Les deux phosphines ont été évaluées d'une part en couplage de Mizoroki-Heck entre aryles bromés et styrène (catalyse au palladium), d'autre part en hydroformylation asymétrique du styrène (en présence de rhodium). L'absence, dans le milieu réactionnel, de complexes comportant deux ligands phosphine au cours de la réaction d'hydroformylation a été démontrée par des études RMN sous pression. La formation sélective de complexes monophosphine dans les deux réactions étudiées influence de manière significative le déroulement de la réaction, et ce aussi bien en terme d'activité que de sélectivité. Ainsi, ces ligands permettent pour la première fois, d'observer à la fois une isosélectivité et une énantiosélectivité élevées en hydroformylation asymétrique du styrène.



IV. 1. Introduction

Sterically encumbered phosphines are of paramount importance in coordination chemistry and catalysis.[1] Such ligands not only allow protection of active sites during a catalytic cycle, but also provide stabilization of undercoordinated species.[2] They may further promote the formation of singly phosphorus-ligated complexes, which act as key intermediates in a number of catalytic processes.[3] Striking examples of phosphines that display a marked tendency to result in high proportions of monophosphine complexes include porphyrin-substituted phosphines,[4] as well as dendrimeric phosphines,[5] bowl-shaped phosphines,[6] calix-phosphines,[7] and hybrid phosphines (Figure 1).[8]

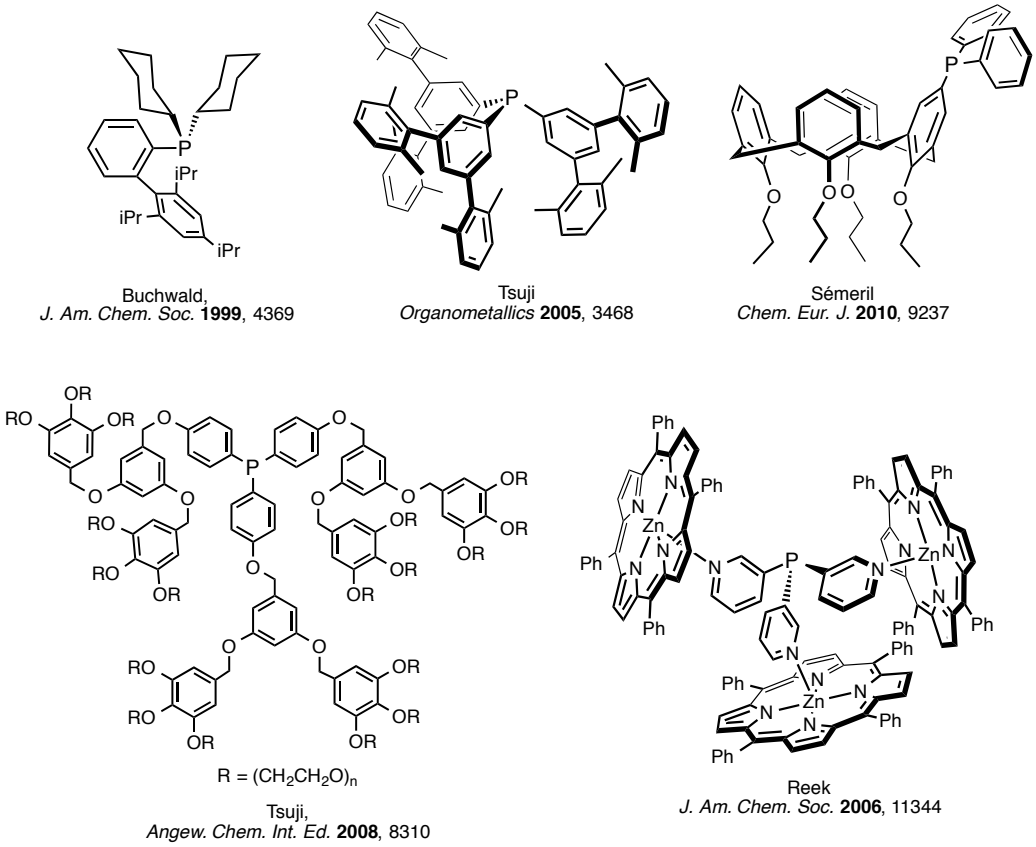


Figure 1. Different types of ligands promoting the formation of monophosphine complexes.

Recently, we have synthesised a new type of confining ligand, namely the cyclodextrin (CD) derivatives α-HUGPHOS[9] and β-HUGPHOS (Figure 2).[10] These ligands have their P(III) atom grafted rigidly to the CD core, with the P lone pair pointing toward the centre of the cavity. In principle, ligands of this type, which have been shown to tightly envelop a metal centre upon complexation and thus behave as bulky ligands, should prevent binding of a second phosphine unit. One may further anticipate that the high degree of confinement created by such chiral cavities will favour efficient chiral induction in asymmetric catalysis.

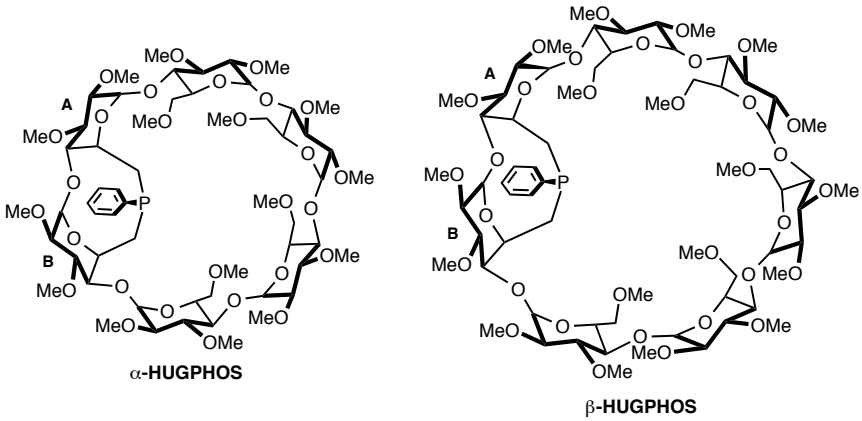


Figure 2. HUGPHOS ligands.

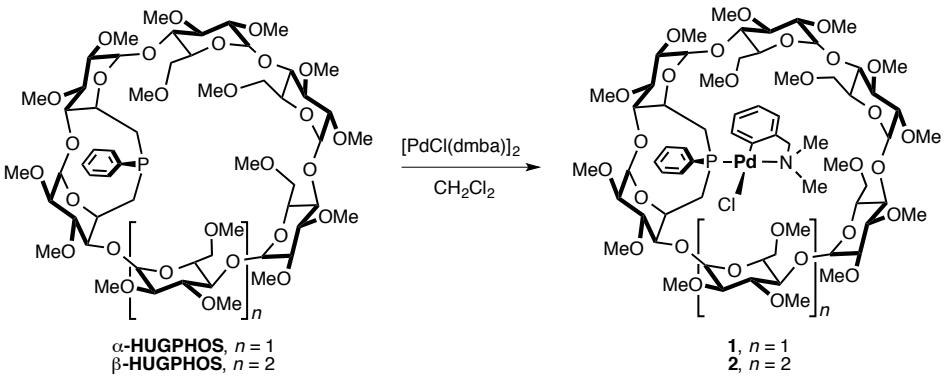
In the present study, we describe the coordinating properties of HUGPHOS ligands towards Pd(II), Pt(II), Rh(I) and Ru(II) centres, and show that these ligands form selectively monophosphine complexes in reactions in which classical phosphines would result in bis(phosphine) complexes. Palladium and rhodium complexes of both ligands have been assessed in Mizoroki-Heck and asymmetric hydroformylation reactions.[§]

[§] *Compounds **2** and **5** mentioned hereafter, as well as the X-Ray diffraction structure of **5** have already been reported in the PhD dissertation of R. Gramage-Doria.*[11]

IV. 2. Results and discussion

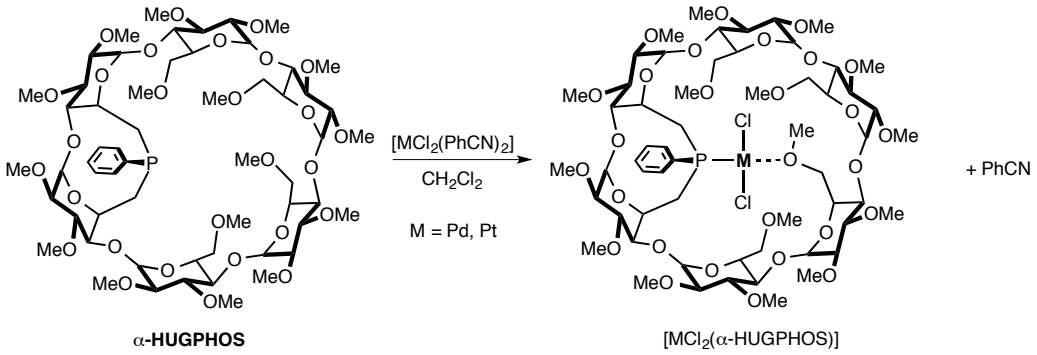
IV. 2. 1. Metal coordination

As shown earlier, α- and β-HUGPHOS are able to accommodate small organometallic moieties, for example the PdCl(dmba) moiety, as in complexes **1**[9] and **2**[11] (Scheme 1). In view of the embracing nature of these cavity-shaped ligands, we wondered whether it would be possible to promote the selective formation of monophosphine complexes with MX_2 (M = Pd, Pt) fragments that normally form $[ML_2X_2]$ complexes with tertiary phosphines.



Scheme 1. Complexation of a "PdCl(dmba)" unit by HUGPHOS ligands.

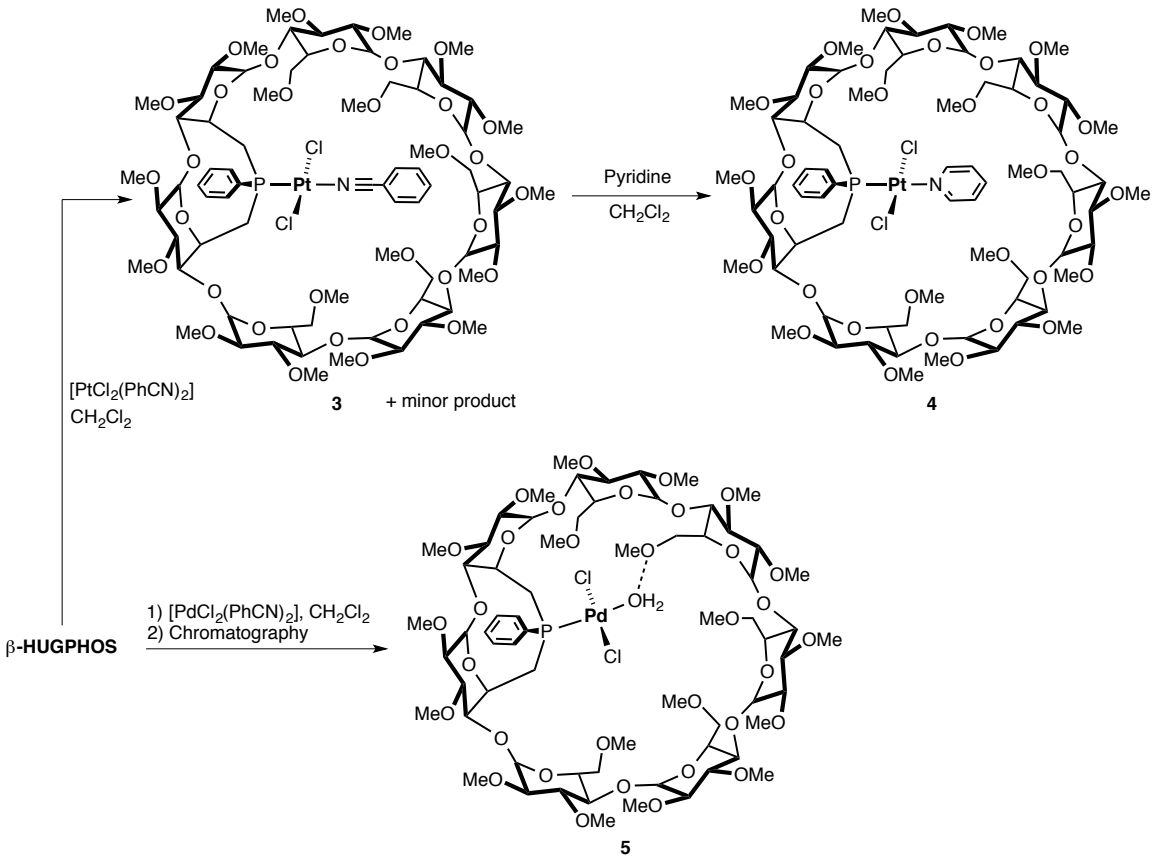
When reacted with α-HUGPHOS in CH_2Cl_2, $[PdCl_2(PhCN)_2]$ and $[PtCl_2(PhCN)_2]$ both afforded a mixture of complexes (Scheme 2). Mass spectroscopic measurements carried out on the crude reaction mixtures showed a peak corresponding to MCl_2(α-HUGPHOS) fragments. There was no indication for the formation of complexes with a molecular weight higher than that of [MCl_2(α-HUGPHOS)], this suggesting that no stable bis(phosphine) complexes had formed. The presence of a unique broad signal in each $^{31}P\{^1H\}$ NMR spectrum is consistent with the presence of several species in equilibrium. This may reflect exchange processes involving methoxy groups of the primary face and/or free benzonitrile (See chapter I, **37**).



Scheme 2. Reaction of α-HUGPHOS with $[MCl_2(PhCN)_2]$ complexes (M = Pd, Pt).

A similar study was carried out with the larger β-HUGPHOS. Its reaction with $[PtCl_2(PhCN)_2]$ in CH_2Cl_2 resulted in the formation of the monophosphine complex $[PtCl_2$(β-HUGPHOS)(PhCN)] (**3**) in 95% yield, but this complex could not be separated from a minor product, probably the benzonitrile-free complex $[PtCl_2$(β-HUGPHOS)] (Scheme 3). The $^{31}P\{^1H\}$ NMR spectrum of **3** showed a sharp signal at 3.2 ppm, with Pt satellites ($^1J_{P,Pt}$ = 3433 Hz). The mass spectrum of the product mixture showed an intense peak at *m/z* = 1866.61 (100%), corresponding to the $[M + Na]^+$ cation, as well as a peak resulting from the loss of PhCN (*m/z* = 1763.57 (11) $[M – PhCN + Na]^+$). No peaks corresponding to compounds with two phosphine ligands were detected in the spectrum.

Addition of 1 equiv. of pyridine to the mixture containing **3** gave quantitatively complex **4** (Scheme 3). The ^1H NMR spectrum of **4** shows that some H-5 signals are significantly lowfield shifted with respect to their counterparts in the free ligand, an observation which is indicative of an entrapped chlorido ligand. Note that the marked affinity of CDs for metal halide bonds is well documented.[12] The trans *P,N* configuration was deduced from a ROESY experiment that showed strong correlations between the pyridinic H-4 proton and some inner cavity H-5 protons. Also, a $^1J_{P,Pt}$ coupling constant typical of this particular geometry ($^1J_{P,Pt}$ = 3542 Hz)[13] unequivocally established the structure of the complex.



Scheme 3. Synthesis of complexes **3**–**5**.

It should be reminded that monophosphine complexes of the general formula [MX_2(phosphine)(pyridine)] usually undergo facile ligand dissociation in solution.[13] This is however not the case for complex **4**. Owing to the protecting role played by the cavity, this complex proved to be particularly robust, to such an extent that it could be purified by column chromatography (this being necessary for removing PhCN) without noticeable decomposition.

Attempts to produce a palladium analogue of **3** starting from [$PdCl_2(PhCN)_2$] failed, the corresponding reaction leading to a mixture of equilibrating species that could not be separated. However, when the reaction mixture was subjected to column chromatography on wet SiO_2, a single aquo palladium complex (**5**) was recovered in high yield (90%). The P-monoligated nature of this complex was inferred from its mass spectrum, which displays a strong peak at *m/z* = 1675.52 corresponding to the $[M + Li]^+$ ion. The $^{31}P\{^1H\}$ NMR spectrum of **5** revealed a single, slightly broad singlet at δ = 34.4 ppm. Although not visible at room temperature, the coordinated water molecule appeared as a broad singlet at δ = 5.64 ppm in the ^1H NMR spectrum recorded at –80 °C.[11] This chemical shift value is typical of aquo palladium complexes.[14] A single crystal X-ray diffraction study confirmed coordination of a {$PdCl_2(H_2O)$} fragment, which lies inside the β-CD cavity (Figure 3). To date, only one other example of [MCl_2(phosphine)(H_2O)] aquo complex has been reported.[15]

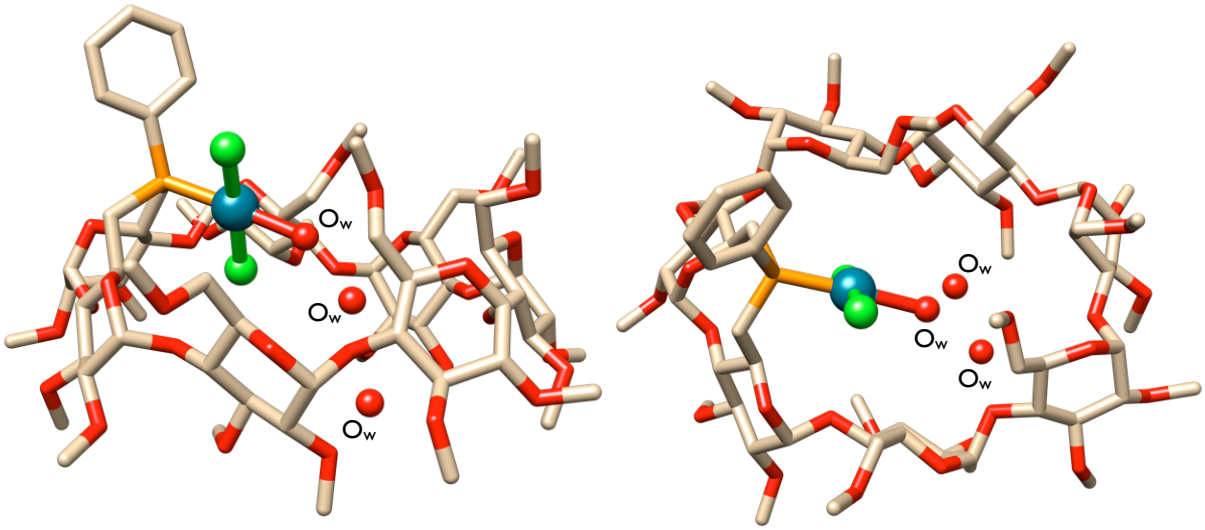


Figure 3. X-ray structure of aquo palladium complex **5** (side view, left, and top view, right). The cavity contains two non-coordinated water molecules.

β-HUGPHOS was further opposed to $[RuCl_2(p\text{-cymene})]_2$. This reaction gave a 57:43 mixture of the two rotamers **6** and **7**, which could be separated by column chromatography (Figure 4). Careful examination of the ROESY spectrum of **6** indicates that the rotations about the P–Ru bond and the Ru–arene bond are both restricted. Thus, the ROESY spectrum of this complex showed correlations between the *Me* group of the *p*-cymene ligand and protons belonging to glucose units G and A, but not with the PPh ring, nor with glucose units B and C. Consistent with these findings, the only cross peaks seen for the C*H*Me_2 proton of **6** were with protons of the PPh ring. Similar observations, which establish the same blocked rotations about the P–Ru and the Ru–arene bonds were made for **7**. It should be emphasised that prolonged heating of **6** in refluxing toluene did not induce its conversion into **7**. Hindered rotation about the Ru–P bond in **6** is possibly caused by the entrapment of one of the chlorido ligand inside the cavity.

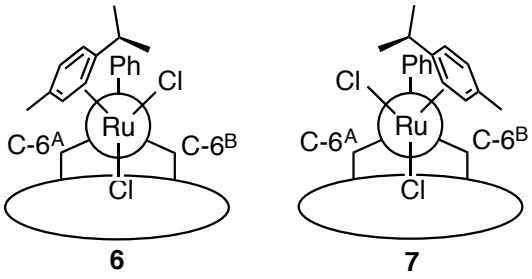


Figure 4. Ruthenium complexes **6** and **7** in Newman projection along the Ru–P bond.

Further proof for the capacity of α-HUGPHOS to *prevent* formation of bis(phosphine) complexes came from the reaction of $[RhCl(CO)_2]_2$ with an excess of ligand, which only produced *cis*-[RhCl(α-HUGPHOS)$(CO)_2$] (**8**) together with free phosphine, rather than the expected complex *trans*-[RhCl(α-HUGPHOS)$_2$(CO)] (Figure 5). The corresponding IR spectrum is typical of CO ligands in relative *cis* positions (strong CO bands at 2009 and 2082 cm^{-1}). Further, with some CD H-5 protons belonging to non bridged glucose units strongly upfield shifted upon metal complexation (Δδ up to 0.7 ppm), the ^{1}H NMR spectrum of **8** is fully consistent with a CD-encapsulated chlorido ligand,[16] which can only mean that two *cis* configured CO ligands are present.[3]

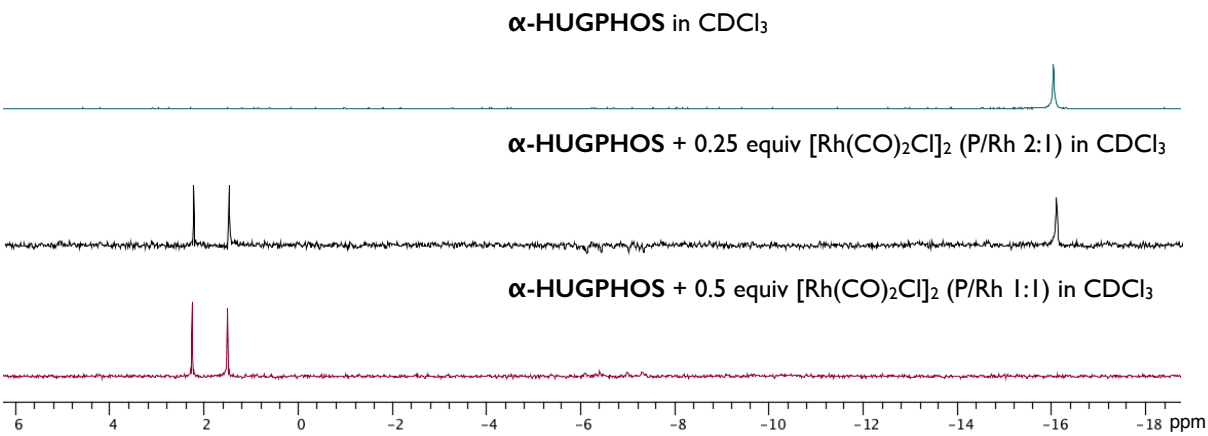
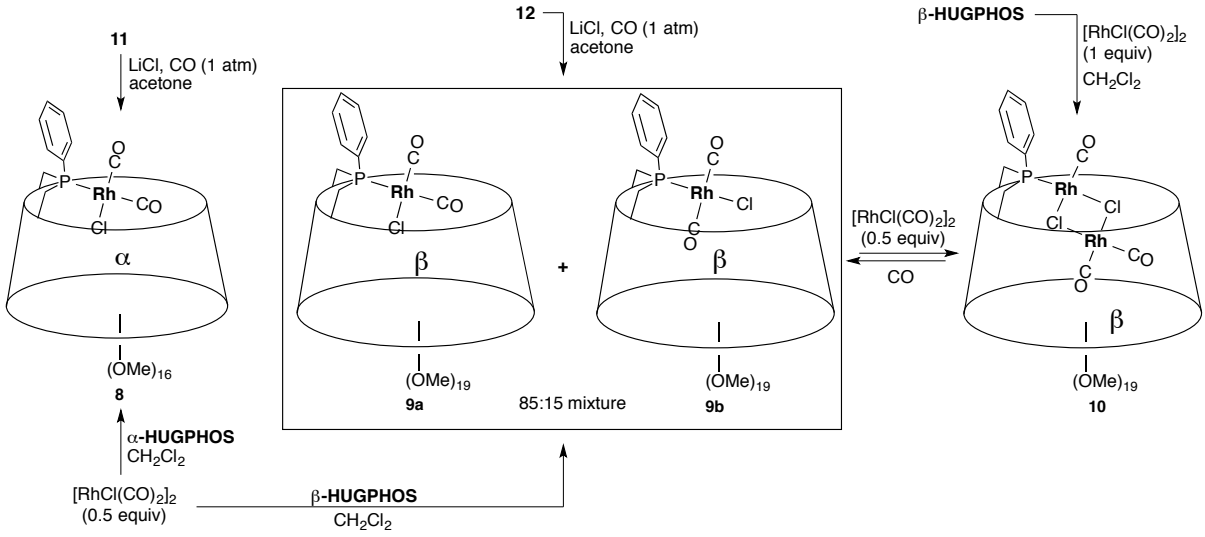


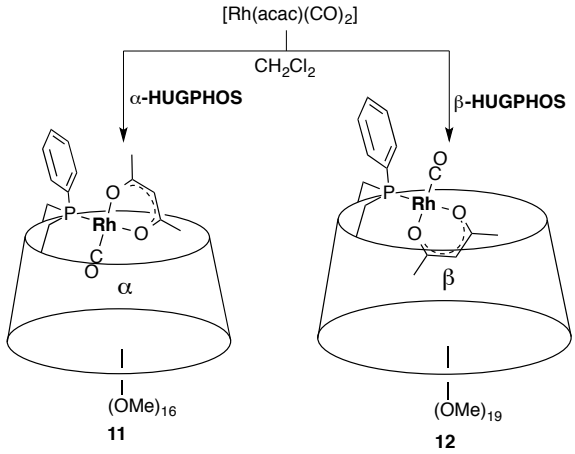
Figure 5. Titration of α-HUGPHOS with $[Rh(CO)_2Cl]_2$ at 25°C.

In the case of β-HUGPHOS, the reaction with 0.5 equiv. of $[RhCl(CO)_2]_2$ resulted in the formation of an 85:15 mixture of the inseparable mononuclear stereoisomeric complexes **9a** and **9b**, in which the two CO ligands are respectively *cis* (strong CO IR bands at 2009 and 2082 cm^{-1}) and *trans* (strong CO IR band at 1985 cm^{-1}) configured (Scheme 4). Assignment of the IR bands was made by comparison with the IR spectrum of **8** and that of other carbonyl phosphine rhodium complexes.[31] Remarkably, the same ratio of stereoisomers was obtained when rhodium complex **12** (see Scheme 5) was treated with LiCl under CO (1 atm). When the reaction between β-HUGPHOS and $[RhCl(CO)_2]_2$ was repeated applying a 1:1 stoichiometry, the dinuclear complex $[Rh_2(\mu\text{-}Cl_2)$(β-HUGPHOS)$(CO)_3]$ (**10**) formed (see experimental part). Clearly, the cavity of β-HUGPHOS is capable of accommodating up to two metal centres, whereas the smaller α-HUGPHOS ligand is unable to do so.



Scheme 4. Synthesis of rhodium biscarbonyl complexes **8**–**10**.

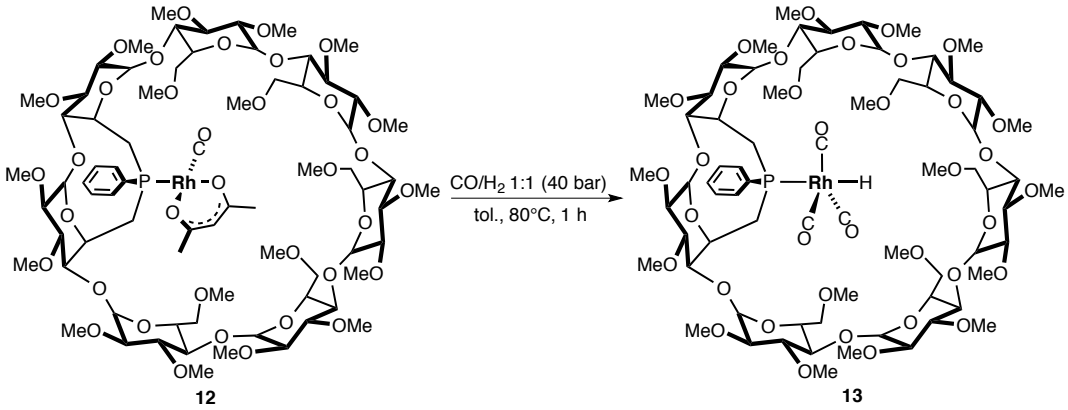
The HUGPHOS ligands were further reacted with $[Rh(acac)(CO)_2]$ (acac = acetylacetonate), this producing quantitatively the singly ligated rhodium complexes **11** and **12**. While in **12** the large β-CD cavity hosts the acac ligand, the same ligand is located outside the α-CD cavity in **11** according to ROESY experiments. On the other hand, the smaller CO rod is nested in the α-CD cavity of **11**, and located outside the β-CD cavity in **12**. Clearly, size selectivity is at work in these metal complexes (Scheme 5). As already observed for complex **4**, both **11** and **12** are remarkably stable and can be purified by column chromatography on SiO_2. This makes them, *a priori*, good candidates for hydroformylation studies.



Scheme 5. Synthesis of rhodium complexes **11** and **12**.

IV. 2. 2. High-pressure NMR studies

In order to find out whether singly phosphorus-ligated species also formed under standard hydroformylation conditions, complex **12** was activated in toluene at 80°C with a CO/H_2 mixture (1:1) at 40 bar (Scheme 6). Under these conditions, a *single* hydrido carbonyl species formed, as revealed by high-pressure NMR (toluene-d_8) and IR studies. Mass spectrometric measurements together with the ^1H and $^{31}P\{^1H\}$ NMR data obtained at high pressure unequivocally proved the formation of the complex *trans*-[$RhH(CO)_3$(β-HUGPHOS)] (**13**). Thus, the mass spectrum recorded from a toluene solution of **13** after CO/H_2 removal displayed a peak at 1663.53 (1%, exact isotopic profile) corresponding to the $[M + H]^+$ ion.



Scheme 6. Selective formation of complex **13** under 40 bar CO/H_2 at 80°C.

The ^{1}H NMR spectrum of **13** (25°C, 40 bar) revealed a hydride signal at –8.8 ppm ($^{1}J_{H,Rh}$ = 6.2 Hz) with a large ^{2}J(H,P) coupling constant ($^{2}J_{H,P}$ = 103 Hz) typical of a linear P-Rh-H arrangement.[17] In the corresponding ^{31}P{^{1}H} NMR spectrum, the P atom appeared as a doublet at 28.1 ppm ($^{1}J_{P,Rh}$ = 95 Hz) (Figure 6). The IR spectrum of **13** measured at 50°C under 40 bar of CO/H_2 showed three close together carbonyl bands at 1982 (vs), 1989 (vs), and 1992 (sh, vs) cm^{-1}, respectively, with an additional Rh–H broad weak band at 2084 cm^{-1} (Figure 7).

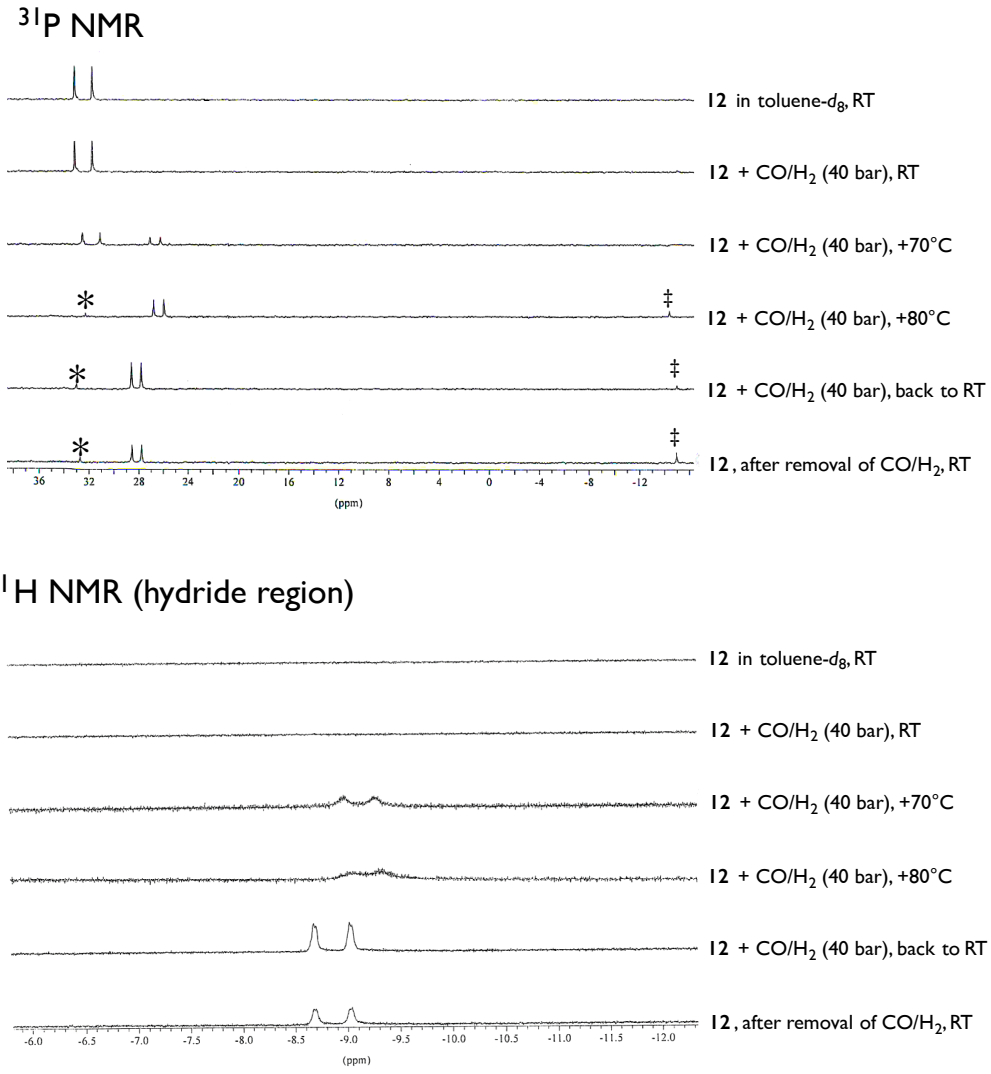


Figure 6. High-pressure NMR spectra of **12** under CO/H_2 (1:1) recorded in toluene–d_8 (at various temperatures and pressures), showing its conversion into *trans*-[RhH(CO)$_3$(β-HUGPHOS)] (**13**). The asterisk and double cross denote traces of oxidized and free β-HUGPHOS, respectively.

These data are consistent with a trigonal bipyramidal complex of C_1 symmetry. Note that the related cobalt complex *trans*-[CoH(CO)$_3$(PCy$_3$)] displays a higher symmetry (D_{3h}), and accordingly, its IR spectrum shows only one carbonyl band.[18] It is worth mentioning that the carbonyl region of the IR spectrum of **13** markedly differs from that of the only other

reported *trans*-[RhH(CO)$_3$L] complex (where L is a bulky phosphoramidite), the observed three carbonyl bands (2055 (sh), 2022 (w) and 1998 (s) cm^{-1}) being here spread over a larger frequency range.[4a]

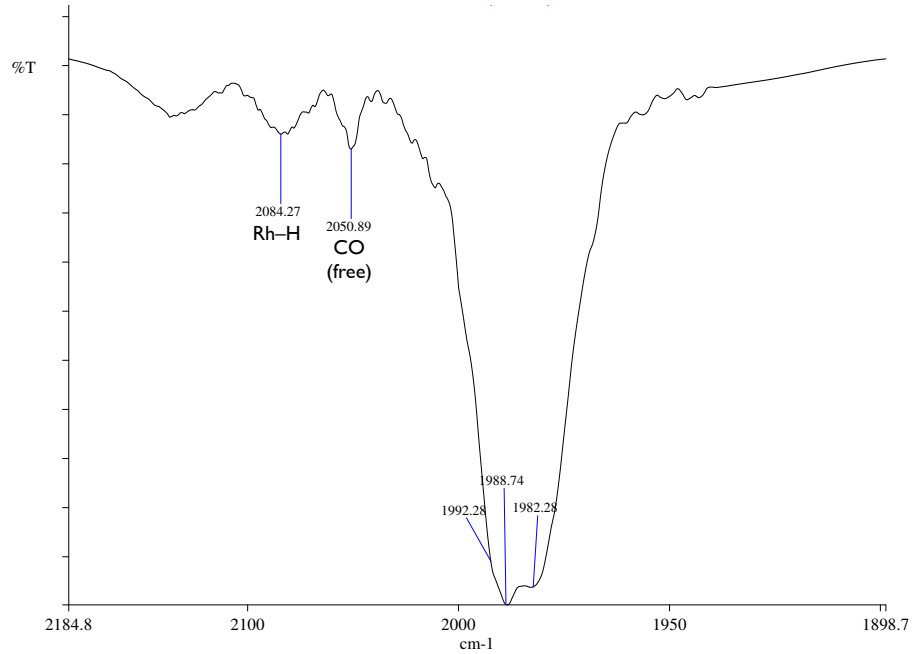


Figure 7. IR spectra of **13** recorded in CH_2Cl_2 at 50°C under 40 bar of CO/H_2 1:1.

The embracing character of the phosphine forces the trigonal bipyramidal complex to adopt a linear P-Rh-H arrangement and is responsible for the apical preference of the phosphorus atom in **13**. Such a feature minimizes steric interactions between the carbonyl ligands and the cavity wall (Figure 8).

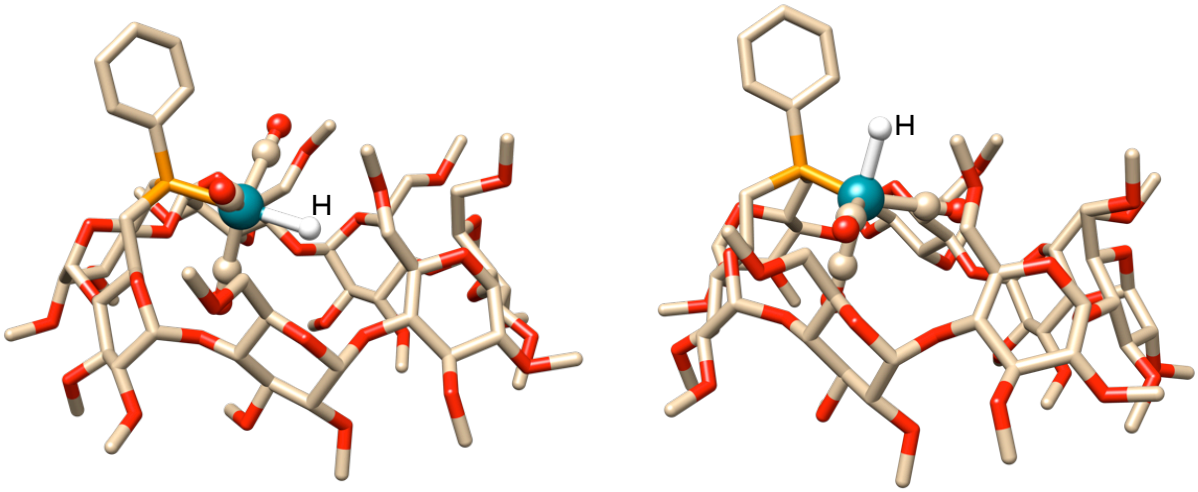


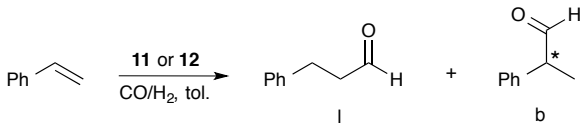
Figure 8. Calculated structures (Spartan 10) of [RhH(CO)$_3$(β-HUGPHOS)] with the phosphorus being either in apical (left) or equatorial (right) position.

IV. 2. 3. Homogeneous catalysis

i) Hydroformylation of styrene

The results of the above HP-NMR studies prompted us to investigate the properties of HUGPHOS ligands in asymmetric hydroformylation.[19] Styrene was chosen as this substrate is compatible in terms of size with both CD cavities. Hydroformylation tests (Table 1 and 2) were performed not only at various temperatures and pressures but also at several CO/H_2 and L/Rh ratios as well as pre-catalyst loadings. When standard hydroformylation conditions (Table 1, entry 1) were applied, next to full conversion was observed after 24 h with **12**. As expected, the branched product was formed predominantly, however with poor enantioselectivity. Surprisingly, raising the CO/H_2 from 1:1 to 1:2, which is known to speed up the reaction, produced the opposite effect and was also detrimental to enantioselectivity,[3] but without significantly altering regioselectivity (Table 1, entry 2). On the other hand, increasing the partial CO pressure led to a marked reaction rate increase, however without enantioselectivity nor regioselectivity increase (Table 1, entry 3). An unexpected observation was that addition of free ligand to the reaction medium maintained at 80°C (20 bar) was detrimental to the catalyst activity, this suggesting that at this temperature unreactive bis(phosphine) complexes formed (Table 1, entries 4 and 5).

Table 1. Rhodium-catalysed hydroformylation of styrene using precatalyst **12** – variation of ligand/Rh and CO/H_2 ratio.[a]



Entry	equiv. of β-HUGPHOS [b]	ratio CO/H_2	Conv[c] [%]	Aldehydes[c] l [%]	b[%]	b/l[d]	*ee*[e] [%]
1	0	1/1	96.8	37.1	62.9	1.7	27 (*R*)
2	0	1/2	71.5	32.0	68.0	2.2	17 (*R*)
3	0	2/1	99.3	32.6	67.4	2.1	26 (*R*)
4	1	1/1	75.1	38.2	61.8	1.6	19 (*R*)
5	4	1/1	12.9	20.3	79.7	3.9	36 (*R*)

[a] Styrene (5 mmol), styrene/complex = 2500, T = 80°C, t = 24 h, $P(CO/H_2)$ = 20 bar, toluene/*n*-decane (15mL/0.5mL), incubation overnight at 80°C under $P(CO/H_2)$ = 20 bar. [b] Equiv. of free ligand β-HUGPHOS added to preformed rhodium complex **12** after overnight incubation. [c] Determined by GC using decane as internal standard. [d] b/l aldehyde ratio. [e] Determined by chiral-phase GC after reduction with $LiAlH_4$.

Raising the temperature to 120 °C caused the catalyst activity to drop significantly and led predominantly to the (*S*)-enantiomer, suggesting a profound transformation of the catalyst upon heating (Table 2, entry 2). However, both regioselectivity and enantioselectivity improved significantly upon lowering the temperature, reaching 63 % *ee* at 60°C (Table 2, entry 3). Increasing the metal to substrate ratio by 10-fold and further lowering the temperature allowed to maintain a reasonable activity while further increasing the *ee* value

and b/l ratio (Table 2, entry 4). Interestingly, complexes **11** and **12** led roughly to the same results (Table 2, entries 5 and 12). This means that the reaction is insensitive to cavity size, this being indicative of a catalytic transformation taking place at the cavity entrance, rather than inside. Pressure had also a dramatic effect on both regioselectivity and enantioselectivity as raising it from 5 to 40 bar increased the *ee* value by a staggering 49 % and the b/l ratio from 3.7 to 24.6 (Table 2, entries 10 and 11). Not surprisingly, the best result (Table 2, entry 12) was obtained at room temperature and high pressure, the *ee* value and the proportion of branched aldehyde reaching then 95 % and 98.3 %, respectively.

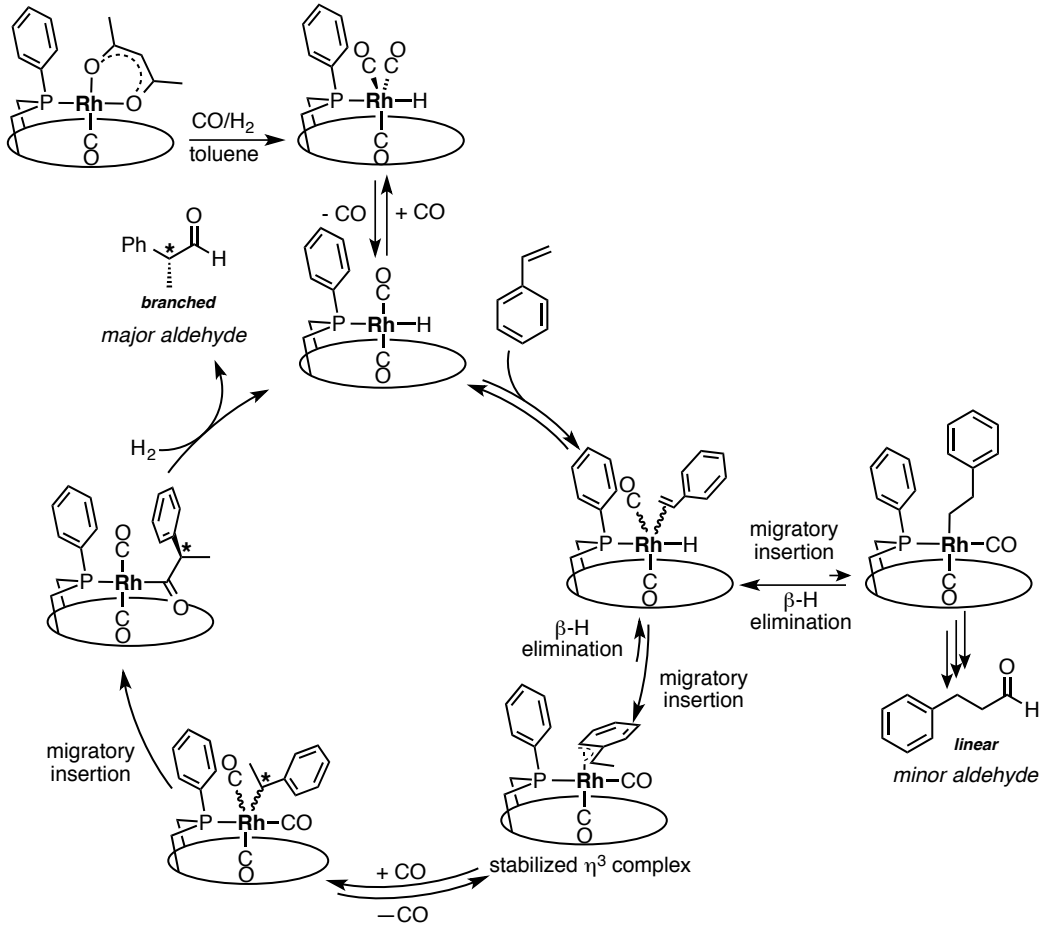
Table 2. Rhodium-catalysed hydroformylation of styrene using precatalysts **13** and **14** – variation of pressure and temperature.[a]

Entry	Complex	$P(CO/H_2)$[b] [bar]	T [°C]	Conv[c] [%]	Aldehydes[c] l [%]	b[%]	b/l[d]	*ee*[g] [%]
1	**12**	20	80	96.8	37.1	62.9	1.7	27 (*R*)
2	**12**	20	120	31.5	43.0	57.0	1.3	34 (*S*)
3	**12**	20	60	43.7	13.9	86.1	6.2	63 (*R*)
4[e]	**12**	20	40	79.0	6.8	93.2	13.7	80 (*R*)
5[e]	**12**	40	20	66.2	1.7	98.3	57.8	92 (*R*)
6	**11**	20	80	86.3	27.2	72.8	2.7	33 (*R*)
7[e]	**11**	20	60	100	11.4	88.6	7.8	62 (*R*)
8[e]	**11**	20	40	99.8	6.3	93.7	14.9	80 (*R*)
9[e]	**11**	20	20	30.6	1.0	99.0	99.0	93 (*R*)
10[e]	**11**	5	40	19.8	21.4	78.6	3.7	41 (*R*)
11[e]	**11**	40	40	99.2	3.9	96.1	24.6	90 (*R*)
12[e]	**11**	40	20	60.7	1.7	98.3	57.8	95 (*R*)
13[e]	**11**	40	4	34.0	traces	100	>100[f]	93 (*R*)

[a] Styrene (5 mmol), styrene/complex = 2500, t = 24 h, toluene/*n*-decane (15mL/0.5mL), incubation overnight at 80°C under $P(CO/H_2)$ = 20 bar. [b] CO/H_2 1:1 v/v. [c] Determined by GC using decane as internal standard. [d] b:l aldehyde ratio. [e] Run carried out with a ratio styrene/complex = 250. [f] Exact value not determined because of a very low amount of linear aldehydes. [g] Determined by chiral-phase GC after reduction with $LiAlH_4$.

Clearly, isoregioselectivity increases concomitantly with enantioselectivity contrary to what is generally observed,[19e] probably because the singly phosphine-ligated active species behaves differently from the usual bis(phosphine) complexes (Scheme 7). To the best of our knowledge, these are the highest combined enantio- and isoregioselectivities ever reported for the asymmetric hydroformylation of styrene.

The presence of monophosphine intermediates (and not bis(phosphine) ones) in the catalytic cycle is likely to favour the formation of a [Rh(η^3-(styrenyl))$(CO)_2$(HUGPHOS)] intermediate,[4a, 17b, 20] precursor of the branched aldehyde, over that of the electron poorer [Rh(η^1-(styrenyl))$(CO)_2$(HUGPHOS)] isomer, which leads to the linear aldehyde. The high enantioselectivities probably arise from the embracing properties of the HUGPHOS ligands, which facilitates chirality transfer.



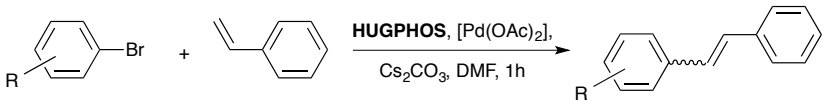
Scheme 7. Possible mechanism for the hydroformylation of styrene when using monophosphine complexes **11** or **12** as precatalysts.

ii) Heck cross-coupling

Phosphine-assisted Heck reactions strongly depend on the bulkiness of the phosphine used.[21] To assess β-HUGPHOS in Heck coupling, we focused on the reaction between styrene and arylbromides using $Pd(OAc)_2$ as palladium source.[22] In a preliminary study, 4-bromoanisole was reacted for 1 h with styrene in the presence of Cs_2CO_3 in *N,N*-dimethylformamide (DMF) at different temperatures and ligand/metal ratios (Table 3). The highest yield (46.5%) was obtained when operating with one equivalent of β-HUGPHOS per palladium (Table 3, entry 5). Higher phosphine/Pd ratios did not improve the catalytic outcome (Table 3, entry 4). These results clearly indicate

that a single phosphine ligand is sufficient to stabilise the active palladium species. Finally, we observed that by raising the temperature to 130º, the conversions remained practically unchanged (Table 3, entry 6).

Table 3. Optimisation of conditions for the Heck cross-coupling of 4-bromoanisole with styrene using β-HUGPHOS as ligand.[a]

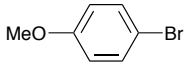
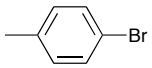
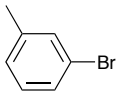
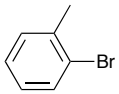
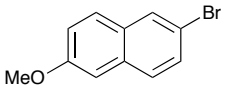


Entry	β-HUGPHOS/ $[Pd(OAc)_2]$	*T* [°C]	Conv[b] [%]
1	0/1	110	4.3
2	1/2	110	17.6
3	1/2	130	22.4
4	2/1	110	45.7
5	1/1	110	46.5
6	1/1	130	45.5

[a] $[Pd(OAc)_2]$ (5×10^{-3} mmol), 4-bromoanisole (0.5 mmol), styrene (1.0 mmol), Cs_2CO_3 (1.0 mmol), DMF (1.5 mL), decane (0.05 mL), 1 h. [b] Conversions were determined by GC using decane as internal standard.

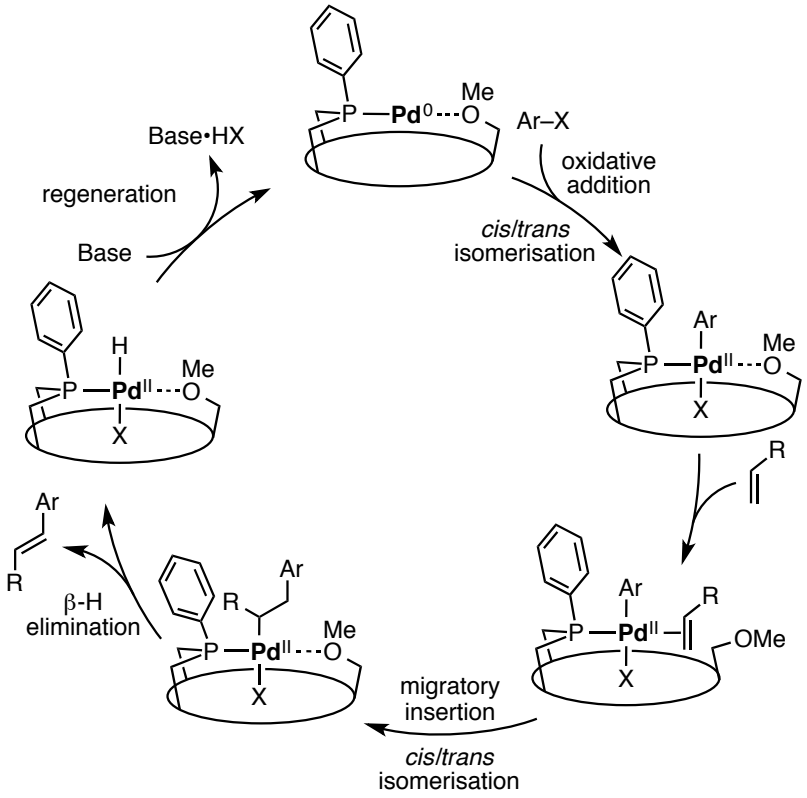
We then applied the aforementioned optimal conditions in the coupling of styrene with substituted arylbromides (Table 4), using either α- and β-HUGPHOS as ligands. In the case of β-HUGPHOS, a conversion of 61.0% was observed for 4-bromotoluene, while the 3- and 2-substituted isomers led to conversions of 37.9% and 28.6%, respectively (Table 4, entries 2–4). As expected, the activated 2-bromo-6-methoxynaphtalene afforded the corresponding coupling product in relatively high yield (71%; Table 4, entry 5). As already observed in the hydroformylation experiments, α-HUGPHOS generally gave slightly better results than β-HUGPHOS, which again points to a catalytic reaction taking place outside the cavity. It is noteworthy that the activities obtained in Mizoroki-Heck coupling with the above catalytic systems lie in the range obtained with other phosphines,[23] these, however, being used in excess.[24] We note that HUGPHOS-derived catalysts are much more active than previously reported CD-based catalysts.[25]

Table 4. Palladium-catalysed Heck cross-coupling of aryl bromides with styrene using α-HUGPHOS and β-HUGPHOS.[a]

Entry	ArBr		HUGPHOS α	HUGPHOS β
1		conv. [%][b]	58.3	45.5
2		conv. [%][b]	50.5	61.0
3		conv. [%][b]	42.4	37.9
4		conv. [%][b]	32.5	28.6
5		conv. [%][b]	80.6	71.1

[a] Ligand (2.5 x 10^{-3} mmol), $[Pd(OAc)_2]$ (2.5 x 10^{-3} mmol), arylbromide (0.25 mmol), styrene (0.50 mmol), Cs_2CO_3 (0.50 mmol), DMF (0.750 mL), decane (0.025 mL), T = 130°C, 1 h. [b] Conversions were determined by GC using decane as internal standard.

According to a number of mechanistic studies, the structure of the catalytic intermediates of Mizoroki-Heck reactions is strongly dependent on the phosphine used.[26] With very bulky phosphines, active species having only one phosphine coordinated to the metal have been proposed.[26h, 27] In view of the above complexation studies, such mono-ligated intermediates are also likely to be operative with HUGPHOS ligands (Scheme 8). The fact that the observed reaction rates were higher with HUGPHOS ligands than with other bulky phosphines may be related to the presence of hemilabile methoxy groups able either to stabilise highly reactive intermediates or assist the reduction-elimination step.[28]



Scheme 8. Possible mechanism of the Heck reaction when using α- or β-HUGPHOS as ligands (right). R = Ar or vinyl; X = Br, I.

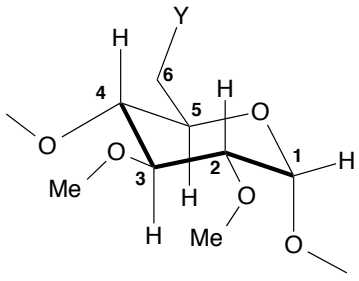
IV. 3. Conclusion

In conclusion, we have shown that the cavity-shaped phosphines α-HUGPHOS and β-HUGPHOS exclusively form *monophosphine* complexes with Pd(II), Pt(II), Rh(I), and Ru(II) centres. In these complexes the CD cavity tightly embraces the metal. Both ligands have been engaged in two carbon-carbon bond forming reactions, in which active species with a single phosphine ligand are likely to be operative. The ability of these CD derivatives to form exclusively monophosphine complexes in the presence of excess ligand turned out to have a significant impact on the catalytic outcome. Thus, when used in the Rh-catalysed hydroformylation of styrene, the HUGPHOS ligands resulted *both* in high regio- and enantioselectivity. Obviously, these two features, which are generally regarded as incompatible, rely on the ligand ability to exclusively generate monophosphine complexes – this inducing high regioselectivity – and to maintain the catalytic centre in a confined, chiral environment that ensures efficient chirality transfer. The enantioselectivities, which were obtained in organic medium for the hydroformylation of styrene outperform those obtained with other CD derived ligands in asymmetric catalysis.[29] Future work will focus on extending the scope of applications based on HUGPHOS ligands to other metal-catalysed reactions, notably olefin polymerization.

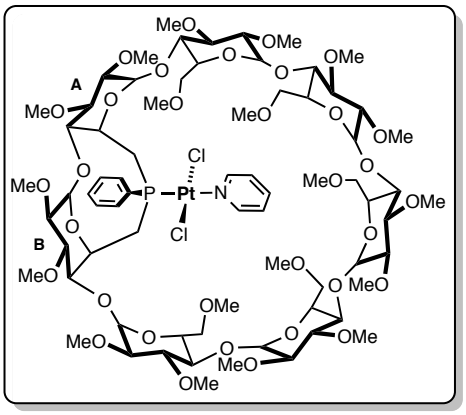
IV. 4. Experimental section

IV. 4. 1. General procedures

All commercial reagents were used as supplied. All manipulations were performed in Schlenk-type flasks under N_2 with degassed solvent. Solvents were dried by conventional methods and distilled immediately prior to use. Column chromatography was performed on silica gel 60 (particle size 40-63 μm, 230-240 mesh). $CDCl_3$ was passed down a 5-cm-thick alumina column and stored under N_2 over molecular sieves (3 Å). Routine ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded with Bruker FT instruments (AVANCE 300, 400, 500, 600 spectrometers). ^1H NMR spectral data were referenced to residual protiated solvents (δ = 7.26 ppm for $CDCl_3$), ^{13}C chemical shifts are reported relative to deuterated solvents (δ = 77.16 ppm for $CDCl_3$) and the $^{31}P\{^1H\}$ NMR data are given relative to external H_3PO_4. Mass spectra were recorded either on a Maldi TOF spectrometer (MALDI-TOF) using α-cyano-4-hydroxycinnamic acid as matrix, or on a Bruker MicroTOF spectrometer (ESI-TOF) using CH_2Cl_2, MeCN or MeOH as the solvent. Elemental analyses were performed by the Service de Microanalyse, Institut de Chimie UMR 7177, Strasbourg. Melting points were determined with a Büchi 535 capillary melting point apparatus. The catalytic solutions containing the aldehyde were analysed by using a Varian 3900 gas chromatograph equipped with a WCOT fused-silica column (25m × 0.25mm). This allowed to determine the b:l ratio. In order to determine the enantiomeric excess, a sample of the reaction mixture (toluene) was treated with $LiAlH_4$ for 0.5 h. After filtration, the solution, which contained enantiomeric alcohols, was analysed by GC with a Chirasil-DEX CB column (25 m × 0.25 mm). α–HUGPHOS,[9] β–HUGPHOS,[10] $[PdCl_2(PhCN)_2]$ and $[PtCl_2(PhCN)_2]$[30] were synthesised according to literature procedures. In this chapter, the cyclodextrins are depicted as seen from the secondary face, the glucose units being ranged counterclocwise in the following order: A, B, C, D, E, F, G. The numbering of the atoms within a glucose unit is as follows:

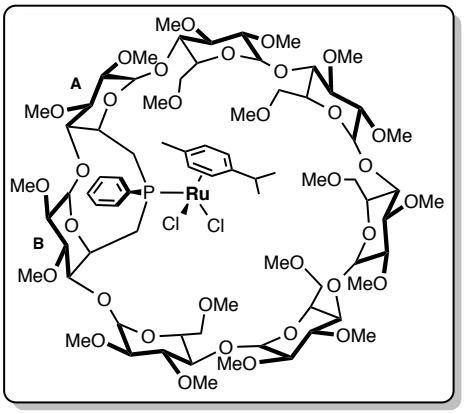


IV. 4. 2. Synthesis and characterisation



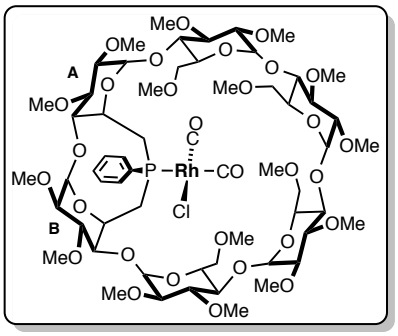
***trans*-Dichlorido-*P*-{6^{A},6^{B}-dideoxy-6^{A},6^{B}-[(*R*)-phenylphosphinidene]-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},2^{G},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},3^{G},6^{C},6^{D},6^{E},6^{F},6^{G}-nonadeca-*O*-methyl-β-cyclodextrin}-pyridine-platinum(II) (4):** A solution of β-HUGPHOS (0.160 g, 0.10 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of $[PtCl_2(PhCN)_2]$ (0.052 g, 0.11 mmol) in CH_2Cl_2 (5 mL) under vigorous stirring at room temperature. After 5 min, pyridine (200 μL, 0.204 g, 2.58 mmol) was added and the reaction mixture was stirred for 1 h before being evaporated to dryness. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH, 95:5, *v*/*v*) affording **4** (0.180 g, 92%) as a pale yellow solid. R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.60; m.p. 210ºC; ^{1}H NMR (500.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY, ROESY and HSQC) = 1.61 (m, 1 H, H-6a^{A}), 2.62 (dd, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 16.8 Hz, $^{2}J_{H\text{-}6a,P}$ = 14.6 Hz, H-6a^{B}), 2.97 (s, 3 H, OMe), 3.26 (s, 3 H, OMe), 3.29 (s, 3 H, OMe), 3.33 (s, 3 H, OMe), 3.35 (s, 3 H, OMe), 3.43 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 3.48 (s, 3 H, OMe), 3.49 (s, 6 H, OMe), 3.51 (s, 3 H, OMe), 3.52 (s, 3 H, OMe), 3.54 (s, 3 H, OMe), 3.58 (s, 3 H, OMe), 3.59 (s, 3 H, OMe), 3.63 (s, 3 H, OMe), 3.68 (s, 3 H, OMe), 3.75 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 2.93–3.82 (32 H, H-2, H-3, H-4, H-5, H-6), 3.96 (t, 1 H, $^{3}J_{H\text{-}4,H\text{-}3}$ = $^{3}J_{H\text{-}4,H\text{-}5}$ = 9.5 Hz, H-4), 4.04 (dd, 1 H, $^{3}J_{H\text{-}6a,H\text{-}6b}$ = 12.2 Hz, $^{3}J_{H\text{-}6,H\text{-}5}$ = 3.0 Hz, H-6), 4.35 (dd, 1 H, $^{3}J_{H\text{-}6b,H\text{-}6a}$ = 12.2 Hz, $^{3}J_{H\text{-}6,H\text{-}5}$ = 1.6 Hz, H-6), 4.38–4.46 (3 H, H-5^{B}, H-5, H-6), 4.57 (d, 1 H, $^{3}J_{H\text{-}5,H\text{-}4}$ = 10.2 Hz, H-5), 4.80 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 2.9 Hz, H-1), 4.96 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 4.4 Hz, H-1), 4.98 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.9 Hz, H-1), 5.04–5.06 (2 H, H-1), 5.10 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 4.0 Hz, H-1), 5.25 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.7 Hz, H-1), 5.32 (dt, 1 H, $^{3}J_{H\text{-}5,H\text{-}6a}$ = $^{3}J_{H\text{-}5,P}$ = 13.2 Hz, $^{3}J_{H\text{-}5,H\text{-}6b}$ = 8.5 Hz, H-5^{A}), 7.44–7.53 (3 H, *m*-H, *p*-H of phenyl), 7.75–7.81 (2 H, H-3,5 of pyridine), 7.91 (t, 1 H, $^{3}J_{H\text{-}4,H\text{-}3,5}$ = 8.2 Hz, H-4 of pyridine), 7.97–8.02 (2 H, *o*-H of phenyl), 9.09–9.13 (2 H, H-2,6 of pyridine) ppm; ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 30.29 (d, $^{1}J_{C,P}$ = 42.1 Hz, C-6^{A}), 32.50 (d, $^{1}J_{C,P}$ = 38.3 Hz, C-6^{B}), 57.54, 57.69, 57.91, 58.37, 58.67, 58.80, 58.97, 59.04, 59.10, 59.14, 59.26, 59.37, 60.30, 60.85, 60.98, 61.31, 61.80, 61.85, 62.18 (OMe), 64.30 (C-5^{A}), 69.49, 69.91 (C-5), 70.06, 70.84, 70.92 [×2] (C-6), 71.09, 71.32 (C-5), 71.57 (C-6), 71.76 (C-5), 72.11 (d, $^{2}J_{C,P}$ = 11.3 Hz, C-5^{B}), 78.97, 79.73, 80.49, 81.34, 82.39, 82.43, 82.46, 82.50, 81.78 [×2], 82.17, 82.24, 82.36, 82.61, 82.64, 83.02, 83.32, 83.91, 84.78 (C-2, C-3, C-4), 81.23 (C-4^{A}), 89.11 (C-4^{B}), 95.76, 99.25 [×2], 99.39, 100.43, 100.79, 101.18 (C-1), 126.19 [×2] (C-3,5 of pyridine), 128.13, 128.21 (C_{meta} of phenyl), 131.11 (C_{para} of phenyl), 132.99, 133.08 (C_{ortho} of phenyl), 133.65 (d, $^{1}J_{C,P}$ = 25.3 Hz, C_{ipso} of phenyl), 138.78 (C-4 of pyridine), 151.55 [×2] (C-2,6 of pyridine) ppm; ^{31}P{^{1}H} NMR (161.9

MHz, $CDCl_3$, 25ºC): δ = 4.3 (s with Pt satellites, $^1J_{P,Pt}$ = 3542 Hz) ppm; elemental analysis (%) calcd for $C_{72}H_{116}Cl_2NO_{33}PPt{\cdot}2CH_2Cl_2$ (1820.64 + 169.87): C 44.65, H 6.08, N 0.70 found: C 44.52, H 5.77, N 0.61; MS (ESI-TOF): *m/z* (%): 1837.63 (25) $[M + H_2O + H]^+$, 1841.61 (100) $[M + Na]^+$.



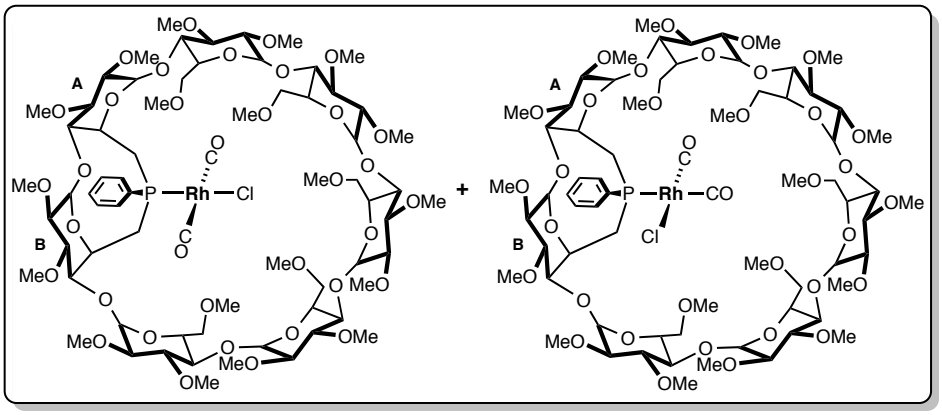
Dichlorido-(η^6-*p*-cymene)-*P*-{6^A,6^B-dideoxy-6^A,6^B-[(*R*)-phenylphosphinidene]-2^A,2^B,2^C,2^D,2^E,2^F,2^G,3^A,3^B,3^C,3^D,3^E,3^F,3^G,6^C,6^D,6^E,6^F,6^G-nonadeca-*O*-methyl-β-cyclodextrin}ruthenium(II) (6 and **7):** A solution of β-HUGPHOS (0.126 g, 0.09 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (0.052 g, 0.08 mmol) in CH_2Cl_2 (5 mL) under vigorous stirring at room temperature. The reaction mixture was stirred for 1 h before being evaporated to dryness. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH, 97:3 to 95:5, *v*/*v*) affording **6** (0.085 g, 56%) and **7** (0.065 g, 42%) as brown solids. **6**: R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.64; m.p. 210ºC; ^{1}H NMR (500.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY, ROESY and HSQC) = 1.13 (d, 3 H, $^3J_{CH3,CH}$ = 7.1 Hz, CH_3^{iPr} of *p*-cymene), 1.15 (d, 3 H, $^3J_{CH3,CH}$ = 7.1 Hz, $CH_3^{iPr'}$ of *p*-cymene), 1.63 (s, 3 H, CH_3 of *p*-cymene), 2.57 (ddd, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 15.3 Hz, $^2J_{H\text{-}6a,P}$ = 11.4 Hz, $^3J_{H\text{-}6a,H\text{-}5}$ = 2.5 Hz, H-6a^A), 2.71 (sept, 1 H, $^3J_{CH,CH3}$ = 7.1 Hz, CH^{iPr} of *p*-cymene), 3.00 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}1}$ = 2.9 Hz, $^3J_{H\text{-}2,H\text{-}3}$ = 9.8 Hz, H-2), 3.19 (s, 3 H, OMe), 3.34 (s, 3 H, OMe), 3.35 (s, 3 H, OMe), 3.40 (s, 3 H, OMe), 3.41 (s, 3 H, OMe), 3.45 (s, 3 H, OMe), 3.46 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 3.48 (s, 3 H, OMe), 3.51 (s, 3 H, OMe), 3.52 (s, 3 H, OMe), 3.53 (s, 3 H, OMe), 3.54 (s, 3 H, OMe), 3.56 (s, 3 H, OMe), 3.58 (s, 3 H, OMe), 3.62 (s, 3 H, OMe), 3.63 (s, 3 H, OMe), 3.69 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 3.06–3.85 (36 H, H-2, H-3, H-4, H-5, H-6), 3.88 (dd, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 10.8 Hz, $^3J_{H\text{-}6a,H\text{-}5}$ = 4.3 Hz, H-6), 3.91–3.95 (m, 1 H, H-5), 4.02–4.10 (2 H, H-5, H-5^A), 4.82 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 2.8 Hz, H-1), 4.88 (dd, 1 H, $^3J_{m\text{-}H,o\text{-}H}$ = 5.6 Hz, $^3J_{m\text{-}H,m\text{-}H'}$ = 2.3 Hz, *m*-H of *p*-cymene), 4.95 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 4.1 Hz, H-1), 5.04 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.9 Hz, H-1), 5.05 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.5 Hz, H-1), 5.06–5.09 (2 H, H-1, *o*-H of *p*-cymene), 5.14–5.18 (2 H, H-1, *o*-H' of *p*-cymene), 5.26–5.29 (m, 1 H, *m*-H' of *p*-cymene), 5.36 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 4.1 Hz, H-1), 7.45–7.56 (3 H, *m*-H, *p*-H), 7.91–7.96 (2 H, *o*-H) ppm; $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 16.32 (CH_3 of *p*-cymene), 21.04, 21.10 (CH_3^{iPr} of *p*-cymene), 27.26 (d, $^1J_{C,P}$ = 27.8 Hz, C-6^A), 27.36 (d, $^1J_{C,P}$ = 23.8 Hz, C-6^B), 29.50 (CH of *p*-cymene), 55.99, 56.99, 57.61, 57.74, 57.77, 57.83, 58.05, 58.13, 58.16, 58.26, 58.33, 59.00, 59.69, 60.01, 60.24, 60.44, 60.61, 60.64, 60.81, 63.79 (d, $^2J_{C,P}$ = 9.4 Hz, C-5^A), 68.48 (d, $^2J_{C,P}$ = 10.1 Hz, C-5^B), 69.88 [×2] (C-6), 69.94 [×2],

70.39 (C-5), 70.46, 70.55 (C-6), 70.70 (C-5), 70.82 (C-6), 71.76 (C-5), 76.84, 78.21, 79.16, 79.80 [×2], 79.93, 80.09, 80.34 [×2], 80.45, 80.61, 80.68, 81.01, 81.20, 81.32 [×2], 81.61 [×2], 81.93, 82.74, 84.46, 87.88 (C-2, C-3, C-4, C_{ortho} of *p*-cymene), 88.64, 90.43 (C_{meta} of *p*-cymene), 91.55 (C_{ipso} of *p*-cymene), 95.27, 96.29, 96.73, 98.54, 98.74, 98.92 [×2] (C-1), 109.23 (C_{ipso} of *p*-cymene), 127.74, 127.81 (C_{meta}), 129.17 (C_{para}), 130.30, 130.35 (C_{ortho}), 132.65 (d, $^{1}J_{C,P}$ = 38.3 Hz, C_{ipso}) ppm; $^{31}P\{^{1}H\}$ NMR (161.9 MHz, $CDCl_3$, 25ºC): δ = 20.4 (s) ppm; elemental analysis (%) calcd for $C_{77}H_{125}Cl_2O_{33}PRu{\cdot}CH_2Cl_2$ (1781.75 + 84.93): C 50.19, H 6.86 found: C 50.05, H 6.80; MS (ESI-TOF): *m/z* (%): 1803.62 (100) $[M + Na]^+$. **7**: R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.60; m.p. 210ºC; ^{1}H NMR (500.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY, ROESY and HSQC) = 0.94 (d, 3 H, $^{3}J_{CH3,CH}$ = 7.1 Hz, CH_3^{iPr} of *p*-cymene), 1.05 (d, 3 H, $^{3}J_{CH3,CH}$ = 7.1 Hz, $CH_3^{iPr'}$ of *p*-cymene), 1.73 (s, 3 H, CH_3 of *p*-cymene), 2.28 (sept, 1 H, $^{3}J_{CH,CH3}$ = 7.1 Hz, CH^{iPr} of *p*-cymene), 2.50 (dt, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 18.2 Hz, $^{2}J_{H\text{-}6a,P} = {}^{3}J_{H\text{-}6a,H\text{-}5}$ = 7.2 Hz, H-$6a^A$), 2.59 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.1 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.9 Hz, H-2^A), 2.75 (ddd, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 14.3 Hz, $^{2}J_{H\text{-}6a,P}$ = 12.0 Hz, $^{3}J_{H\text{-}6a,H\text{-}5}$ = 2.6 Hz, H-$6a^B$), 2.88 (t, 1 H, $^{3}J_{H\text{-}4,H\text{-}3} = {}^{3}J_{H\text{-}4,H\text{-}5}$ = 9.5 Hz, H-4^A), 3.12–3.27 (7 H, H-2, H-$6b^B$), 3.35 (s, 3 H, OMe), 3.36 (s, 3 H, OMe), 3.38 (s, 3 H, OMe), 3.39 (s, 3 H, OMe), 3.40 (s, 3 H, OMe), 3.41 (s, 3 H, OMe), 3.45 (s, 3 H, OMe), 3.46 (s, 3 H, OMe), 3.48 (s, 6 H, OMe), 3.49 (s, 3 H, OMe), 3.53 (s, 3 H, OMe), 3.56 (s, 3 H, OMe), 3.57 (s, 3 H, OMe), 3.58 (s, 3 H, OMe), 3.61 (s, 3 H, OMe), 3.62 (s, 3 H, OMe), 3.63 (s, 3 H, OMe), 3.64 (s, 3 H, OMe), 3.33–3.87 (26 H, H-3, H-4, H-5, H-6), 3.92 (dd, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 10.3 Hz, $^{3}J_{H\text{-}6a,H\text{-}5}$ = 2.5 Hz, H-6), 4.10 (d, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 10.3 Hz, H-6), 4.21–4.32 (2 H, H-5^B, H-6), 4.35 (ddd, 1 H, $^{2}J_{H\text{-}5,H\text{-}6a}$ = 7.2 Hz, $^{2}J_{H\text{-}5,H\text{-}6b}$ = 26.1 Hz, $^{3}J_{H\text{-}5,H\text{-}4}$ = 10.9 Hz, H-5^A), 4.73 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 5.1 Hz, H-1), 4.74 (d, 1 H, $^{3}J_{o\text{-}H,m\text{-}H}$ = 5.9 Hz, *o*-H' of *p*-cymene), 4.95 (d, 1 H, $^{3}J_{m\text{-}H,o\text{-}H}$ = 5.9 Hz, *m*-H' of *p*-cymene), 4.96 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 2.4 Hz, H-1), 4.98 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 2.7 Hz, H-1), 5.06 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.1 Hz, H-1), 5.10 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1), 5.13 (d, 1 H, $^{3}J_{m\text{-}H,o\text{-}H}$ = 6.5 Hz, *m*-H of *p*-cymene), 5.15 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.4 Hz, H-1), 5.16 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.4 Hz, H-1), 5.25 (d, 1 H, $^{3}J_{o\text{-}H,m\text{-}H}$ = 6.5 Hz, *o*-H of *p*-cymene), 7.32–7.40 (3 H, *m*-H, *p*-H), 8.03–8.11 (2 H, *o*-H) ppm; $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 16.77 (CH_3 of *p*-cymene), 20.80, 21.24 (CH_3^{iPr} of *p*-cymene), 23.46 (d, $^{1}J_{C,P}$ = 25.8 Hz, C-6^A), 28.57 (d, $^{1}J_{C,P}$ = 26.0 Hz, C-6^B), 28.95 (CH of *p*-cymene), 56.36, 56.97, 57.09, 57.63, 57.68, 57.83 [×2], 57.99, 58.03, 58.12, 58.19, 58.61, 59.40, 60.19, 60.31, 60.42, 60.46, 60.93, 60.97 (OMe), 65.82 (d, $^{2}J_{C,P}$ = 11.1 Hz, C-5^B), 67.61 (d, $^{2}J_{C,P}$ = 9.3 Hz, C-5^A), 69.61 (C-5), 69.63 (C-6), 69.75, 69.93 (C-5), 69.99, 70.06 [×2], 70.13 (C-6), 70.34, 70.96 (C-5), 74.88 (d, $^{3}J_{C,P}$ = 4.4 Hz, C-4^A), 79.29, 79.34, 79.40, 79.55, 80.06 [×2], 80.48, 80.53, 80.62 [×2], 80.67, 80.69, 80.81, 80.85, 80.95, 81.23, 81.26, 81.41, 82.89 (C-2, C-3, C-4), 83.45, 83.65 (C_{ortho} of *p*-cymene), 83.84 (C_{meta} of *p*-cymene), 84.43 (C-4^B), 88.01 (C_{meta} of *p*-cymene), 95.54 (C-1), 95.62 (C_{ipso} of *p*-cymene), 96.42, 97.94, 98.35, 98.76 [×2], 98.86 (C-1), 108.11 (C_{ipso} of *p*-cymene), 126.06, 126.13 (C_{meta}), 128.94 (C_{para}), 130.68, 130.82 (C_{ortho}), 134.91 (d, $^{1}J_{C,P}$ = 38.5 Hz, C_{ipso}) ppm; $^{31}P\{^{1}H\}$ NMR (161.9 MHz, $CDCl_3$, 25ºC): δ = 22.8 (s) ppm; elemental analysis (%) calcd for $C_{77}H_{125}Cl_2O_{33}PRu{\cdot}CH_2Cl2$ (1781.75 + 84.93): C 50.19, H 6.86 found: C 50.03, H 6.78; MS (ESI-TOF): *m/z* (%): 1803.62 (100) $[M + Na]^+$.

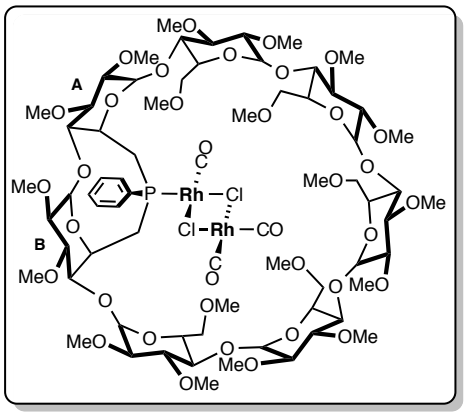


***cis*-dicarbonyl-chlorido-P-{6^{A},6^{B}-dideoxy-6^{A},6^{B}-[(*R*)-phenylphosphinidene]-2^{A},2^{B},2^{C},2^{D}, 2^{E},2^{F},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F} ,6^{C},6^{D},6^{E},6^{F}-hexadeca-*O*-methyl-α-cyclodextrin}-rhodium(I) (8):**

A solution of α-HUGPHOS (0.110 g, 0.09 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of $[Rh(CO)_2Cl]_2$ (0.027 g, 0.10 mmol) in CH_2Cl_2 (5 mL) under vigorous stirring at room temperature. Carbon monoxide was bubbled into the resulting yellow solution for 5 min. Removal of the solvent in vacuo afforded quantitatively **8** (126 mg, 99%) as a bright yellow solid. R_f (SiO_2) = dec; m.p. dec.; ^{1}H NMR (500.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY and HSQC) = 2.01 (dt, 1 H, $^2J_{H\text{-}6a,H\text{-}6b} = {}^2J_{H\text{-}6a,P}$ = 12.8 Hz, $^3J_{H\text{-}6a,H\text{-}5}$ = 11.0 Hz, H-6a^B), 2.55 (ddd, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 14.9 Hz, $^2J_{H\text{-}6a,P}$ = 8.0 Hz, $^3J_{H\text{-}6a,H\text{-}5}$ = 2.1 Hz, H-6a^A), 3.05 (t, 1 H, $^3J_{H\text{-}4,H\text{-}3} = {}^3J_{H\text{-}4,H\text{-}5}$ = 8.9 Hz, H-4^B), 3.08–3.23 (6 H, H-2), 3.25 (t, 1 H, $^3J_{H\text{-}4,H\text{-}3} = {}^3J_{H\text{-}4,H\text{-}5}$ = 9.1 Hz, H-4^A), 3.38 (s, 3 H, OMe), 3.39 (s, 3 H, OMe), 3.45 (s, 6 H, OMe), 3.46 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 3.49 (s, 6 H, OMe), 3.50 (s, 3 H, OMe), 3.51 (s, 3 H, OMe), 3.61 (s, 3 H, OMe), 3.64 (s, 9 H, OMe), 3.65 (s, 3 H, OMe), 3.68 (s, 3 H, OMe), 3.37–3.84 (18 H, H-3, H-4, H-6), 3.88 (dt, 1 H, $^3J_{H\text{-}5,H\text{-}6a}$ = 9.7 Hz, $^3J_{H\text{-}5,H\text{-}6b} = {}^3J_{H\text{-}5,H\text{-}4}$ = 1.7 Hz, H-5), 3.99 (dt, 1 H, $^3J_{H\text{-}5,H\text{-}4}$ = 9.1 Hz, $^3J_{H\text{-}5,H\text{-}6a} = {}^3J_{H\text{-}5,H\text{-}6b}$ = 1.8 Hz, H-5), 4.05–4.13 (2 H, H-5, H-6), 4.29 (dt, 1 H, $^3J_{H\text{-}5,H\text{-}4}$ = 9.4 Hz, $^3J_{H\text{-}5,H\text{-}6a} = {}^3J_{H\text{-}5,H\text{-}6b}$ = 2.7 Hz, H-5), 4.52 (ddd, 1 H, $^3J_{H\text{-}5,H\text{-}6a}$ = 11.0 Hz, $^3J_{H\text{-}5,H\text{-}6b}$ = 18.4 Hz, $^3J_{H\text{-}5,H\text{-}4}$ = 9.2 Hz, H-5^B), 4.60 (dd, 1 H, $^2J_{H\text{-}6b,H\text{-}6a}$ = 10.5 Hz, $^3J_{H\text{-}6b,H\text{-}5}$ = 2.3 Hz, H-6), 4.89–4.96 (m, 1 H, H-5^A), 4.95 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.6 Hz, H-1), 4.99 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.9 Hz, H-1), 5.06–5.10 (4 H, H-1), 7.45–7.49 (3 H, *m*-H, *p*-H), 7.58–7.64 (2 H, *o*-H) ppm; ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 31.46 (d, $^1J_{C,P}$ = 22.2 Hz, C-6^B), 36.0 (d, $^1J_{C,P}$ = 23.4 Hz, C-6^A), 57.35, 57.51, 57.67 [×2], 57.88, 58.00, 59.01, 59.06, 59.16, 59.40, 61.74 [×2], 61.76, 61.86, 62.10, 62.33 (OMe), 66.71 (d, $^2J_{C,P}$ = 6.7 Hz, C-5^B), 67.92 (d, $^2J_{C,P}$ = 4.8 Hz, C-5^A), 69.95, 70.48, 70.94 (C-5), 71.02, 71.12 (C-6), 71.21 (C-5), 71.80, 73.26 (C-6), 80.04, 80.83 [×2], 81.00, 81.23, 81.35, 81.63, 81.92 [×2], 82.10, 82.19, 82.21, 82.28, 82.46, 82.49, 82.53 (C-2, C-3, C-4), 88.54 (d, $^3J_{C,P}$ = 7.8 Hz, C-4^B), 90.60 (d, $^3J_{C,P}$ = 3.3 Hz, C-4^A), 97.53, 99.79, 100.05, 100.23 [×2], 101.43 (C-1), 129.09, 129.18 (C_{meta}), 130.23 (C_{para}), 130.31, 130.70 (C_{ortho}), 136.57 (d, $^1J_{C,P}$ = 46.4 Hz, C_{ipso}), 180.72 ,184.41 (CO) ppm; ^{31}P{^{1}H} NMR (161.9 MHz, $CDCl_3$, 25ºC): δ = 1.9 (d, $^1J_{P,Rh}$ = 120.6 Hz) ppm; IR: 2009 (s, CO), 2082 (s, CO) cm^{-1}; We do not provide microanalysis for this compound because of its rapid decomposition; MS (ESI-TOF): *m/z* (%): 1443.46 (45) [*M* – CO + Li]$^+$, 1459.43 (100) [*M* $^{P\ oxide}$ – CO + Li]$^+$ or [*M* – CO + Na]$^+$,1471.45 (1) [*M* + Li]$^+$, 1475.43 (10) [*M* $^{P\ oxide}$ – CO + Na]$^+$, 1489.46 (2) [*M* + H_2O + Li]$^+$.

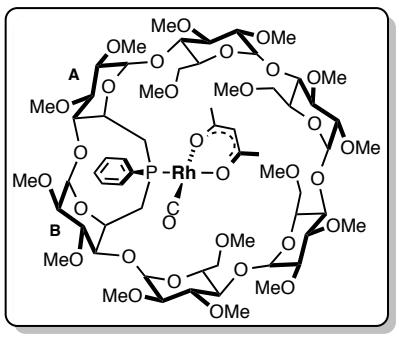


***cis*-Dicarbonyl-chlorido-*P*-{6^{A},6^{B}-dideoxy-6^{A},6^{B}-[(*R*)-phenylphosphinidene]-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},2^{G},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},3^{G},6^{C},6^{D},6^{E},6^{F},6^{G}-nonadeca-*O*-methyl-β-cyclodextrin}rhodium(I) (9a) and *trans*-dicarbonyl-chlorido-*P*-{6^{A},6^{B}-dideoxy-6^{A},6^{B}-[(*R*)-phenylphosphinidene]-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},2^{G},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},3^{G},6^{C},6^{D},6^{E},6^{F},6^{G}-nonadeca-*O*-methyl-β-cyclodextrin}rhodium(I) (9b):** A solution of β-HUGPHOS (0.100 g, 0.07 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of $[Rh(CO)_2Cl]_2$ (0.016 g, 0.04 mmol) in CH_2Cl_2 (5 mL) under vigorous stirring at room temperature. The reaction mixture was stirred for 1 h before being evaporated to dryness *in vacuo* to afford quantitatively a mixture of **9a** and **9b** (**9a**/**9b**, 85:15, 0.114 g, 99%) as a brown solid. R_f (SiO_2) = dec; m.p. > 250°C; Selected spectroscopic data: $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$, 25ºC): δ = 181.12–182.82 (m, CO), 187.24–189.73 (m, CO) ppm; $^{31}P\{^1H\}$ NMR (161.9 MHz, $CDCl_3$, 25ºC): δ = 13.9 (**9b**, d, $^1J_{P,Rh}$ = 121 Hz), 20.1 (**9a**, d, $^1J_{P,Rh}$ = 124 Hz) ppm; IR: 2090 (s, CO), 2005 (s, CO), 1985 (s, CO) cm^{-1}; elemental analysis (%) calcd for $C_{69}H_{111}ClO_{35}PRh{\cdot}3CH_2Cl_2$ (1669.93 + 254.80): C 44.99, H 6.31 found: C 45.01, H 6.99; MS (ESI-TOF): *m/z* (%): 1605.58 (100) $[M - CO - Cl]^+$, 1663.54 (20) $[M - CO + Na]^+$; MS (ESI-TOF): *m/z* (%): 1675.55 (100) $[M - CO + Cl]^-$; MS (MALDI-TOF): *m/z* (%): 1605.58 (100) $[M - CO - Cl]^+$, 1719.69 (5) $[M + CO + Na]^+$.



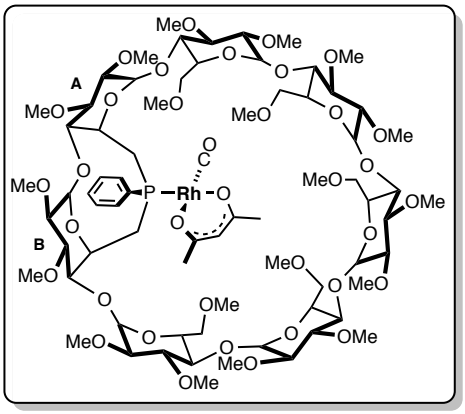
Tricarbonyl-di-μ-chlorido-*P*-{6^{A},6^{B}-dideoxy-6^{A},6^{B}-[(*R*)-phenylphosphinidene]-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},2^{G},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},3^{G},6^{C},6^{D},6^{E},6^{F},6^{G}-nonadeca-*O*-methyl-β-cyclodextrin}dirhodium(I) (10): A solution of $[Rh(CO)_2Cl]_2$ (0.080 g, 0.20 mmol) in CH_2Cl_2 (7 mL) was added dropwise to a solution of β-HUGPHOS (0.100 g, 0.07 mmol) in CH_2Cl_2 (5 mL) under vigorous stirring, at room temperature. After 1 h, the volume of the reaction mixture was reduced to 5 mL and pentane (40 mL) was added in order to precipitate

excess of metallic precursors, which was removed by filtration through a pad of Celite. The resulting solution was finally evaporated to dryness *in vacuo* to afford quantitatively **10** as a brown powder (0.103 g, 83 %). R_f (SiO_2) = dec; m.p. > 250°C; ^{1}H NMR (500.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY and HSQC) = 1.91 (q, 1 H, $^2J_{H\text{-}6a,H\text{-}6b} = {}^2J_{H\text{-}6a,P} = {}^3J_{H\text{-}6a,H\text{-}5}$ = 15.4 Hz, H-6a^B), 2.17 (t, 1 H, $^2J_{H\text{-}6a,H\text{-}6b} = {}^2J_{H\text{-}6a,P}$ = 14.2 Hz, H-6a^A), 3.02 (m, 1 H, H-6b^B), 3.20 (s, 3 H, OMe), 3.30 (s, 3 H, OMe), 3.32 (s, 3 H, OMe), 3.36 (s, 3 H, OMe), 3.45 (s, 6 H, OMe), 3.46 (s, 3 H, OMe), 3.48 (s, 3 H, OMe), 3.50 (s, 6 H, OMe), 3.52 (s, 3 H, OMe), 3.53 (s, 3 H, OMe), 3.59 (s, 6 H, OMe), 3.62 (s, 3 H, OMe), 3.64 (s, 3 H, OMe), 3.65 (s, 3 H, OMe), 3.68 (s, 3 H, OMe), 3.76 (s, 3 H, OMe), 3.13–3.79 (26 H, H-2, H-3, H-4, H-6), 3.80–3.92 (4 H, H-6), 3.93–4.01 (4 H, H-5, H-6), 4.07–4.13 (3 H, H-5, H-6), 4.36 (dt, 1 H, $^3J_{H\text{-}5,H\text{-}4} = {}^3J_{H\text{-}5,H\text{-}6b}$ = 10.5 Hz, $^3J_{H\text{-}5,H\text{-}6a}$ = 15.4 Hz, H-5^B), 4.95 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.7 Hz, H-1), 5.00 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 4.6 Hz, H-1), 5.03 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.7 Hz, H-1), 5.08–5.11 (3 H, H-1), 5.20 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.7 Hz, H-1), 5.35–5.45 (m, 1 H, H-5^A), 7.42–7.46 (3 H, *m*-H, *p*-H), 7.82–7.87 (2 H, *o*-H) ppm; ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 32.32 (d, $^1J_{C,P}$ = 29.3 Hz, C-6^A), 35.77 (d, $^1J_{C,P}$ = 29.3 Hz, C-6^B), 56.74, 57.18, 57.26, 57.63 [×2], 57.78, 57.91, 57.96, 57.99, 58.06, 58.08, 58.29, 60.13, 60.31, 60.54 [×2], 60.56, 60.70, 60.83 (OMe), 63.30 (C-5^A), 69.43, 69.50, 69.68, 69.90, 69.94 (C-5), 70.01, 70.24, 70.44, 70.60, 70.76 (C-6), 71.31 (d, $^2J_{C,P}$ = 15.9 Hz, C-5^B), 78.57, 79.04, 79.79 [×2], 80.17, 80.23 [×2], 80.47, 80.51, 80.57, 80.90, 81.05, 81.12, 81.32, 81.40, 81.68, 81.76, 82.14, 83.09 (C-2, C-3, C-4), 84.17 (d, $^3J_{C,P}$ = 10.7 Hz, C-4^B), 88.02 (d, $^3J_{C,P}$ = 4.6 Hz, C-4^A), 96.39, 97.66, 97.70, 98.52, 98.66, 99.37, 99.79 (C-1), 127.62, 127.70 (C_{meta}), 130.08 (C_{para}), 130.56, 130.64 (C_{ortho}), 135.13 (d, $^1J_{C,P}$ = 57.5 Hz, C_{ipso}), 176.16 [×2] (d, $^1J_{C,Rh}$ = 77.2 Hz, CO) 177.63 (dd, $^1J_{C,Rh}$ = 71.9 Hz, $^2J_{C,P}$ = 22.8 Hz, CO) ppm; ^{31}P{^{1}H} NMR (161.9 MHz, $CDCl_3$, 25ºC): δ = 40.5 (d, $^1J_{P,Rh}$ = 172 Hz) ppm; IR: 2086 (vs, CO), 2026 (vs, CO), 2004 (s, CO) cm^{-1}; We do not provide microanalytical data for this compound because of strong hydration; MS (ESI-TOF): *m/z* (%): 1799.44 (70) $[M - Cl]^+$, 1857.40 (100) $[M + Na]^+$.



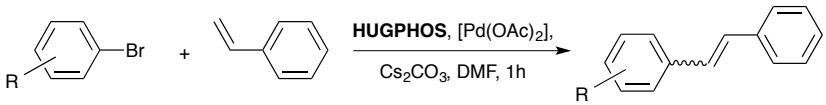
Acetylacetonato-carbonyl-P-{6^A,6^B-dideoxy-6^A,6^B-[(*R*)-phenylphosphinidene]-2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^C,6^D,6^E,6^F-hexadeca-*O*-methyl-α-cyclodextrin}-rhodium(I) (11):
A solution of α-HUGPHOS (0.110 g, 0.09 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of [Rh(acac)(CO)$_2$] (0.027 g, 0.10 mmol) in CH_2Cl_2 (5 mL) under vigorous stirring at room temperature. The reaction mixture was further stirred for 1 h before being concentrated to *c.a.* 2 mL. Pentane (50 mL) was then added causing complex **11** to precipitate. The rhodium complex was collected by filtration and further purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 95:5 to 93:7, *v/v*) to afford **11** as a brown solid (0.098 g, 76%). R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v/v*) = 0.63; m.p. 168°C; ^{1}H NMR (500.1 MHz, $CDCl_3$, 25ºC): δ

(assignment by combined COSY, TOCSY, ROESY and HSQC) = 1.44 (s, 3 H, Me of acac), 2.09 (s, 3 H, Me of acac), 2.28 (q, 1 H, $^{2}J_{\text{H-6a,H-6b}} = {}^{2}J_{\text{H-6a,P}} = {}^{3}J_{\text{H-6a,H-5}} = 12.8$ Hz, H-6a^{B}), 2.70–2.77 (m, 1 H, H-6a^{A}), 2.98 (d, 1 H, $^{2}J_{\text{H-6a,H-6b}} = 12.8$ Hz, H-6b^{B}), 3.09 (t, 1 H, $^{3}J_{\text{H-4,H-3}} = {}^{3}J_{\text{H-4,H-5}} = 9.0$ Hz, H-4^{B}), 3.12 (s, 3 H, OMe), 3.41 (s, 3 H, OMe), 3.44 (s, 3 H, OMe), 3.45 (s, 3 H, OMe), 3.46 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 3.48 (s, 3 H, OMe), 3.49 (s, 3 H, OMe), 3.50 (s, 6 H, OMe), 3.61 (s, 6 H, OMe), 3.64 (s, 3 H, OMe), 3.67 (s, 3 H, OMe), 3.69 (s, 3 H, OMe), 3.70 (s, 3 H, OMe), 3.13–3.84 (25 H, H-2, H-3, H-4, H-5, H-6), 3.89 (m, 1 H, H-6), 3.93 (m, 1 H, H-5), 4.02 (d, 1 H, $^{3}J_{\text{H-5,H-4}} = 9.7$ Hz, H-5), 4.06 (d, 1 H, $^{2}J_{\text{H-6a,H-6b}} = 10.9$ Hz, H-6), 4.26 (m, 1 H, H-5^{A}), 4.50 (m, 1 H, H-5^{B}), 4.72 (dd, 1 H, $^{2}J_{\text{H-6b,H-6a}} = 11.1$ Hz, $^{3}J_{\text{H-6,H-5}} = 1.8$ Hz, H-6), 4.95 (d, 1 H, $^{3}J_{\text{H-1,H-2}} = 3.8$ Hz, H-1), 5.04 (d, 1 H, $^{3}J_{\text{H-1,H-2}} = 3.1$ Hz, H-1), 5.06 (d, 1 H, $^{3}J_{\text{H-1,H-2}} = 2.7$ Hz, H-1), 5.07–5.09 (2 H, H-1), 5.12 (d, 1 H, $^{3}J_{\text{H-1,H-2}} = 3.0$ Hz, H-1), 5.36 (s, 1 H, CH of acac), 7.32–7.36 (3 H, *m*-H, *p*-H), 7.73–7.79 (2 H, *o*-H) ppm; $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 25.66, 27.19 (d, $^{3}J_{\text{C,Rh}} = 5.5$ Hz, Me of acac), 32.92 (dd, $^{1}J_{\text{C,P}} = 30.8$ Hz, $^{2}J_{\text{C,Rh}} = 5.1$ Hz, C-6^{B}), 36.1 (d, $^{1}J_{\text{C,P}} = 24.4$ Hz, C-6^{A}), 56.25, 56.52, 56.70, 56.77, 56.98, 57.28, 57.32, 58.16, 58.35, 58.37, 60.65, 60.78, 60.81, 60.86, 61.03, 61.09 (OMe), 63.46 (d, $^{2}J_{\text{C,P}} = 6.2$ Hz, C-5^{B}), 68.04 (d, $^{2}J_{\text{C,P}} = 6.5$ Hz, C-5^{A}), 69.61 (C-5), 69.63, 69.71, 69.79 (C-6), 69.97 [×2], 70.40 (C-5), 71.54 (C-6), 79.55, 79.82, 79.97 [×2], 80.31 [×2], 80.36, 80.81, 80.89, 80.91, 80.94, 81.04, 81.33 [×2], 81.83 [×2] (C-2, C-3, C-4), 87.21 (d, $^{3}J_{\text{C,P}} = 8.5$ Hz, C-4^{B}), 88.94 (d, $^{3}J_{\text{C,P}} = 8.5$ Hz, C-4^{A}), 96.14, 98.19, 98.76, 99.08 (C-1), 99.42 [×2] (C-1, CH of acac), 100.80 (C-1), 126.81, 126.89 (C_{meta}), 128.57 (C_{para}), 131.05, 131.12 (C_{ortho}), 135.94 (d, $^{1}J_{\text{C,P}} = 52.9$ Hz, C_{ipso}), 183.76, 185.87 (C=O of acac), 189.82 (dd, $^{1}J_{\text{C,Rh}} = 76.6$ Hz, $^{2}J_{\text{C,P}} = 26.0$ Hz, CO) ppm; $^{31}P\{^{1}H\}$ NMR (161.9 MHz, $CDCl_3$, 25ºC): $\delta = 34.3$ (d, $^{1}J_{\text{P,Rh}} = 167$ Hz) ppm; IR: 1960 (s, CO) cm^{-1}; elemental analysis (%) calcd for $C_{64}H_{102}O_{31}PRh{\cdot}1.5CDCl_3$ (1501.36 + 180.57): C 46.77, H 6.29 found: C 46.71, H 6.39; MS (ESI-TOF): *m/z* (%): 1518.58 (100) $[M + H_2O]^+$,1523.51 (5) $[M + Na]^+$.

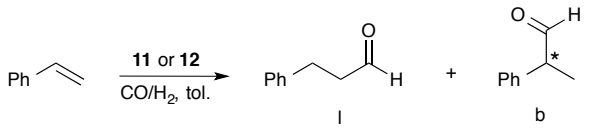


Acetylacetonato-carbonyl-P-{6^{A},6^{B}-dideoxy-6^{A},6^{B}-[(*R*)-phenylphosphinidene]-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},2^{G},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},3^{G},6^{C},6^{D},6^{E},6^{F},6^{G}-nonadeca-*O*-methyl-β-cyclodextrin}-rhodium(I) (12): A solution of β-HUGPHOS (0.160 g, 0.11 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of $[Rh(acac)(CO)_2]$ (0.034 g, 0.13 mmol) in CH_2Cl_2 (5 mL) under vigorous stirring at room temperature. The reaction mixture was further stirred for 1 h before being concentrated to *c.a.* 2 mL. Pentane (50 mL) was then added causing complex **12** to precipitate. The rhodium complex was collected by filtration and further purified by column chromatography (SiO_2; CH_2Cl_2/MeOH, 95:5 to 93:7, *v/v*) to afford **12** as a

brown solid (0.160 g, 87%). R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.60; m.p. 172°C; ^{1}H NMR (500.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY, TOCSY, ROESY and HSQC) = 1.85 (q, 1 H, $^2J_{H\text{-}6a,H\text{-}6b} = {}^2J_{H\text{-}6a,P} = {}^3J_{H\text{-}6a,H\text{-}5}$ = 12.8 Hz, H-6a^B), 2.12 (s, 3 H, Me of acac), 2.22 (dd, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 12.2 Hz, $^2J_{H\text{-}6a,P}$ = 14.6 Hz, H-6a^A), 2.37 (s, 3 H, Me of acac), 3.11–3.29 (10 H, H-2, H-3), 3.32 (s, 3 H, OMe), 3.38 (s, 3 H, OMe), 3.39 (s, 3 H, OMe), 3.40 (s, 3 H, OMe), 3.41 (s, 3 H, OMe), 3.43 (s, 3 H, OMe), 3.44 (s, 3 H, OMe), 3.50 (s, 3 H, OMe), 3.51 (s, 3 H, OMe), 3.52 (s, 3 H, OMe), 3.53 (s, 3 H, OMe), 3.54 (s, 3 H, OMe), 3.55 (s, 3 H, OMe), 3.58 (s, 3 H, OMe), 3.60 (s, 6 H, OMe), 3.61 (s, 3 H, OMe), 3.66 (s, 3 H, OMe), 3.67 (s, 3 H, OMe), 3.32–3.72 (18 H, H-3, H-4, H-5, H-6), 3.72–3.85 (4 H, H-4, H-5, H-6), 3.90–4.02 (3 H, H-5, H-6), 4.13 (d, 1 H, $^3J_{H\text{-}5,H\text{-}6}$ = 10.1 Hz, H-5), 4.34 (d, 1 H, $^3J_{H\text{-}6,H\text{-}5}$ = 10.1 Hz, H-6), 4.42 (d, 1 H, $^3J_{H\text{-}6,H\text{-}5}$ = 11.1 Hz, H-6), 4.99 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 4.0 Hz, H-1), 5.01 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 4.5 Hz, H-1), 5.05 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.1 Hz, H-1), 5.08 (m, 1 H, H-5^B), 5.12–5.16 (3 H, H-1), 5.40 (m, 1 H, H-5^A), 5.42 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 4.2 Hz, H-1), 5.58 (s, 1 H, CH of acac), 7.40–7.45 (3 H, *m*-H, *p*-H), 7.65–7.72 (2 H, *o*-H) ppm; ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 26.94, 28.61 (d, $^3J_{C,Rh}$ = 4.9 Hz, Me of acac), 32.08 (d, $^1J_{C,P}$ = 25.9 Hz, C-6^B), 34.11 (d, $^1J_{C,P}$ = 28.3 Hz, C-6^A), 57.49, 57.57, 57.83, 58.52, 58.78, 58.89, 58.95, 59.11 [×3], 59.15, 59.96, 60.25 [×2], 60.74, 61.42, 61.67, 61.91, 62.10 (OMe), 64.59 (C-5^A), 69.73 (C-5), 70.59 (d, $^2J_{C,P}$ = 12.6 Hz, C-5^B), 70.82 [×4] (C-5), 70.88, 70.96, 71.09, 71.20, 71.58 (C-6), 74.02 (C-4), 78.55, 78.97, 80.89, 80.93, 81.39, 81.63, 81.85, 81.92, 81.99 [×3], 82.24, 82.30, 82.41, 82.61, 82.64, 83.03, 84.10 (C-2, C-3, C-4), 87.20 (d, $^3J_{C,P}$ = 11.5 Hz, C-4^A), 88.53 (d, $^3J_{C,P}$ = 4.3 Hz, C-4^B), 97.50, 97.54, 97.61, 97.93, 99.92 [×2], 100.23 (C-1), 101.29 (CH of acac), 128.57, 128.67 (C_{meta}), 130.25 (C_{para}), 130.37, 130.47 (C_{ortho}), 136.95 (d, $^1J_{C,P}$ = 55.0 Hz, C_{ipso}), 184.06 (C=O of acac), 188.73 (C=O of acac), 189.82 (dd, $^1J_{C,Rh}$ = 76.4 Hz, $^2J_{C,P}$ = 26.3 Hz, CO) ppm; ^{31}P{^{1}H} NMR (161.9 MHz, $CDCl_3$, 25ºC): δ = 31.5 (d, $^1J_{P,Rh}$ = 168 Hz) ppm; IR: 1971 (s, CO) cm^{-1}; elemental analysis (%) calcd for $C_{73}H_{118}O_{36}PRh{\cdot}1.5CDCl_3$ (1705.58 + 180.57): C 47.44, H 6.47 found: C 47.49, H 6.26; MS (ESI-TOF): *m/z* (%): 1727.59 (100) $[M + Na]^+$.



General procedure for palladium-catalysed Heck cross-coupling reactions: In an oven-dried Schlenk tube, a solution of [$Pd(OAc)_2$] in DMF, a solution of α– or β–HUGPHOS in DMF, aryl bromide (1 equiv.), styrene (2 equiv.), Cs_2CO_3 (2 equiv.), decane (internal reference) and additional DMF were introduced under an inert atmosphere. The reaction mixture was heated for 1 h. After cooling to room temperature, a small amount (0.5 mL) of the resulting solution was passed through a Millipore filter and analyzed by GC.



General procedure for the hydroformylation experiments: The hydroformylation experiments were carried out in a glass-lined, 100 mL stainless steel autoclave containing a magnetic stirring bar. In a typical run, the autoclave was charged with preformed rhodium complex **11** or **12** then closed and flushed twice with vacuum/N_2. Toluene (15 mL) was added under N_2 and the autoclave was flushed twice with syngas (CO/H_2 1:1 v/v), before being pressurised with 20 bar of a CO/H_2 mixture and heated under stirring at 80°C. After 16 h, the autoclave was cooled to r.t. and depressurised. Styrene (1 equiv.) and decane (0.513 equiv.) were added to the reaction mixture. The autoclave was then pressurised and heated as mentioned in Table. Progress of the reaction was monitored by sampling the reaction mixture and analysing it by gas chromatography using a WCOT fused-silica column (25m × 0.25mm). This also allowed to determine the b:l ratio. In order to determine the enantiomeric excess, a sample of the reaction mixture (toluene) was treated with $LiAlH_4$ for 0.2 h. After filtration, the solution containing enantiomeric alcohols was analysed by GC with a Chirasil-DEX CB column (25 m × 0.25 mm).

IV. 5. References

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Chapter V

Regiospecific installation of unsymmetrical imine-enamine and imidazole caps on cyclodextrins using a symmetrical diketone reagent

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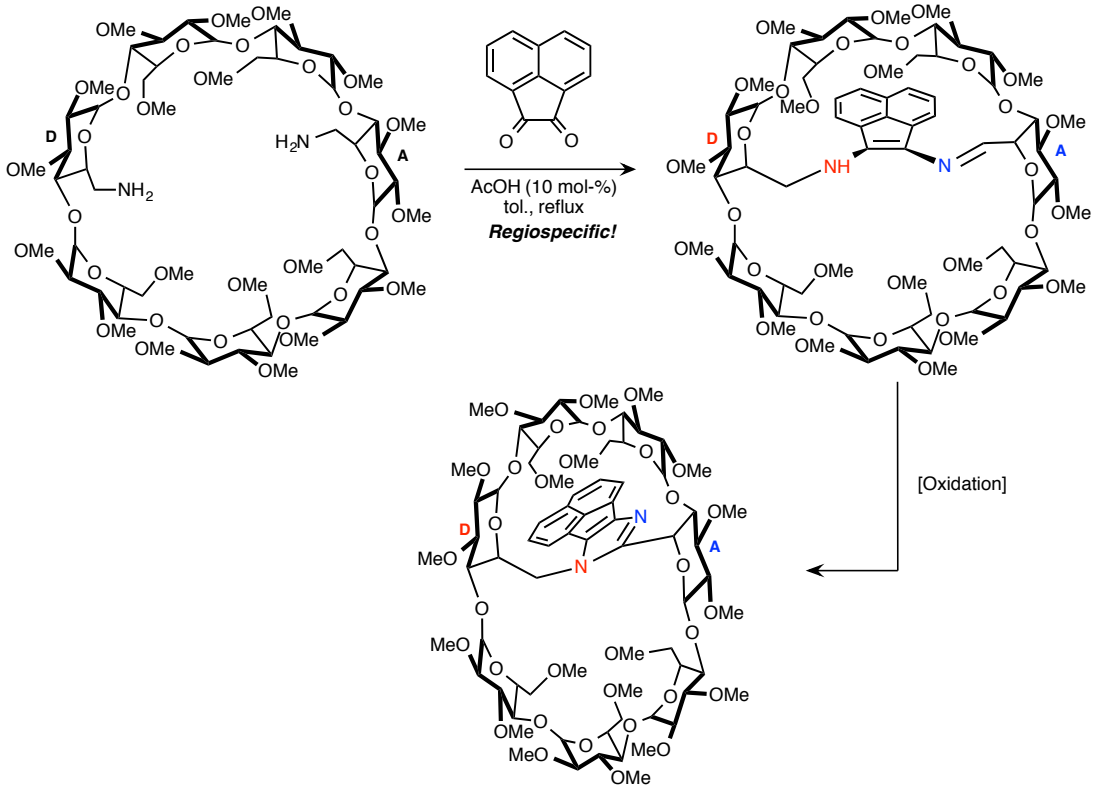
Summary – Chapter V

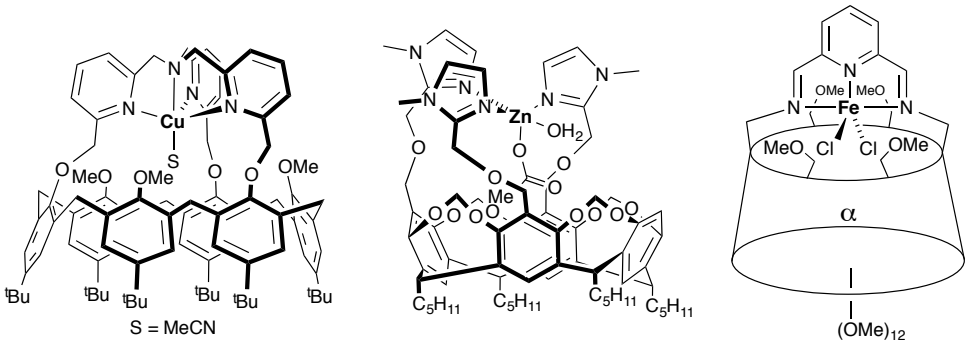
Methylated α- and β-cyclodextrin skeletons were equipped with an unsymmetrical *N*-(2-*N*'-alkylaminoacenaphthenyl)alkylimine rigid handle. The capping reaction, which consists in condensing a diaminocyclodextrin with highly symmetrical acenaphthenequinone, was found to be regiospecific when starting from cyclodextrin-diamines with no symmetry element. All modified cyclo-oligosaccharides possess intra-annular nitrogen donor atoms. They undergo further cyclization upon oxidation, whether chemically with DDQ or electrochemically, to give highly strained cyclodextrins capped with an unsymmetrical 1,2-disubstituted 1*H*-imidazole unit.

Des plateformes de type α- ou β-cyclodextrine (CD) ont été pontées avec une anse dissymétrique rigide N-(2-N'-alkylaminoacenaphthenyl)alkylimine. La réaction de pontage, qui consiste en une condensation entre une CD substituée par deux groupements amine primaire positionnés sur la face primaire et l'acenaphthènequinone, s'est avérée régiospécifique pour des diamino-cyclodextrines de symétrie C_1. Dans tous les cas, elle conduit à des imine-énamines dont les doublets libres sont orientés vers l'intérieur de la cavité. Ces composés azotés donnent lieu à une réaction de cyclisation lorsqu'ils sont soumis à une oxydation chimique ou électrochimique, produisant alors des CD pontées par une anse dissymétrique de type "1H-imidazole 1,2-disubstitué". Ces dernières sont très déformées.



V. 1. Introduction

As seen in the previous chapter, cavity-shaped molecules with *endo*-oriented donor atoms are capable of confining a metal centre within their hollow space.[1] Complexes obtained from such ligands have recently proven useful in catalysis[2] and molecular recognition.[3] Their synthesis is usually achieved by grafting coordinating subunits onto a cavity-shaped structure in such a way that their lone pairs are forced to point towards the hollow centre (Figure 1),[1, 4] although the cavity can also be constructed around the donor atoms.[5] Nitrogen-based ligands of this type are by far the most numerous since nitrogen is a ubiquitous donor atom, present in a variety of useful metal complexes.



Reinaud *Chem. Commun.* **2007**, 810 | Reinaud *Org. Lett.* **2012**, 2044 | Armspach *Eur. J. Inorg. Chem.* **2003**, 805

Figure 1. Various confining ligands with their metal built upon cavity shaped molecules.

One of the most efficient strategies for orientating the donor atoms toward the cavity interior is by capping a cavity-shaped molecule such as a CD with a rigid coordinating handle (see chapter IV).[1, 4b] Access to CD derivatives that can be capped with a coordinating handle[6] has been made possible in recent years by the development of highly regioselective CD difunctionalization methods.[7] The capping unit has usually a high degree of symmetry causing the coordinating atoms to be equivalent or at least of identical nature. Installing an unsymmetrical coordinating handles is highly relevant in homogeneous catalysis, but is synthetically more challenging and can be impractical if the macrocyclic platform is itself nonsymmetric as it will lead to at least two distinct regioisomers that can only be separated with great difficulty. Difunctionalized CD derivatives lacking any element of symmetry fall into this category.[4b, 8] Hereafter we wish to report the regiospecific synthesis of methylated α- and β-CD derivatives, AC and AD-capped with the unknown, unsymmetrical 1,4-diazapenta-2,4-diene motive.[§] The ligands described in this study contrast with other dinitrogen ligands, notably acenaphthenequinonediimines (BIAN),[10] β-diketimidate (nacnac)[11] and aminotroponiminate (ATI^-)[12] ligands which have a symmetrical structure (Figure 2).

[§] To the best of our knowledge, this is the first time that a highly symmetrical capping agent, namely acenaphthenequinone, has been employed to install a non-symmetrical handle onto a macrocyclic scaffold in a regiospecific manner.[9]

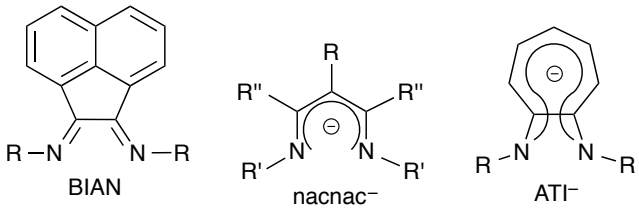


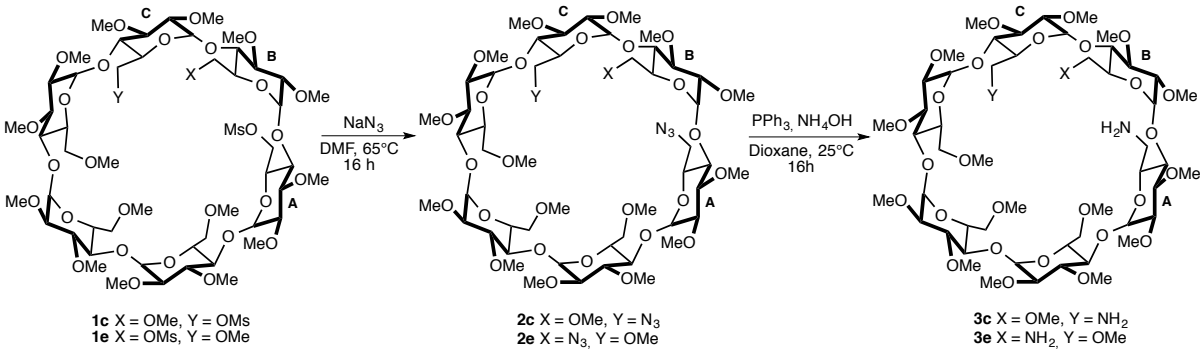
Figure 2. BIAN, nacnac⁻ and ATI⁻ ligand types.

Finally, we also report an unprecedented cyclization process that takes place upon oxidation of all *N*-(2-aminoacenaphthenyl)imino-capped CDs, whether chemically with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or electrochemically, to give highly strained CDs equipped with a 1,2-disubstituted 1*H*-imidazole cap.

V. 2. Results and discussion

V. 2. 1. Synthesis of diamino CD derivatives

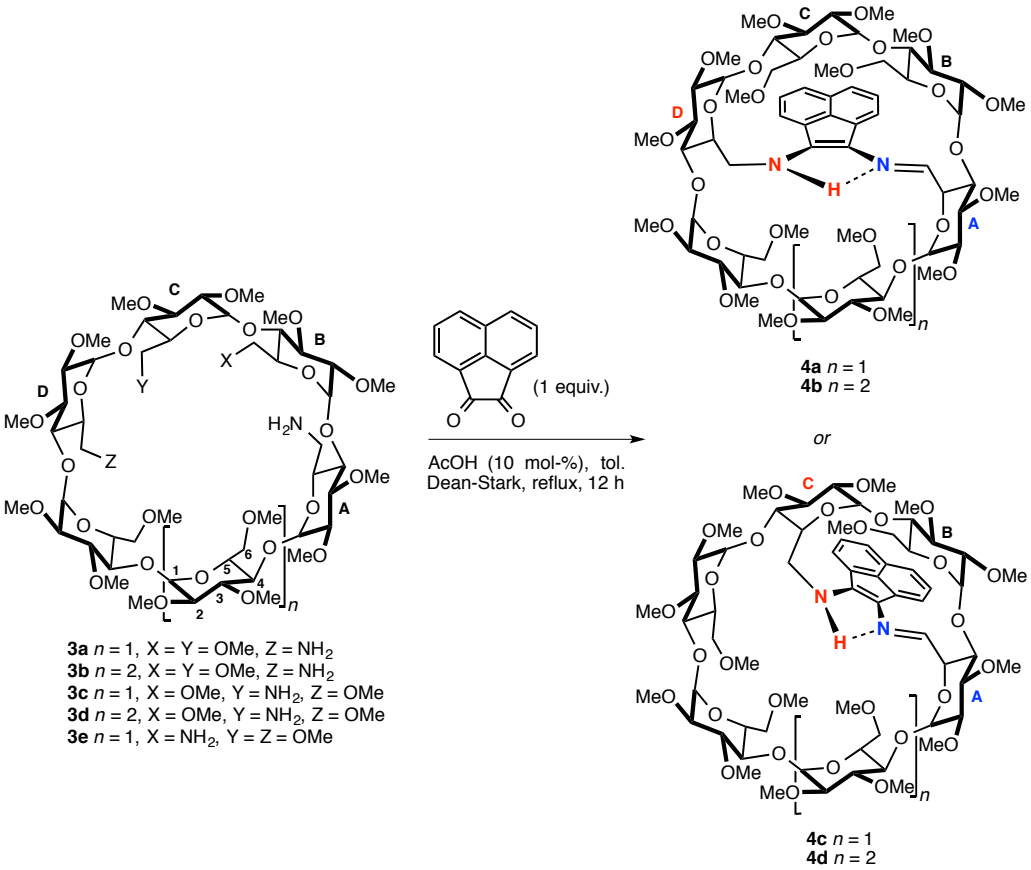
Diamines **3c**,**e** were synthesised according to the procedure describe for **3a,b,d** in two steps from the corresponding dimesylate **1c**,**e** (Scheme 1). First, substitution of the methylsulfonyl groups with sodium azide in DMF led to diazide **2c**,**e**. Subsequent Staudinger reduction with PPh_3 in aqueous ammonia produced water-soluble diamines **3c**,**e** in 85 % yields over two steps.



Scheme 1. Synthesis of diamines **3c**,**e**.

V. 2. 2. Capping reaction

C_2-Symmetric $6^A,6^D$-diamino- α-CD **3a** reacts with acenaphthenequinone in toluene under Dean Stark conditions to give capped CD **4a** in 58 % isolated yield in the presence of catalytic amounts of acetic acid (Scheme 2). The deep violet compound is stable enough to be separated from polymeric material by column chromatography. The ^{1}H NMR of **4a**, recorded in $CDCl_3$, reflects the desymmetrization of the α-CD scaffold upon capping as exemplified by the presence of 6 doublets for the anomeric protons (instead of 3 for the C_2-symmetric **3a**). MS measurements and complete ^{1}H NMR assignment of **4a** were undertaken using a whole range of 2D NMR techniques, including COSY, TOCSY, edited HSQC, HMBC and ROESY to determine the exact nature of the capping unit and its position with respect to the CD cavity. Apart from being fully compatible with the whole set of 2D NMR and ESI-MS spectra, the presence of the unprecedented 2,3-(1,8-naphthylene)-1,4-diazapenta-2,4-diene motive was univocally inferred from the following observations: i) The disappearance of the dd signal integrating for one N*H* proton at δ = 5.74 ppm upon D_2O exchange indicates the presence of a CH_2NH group; ii) The presence of a single downfield shifted proton (δ = 7.98 ppm) bonded to a sp^2 C-6 CD carbon atom is indicative of an imino group; iii) Apart from the sp^2 carbon atoms of the naphthalene unit, there are three sp^2 carbon atoms that can only belong to a 1,4-diazapenta-2,4-diene moiety when taking into account the two former observations.



Scheme 2. Synthesis of non-symmetrically capped CDs **4a**–**d**.

Careful examination of the ROESY spectrum of **4a** allowed us to establish the *endo* orientation of both nitrogen lone pairs (Figure 3). Indeed, the N*H* proton only correlates through-space with neighbouring methylene protons and more strikingly with inner cavity H-$5^{A,C,D,E,\text{ and }F}$ protons, but not with the naphthalene $H^{a'}$ proton. On the contrary, strong cross-peaks arise from through-space correlations between the latter and the outward-looking methylenic CH_2N protons. Similarly, the *endo* orientation of the imino lone pair was inferred from strong correlations between the *exo*-oriented iminic CH proton and the naphthalene H^{a} proton.

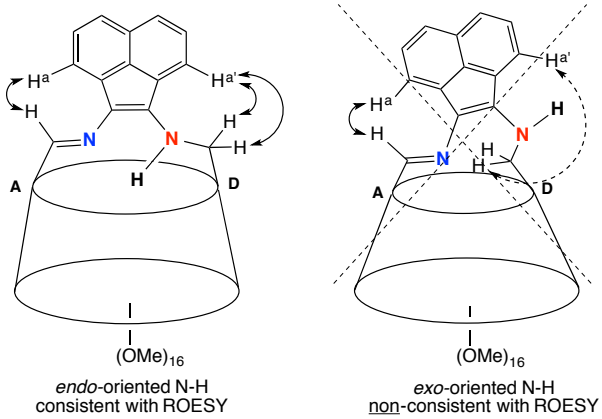


Figure 3. Possible conformation of **4a** consistent with ROESY experiments (left) and non-consistent (right).

Moreover, the acenaphthene plane was found to be strongly tilted towards the CD primary face (Figure 4), in keeping with ROESY cross-peaks originating from through-space correlations between the OMe-6 protons of non-bridged B glucose unit and naphthalene H^a, H^b, H^c protons, as well as OMe-6 protons of non-bridged C glucose unit and naphthalene $H^{a'}$, $H^{b'}$ and $H^{c'}$ protons. Because of the acenaphthene tilt, the B and C glucose units lie in the shielding cone of the aromatic system as revealed by the abnormally low chemical shift value of their OMe-6 protons (respectively δ = 2.75 and 2.76 ppm). The capping reaction is insensitive to cavity size as both 6^A,6^D-diamino- α-CD **3a** and β-CD analogue **3b** react in the same way. However, the location of the amino functionalities on the CD proved to be crucial for the success of the macrocyclisation. While both 6^A,6^C-diamino- α- and β-CDs **3c** and **3d** produced the same type of capped species, respectively **4c** and **4d**, as beforehand, only an inseparable mixture of polymeric material was recovered in the case of 6^A,6^B-diamino- α-CD **3e**. Clearly the two amino functionalities have to be wide enough apart to allow effective capping.

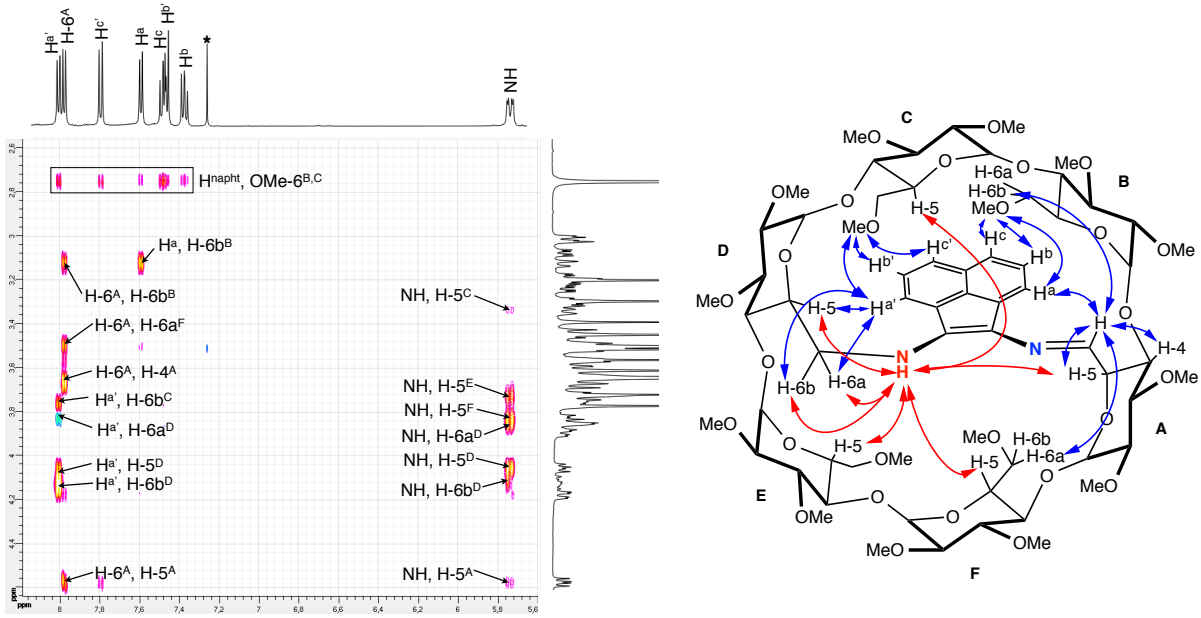


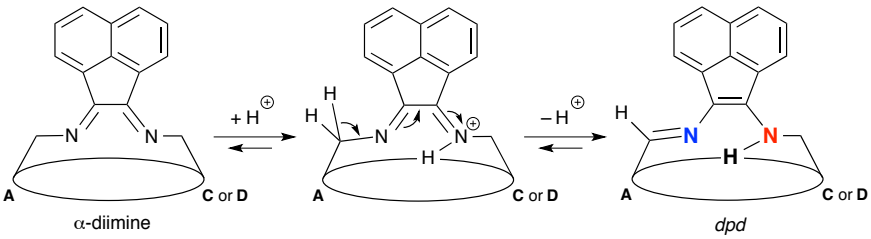
Figure 4. Part of the ROESY spectrum of compound **4a** recorded in $CDCl_3$ at 500.1 MHz. The drawing right to the spectrum shows a selection of ROESY cross peaks arising from through-space correlations between CD and protons of the capping unit proving the *endo* orientation of the NH proton (correlations in red) and the *exo* orientation of the CH=N proton (correlations in blue). Asterisk denotes residual solvent peaks.

Remarkably, the capping reaction is regiospecific when starting from diamines **3b-d** as in each case only one regioisomer out of the two possible ones is formed. Again, full assignment of the ^{1}H NMR spectra of **4b-d** was undertaken to identify the regioisomer formed. The fact that the C*H* imino proton always correlates through space with the H-4 proton of glucose unit A and scalarly with the H-5 proton of the same glucose unit is clear evidence for the presence of the imino group on glucose unit A, while through-space correlations between the N*H* proton and H-5 proton of glucose unit C or D are consistent with the presence of the N*H* group on unit D in **4b** and C in **4c–d**. Again, ROESY spectra gave a

clear picture of the position of the acenaphthene plane with respect to the cavity. Invariably, it lies flat, on glucose unit C in **4b** and on unit B in **4c** and **4d**. Such a feature is also confirmed by the high-field shifts of the OMe-6^C protons in **4b** (δ = 2.53 ppm) and OMe-6^B protons in **4c–d** (δ = 2.31 and 2.35 ppm, respectively).

V. 2. 3. Possible explanation for the regiospecificity of the capping reaction

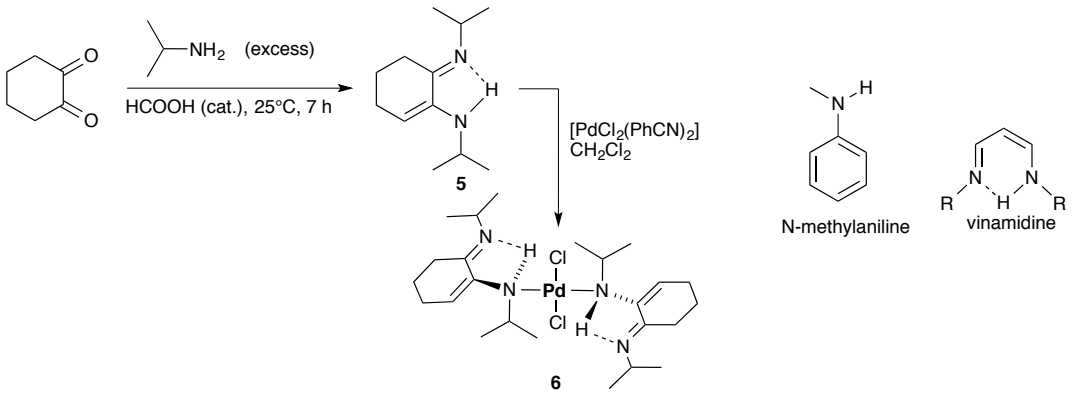
Although the chemistry of Ar-BIAN ligands (Ar-BIAN = bis(aryl)-acenaphthenequinonediimine) is well documented,[11] the synthesis of alkyl-BIAN derivatives,[10, 13] has remained elusive because of their tendency to isomerize when a proton is present on the carbon atom α to nitrogen, this leading to mixtures of products. We believe that in our case α-diimines are formed in the first place, but a thermodynamically-driven prototropic tautomerism then occurs, resulting in the conjugated 1,4-diazapenta-2,4-diene (*dpd*) system, a motive that has not been encountered before (Scheme 3). The fact that this prototropy is regiospecific, resulting in a single capped species (with the NH bond connected either to the C or the D glucose unit), is clear evidence for the templating role of the CD in this rearrangement.



Scheme 3. Proposed prototropic isomerism of CD-alkyl-BIANs leading to **4a-d**.

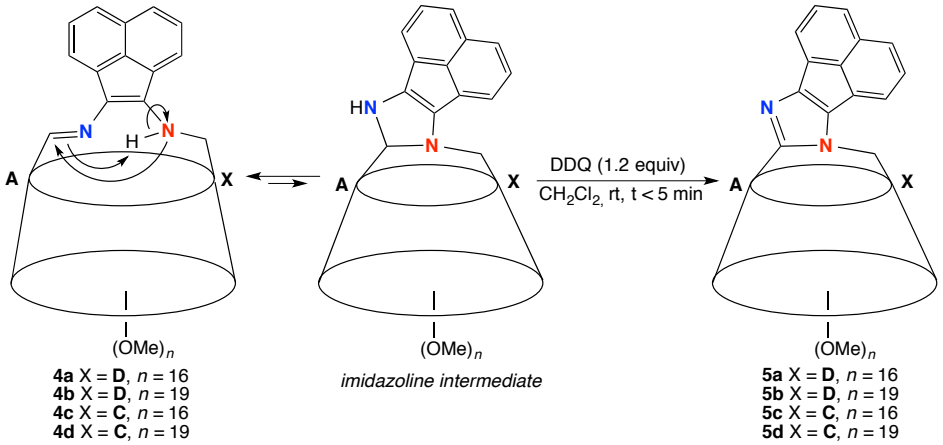
V. 2. 4. Attempts to chelate a transition metal with imine-enamines 4

As mentioned in the introduction, imine-enamines **4** are similar to nacnac$^-$ and ATI$^-$ ligands. While the latter have found many applications in coordination chemistry and in metallo-catalysed reactions, no coordination occurred when compounds **4** were opposed to transition metal complexes such as or [Rh(acac)$(CO)_2$], even in the presence of a strong base such as sodium hydride, lithium diisopropylamidure or even *n*BuLi. In fact, a similar lack of reactivity was already observed by Elsevier and co-workers for the closely related imine-enamine **5**,[14] which was obtained as the only product upon condensing 1,2-cyclohexanedione with excess isopropylamine. Reaction of **5** with [$PtCl_2(PhCN)_2$] did not result in the expected chelate complex but instead afforded complex **6**, which features two amine ligands bonded to palladium (Scheme 4). Another confirmation of this abnormal reactivity comes from the chemical shift value of the NH proton of **5** (δ = 4.8 ppm in $CDCl_3$) which lies very closed to those of **4** (δ = 5.8 ppm in $CDCl_3$) but in an unusual chemical shift range, halfway between the non-hydrogen bonded NH proton of *N*-methylaniline (δ = 3.6 ppm in $CDCl_3$) and that of strongly conjugated vinamidines (~ 12 ppm in $CDCl_3$).



Scheme 4. Elsevier's imine-enamine ligand **5** with its palladium complex **6**.

Surprisingly, when reacted $AgBF_4$, **4a** did not coordinate the Ag(I) cation. Instead, oxidation into imidazole **5a** occurred with concomitant formation of metallic silver (Scheme 5). In order to confirm the tendency of **4a** to undergo oxidative cyclisation, $AgBF_4$ was replaced with the non-metallic oxidant DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone). As expected, the same cyclization product was obtained in high yield (85 %). All other capped CDs (**4b-d**) undergo this type of cyclisation upon treatment with DDQ to afford 1,2-disubstituted 1*H*-imidazoles **5b–d** in 85 % yield. Although not detected in the reaction mixture, the reaction proceeds most probably via an imidazoline intermediate, the oxidation of which is highly favourable as it leads to an aromatic 1,2-dialkyl-1*H*-imidazole ring. It is to note that only a 4-imidazoline is depicted in Scheme 5 as an intermediate. Possibly, 2-imidazoline or 3-imidazoline intermediates are also formed as both of them are accessible from 4-imidazoline by prototropy.



Scheme 5. Synthesis of 1,2-disubstituted 1*H*-imidazoles **5a-d** by oxidation of **4a-d.**

The significant red shift of the IR stretching band associated with the C=N bond on going from **4a** to **5a** (1564 and 1500 cm^{-1}, respectively) is consistent with the proposed cyclization process. Direct evidence for the latter came from an X-Ray diffraction study on Cu(I) complex $[Cu(\mathbf{5a})_2]BF_4$, which was obtained by reacting $[Cu(MeCN)_4]BF_4$ with 2 equiv. of ligand **5a** (Figure 5). As a result of the installation of the shortest thinkable bridge (a single atom) between the two C-6 atom of distal glucose units, the two CD scaffolds are heavily

distorted, both adopting an elongated shape (distances between diametrically opposed O-4 atoms ranging from 4.58 to 10.80 Å for the CD ligands) instead of the usual circular one. Despite the CD deformation, all glucose units keep their standard $^4C_1$ conformation. The rigid acenaphthimidazole cap, which is almost planar is markedly tilted towards one side of the CD macrocycle as observed for acenaphathene-capped CDs **4a–d**. Steric congestion is most probably responsible for the almost linear geometry (N(2)–Cu–N(11) angle = 174.36°) adopted by the rare coordinatively-unsatured 14 VE complex, as evidenced by the location of the Cu(I) centre, which is literally buried between the two CD ligands. The two Cu-N bonds (1.900(9) and 1.913(9) Å) are somewhat longer than those found in two other reported two-coordinate Cu(I) imidazole complexes.[15] The nearest oxygen atom to copper is at 2.95 Å (O(35)), which means there is no stabilization of the complex by donor atoms other than the two imidazole nitrogen ones.

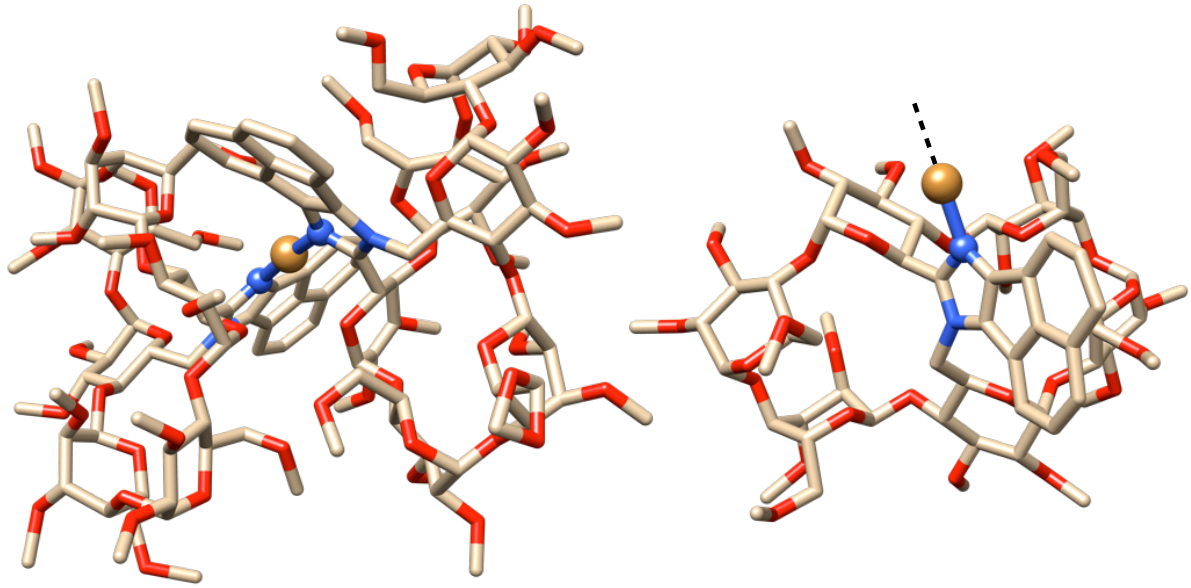


Figure 5. Molecular structure of [Cu(**5a**)$_2$]BF$_4$: (left) whole view showing both cyclodextrin units; (right) partial view illustrating the pinched structure of one of the cyclodextrin cores. The solvent molecules and the BF$_4$ counterion, all located outside the cavity, have been omitted for clarity.

Evidence for cavity distortion in solution could be inferred from the wide chemical shift range in which the anomeric H-1 protons resonate in both **5a** ($\Delta\delta$ = 1.05 ppm) and [Cu(**5a**)$_2$]BF$_4$ ($\Delta\delta$ = 0.97 ppm) as opposed to that of more relaxed **4a** ($\Delta\delta$ = 0.36 ppm). The same observation holds for all other capped CDs ($\Delta\delta$ = 0.97 ppm on average for **5b–d** vs. $\Delta\delta$ = 0.57 ppm for **4b–d**). All imidazole derivatives **5a–d** display a bent acenaphthene cap similar to that observed for **4b–d** in keeping with the high-field shifted OMe-6 protons of glucose unit C in **5a,b** and [Cu(**5a**)$_2$]BF$_4$ (δ = 2.37, 1.92 and 1.93 ppm, respectively) and unit B in **5c,d** (δ = 2.65 and 2.61 ppm, respectively).

V. 2. 5. Electro- and spectroelectrochemical studies

To have a clearer understanding of the cyclization/oxidation process, we decided to conduct electrochemical (Figure 6) and spectroelectrochemical (Figure 7) studies on compounds **4a** and **5a**. The cyclic voltammogram (CV) of **4a**, recorded in the range 0–1600 mV, shows one well-defined reversible one-electron oxidation at E_{pa} = 850 mV (characterised by a potential difference of 60 mV between the corresponding oxidation (1) and reduction (2) peaks). An ill-defined peak (3) with reduced intensity was also detected at a much more positive potential (ca. 1500 mV). The same redox process (1') was also present in the CV of **5a**, but was found to be much more intense. It corresponds to the much harsher, reversible one-electron oxidation of the imidazole cap. Clearly, the oxidation of **4a** is very facile and the first one-electron process is immediately followed by a chemically irreversible one-electron oxidation of the deprotonated radical cation to generate **5a**, the oxidation of which can already be detected in the CV of **4a**.

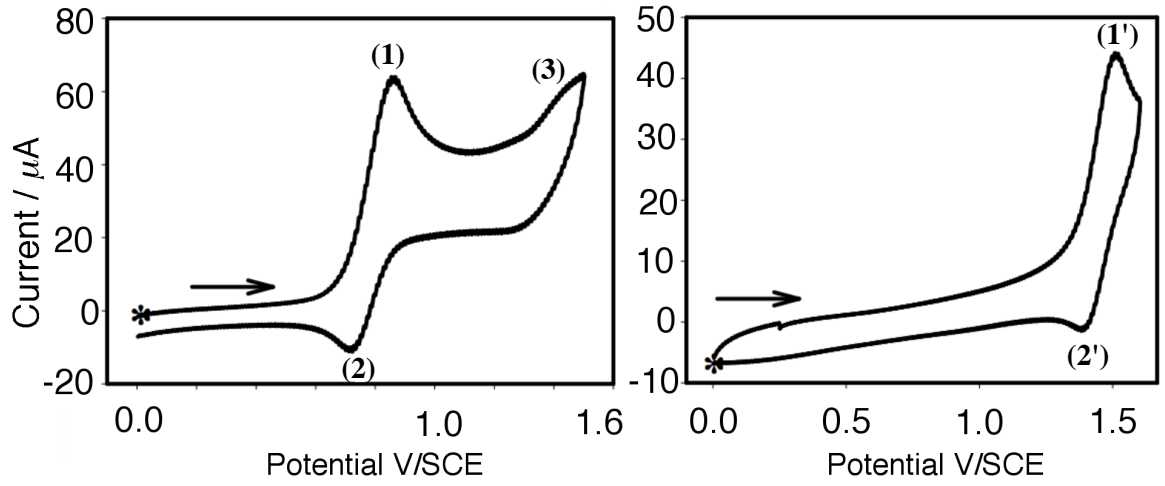


Figure 6. Cyclic voltammograms of **4a** (left) and **5a** (right) (1.2 mM) in CH_2Cl_2 (0.1 M Bu_4NPF_6) recorded with a scan rate of 100 mV/s. (∗) denotes the initial and final potential.

Figure 7 shows the UV-vis spectra of **4a** recorded every 10 seconds upon a potential increase of 10 mV s^{-1} from 0 to 1.5 V. As the oxidation of **4a** proceeded, the absorption bands at 321 nm (ε = 17750; ε: molar extinction coefficient in M^{-1} cm^{-1}) and 529 nm (ε = 1840) decreased. At the same time a new absorption band at 279 nm appeared. In addition, four well-defined isosbestic points at 257 nm, 296 nm, 382 nm and 444 nm were observed. The stepping back of the potential from 1.5 to 0 V did not regenerate the starting material. This indicates that the anodic oxidation of **4a** leads ultimately and irreversibly to a very stable product, the spectrum of which is identical to that of **5a** (absorption bands at 233 nm (ε = 26830) and 279 nm (ε = 14840)).

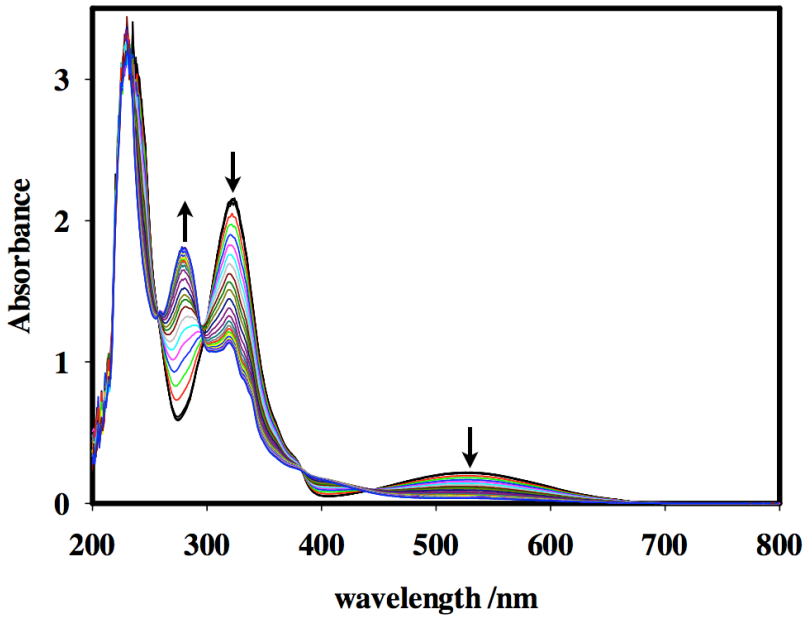


Figure 7. Thin-layer spectral changes of **4a** in CH_2Cl_2 (0.1 M Bu_4NPF_6) observed when the potential is scanned from 0 to 1.50 V (Scan rate 10 mV s^{-1}).

Electrochemical studies were also conducted on complex [Cu(**5a**)$_2$]BF_4 (Figure 8). The CV of the latter was recorded in the range 0–1000 mV and shows a one-electron oxidation at E_{pa} = 810 mV (characterised by a potential difference of 180 mV between the corresponding oxidation (1) and reduction (2) peaks). It corresponds to the one-electron reversible oxidation of Cu(I) in Cu(II), which lies in the range observed for tetrahedral Cu(I) imidazole complexes.[16] When recorded in the range -1000– +1000 mV, CV showed that complex decomposed readily upon reduction of Cu(I) in Cu(0) but the precise potential of this reduction could not be properly determined.

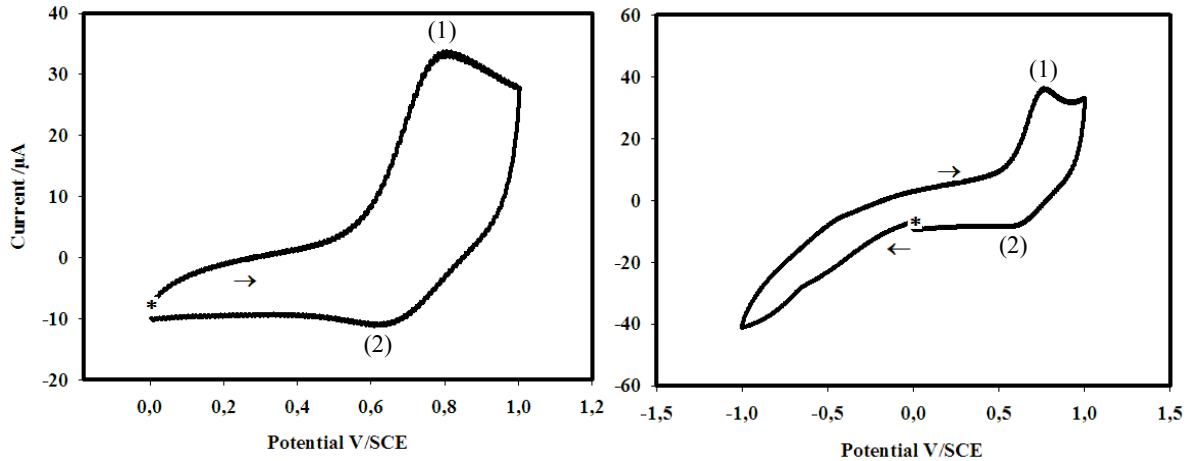


Figure 8. Cyclic voltammograms of [Cu(**5a**)$_2$]BF_4 in 0–1000 mV (left) and -1000– +1000 mV range (right) (1.2 mM) in CH_2Cl_2 (0.1 M Bu_4NPF_6) recorded with a scan rate of 100 mV/s. (∗) denotes the initial and final potential.

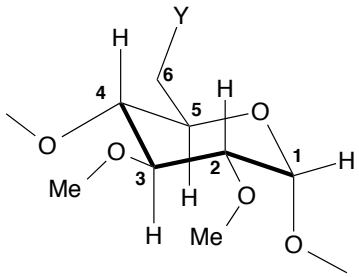
V. 3. Conclusion

In summary, we have demonstrated the capacity of the CD torus to promote the formation of *unsymmetrical* imine-enamine caps in condensation reactions involving diamino-CDs and the *symmetrical* acenaphthenequinone. These reactions, which occurred in a regiospecific manner, resulted in the first molecules containing a 1,4-diazapenta-2,4-diene motive. Because of their nitrogen functionalities oriented towards the cavity interior, these capped CDs may create new opportunities for performing catalytic reactions within a confined, chiral environment. However, so far, we were not able to chelate a metal centre with these ligands even in the presence of a strong base. Possibly, the use of highly reactive metal precursors such as $[Zn(Et)_2]$ should allow to reach this goal, although, *a priori*, nucleophilic addition of this reagent to the C=N double bond cannot be ruled out. We further showed that such imine-enamines readily undergo one-electron oxidation leading to unprecedented, 1,2-disubstituted 1*H*-imidazole units capping a highly distorted CD skeleton with a very short bridge.

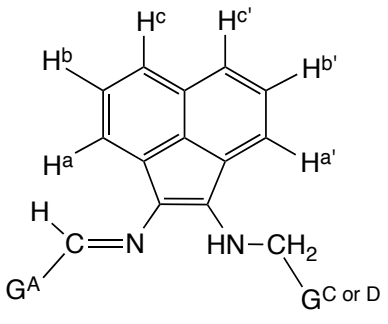
V. 4. Experimental section

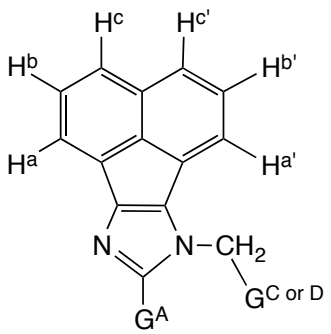
V. 4. 1. General procedures

All commercial reagents were used as supplied. All reactions were performed in Schlenk-type flasks under N_2 with degassed solvent. Solvents were dried by conventional methods and distilled immediately prior to use. Column chromatography was performed on silica gel 60 (particle size 40-63 μm, 230-240 mesh), beforehand dried overnight at 250 °C. $CDCl_3$ was passed down a 5 cm thick alumina column and stored under N_2 over molecular sieves (3 Å). IR spectra were recorded with Bruker Alpha spectrophotometer. Routine ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded with Bruker FT instruments (AVANCE 300, 400, 500 spectrometers). ^1H NMR spectral data were referenced to residual protiated solvents (δ = 7.26 ppm for $CDCl_3$) and ^{13}C chemical shifts are reported relative to deuterated solvents (δ = 77.00 ppm for $CDCl_3$). Mass spectra were recorded with a Bruker MicroTOF spectrometer (ESI) using CH_2Cl_2, MeCN or MeOH as solvent or with a Bruker Autoflex II TOF/TOF (MALDI) using α-cyano-4-hydroxycinnamic acid as matrix. Elemental analyses were performed by the Service de Microanalyse, Institut de Chimie UMR 7177, Strasbourg. Melting points were determined with a Büchi 535 capillary melting point apparatus. Compounds **1c** and **1e**, [17] **3a**,[6a] **3b**,[6c] **3d**[18] and $[Cu(MeCN)_4]$[19] were prepared according to literature procedures. In this publication, cyclodextrins are depicted as seen from the secondary face, the glucose units being ranged counterclockwise in the following order: A, B, C, D, E, F and G. The numbering of the atoms within a glucose unit is as follows:



The labelling of aromatic protons in the A,C or A,D cap is as follows:

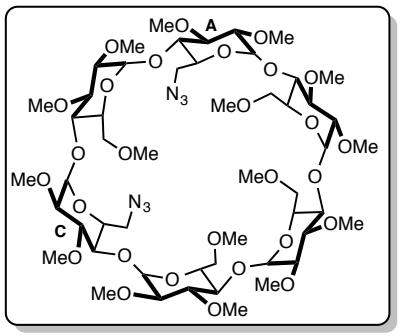




V. 4. 2. Procedure for determining the glucose units linked by a given capping unit

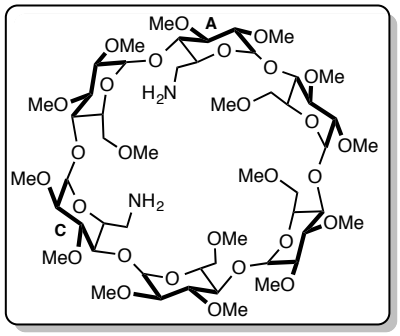
Our strategy for full structural assignment began with the differentiation between capped and non-capped C-6 carbon atoms by DEPT 135. These appear as two distinct sets of signals. The H-6 protons could then be identified using ^{1}H-^{13}C HMQC (Heteronuclear Multiple Quantum Coherence spectroscopy) or edited HSQC (Heteronuclear Single Quantum Coherence spectroscopy). By using TOCSY (TOtal Correlation SpectroscopY) and COSY (COrrelated SpectroscopY), each H-6 proton was correlated to the set of protons belonging to the same glucose residue. The connectivity between individual glucose units was then established via a ROESY (Rotating frame Overhause Effect SpectroscopY) experiment showing the proximity between H-4$_N$ and H-1$_{N+1}$ protons (N and N+1 standing for neighbouring glucose moieties labeled in the alphabetical order).[20]

V. 4. 3. Synthesis and characterisation

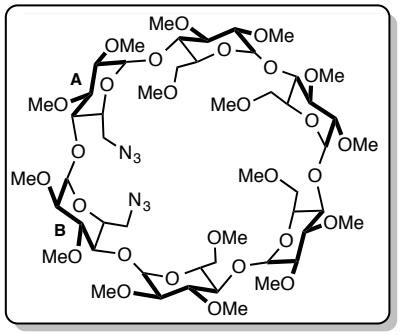


6^{A},6^{C}-Dideoxy-6^{A},6^{C}-diazido-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},6^{B},6^{D},6^{E},6^{F}-hexadeca-*O*-methyl-α-cyclodextrin (2c): Sodium azide (2.590 g, 39.82 mmol) was added to a solution of **1c** (2.440 g, 1.81 mmol) in DMF (40 mL). The reaction mixture was stirred at 65 °C for 18 h before being cooled down to 25 °C. An ice-water slurry was added to the reaction mixture (200 mL), which was then extracted with Et_2O (4 × 100 mL). The organic extract was washed once with water (200 mL) before being dried ($MgSO_4$) and evaporated to dryness in vacuo to afford analytically pure **2c** (2.257 g, 100%) as a colorless solid. R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.71; m.p. 188–190 °C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25 ºC): δ (assignment by combined COSY and HSQC) = 3.09–3.14 (6 H, H-2), 3.35 (s, 6 H, OMe), 3.36 (s, 3 H, OMe), 3.37 (s, 3 H, OMe), 3.42 (s, 3 H, OMe), 3.43 (s, 3 H, OMe), 3.44 (s, 3 H, OMe), 3.45 (s, 6 H, OMe), 3.46 (s, 3 H, OMe), 3.57 (s, 3 H, OMe), 3.58 (s, 6 H, OMe), 3.59 (s, 3 H, OMe), 3.60 (s, 3 H, OMe), 3.61 (s, 3 H, OMe), 3.32–3.90 (30 H, H-3, H-4, H-5, H-6), 4.95 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1), 4.96–4.99 (3 H, H-1), 5.00–5.02 (2 H, H-1) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ (assignment by HSQC) = 52.11, 52.20 (C-6^{A,C}), 57.91, 57.93, 57.97, 57.99, 58.03, 58.15, 59.04, 59.08, 59.10, 59.15, 61.77, 61.78, 61.85 [×2], 61.87, 61.92 (OMe), 70.99, 71.05 (C-5), 71.14 (C-6), 71.20, 71.23 (C-5), 71.26, 71.32 (C-6), 71.36, 71.38 (C-5), 71.52 (C-6), 81.10, 81.13, 81.18, 81.26 [×2], 81.34, 81.93, 82.09 [×3], 82.17, 82.23 [×2],

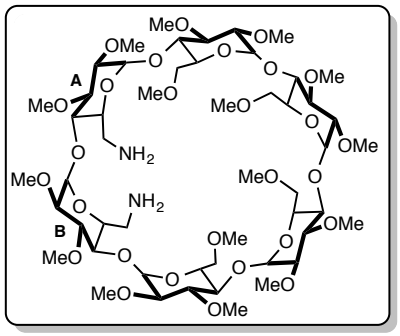
82.31, 82.45, 82.67, 83.60 [×2] (C-2, C-3, C-4), 99.60 [×2], 100.16 [×3], 100.29 (C-1) ppm; elemental analysis (%) calcd for $C_{52}H_{90}N_6O_{28}$•CH_2Cl_2 (1247.29 + 84.93): C 47.78, H 6.96, N 6.31, found: C 47.79, H 7.00, N 6.49; MS (ESI-TOF): *m/z* (%): 1264.61 (100) $[M + H_2O]^+$, 1269.57 (78) $[M + Na]^+$.



6^A,6^C-Dideoxy-6^A,6^C-diamino-2^A,2^B,2^C,2^D,2^E,2^F,3^A,3^B,3^C,3^D,3^E,3^F,6^B,6^D,6^E,6^F-hexadeca-*O*-methyl-α-cyclodextrin (3c): Triphenylphosphine (2.850 g, 10.86 mmol) was added to a solution of **2c** (2.257 g, 1.81 mmol) in dioxane (25 mL). The solution was stirred for 1 h at 25 °C before adding ammonium hydroxide (1.630 g, 1.81 mL of 30 % *wt/wt* solution, 13.94 mmol). The reaction mixture was stirred at 25 °C for a further 16 h before being poured into water (300 mL). The pH of the resulting suspension was made alkaline by adding 2 M NaOH (50 mL) before being extracted with $CHCl_3$ (4 × 100 mL). The organic extract was dried over $MgSO_4$ before being evaporated to dryness and the resulting crude was subjected to column chromatography (SiO_2, CH_2Cl_2/MeOH/NH_4OH, 95:4:1 to 89:10:1, *v*/*v*) to afford **3c** (1.940 g, 90%) as a colorless fluffy solid. R_f (SiO_2, CH_2Cl_2/MeOH/NH_4OH, 89:10:1, *v*/*v*) = 0.34; m.p. 184–186 °C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY and HSQC) = 1.42 (br. s, 4 H, NH_2), 3.00–3.12 (6 H, H-2), 3.21 (s, 3 H, OMe), 3.26 (s, 3 H, OMe), 3.27 (s, 3 H, OMe), 3.29 (s, 3 H, OMe), 3.36 (s, 3 H, OMe), 3.37 (s, 3 H, OMe), 3.38 (s, 9 H, OMe), 3.39 (s, 3 H, OMe), 3.52 (s, 3 H, OMe), 3.53 (s, 3 H, OMe), 3.54 (s, 6 H, OMe), 3.55 (s, 6 H, OMe), 3.23–3.93 (30 H, H-3, H-4, H-5, H-6), 4.85–4.86 (2 H, H-1), 4.94–4.97 (4 H, H-1) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 52.18, 52.35 (C-$6^{A,B}$), 57.52 [×2], 57.55 [×2], 57.60 [×2], 58.66, 58.72, 58.74, 58.82, 61.54, 61.57 [×2], 61.61 [×3] (OMe), 70.62 (C-5), 70.80 (C-6), 70.82, 70.88 (C-5), 70.92, 70.96 (C-6), 71.06 (C-5), 71.20 (C-6), 71.33, 71.41 (C-5), 80.87, 80.91 [×2], 80.93 [×2], 81.03 [×2], 81.07, 82.04 [×3], 82.09 [×4], 82.20, 84.16, 84.94 (C-2, C-3, C-4), 99.90, 100.01, 100.10, 100.13, 100.20 [×2] (C-1) ppm; elemental analysis (%) calcd for $C_{52}H_{94}N_2O_{28}$•$2CH_2Cl_2$ (1195.30 + 169.86): C 47.51, H 7.24, N 2.05, found: C 47.44, H 7.25, N 1.93; MS (ESI-TOF): *m/z* (%): 1195.61 (100) $[M + H]^+$, 1235.63 (25) $[M + MeCN]^+$.

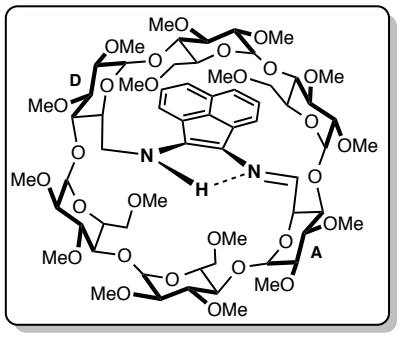


6^{A},6^{B}-Dideoxy-6^{A},6^{B}-diazido-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},6^{C},6^{D},6^{E},6^{F}-hexadeca-*O*-methyl-α-cyclodextrin (2e): 2e (colorless solid, 1.296 g, 100%) was synthesised from **1e** (1.400 g, 1.04 mmol) and sodium azide (1.360 g, 20.82 mmol) according to the procedure used for preparing **2c**. R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.71; m.p. 188–190 °C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25 ºC): δ (assignment by combined COSY and HSQC) = 3.08–3.16 (6 H, H-2), 3.36 (s, 3 H, OMe), 3.37 (s, 6 H, OMe), 3.38 (s, 3 H, OMe), 3.43 (s, 3 H, OMe), 3.44 (s, 3 H, OMe), 3.45 (s, 3 H, OMe), 3.46 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 3.48 (s, 3 H, OMe), 3.59 (s, 6 H, OMe), 3.60 (s, 6 H, OMe), 3.61 (s, 3 H, OMe), 3.62 (s, 3 H, OMe), 3.26–3.89 (30 H, H-3, H-4, H-5, H-6), 4.95 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1), 4.97–4.99 (2 H, H-1), 5.01 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.1 Hz, H-1), 5.02 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1), 5.04 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ (assignment by HSQC) = 51.97, 52.25 (C-6^{A,B}), 57.81, 57.84, 57.93, 58.00, 58.04, 58.07, 58.97 [×2], 59.04, 59.08, 61.67, 61.79 [×3], 61.84 [×2] (OMe), 71.02, 71.11 (C-5), 71.15 [×2] (C-6), 71.16, 71.20 [×2] (C-5), 71.28 (C-6), 71.35 (C-5), 71.45 (C-6), 80.93, 80.96, 81.18, 81.23, 81.29, 81.31, 81.95, 81.98 [×2], 82.11 [×2], 82.19 [×2], 82.25, 82.31, 82.59, 83.47, 83.88 (C-2, C-3, C-4), 99.65, 99.72, 100.01, 100.08, 100.17 [×2] (C-1) ppm; elemental analysis (%) calcd for $C_{52}H_{90}N_6O_{28}$•2MeOH (1247.29 + 64.08): C 49.46, H 7.53, N 6.41, found: C 49.33, H 7.31, N 6.24; MS (ESI-TOF): *m/z* (%): 1269.57 (100) $[M + Na]^+$.



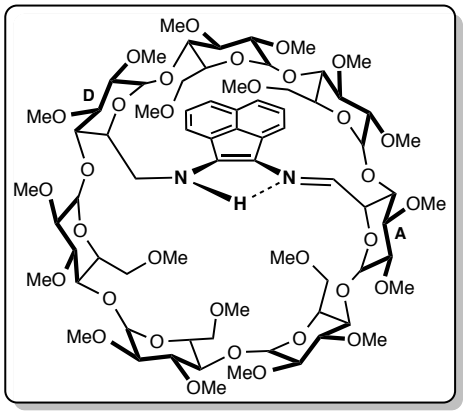
6^{A},6^{B}-Dideoxy-6^{A},6^{B}-diamino-2^{A},2^{B},2^{C},2^{D},2^{E},2^{F},3^{A},3^{B},3^{C},3^{D},3^{E},3^{F},6^{C},6^{D},6^{E},6^{F}-hexadeca-*O*-methyl-α-cyclodextrin (3e): (colorless solid, 0.730 g, 90%) was synthesised from **2e** (0.850 g, 0.68 mmol), triphenylphosphine (0.860 g, 3.27 mmol) and ammonium hydroxide (0.585 g, 0.65 mL of 30% *wt/wt* solution, 5.00 mmol) according to the procedure used for preparing **3c**. R_f (SiO_2, CH_2Cl_2/MeOH/NH_4OH, 89:10:1, *v*/*v*) = 0.34; m.p. 184–186 °C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY and HSQC) = 1.62 (br. s, 4 H, NH_2), 2.96–3.15 (10 H, H-2, H-6^{A,B}), 3.34 (s, 3 H, OMe), 3.35 (s, 3 H, OMe), 3.36 (s, 3 H, OMe), 3.37 (s, 3 H, OMe), 3.43 (s, 3 H, OMe), 3.44 (s, 6 H, OMe), 3.45 (s, 3 H, OMe), 3.46 (s, 6 H,

OMe), 3.59 (s, 3 H, OMe), 3.60 (s, 12 H, OMe), 3.61 (s, 3 H, OMe), 3.31–3.85 (26 H, H-3, H-4, H-5, H-$6^{C,D,E,F}$), 4.98–5.03 (6 H, H-1) ppm; $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 42.44, 42.48 (C-$6^{A,B}$), 57.72, 57.81 [×2], 57.84, 57.87 [×2], 58.97 [×3], 59.11, 61.72 [×3], 61.75, 61.80, 61.83 (OMe), 71.00 (C-6), 71.11, 71.15, 71.17, 71.28 (C-5), 71.37 [×3] (C-6), 72.27, 72.45 (C-5), 81.14, 81.18 [×3], 81.23, 81.25, 82.03, 82.07 [×2], 82.14 [×2], 82.20, 82.23, 82.30, 82.35 [×2], 82.99, 83.28 (C-2, C-3, C-4), 99.79, 99.92, 99.93, 100.00, 100.02 [×2] (C-1) ppm; elemental analysis (%) calcd for $C_{52}H_{94}N_2O_{28}$ (1195.30): C 52.23, H 7.95, N 2.20, found: C 52.25, H 7.93, N 2.34; MS (ESI-TOF): *m/z* (%): 1195.61 (100) $[M + H]^+$.



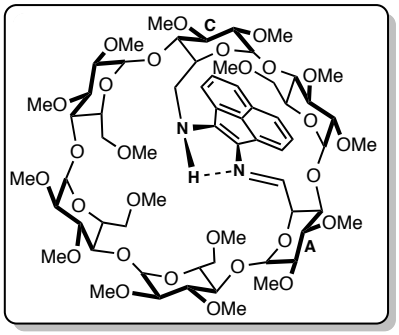
4a: Acenaphthenequinone (0.137 g, 0.75 mmol) and glacial acetic acid (4 μL, 0.004 g, 0.08 mmol) was added to a solution of **3a** (0.900 g, 0.75 mmol) in 200 mL of toluene. The reaction mixture, which rapidly turned violet, was then refluxed for 12 h under Dean-Stark conditions. After cooling down to 25 °C, the deep violet solution was evaporated to dryness under vacuum and the residue subjected to column chromatography (SiO_2; CH_2Cl_2/MeOH, 96:4, *v/v*) to afford **4a** (0.530 g, 53%) as a deep violet solid. R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v/v*) = 0.61; m.p. >250 °C; ^1H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY, TOCSY, HSQC and ROESY) = 2.05 (d, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 11.5 Hz, H-$6a^C$), 2.75 (s, 3 H, OMe-6^B), 2.76 (s, 3 H, OMe-6^C), 3.02 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}1}$ = 3.5 Hz, $^3J_{H\text{-}2,H\text{-}3}$ = 10.0 Hz, H-2^C), 3.03 (1H, H-$6a^B$), 3.08 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}1}$ = 3.5 Hz, $^3J_{H\text{-}2,H\text{-}3}$ = 9.9 Hz, H-2^B), 3.13 (d, 1 H, $^2J_{H\text{-}6a,H\text{-}6b}$ = 10.6 Hz, H-$6b^B$), 3.19 (1 H, H-2^E), 3.21 (s, 3 H, OMe-6^F), 3.22 (1 H, H-2^F), 3.25 (dd, 1 H, $^3J_{H\text{-}2,H\text{-}1}$ = 3.4 Hz, $^3J_{H\text{-}2,H\text{-}3}$ = 9.5 Hz, H-2^D), 3.30 (s, 3 H, OMe-6^E), 3.30 (1 H, H-4^D), 3.31 (1 H, H-2^A), 3.33 (1 H, H-5^C), 3.34 (1 H, H-5^B), 3.40 (s, 3 H, OMe), 3.45 (1 H, H-3^C), 3.46 (1 H, H-$6a^F$), 3.47 (s, 3 H, OMe), 3.49 (1 H, H-3^B), 3.50 (s, 3 H, OMe), 3.51 (s, 3 H, OMe), 3.51 (1 H, H-3^D), 3.52 (s, 3 H, OMe), 3.57 (s, 3 H, OMe), 3.58 (1 H, H-4^B), 3.61 (1 H, H-3^F), 3.62 (s, 3 H, OMe), 3.63 (1 H, H-3^A), 3.64 (1 H, H-$6a^E$), 3.65 (s, 6 H, OMe), 3.66 (s, 3 H, OMe), 3.67 (1 H, H-4^E), 3.69 (1 H, H-4^A), 3.73 (s, 3 H, OMe), 3.74 (1 H, H-3^E), 3.74 (1 H, H-5^E), 3.75 (1 H, H-4^C), 3.77 (1 H, H-$6b^C$), 3.78 (s, 3 H, OMe), 3.84 (1 H, H-$6a^D$), 3.85 (1 H, H-4^F), 3.86 (1 H, H-5^F), 3.91 (dd, 1 H, $^2J_{H\text{-}6b,H\text{-}6a}$ = 10.8 Hz, $^3J_{H\text{-}6b,H\text{-}5}$ = 3.2 Hz, H-$6b^E$), 4.06 (m, 1 H, H-5^D), 4.13 (m, 1 H, H-$6b^D$), 4.18 (dd, 1 H, $^2J_{H\text{-}6b,H\text{-}6a}$ = 11.4 Hz, $^3J_{H\text{-}6b,H\text{-}5}$ = 3.2 Hz, H-$6b^F$), 4.58 (dd, 1 H, $^3J_{H\text{-}5,H\text{-}6}$ = 6.9 Hz, $^3J_{H\text{-}5,H\text{-}4}$ = 10.2 Hz, H-5^A), 4.86 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1^C), 4.89 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.4 Hz, H-1^D), 5.05 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1^F), 5.06 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1^A), 5.18 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.6 Hz, H-1^B), 5.22 (d, 1 H, $^3J_{H\text{-}1,H\text{-}2}$ = 3.6 Hz, H-1^E), 5.74 (dd, 1 H, $^3J_{N\text{-}H,H6a}$ = 4.2 Hz, $^3J_{N\text{-}H,H6b}$ = 11.9 Hz, NH), 7.38 (t, 1 H, $^3J_{Hb,Ha}$ = $^3J_{Hb,Hc}$ = 7.7 Hz, H^b), 7.49 (t, 1 H, $^3J_{Hb,Ha}$ = $^3J_{Hb,Hc}$ = 7.7 Hz, $H^{b'}$), 7.47 (d, 1 H, $^3J_{Hc,Hb}$ = 7.7 Hz, H^c), 7.60

(d, 1 H, $^{3}J_{Ha,Hb}$ = 7.7 Hz, H^{a}), 7.80 (d, 1 H, $^{3}J_{Hc,Hb}$ = 7.7 Hz, H$^{c'}$), 7.98 (d, 1 H, $^{3}J_{H\text{-}6,H\text{-}5}$ = 6.9 Hz, H-6^{A}), 8.01 (d, 1 H, $^{3}J_{Ha,Hb}$ = 7.7 Hz, H$^{a'}$) ppm; $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 47.28 (C-6^{D}), 57.51, 57.66 [×2], 57.84, 58.30, 58.77, 59.01, 59.14 [×2], 59.71, 61.20, 61.34, 61.68, 61.89, 61.92, 62.13 (OMe), 70.27 (C-6), 70.41 (C-5), 70.57, 70.81, 71.16 (C-6), 71.23, 71.44, 71.54, 74.90, 75.30 (C-5), 80.30, 80.79, 80.96, 81.14, 81.25 [×2], 81.43 [×2], 81.63, 81.79 [×2], 81.90, 82.30, 82.59, 82.64, 82.69, 82.86 [×2] (C-2, C-3, C-4), 96.84, 97.69, 99.25, 99.45, 100.09, 100.13 (C-1), 119.04 (C-*quat*), 119.38, 123.01, 124.26, 126.79 (CH-*arom*), 127.09 (C-*quat*), 128.00 (CH-*arom*), 128.44 (C-*quat*), 129.71 (CH-*arom*), 131.42, 134.75 (C-*quat*), 144.41 (C-6^{A}, iminic C), 149.02 (C-*quat*) ppm; IR: 1564 (s, C=N) cm^{-1}; elemental analysis (%) calcd for $C_{64}H_{96}N_2O_{28}$•C_5H_{12} (1341.44 + 72.15): C 58.63, H 7.70, N 1.98, found: C 58.42, H 7.55, N 1.68; MS (ESI-TOF): *m/z* (%): 1341.61 (100) $[M + H]^{+}$.



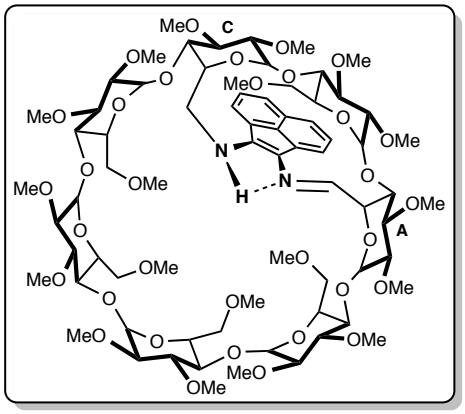
4b: 4b (violet solid, 0.358 g, 54%) was synthesised from **3b** (0.600 g, 0.43 mmol), acenaphthenequinone (0.078 g, 0.43 mmol), and glacial acetic acid (3 μL, 0.003 g, 0.06 mmol) according to the procedure used for preparing **4a**. R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.62; m.p. >250 °C; ^{1}H NMR (400.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY, TOCSY, HSQC, and ROESY) = 1.89 (d, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 12.2 Hz, H-6a^{C}), 2.53 (s, 3 H, OMe-6^{C}), 2.96 (s, 3 H, OMe-6^{B}), 3.02 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.2 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.8 Hz, H-2^{C}), 3.11 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 4.1 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.9 Hz, H-2^{B}), 3.17 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.3 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 10.6 Hz, H-2^{G}), 3.19 (1 H, H-2^{F}), 3.20 (s, 3 H, OMe-6^{E}), 3.20 (1 H, H-6b^{C}), 3.21 (1 H, H-2^{E}), 3.25 (1 H, H-2^{D}), 3.27 (3 H, H-6a^{B}, H-6^{F}), 3.28 (1 H, H-2^{A}), 3.32 (s, 3 H, OMe-6^{F}), 3.34 (1 H, H-3^{C}), 3.35 (s, 3 H, OMe-6^{G}), 3.37 (1 H, H-5^{C}), 3.40 (s, 3 H, OMe), 3.41 (1 H, H-3^{B}), 3.44 (s, 3 H, OMe), 3.45 (1 H, H-6a^{E}), 3.46 (1 H, H-4^{D}), 3.48 (1 H, H-4^{E}), 3.49 (s, 3 H, OMe), 3.50 (1 H, H-3^{F}), 3.51 (s, 3 H, OMe), 3.51 (1 H, H-4^{F}), 3.52 (1 H, H-4^{B}), 3.53 (s, 3 H, OMe), 3.54 (1 H, H-3^{D}), 3.55 (2 H, H-3^{G}, H-5^{E}), 3.56 (s, 3 H, OMe), 3.57 (1 H, H-6a^{G}), 3.58 (s, 6 H, OMe), 3.59 (1 H, H-3^{E}), 3.60 (1 H, H-5^{G}), 3.63 (s, 3 H, OMe), 3.66 (s, 6 H, OMe), 3.67 (s, 3 H, OMe), 3.69 (1 H, H-4^{G}), 3.71 (s, 3 H, OMe), 3.72 (s, 3 H, OMe), 3.74 (1 H, H-4^{C}), 3.76 (1 H, H-3^{A}), 3.78 (2 H, H-4^{A}, H-6b^{B}), 3.79 (1 H, H-5^{C}), 3.82 (1 H, H-5^{F}), 3.92 (2 H, H-6a^{D}, H-6b^{E}), 3.96 (1 H, H-6b^{G}), 4.04 (1 H, H-6b^{D}), 4.14 (t, 1 H, $^{3}J_{H\text{-}5,H\text{-}4}$ = $^{3}J_{H\text{-}5,H\text{-}6}$ = 9.7 Hz, H-5^{D}), 4.43 (dd, $^{3}J_{H\text{-}5,H\text{-}4}$ = 8.7 Hz, $^{3}J_{H\text{-}5,H\text{-}6}$ = 7.0 Hz, H-5^{A}), 4.78 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.6 Hz, H-1^{D}), 4.85 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1^{C}), 5.02 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1^{F}), 5.06 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.1 Hz, H-1^{A}), 5.12 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1^{G}), 5.45 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 4.1 Hz,

H-1^{B}), 5.46 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 4.2 Hz, H-1^{E}), 6.04 (dd, 1 H, $^{3}J_{NH,H\text{-}6a}$ = 9.7 Hz, $^{3}J_{NH,H\text{-}6b}$ = 6.4 Hz, NH), 7.37 (t, 1 H, $^{3}J_{Hb,Ha}$ = $^{3}J_{Hb,Hc}$ = 7.7 Hz, H^{b}), 7.45 (d, 1 H, $^{3}J_{Hc,Hb}$ = 7.7 Hz, H^{c}), 7.49 (t, 1 H, $^{3}J_{Hb',Ha'}$ = $^{3}J_{Hb',Hc'}$ = 7.5 Hz, H$^{b'}$), 7.59 (d, 1 H, $^{3}J_{Ha,Hb}$ = 7.7 Hz, H^{a}), 7.78 (d, 1 H, $^{3}J_{Hc',Hb'}$ = 7.5 Hz, H$^{c'}$), 7.99 (d, 1 H, $^{3}J_{H\text{-}6,H\text{-}5}$ = 7.1 Hz, H-6^{A}), 8.09 (d, 1 H, $^{3}J_{Ha',Hb'}$ = 7.5 Hz, H$^{a'}$) ppm; $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 46.09 (C-6^{D}), 57.87, 57.99, 56.01, 58.10, 58.40, 58.65, 58.80, 58.88, 59.10, 59.27, 60.21, 60.28, 60.82, 60.86, 61.61, 61.67, 62.00, 62.06 [×2] (OMe), 70.21 (C-5), 70.36 (C-6), 70.82 (C-5), 71.00 [×2] (C-6), 71.05 (C-5), 71.37 (C-6), 71.48 [×2] (C-5), 71.61 (C-6), 74.33, 75.14 (C-5), 78.65, 78.80, 80.45, 80.66, 81.19, 81.40, 81.60 [×3], 81.66 [×3], 81.72, 82.09, 82.23 [×2], 82.36, 82.54, 82.98, 83.17, 83.30 (C-2, C-3, C-4), 95.02, 98.45, 98.58 [×2], 99.23 [×2], 100.10 (C-1), 118.78 (C-*quat*), 119.10 (CH-*arom*), 119.24 (C-*quat*), 122.81, 125.67, 126.79, 127.24, 127.92 (CH-*arom*), 128.36, 129.51, 134.99 (C-*quat*), 146.66 (C-6^{A}, iminic C), 149.48 (C-*quat*) ppm; elemental analysis (%) calcd for $C_{73}H_{112}N_2O_{33}$•$2H_2O$ (1341.44 + 36.02): C 55.43, H 7.39, N 1.77, found: C 55.51, H 7.33, N 1.49; MS (ESI-TOF): *m/z* (%): 1567.69 (100) [*M* + Na]$^{+}$.



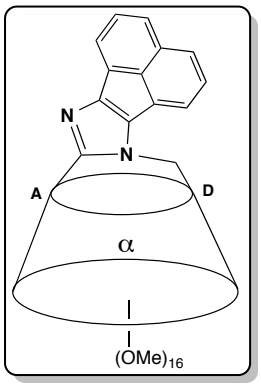
4c: **4c** (violet solid, 0.358 g, 54%) was synthesised from **3c** (0.565 g, 0.47 mmol), acenaphthenequinone (0.086 g, 0.47 mmol), and glacial acetic acid (3 μL, 0.003 g, 0.06 mmol) according to the procedure used for preparing **4a**. R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.61; m.p. >250 °C; ^{1}H NMR (500.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY, TOCSY, HSQC, and ROESY) = 2.31 (s, 3 H, OMe-6^{B}), 2.44 (d, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 11.4 Hz, H-6a^{B}), 3.04 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 4.0 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 10.1 Hz, H-2^{B}), 3.08 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.5 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.8 Hz, H-2^{C}), 3.14 (t, 1 H, $^{3}J_{H\text{-}4,H\text{-}3}$ = $^{3}J_{H\text{-}4,H\text{-}5}$ = 8.7 Hz, H-4^{C}), 3.18 (1 H, H-2^{D}), 3.19 (1 H, H-2^{F}), 3.19 (1 H, H-6b^{B}), 3.20 (1 H, H-2^{E}), 3.25 (s, 3 H, OMe-6^{F}), 3.30 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.6 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.9 Hz, H-2^{A}), 3.32 (s, 3 H, OMe-6^{D}), 3.36 (s, 3 H, OMe), 3.40 (s, 3 H, OMe-6^{E}), 3.44 (1 H, H-3^{C}), 3.49 (s, 3 H, OMe), 3.50 (s, 3 H, OMe), 3.51 (s, 3 H, OMe), 3.52 (s, 3 H, OMe), 3.53 (s, 3 H, OMe), 3.54 (1 H, H-6a^{F}), 3.56 (s, 3 H, OMe), 3.57 (1 H, H-3^{B}), 3.61 (1 H, H-3^{E}), 3.62 (1 H, H-4^{A}), 3.64 (s, 3 H, OMe), 3.64 (2 H, H-4^{E}, H-6a^{D}), 3.65 (2 H, H-3^{D,F}), 3.66 (1 H, H-5^{B}), 3.67 (s, 3 H, OMe), 3.67 (1 H, H-4^{F}), 3.68 (2 H, H-3^{A}, H-4^{D}), 3.71 (s, 3 H, OMe), 3.73 (1 H, H-6a^{E}), 3.74 (s, 6 H, OMe), 3.80 (2 H, H-4^{B}, H-5^{F}), 3.82 (1 H, H-6b^{D}), 3.86 (2 H, H-5^{D}, H-6b^{E}), 3.92 (1 H, H-5^{C}), 3.94 (H-6a^{C}), 3.95 (1 H, H-5^{E}), 4.01 (1 H, H-6b^{F}), 4.02 (1 H, H-6b^{C}), 4.50 (dd, 1 H, $^{3}J_{H\text{-}5,H\text{-}4}$ = 9.6 Hz, $^{3}J_{H\text{-}5,H\text{-}6}$ = 7.2 Hz, H-5^{A}), 4.61 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.5 Hz, H-1^{C}), 5.05 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.2 Hz, H-1^{E}), 5.08 (1 H, H-1^{A}), 5.09 (1 H, H-1^{F}), 5.10 (1 H, H-1^{B}), 5.11 (1 H, H-1^{D}), 5.17 (br. d, 1 H, $^{3}J_{N\text{-}H,H6a}$ = $^{3}J_{N\text{-}H,H6b}$ = 10.8 Hz, NH), 7.39 (m, 1 H, H^{b}), 7.48 (d, 1 H, $^{3}J_{Hc,Hb}$ = 8.7 Hz, H^{c}), 7.52 (t, 1 H, $^{3}J_{Hb',Ha'}$ = $^{3}J_{Hb',Hc'}$ = 7.7 Hz, H$^{b'}$), 7.58 (d, 1 H, $^{3}J_{Ha,Hb}$ = 7.0 Hz, H^{a}), 7.76 (d, 1 H, $^{3}J_{Hc',Ha'}$ = 7.7 Hz, H$^{c'}$),

7.83 (d, 1 H, $^{3}J_{Ha',Hb'}$ = 7.7 Hz, H$^{a'}$), 8.02 (d, 1 H, $^{3}J_{H\text{-}6,H\text{-}5}$ = 7.2 Hz, H-6^{A}) ppm; $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 48.30 (C-6^{C}), 57.47, 57.62, 57.73 [×2], 58.08, 58.78, 59.83, 58.84, 59.04, 59.34, 61.27 [×2], 61.42, 61.67, 61.90, 62.00 (OMe), 70.14 (C-5), 70.64, 70.83 (C-6), 70.96 (C-5), 71.02, 71.20 (C-6), 71.23, 71.30 (C-5), 75.13 (C-5^{A}), 75.19 (C-5^{C}), 79.32, 80.79, 81.34, 81.41, 81.54, 81.59, 81.63 [×2], 81.88, 82.01, 82.09, 82.12, 82.24 [×2], 82.43, 82.54, 82.95, 83.37 (C-2, C-3, C-4), 95.20, 99.04, 99.13 , 99.92, 100.13, 100.31 (C-1), 119.31 (CH-*arom*), 121.51 (C-*quat*), 123.29, 123.69, 126.91 (CH-*arom*), 127.00 (C-*quat*), 127.99 (CH-*arom*), 128.58 (C-*quat*), 129.02 (CH-*arom*), 132.07, 135.10 (C-*quat*), 147.09 (C-6^{A}, iminic C), 150.67 (C-*quat*) ppm; elemental analysis (%) calcd for $C_{64}H_{96}N_2O_{28}$•C_5H_{12} (1341.44 + 72.15): C 58.63, H 7.70, N 1.98, found: C 58.42, H 7.55, N 1.68; MS (ESI-TOF): *m/z* (%): 1363.60 (100) $[M + Na]^{+}$.



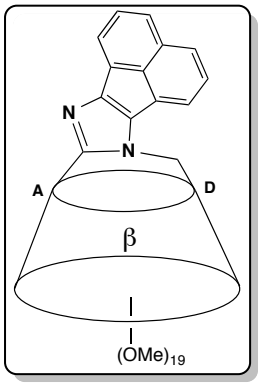
4d: 4d (violet solid, 0.494 g, 56%) was synthesised from **3d** (0.805 g, 0.58 mmol), acenaphthenequinone (0.105 g, 0.58 mmol), and glacial acetic acid (3 μL, 0.003 g, 0.06 mmol) according to the procedure used for preparing **4a**. R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.62; m.p. >250 °C; ^{1}H NMR (500.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY, TOCSY, HSQC, and ROESY) = 2.35 (s, 3 H, OMe-6^{B}), 2.53 (d, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 11.8 Hz, H-6a^{B}), 3.06 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 4.3 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.9 Hz, H-2^{B}), 3.07 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.8 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 10.0 Hz, H-2^{C}), 3.18 (1 H, H-6b^{B}), 3.19 (1 H, H-2^{G}), 3.20 (2 H, H-2^{E,F}), 3.23 (1 H, H-4^{C}), 3.25 (1 H, H-2^{D}), 3.26 (s, 3 H, OMe), 3.27 (1 H, H-2^{A}), 3.32 (s, 3 H, OMe-6^{F}), 3.36 (s, 3 H, OMe-6^{D}), 3.37 (s, 3 H, OMe), 3.39 (1 H, H-3^{C}), 3.44 (s, 3 H, OMe-6^{G}), 3.45 (1 H, H-3^{B}), 3.46 (1 H, H-3^{G}), 3.48 (1 H, H-3^{F}), 3.49 (s, 3 H, OMe), 3.50 (1 H, H-6a^{F}), 3.51 (s, 3 H, OMe-6^{E}), 3.52 (s, 3 H, OMe), 3.53 (s, 3 H, OMe), 3.53 (1 H, H-3^{E}), 3.54 (s, 3 H, OMe), 3.55 (1 H, H-6a^{E}), 3.57 (s, 3 H, OMe), 3.59 (s, 3 H, OMe), 3.60 (1 H, H-4^{A}), 3.61 (1 H, H-4^{D}), 3.62 (2 H, H-3^{D}, H-4^{G}), 3.63 (s, 3 H, OMe), 3.63 (2 H, H-4^{F}, H-6a^{D}), 3.64 (s, 6 H, OMe), 3.65 (1 H, H-5^{B}), 3.66 (s, 3 H, OMe), 3.67 (1 H, H-4^{E}), 3.69 (3 H, H-3^{A}, H-6^{G}), 3.71 (s, 3 H, OMe), 3.74 (1 H, H-5^{G}), 3.75 (s, 3 H, OMe), 3.76 (1 H, H-4^{B}), 3.81 (1 H, H-5^{F}), 3.85 (1 H, H-6b^{E}), 3.91 (2 H, H-5^{C}, H-6b^{F}), 3.92 (1 H, H-5^{E}), 3.96 (dd, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 14.0 Hz, $^{3}J_{H\text{-}6a,NH}$ = 11.7 Hz, H-6a^{C}), 3.97 (1 H, H-6b^{D}), 4.04 (m, 1 H, H-5^{D}), 4.30 (dd, 1 H, $^{2}J_{H\text{-}6b,H\text{-}6a}$ = 14.0 Hz, $^{3}J_{H\text{-}6b,NH}$ = 1.7 Hz, H-6b^{C}), 4.39 (dd, 1 H, $^{3}J_{H\text{-}5,H\text{-}4}$ = 9.8 Hz, $^{3}J_{H\text{-}5,H\text{-}6}$ = 7.0 Hz, H-5^{A}), 4.64 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.8 Hz, H-1^{C}), 5.06 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.5 Hz, H-1^{F}), 5.07 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.5 Hz, H-1^{G}), 5.12 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.6 Hz, H-1^{D}), 5.13 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1^{A}), 5.16 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 4.3 Hz, H-1^{B}), 5.29 (dd, 1 H, $^{3}J_{NH,H\text{-}6a}$ = 11.7 Hz, $^{3}J_{NH,H\text{-}6b}$ = 1.7

Hz, NH), 5.39 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.4 Hz, H-1^{E}), 7.34 (dd, 1 H, $^{3}J_{Hb,Ha}$ = 7.0 Hz, $^{3}J_{Hb,Hc}$ = 8.2 Hz, H^{b}), 7.44 (d, 1 H, $^{3}J_{Hc,Hb}$ = 8.2 Hz, H^{c}), 7.47 (dd, 1 H, $^{3}J_{Hb',Ha'}$ = 7.4 Hz, $^{3}J_{Hb',Hc'}$ = 8.2 Hz, H$^{b'}$), 7.53 (d, 1 H, $^{3}J_{Ha,Hb}$ = 7.0 Hz, H^{a}), 7.74 (d, 1 H, $^{3}J_{Hc',Hb'}$ = 8.2 Hz, H$^{c'}$), 7.83 (d, 1 H, $^{3}J_{Ha',Hb'}$ = 7.4 Hz, H$^{a'}$), 7.99 (d, 1 H, $^{3}J_{H\text{-}6,H\text{-}5}$ = 7.0 Hz, H-6^{A}) ppm; $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$, 25ºC): δ (assignment by HSQC) = 46.93 (C-6^{C}), 57.77, 57.93 [×2], 58.24 [×2], 58.37, 58.87, 58.98, 59.03, 59.19, 59.50, 59.95, 60.76, 61.00, 61.60, 61.62, 61.77, 61.79, 61.87 (OMe), 69.56, 70.37 (C-5), 70.91, 71.00, 71.02, 71.10 (C-6), 71.16, 71.23, 71.39 (C-5), 72.22 (C-6), 73.46, 74.81 (C-5), 77.04, 78.50, 79.96, 80.57, 81.04, 81.45, 81.59, 81.66, 81.72, 81.78 [×3], 82.09, 82.16, 82.25 [×2], 82.31, 82.53, 82.70, 83.33, 83.86 (C-2, C-3, C-4), 94.08, 98.31, 99.12, 99.22, 99.41, 99.59, 100.04 (C-1), 118.79 (CH-*arom*), 120.46 (C-*quat*), 122.91, 124.16, 126.83 (CH-*arom*), 127.01 (C-*quat*), 127.92 (CH-*arom*), 128.42 (C-*quat*), 128.86 (CH-*arom*), 132.40, 135.41 (C-*quat*), 148.28 (C-6^{A}, iminic C), 149.95 (C-*quat*) ppm; IR: 1562 (s, C=N) cm^{-1}; elemental analysis (%) calcd for $C_{73}H_{112}N_2O_{33}$•0.5C_7H_8 (1341.44 + 46.07): C 57.72, H 7.35, N 1.75, found: C 57.88, H 7.25, N 1.45; MS (ESI-TOF): *m/z* (%): 1567.69 (100) $[M + Na]^{+}$.



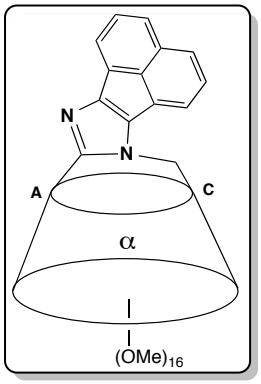
5a: Powdered 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.067 g, 0.30 mmol) was added to a solution of **4a** (0.330 g, 0.25 mmol) in CH_2Cl_2 (15 mL). After 5 min, the deep brown mixture was quenched with MeOH (10 mL) before being evaporated to dryness under vacuum. The residue was subjected to column chromatography (SiO_2; CH_2Cl_2/MeOH, 96:4, *v/v*) to afford **5a (**0.280 g, 85%) as a yellow powder. R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v/v*) = 0.61; m.p. >250°C; ^{1}H NMR (500.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY, TOCSY, HSQC, and ROESY) = 1.71 (dd, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 11.5 Hz, $^{3}J_{H\text{-}6a,H\text{-}5}$ = 1.9 Hz, H-6a^{C}), 2.28 (dd, 1 H, $^{2}J_{H\text{-}6b,H\text{-}6a}$ = 11.5 Hz, $^{3}J_{H\text{-}6b,H\text{-}5}$ = 1.6 Hz, H-6b^{C}), 2.37 (s, 3 H, OMe-6^{C}), 2.92 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 2.7 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.1 Hz, H-2^{C}), 3.05 (1 H, H-5^{C}), 3.06 (1 H, H-5^{B}), 3.08 (s, 3 H, OMe-6^{F}), 3.13 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 2.7 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.8 Hz, H-2^{F}), 3.14 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.5 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.5 Hz, H-2^{B}), 3.22 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.1 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.7 Hz, H-2^{D}), 3.26 (s, 3 H, OMe), 3.34 (1 H, H-3^{B}), 3.35 (s, 3 H, OMe-6^{B}), 3.42 (s, 3 H, OMe), 3.45 (1 H, H-2^{E}), 3.46 (2 H, H-2^{A}, H-6a^{B}), 3.47 (s, 6 H, OMe, OMe-6^{E}), 3.48 (s, 3 H, OMe), 3.50 (s, 3 H, OMe), 3.51 (1 H, H-3^{C}), 3.51 (s, 3 H, OMe), 3.52 (1 H, H-6a^{F}), 3.54 (s, 3 H, OMe), 3.56 (s, 3 H, OMe), 3.60 (s, 3 H, OMe), 3.61 (1 H, H-6b^{B}), 3.62 (s, 3 H, OMe), 3.63 (1 H, H-6a^{E}), 3.64 (1 H, H-4^{F}), 3.65 (1 H, H-4^{B}), 3.66 (1 H, H-3^{D}), 3.68 (1 H, H-4^{C}), 3.70 (s, 3 H, OMe), 3.72 (s, 3 H, OMe), 3.74 (1 H, H-4^{D}), 3.77 (1 H, H-4^{E}), 3.78 (1 H, H-3^{F}), 3.81 (dd, 1 H, $^{2}J_{H\text{-}6b,H\text{-}6a}$ = 10.7 Hz, $^{3}J_{H\text{-}6b,H\text{-}5}$ = 7.3 Hz, H-6b^{E}), 3.84 (t, 1 H, $^{3}J_{H\text{-}3,H\text{-}2}$ = $^{3}J_{H\text{-}3,H\text{-}4}$ = 9.4 Hz, H-

3^{A}), 3.86 (dd, 1 H, $^{2}J_{H\text{-}6b,H\text{-}6a}$ = 10.2 Hz, $^{3}J_{H\text{-}6b,H\text{-}5}$ = 3.2 Hz, H-6b^{F}), 3.94 (m, 1 H, H-3^{E}), 3.99 (br. t, 1 H, $^{3}J_{H\text{-}5,H\text{-}4}$ = $^{3}J_{H\text{-}5,H\text{-}6a}$ = 9.8 Hz, H-5^{D}), 4.12 (dd, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 14.9 Hz, $^{3}J_{H\text{-}6a,H\text{-}5}$ = 9.8 Hz, H-6a^{D}), 4.69 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.1 Hz, H-1^{D}), 4.74 (dt, 1 H, $^{3}J_{H\text{-}5,H\text{-}4}$ = 9.3 Hz, $^{3}J_{H\text{-}5,H\text{-}6a}$ = $^{3}J_{H\text{-}5,H\text{-}6b}$ = 3.2 Hz, H-5^{F}), 4.81 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 2.7 Hz, H-1^{C}), 4.82 (1 H, H-6b^{D}), 4.83 (1 H, H-4^{A}), 4.91 (t, 1 H, $^{3}J_{H\text{-}5,H\text{-}4}$ = $^{3}J_{H\text{-}5,H\text{-}6a}$ = 7.3 Hz, H-5^{E}), 4.93 (d, 1 H, $^{3}J_{H\text{-}5,H\text{-}4}$ = 9.3 Hz, H-5^{A}), 4.96 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.4 Hz, H-1^{A}), 5.04 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 2.7 Hz, H-1^{F}), 5.39 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 1.2 Hz, H-1^{E}), 5.74 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.5 Hz, H-1^{B}), 7.51 (dd, 1 H, $^{3}J_{Hb,Ha}$ = 6.8 Hz, $^{3}J_{Hb,Hc}$ = 8.2 Hz, H^{b}), 7.52 (dd, 1 H, $^{3}J_{Hb',Ha'}$ = 6.8 Hz, $^{3}J_{Hb',Hc'}$ = 8.2 Hz, H$^{b'}$), 7.66 (d, 1 H, $^{3}J_{Hc,Hb}$ = 8.2 Hz, H^{c}), 7.70 (d, 1 H, $^{3}J_{Hc',Hb'}$ = 8.2 Hz, H$^{c'}$), 7.76 (d, 1 H, $^{3}J_{Ha,Hb}$ = 6.8 Hz, H^{a}), 7.85 (d, 1 H, $^{3}J_{Ha',Hb'}$ = 6.8 Hz, H$^{a'}$) ppm; $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$, 25ºC): δ (assignment by combined HSQC and HMBC) = 48.77 (C-6^{D}), 58.53, 58.58, 59.07, 59.27, 59.28, 59.86, 59.96, 59.99, 60.13, 60.41, 60.75, 61.24, 61.26, 61.65, 62.13, 63.02 (OMe), 66.35 (C-5^{A}), 70.76 (C-6), 71.71 (C-5^{B}), 71.91, 72.04, 72.10 (C-6), 72.40 (C-5^{F}), 73.72 (C-5^{C}), 74.22 (C-4^{E}), 74.87 (C-4^{A}), 75.12 (C-4^{D}), 75.46 (C-5^{D}), 75.58 (C-5^{E}), 77.02, 78.95, 80.31, 81.44, 81.54, 81.94, 82.57, 82.91, 82.99, 83.19, 83.40, 83.72, 83.89, 83.95, 84.64 (C-2, C-3, C-4), 94.83, 97.49, 97.56, 97.85, 97.87, 100.48 (C-1), 121.41, 121.91, 127.14, 127.64, 128.02, 128.79, (CH-*arom*), 130.36, 130.72, 131.70, 133.06, 140.66, 148.41 (C-*quat*), 150.05 (C-6^{A}) ppm; IR: 1500 (vw, C=N) cm^{-1}; elemental analysis (%) calcd for $C_{64}H_{94}N_2O_{28}$•$3CH_2Cl_2$ (1339.44 + 254.79): C 50.48, H 6.32, N 1.76, found: C 50.38, H 6.34, N 1.63; MS (ESI-TOF): *m/z* (%): 1339.60 (100) $[M + H]^{+}$.



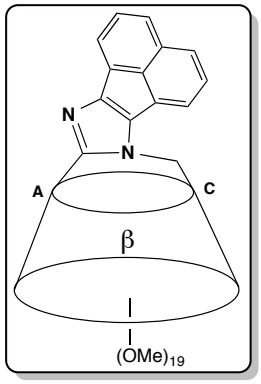
5b: 5b (yellow solid, 0.068 g, 85%) was synthesised from **4b** (0.080 g, 0.05 mmol) and DDQ (0.014 g, 0.06 mmol) according to the procedure used for preparing **5a**. R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.62; m.p. >250°C; ^{1}H NMR (500.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY, TOCSY, HSQC, and ROESY) = 1.92 (s, 3 H, OMe-6^{C}), 2.05 (br. d, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 11.6 Hz, H-6a^{C}), 2.53 (br. d, 1 H, $^{2}J_{H\text{-}6b,H\text{-}6a}$ = 11.6 Hz, H-6b^{C}), 2.65 (s, 3 H, OMe-6^{G}), 2.93 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 2.6 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 8.9 Hz, H-2^{G}), 3.12 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 2.9 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.4 Hz, H-2^{C}), 3.17 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.0 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.4 Hz, H-2^{F}), 3.21 (dd, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 10.3 Hz, $^{3}J_{H\text{-}6a,H\text{-}5}$ = 3.9 Hz, H-6a^{G}), 3.25 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 2.9 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 7.1 Hz, H-2^{B}), 3.28 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.2 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.5 Hz, H-2^{D}), 3.33 (s, 3 H, OMe-6^{F}), 3.35 (s, 3 H, OMe-6^{E}), 3.36 (s, 3 H, OMe-6^{B}), 3.37 (1 H, H-5^{C}), 3.38 (1 H, H-6b^{G}), 3.40 (s, 3 H, OMe), 3.42 (s, 3 H, OMe), 3.44 (s, 3 H, OMe), 3.45 (1 H, H-2^{E}), 3.48 (1 H, H-4^{G}), 3.49 (s, 3 H, OMe), 3.50 (1 H, H-3^{G}), 3.51 (s, 3 H, OMe), 3.52 (1 H, H-4^{C}), 3.53 (s, 3 H, OMe), 3.54 (s, 3 H, OMe), 3.54 (1 H, H-3^{C}), 3.55 (s, 3 H, OMe), 3.56 (1 H,

H-2^{A}), 3.57 (s, 6 H, OMe), 3.58 (s, 3 H, OMe), 3.59 (s, 3 H, OMe), 3.60 (2 H, H-3^{B}, H-6a^{F}), 3.62 (1 H, H-3^{F}), 3.63 (2 H, H-6a^{B}, H-6a^{E}), 3.64 (1 H, H-3^{A}), 3.65 (2 H, H-3^{D}, H-4^{D}), 3.66 (s, 3 H, OMe), 3.69 (1 H, H-4^{F}), 3.71 (1 H, H-6b^{B}), 3.72 (s, 3 H, OMe), 3.73 (1 H, H-6b^{E}), 3.79 (1 H, H-5^{E}), 3.85 (1 H, H-3^{E}), 3.87 (1 H, H-5^{G}), 3.88 (2 H, H-4^{B}, H-6b^{F}), 3.98 (t, 1 H, $^{3}J_{H\text{-}5,H\text{-}4} = {}^{3}J_{H\text{-}5,H\text{-}6} = 8.9$ Hz, H-5^{D}), 4.17 (1 H, H-6a^{D}), 4.18 (1 H, H-5^{F}), 4.21 (m, 1 H, H-5^{B}), 4.57 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2} = 3.2$ Hz, H-1^{D}), 4.60 (m, 1 H, H-4^{E}), 4.70 (t, 1 H, $^{3}J_{H\text{-}4,H\text{-}3} = {}^{3}J_{H\text{-}4,H\text{-}5} = 8.5$ Hz, H-4^{A}), 4.83 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2} = 2.6$ Hz, H-1^{G}), 4.85 (1 H, H-6b^{D}), 4.92 (d, 1 H, $^{3}J_{H\text{-}5,H\text{-}4} = 8.5$ Hz, H-5^{A}), 4.98 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2} = 2.9$ Hz, H-1^{C}), 4.99 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2} = 3.0$ Hz, H-1^{F}), 5.01 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2} = 3.5$ Hz, H-1^{A}), 5.48 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2} = 2.9$ Hz, H-1^{B}), 5.52 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2} = 2.2$ Hz, H-1^{E}), 7.47 (dd, 1 H, $^{3}J_{Hb',Ha'} = 7.0$ Hz, $^{3}J_{Hb',Hc'} = 8.2$ Hz, H$^{b'}$), 7.48 (dd, 1 H, $^{3}J_{Hb,Ha} = 7.0$ Hz, $^{3}J_{Hb,Hc} = 8.2$ Hz, H^{b}), 7.61 (d, 1 H, $^{3}J_{Hc,Hb} = 8.2$ Hz, H^{c}), 7.65 (d, 1 H, $^{3}J_{Hc',Hb'} = 8.2$ Hz, H$^{c'}$), 7.68 (d, 1 H, $^{3}J_{Ha',Hb'} = 7.0$ Hz, H$^{a'}$), 7.83 (d, 1 H, $^{3}J_{Ha,Hb} = 7.0$ Hz, H^{a}) ppm; $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$, 25ºC): δ (assignment by combined HSQC and HMBC) = 48.05 (C-6^{D}), 57.46, 57.62, 58.06, 58.09, 58.34, 58.66, 58.76, 58.79, 58.98, 59.04, 59.15, 59.35, 59.41, 59.43, 59.95, 60.08, 61.03, 61.21, 61.41 (OMe), 66.61 (C-5^{A}), 70.06, 70.68, 70.83 (C-6), 71.34, 71.57 (C-5), 71.68, 71.90 (C-6), 72.21, 72.34, 72.64, 73.17 (C-5), 74.42, 74.74, 76.44, 76.61, 77.38, 79.10, 79.97, 80.79, 81.26 [×2], 81.52, 81.57, 81.60, 81.83, 82.03, 82.14, 82.80, 82.86, 82.99, 83.02, 83.17 (C-2, C-3, C-4), 93.15, 95.18, 96.51, 97.38, 97.65, 98.24, 100.23 (C-1), 120.47 [×2], 126.11, 126.57, 127.10, 127.88 (CH-*arom*), 129.27, 129.83, 130.98, 132.02, 140.03, 147.02 (C-*quat*), 148.96 (C-6^{A}) ppm; elemental analysis (%) calcd for $C_{73}H_{110}N_2O_{33}$•0.5CH_2Cl_2 (1543.65 + 180.10): C 55.66, H 7.05, N 1.77, found: C 55.38, H 7.11, N 1.60; MS (ESI-TOF): *m/z* (%): 1565.69 (100) $[M + Na]^{+}$.



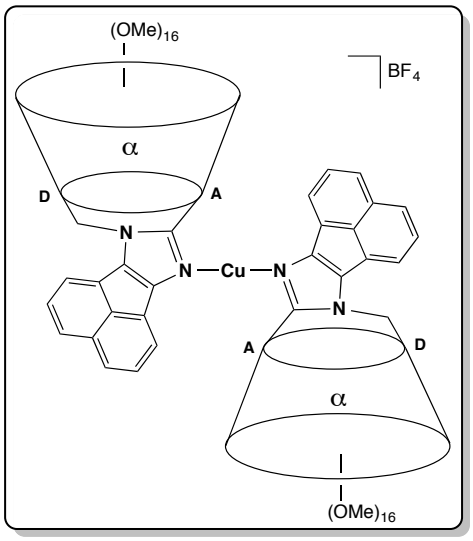
5c: 5c (yellow solid, 0.119 g, 85%) was synthesised from **4c** (0.140 g, 0.10 mmol) and DDQ (0.029 g, 0.125 mmol) according to the procedure used for preparing **5a**. R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v/v*) = 0.61; m.p. >250°C; ^{1}H NMR (500.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY, TOCSY, HSQC, and ROESY) = 2.47 (dd, 1 H, $^{2}J_{H\text{-}6a,H\text{-}6b} = 11.8$ Hz, $^{3}J_{H\text{-}6a,H\text{-}5} = 2.8$ Hz, H-6a^{B}), 2.65 (s, 3 H, OMe-6^{B}), 2.75 (dd, 1 H, $^{2}J_{H\text{-}6b,H\text{-}6a} = 11.8$ Hz, $^{3}J_{H\text{-}6b,H\text{-}5} = 2.3$ Hz, H-6b^{B}), 2.96 (m, 1 H, H-5^{B}), 3.03 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1} = 4.5$ Hz, $^{3}J_{H\text{-}2,H\text{-}3} = 9.1$ Hz, H-2^{C}), 3.06 (s, 3 H, OMe-6^{F}), 3.07 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1} = 3.7$ Hz, $^{3}J_{H\text{-}2,H\text{-}3} = 10.1$ Hz, H-2^{B}), 3.14 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1} = 2.8$ Hz, $^{3}J_{H\text{-}2,H\text{-}3} = 10.0$ Hz, H-2^{E}), 3.20 (dd, 1 H, $^{3}J_{H\text{-}2,H\text{-}1} = 3.7$ Hz, $^{3}J_{H\text{-}2,H\text{-}3} = 9.7$ Hz, H-2^{F}), 3.23 (s, 3 H, OMe-6^{D}), 3.30 (s, 3 H, OMe-6^{E}), 3.32 (s, 3 H, OMe), 3.38 (m, 1 H, H-6a^{F}), 3.46 (s, 3 H, OMe), 3.47 (1 H, H-4^{D}), 3.51 (s, 3 H, OMe), 3.52 (s, 3 H, OMe), 3.53 (s, 3 H, OMe), 3.54 (1 H, H-2^{A}), 3.55 (1 H, H-3^{F}), 3.56 (1 H, H-4^{E}), 3.57 (s, 3 H,

OMe), 3.57 (2 H, H-3^{B,C}), 3.58 (s, 3 H, OMe), 3.58 (1 H, H-6a^{D}), 3.59 (s, 3 H, OMe), 3.60 (1 H, H-2^{D}), 3.65 (s, 3 H, OMe), 3.66 (1 H, H-6a^{E}), 3.67 (s, 3 H, OMe), 3.68 (s, 3 H, OMe), 3.69 (1 H, H-4^{C}), 3.70 (1 H, H-5^{F}), 3.71 (3 H, H-3^{E}, H-4^{F}, H-6b^{F}), 3.72 (s, 3 H, OMe), 3.73 (1 H, H-6b^{D}), 3.75 (1 H, H-6b^{E}), 3.78 (1 H, H-3^{D}), 3.83 (1 H, H-3^{A}), 3.85 (m, 1 H, H-5^{E}), 3.94 (dd, 1 H, $^{3}J_{H\text{-}4,H\text{-}3}$ = 6.2 Hz, $^{3}J_{H\text{-}4,H\text{-}5}$ = 8.0 Hz, H-4^{B}), 4.08 (td, 1 H, $^{3}J_{H\text{-}5,H\text{-}4}$ = $^{3}J_{H\text{-}5,H\text{-}6a}$ = 7.6 Hz, $^{3}J_{H\text{-}5,H\text{-}6b}$ = 1.9 Hz, H-5^{D}), 4.37 (t, 1 H, $^{3}J_{H\text{-}4,H\text{-}3}$ = $^{3}J_{H\text{-}4,H\text{-}5}$ = 9.5 Hz, H-4^{A}), 4.42 (m, 1 H, H-5^{C}), 4.61 (m, 1 H, H-6a^{C}), 4.64 (m, 1 H, H-6b^{C}), 4.65 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 4.5 Hz, H-1^{C}), 4.90 (d, 1 H, $^{3}J_{H\text{-}5,H\text{-}4}$ = 9.5 Hz, H-5^{A}), 4.97 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.7 Hz, H-1^{F}), 5.01 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 2.8 Hz, H-1^{E}), 5.15 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.6 Hz, H-1^{A}), 5.36 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.7 Hz, H-1^{B}), 5.50 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 4.5 Hz, H-1^{D}), 7.48 (1 H, H$^{b'}$), 7.50 (1 H, H^{b}), 7.53 (1 H, H$^{a'}$), 7.66 (d, 1 H, $^{3}J_{Hc,Hb}$ = 8.2 Hz, H^{c}), 7.69 (d, 1 H, $^{3}J_{Hc',Hb'}$ = 8.2 Hz, H$^{c'}$), 7.85 (d, 1 H, $^{3}J_{Ha,Hb}$ = 6.7 Hz, H^{a}) ppm; $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$, 25ºC): δ (assignment by combined HSQC and HMBC) = 47.75 (C-6^{C}), 57.95, 58.20, 58.53, 58.75 [×2], 59.07, 59.12, 59.19, 59.30, 59.41, 59.70, 60.25, 61.09, 61.31, 61.64, 62.28 (OMe), 66.13 (C-5^{A}), 66.95 (C-5^{C}), 67.92 (C-5^{B}), 70.70 (C-6), 71.38, 72.82 (C-5), 72.85 [×2] (C-6), 72.95 (C-5), 73.10 (C-6), 77.44, 78.25, 78.38, 79.59, 79.75, 80.31, 81.31, 81.53, 81.60, 81.78, 81.88, 81.98, 82.55, 82.65, 82.71, 82.95, 83.49, 83.64 (C-2, C-3, C-4), 93.52, 97.99, 98.06, 98.52, 99.01, 99.91 (C-1), 119.40, 120.64, 126.23, 126.61, 127.16, 127.93 (CH-*arom*), 128.38, 129.59, 130.85, 131.97, 140.14, 146.62 (C-*quat*), 148.68 (C-6^{A}) ppm; elemental analysis (%) calcd for $C_{64}H_{94}N_2O_{28}$•CH_2Cl_2 (1339.44 + 84.93): C 54.81, H 6.79, N 1.97, found: C 54.54, H 6.72, N 1.98; MS (ESI-TOF): *m/z* (%): 1361.59 (100) $[M + Na]^+$.



5d: 5d (yellow solid, 0.305 g, 85%) was synthesised from **4d** (0.360 g, 0.23 mmol) and DDQ (0.069 g, 0.30 mmol) according to the procedure used for preparing **5a**. R_f (SiO_2, CH_2Cl_2/MeOH, 90:10, *v*/*v*) = 0.62; m.p. >250°C; ^{1}H NMR (500.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY, TOCSY, HSQC, and ROESY) = 2.53 (1 H, H-6a^{B}), 2.58 (1 H, H-6b^{B}), 2.61 (s, 3 H, OMe-6^{B}), 2.78 (m, 1 H, H-5^{B}), 3.01 (s, 3 H, OMe-6^{D}), 3.02 (1 H, H-2^{B}), 3.10 (1 H, H-2^{F}), 3.12 (1 H, H-2^{C}), 3.15 (1 H, H-6a^{D}), 3.17 (1 H, H-2^{G}), 3.18 (1 H, H-2^{E}), 3.20 (s, 3 H, OMe-6^{E}), 3.27 (s, 3 H, OMe-6^{G}), 3.31 (s, 3 H, OMe), 3.32 (1 H, H-4^{D}), 3.33 (s, 3 H, OMe-6^{F}), 3.34 (1 H, H-6b^{D}), 3.35 (1 H, H-2^{D}), 3.39 (1 H, H-6a^{E}), 3.40 (s, 3 H, OMe), 3.44 (s, 3 H, OMe), 3.47 (1 H, H-3^{F}), 3.49 (s, 3 H, OMe), 3.50 (1 H, H-4^{G}), 3.53 (2 H, H-6a^{F}, H-6a^{G}), 3.54 (s, 3 H, OMe), 3.55 (s, 3 H, OMe), 3.55 (1 H, H-2^{A}), 3.56 (1 H, H-4^{E}), 3.57 (s, 3 H, OMe), 3.57 (1 H, H-3^{B}), 3.58 (s, 3 H, OMe), 3.59 (s, 3 H, OMe), 3.60 (s, 3 H, OMe), 3.61 (1 H, H-3^{G}), 3.66 (s, 3 H, OMe), 3.67 (s, 3 H, OMe), 3.69 (1 H, H-6b^{G}), 3.70 (s, 3 H, OMe), 3.71

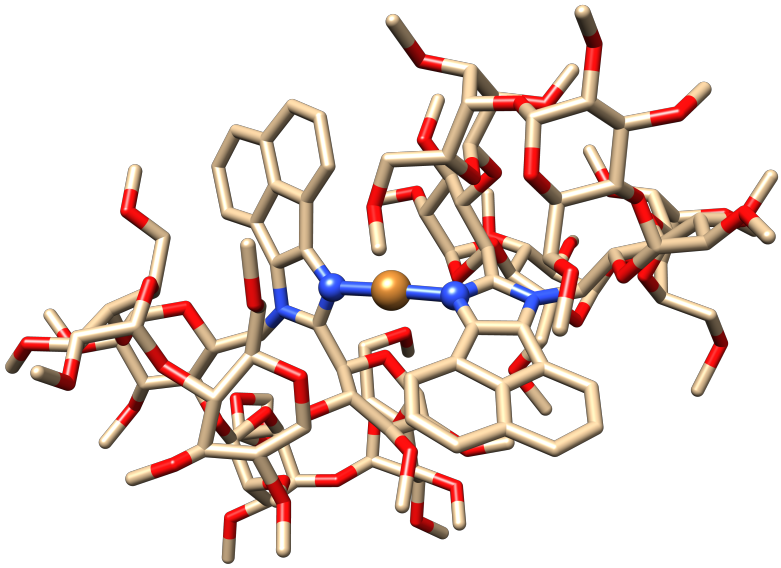
(1 H, H-3^{C}), 3.72 (1 H, H-3^{D}), 3.73 (2 H, H-3^{A}, H-5^{E}), 3.74 (1 H, H-4^{F}), 3.75 (1 H, H-5^{F}), 3.77 (s, 3 H, OMe), 3.79 (1 H, H-3^{E}), 3.80 (2 H, H-6b^{E,F}), 3.81 (2 H, H-4^{C}, H-5^{D}), 3.89 (1 H, H-5^{G}), 3.90 (1 H, H-4^{B}), 4.50 (1 H, H-5^{C}), 4.51 (1 H, H-6a^{C}), 4.70 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 2.7 Hz, H-1^{C}), 4.71 (1 H, H-6b^{C}), 4.80 (t, 1 H, $^{3}J_{H\text{-}4,H\text{-}3}$ = $^{3}J_{H\text{-}4,H\text{-}5}$ = 9.2 Hz, H-4^{A}), 4.90 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.7 Hz, H-1^{G}), 4.92 (d, 1 H, $^{3}J_{H\text{-}5,H\text{-}4}$ = 9.2 Hz, H-5^{A}), 4.99 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 2.9 Hz, H-1^{F}), 5.01 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.6 Hz, H-1^{E}), 5.23 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 1.7 Hz, H-1^{A}), 5.25 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.1 Hz, H-1^{B}), 5.80 (d, 1 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 4.9 Hz, H-1^{D}), 7.47 (dd, 1 H, $^{3}J_{Hb',Ha'}$ = 6.8 Hz, $^{3}J_{Hb',Hc'}$ = 8.1 Hz, H$^{b'}$), 7.50 (dd, 1 H, $^{3}J_{Hb,Ha}$ = 7.0 Hz, $^{3}J_{Hb,Hc}$ = 8.2 Hz, H^{b}), 7.58 (d, 1 H, $^{3}J_{Ha',Hb'}$ = 6.8 Hz, H$^{a'}$), 7.66 (d, 1 H, $^{3}J_{Hc,Hb}$ = 8.2 Hz, H^{c}), 7.70 (d, 1 H, $^{3}J_{Hc',Hb'}$ = 8.1 Hz, H$^{c'}$), 7.80 (d, 1 H, $^{3}J_{Ha,Hb}$ = 7.0 Hz, H^{a}) ppm; $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$, 25ºC): δ (assignment by combined HSQC and HMBC) = 45.19 (C-6^{C}), 54.76, 55.33, 55.80, 55.81, 55.95, 56.21, 56.30, 56.33, 56.50, 56.71, 56.88, 56.93, 57.41, 57.80, 58.31, 58.37, 59.38 [×2], 59.69 (OMe), 64.67, 65.66, 67.35, 68.01 (C-5), 68.56 (C-6), 68.64 (C-5), 68.76 (C-6), 68.87, 69.04 (C-5), 69.57, 69.99, 70.15 (C-6), 74.70, 75.01, 77.02, 77.71, 78.09, 78.53, 78.76 [×2], 78.82, 79.02, 79.34, 79.44, 79.55, 79.86, 80.18, 80.30, 80.52, 80.87, 81.40, 81.80, 83.18 (C-2, C-3, C-4), 91.90, 93.96, 94.38, 95.36, 96.48, 97.45, 99.53 (C-1), 116.81, 118.00, 123.86, 124.47, 124.61, 125.13 (CH-*arom*), 125.50, 127.11, 128.44, 129.43, 137.46, 144.10 (C-*quat*), 146.49 (C-6^{A}) ppm; IR: 1499 (vw, C=N) cm^{-1}; elemental analysis (%) calcd for $C_{73}H_{110}N_2O_{33}$•3.5CH_2Cl_2 (1543.65 + 297.26): C 49.91, H 6.41, N 1.52, found: C 49.96, H 6.45, N 1.48; MS (ESI-TOF): *m/z* (%): 1565.69 (100) $[M + Na]^{+}$.



[Cu(**5a**)$_2$]BF_4: A solution of [Cu(MeCN)$_4$] (0.013 g, 0.04 mmol) in CH_2Cl_2 (3 mL) was added dropwise to a solution of **5a** (0.055 g, 0.04 mmol) in CH_2Cl_2 (3 mL). After stirring the reaction mixture overnight at 25 °C, the solution was filtered through a pad of Celite and the resulting solution concentrated under vacuum to ca. 1 mL. Addition of pentane gave quantitatively [Cu(**5a**)$_2$]BF_4 (0.058 g, 100%) as a bright green powder. m.p. >250°C; ^{1}H NMR (500.1 MHz, $CDCl_3$, 25ºC): δ (assignment by combined COSY, TOCSY, HSQC, and ROESY) = 1.93 (s, 6 H, OMe), 1.94 (t, 2 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = $^{3}J_{H\text{-}6,H\text{-}5}$ = 11.6 Hz, H-6a), 2.94 (dd, 2 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 2.2 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 10.0 Hz, H-2), 2.97 (s, 6 H, OMe), 3.09 (m, 2 H, H-5), 3.11 (dd, 2 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 2.3 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 9.8 Hz, H-2), 3.18 (dd, 2 H, $^{3}J_{H\text{-}2,H\text{-}1}$ = 3.4 Hz, $^{3}J_{H\text{-}2,H\text{-}3}$ = 8.5 Hz, H-2), 3.22–3.28 (4 H, H-2, H-4), 3.36 (s, 6 H, OMe), 3.43 (s, 6 H, OMe), 3.47 (s, 6 H,

OMe), 3.48 (s, 6 H, OMe), 3.49 (s, 6 H, OMe), 3.50 (s, 6 H, OMe), 3.54 (s, 6 H, OMe), 3.56 (s, 6 H, OMe), 3.58 (s, 6 H, OMe), 3.59 (s, 6 H, OMe), 3.65 (s, 12 H, OMe), 3.67 (s, 6 H, OMe), 3.68 (s, 6 H, OMe), 3.34 –3.78 (34 H, H-2, H-3, H-4, H-6), 3.79–3.88 (4 H, H-5, H-6), 3.98 (m, 2 H, H-4), 4.15–4.24 (4 H, H-5^{A}, H-$6a^{A}$), 4.60 (dd, 2 H, $^{3}J_{H\text{-}5,H\text{-}4}$ = 9.6 Hz, $^{3}J_{H\text{-}6,H\text{-}5}$ = 3.0 Hz, H-5), 4.63 (d, 2 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1^{A}), 4.70 (br s, 2 H, H-1), 4.83–4.86 (4 H, H-4^{B}, H-5), 4.87 (d, 2 H, $^{2}J_{H\text{-}6a,H\text{-}6b}$ = 12.7 Hz, H-$6b^{A}$), 4.97 (d, 2 H, $^{3}J_{H\text{-}5,H\text{-}4}$ = 10.8 Hz, H-5^{B}), 4.99 (d, 2 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 3.3 Hz, H-1), 5.04 (d, 2 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 2.3 Hz, H-1), 5.32 (br s, 2 H, H-1), 5.60 (d, 2 H, $^{3}J_{H\text{-}1,H\text{-}2}$ = 2.2 Hz, H-1), 7.61 (t, 2 H, $^{3}J_{Hb,Ha}$ = $^{3}J_{Hb,Hc}$ = 7.7 Hz, $H^{b \text{ or } b'}$), 7.74 (t, 2 H, $^{3}J_{Hb,Ha}$ = $^{3}J_{Hb,Hc}$ = 7.7 Hz, $H^{b' \text{ or } b}$), 7.80 (d, 2 H, $^{3}J_{Ha',Hb'}$ = 7.7 Hz, $H^{a' \text{ or } a}$), 7.83 (d, 2 H, $^{3}J_{Ha,Hb}$ = 7.7 Hz, $H^{a \text{ or } a'}$), 7.87 (d, 2 H, $^{3}J_{Hc,Hb}$ = 7.7 Hz, $H^{c \text{ or } c'}$), 8.09 (d, 2 H, $^{3}J_{Hc',Hb'}$ = 7.7 Hz, $H^{c' \text{ or } c}$) ppm; $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$, 25ºC): δ (assignment by combined HSQC and HMBC) = 48.83 (C-6^{A}), 57.48, 57.93, 57.98, 58.11, 58.16, 58.69 [×2], 58.94, 59.12, 60.13, 60.22, 60.63, 60.93, 61.12, 61.24, 61.82 (OMe), 64.15 (C-5^{A}), 69.34, 69.69, 71.14 (C-6), 71.23, 72.24 [×2], 72.93, 73.07 (C-5), 73.43 (C-6), 74.51, 75.67, 75.96, 76.39, 77.22, 77.43, 78.88, 79.82, 80.34, 80.48, 81.68, 81.99, 82.05, 82.32 [×2], 82.49, 82.54, 83.11 (C-2, C-3, C-4), 94.08, 96.86, 96.99, 97.28, 98.09, 99.54 (C-1), 122.13, 122.33 (CH-*arom*), 126.94, 127.28 (C-*quat*), 127.34, 127.91, 128.21, 128.51 (CH-*arom*), 129.88, 130.93, 139.88, 145.17 (C-*quat*), 147.60 (C-6^{A}) ppm. We do not provide microanalytical data for this compound because of strong hydration; MS (MALDI-TOF): *m/z* (%): 2740.17 (100) $[M–BF_4]^{+}$.

V. 4. 4. Crystal structure analyses



X-ray crystallographic data of [Cu(**5a**)$_2$]BF$_4$: Single crystals of [Cu(**5a**)$_2$]BF$_4$ were obtained by slow diffusion of pentane into a dichloromethane solution of the compound. Crystal data for $C_{132.5}H_{191}BCl_3CuF_4N_4O_{56}$ ([Cu(**5a**)$_2$]BF$_4$·1.5CH$_2$Cl$_2$·0.5C$_6$) (from disordered C_5H_{12}), M_r = 2992.59; monoclinic; space group $P2_1$; a = 16.7370(10), b = 17.8760(10), c = 29.435(2) Å, β = 105.429(7) °; V = 8489.3(9) Å^3; Z = 2; ρ_{calcd} = 1.171 Mg m^{-3}; $\lambda(Mo_{K\alpha})$ = 0.71073 Å; μ = 0.258 mm^{-1}; $F(000)$ = 3166; T = 100 K. The sample (0.42 × 0.36 × 0.32 mm) was studied with an Oxford Diffraction Xcalibur Saphir 3 CCD with graphite monochromatised $Mo_{K\alpha}$ radiation. The structure was solved with SIR-97,[21] which revealed the non-hydrogen atoms of the molecule. After anisotropic refinement, many hydrogen atoms were found with a Fourier difference analysis. The whole structure was refined with SHELX-97[22] and full-matrix least-square techniques. Use of F^2 magnitude; x, y, z, β_{ij} for C, B, Cl, Cu, F, N, O atoms, x, y, z, in riding mode for H atoms, 1785 variables and 10086 observations with [$I > 2.0\sigma(I)$], calcd $w = 1/[\sigma^2(F_o^2) + (0.1186\ P)^2]$ where $P = (F_o^2 + 2\ F_o^2)/3$ with the resulting R = 0.1123, R_W = 0.3526, and S_w = 0.829, $\Delta\rho < 0.470$ e Å^{-3}. The level A and B alerts are mainly due to the disordered external pentane molecule and to a large thermal motion occurring in one of the CD units. This produces a low diffraction of the samples at high theta. It was not possible to improve the final R values. CCDC-936286.

V. 5. References

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Conclusion générale et perspectives

Conclusion générale et perspectives

Dans ce mémoire, nous avons décrit la synthèse de plusieurs systèmes catalytiques dérivés de métallocyclodextrines. Dans chacun des dérivés de cyclodextrines présentés, le(s) groupement(s) coordinateur(s), qu'il soit phosphoré ou azoté, est (sont) greffé(s) sur la face primaire du macrocycle. Pour les plus préorganisés d'entre eux, c'est a dire ceux dans lesquels l'anse coordinante est fixée de manière rigide à la CD, les doublets non liants des atomes donneurs sont orientés vers le cœur de la cavité. Ces systèmes se sont avérés être des coordinats de choix pour l'étude de réactions de formation de liaisons carbone-carbone métallo-catalysées en milieu confiné, en particulier dans leurs versions asymétriques.

La mise au point que constitue le *premier chapitre* de cette thèse a permis de mettre en évidence la capacité des systèmes hybrides P(III)/CD à se comporter comme première et deuxième sphère de coordination vis-à-vis d'un grand nombre de métaux de transition. A travers de nombreux exemples, cette revue illustre le fait que la présence d'une cavité cyclodextrine a un impact positif sur les sélectivités des réactions et la durée de vie des catalyseurs.

La première partie des travaux présentés dans ce mémoire porte sur le développement de ligands hybrides à chiralité inhérente bâtis sur plateforme CD. Pour atteindre cet objectif, une nouvelle méthode d'hétérodifférenciation de la face primaire des CD méthylées par ouverture régiosélective d'un pont sulfate a été développée (*chapitre II*). Ces ouvertures sont régiosélectives lorsque les nucléophiles sont stériquement encombrés, voire régiospécifiques dans le cas du diphenylphosphure de lithium. Les dérivés ainsi obtenus possèdent un groupement diphénylphosphino ainsi qu'une fonction hydroxyle résiduelle et constituent d'excellents produits de départ pour la préparation de coordinats hybrides *phosphine-phosphite*. La synthèse et les propriétés chélatantes et catalytiques de ces derniers sont décrites dans le *troisième chapitre*. Malgré leur relative flexibilité, ces coordinats ont permis de former quantitativement des complexes *cis*-chélatés à 12 chaînons avec des précurseurs métalliques cationiques (Rh(I)) ou neutres (Pt(II)). Dans ces complexes, le plan métallique décrit un mouvement d'éventail autour de l'axe P···P', concomitamment à une atropoisomérisation rapide du groupement biaryle de l'entité phosphite. Dans les complexes comportant l'entité 2,2'-binaphthyloxyphosphinoxy, l'atropoisomérisation est empêchée et le mouvement d'éventail n'est plus observé. Les complexes de rhodium dérivés de ces ligands hybrides ont été évalués en hydrogénation asymétrique d'esters de déhydroaminoacides N-substitués ainsi qu'en hydroformylation du styrène. Les meilleurs excès énantiomériques (92 %) ont été obtenus avec les chélates présentant une forte rigidité et dans lesquels les différentes unités chirales agissent en synergie.

Le *chapitre IV* a trait à l'étude des propriétés coordinantes et catalytiques des ligands α- et β-HUGPHOS, deux cyclodextrines équipées chacune d'un atome de phosphore dont le doublet pointe vers le cœur de la cavité CD. Leur réaction avec des cations des groupes 8-10 conduit exclusivement à des complexes mono-ligandés en phosphine dont le centre métallique est confiné dans le ligand macrocyclique. Les complexes monophosphine de rhodium (I) de ce type ont été évalués en hydroformylation asymétrique du styrène. Il a été établi pour la première fois, que l'hydroformylation du styrène pouvait conduire à la fois à une haute sélectivité en produit branché (98.3 %) et à une énantiosélectivité élevée (95 %). Des études par RMN et IR haute pression ont mis en évidence la formation exclusive d'espèces mono-ligandées en phosphore dans les conditions de la catalyse.

Dans le dernier chapitre de ce manuscrit (*chapitre V*) est décrit le pontage distal de diaminocyclodextrines par l'acénaphtènequinone. Cette réaction régiospécifique fournit des ligands présentant une anse azotée de type N-(2-N'-alkylaminoacenaphthenyl)alkylimine dissymétrique sur la face primaire du macrocycle. Ces derniers sont potentiellement confinants car les doublets libres des deux atomes d'azote sont orientés vers le centre de la cavité. L'oxydation par voie chimique ou électrochimique provoque la transformation de l'anse azotée en un pont imidazole 1,2-disubtitué très court à l'origine d'une très forte déformation du squelette cyclodextrine.

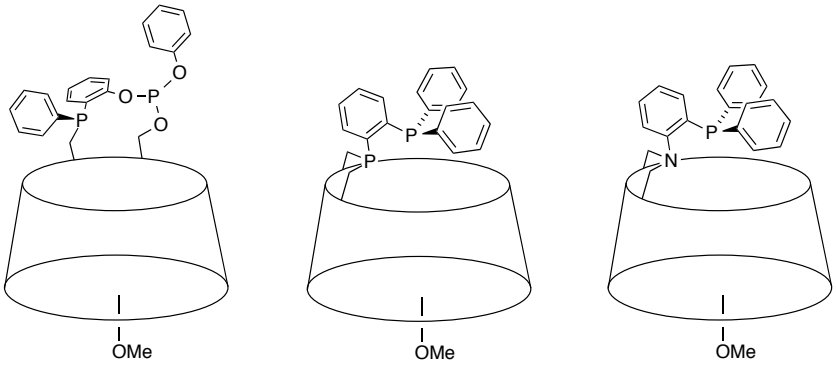
Les différents travaux réalisés au cours de cette thèse ont montré que le confinement d'un centre métallique à l'intérieur d'une cavité moléculaire est de nature à améliorer les propriétés d'un catalyseur métallique, notamment en terme de sélectivité. On peut anticiper que des systèmes plus performants pourront être obtenus en augmentant le degré de confinement du métal, et ce afin de maximiser les effets stériques. Il conviendra toutefois d'opérer dans des cavités dont la taille reste compatible avec une activité raisonnable.

Parmi les modifications qui pourraient améliorer les performances des catalyseurs existants et diversifier la palette de ligands confinants, on peut citer :

– le pontage proximal des deux groupements coordinants des ligands hétérodentates du chapitre III par un espaceur rigide afin de bloquer le mouvement d'éventail observé.

– Le développement de diphosphines introverties dérivées des ligands HUGPHOS. En raison de leur caractère cis-chélatant, ces dernières devraient (logiquement) former des complexes susceptibles de catalyser de nombreuses réactions de couplage en milieu confiné.

– Le remplacement de l'atome de phosphore pontant par un atome d'azote dans les ligands HUGPHOS et leurs analogues diphosphine pour obtenir des systèmes hybrides *P*,*N* confinants.



Matthieu JOUFFROY

Cyclodextrines confinantes : synthèse, propriétés complexantes et utilisation en catalyse asymétrique.

Résumé

Ce mémoire de thèse est consacré au développement de nouveaux systèmes catalytiques dérivés de métallocyclodextrines. Les travaux qui y sont décrits ont trait à la mise au point de méthodes de fonctionnalisation régiosélective de la face primaire des cyclodextrines donnant accès à des ligands hétérodentés de type P,P' à chiralité inhérente. Ces derniers forment quantitativement des complexes chélate de géométrie cis, dont les versions rhodiées ont été testées en hydrogénation et en hydroformylation asymétriques d'oléfines prochirales. L'étude des propriétés complexantes et catalytiques de deux phosphines confinantes dérivées d'α- et de β-cyclodextrine a également été réalisée. L'ancrage rigide de l'atome de phosphore (III) au sein de la matrice cyclodextrine permet de confiner le centre métallique au cœur du macrocycle, ce qui se traduit par la formation exclusive de complexes mono-ligandés en phosphore. Les complexes monophosphine de rhodium (I) catalysent l'hydroformylation asymétrique du styrène avec une très forte sélectivité en produit branché et une énantiosélectivité très élevée. Le pontage de diaminocyclodextrines par l'acénaphtènequinone permet d'obtenir des ligands potentiellement confinants dans lesquels l'anse azotée de type N-(2-N'-alkylaminoacenaphthenyl)alkylimine est dissymétrique. L'oxydation du pont par voie chimique ou électrochimique conduit à une anse imidazole 1,2-disubstitué très courte qui provoque une forte déformation du squelette cyclodextrine.

Mot clés: cyclodextrine • phosphore (III) • azote • ligand confinant • catalyse homogène • hydroformylation asymétrique • hydrogénation asymétrique • rhodium

Abstract

This manuscript is concerned with the design of novel catalytic systems derived from metallocyclodextrins. The first part describes new ways of functionalising the cyclodextrin primary face regioselectively for accessing inherently chiral *P*,*P'* chelators. These heterodentate ligands gave quantitatively *cis*-chelate complexes with various d^8 cations. Their rhodium(I) complexes were assessed in the asymmetric hydrogenation and hydroformylation of prochiral olefins. The coordination and catalytic properties of two phosphines derived from a- and b-cyclodextrin are also reported. With their phosphorus lone pair pointing toward the CD core, these confining ligands force the coordinated metal centre to stay within the CD hollow and promote the formation of singly phosphorus-ligated complexes. Rhodium (I) monophosphine complexes of this type catalyse the asymmetric hydroformylation of styrene with both very high isoselectivity and enantioselectivity. Capping of diaminocyclodextrins with acenaphthenequinone resulted in the formation of a non-symmetric N-(2-N'-alkylaminoacenaphthenyl)alkylimine handle with two intra-annular nitrogen atoms. A strong deformation of the cyclodextrin scaffold was shown to take place upon chemical or electrochemical oxidation of the bridging unit into the very short 1,2-disubstituted imidazole moiety.

Key words: cyclodextrin • phosphorus (III) • nitrogen • confining ligand • homogeneous catalysis • asymmetric hydroformylation • asymmetric hydrogenation • rhodium