Asymmetric Transfer Hydrogenation to Aromatic and Aliphatic Ketones Catalyzed by Ruthenium Complexes Linked to both Faces of β-Cyclodextrin

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Theoretical Part

1 Introduction

1.1 Asymmetric Transfer Hydrogenation Reaction to Carbonylbonds

1.1.1 Transfer Hydrogenation versus Hydrogenation

The asymmetric reduction of prochiral ketones to their corresponding optical active alcohols is one of the most important molecular transformations in modern synthetic chemistry[1,2]. The products are common intermediates for pharmaceuticals, biologically active compounds and fine chemicals. For example, they are used in the synthesis of *Aprepitant* (**1**, a NK-1 receptor antagonist)[3] and herbicide **2**[4] *(figure 1)*.

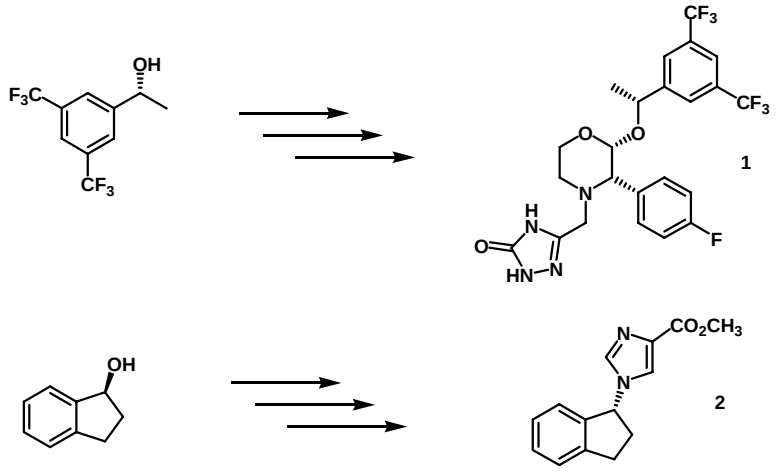
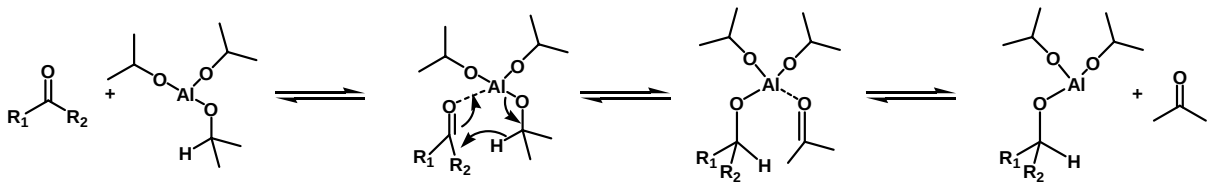


Figure 1 *The importance of chiral secondary alcohols in chemical synthesis*

The racemic reversible reduction of carbonyls to carbinols with superstoichiometric amounts of aluminium alkoxides in alcohols was found independently by *Meerwein*, *Ponndorf* and *Verley* in 1925[5,6,7]. *Scheme 1* shows the accepted mechanism of the *Meerwein-Ponndorf-Verley* reaction (MPV) involving a six-membered transition state[8].



Scheme 1 *MPV: reversible reaction and mechanism*

Only in the early 1990's, first successful versions of catalytic asymmetric MPV reactions have been reported using C_2 symmetric chiral ligands. Pioneering efforts were made by the group of *Pfaltz* using Ir(I) dihydrooxazole complexes **3**[9] and the group of *Genêt* with chiral diphosphine Ru(II) catalysts **4**[10]. *Evans* showed that lanthanide complexes of tridentate ligand **5**[11] reduce aromatic ketones with enantioselectivities up to 97% (*figure 2*).

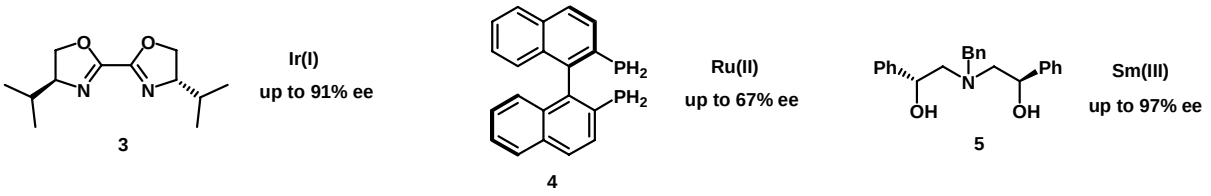
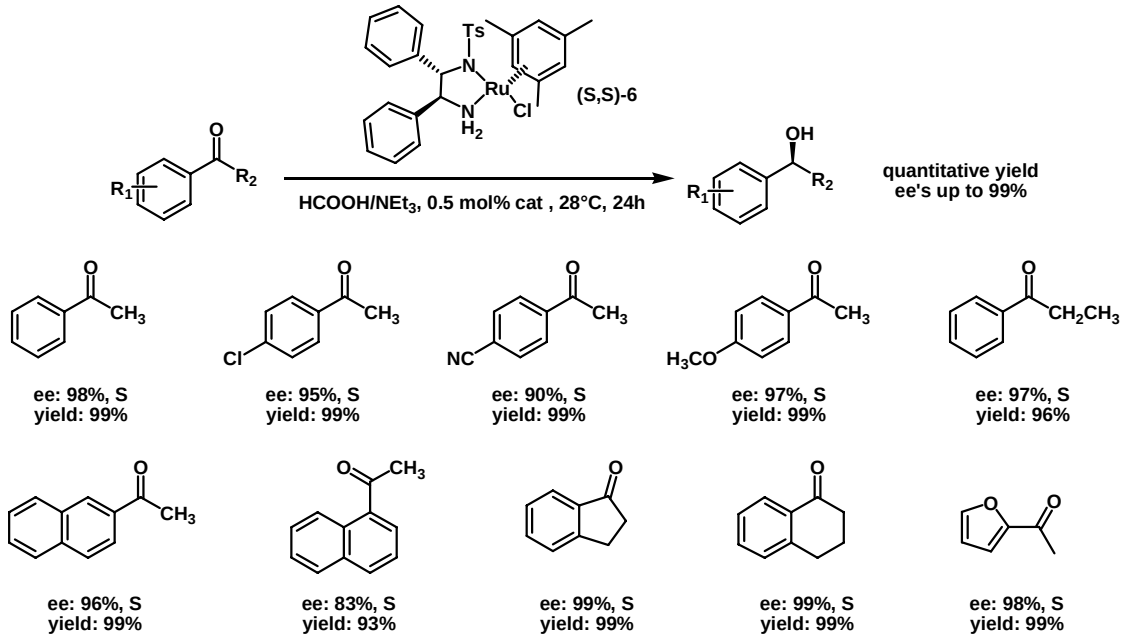


Figure 2 *Primary chiral ligands in the asymmetric catalytic version of MPV*

In 1996, *Noyori* and co-workers found that Ru(II) complexe **(S,S)-6** modified with a $^6\eta$- arene and a chiral N-monotosylated 1,2-diamine serve as excellent catalysts. It was a breakthrough for catalytic asymmetric transfer hydrogenation (ATH) reactions to ketones in terms of enantioselectivities, catalyst loading and substrate scope[12]. For example, acetophenone can be reduced quantitatively to its corresponding (S)-alcohol with up to 98% ee (*scheme 2*).



Scheme 2 *Noyori's Ru(II) based ATH system using chiral monotosylated 1,2-diamines as chiral ligands*

This ATH system is strongly chemoselective. Olefinic bonds, halogen atoms, nitro groups and ester functionalities are not affected under such conditions. Several efforts have been made in the last decade to improve the catalytic properties by designing and employing new chiral ligands. Nevertheless, the system described by *Noyori* remains the method of choice for many substrates up to date due to excellent reactivity, selectivity, low costs and readily availability of chiral ligands. Chiral amino alcohols like indanol **7**[13] and 2-azanorbornyl alcohol **8**[14] are also known to act as ligands in ATH. The stereoselectivities are comparable with the monotosylated diamine analogue but the reactivities are slightly lower. Another interesting difference between 1,2-amino alcohols and 1,2-monotosylated diamines is the function of the two stereogenic centres R_1 and R_2 (*figure 3)*. Amino alcohols (X = O) show high enantioselectivities for both *cis* and *anti* configured ligands, whereas monotosylated diamines (X = NTs) require *anti* configuration for high optical purity of the products. Furthermore it could be demonstrated that the stereogenic centre R_2 is more important for the stereo outcome of the reaction than R_1 with amino alcohol ligands. For 1,2-monotosylated diamines it's directly the opposite[15].

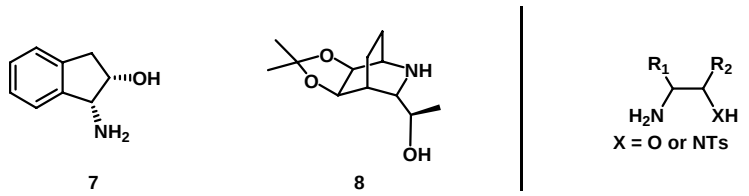


Figure 3 left: *Amino alcohols as ligands in Ru(II) catalyzed ATH reactions; right: monotosylated diamine vs. amino alcohol*

Wills[16] showed that a tethered Ru(II) complex containing an arene ligand which is covalently bound to the amine functionality in **9** shows higher reactivity than non tethered complex **6** *(figure 4)*. This contribution illustrates a rare example in which the original *Noyori* system could be improved in terms of catalyst loading (0.01 mol%) and reactivity. Interestingly, ligand **10** which is connected via the tosyl motif, is less reactive than **6** and **9**. The role of the tether is not fully understood at the moment. However, it is speculated that the chiral elements of the catalyst are locked due to the decreased flexibility of the system.

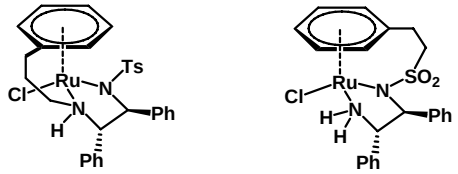
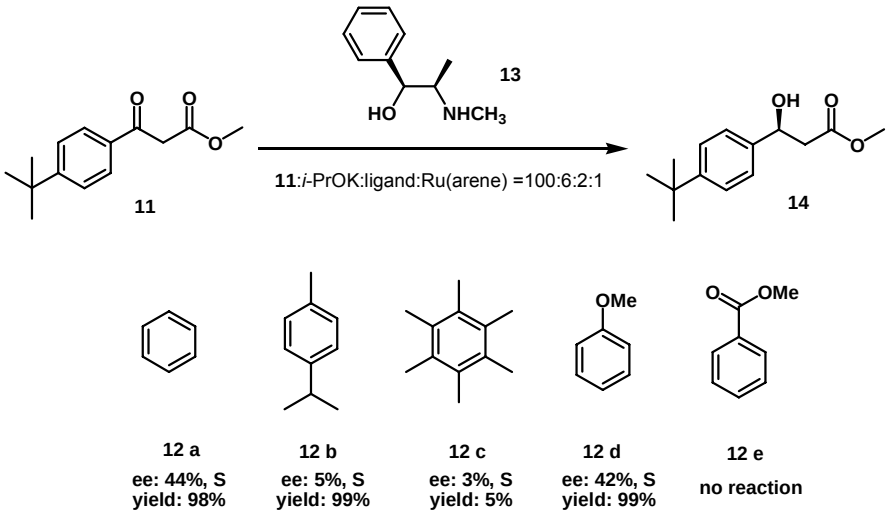


Figure 4 *Tethered ligands can improve the reactivity and lower the catalyst loading*

Arenes are known to coordinate to many transition metals in hexahapto fashion[17]. Several features make them popular ligands in asymmetric catalysis: (1) they occupy three out of six coordination sites of Ru in its octahedral environment, leaving two sites for a chiral bidentate ligand and one site for the halide/hydride; (2) they are easily modified; (3) the dimeric dihalide precursors are readily available.

Their role in the catalytic process was investigated by *Mortreux et al*[18]. Model substrate **11** was reduced with a variety of substituted arenes **12 a-e** using *i*-PrOH as hydrogen source and chiral amino alcohol **13** as ligand (*scheme 3*). There is no direct correlation between steric bulkiness of the arene and the optical purity of β-hydroxy ester **14**. Anyway, bulky arene **12 c** and the arene containing a strong electron withdrawing group **12 e** lower the reactivity dramatically.

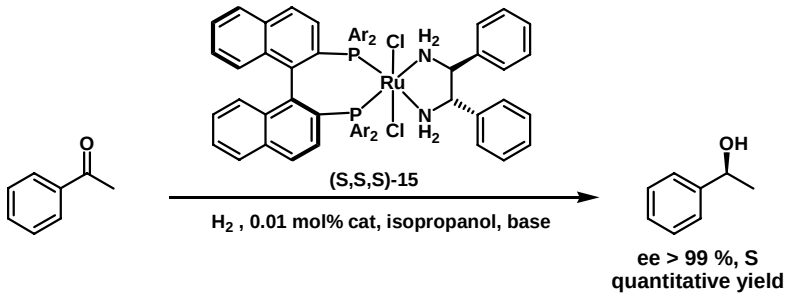


Scheme 3 *Influence of substitution pattern of arenes in ATH*

Isopropanol was chosen as a hydrogen source in initial studies[19]. An additional base (alkoxides) was required to obtain reactivity but the conversions remained moderate due to reversibility of the reaction. A simple solution to solve this problem is the use of an azeotropic mixture of formic acid and triethylamine. The evolution of carbon dioxide makes the process irreversible and increases the yields

to a satisfying level[12]. Isopropanol and formic acid avoid the use of hazardous molecular hydrogen and the special technical equipment. The low costs and operational simplicity are two other advantages of organic hydrogen sources, which are applied to all ligands mentioned so far.

Nevertheless, asymmetric hydrogenation (AH) using molecular hydrogen exists and is illustrated in *scheme 4*. It was again *Noyori* who developed ruthenium based catalyst **(S,S,S)-15** bearing a chiral diphosphine and a chiral diamine[20]. This system is able to reduce a wide range of aromatic ketones with outstanding stereocontrol (up to 99% ee) in the presence of a base.



Scheme 4 *Asymmetric hydrogenation using molecular hydrogen*

Huge endeavours have been made to employ new chiral ligands in AH as well. Only few of them could improve the catalytic activity (*figure 5*). Combinations of diphosphines such as **16** xyl-BINAP[21], **17** P-Phos[22] and **18** PhanePhos[23] with 1,2- or 1,4-diamines such as **19** DAIPEN[21] and **20** IPHAN[24] lead to excellent reduction results for numerous aromatic ketones. However, the proper catalyst has to be found for each substrate since no universal catalyst is known up to date.

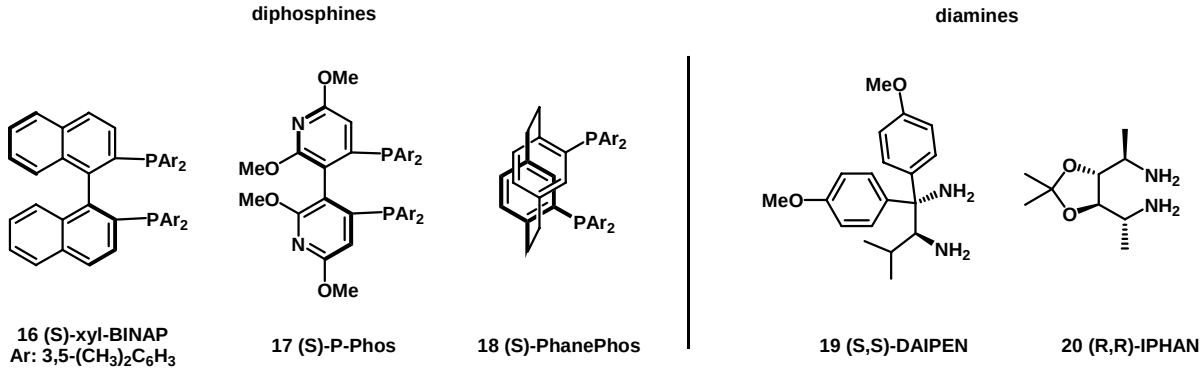


Figure 5 *Advanced ligands for asymmetric hydrogenation*

Table 1 compares the two different methodologies (ATH vs. AH). Hydrogenations are still favoured in industrial applications due to lower catalyst loading, higher substrate concentration and slightly shorter reaction times.

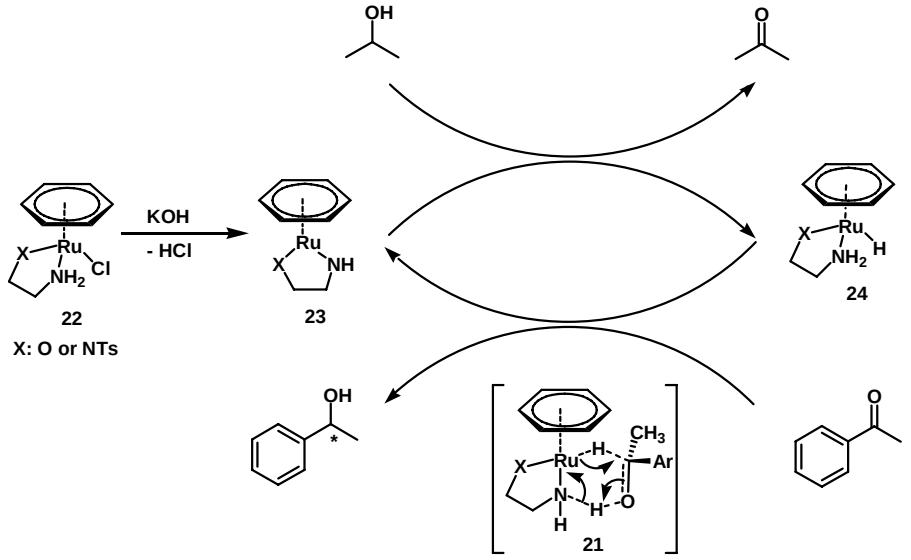
	Transfer Hydrogenation	Hydrogenation
Stereoselectivity	aromatic: 95-98%	aromatic: > 98%
Substrate concentration	up to 1M	up to 10M
Reactivity	slower than AH	faster than ATH
Solvent	organics; H_2O is possible	limited to organic solvents
Large scale synthesis	small-medium scale	large scale
Turn over Number (TON)	up to 10^4	up to 10^6
Catalyst loading	10^{-2} mol%	10^{-4} mol%
Hydrogen source	*i*-PrOH or formic acid	molecular H_2
External base	*i*-PrOH: 10^{-1} eq. of *i*-PrOK	10^{-3} eq. of *i*-PrOK

Table 1 *Transfer Hydrogenation versus Hydrogenation*

Asymmetric transfer hydrogenation and asymmetric hydrogenation are powerful methods for the enantioselective reduction of prochiral ketones. They will probably replace aluminium hydride and boron hydride systems using stoichiometric amounts of reductant like BINAL-H[25] or CBS[26] in the future. Nevertheless, there is still room for improvement. Aliphatic substrates are only reduced in poor to moderate enantioselectivities. Water as solvent can't compete with organic solvents yet. The attention will be turned to these two special features after discussion of the mechanism of AH and ATH.

1.1.2 Mechanistic Aspects

Experimental and theoretical studies revealed that ATH occurs via newly discovered metal-ligand bifunctional catalysis[27], which is in contrast to accepted classical pathways involving metal coordinated alkoxides[28]. The mechanism is based on a concerted transfer of both a hydride and a proton from the catalyst to the carbonyl bond over a pericyclic transition state **21** (*scheme 5*).



Scheme 5 *Metal-ligand bifunctional mechanism in ATH*

An external base is necessary to transform 18-electron precatalyst **22** into complex **23** under elimination of HCl whereas no further base is needed in all remaining catalytic steps. Coordinatively unsaturated complex **23** reacts with isopropanol to Ru(II) hydride species **24**, which then reduces the substrate to the corresponding alcohol. Simultaneous transfer of the hydride and one proton of the amino group to the substrate occurs via transition state **21** and regenerates **23**. Ruthenium complexes **22-24** could be isolated and characterised by x-ray analysis[29]. **22** possesses a distorted octahedral structure containing an intramolecular hydrogen bond between the chloride and the axial proton of the amino functionality. Square planar 16-electron intermediate **23** contains a short ruthenium-nitrogen bond (1.897 Å) indicating a double bond character between the metal centre and the amino nitrogen. Octahedral 18-electron complex **24** is structurally very similar to **22**. ^{1}H-NMR-spectroscopy studies in deuterated toluene showed a resonance at -5.47 ppm corresponding to the metal hydride and moreover demonstrated that the diastereomeric purities of **22** and **24** are higher than 98% with chiral ligand **(S,S)-6**.

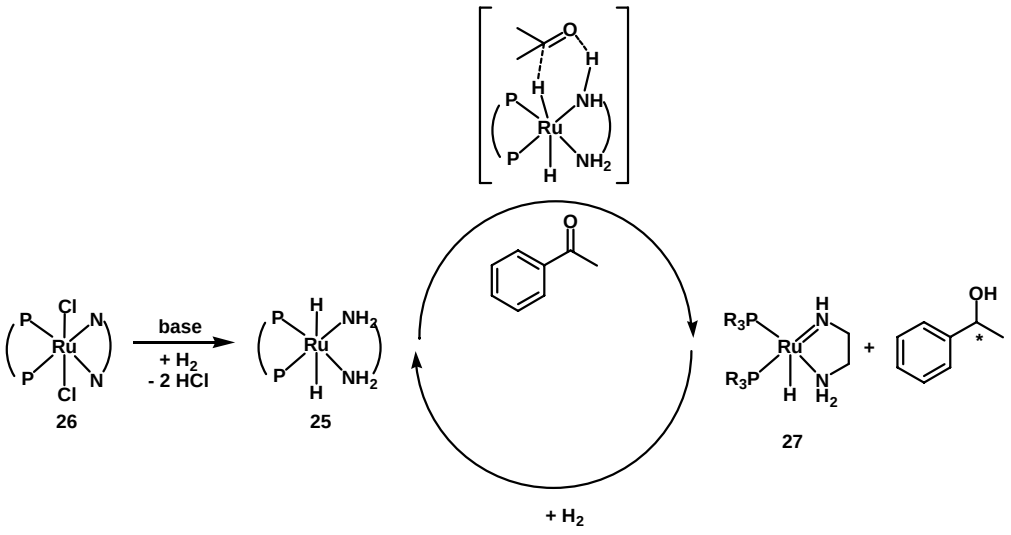
The presence of a NH or NH_2 in the chelating ligand is crucial for catalytic activity. Corresponding dialkylated analogues are totally inactive[27]. The NH moiety forms a hydrogen bond with the oxygen of the carbonyl compound to facilitate the nucleophilic hydride transfer to the carbon atom in **21**. Experimental data disclose that 1,2-amino alcohols and 1,2-monotosylated diamines serve as exquisite ligands, while 1,2-diols or 1,2-diamines do not show any catalytic activity at all in ATH. Kinetic

isotope effect investigations pointed out that the formation of hydride species **24** is the rate limiting step in the catalytic cycle[29]. Furthermore, it could be demonstrated that the reduction is concerted and doesn't proceed stepwise[30].

The chirality of the ligand determines the enantioselection of this asymmetric process. But this differentiation caused by steric interactions between the chiral ligand and the ketone is not the only source of enantioselectivity[31]. An attractive CH/π interaction[32] between the arene ligand and the aromatic ring of the carbonyl substrate seems to play an important role in the enantioselection. This fact is supported by the certainty that alcoholic products lacking an aromatic moiety show only very poor ee's[31].

An alternative mechanism involving a direct hydride transfer from an alcohol can be ruled out by computational studies and the fact that the stereochemical outcome of the reduction is independent from the chirality of the hydrogen donor[33]. Another proposed pathway is the migratory insertion mechanism[33] which can be excluded because coordinatively saturated hydride species like **24** don't bind an additional required alkoxide ligand.

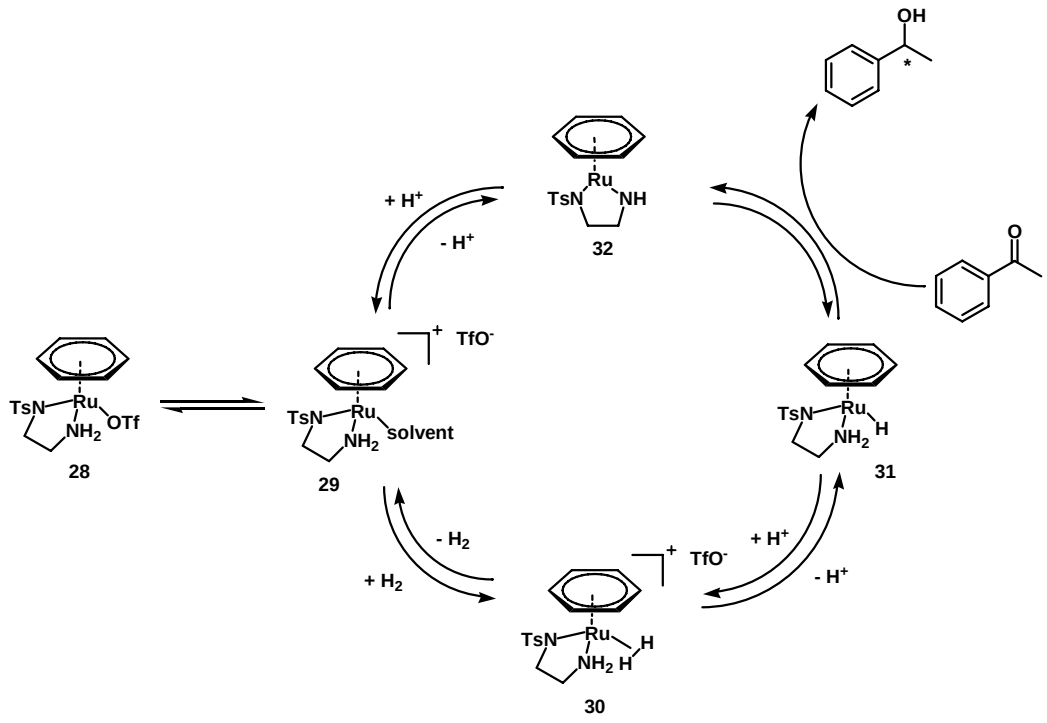
Asymmetric hydrogenation is proposed to proceed in a similar way to the one described above for the ATH[34]. Octahedral complex **25** is formed from dihalide precursor **26** by successive loss of chloride, coordination of hydrogen and heterolytic cleavage under basic conditions (*scheme 6*). *Trans* Ru(II) dihydride species **25** could be characterised by x-ray and NMR analysis[35].



Scheme 6 *Proposed mechanism in asymmetric hydrogenation*

In contrast to classical diamine free BINAP hydrogenation[28] neither the ketone nor the alcohol interacts with the metal centre throughout the process. This metal-ligand bifunctional mechanism involves simultaneous transfer of hydridic Ru-H and protic N-H from **25** via a six-membered transition state. Complex **27** stabilized by a Ru-N double bond reacts with molecular hydrogen and regenerates **25**[36].

One aspect remained a mystery for many years. Although the two methodologies are linked mechanistically, transfer hydrogenation catalysts showed no reactivity with H_2 as hydrogen source. Similar observations have been made for the opposite case. This result is surprising because the precursor and metal hydride of both processes are viewed to be essentially the same[37]. However generating a cationic Ru species by switching the reaction conditions from basic to acidic seems to overwhelm the problem using molecular hydrogen in combination with transfer hydrogenation catalysts[38] (*scheme 7*).



Scheme 7 *Use of a transfer hydrogenation catalyst with H_2 by changing the catalytic conditions from basic to acidic*

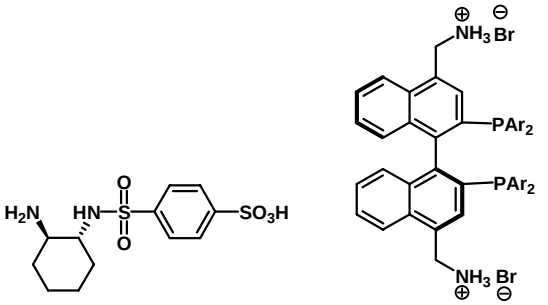
The catalytic cycle starts with ionisation of **28** in methanol to give ion pair complex **29**. Ruthenium reversibly coordinates an H_2 molecule to form $^2\eta$-complex **30**. Deprotonation by the solvent leads to Ru hydride complex **31**, which reduces enantioselectively aromatic ketones to give the corresponding alcohols and **32**.

Finally, **29** is regenerated by protonation of **32** with TfOH. This finding opens the way to hydrogenate base sensitive substrates as well[39]. In addition to this, it suggests that a second catalytic cycle exists in hydrogenation under acidic conditions. Future studies will teach us more about this system and show if determined combination of AH conditions and ATH catalysts (and the other way round) lead to more sophisticated methods.

1.1.3 ATH performed in Water

The considerable interest in the development of water soluble catalysts has two main reasons. Firstly, the separation and recovery of the catalyst is much easier. The product is extracted with organic solvents while the catalyst remains in the aqueous phase. Secondly, water which replaces organic solvents fulfils the criteria of environmentally friendly chemistry. Catalysis performed in water includes the use of biphasic systems as well as the addition of surfactants[40].

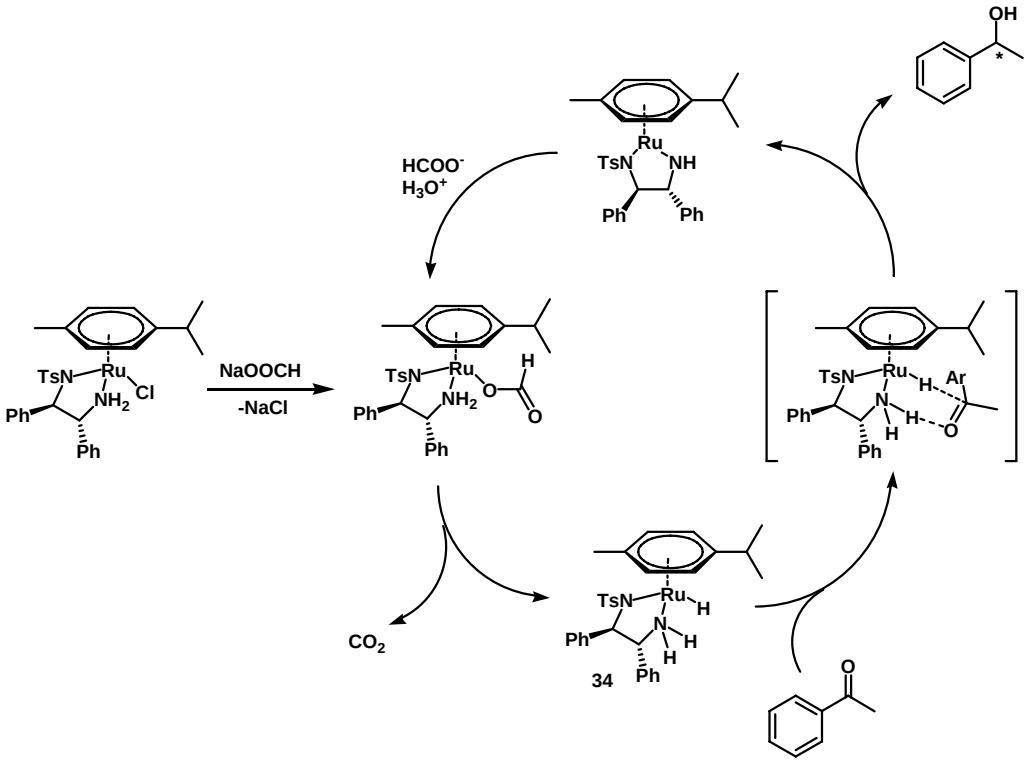
Most of reported chiral water soluble ligands have been prepared by incorporation of charged groups such as sulfonates[41] **33 a** and ammonium ions[42] **33 b** to known ligands (*figure 6*). The conversions and enantioselectivities are generally lower in aqueous phase than in organic solvents.



33 a 33 b

Figure 6 *Chiral water soluble ligands in ATH*

Xiao demonstrated in 2004 that unmodified ligand **6** shows high catalytic activity in water using sodium formate instead of formic acid/triethylamine[43]. For example acetophenone is reduced to the (S)-alcohol with 76% yield and 95% ee within 12 hours. The proposed mechanism is based on *Noyori's* findings and involves again an 18-electron Ru hydride **34** as key intermediate (*scheme 8*).



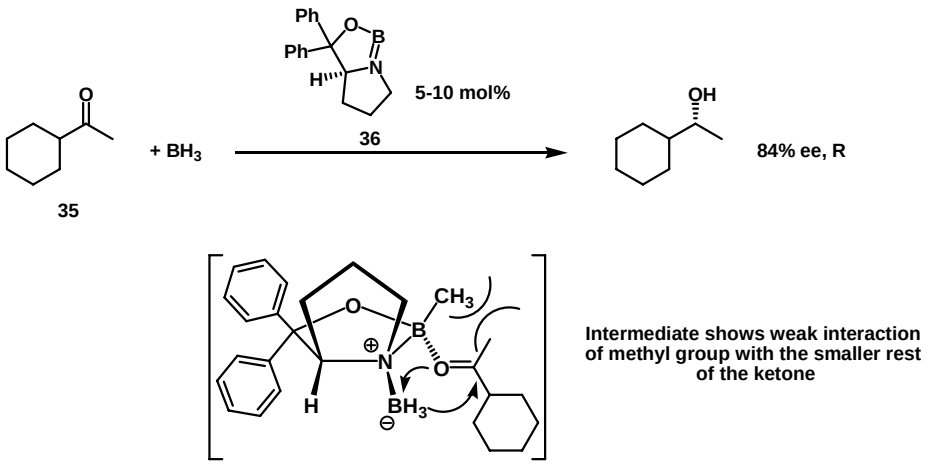
Scheme 8 *Possible mechanism of ATH in water using sodium formate*

1.1.4 Reduction of Aliphatic Substrates

Reduction of aliphatic ketones remains a major challenge in asymmetric hydrogenation. Because the aromatic moiety is missing, totally aliphatic substrates are lacking of sp^2-orbitals, which can interact with d-orbitals of the metal centre of the catalyst. But right these interactions are the origin of enantioselectivity in most asymmetric reduction processes. This chapter shows four rare examples of asymmetric hydrogenations of alkyl-alkyl ketones with satisfying ee values, including a short summary about asymmetric enzymatic reductions.

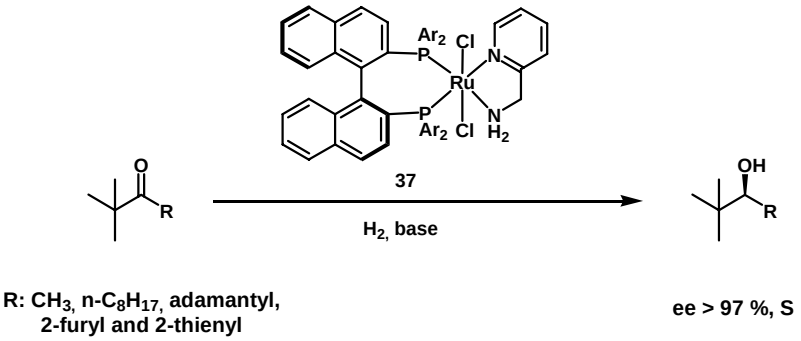
In 1987, *Corey* reported a borane based reduction using chiral oxazoborolidines, derived from simple amino acids (*scheme 9*)[44]. This system is able to reduce various aryl ketones with ee's higher than 95%. In addition to this, 1-cyclohexylethanone **35** is reduced with 84% ee. The reaction is very fast. All starting material is converted to the corresponding alcohol within 10 minutes. Oxazoborolidine structure **36** offers both, lewis acidity and lewis basicity in one single molecule. The boron of the ring fixes the oxygen of the carbonyl bond. The nitrogen next to the boron of the ring binds the boronhydride and thus brings the hydride close

to the carbonyl bond. The hydride transfer occurs preferentially from one face because the methyl group at the heterocyclic boron atom directs the small alkyl group of the ketone upwards. The larger alkyl rest of the ketone is pointed downwards due to unfavourable steric interactions with the B-CH_3 group.



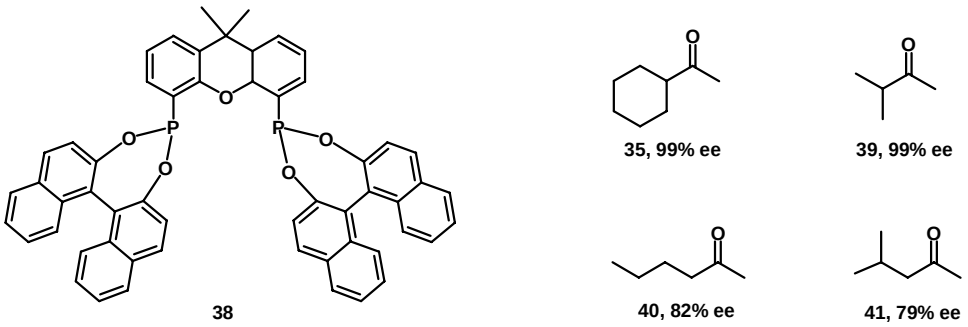
Scheme 9 *A first example of a reduction of an aliphatic ketone and the face specific hydride transfer model from Corey*

Almost 20 years later, *Noyori* observed that a system comprising the combination of BINAP and α-picolyl amine in **37** reduces *tert*.-alkyl ketones with very high ee's[45]. But the substrate scope of this AH catalyst is very narrow. Only *tert*.-alkyl ketones can be reduced in a satisfying manner. Other aliphatic and even aromatic ketones show very poor enantioselection (*scheme 10*).



Scheme 10 *Asymmetric reduction of tert.-alkyl ketones*

In 2006, *Reetz* dramatically increased the substrate scope of aliphatics using Ru(II)-diphosphonite catalyst **38**[46]. Challenging substrates like 1-cyclohexylethanone **35** and 3-methylbutan-2-one **39** are reduced with essentially complete enantioselectivity under AH conditions. Whereas linear aliphatic substrates like 2-hexanone **40** and 4-methyl-pentan-2-one **41** can still not be reduced with ee's higher than 82% nowadays. The BINOL-derived diphosphonite ligand is shown in *scheme 11*. The active ruthenium species and the mechanism are not clear yet up to date.



Scheme 11 *Diphosphonite ligand **38** in AH to aliphatic ketones*

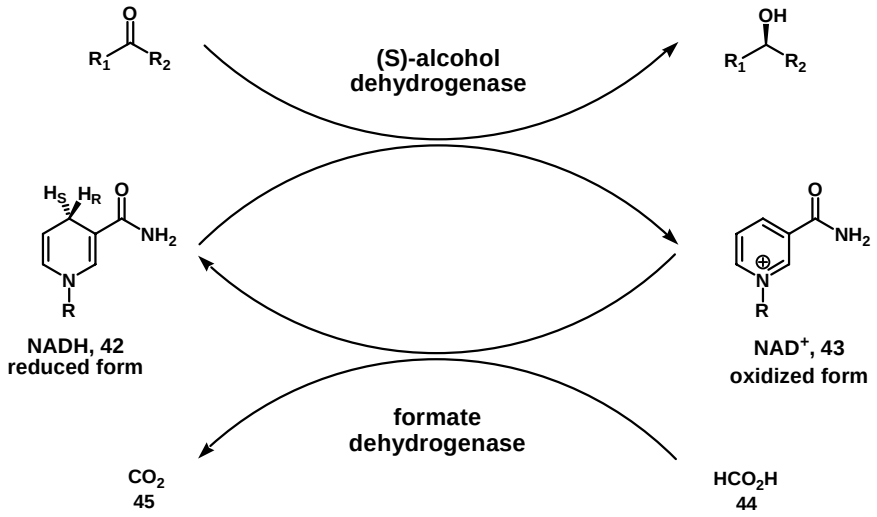
The catalysts for the asymmetric reduction of ketones can be classified into two categories: chemical catalysts and biological catalysts[47]. Before an impressive example of a biocatalytic reduction of aliphatic ketones is presented, the two different methodologies are compared in *table 2*.

	Chemical catalyst	Bio catalyst
Stereoselectivity & Substrate scope	aromatics: excellent ee's, aliphatics: moderate ee's	aromatics and aliphatics up to 99% ee
Substrate concentration	in the M range	in the mM range
Reaction times	faster than bio cat.	slower than chem. cat.
Solvent	several organic solvents	often water
Large scale synthesis	well established	problematic
Hydrogen source	H_2, alcohols, formate	alcohols, glucose, formic acid
Modification methods	by chemical design and synthesis	by mutagenesis
Availability	many catalysts available for a broad reaction scope	still difficult to get enough coenzyme (NADH)
Green chemistry	produces a lot of metal waste; organic solvents are not optimal	no metal waste; very environmentally friendly when run in water
Price	cheap-moderate	moderate-expensive

Table 2 *Advantages and disadvantages of chemical catalysts*

One of the major disadvantages using bio catalysts is the difficult application to large scale synthesis, which is caused by solubility problems of the substrates in water and the long reaction times. In addition to this, it's troublesome to isolate the product from the reaction mixture. Nevertheless, the advantages are obvious: excellent stereoselectivities for a broad substrate scope including challenging aliphatics and environmentally friendly and safe procedures (no molecular hydrogen in use).

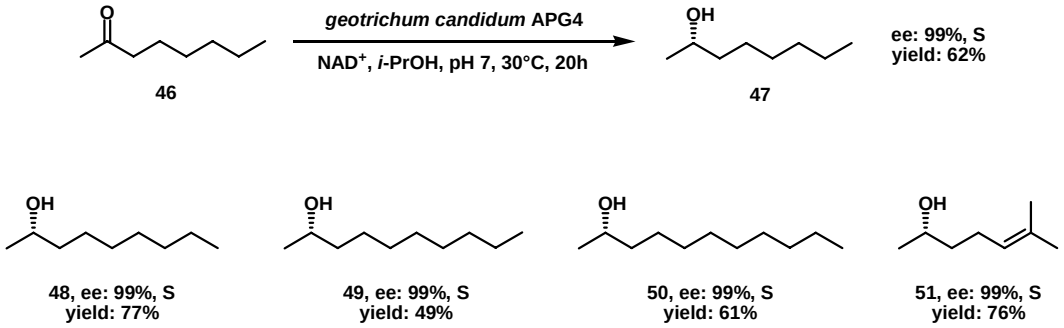
Dehydrogenases are enzymes that catalyse the reversible reduction of carbonyl bonds. Natural substrates of the enzymes are alcohols like ethanol, lactate and glycerol and their corresponding carbonyl compounds. It's noteworthy that the substrate scope is not limited to natural products. To exhibit catalytic activities, enzymes require a coenzyme such as NADH **42** (nicotinamide adenine dinucleotide) which transfers a hydride to the carbonyl bond (*scheme 12*). NAD^+ **43** is reduced by FAD (formate dehydrogenase), which oxidizes formic acid **44** to carbon dioxide **45**. Depending on the enzyme, either the pro-H-(S)-hydride or pro-H-(R)-hydride is transferred from the *re*- or *si*-face. These four possibilities allow nature to biosynthesise (S)-alcohols and (R)-alcohols in high enantiomeric purity.



Scheme 12 *Reversible NAD^+/NADH redox process in dehydrogenase*

Harada demonstrates that excellent stereoselectivities can be obtained using biocatalysts[48,49]. Reduction of several aliphatic alcohols with a powder of *geotrichum candidum* APG4 leads to ee's of 99% (*scheme 13*). He used NAD^+ as cofactor and isopropanol as hydrogen source. The reductions are performed at 30°C in a buffer at

pH 7 for 20 hours. The yields are only moderate but such high stereoselectivities have no precedent in metal catalyzed systems up to date. For example 2-octanone **46** is reduced to (S)-2-octanol **47** in 99% ee. Four more aliphatic alcohols **48-51** are obtained with complete enantioselectivity.



Scheme 13 *The reduction of aliphatic ketones with geotrichum candidum APG4*.

1.2 Cyclodextrins

1.2.1 Chemical Structure, Production and Properties

Cyclodextrins (CD's) are cyclic oligosaccharides comprised of α-1,4-linked glucopyranose units (*figure 7*). The major industrially produced CD is β-CD **52** consisting of seven glucose units. Two other CD's are also produced in reasonable quantities: α-CD (six glucose units) and γ-CD (eight glucose units) [50,51,52].

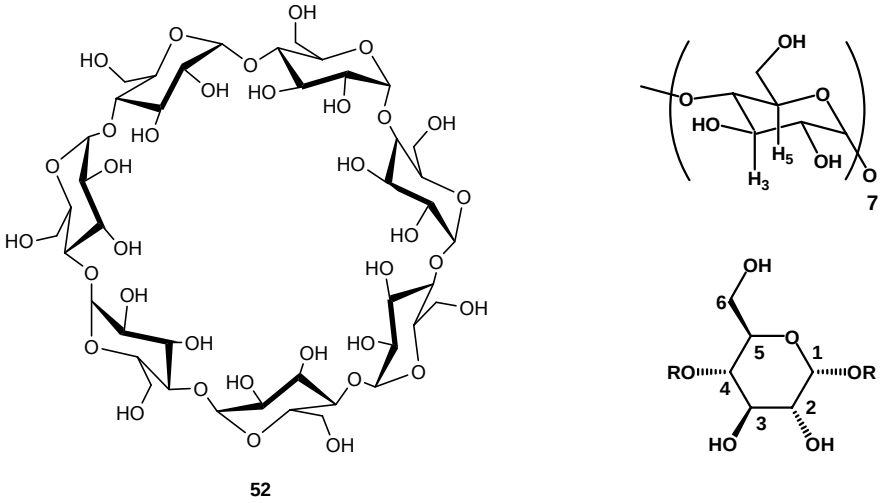


Figure 7 *Left: structure of β-CD; right top: $^4C_1$-conformation of glucose unit in β-CD; right bottom: numbering of carbon atoms in glucose*

As a consequence of the $^4C_1$-conformation of the glucopyranose units, all primary hydroxy groups are situated on one of the two edges of the ring, whereas all secondary hydroxy groups are located on the other edge[50].

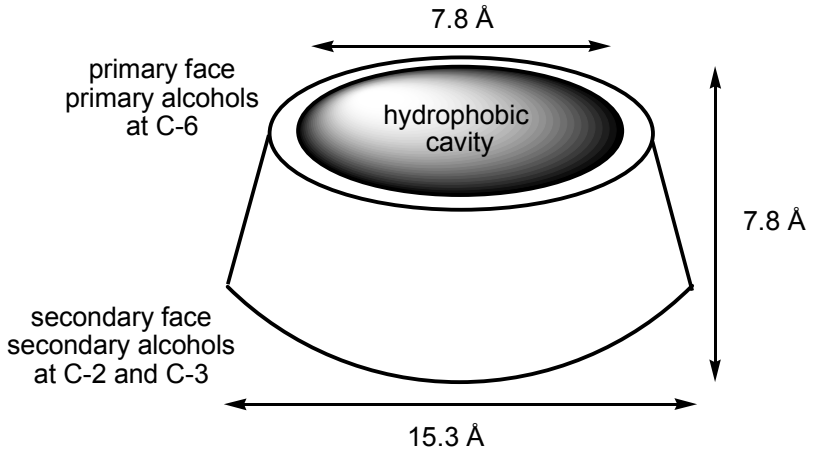


Figure 8 *Doughnut shape icon of CD illustrating the size and dimensions of β-CD **52***

The resulting doughnut shaped form offers a polar surface because all (primary and secondary) hydroxy groups are pointed outside *(figure 8).* This makes CD's water soluble. The cavity is hydrophobic, because only the axial hydrogen atoms H_3 and H_5 are pointed inside. The diameter of β-CD's hydrophobic cavity is 7.8 Å and allows inclusion complex formation with various guest molecules. *Table 3* shows that aromatic (**53**, **54**, **55**, **57**) and aliphatic **56** compounds form inclusion complexes with binding constants[53] up to 10^3 M^{-1}. Structures containing a *tert*.-butyl or adamantly rest show especially good binding affinities. The complexes are formed by non covalent interactions such as hydrogen bonds, dipole-dipole interactions and hydrophobic interactions. This feature makes CD's attractive for *supramolecular chemistry*, which was defined by *J. M. Lehn*[54] as: *chemistry beyond the molecule, the designed chemistry of the intermolecular bond*. It's noteworthy that intermolecular interactions (~0.5-5 kcal/mol) are about an order of magnitude weaker than covalent chemical bonds (~40-250 kcal/mol). This affords the involvement of multiple types of interactions in one binding mode.

Compound	α-CD	β-CD	γ-CD
benzoic acid, **53**	16 M^{-1}	23 M^{-1}	3 M^{-1}
4-methylbenzoic acid, **54**	36 M^{-1}	66 M^{-1}	8 M^{-1}
4-*tert*-butylbenzoic acid, **55**	51 M^{-1}	457 M^{-1}	59 M^{-1}
1-adamantanecarboxylic acid, **56**	114 M^{-1}	501 M^{-1}	42 M^{-1}
Ibuprofen, **57**	55 M^{-1}	2600 M^{-1}	59 M^{-1}

Table 3 *Inclusion complex formation constants of CD's with various guest molecules*

The structures of unmodified CD's are fairly rigid, due to intramolecular hydrogen bonds between C-2-OH and C-3-OH of adjacent glucose units[55].

CD's are industrially produced from starch and the enzyme *cyclodextrin glucosyl transferase* (CTG), which can be isolated from several bacteria like *Bacillus macerans, Klebsiella oxytoca or Bacillus circulans*[53]. This enzymatic reaction results in a complicated mixture of several cyclic and linear oligosaccharides. Isolation and purification of CD's is performed with the addition of an appropriate complex forming agent (e.g. toluene for the isolation of β-CD), filtration and crystallization. Several 1000 tons of CD's are produced per year. They are widely used as additives in

pharmaceuticals, food and cosmetics, as well as in analytical chemistry (e.g. separation of enantiomers by chiral HPLC)[53].

1.2.2 Use of Cyclodextrins in Organic Reactions

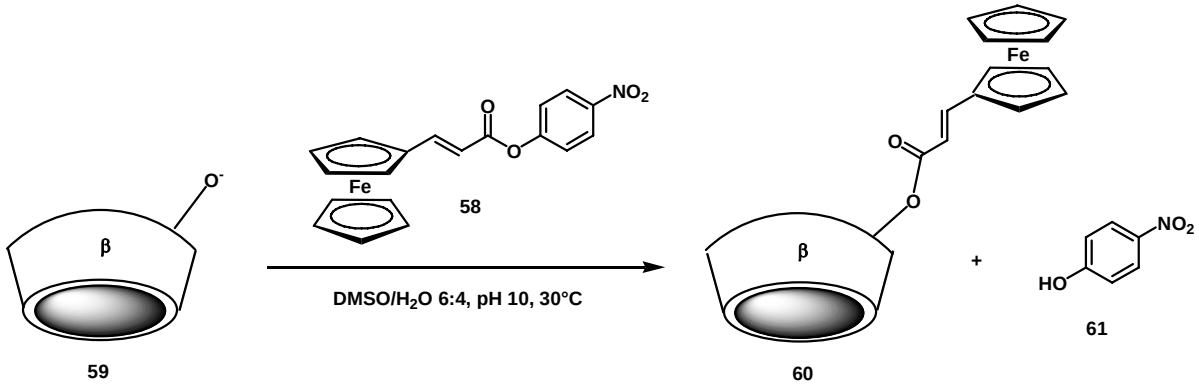
The properties discussed above make CD's attractive components in organic chemistry and supramolecular catalysis/enzyme mimics in particular[56]. A short summary follows here:

1) CD's are water soluble
2) their hydrophobic cavity can host a variety of guest molecules
3) their structure is well defined due to intramolecular H bonds
4) the hydroxyl groups allow functionalisation
5) CD's are chiral and therefore applicable to enantioselective reactions

Since β-CD is employed in this thesis, the following chapters are only dealing with β-CD-examples. α-CD's and γ-CD's are not mentioned because they are much more expensive than β-CD. In addition to this, α-CD offers a smaller binding cavity, which limits the potential substrate scope.

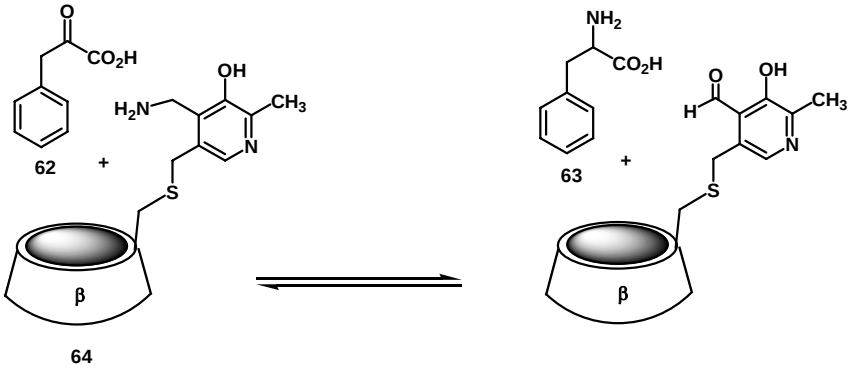
1.2.2.1 CD's in Enzyme Mimic Reactions

Breslow[57] started his pioneering work mimicking enzymatic reactions using the appropriate features of β-CD in the late 1970s. He showed that unmodified β-CD accelerates the hydrolysis of various esters at pH 10. The *p*-nitrophenyl ester of (E)-3-(carboxymethylene)-1,2-ferroceneocyclopentene **58** hydrolyzes 1.5 x 10^8 faster in the presence of β-CD *(scheme 14).* Interestingly one of the two enantiomers reacts 62-fold faster than the other one. This stereoselection is explained by the fact that β-CD forms a stronger inclusion complex with one of the two enantiomers. β-CD-oxyanion **59** attacks the carbonyl group of the ester producing acylated β-CD **60** and *p*-nitrophenol **61**. It's important to note that this reaction is not catalytic, nevertheless it can be regarded as a first imitation of an enzymatic reaction (*esterase*) using the properties of β- CD.



Scheme 14 *Hydrolysis of esters with CD-oxyanion **59***

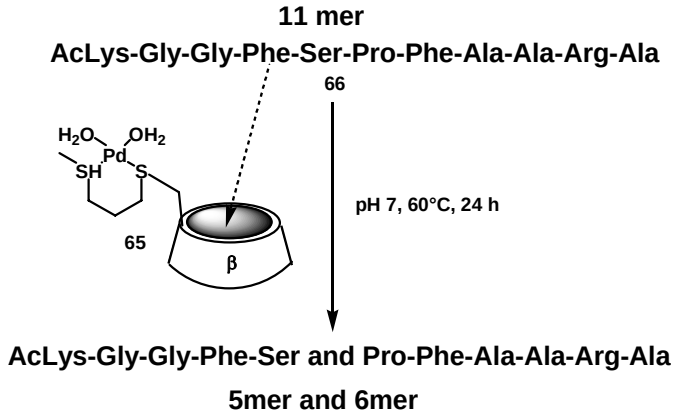
A development of so called naked CD models is the attachment of functional groups, which are able to catalyse a reaction. This leads to more sophisticated enzyme models. The functional group can either be linked to the primary or to the secondary face of CD. *Scheme 15* shows the enzyme mimic of *transaminase*, which converts α-keto acid **62** to α-amino acid **63**[58]. The cofactor pyridoxamine has been attached covalently to both sides of β-CD. Pyridoxamine derivative **64** is modified on the primary face. It was found that both model compounds were effective in the transamination process.



Scheme 15 *Transaminase model with pyridoxamine cofactor covalently attached to the primary face of CD*

An excellent example for a *peptidase* model combining a metal complex as cofactor and CD as binding site is shown in *scheme 16*[59]. *Kostic* used palladium(II) complexes attached to β-CD in **65** for the hydrolytic cleavage of non activated amide bonds at neutral pH. The selective cleavage of the 11mer peptide **66** is explained like

this: β-CD binds the aromatic side chain of the only phenylalanine (Phe) present in the peptide and thus brings the Pd(II) aqua complex near the carbonyl oxygen of proline. The Lewis acid Pd(II) ion binds to the carbonyl oxygen of proline and activates the carbonyl carbon for nucleophilic attack by a water molecule. The 11mer has been successfully cleaved into a pentamer and a hexamer.

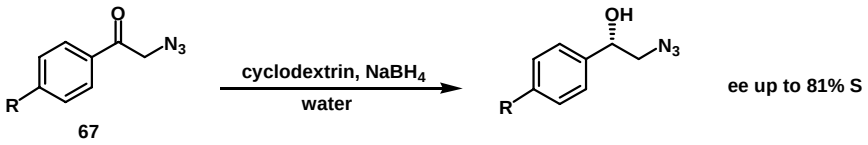


Scheme 16 *A protease model for selective cleaving of a non activated amide bond*

1.2.2.2 Asymmetric Reduction of Ketones

Furthermore, CD's are used as binding sites for dehydrogenase models. In 1978, *Sugimoto* compared the reduction of aryl trifluoromethyl ketones with either NAH (nicotinamide without the dinucleotide part) or sodium borohydride in the presence of β-CD. No ee-value higher than 10% could be observed at conversions from 20-99%[60].

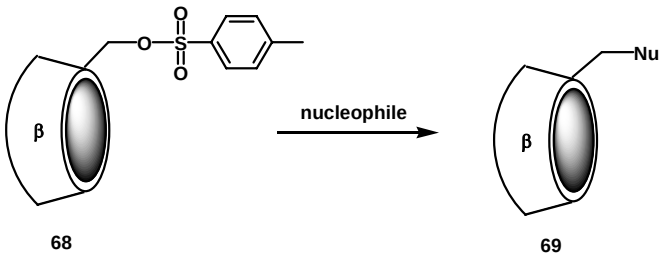
Since then, several efforts have been made to reduce ketones to their optically active secondary alcohols using β-CD as the only chiral source[61,62,63]. A rare example with enantioselectivities higher than 50% is shown in *scheme 17*. *Rao* describes the asymmetric reduction of azido arylketones **67** using sodium borohydride as the hydrogen source and stoichiometric amounts of β-CD[64]. Only three out of 17 substrates show ee's higher than 60% and no aliphatic substrates are reported. Reactive groups which can catalyze the reduction have not been covalently attached to β-CD. This is probably the reason why the stereo outcome of this reduction system is not satisfying.



Scheme 17 *Asymmetric reduction of azido arylketones using stoichiometric amounts of β-CD and $NaBH_4$*

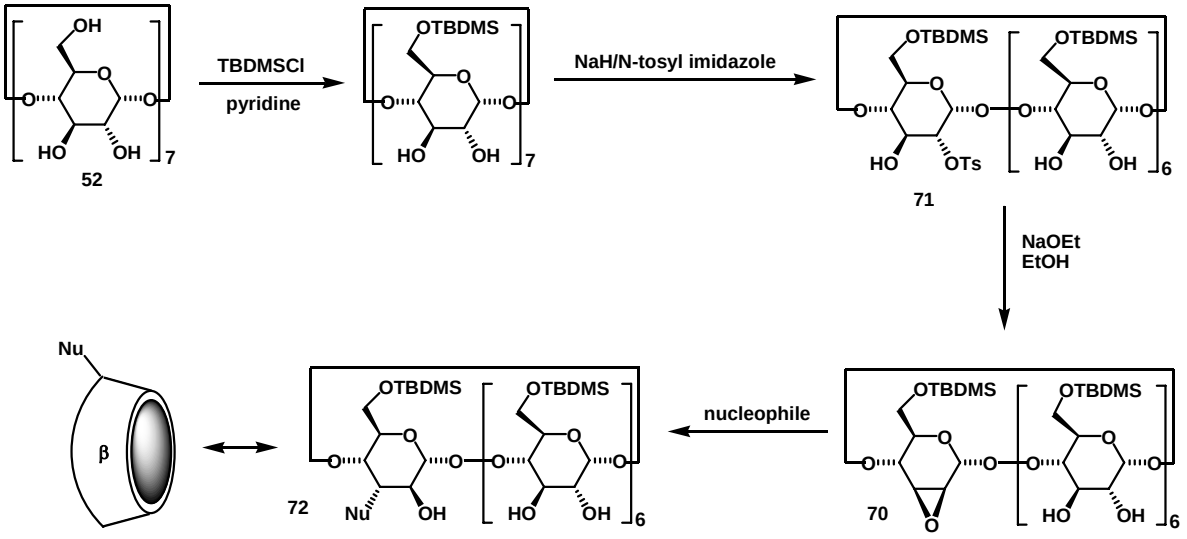
1.2.2.3 CD modified on Secondary Face

The primary face is easier to modify than the secondary one. Substitution reaction of commercially available mono-6-tosyl-β-CD **68** with various nucleophiles leads to desired product **69** in only one step (*scheme 18*). That's why much more publications are available dealing with CD's modified on the primary face.



Scheme 18 *Modification at position 6 on the primary face of β-CD*

Extremely difficult, selective one step functionalizations of unprotected CD have been reported (e.g. mono-2-tosyl-β-CD). Nevertheless they are neither reproducible nor reliable[65]. An alternative strategy was developed by *Bruncel* and goes via protection of primary alcohols[66]. The modification on the secondary face takes at least four steps (*scheme 19*).



Scheme 19 *Modification of position 3 on the secondary face of β-CD*

The key intermediate for the modification on the secondary face is 2,3-mannoepoxy-β-CD **70**, which is synthesized from β-CD **52** in three steps: protection of all seven primary hydroxyl groups with TBDMSCl followed by selective sulfonation of more acidic hydroxyl group at position 2 leads to compound **71**. Under alkaline conditions one observes **70** in an overall yield of 25%. Epoxide opening with a nucleophile leads to β-CD modified at position 3, **72**. Regioisomer (modified at position 2) is only formed in minor amounts with various nitrogen- and sulfur nucleophiles[67]. Deprotection on the primary face with fluoride finishes the synthesis of CD's modified at position 3, which undergo an interesting change in their cavity form[68]. Epoxide opening with a nucleophile of choice inverts two stereo centres (C-2 and C-3). This transforms the modified glucose into an altrose unit, which adopts no more $^4C_1$-conformation **73** but energetically more stable $^1C_4$-conformation **74**. The conformational flip occurs because three unfavourable axial substituents (at C1, C2 and C3) change to preferred equatorial positions (*figure 9*).

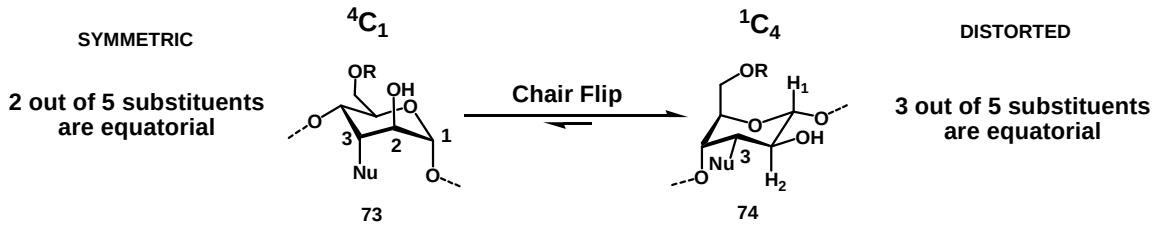
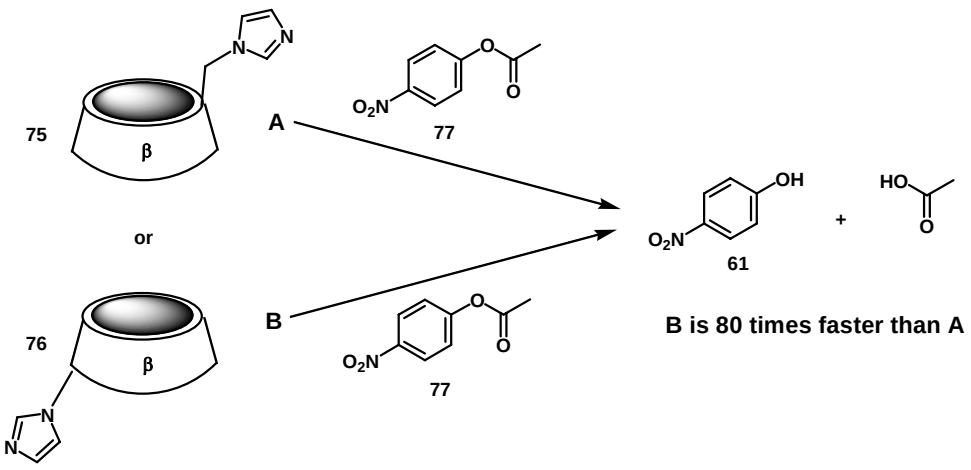


Figure 9 *Altrose-flip from $^4C_1$-conformation to the more stable $^1C_4$-conformation*

This flip causes a desymmetrization respectively a distortion of the hydrophobic cavity of β-CD. *Lichtenthaler* recently proved the distorted cavity in solid state with a crystal structure of mono[3-(2-imidazolylthio)]-altro-β-CD[69]. The conformational change can also be followed by ^{1}H-NMR spectroscopy. The coupling constant between H_1 and H_2 increases significantly from the di-equatorial ($^3J_{H1H2}$ = 3.2-3.6 Hz) to the di-axial situation ($^3J_{H1H2}$ = 6.4-7.6 Hz). *Lichtenthaler* suggested that distorted mono-altrose-CD's had interesting molecular recognition properties[69]. They are supposed to restrict the orientation of a guest molecule, and altering its own conformation to fit better the geometry of the spherical guests.

Despite of these interesting properties only few model compounds modified on the secondary face have been published so far[58,70]. It's still not clear if modification on the secondary face brings advantages compared to the easier accessible primary face. *Rao et al* covalently linked imidazole to both sides of β-CD e.g. in **75** (primary face) and in **76** (secondary face) (*scheme 20*). He observed that the hydrolysis of *p*-nitrophenylacetate **77** is 80 times faster when imidazole is bound to the secondary face instead to the primary one. *Breslow* reported similar acceleration rates using CD's modified on the secondary face (in the range of 10-100), but neither of them explained their findings.



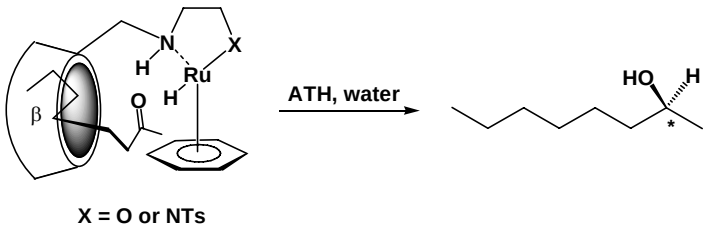
Scheme 20 *Comparison of primary and secondary face modified CD in hydrolysis of ester **77***

Three arguments indicating that the synthesis of secondary face modified CD's offer newly attractive properties are listed here:

1) The opening of the cavity on the secondary face is slightly bigger, which facilitates the penetration of the guest molecule
2) The chiral environment of secondary face modified CD's is closer to the guest, because secondary alcohols have one methylene group less
3) Unique binding properties are proposed due to a conformational flip of the modified altrose unit

2 Aim of the Work

A wide range of chiral aromatic secondary alcohols is available through ATH and AH nowadays. However these catalytic systems fail in the reduction of totally aliphatic ketones, which serve as important intermediates in modern chemistry. The goal was to design and synthesize a novel class of catalysts for the reduction of aromatic and challenging aliphatic substrates in particular. Within this context β-CD was attached covalently to Ru(II) complexes (*scheme 21*). The special binding and solubility properties of CD and the well known reactivity of ruthenium catalysts towards carbonyl bonds opens the way for the asymmetric reduction of aliphatic ketones in water.

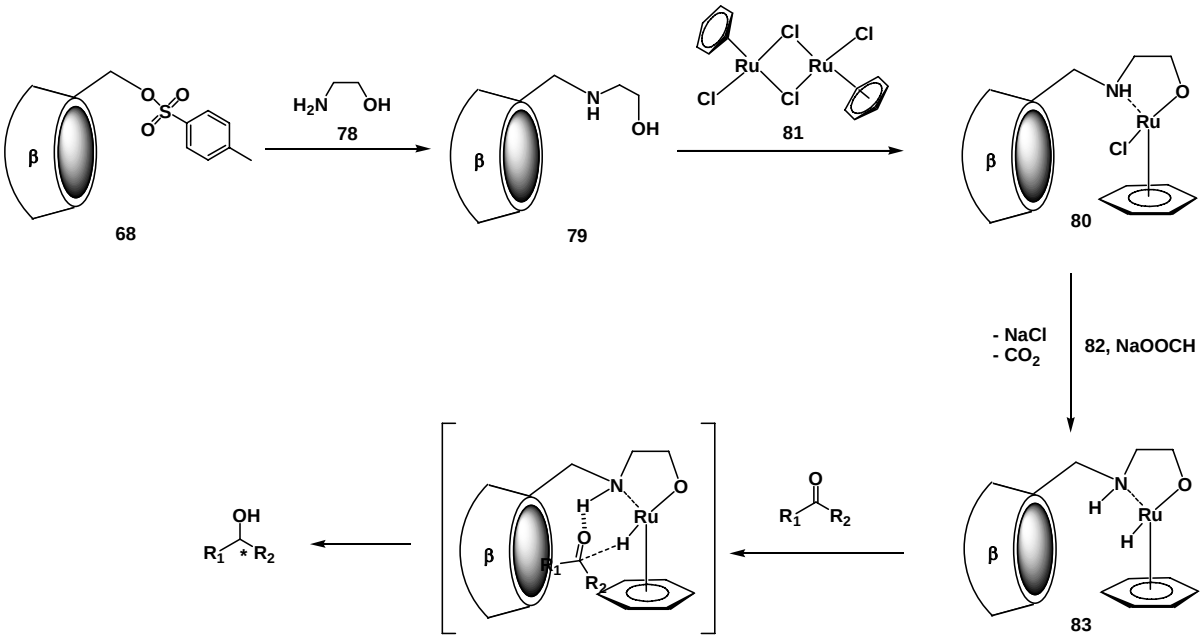


Scheme 21 *Design of new class of water soluble ATH catalyst*

3 Results and Discussion

3.1 Concept and Design of Catalyst

The idea behind this new concept is illustrated in *scheme 22*. Substitution of β-CD tosylate **68** with aminoethanol **78** leads to modified β-CD **79**, which reacts further to **80** with ruthenium dimer **81**. Ru chloride **80** undergoes hydride exchange upon treatment with excess of sodium formate **82**. Ruthenium hydride **83** consisting of a β-CD unit which is covalently linked[71] over aminoethanol **78** to a ruthenium arene complex should act as catalyst for the asymmetric reduction of various ketones. It's expected that the aryl- or alkyl rest of the ketone enters the hydrophobic cavity of β-CD and the reduction occurs according to metal-ligand bifunctional mechanism[27] involving a H bond between the carbonyl oxygen of the ketone and the amino proton of the ligand and a hydride transfer from the metal to the carbonyl carbon. **83** can be regarded as an enzyme model: the metal serves as the active site while β-CD offers the binding site. The huge advantage of this novel catalyst is that it provides not only the possibility to reduce aromatic but also notorious difficult aliphatic substrates[45,46].



Scheme 22 *Design of novel catalyst*

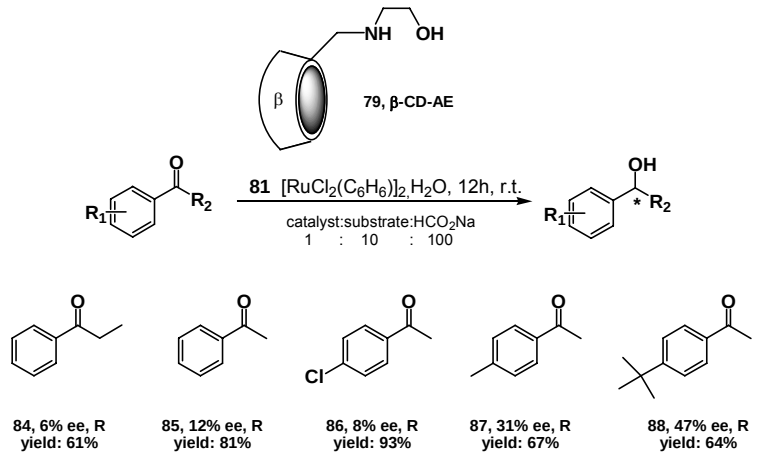
Several β-CD's modified on the primary and secondary face have been synthesised during these studies, including amino alcohols, monosulfonated diamines and α-pycolyl amines. Their ruthenium complexes have been tested for reactivity in ATH reactions to prochiral carbonyl compounds.

3.2 CD modified on Primary Face

3.2.1 Amino Alcohols as Side Chains

3.2.1.1 Initial Catalysis Results

Initially it was decided to attach cheap achiral amino ethanol **78** to the primary face of β-CD according to a known procedure[71]. Monotosylated β-CD **68** was stirred with 80 times excess **78** for 12 hours at 70°C. After precipitation of the reaction mixture in acetone and recrystallisation in water one obtained desired product β-CD-AE **79** in 53% yield as a white solid. ^{1}H-NMR spectroscopy and ESI-MS measurements clarified the structure. For catalytic reactions the Ru complexes were formed *in situ* and ketones reduced in the presence of excess of sodium formate as hydrogen source at room temperature (*scheme 23*). The reductions were performed with 10 mol% of catalyst in water at pH 8.7. The enantioselectivities of all aromatic alcohols were measured by chiral HPLC (A general catalytic procedure is given in chapter 5).



Scheme 23 *ATH with β-CD-EA and Ru(II) arene in water*

Successful reduction of five aromatic ketones **84-88** proved the concept and showed that even with β-CD as the only chiral unit of the Ru complex remarkable ee values of alcohols with predominantly (R)-configuration are accomplished. Obviously the observed ee values correlate with binding constants of ketones to β-CD[50] reflecting preorganization of substrates such that *si* addition of the hydride to the carbonyl group is preferred in the reactive complex. This reaction proceeds in a very clean way, no side products were recorded by gas chromatographic analysis

With these promising results in hand, it was decided to introduce chirality to the amino alcohol side chain. It's known from other groups[15] that the stereo outcome of Ru based ATH reactions lacking of β-CD are strongly influenced by the chirality of both carbons of the amino alcohol motif. Therefore ligands **89-92** were prepared in comparable yields according to β-CD-AE **79** (*figure 10*).

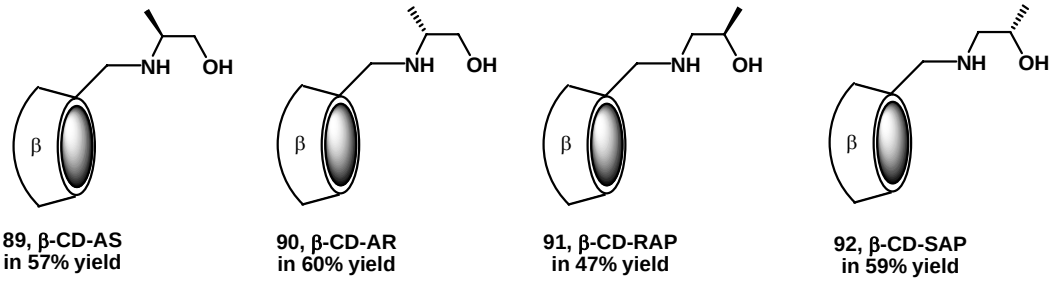


Figure 10 *β-CD bearing chiral amino alcohols*

89-92 were tested in the reduction of *p*-Cl-acetophenone **86** as standard substrate. The only difference to the conditions mentioned above is the solvent. A mixture of H_2O/DMF 3:1 was used due to solubility problems of the ligand in water only. *Table 4* shows that β-CD-SAP **92** is the best ligand in terms of yield (80%) and enantioselectivity (87% ee, S). (R)-alcohols using Ru complexes of ligand **90** and **92** and (S)-alcohols using ligands **89** and **91** were obtained. These results suggest a clear dominance of chirality of the amino alcohol on the outcome of enantioselectivity whereas the influence of the chiral centre next to the hydroxyl group of the amino alcohol is stronger than the one next to the nitrogen

Entry	Ligand	Solvent	Yield [%]	ee [%]
1	β-CD-AS	H_2O/DMF 3:1	45	72 (R)
2	β-CD-AR	H_2O/DMF 3:1	70	62 (S)
3	β-CD-RAP	H_2O/DMF 3:1	80	24 (R)
4	β-CD-SAP	H_2O/DMF 3:1	80	87 (S)

Table 4 *ATH to **86** with four chiral amino alcohols attached to β-CD in H_2O/DMF 3:1*

3.2.1.2 Optimization of Catalytic Conditions

Several attempts have been made to optimize the catalytic reduction using β-CD-SAP **92** as ligand and *p*-Cl-acetophenone **86** as standard substrate by varying the following parameters: catalyst loading and solvent (*table 5*), temperature (*table 6*), pH value (*table 7*), Ru precursor (*table 8*) and using schlenk conditions (*table 9*).

Table 5 shows that 5 mol% of catalyst lead to unsatisfying yields. β-CD-SAP is not soluble in reasonable amounts of water. To avoid rather diluted conditions with 10 mol% the transfer hydrogenation reactions were carried out in a mixture of H_2O-DMF 3:1.

Entry	Ligand	mol%	Solvent	Yield [%]	ee [%]
1	β-CD-SAP	5	H_2O (0.25 ml)	45	82
2	β-CD-SAP	5	H_2O/MeOH 3:1 (0.25 ml)	32	81
3	β-CD-SAP	5	H_2O/DMF 3:1 (0.25 ml)	33	83
4	β-CD-SAP	10	H_2O (0.50 ml)	65	82
5	β-CD-SAP	10	H_2O/DMF 3:1 (0.25 ml)	80	87

Table 5 *Optimization of catalyst loading and solvent*

An unexpected result was obtained at elevated temperatures (*table 6*). The yield at 50°C is not better compared to the one performed at room temperature. However the chiral induction decreases as expected from 87% ee to 75% ee. Indeed the ee value at 4°C is 2% higher than at 22°C but the yield is very poor.

Entry	Ligand	mol%	Temperature	Yield [%]	ee [%]
1	β-CD-SAP	10	4°C	5	89
2	β-CD-SAP	10	22°C	80	87
3	β-CD-SAP	10	50°C	76	75

Table 6 *Optimization of temperature*

In order to optimize the pH value for this specific system several formate species were tested in the presence and absence of an alkaline base (*table 7*). No product formation was observed with ammonium formate (pH 6.8, *entry 2*) or formic acid (pH 2.0, *entry 3*) as hydrogen source. Reductions performed at several pH values between 5.7 and 11.8 (*entries 4-9*) could not increase the yield. So the use of 100 equivalents of NaOOCH in H_2O/DMF 3:1 at pH 8.7 is the optimum (*entry 1*). These results correlate with studies from other groups reporting that the reduction using formate in water is pH dependent[72] and high reactivity is only observed at pH 5-9 while it drops dramatically down at lower pH values. The main problem at low pH is that the formate species exists predominantly in the protonated form at pH < 3 due to a pK_a value of 3.6 for HCOOH in water, which makes the formation of the Ru formato complex more difficult. Furthermore the oxygen of the amino alcohol is protonated at low pH, which results in decomposition of the Ru complex.

Entry	Ligand	mol%	Formate	Additive	eq.	pH	Yield [%]	ee [%]
1	β-CD-SAP	10	NaCOOH	No	100	8.7	80	87 (S)
2	β-CD-SAP	10	NH_4COOH	No	100	6.8	0	n.d.
3	β-CD-SAP	10	HCOOH	No	100	2.0	0	n.d.
4	β-CD-SAP	10	NaCOOH	No	10	7.9	57	87 (S)
5	β-CD-SAP	10	NaCOOH	5% HCOOH	100	5.7	73	87 (S)
6	β-CD-SAP	10	NaOOCH	1mM NaOH	100	8.9	63	87 (S)
7	β-CD-SAP	10	NaOOCH	2mM NaOH	100	10.4	73	87 (S)
8	β-CD-SAP	10	NaOOCH	2mM NaOH	10	11.1	68	88 (S)
9	β-CD-SAP	10	NaOOCH	10mM NaOH	10	11.8	56	87 (S)

Table 7 *Optimization of pH value*

Ru cymene reduces model substrate **86** in similar ee's as Ru arene **81** does (*table 8*). The lower yield can be addressed to the steric hindrance of *p*-cymene which hampers the substrate to enter the cavity and form the inclusion complex. Ru(COD) halide precursor shows no activity at all, most likely due to solubility problems of the complex in aqueous solution.

Entry	Ligand	mol%	Ru precursor	Yield [%]	ee [%]
1	β-CD-SAP	10	$Ru[Cl_2(arene)]_2$	80	87 (S)
2	β-CD-SAP	10	$Ru[Cl_2(p\text{-cymene})]_2$	53	82 (S)
3	β-CD-SAP	10	$RuCl_2(COD)$	0	n.d.

Table 8 *Varying the Ru precursor*

The reduction was also tested with so called schlenk technique using degassed solvents under an argon atmosphere (*table 9*). The values under air atmosphere are given in parentheses. Actually the yields could be increased about 20% with a slight loss of enantioselectivity. The Ru complex is probably oxidised in the presence of oxygen and loses therefore some catalytic activity.

Entry	Substrate	Ligand	mol%	Yield [%]	ee [%]
1	**86**	β-CD-SAP	10	99 (80)	82 (S), 87 (S)
2	**86**	β-CD-SAP	5	42 (33)	76 (S), 83 (S)
3	**88**	β-CD-SAP	10	65 (51)	96 (S), 97 (S)

Table 9 *Catalysis under schlenk conditions*

3.2.1.3 Reduction of Aromatic and Aliphatic Ketones with β-CD-SAP

β-CD-SAP was chosen to testify that this system is not limited for one substrate. Several aromatic prochiral ketones were reduced under standard conditions: 10 mol% catalyst, H_2O/DMF 3:1 as solvent, Ru arene as metal precursor, at room temperature under an air atmosphere for 12 hours at pH 8.7.

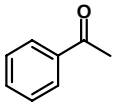
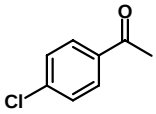
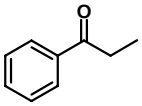
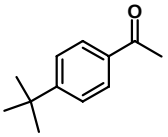
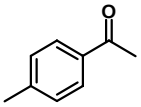
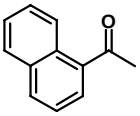
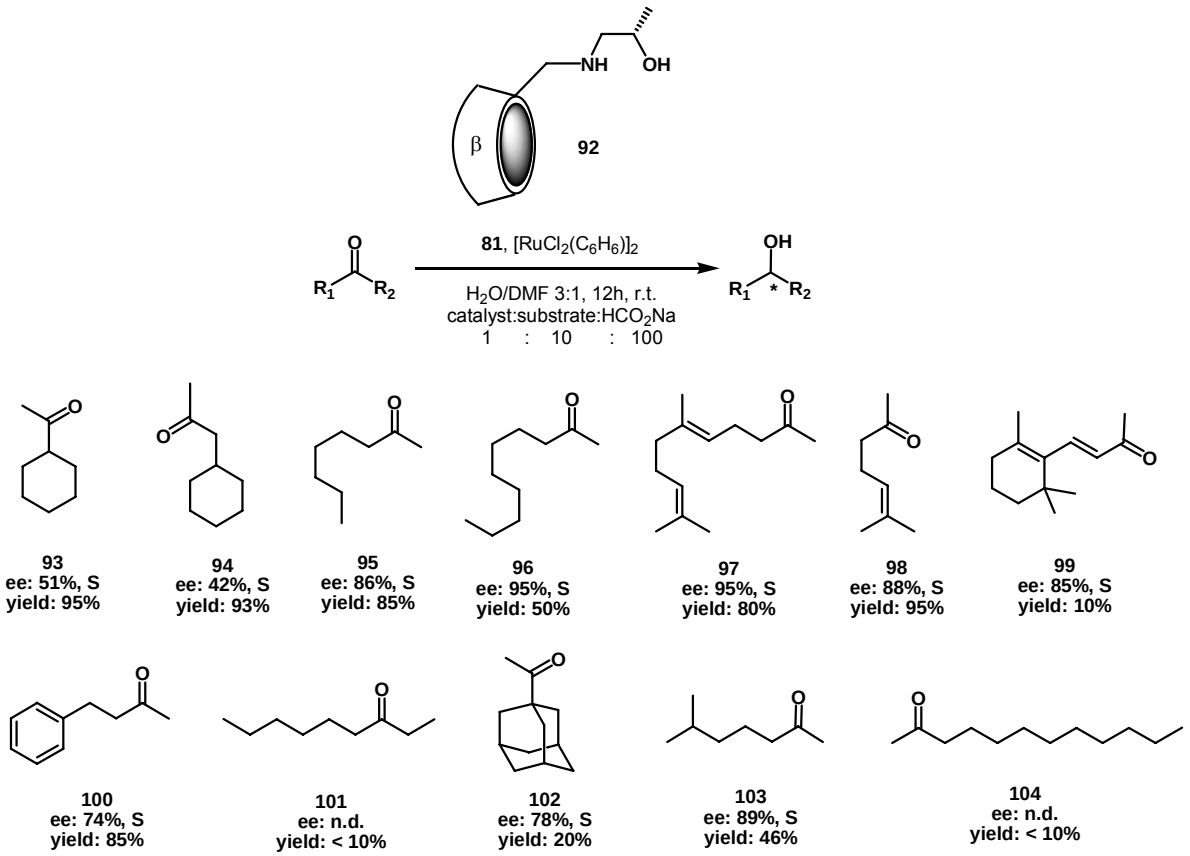
Entry	Substrate	Yield [%]	ee [%]	Entry	Substrate	Yield [%]	ee [%]
1		90	77 (S)	4		80	87 (S)
2		63	80 (S)	5		51	97 (S)
3		69	94 (S)	6		40	87 (S)

Table 10 *Catalysis with β-CD-SAP*

According to results summarized in *table 10* employing β-CD-SAP enantiomeric purity of products was achieved as high as 97% and in acceptable yield. It is interesting to note that using **92** as a Ru ligand, acetophenone **85** was reduced to the (*S*)-alcohol exhibiting 77% ee, in contrast the Ru complex of (*S*)-1-amino-2-propanol lacking the β-CD unit gave the (S)-product in only 35% ee[18].

Demonstrated that this novel catalytic system is able to reduce prochiral aromatic ketones with high enantioselectivities the ultimate goal of this project was envisaged: The asymmetric reduction of challenging totally aliphatic carbonyl compounds. For initial studies non prochiral aliphatic substrates were used, just to check if they show any reactivity under the described conditions. 4-Methyl-cyclohexanone (100% yield) and cycloheptanone (50% yield) demonstrated that it's possible to reduce aliphatic ketones as well. This positive outcome encouraged to test various prochiral aliphatics **93-104**. The results using standard conditions are summarised in *scheme 24*.



Scheme 24 *The reduction of challenging aliphatic ketones*

Most substrates could be reduced in good yields. The unsatisfying yields of **99**, **101, 102** and **105** are probably caused by solubility problems of long alkyl chains in aqueous solution. But more importantly the enantioselectivities of six alcoholic products are higher than 85%. 2-Decanone **95** and geranylacetone **97** showed even ee's of 95%, indicating that the concept works for non aromatics as well. No conventional metal catalyst lacking of β-CD achieves such good selectivities for the reduction of totally aliphatic ketones up to date[73].

The olefinic bonds were not reduced in compounds **97**, **98** and **99** at all. Furthermore styrene was stirred at 50°C in the presence of the catalyst. No alkane was detected after 3 days confirming that the reaction occurs strongly chemoselective.

Those enantiomers which could not be separated by chiral gas chromatography were converted to mosher esters using enantiomerically pure (R)-α-methoxy-α-trifluoromethylphenylacetic chloride to determine their ee values (*figure 11*)[74]. *Mosher* explained that the non-equivalence of the α-CF_3 resonances in the

two resulting diastereomeric esters is based on anisotropic deshielding of the α-CF_3 substituent by the ester carbonyl.

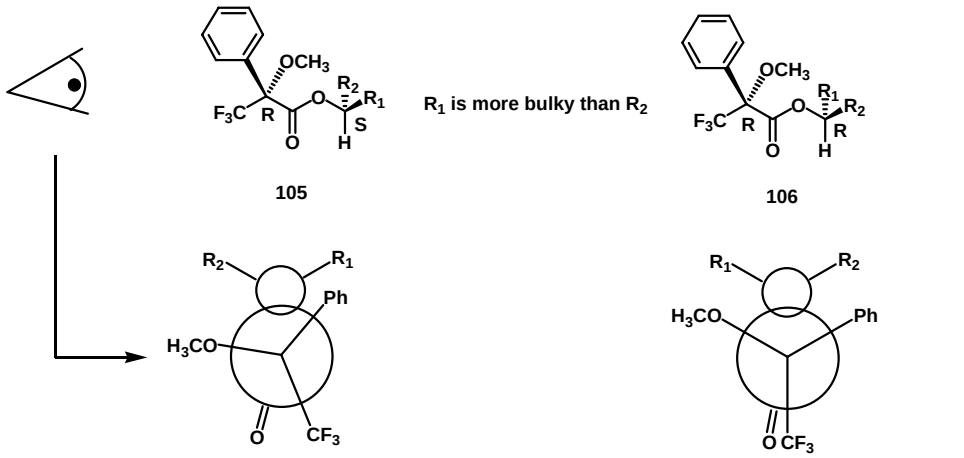


Figure 11 *Explains the relative up- and downfield shift in mosher esters*

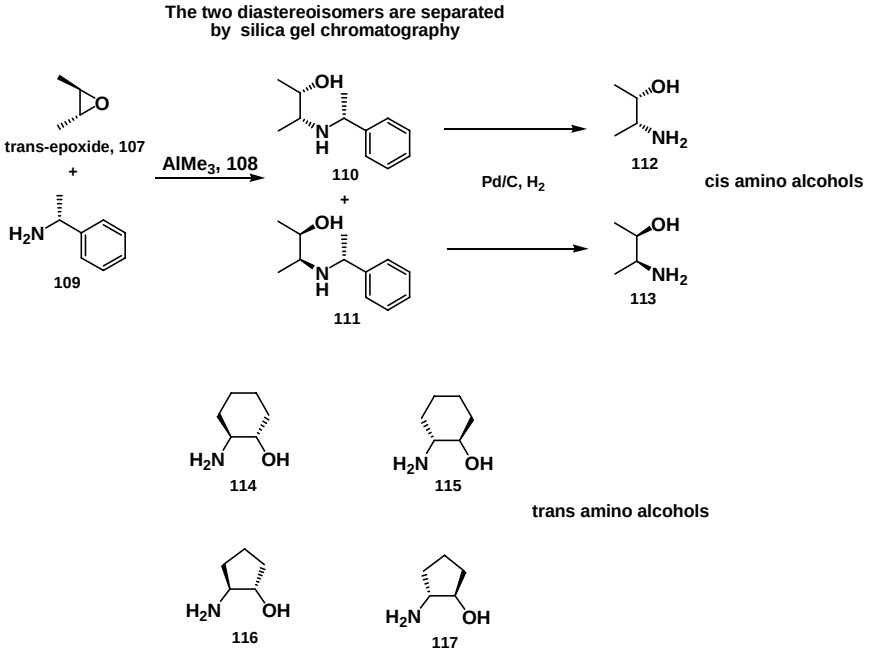
The following assumptions are made:

1) R_1 is bulkier than R_2
2) The phenyl group is bulkier than the methoxy group
3) All interactions are of steric nature.

The CF_3 group is normally coplanar with the carbonyl of the ester and therefore strongly deshielded by the anisotropic field of the polar C=O double bond. We now compare the steric interactions of the two diastereomeric esters **105** and **106**. The interactions are stronger in the case of **105**, because of bulky phenyl group is interacting with bulky R_1. On the contrary steric interactions are minimized in ester **106**. As a result of this the CF_3 group of ester **105** is much more forced out of coplanarity with the carbonyl bond, which explains the relative upfield shift. Treating an alcohol with enantiomerically pure mosher chloride allows determination of the ee and the absolute configuration of the alcohol in an elegant way.

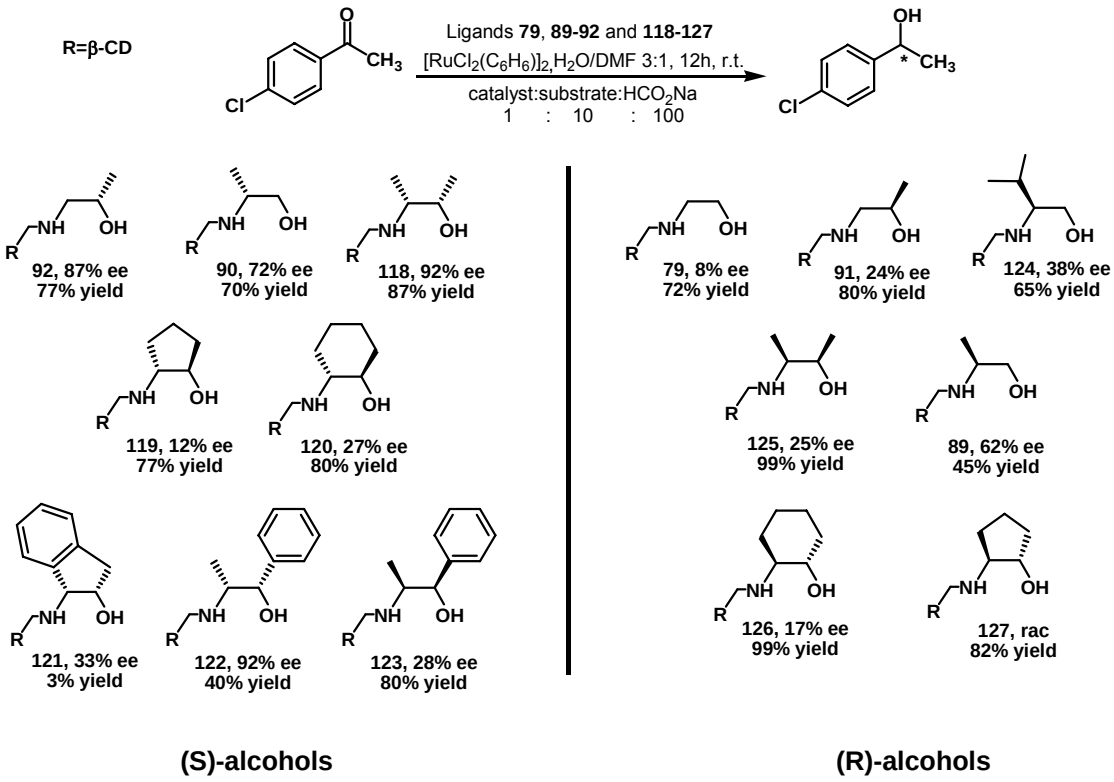
3.2.1.4 Ligand Screening with various chiral Amino Alcohols

Ligand screening with numerous amino alcohols attached to β-CD was performed in order to increase the reactivity and selectivity of the catalytic process. Some amino alcohols were not commercially available and had to be synthesised by epoxide opening with chiral nitrogen nucleophiles[75] (*scheme 25*). For example *trans*-epoxy-butane **107** was opened using stoichiometric amounts trimethylaluminium **108** and enantiopure (R)-(+)-methylbenzylamine **109**. The two diastereotopic secondary amines **110** and **111** could be separated by silica gel chromatography. Removal of the protecting group with palladium on charcoal under hydrogen atmosphere lead to desired products **112** and **113** in overall yields of 50%. The enantiomeric purity of the *cis*-amino alcohols was shown to be higher than 98% by ^{1}H-NMR analysis of diastereomeric precursors **110** and **111**. The absolute configuration of this novel compound was obtained by x-ray analysis of intermediates **110** and **111**. *Trans*-analogues **114-117** were prepared in the same manner starting from cyclohexene oxide and cyclopentene oxide in similar yields. Comparison of the optical rotation with reported values let assign the enantiomers[76].



Scheme 25 *Synthesis of chiral cis- and trans-amino alcohols*

Modified cyclodextrins **118-127** were obtained from tosylated β-CD **68** in yields around 50%. The ligands were applied to ATH with Ru arene complexe **81** under standard conditions using *p*-Cl-acetophenone **86** (*scheme 26*). The model substrate was selected because the ee values could be determined easily by chiral HPLC chromatography. Furthermore the observed ee values of 87% with **92** leaves some room for improvement.

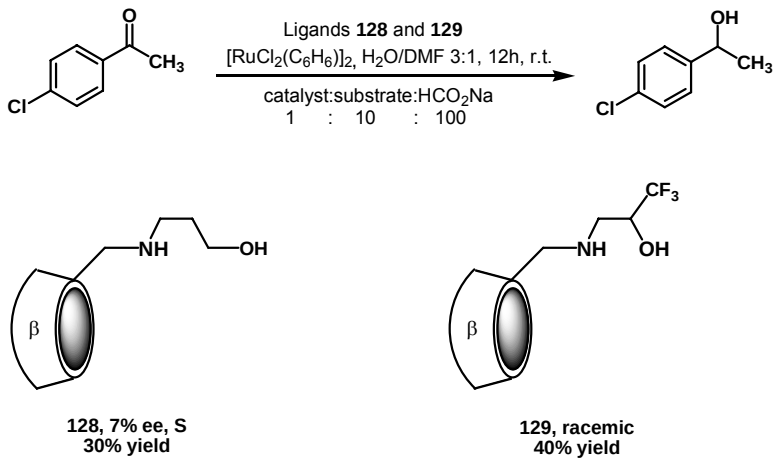


Scheme 26 *Ligand screening with various chiral amino alcohols*

12 out of 15 ligands show good to excellent yields. The only unreactive amino alcohol is indanol with only 3% conversion. *Scheme 26* is divided in two parts: ligands on the left side having alkyl groups looking to the back produce (S)-alcohols, ligands on the right side possessing bulky substituents looking to the front lead to (R)-products. It's interesting to note that norephedrine derivative **121** is the only exception (28% ee, S). Cyclic *trans*-amino alcohols (**119**, **120**, **126** and **127**) are not competitive with open chained *cis* analogues indicated by very poor enantioselection reaching from racemic to 27% ee only. It's not necessary to introduce bulkier alkyl groups than methyl. For example **124** bearing an isopropyl rest (38% ee, R) is less enantioselective than alaninol based **89** (62% ee, R) and **122** (92% ee, S) gives the

same ee value as **118** bearing less hindered substituents. So one can summarise that CD preorganizes the substrate in the hydrophobic cavity and the *si*- respectively *re*-face attack of the hydride is strongly affected by the stereo centres of the chiral side chains. The absolute configuration of the alcoholic product can be controlled by proper adjustment of the stereogenic centres of the amino alcohol motif. Only two examples lead to higher ee's than β-CD-SAP **92**. *Cis*-amino alcohols **122** and **118** could improve the stereo outcome from 87% to 92%. Unfortunately both ligands have a disadvantage. 40% yield is not satisfying in case of norephedrine derived **122**. And an increase of 5% ee doesn't legitimate the additional expense of two more synthetic steps to obtain ligand **118**.

Two more ligands were prepared for the purpose of improving the system. 1,3-amino alcohol **128** was linked to β-CD to see if a six membered chelate ring of the amino alcohol with the metal centre is better than the five membered described by Noyori[13]. Trifluoromethyl group was introduced in ligand **129** by reacting racemic 1,1,1-trifluoro-3-amino-2-propanol with tosylate **68** to check the influence of an electron withdrawing group at the side chain. The reactivity was tested with aromatic standard ketone **86** under standard conditions (*scheme 27*).



Scheme 27 *ATH with β-CD bearing a γ–amino alcohol respectively a CF_3 group*

Both ligands **128** and **129** gave 1-(4-chlorophenyl)ethanol in lower yields (30%, 40% respectively) and poorer enantioselectivities (7% ee R, racemic respectively) than **79**.

3.2.1.5 Aromatic vs. Aliphatic Standard Substrate

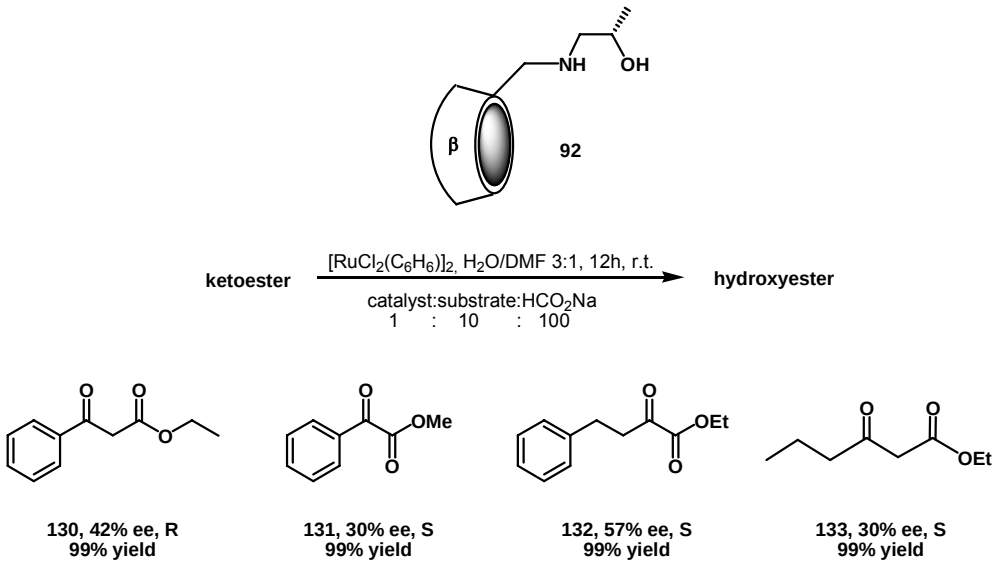
Aliphatic model compound 6-methyl-5-ene-2-heptanone **98** which can be analyzed by chiral GC was reduced with six of the ligands mentioned above and compared with the results obtained with aromatic **86**. *Table 11* shows that the enantioselectivities of the two ketones are matching very well. This obvious trend is important because the risk to miss a good ligand for aliphatics is very small testing the ligands with aromatic substrate **86** which is easier to analyze with the equipment available in our laboratories.

Ligand	*p*-Cl-acetophenone, 86	6-methyl-5-ene-2-heptanone, 98
79, β-CD-AE	8% ee (R); 73% yield	27% ee (S); 52% yield
92, β-CD-SAP	87% ee (S); 88% yield	88% ee (S); 90% yield
90, β-CD-AR	62% ee (S); 70% yield	88% ee (S); 37% yield
118, β-CD-SRDM	92% ee (S); 87% yield	90% ee (S); 60% yield
125, β-CD-RSDM	25% ee (R); 99% yield	24% ee (R); 84% yield
128, β-CD-AP	7% ee (S); 30% yield	13% ee (S); 30% yield

Table 11 *Aromatic **86** versus aliphatic **98** standard compound*

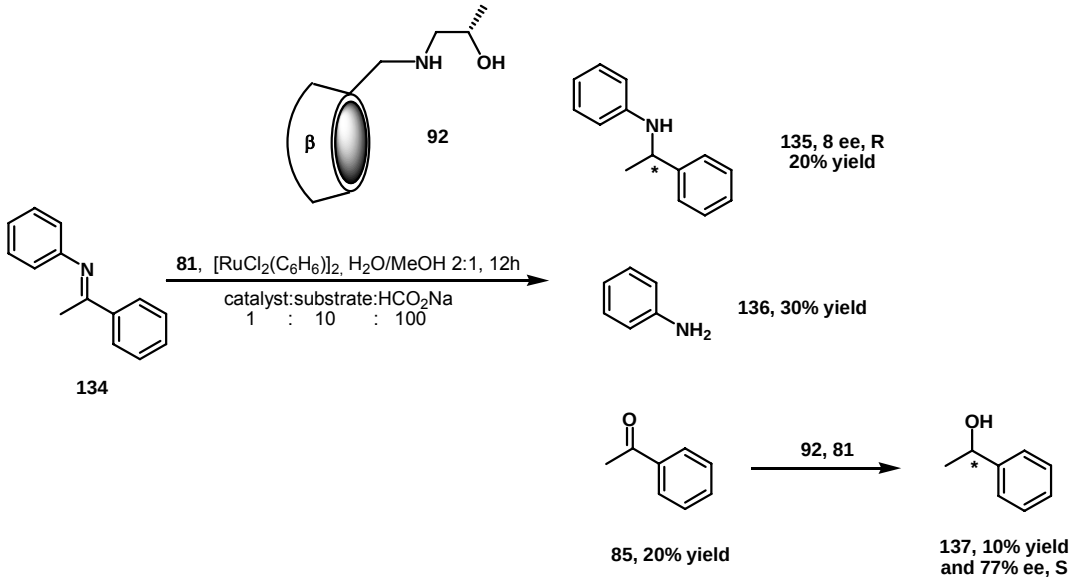
3.2.1.6 Substrate Scope

The substrate scope was extended by applying the new catalytic system to ketoesters. Quantitative conversions were observed for all four substrates, including one aromatic β-ketoester (**130)**, two aromatic α-ketoesters (**131** and **132**) and aliphatic α-ketoester **133**. The enhanced reactivity is probably caused by the higher electrophilicity of the carbonyl carbon due to electron withdrawing properties of the neighbouring ester functionality. The stereoselectivities remained on a moderate level reaching 57% ee as a maximum for **132**. All reductions were performed under standard conditions using β-CD-SAP as a ligand (*scheme 28*). The ee values were determined by chiral HPLC chromatography.



Scheme 28 *ATH to ketoesters **130-133***

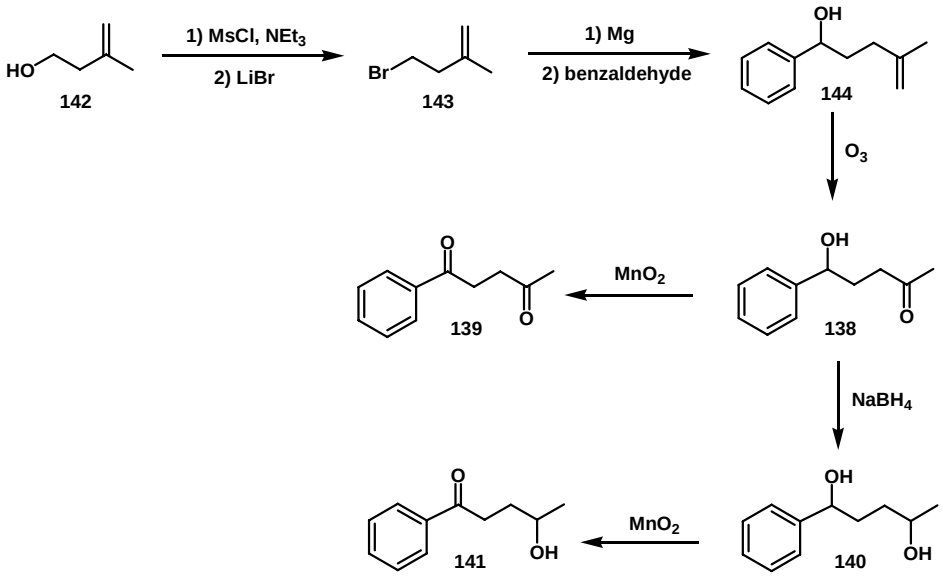
ATH reactions are not limited to carbonyl compounds. Hydride transfer to the carbon-nitrogen double bond of imines results in chiral amines, which are important precursors for fine chemicals and agrochemicals in particular[2,13]. Hence β-CD based catalyst **92** was tested with aromatic imine **134** using slightly modified standard conditions. The reduction was performed in a water/methanol mixture 2:1 due to solubility problems of the substrate (*scheme 29*).



Scheme 29 *ATH to prochiral imine **134***

The reaction gave a mixture of five compounds as could be analyzed by HPLC chromatography. The peaks were identified as starting material **134** (20%), desired secondary amine **135** (20%), aniline **136** (30%), acetophenone **85** (20%) and alcohol **137** (10%). This means that imine **134** is hydrolyzed under basic conditions and the corresponding ketone **85** reacts further to (S)-**137** in 77% ee as could be demonstrated earlier. The optical yield of the secondary amine **135** is very poor (8%, R). The loss of chiral induction compared to the reduction of carbonyl bonds can be addressed to the weaker H bond and there from less distinctive preorganization of the substrate in the hydrophobic cavity of CD.

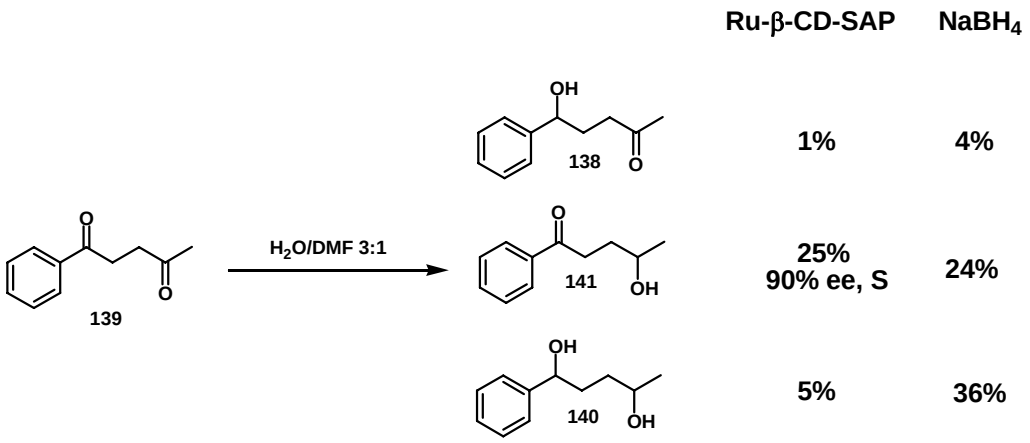
Compounds **138-141** were synthesised to discover if it's possible to reduce unsymmetrical diketones regioselectively, like enzymes can do[47] (*scheme 30*). 3-Methylbut-3-en-1-ol **142** was transformed to bromide **143**. *Grignard* reaction with benzaldehyde gave secondary alcohol **144** in 66% yield. Ozonolysis afforded 1,4-hydroxyketone **138** which opened the way for the synthesis of diketone **139** via allylic oxidation and diol **140** via $LiAlH_4$ reduction. Oxidation with manganese dioxide gave 1,4-hydroxyketone **141** in 62%.



Scheme 30 *Synthesis of diketone **139** and possible reduction products*

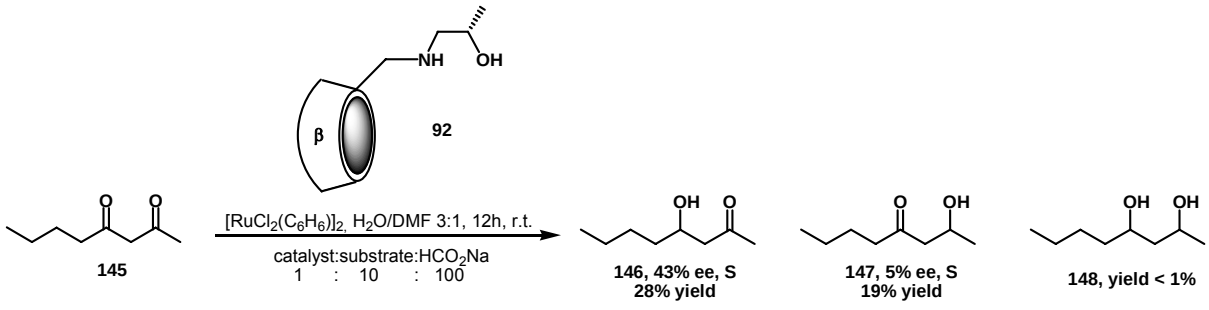
The reduction of diketone **139** was performed with stoichiometric amounts of $NaBH_4$ respectively 10 mol% of β-CD-SAP **92** (*scheme 31*). $NaBH_4$ produces much

more diol **140** than β-CD-SAP and the ratio of **141** to **138** is 24:4. This selectivity can be explained with electron donating properties of the phenyl ring which lowers the electrophilicity of the carbon close to the aromatic moiety. The ratio of 25:1 for **141** to **138** using β-CD-SAP (four times as selective as $NaBH_4$) suggests that the hydrogen bond from the amine of the ligand to the carbonyl oxygen closer to phenyl ring is less preferred than to the other one. This results in a considerable regioselective outcome of the reduction.



Scheme 31 *Regioselective reduction of aromatic diketone **139***

The reduction of aliphatic octan-2,4-dione **145** using β-CD-SAP was less regioselective. The ratio of the formation of **146** to **147** is only 3:2 (*scheme 32*). This result is not surprising since the difference in electrophilicity of the two carbonyl carbons is marginal. Again, only traces of diol **148** were produced demonstrating that hydroxylketones do not react further with β-CD-SAP. This is in contrast to conventional sodium borohydride reduction yielding predominantly diol **148**.



Scheme 32 *Regioselective reduction of aliphatic diketone **145***

3.2.1.7 Structure Elucidation and Mechanistic Aspects

The structure of β-CD ligands could be elucidated by ^{1}H-NMR (1-D and 2-D), ESI mass spectroscopy and sometimes also with x-ray diffraction. The special analysis features of modified β-CD's are discussed on the basis of β-CD-SAP **92**. 500 MHz ^{1}H-NMR spectra were measured in D_2O (solvent peak 4.79 ppm). All hydroxy protons are exchanged with deuterium and are therefore not visible (*figure 12*). The region around 5.0 ppm shows all seven anomeric protons H_1 of **92** which are characteristically shifted downfield and well separated from all other sugar protons (H_3, H_5, H_6, H_2 and H_4) between 4.0 and 3.5 ppm. The doublet at 1.09 ppm with a coupling constant of 6.3 Hz belongs to the methyl group of the amino alcohol. The multiplet at 2.56 ppm corresponds to the two protons α to nitrogen. Three other resonances are separated from the huge sugar peak: Both H_6 (2.81 and 3.02 ppm) of the modified sugar unit and one H_4 (3.38 ppm) of a neighbouring glucose as could be revealed by additional 2-D experiments (COSY and TOCSY). The α-proton of the hydroxy group of the side chain is hidden under the sugar peak at 3.89 ppm.

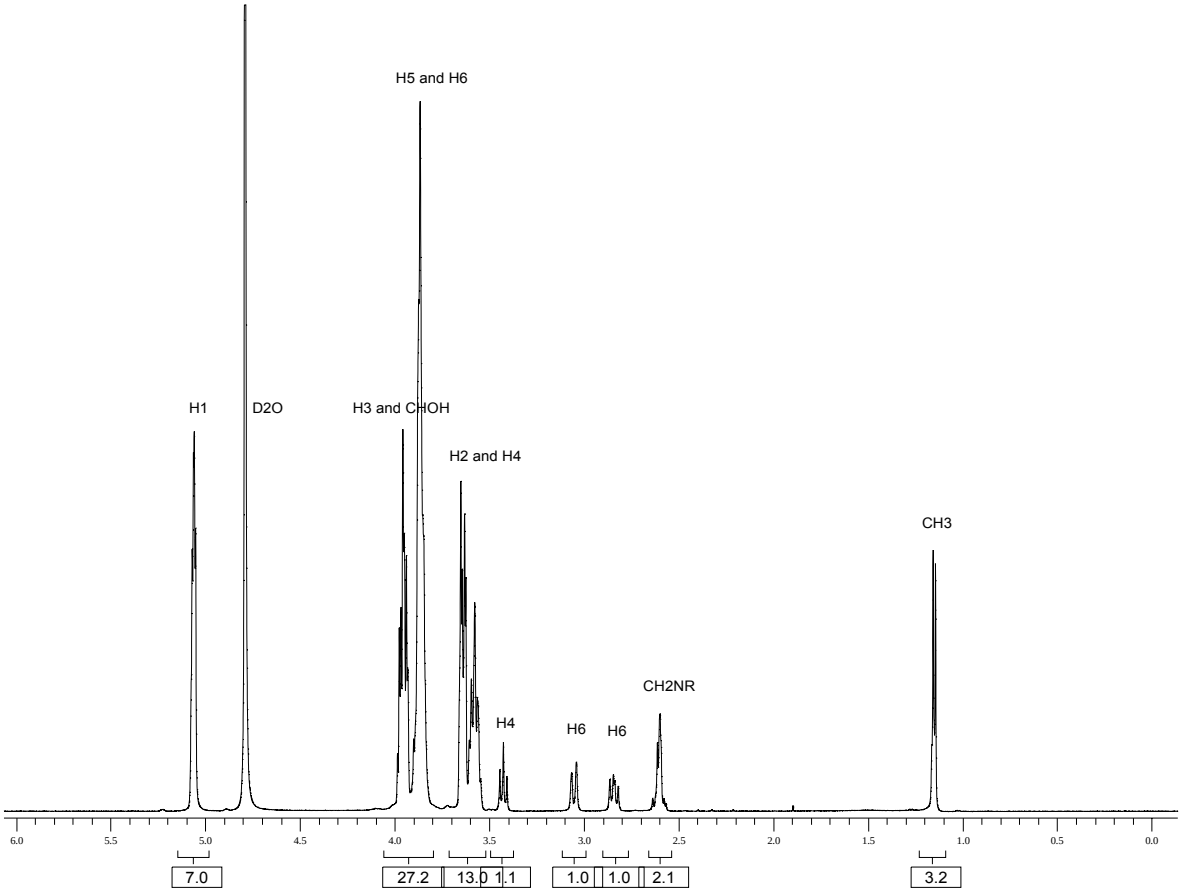


Figure 12 *^{1}H-NMR spectroscopy of β-CD-SAP **92***

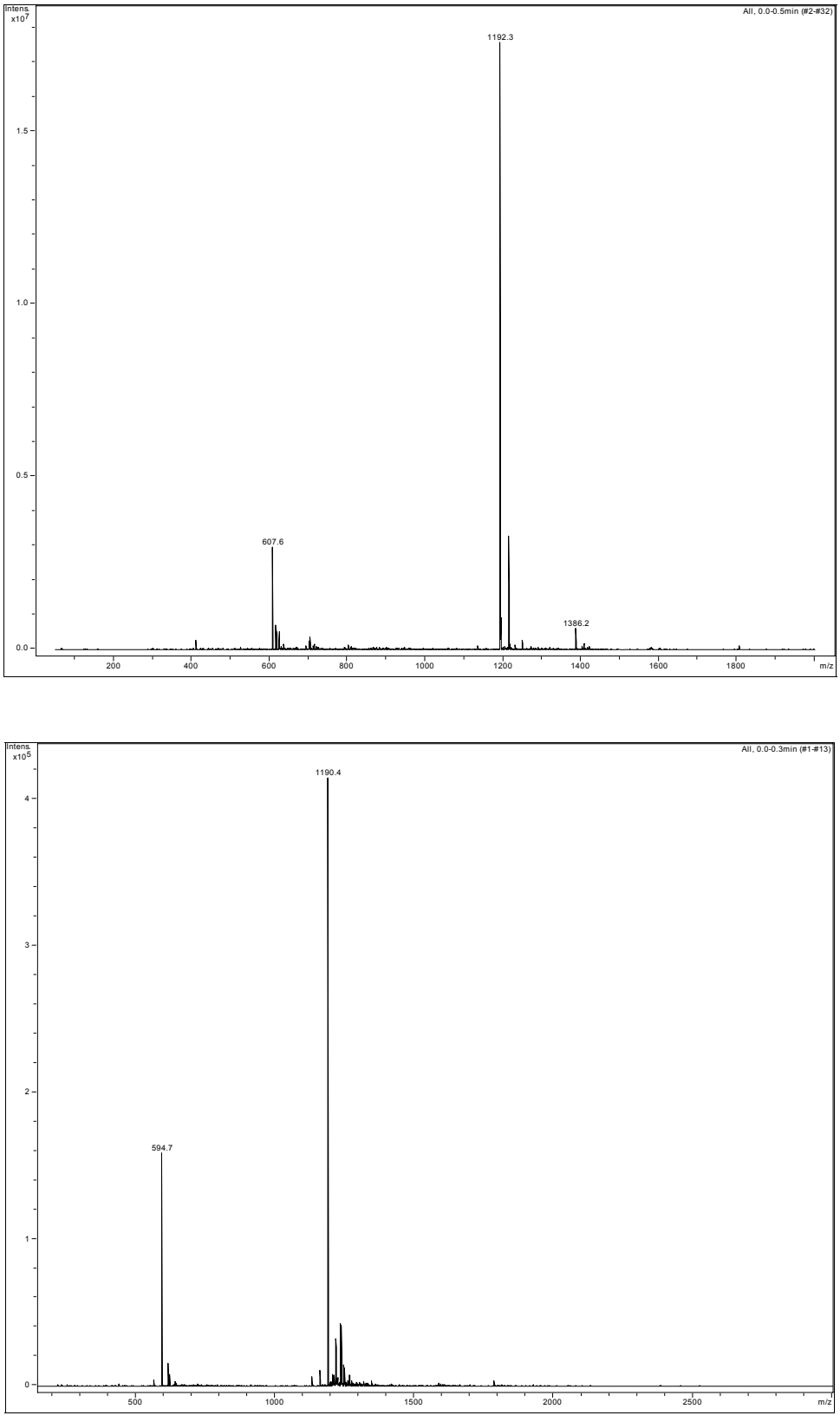


Figure 13 *ESI-MS with β-CD-SAP: top: positive mode; bottom: negative mode*

The exact mass of β-CD-SAP **92** is (1191.43 g/mol). Since all amino alcohol modified β-CD's are carrying nitrogen atoms which can easily be ionized, ESI-MS positive mode spectra showed usually good intensities (*figure 13*). Beside the molecule ion m/z = 1192.3 $[M+H]^+$ it was possible to identify two other peaks: $[M+Na]^{2+}$ at 607.6 and $[M+Na]^+$ at 1214.3. Ionization in the negative mode shows m/z = 1190.4 $[M-H]^-$ and m/z = 594.7 $[M-H]^{2-}$.

The x-ray structure of β-CD-SAP clearly shows the newly formed covalent bond between the nitrogen of the amino alcohol and β-CD (*figure 14 and 15*). The absolute configuration of the stereo centre on the side chain is S. The cavity of β-CD is symmetric and the opening of the primary face is significantly smaller than on the secondary face.

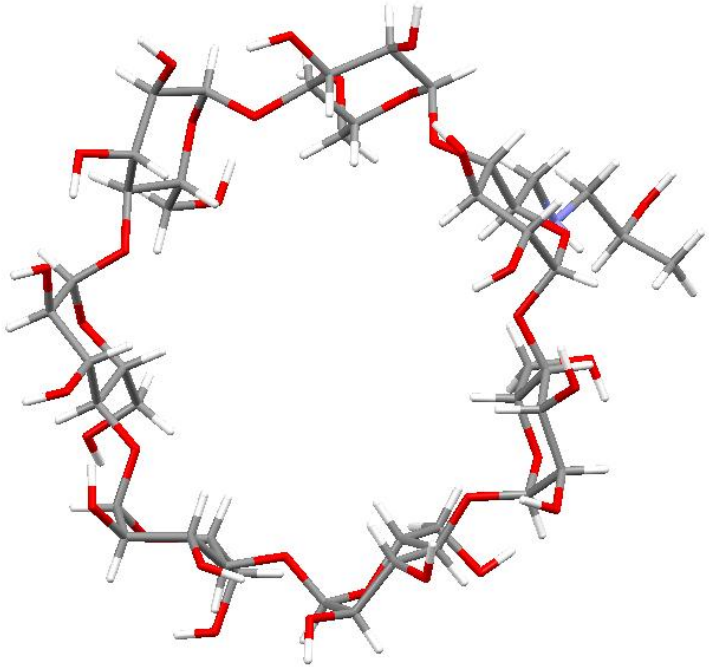


Figure 14 *X-ray front view of β-CD-SAP* ***92***

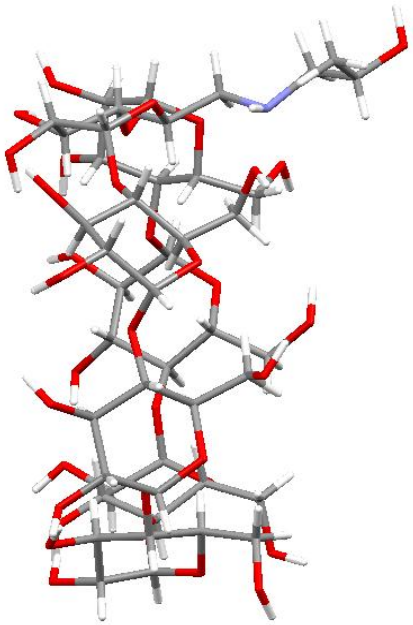


Figure 15 *X-ray side view of β-CD-SAP* ***92***

In addition to the three methods mentioned above modified CD's were analyzed by TLC on silica gel in a very polar solvent system (EtOAc/*i*-PrOH/NH_4OH/H_2O 7:7:5:4). The spots were visualized by spraying the plates with a solution of 250 ml ethanol and 6 g anisaldehyde in 2.5 ml concentrated sulphuric acid. In this way it was possible to follow the reaction as well as to get an idea of the purity of the products. HPLC analysis was not possible because the compounds are lacking a chromophore while GC analysis could not be performed due to unpractical high boiling points of CD.

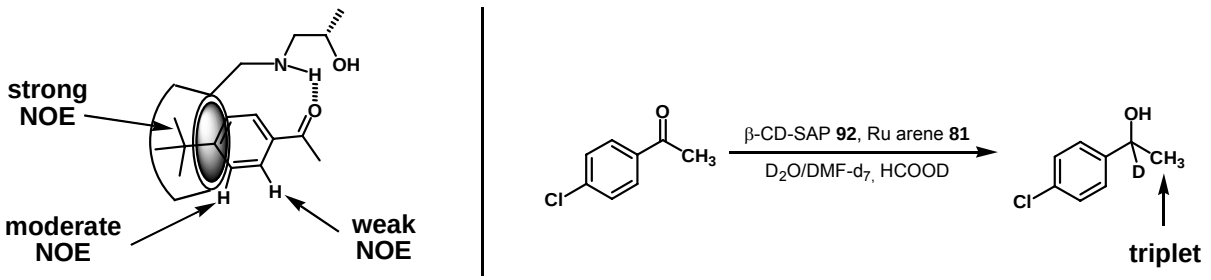
Formation of Ru chloro complex **149** (according to structure **80**, page 26) from β-CD-SAP **92** and metal precursor **81** was demonstrated to be quantitative by ^{1}H-NMR measurements. Significant downfield shifts of several protons relative to free ligand **92** are shown in *table 12*. The two protons H_6 belong to the primary alcohol of the modified sugar unit of β-CD and C_1-H stands for the protons next to the nitrogen of the amino alcohol. A second argument for complex formation are the two peaks in the ESI-MS positive mode which could be identified as m/z = 1406 [**149**]$^+$ and 1371 [**149**-Cl]$^+$.

Proton	H'_6	H''_6	C_1-H'	C_1-H''
Shift (ppm)	0.56	0.51	0.36	0.51

Table 12 *^{1}H-NMR downfield shifts of Ru complex **149** relative to **92***

Although all aromatic protons of the arene moiety in **149** appeared in a single singlet at 5.34 ppm one can not take this as an evidence for diastereopure metal complex formation, since one could not observe the other diastereomeric Ru complex. However, catalysis results with enantioselectivities up to 98% suggest an explicit dominance of one Ru diastereoisomer.

Binding constants of *p*-Cl-acetophenone (1040 M^{-1}) **86** and 1-(4-chlorophenyl)ethanol (400 M^{-1}) **150** with β-CD-SAP were measured by ^{1}H-NMR titrations in D_2O/DMF-d_7. Protons H_3 and H_5 of β-CD which are pointed inside the cavity showed significant downfield shifts by increasing the guest concentration. The alcoholic product binds less than halve as strong as the starting material. This result is very essential for the catalytic process since a higher binding constant of the alcohol would inhibit the reaction by occupying the cavity of β-CD. The better binding affinities of **86** can be ascribed to the additional H bond from the carbonyl oxygen to the amino proton of the amino alcohol. A ROESY spectra of ligand **92** and *p-tert*.-butylacetophenone **88** provided evidence that the substrate really enters the cavity. Strong cross peaks of H_3 and H_5 from β-CD could be observed with the *tert.*-butyl group of the ketone. Furthermore moderate respectively weak cross peaks were found for *meta*- and *ortho* protons of the aromatic ring, indicating that the carbonyl compound enters the cavity with the hydrophobic *tert.*-butyl rest ahead (*scheme 33: left*).



Scheme 33 *left: Substrate **88** enters the cavity; right: incorporation of D$^-$*

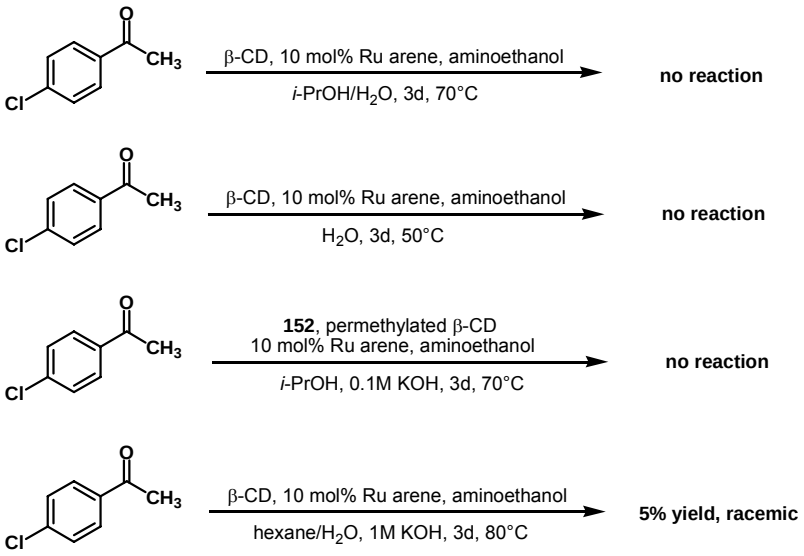
The Ru hydride signal of **151** could not be detected in the ^{1}H-NMR spectra after addition of excess NaOOCH to **149**. Nevertheless a hydride transfer from the metal to the substrate seems very likely since reduction of **86** in H_2O and excess NaCOOD results in a triplet splitting of the alcoholic methyl group due to incorporation of deuterium (*scheme 33*: right). No alcohol is formed at all in the absence of NaCOOD.

In contrast to Ru-H complex **83,** Ru-Cl **80** species is stable in water under an air atmosphere for several hours (*table 13*). Addition of NaOOCH 12 hours after mixing Ru-Cl precursor **81** and β-CD-AE **79** followed by addition of the ketone 15 minutes later (*entry 3*) lead to identical yield and ee's in ATH under standard conditions as observed for standard procedures (*entry 1*). Whereas only 35% yield was gained when the Ru-H **83** was stirred for 12 hours before addition of the ketone (*entry 2*), indicating a decomposition of the active Ru-H species.

Entry	Addition of NaCOOH	Addition of Ketone	Yield [%]/ee [%]
1	1 hour after mixing **79** and **81**	15 minutes later	93/8
2	1 hour after mixing **79** and **81**	12 hours later	35/7
3	12 hours after mixing **79** and **81**	15 minutes later	94/8

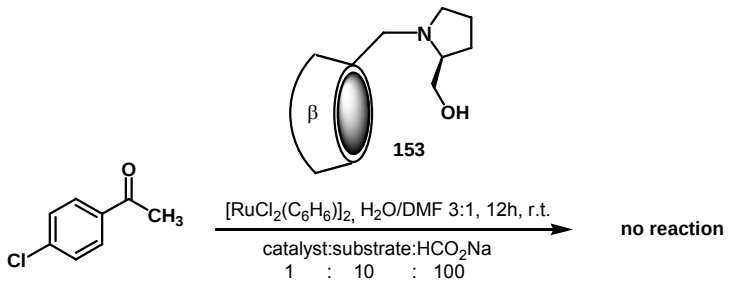
Table 13 *Stability of Ru-Cl **80** and Ru-H **83***

Scheme 34 summarises experiments using unmodified β-CD. No product formation was observed for several test reductions using Ru precursor **81**, aminoethanol **79** and stoichiometric amounts of free β-CD **52** or protected β-CD **152** under various conditions. Since the reaction occurs only with covalently linked amino alcohols these results support the original concept: β-CD forms an inclusion complex with the ketone and thus brings the carbonyl bond in close proximity to the reactive metal centre where the stereoselective reduction occurs.



Scheme 34 *Test experiments with free CD show no activity*

Proline was linked to the primary face of β-CD yielding tertiary amine **153** which was applied to ATH under standard conditions (*scheme 35*). The fact that no product was formed at all is in good agreement with observations done by other groups[27,33]. The so called NH-effect postulates that ATH catalysts lacking a NH motif are totally inactive in the reduction process. This implies that the mechanism of our novel transformation resembles the metal-ligand bifunctional mechanism proposed by Noyori[27].



Scheme 35 *Proline derivative **153** shows no reactivity in ATH*

As expected from reported results[12,37] Ru catalyst showed very poor reactivity changing the hydrogen source from formate to molecular H_2 (*table 14*). A recent explanation is given in chapter 1.1.2[38,39]. Systems using an azeotropic mixture of Et_3N/HCOOH or pure *i*-PrOH instead of NaCOOH failed as well and gave no product.

Substrate	Ligand	Solvent	mol%	Bar	Yield [%]
p-Cl-acetophenone	β-CD-SAP	H_2O/DMF 3:1	10	50	3
p-Cl-acetophenone	β-CD-SAP	1M KOH	10	50	0
p-Cl-acetophenone	β-CD-SAP	*i*-PrOH/MeOH	10	50	2

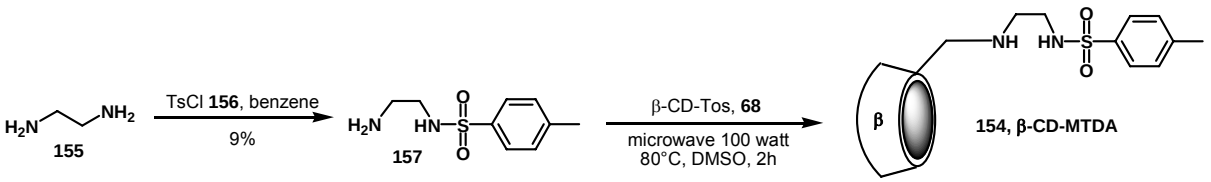
Table 14 *Reductions with molecular hydrogen*

A back reaction from the alcohol to the ketone according to reversible MPV reaction can be excluded since no optical resolution at all occurred when racemic 1-(4-chlorophenyl)ethanol **150** was applied to standard reduction conditions with β-CD-SAP for 12 hours.

3.2.2 Monosulfonated Diamines as Side Chains

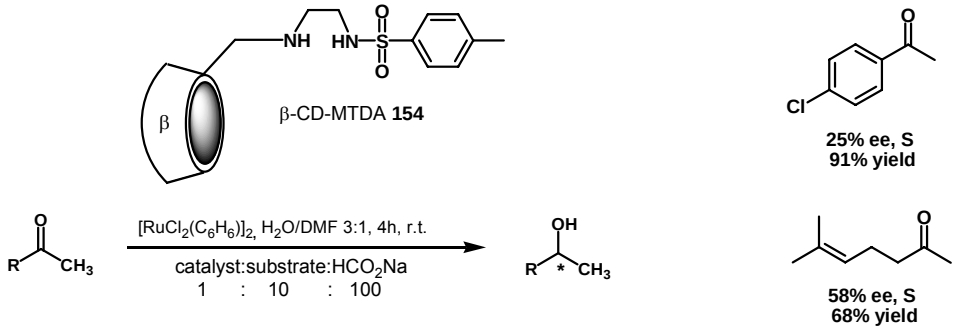
3.2.2.1 Catalysis Results with Monotosylated Diamines

It was obvious to link monotosylated diamines to β-CD as well, because Ru catalysts bearing such ligands are known to be very reactive in ATH[12]. Modified β-CD **154** was synthesised in two steps starting from achiral ethan-1,2-diamine **155** (*scheme 36*). Monosulfonation[77] using tosylchloride **156** afforded **157** in low yield which is less nucleophilic than amino alcohols, due to electron withdrawing properties of the tosyl group. Therefore substitution with β-CD-Tos **68** was performed in the microwave at 80°C (constant irradiation with 100 watt) and gained β-CD-MTDA **154** in 47%. The advantage of the microwave assisted substitution reaction is that the excess of nucleophile could be decreased from originally 80 times to 5 times, while the reaction time dropped down from 12 hours to 2 hours.



Scheme 36 *Synthesis of β-CD-MTDA **154***

With β-CD as the only chiral unit aromatic and aliphatic standard ketones **86** and **98** could be reduced in 91% yield and 25% ee (S) respectively 68% yield and 58% ee (S) within only 4 hours under standard conditions (*scheme 37*).



Scheme 37 *ATH with monotosylated β-CD **154***

The difference in reactivity between amino alcohol- and monotosylated diamine modified β-CD was investigated by comparing the conversions at several times. *p*-Cl-acetophenone **86** was reduced with ligands **79** and **154** under standard conditions (*table 15*). Monotosylated diamine analogue **154** reacts about three times faster than amino alcohol derived **79**.

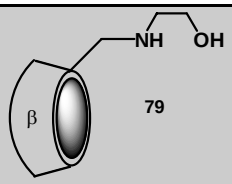
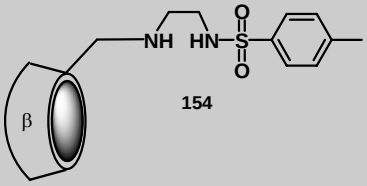
	 79	 154
1h	18% conversion	64% conversion
2h	39% conversion	84% conversion
3h	58% conversion	90% conversion
4h	77% conversion	91% conversion
6h	86% conversion	91% conversion
12h	93% conversion	91% conversion

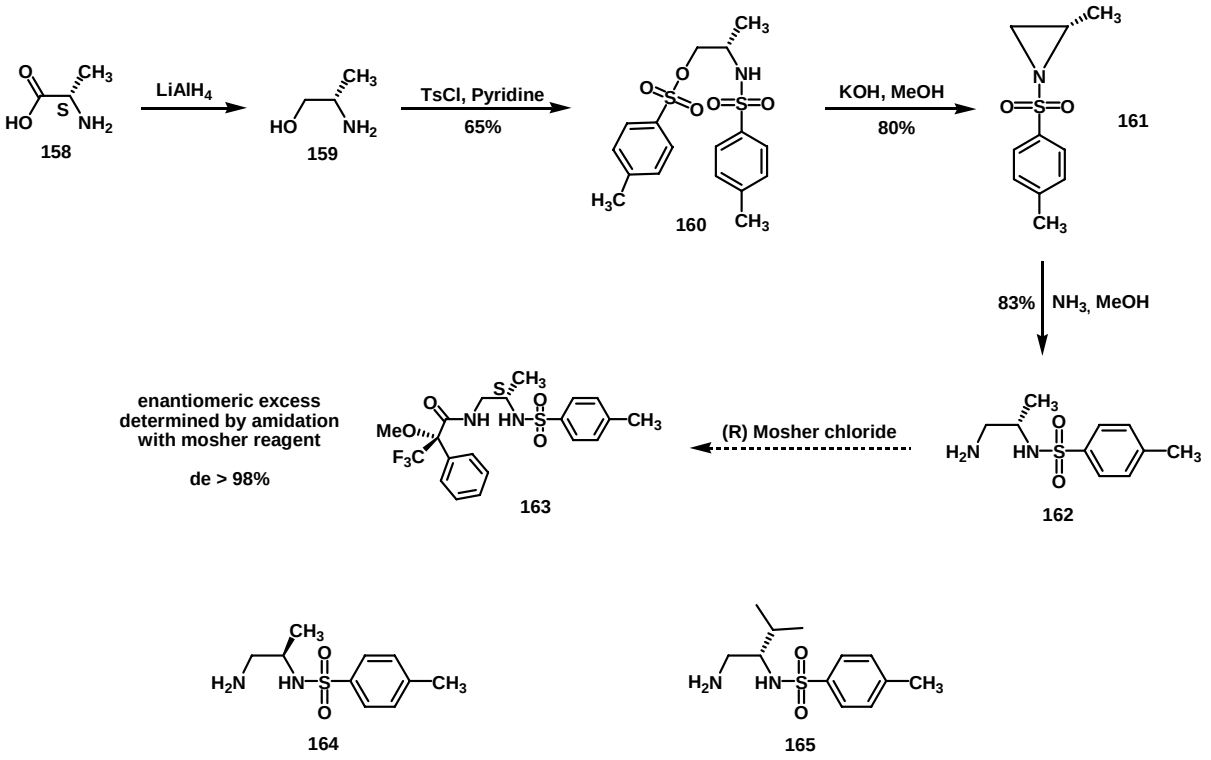
Table 15 *Amino alcohol vs. monotosylated diamine*

Table 16 summarises some efforts which have been made in order to lower the catalyst loading using β-CD-MTDA **154** and standard reduction conditions. Respectable 56% yield was obtained with 5 mol% catalyst whereas it could be increased to 67% performing the reduction in a twice as concentrated solvent system. 34% yield was afforded decreasing the catalyst loading to 2% which corresponds to a turn over number of 17.

Entry	Ligand	mol%	Solvent	Yield [%]	ee [%]
1	β-CD-SAP	10	H_2O/MeOH 3:1 (0.25 ml)	91	25 (S)
2	β-CD-SAP	5	H_2O/MeOH 3:1 (0.25 ml)	56	24 (S)
3	β-CD-SAP	5	H_2O/MeOH 3:1 (0.125 ml)	67	19 (S)
4	β-CD-SAP	2	H_2O/MeOH 3:1 (0.25 ml)	34	23 (S)
5	β-CD-SAP	1	H_2O/MeOH 3:1 (0.25 ml)	8	3 (S)

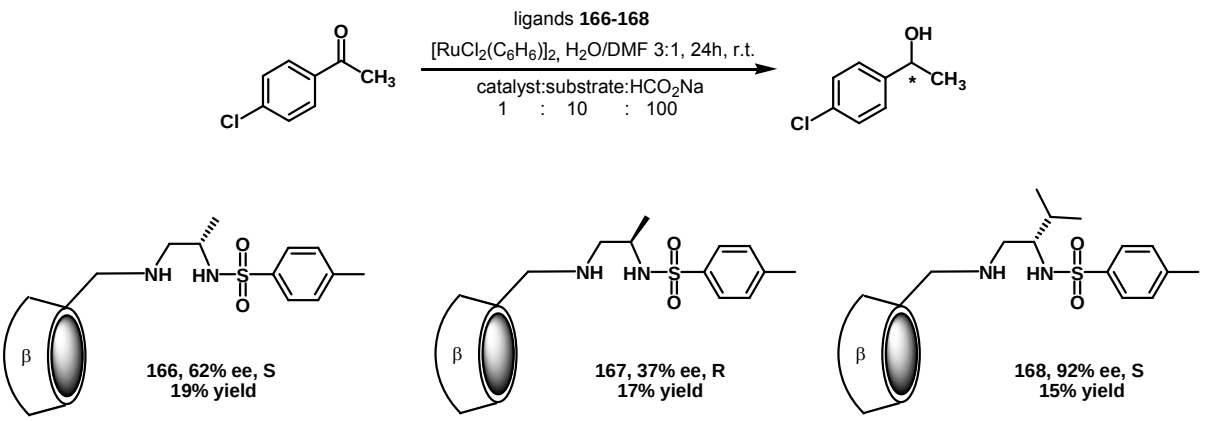
Table 16 *Efforts to decrease of catalyst loading*

The acceleration of ATH with β-CD-MTDA **154** compared to **79** prompted the introduction of chirality in the side chain for the purpose of increasing the stereoselectivity. With the knowledge of the amino alcohol ligand system it was obvious to test monotosylated diamines with a chiral centre next to the tosyl motif. Such compounds are neither commercially available nor precedent in the literature and had to be prepared by opening of chiral tosylaziridines (*scheme 38*). (S)-Alanine **158** was reduced with lithium aluminium hydride[78]. The hydroxy- and amino group of (S)-alaninol **159** were both tosylated to obtain intermediate **160** in 65% yield[79]. Ring closure under basic conditions lead to chiral tosylaziridine[79] **161**, which was regioselectively opened with ammonia to get desired compound **162** in 46% overall yield. It's noteworthy that the optical purity of **162** could be shown to be higher than 98% by treatment with optical pure (R)-mosher chloride although the chiral centre is in β-position to mosher amide **163**.



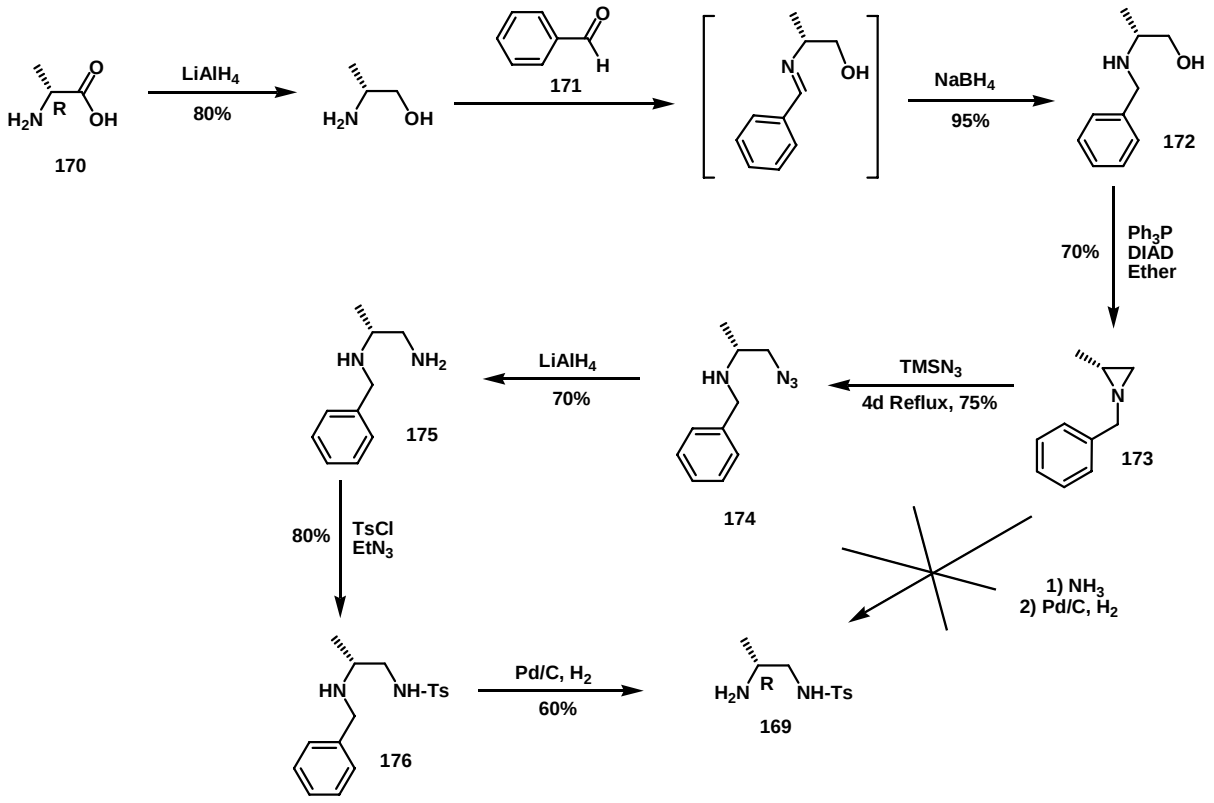
Scheme 38 *Synthesis of chiral monotosylated diamines*

Compound **162**, enantiomer **164** (derived from (R)-alanine) and valine based **165** were all linked to β-CD in moderate yields using the same one step procedure as mentioned above. Unexpected poor reactivities in ATH were obtained with all three ligands (*scheme 39*). Since several efforts to get appropriate crystals for x-ray analysis of the Ru complex with ligands **166-168** failed it can only be speculated that the methyl respectively *iso*-propyl group affects somehow the proper formation of the five membered chelate ring with the metal and therefore significantly lowers the reactivity. However the absolute configuration of the alcoholic product is comparable with the amino alcohol system. **166** bearing a (S)-centre at the side chain leads to 62% ee (S), **167** with the (R)-chirality results in 37% ee (R). In contrast to amino alcohol ligands the stereo outcome of the reduction could be enhanced with bulkier alkyl rest at the side chain from methyl **166** (62% ee, S) to *iso*-propyl **168** (92% ee, S)



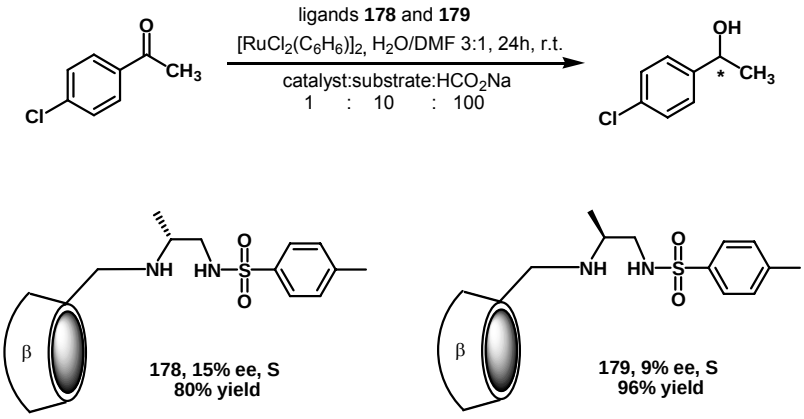
Scheme 39 *ATH with chiral monotosylated CD's* ***166-168***

The chiral centre was moved next to the amino nitrogen to ascertain if this change leads to a better reactivity. A seven step synthesis of free chiral monotosylated diamine **169** starting from cheap (R)-alanine **170** is illustrated in *scheme 40*. Reductive amination[80] with benzaldehyde **171** gained protected amino alcohol **172**. Aziridine formation was observed under *Mitsunobu* conditions[80]. In contrast to tosylated aziridine **161** benzylaziridine **173** is electron rich and deactivated for nucleophilic ring opening. A saturated solution of ammonia in methanol failed to open the ring. So an excess of more nucleophilic $TMSN_3$ in refluxing acetonitrile was used[81]. Reduction of azide **174** with lithium aluminium hydride[81] followed by tosylation of the primary amine in **175** and cleavage of the phenyl group in **176** gave free (R)-amine **169** in an overall yield of 13% and optical purity of > 98% (mosher method).



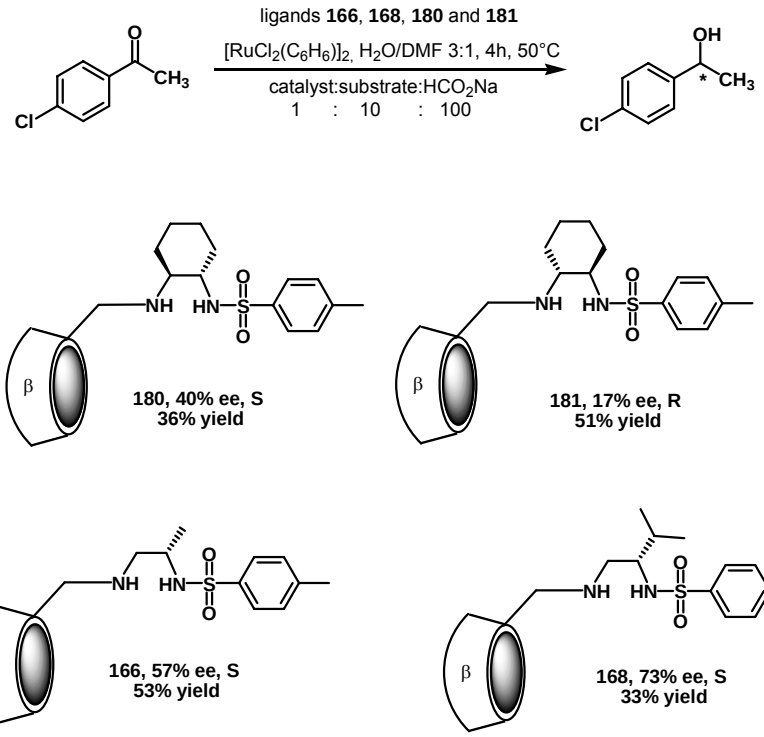
Scheme 40 *Moving the stereo centre closer to β-CD*

Compound **169** and (S)-enantiomer **177** were attached to β-CD and applied to ATH under standard conditions (*scheme 41*). Interestingly the yields increased to 80% and 96% respectively. But unfortunately both ligands gave quasi racemic mixtures of the alcoholic product. The fact that a chiral centre next to the amino nitrogen shows a lower chiral induction than next to the sulfonated nitrogen is in agreement with the amino alcohol system.



Scheme 41 *ATH with novel ligands **178** and **179***

It was decided to prepare cyclic monotosylated diamines bearing two chiral centres from commercially available trans-1,2-cyclohexyl-diamine[82] and attach them to β-CD (**180** and **181**). Surprisingly both ligands were totally inactive for the reduction of standard substrate **86** at 22°C even at elongated reaction times. However at 50°C one observed moderate yields and low ee's (*scheme 42*). Due to this reaction acceleration at elevated temperatures also ligands **166** and **168** which showed good (62% ee, S) respectively excellent (92% ee, S) chiral induction at room temperature were tested at 50°C. Actually the yields increased up to 53% with significant loss of enantioselectivity.



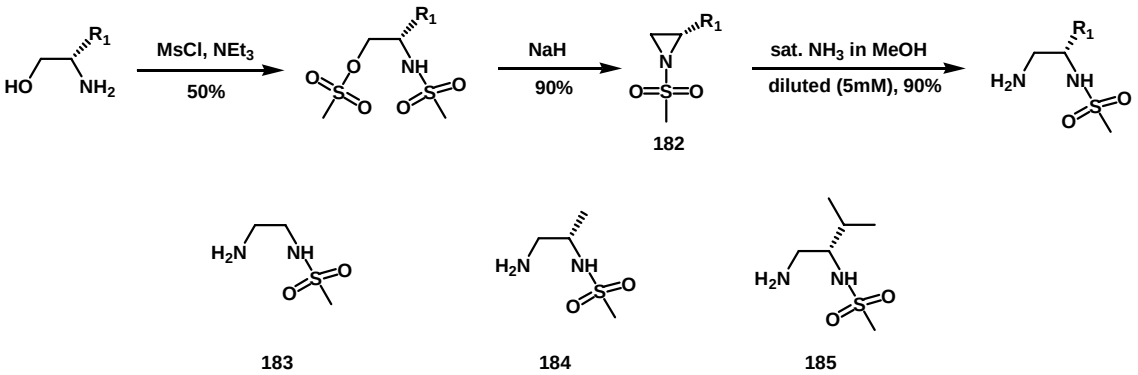
Scheme 42 *ATH at elevated temperatures*

It could be demonstrated that monotosylated diamines linked to β-CD can also act as ligands in ATH to ketones. Indeed **154** (without a chiral centre at the side chain), **178** and **179** (with a chiral centre next to the amino nitrogen) revealed to be three times faster than their amino alcohol analogues. But the chiral induction with these ligands is very poor. In contrast to this ligands bearing a chiral centre in α-position to the sulfonamide nitrogen **166-168** show good chiral induction but low

yields. At this point it is not clear why these structural similar compounds behave so differently in ATH in terms of the stereo outcome and reactivity.

3.2.2.2 Catalysis Results with Monomesylated Diamines

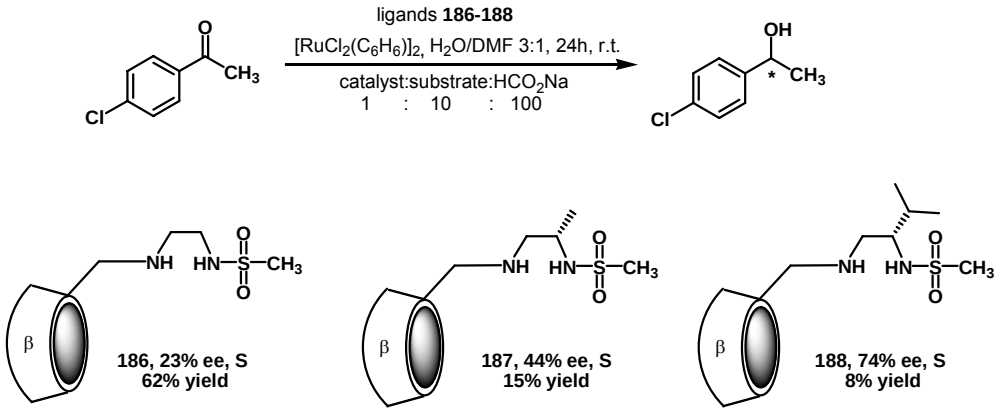
Monomesylated diamines were introduced as a new ligand class. Mesylates are lacking an aromatic moiety which can theoretically form self assembled structures by inclusion complex formation of a tosyl rest of one ligand with the hydrophobic cavity of β-CD of another one and thus inhibit the reduction. Monomesylated diamines were prepared as described in *scheme 43*. Mesylation of the hydroxy and amino group of amino alcohols followed by aziridine ring closure under basic condition afforded intermediate **182**[79]. Ring opening with a saturated solution of ammonia in methanol had to be performed under diluted conditions to avoid the formation of bis- and tris by products. The free amines **183-185** were linked to β-CD in the microwave as described above. Achiral **183** had to be prepared in the same manner since direct mesylation of ethan-1,2-diamine gave exclusively undesired dimesylated product.



Scheme 43 *Synthesis of monomesylated diamines*

Scheme 44 summarises the catalysis results with β-CD modified ligands **186-188** under standard conditions. They show comparable reactivities and stereoselectivities as their monotosylated analogues **154**, **166** and **168**. Ligand **186** without chirality on the side chain gives the alcohol in respectable 62% yield, whereas the introduction of a chiral centre next to the sulfonamide nitrogen again dramatically decreases the yield to 15% respectively 8%. Valine derived **188** gave

better ee's than **187** having a less bulky methyl substituent, which is in agreement with observations made with **168** and **166**.



Scheme 44 *ATH with monomesylated diamines*

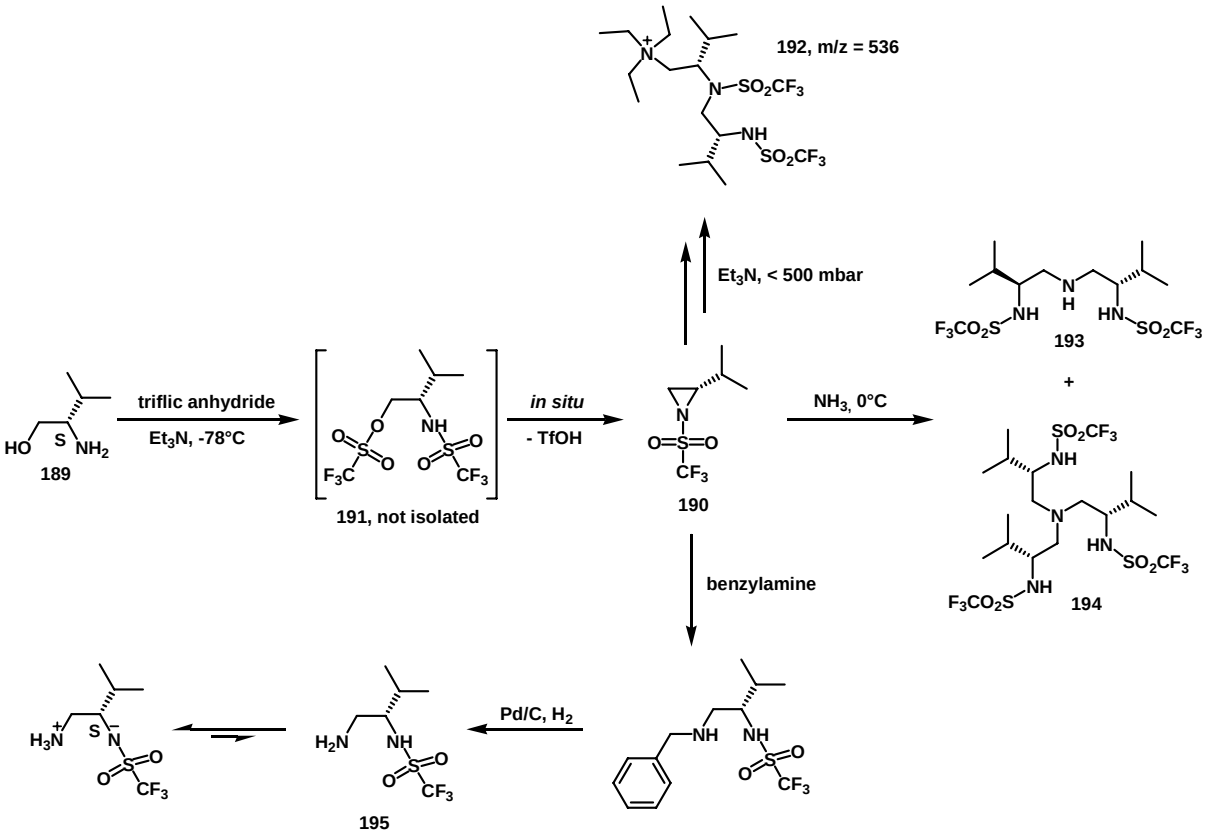
With these results in hand one can argue that the aromatic ring in monotosylated ligands is not responsible for the low reactivity of ligands **168**-**168**. In other words: self assembling of the ligands seems very unlikely.

3.2.2.3 Catalysis Results with Monotriflated Diamines

Triflate has stronger electron withdrawing properties than mesylates or tosylates[83]. With the aim of increasing the reduction rate even more, a monotriflated diamine was linked to β-CD. The synthesis was much more problematic and started again from an amino alcohol (*scheme 45*). Treatment of **189** with triflic anhydride at -78°C gave directly valine based aziridine **190** without isolation of reactive intermediate **191**[79]. Aziridine **190** is an unstable compound and could not be chromatographed or dried properly. Decomposition was observed below 500 mbar. In fact triethylamine acted as nucleophile and opened the aziridine ring as could be demonstrated by ESI-MS analysis (m/z = 536 [**192**]$^+$). So crude product **190** was dried for 5 minutes at 650 mbar and tried to open directly with ammonia. A lot of bis-**193** and tris **194** side product was observed. So the strategy was changed and the aziridine opened regioselectively with benzylamine followed by deprotection to desired compound **195** in an overall yield of 48% (for three steps) as a white powder. Free amine **195** could not be attached to β-CD using conventional microwave

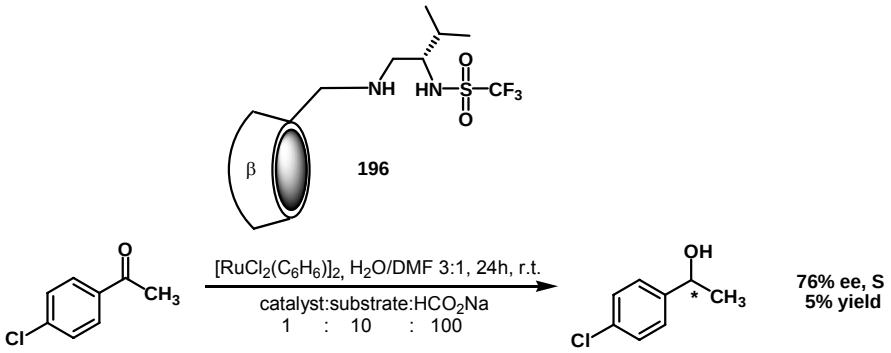
conditions which were applied for tosylates and mesylates. The remaining proton at the sulfonamido nitrogen is so acidic that it's probably located on the amino functionality. The resulting positively charged nitrogen is no more nucleophilic at all. Addition of superstoichiometric amounts *Hünig* base was necessary to get a proper reaction with β-CD.

The corresponding aziridine intermediate of the non chiral triflate analogue starting from aminoethanol **78** was so unstable that it could not be isolated.



Scheme 45 *Synthesis of chiral monotriflated diamine **195***

The reactivity of **196** in ATH was very poor but comparable with other monosulfonated diamine ligands bearing a chiral centre in α-position to the sulfonamido nitrogen. 5% yield and 76% ee (S) were observed for the reduction of standard ketone **86** (*scheme 46*). ATH with the free monotriflate lacking the β-CD unit resulted in 5% yield and 88% ee (S). So the CD moiety lowers the enantioselectivity and is therefore useless for this ligand class.

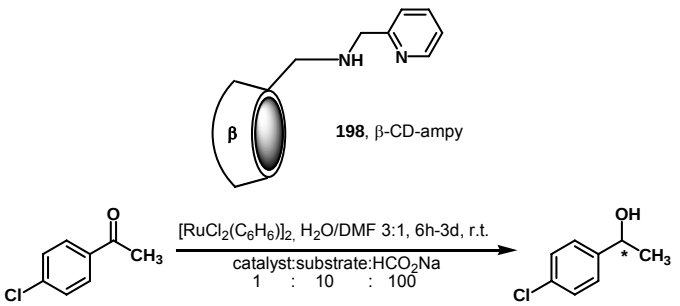


Scheme 46 *ATH with monotriflated **196***

3.2.3 α-Pycolyl Amines Side Chains

3.2.3.1 Catalysis Results with α-Pycolyl Amines

Replacing the OH- respectively the $NHSO_2R$ functionality of the side chain by a pyridine ring leads to α-pycolyl amines. It was mentioned in the introduction part of this thesis[45] that such structures can also serve as ligands for Ru catalysed ATH. Commercially available non chiral pyridin-2-ylmethanamine **197** was directly linked to β-CD yielding ligand **198** in 48%. Initial ATH experiments at room temperature showed only very poor activity (*scheme 47*). The yield increased only slightly by heating till 60°C but got quantitative at 70°C.



	RT	50°	60°	70°C
yield	3%	4%	6%	99%
ee	58%, S	48%, S	46%, S	42%, S

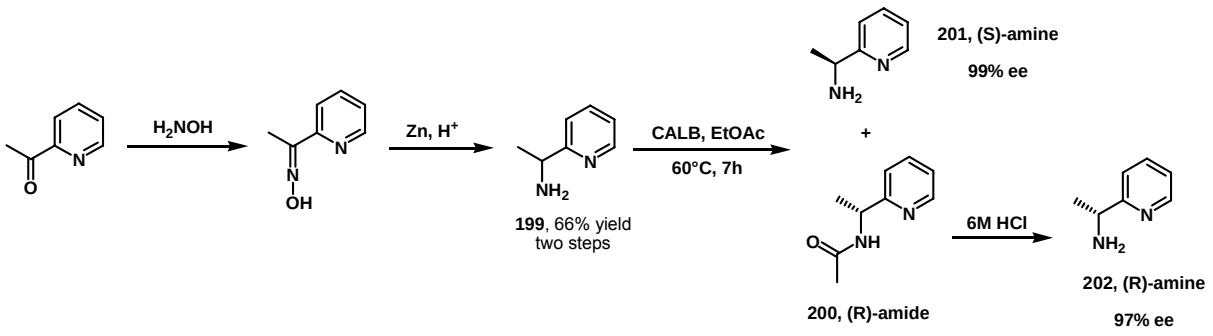
Scheme 47 *ATH with α-pycolyl amine attached to β- CD*

Since it was suggested that the active Ru complex is only formed at higher than 70°C, β-CD-ampy **198**, Ru arene **81** and excess sodium formate **82** were stirred for 1 hour at 70°C in H_2O/DMF 3:1 prior to use in catalytic reactions. After cooling down to 22°C respectively 50°C one could observe somewhat better yields after three days (*table 17*). Lowering the catalyst loading to 5% gave unsatisfying 18% yield.

Entry	Ligand	mol%	1h at 70°C prior to use	T during catalysis	Yield [%]	ee [%]	Time
1	β-CD-ampy	10	yes	70	99	42 (S)	6h
2	β-CD-ampy	10	yes	50	18	46 (S)	3d
3	β-CD-ampy	10	yes	22	6	58 (S)	3d
4	β-CD-ampy	5	no	70	18	28 (S)	3d

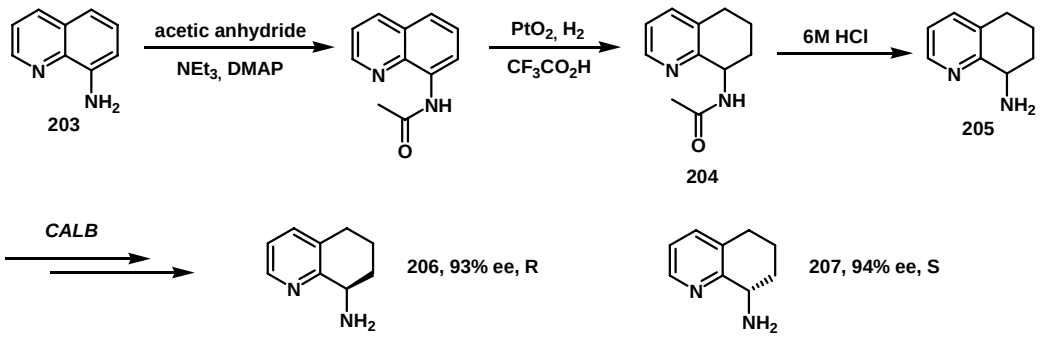
Table 17 *ATH 1h at 70°C prior catalysis is started*

However β-CD-ampy having no chirality at the side chain showed already respectable 58% ee (S) at 22°C. This result encouraged the introduction of a chiral centre in the pyridyl moiety by enzymatic resolution with *candida antarctica lipase B* (*CALB*). Racemic pyridine derivative **199** was synthesised in two steps and good yield according a literature procedure[84] (*scheme 48*). *CALB* selectively transformed the (R)-amine to the amide **200** leaving enantiomerically pure free (S)-amine **201**[85]. **200** was hydrolyzed to the free (R)-amine **202** in the presence of 6M HCl without loss of optical purity as could be demonstrated by mosher method.



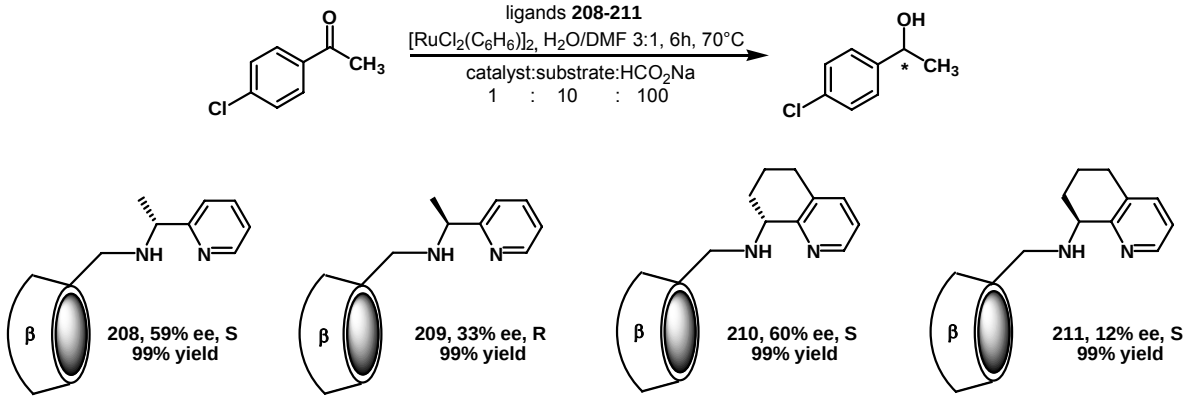
Scheme 48 *Synthesis of chiral α-pycolyl amines **201** and **202***

Another pair of pycolyl enantiomers was prepared starting from 8-aminoquinoline **203**. Acetylation followed by hydrogenation gained tetrahydroquinoline **204** in 40% yield (*scheme 49*)[86]. Hydrolysis in aqueous HCl gave racemic amine **205** which was resolved with *CALB* as described above yielding free (S)-amine **206** in 93% ee and the (R)-enantiomer **207** in 94% ee[85].



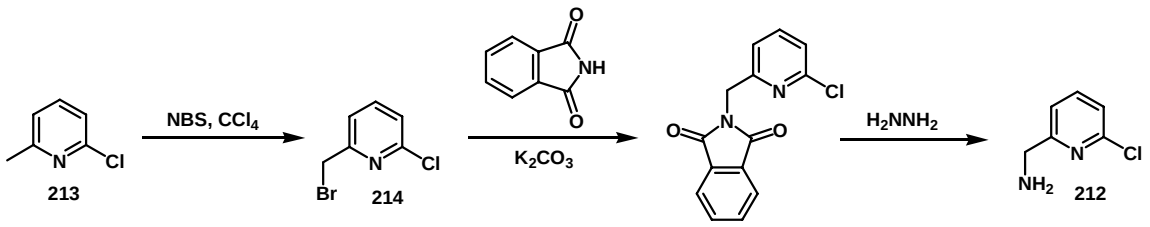
Scheme 49 *Synthesis of chiral tetrahydroquinolines **206** and **207***

Free amines **201**, **202**, **206** and **207** were attached to β-CD in the microwave as discussed earlier. New ligands **208-211** were applied to ATH under standard conditions (*scheme 50*). Because all four ligands showed very poor reactivities at 22°C (1-3% yield) the catalyses were performed at 70°C again. Quantitative conversions and enantioselectivities up to 60% were observed. (R)-configuration at the pycolyl moiety leads to (S)-alcohols and (S)-chirality in the ligand gains the (R)-product. **211** represents the only exception but can be neglected due to the low ee value of 12%. The absolute configurations are in agreement with amino alcohol- and monosulfonated diamine analogues.



Scheme 50 *ATH with chiral α-pycolyl amines*

Apparently steric modification can only influence the stereo outcome but not accelerate the reduction process. So it was decided to change the electronic properties of the pycolyl ligand. Since direct chlorination of α-pycolyl amine **197** with NCS failed compound **212** was prepared in three steps as illustrated in *scheme 51*. Allylic bromination[87] of chloropyridine **213** gave a mixture of mono- and dibrominated intermediate **214**. *Gabriel* reaction including nucleophilic attack of potassium phtalimide followed by hydrazinolysis gave (6-chloropyridin-2-yl)methanamine **212** in 30% overall yield[87].



Scheme 51 *Synthesis of halogenated α-pycolyl amines*

Compound **212** and fluorinated analogue **215** (derived from 2-fluoro-6-methylpyridine[87]) were both connected to β-CD to test their reactivity towards ATH. Catalytic results with chloro- **216** and fluoro modified β-CD **217** are summarised in *table 18*. Neither Cl-**216** nor F-**217** is more reactive than non halogenated β-CD-ampy **198**. Despite the low yield *entry 1* is a remarkable result. Asymmetric inductions higher than 50% ee with β-CD as the only chiral unit are quite rare[70].

Entry	Ligand	mol%	T [°C]	Yield [%]	ee [%]	Time
1	Cl-**216**	10	22	7	70 (S)	3d
2	Cl-**216**	10	50	9	56 (S)	1d
3	Cl-**216**	10	70	51	42 (S)	1d
4	F-**217**	10	22	9	57 (S)	3d
5	F-**217**	10	70	62	28 (S)	1d

Table 18 *ATH with halogenated α-pycolyl amines*

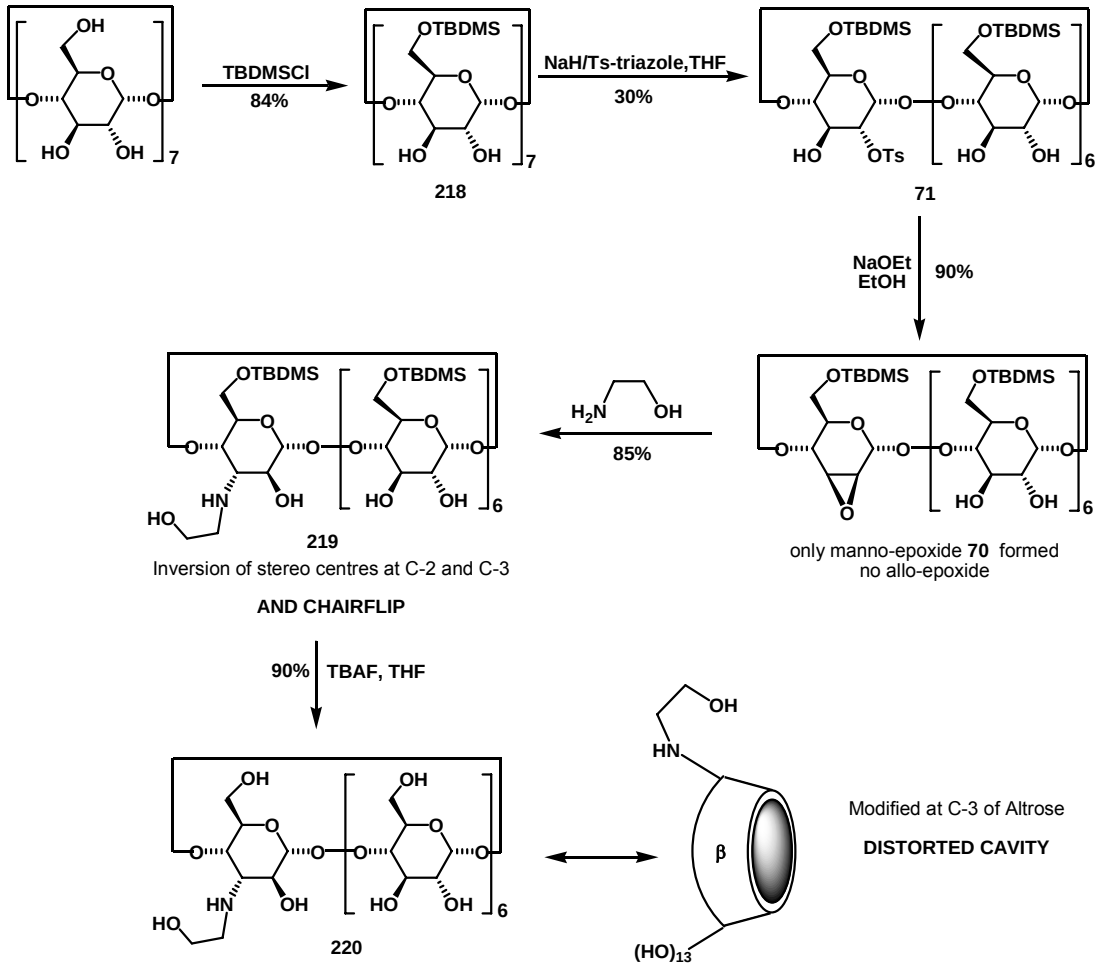
At this point it was decided to change the strategy and no more attach the side chains on the primary face but on the secondary face.

3.3 CD modified on Secondary Face

3.3.1 Amino Alcohols as Side Chains

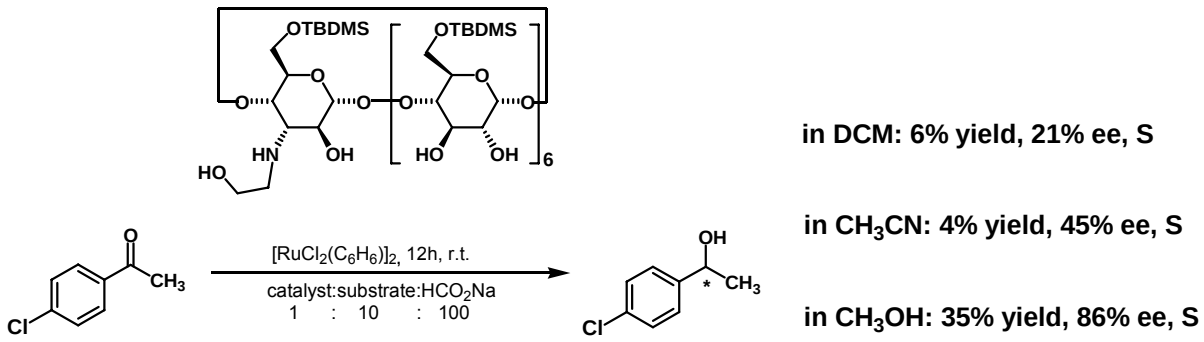
As explained in chapter 1.2.2.3 the cavity of β-CD's modified on the secondary face is not symmetric[67]. Thus it was decided to link the side chains, which have been linked successfully to the primary face, to the secondary face as well. It was assumed that a desymmetrization of the cavity changes the binding properties of the guest and therefore influences the stereo outcome of the reduction. Importantly, it could not be predicted whether this leads to better or worse stereoselectivities, since the influence of this distortion is still not explored properly nowadays[70].

Aminoethanol **78** was attached to the secondary face of β-CD as illustrated in *scheme 52*. β-CD was selectively protected on the primary face by treatment with TBDMSCl in pyridine[65]. Hepta protected **218** is soluble in various organic solvents which simplifies the purification procedure drastically. **218** could be chromatographed on silica gel using a mixture of ethyl acetate/ethanol/water as eluent. Deprotonation of the hydroxy group at position 2 followed by tosylation with 1-tosyl-1,2,4-triazole lead to monosulfonated **71** in moderate yield[65]. However a lot of starting material could be isolated and reused. Treatment with sodium ethylate in ethanol gave manno-epoxide **70** in 90% yield. The modified sugar unit is no more of glucose type because the stereo centre at position 3 has been inverted. Confirmation of the manno unit arose from ^{1}H-NMR experiments and the coupling constant between H_1 and H_2 (J_{H1H2} = 0 Hz). In addition to this ^{13}C-NMR spectra showed solely two peaks (53.2 ppm and 49.2 ppm) in the epoxide region indicating that there is only one isomer present[65]. Manno epoxide **70** was opened regioselectively with aminoethanol yielding protected β-CD **219**. Evidence for the $^{1}C_4$ conformation of the altrose unit in **219** rests on the coupling constant of the two di-axial protons H_1 and H_2 (J_{H1H2} = 7.3 Hz) which is about three times the value observed for the di-equatorial situation (J_{H1H2} = 2.3 Hz)[88]. Accordingly, the initially formed $^{4}C_1$ conformation flips over to the more stable $^{1}C_4$ form changing the interior of β-CD to a distorted ellipsoid cavity. Deprotection[89] of all seven silyl ethers with tetrabutyl ammonium fluoride in THF followed by purification by RP-18 chromatography gave β-CD modified at position 3 **220** in an overall yield of 17% (five steps).



Scheme 52 *Synthesis of β-CD modified on the secondary face*

Initial catalytic reactions were performed with protected **219** in various organic solvents to check if the distortion can really enhance the ee's in ATH to standard ketone **86**. Excellent 86% ee (S) were observed in methanol (*scheme 53*). This is an intriguing result since β-CD is the only chiral unit in the catalytic system. The lower chiral induction in less polar CH_2Cl_2 or CH_3CN is not surprising, since hydrophobic guests form stronger inclusion complexes with β-CD in polar solvents like water or alcohols[50]. The poor yields in CH_2Cl_2 and CH_3CN can be explained by solubility problems of sodium formate in the corresponding solvents.



Scheme 53 *ATH with protected CD **219** modified on the secondary face*

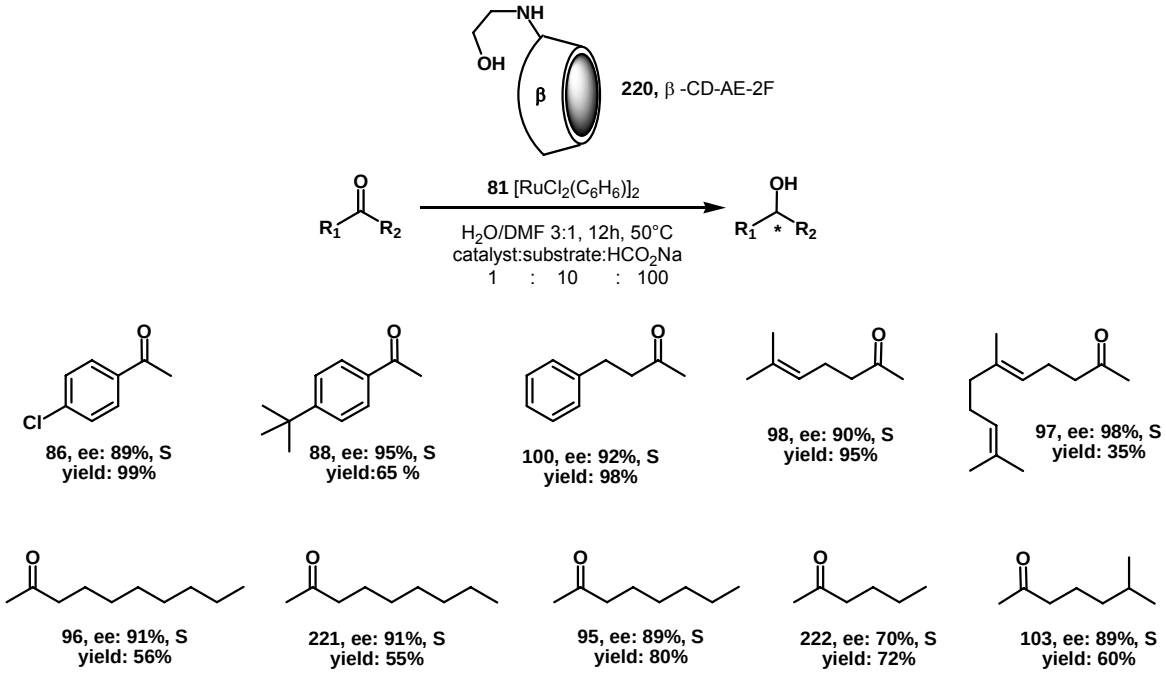
With this promising result in hand deprotected β-CD-AE-2F **220** was applied to ATH under standard conditions. Distortion of the cavity was again proven by ^{1}H-NMR measurements. A selective TOCSY experiment in D_2O revealed that J_{H1H2} is 6.6 Hz. *Table 19* summarises efforts to optimize the reaction conditions. Catalysis with 10 mol% of catalyst at room temperature gives 79% yield and 91% ee (S). This is a dramatically increase compared to non chiral aminoethanol linked to the primary face of β-CD (8% ee, R). Quantitative yields were observed at 50°C with a slight loss of enantioselectivity. Decreasing the catalyst loading to 5 mol% lead to 30% yield at 22°C respectively 78% yield at 50°C. Identical temperature and catalyst loading dependency was observed for three other substrates including two aliphatics.

Entry	Ligand	mol%	Solvent	T [°C]	Yield [%]	ee [%]
1	β-CD-AE-2F	10	H_2O/DMF 3:1 (0.25ml)	22	79	91 (S)
2	β-CD-AE-2F	10	H_2O/DMF 3:1 (0.25ml)	50	99	89 (S)
3	β-CD-AE-2F	10	H_2O (0.25ml)	22	48	92 (S)
4	β-CD-AE-2F	5	H_2O/DMF 3:1 (0.25ml)	22	30	93 (S)
5	β-CD-AE-2F	5	H_2O/DMF 3:1 (0.25ml)	50	78	89 (S)
6	β-CD-AE-2F	5	H_2O/DMF 3:1 (0.125ml)	22	30	92 (S)

Table 19 *ATH with deprotected **220** under various conditions*

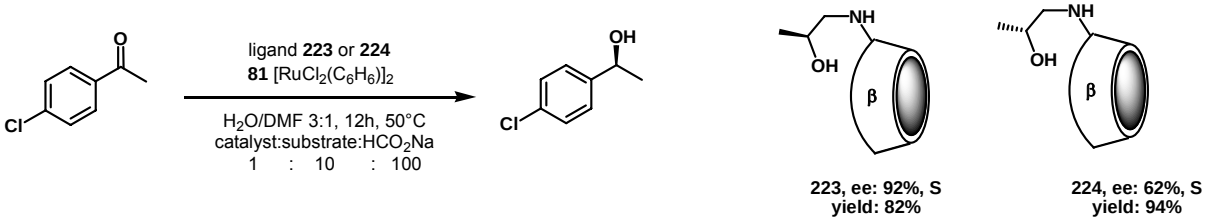
β-CD-AE-2F **220** was tested with three aromatic and seven aliphatic ketones to explore the substrate scope. The catalysis results performed in H_2O/DMF 3:1 at 50°C with 10 mol% of catalyst are shown in *scheme 54*. The ee's of most substrates

are around 90%, reaching a maximum value of 98% (S) for the reduction of geranyl acetone **97**. Only 2-hexanone **222** was reduced in moderate ee's (70%, S). All alcoholic products showed (S)-configuration and the yields correlate with solubilities of the substrates in H_2O/DMF. It's worth mentioning that the ee values with ligand **220** bearing non chiral aminoethanol on the secondary face are on the same high level as observed with chiral amino alcohols linked to the primary face (ligand **92**).



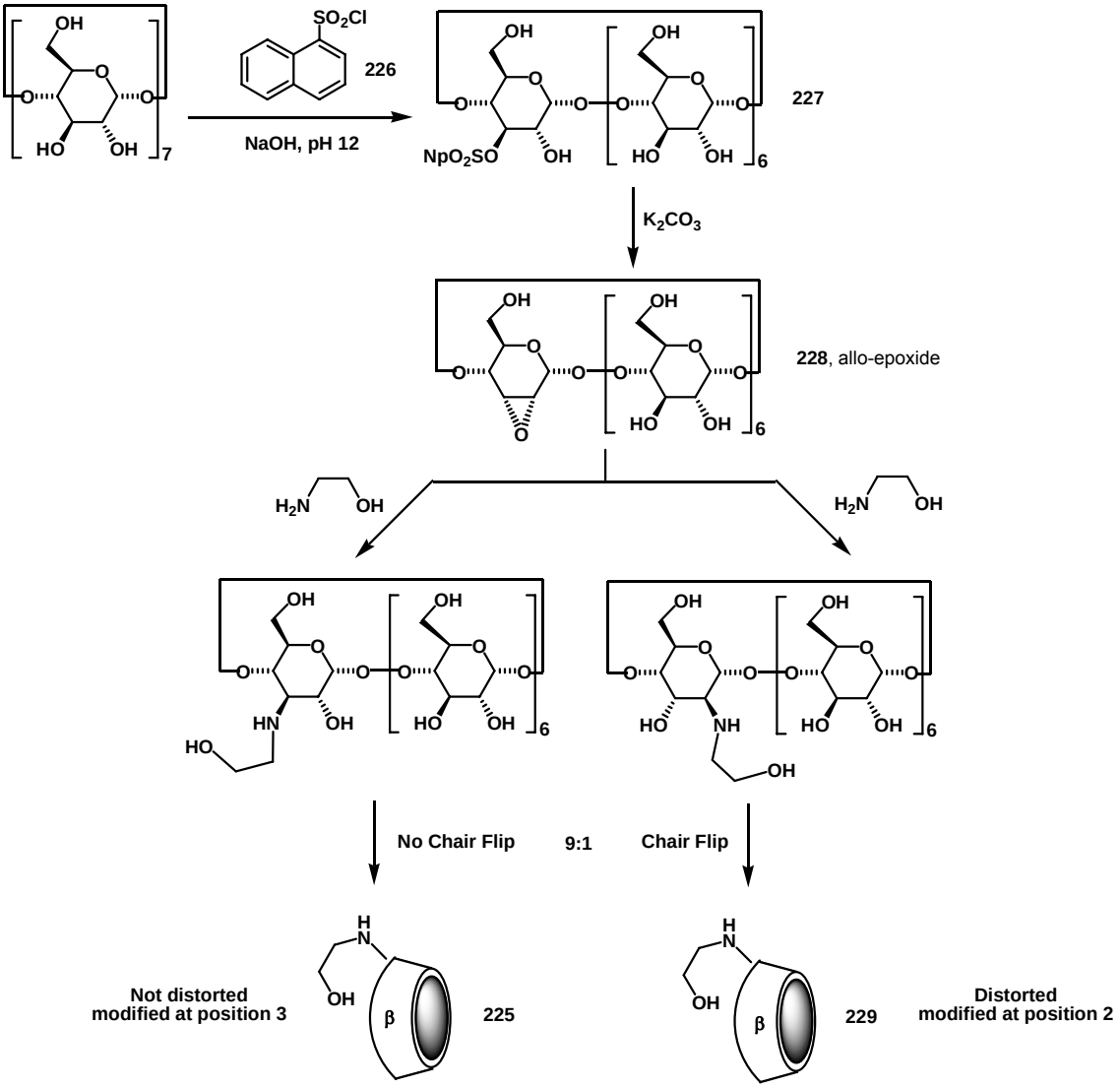
Scheme 54 *ATH with various aromatic and aliphatic ketones*.

These nice results prompted the insertion of chirality in the side chain with the aim of improving the stereoselection even more. For this purpose (S)-1-amino-2-propanol and the (R)-enantiomer were attached to the secondary face of β-CD as described earlier. The result shown in *scheme 55* was kind of unexpected. Both catalysts **223** and **224** lead to the (S)-alcohol in 92% ee respectively 62% ee.



Scheme 55 *ATH with chiral amino alcohols attached to 2° face of β-CD*

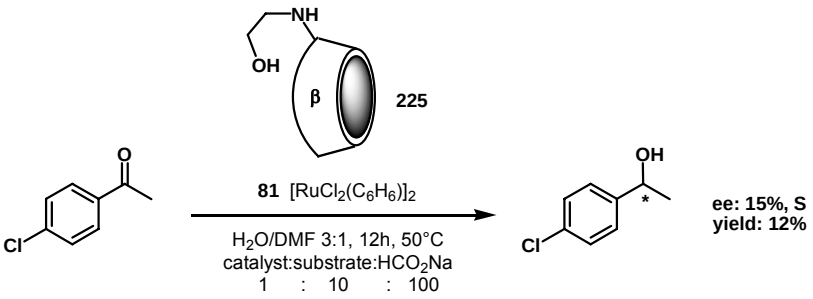
In contrast to primary face modified CD catalysts the chiral centre at the side chain of β-CD-AE-2F **220** seems to play an inferior role and chiral induction is mainly caused by the β-CD unit. To demonstrate that the distortion of the CD cavity is responsible for the enhanced stereo outcome, compound **225** was synthesised bearing aminoethanol at position 3 with an intact symmetric cavity (*scheme 56*).



Scheme 56 *Synthesis of symmetric modified CD **225***

Unprotected β-CD was sulfonated selectively at position 3 using 2-naphtalenesulfonyl chloride **226**[90]. This reaction is a little bit odd because the hydroxy proton at position 3 is less acidic than the one at position 2[55]. However regioselective sulfonation in **227** could be proven with elucidation of allo-epoxide structure **228**. In contrast to manno-epoxide **70** coupling constant between H_1 and H_2

is J_{H1H2} = 3.3 Hz which is in agreement with an equatorial-axial conformation[90]. Epoxide opening with amino ethanol gave a 9:1 mixture of β-CD modified at position 3 (**225**) respectively position 2 (**229**)[66]. The two regioisomers could be separated by chromatography on RP-18 with a gradient system H_2O/MeOH. **225** offers a symmetric cavity since all seven sugars are of $^4C_1$ glucose type. On the other hand the modified sugar unit of compound **229** flips to the more stable $^1C_4$ conformation resulting in a desymmetrization of the cavity. Since latter compound was obtained only in very small amounts catalytic reactions were exclusively performed with ligand **225**. Only 15% ee (S) was obtained for the reduction of standard ketone **86** with ligand **225** (*scheme 57*). Since this chiral induction is much lower than with ligand **220** (89% ee, S) one can assume that the distortion of the cavity really enhances the stereo outcome of the reduction by modifying the inclusion complex formation in a positive way.

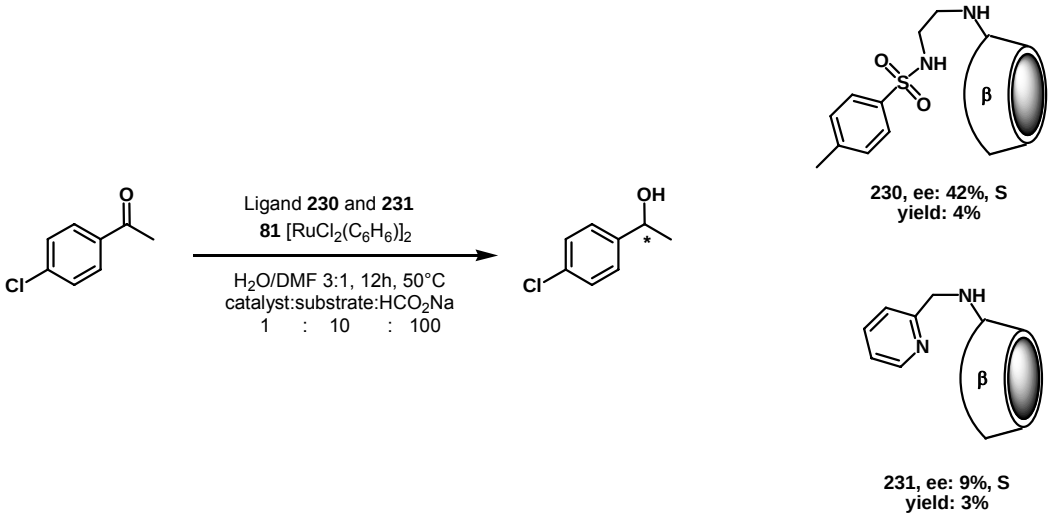


Scheme 57 *ATH with secondary face modified CD with a non distorted cavity*

The yield was also significantly lower with **225** than with **220**. Obviously, the nitrogen of the amino alcohol attached to a sugar unit with glucose $^4C_1$ conformation is pointed to another direction than to one with altrose $^1C_4$ conformation. It can be speculated that the combination of the two inclusion complex forming interactions (hydrophobic interaction of cavity/substrate and additional H bond of substrate to N-H) do not fit nicely due to inappropriate geometries.

3.3.2 Monosulfonated Diamines and α-pycolyl Amines as Side Chains

With the knowledge in hand that a distorted cavity enhances the enantioselectivities it was decided to attach achiral monotosylated diamine **157** and α-pycolyl amine **197** to the secondary face of β-CD as described earlier. Surprisingly, both ligands were inactive in ATH to ketone **86** at 50°C (*scheme 58*).



Scheme 58 *ATH with ligands **230** and **231***

As a result of the poor reactivities and low stereoselectivities of ligands **230** and **231** in ATH the project was continued with a new ligand class (see chapter 3.3.3)

3.3.3 Alkyl Amines as Side Chains

With respect to the two following findings it was decided to prepare ligands bearing alkyl amines on the secondary face of β-CD: Firstly, ^{1}H-NMR experiments of Ru complex β-CD-AE-2F **220** revealed no chemical shifts for any proton of the ligand which is in contrast to metal complexes with β-CD's modified on the primary face (see chapter 3.2.1.7). Secondly, ligand **220** offers more than just one β-amino alcohol motif. Thus the metal can theoretically bind in three different modes, two of them involving oxygen atoms of CD's glucose unit (*figure 16*).

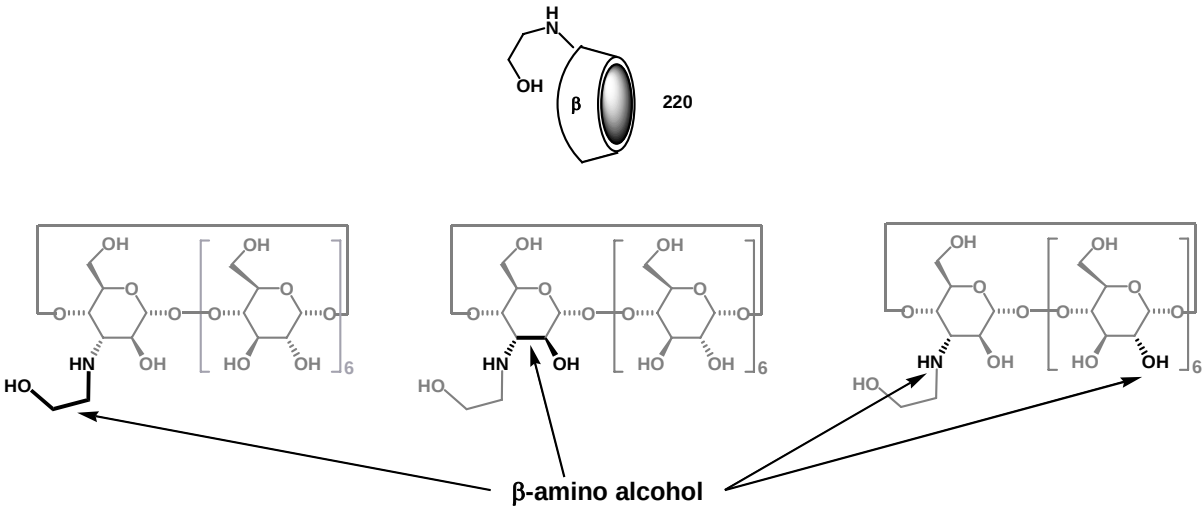
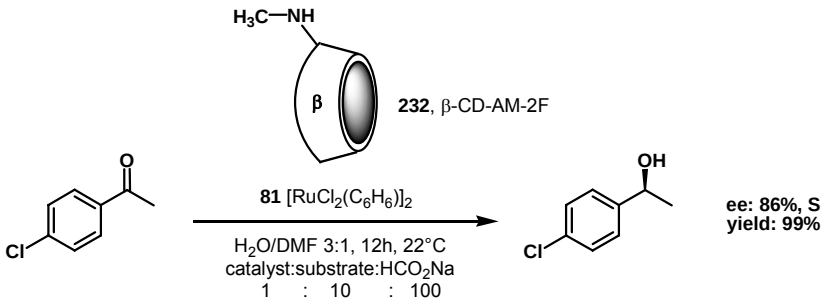


Figure 16 *Three possible binding modes with ligand **220***

Accordingly methyl amine was linked to β-CD as described above yielding new ligand **232**. If this ligand was inactive in ATH one could exclude the two proposed binding modes incorporating hydroxy groups of the β-CD unit (*figure 16; middle and right structure*). Moreover it would demonstrate conventional complex formation of the metal with the amino alcohol side chain as observed for the primary face. Interestingly, quantitative conversion and 86% ee (S) was observed using ligand **232** in ATH reaction under standard conditions (*scheme 59*).



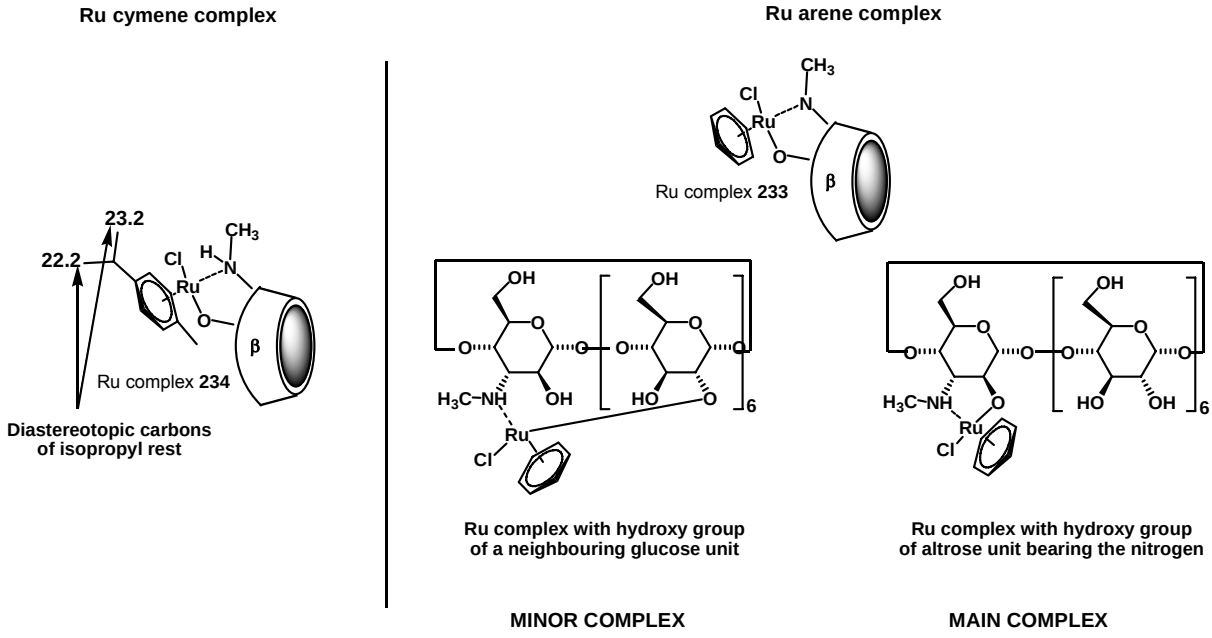
Scheme 59 *ATH with methyl amine derived CD **232***

Furthermore the ^{1}H-NMR spectra of Ru complex **233** in D_2O showed noticeable downfield shifts of several protons (*table 20, scheme 60*). As expected H_3 (0.63 ppm) and N-CH_3 (0.38 ppm) show the largest downfield shifts relative to free ligand **232**. Downfield shifts of 0.14 (H_1), 0.23 (H_2) and 0.22 (H_4) are in agreement with proposed binding mode shown on the very right in *scheme 60*.

Proton	H_1	H_2	H_3	H_4	H_5	N-CH_3
Shift (ppm)	0.14	0.23	0.63	0.22	0.01	0.38

Table 20 *Downfield shifts of several protons of Ru complex **233** relative to **232***

In addition to this, 1-D and 2-D ^{1}H-NMR spectra of Ru cymene complex **234** were measured. The downfield shifts relative to free ligand **220** are in the same range as observed for the arene analogue. Moreover metal complex **233** showed similar catalytic properties (97% yield and 63% ee (S) at 50°C). Importantly, the presence of a methyl- and especially of an isopropyl group on the aromatic ring facilitates the interpretation of the spectra (*scheme 60; left side*). HMQC spectra showed cross peaks of diastereotopic CH_3 isopropyl carbons at 22.2 ppm respectively 23.3 ppm to the protons at 1.54 ppm respectively 1.52 ppm. Only two supplementary cross peaks with intensities of less than 5% appeared in the same region and thus evidence that one main complex is formed.



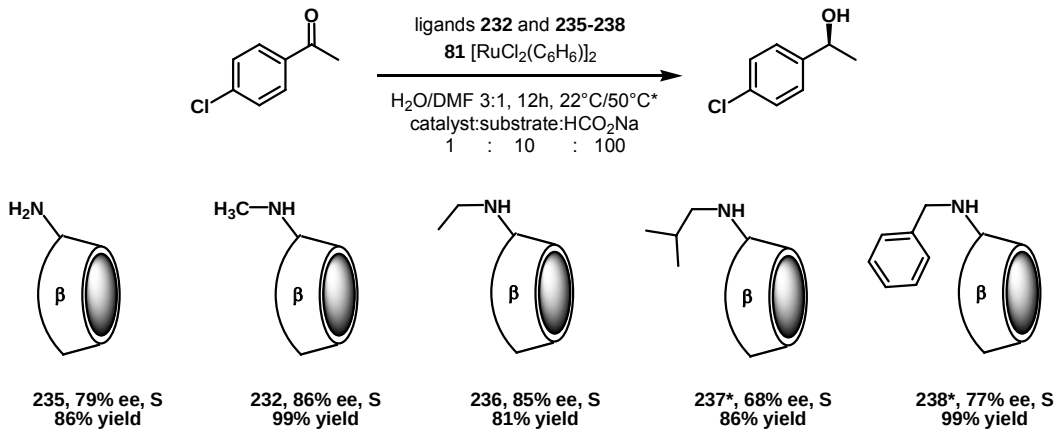
Scheme 60 *Left: Ru cymene complex; right two possible Ru arene binding modes*

Hence it was concluded that Ru coordinates to N-H and the adjacent OH group at C-2 of the altrose unit (*scheme 61*; *right structure*). The stereo outcome of the reduction of standard ketone **86** with amino ethanol based ligand **220** is only 3%

higher than with methyl amine ligand **232**. So it can be assumed that ATH performed with amino alcohol ligand **220** involves a mixture of the proposed three complexes which are specified in *figure 16*. Since the enantioselectivities are almost identical a main species according to the methyl amine analogue is very likely. This finding explains the poor reactivity of monotosylated- and α-pycolyl diamines. The bulky tosyl- respectively pyridine rest disturbs the formation of the Ru complex incorporating a hydroxy group of β-CD and therefore lowers the activity dramatically.

In order to exclude similar binding modes on the other face of β-CD, methyl amine was attached to the primary face as well. Reduction of standard ketone **86** gave no alcohol after 3 days at 50°C. Thus incorporation of a hydroxy group from β-CD in the reactive Ru complex can be ruled out for the primary face.

Unlike amino alcohol modified β-CD's, the structure of the active catalyst could be elucidated for methyl amine based CD. That's why several alkyl amines were linked to the secondary face of β-CD in order to get more sophisticated ligands for ATH. *Scheme 61* summarises the catalytic results of novel ligands **235-238**. Neither a primary amine in **235** nor a bulkier alkyl chain in **236** and **237** nor a phenyl rest in **238** could improve the stereoselectivity of the reduction compared to initially prepared methyl amine β-CD **232**.



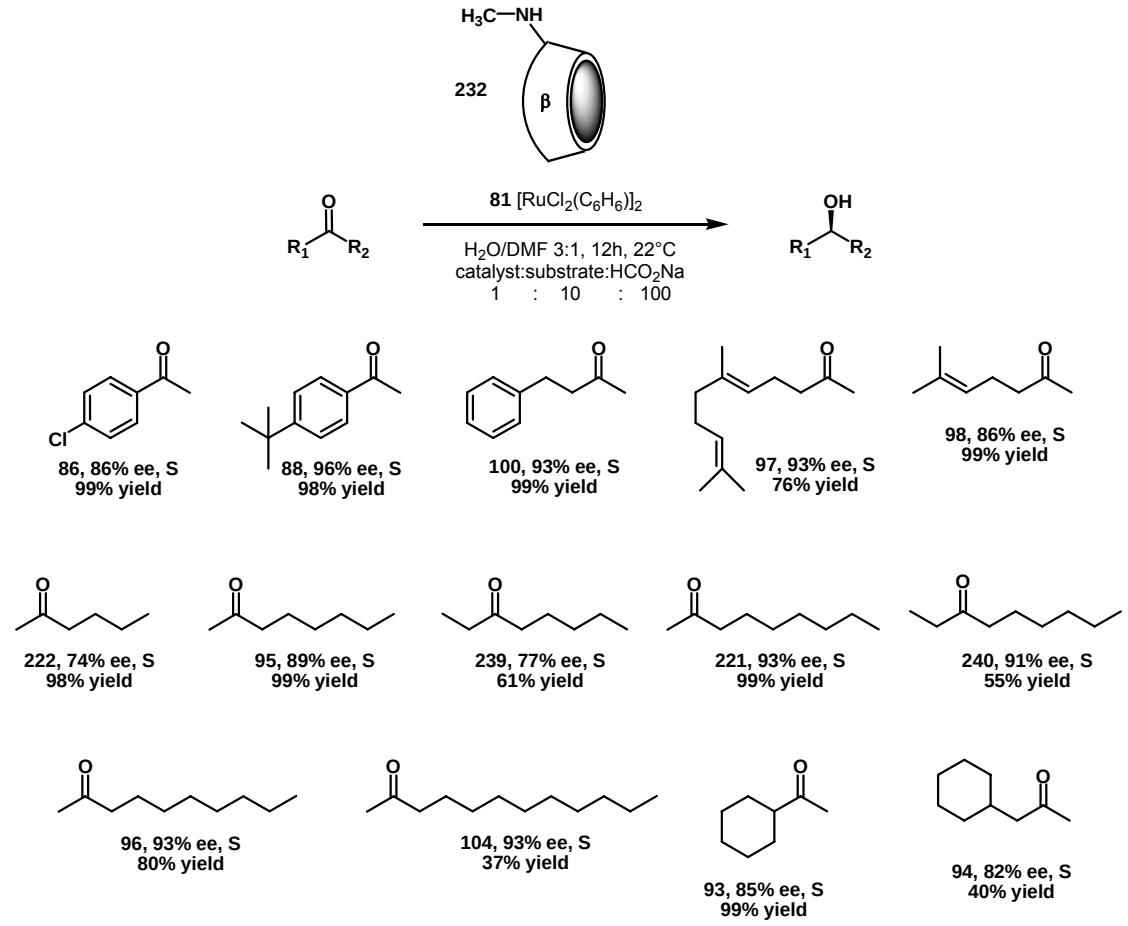
Scheme 61 *ATH with alkyl amines attached to the secondary face of β-CD*

Optimization of β-CD-AM-2F **232** carrying a methyl amine group is shown in *table 21*. As expected aromatic **86** and aliphatic standard substrate **98** behave similar. Best results for both substrates were obtained at room temperature using 10 mol% catalyst loading.

Entry	Ligand	mol%	Substrate	Solvent	T [°C]	Yield [%]	ee [%]
1	β-CD-AM-2F	10	aromatic **86**	H_2O/DMF 3:1	4	4	89 (S)
2	β-CD-AM-2F	10	aromatic **86**	H_2O/DMF 3:1	22	99	86 (S)
3	β-CD-AM-2F	10	aromatic **86**	H_2O/DMF 3:1	50	99	83 (S)
4	β-CD-AM-2F	5	aromatic **86**	H_2O/DMF 3:1	22	49	86 (S)
5	β-CD-AM-2F	5	aromatic **86**	H_2O/DMF 3:1	50	83	82 (S)
6	β-CD-AM-2F	10	aliphatic **98**	H_2O/DMF 3:1	22	98	86 (S)
7	β-CD-AM-2F	10	aliphatic **98**	H_2O/DMF 3:1	50	99	84 (S)

Table 21 *Optimization of ATH with ligand β-CD-AM-2F **232***

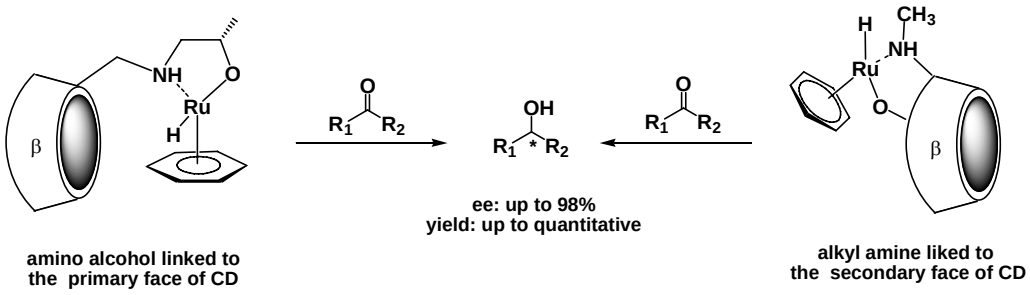
β-CD-AM-2F **232** was applied to ATH of various aromatic and notorious difficult aliphatic substrates under optimized conditions mentioned above (*scheme 62*). Generally, the yields are better with β-CD-AM-2F **232** than with β-CD-SAP **92**. Eight out of fourteen substrates showed quantitative yield, the six remaining ones moderate till good yield. Especially the yields of ketones bearing long alkyl chains could be improved. All alcoholic products show (S)-configuration and only two substrates are reduced with less than 82% ee. There is a trend that the bigger the difference between the two linear alkyl chains attached to the carbonyl functionality the higher the enantioselectivities. Example given, 3-octanone **239** (77% ee) is worse than 2-octanone **95** (89% ee) or 2-hexanone **222** (74% ee) is worse than 2-octanone **95** (89% ee) and this again worse than 2-nonanone **221** (93% ee). Highest enantioselectivities are observed for aromatic **88** (96% ee) and aliphatic **100**, **97** and (all 93% ee). Thus the stereo outcome is comparable to the one performed with β-CD-SAP **92** bearing a chiral amino alcohol side chain on the primary face and β-CD-AE-2F **220** carrying a non chiral amino alcohol on the secondary face. This is a remarkable result since CD is the only chiral unit in β-CD-AM-2F **232**.



Scheme 62 *ATH to several ketones under optimized conditions*

4 Summary

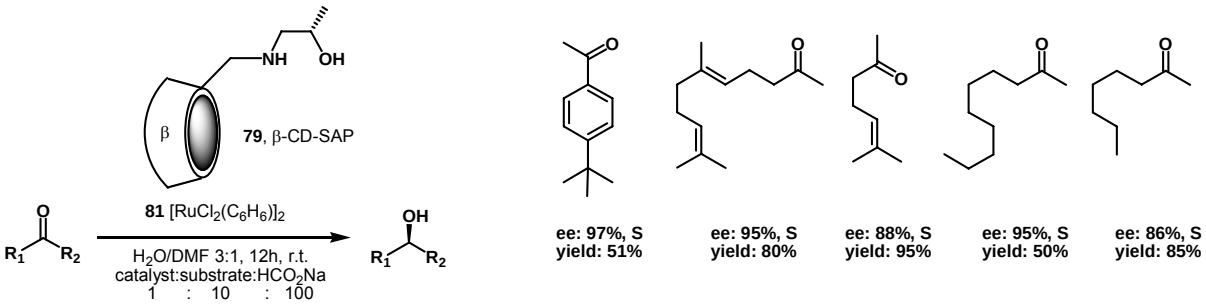
A novel ATH catalyst comprising of Ru(II) complexes linked to both faces of β-CD is presented. The huge advantage of this system is that it is possible to reduce aromatic as well as notorious difficult aliphatic ketones in good to excellent enantioselectivities (*scheme 63*). The catalytic reactions were performed in aqueous solution in the presence of 10 mol% catalyst and excess sodium formate.



Scheme 63 *Ru(II) complexes of β-CD's modified on primary and secondary face*

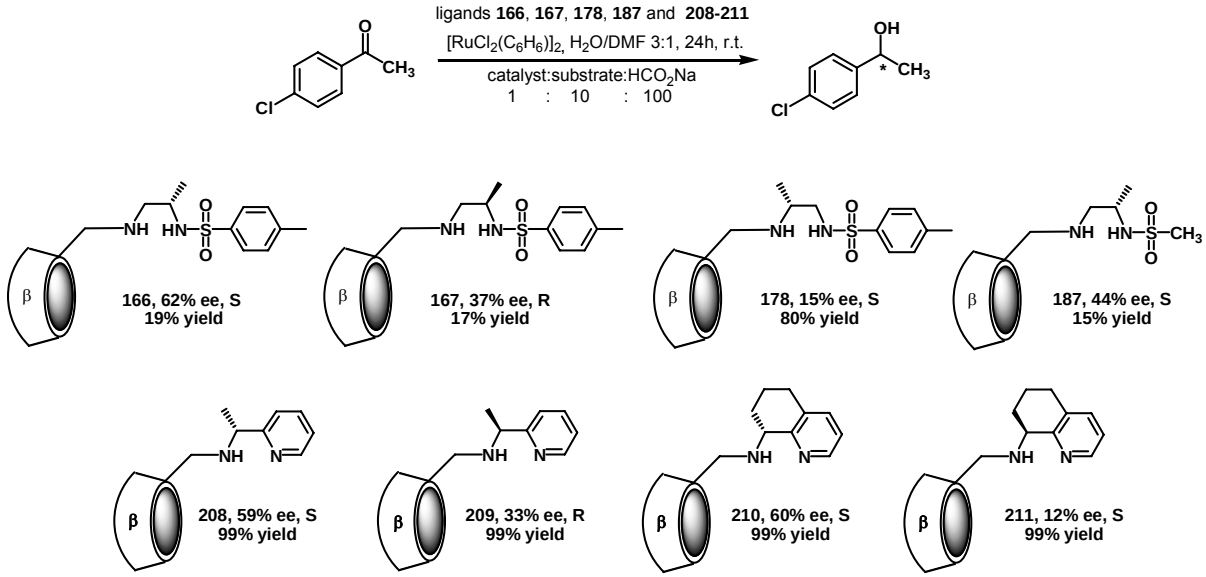
Initial studies were performed with ligand **79** carrying non chiral aminoethanol on the primary face of β-CD synthesised in one step from monotosylated β-CD **68**. The stereoselection varying from 6% ee (R) to 47% (R) for various aromatic carbonyl compounds was addressed to preorganization of the substrate in the hydrophobic cavity of β-CD such that *si* addition of the hydride to the carbonyl group is preferred in the reactive complex.

Screening of several chiral amino alcohols revealed that β-CD-SAP **92** bearing relatively little sterically demanding chiral methyl group serves as excellent ligand for the ATH to various aromatic and challenging aliphatic ketones (*scheme 64*). A drastically increase of enantioselectivities up to 97% ee (S) was observed in a mixture of H_2O/DMF 3:1 with moderate to good conversions. The chiral centre in α-position to the hydorxy group at the side chain has a strong influence on the stereo outcome. Furthermore the catalytic system was able to reduce β-ketoesters enantioselectively and diketones regioselectively.



Scheme 64 *ATH of aromatic and aliphatic ketones with β-CD-SAP **79***

A number of monosulfonated diamines and α-pycolyl amines were connected to the primary face of β-CD and applied to ATH. Neither of them could improve β-CD-SAP **79** in terms of reactivity and stereoselectivity. A selection of these ATH ligands is shown in *scheme 65*.

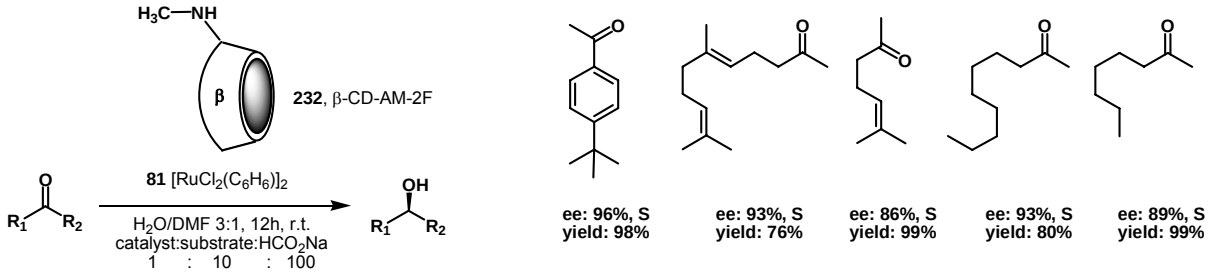


Scheme 65 *ATH with monosulfonated and α-pycolyl derived ligands*

In continuing studies amino alcohols were linked in five steps and overall yields up to 20% to the secondary face of β-CD. It was anticipated that the stereo outcome of ATH reactions with such ligands would differ from the one's observed with ligands modified on the primary face due to a distortion of the hydrophobic cavity of β-CD. This desymmetrization is caused by a conformational change of the modified sugar ring from $^4C_1$ to more stable $^1C_4$. Interestingly enantioselectivities up

to 98% (S) were achieved using β-CD-AE-2F **220** carrying non chiral amino ethanol on the secondary face. This is a striking result since asymmetric reactions using β-CD's as the only chiral unit are rarely exceeding 50% ee.

In addition to this it was found that methyl amine attached to the secondary face of β-CD act as excellent ligand in ATH reactions. It could be demonstrated that Ru binds to the amino nitrogen and the hydroxyl group at position 2 of the modified sugar unit. Various aromatic and aliphatic ketones were reduced in exquisite yields and enantioselectivities around 90% (*scheme 66*).



Scheme 66 *ATH with methyl amine linked to the secondary face of β-CD*

Experimental Part

5 Experimental Part

5.1 General

5.1.1 Abbreviations

AIBN	azobisisobutyronitrile
Alox	aluminium oxide
CALB	*candida antarctica lipase B*
CCl_4	tertrachloromethane
$CuSO_4$	copper sulfate
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DMAP	N,N-dimethylpyridin-4-amine
DMSO	dimethylsulfoxide
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
H_2SO_4	sulfuric acid
HCl	hydrochloric acid
Hx	hexane
K_2CO_3	potassium carbonate
KBr	potassium bromide
KOH	potassium hydroxide
$LiAlH_4$	lithium aluminiumhydride
MeOH	methanol
Na_2SO_4	sodium sulfate
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
NBS	N-bromosuccinimide
NH_4Cl	ammonium chloride
Pd/C	palladium on charcoal
Si_2O	silica gel
TBAF	tetrabutylammonium fluoride
TBME	*tert*.-butylmethylether

5.1.2 Solvents and Chemicals

Reagents were used as received from *Fluka AG, Acros Organics* and *Aldrich Chemie* unless otherwise stated. Chemicals of the quality *purum*, *purum p.a.* or > 98% were used without further purification. 6-*O*-monotosyl-β-CD **68** was purchased from *CycloLab Ltd* (Budapest, Hungary). Dichloro(benzene)ruthenium (II) dimer **81** was purchased from *Strem*. Mono-3-deoxy heptakis(6-O-*tert*.-butyldimethylsilyl)-3-amino-β-CD **235** was available in the group and used without further purification.

Solvents for chromatography and extractions were distilled prior to use. Dry dichloromethane (CH_2Cl_2) was distilled from CaH_2, diethyl ether (Et_2O) and tetrahydrofuran (THF) from Na/benzophenone. All freshly dried solvents were stored over activated molecular sieves (4Å). Further solvents (dimethylformamide, dimethylsolfoxide, methanol, ethanol) used for reactions corresponded to the quality *puriss p.a.*, *abs.*, *over Molecular Sieves* from *Fluka AG*. HPLC-grade solvents were purchased and used for analytical HPLC on chiral phase (Chiracel OD-H). Degassed solvents for catalysis under oxygen-free condition were obtained by five freeze-pump-thaw cycles in high-vacuum.

For an inert atmosphere Argon 56 (< 4 ppm other gases) from *Carbagas AG* (Lenzburg, Switzerland) or Argon 6.0 (<1.5 ppm other gases) from *PanGas AG* (Dagmersellen, Switzerland) were used.

5.1.3 Materials and Instruments

Solvents were removed with a *Büchi* (Switzerland) rotary evaporator (Waterbath 461, Rotavapor RE 111 and Vauum Controller 168) and a MZ 2C membrane pump (*Vacuubrand*). For cooling a mixture of EtOH and water was kept at 2°C with a UKW 300 thermostat (*Vacuubrand*).

For weighing compounds and reagents *Mettler* (Switzerland) balances P1200 (>1g), AE 163 (<1g), and AX205 (<100mg) were used.

A high-vacuum pump D5E from *Trivac* (Köln, Germany) was used for drying compounds and degassing solvents.

Slow addition of reagents to a reaction mixture was achieved with a Precidor 5003 syringe pump (*Informs HT*, Switzerland).

For all non-aqueous reactions glassware was dried with a heat gun for several minutes under vacuum, and the atmosphere was exchanged by three cycles of evacuating and flushing with argon.

Melting points (mp) were determined on a *büchi* 510 apparatus and are uncorrected.

Chromatographic Methods

Analytical thin layer chromatography (TLC) was performed on 0.25 mm precoated glass plates (5×10 cm, silica gel 60 F_{254}, *Merck AG*, Germany), 0.25 mm precoated glass plates (5×10 cm, aluminium oxide 60 F_{254}, *Merck AG*, Germany), or on 0.25 mm precoated glass plates (5×10 cm, RP-18 F_{254s}, *Merck AG*, Germany). Compounds were detected at 254 nm (UV) or at 366 nm (fluorescence). For carbohydrates, compounds were visualized by *p*-anisaldehyde dip (6 g *p*-anisaldehyde and 3 ml concentrated sulphuric acid in 250 ml ethanol). Description: (solvent): R_f.

For **normal phase column chromatography** silica gel 60 from *Merck* (0.040-0.063 mm, 230-400 mesh) or aluminum oxide 90 from *Merck* (standardized (activity II-III), 0.063-0.2 mm, 70-230 mesh) were used. For **reversed phase column chromatography**, RP-18 silica gel (fully endcapped) from *Fluka* (0.040-0.063mm, 230-400 mesh) was used. For **ion-exchange column chromatography**, Amberlite CG-50 from *Fluka* (weak acidic, H^+-Form, 100-200 mesh) or Amberlite IRA-68 (weakly basic, free base) were washed five times with nanopure water prior to use. Flash chromatography was performed under pressure with an aquarium pump.

Analytical chiral phase HPLC (ee determination) was performed with a *Chiralcel* OD-H column using HPLC-grade solvents on a *Agilent* 1100 Series HPLC system with Solvent degasser G1322A, BinPump G1312A, Autosampler G1313A, Thermostatic column housing G1316A, Diode array UV detector G1315B. All samples were filtrated prior to injection.

Spectroscopic Methods

Ultra Violet-Visible absorption spectras (UV/Vis) were recorded on an *Agilent* 8453 Diode Array spectrophotometer using optical 110 QS *Hellma* cuvettes (10 mm light path). Description: UV/Vis (solvent): wavelength of maxima (λ_{max}) in nm (relative extinction coefficient in %).

Infrared spectras (IR) were measured on a *Perkin-Elmer* 1600 series FTIR spectrometer in KBr or on a *FTIR-8400S* from *SHIMADZU*. Description: IR (medium): wavenumbers of transmission maxima in cm^{-1}.

Electron spray ionization mass spectras (ESI-MS) were recorded on a *Bruker* Esquire 3000^{plus}. Description: ESI-MS (solvent): mass peaks in *m/z* (relative intensity in %). Peaks with an intensity of less than 5% were not considered.

^{1}H-Nuclear magnetic resonance spectroscopy (^{1}H-NMR) was performed using either a *Bruker* av250 (250MHz), *Bruker* DPX-NMR (400MHz), *Bruker* DRX-500 (500MHz) or *Bruker* DRX-600 (600MHz) spectrometer. Solvents for NMR were obtained from *Cambridge Isotope Laboratories* (Andover, MA, USA). $CDCl_3$ was filtered through basic alumina prior to use. All spectra were recorded at 298 K. COSY, TOCSY, NOESY and ROESY were recorded if necessary. Selective TOCSY experiments were performed by Dr. Daniel Häussinger. Descripition: ^{1}H-NMR (frequency, solvent): δ_H in ppm relative to TMS or residual solvent peaks ($CDCl_3$: 7.26, D_2O: 4.79). Peak multiplicity: *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet; coupling constants *J* in Hertz.

^{13}C-Nuclear magnetic resonance spectroscopy (^{13}C-NMR) was ^{1}H-decoupled and recorded on a *Bruker* DPX-NMR (100MHz) or *Bruker* DRX-500 (125 MHz) spectrometer. For the assignment of carbons ATP, DEPT, HETCOR, HMQC and HMBC experiments were carried out. Descripition: ^{13}C-NMR (frequency, solvent): δ_C in ppm relative to residual solvent peaks.

^{19}F-Nuclear magnetic resonance spectroscopy (^{19}F-NMR) was recorded on a *Bruker* DPX-NMR (400MHz).

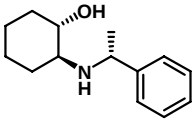
Single crystal *X*-ray structures were determined by *Dr. Markus Neuburger* and *Dr. Silvia Schaffner* in the chemical crystallography laboratory of the inorganic department. Data collection was carried out on a *Nonius KappaCCD* diffractometer using the COLLECT software suite. The usual corrections were applied. No absorption correction was determined. The structures were solved by direct method using the program DIRDIF-99. Anisotropic least-squares refinement was carried out on all non-hydrogen atoms using the program CRYSTALS. Hydrogen atoms were in calculated positions.

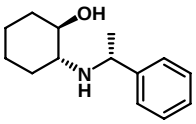
5.2 Synthesis

5.2.1 Synthesis of Cyclodextrin Side Chains

5.2.1.1 Amino alcohols

(1S,2S)-2-((R)-1-phenylethylamino)cyclohexanol (241) and (1R,2R)-2-((R)-1-phenylethylamino)cyclohexanol (242)[75] 12.4 ml of a 2M solution of trimethylaluminium in heptane (24.82 mol, 1.0 eq.) were added slowly to 3.15 ml (R)-(+)-methylbenzylamine (24.82 mol, 1.0 eq.) in 20 ml DCM at -5°C. After stirring for an additional hour at 0°C, 2.56 g cyclohexeneoxide (26.10 mol, 1.05 eq.) dissolved in 20 ml DCM were added over a period of 30 minutes to the cold solution and let stir for 3 h at 0°C and 18 h at r.t. The white suspension was then cooled to 0°C and 4.4 g NaF were added. 2.8 ml water were added very carefully and the solution was stirred for 90 minutes at r.t. After filtration over Celite and washing with DCM, the organic phase was dried over K_2CO_3 and concentrated. The crude product was purified by column chromatography (SiO_2, Hx/EtOAc/Et_3N 1:1:0.1), yielding 1.45 g **242** (25% yield) and 1.34 g **241** (23% yield) as white solids.

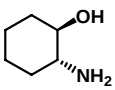




(1S,2S): **TLC** (SiO_2, Hx/EtOAc/Et_3N 1:1:0.1): R_f = 0.38; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.19-7.32 (*m*, 5H, H_{ar}); 3.83 (*q*, *J* = 6.3, 1H, PhC*H*(CH_3)NH); 3.00 (*m*, 1H); 2.25 (*m*, 1H, CH_2); 1.97 (*m*, 1H); 1.86 (*m*, 1H); 1.63 (*m*, 2H); 1.60 (*d*, *J* = 6.3, 3H, CH_3); 1.20-1.58 (*m*, 3H) 0.76 (*m*, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): 147.2, 128.9, 127.5, 126.9, 74.5, 62.0, 55.6, 33.4, 31.7, 25.8, 24.7, 23.9 ; **ESI-MS** (MeOH): positive ion mode: 220 (100, $[M+H]^+$)

(1R,2R): **TLC** (SiO_2, Hx/EtOAc/Et_3N 1:1:0.1): R_f = 0.31; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.18-7.32 (*m*, 5H, H_{ar}); 3.92 (*q*, *J* = 6.6, 1H, PhC*H*(CH_3)NH); 3.06 (*m*, 1H); 2.10 (*m*, 2H, CH_2); 1.89-1.92 (*m*, 2H); 1.27 (*d*, *J* = 6.6, 3H, CH_3); 1.16 (*m*, 2H); 1.00-1.04 (*m*, 2H) 0.80-0.84 (*m*, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): 145.8, 129.0, 127.4, 127.1, 74.6, 60.5, 54.5, 33.4, 30.9, 26.2, 25.5, 24.6; **ESI-MS** (MeOH): positive ion mode: 220 (100, $[M+H]^+$)

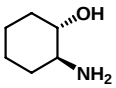
(1R,2R)-2-aminocyclohexanol (115)[75] 1.0 g **241** (4.57 mmol) was dissolved in 50 ml MeOH and stirred for 4 h under a hydrogen atmosphere in the presence of 0.30 g Pd/C. The mixture was filtrated over Celite and basic alox,



yielding 0.51 g **115** (85% yield) as a yellow oil.

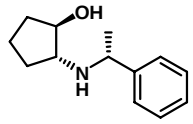
TLC (SiO_2, EtOAc/MeOH/NH_4OH 8:1:1): R_f = 0.18; **^{1}H-NMR** (400 MHz, $CDCl_3$): 3.10 (*m*, 1H, C*H*OH); 2.40 (*m*, 1H, C*H*NH); 1.80-1.96 (*m*, 2H); 1.60-1.66 (*m*, 2H); 1.09-1.21 (*m*, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): 75.6, 57.5, 34.8, 34.0, 25.5, 25.0; **ESI-MS** (MeOH): positive ion mode: 116 (100, $[M+H]^+$)

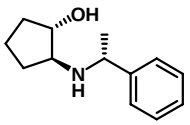
(1S,2S)-2-aminocyclohexanol (114)[75] 1.0 g **241** (4.57 mmol) were dissolved in 50 ml MeOH and stirred for 4 h under a hydrogen atmosphere in the presence of 0.30 g Pd/C. The mixture was filtrated over Celite and basic alox, yielding 0.53 g **114** (86% yield) as a yellow oil.



TLC (SiO_2, EtOAc/MeOH/NH_4OH 8:1:1): R_f = 0.18; **^{1}H-NMR** (400 MHz, $CDCl_3$): 3.10 (*m*, 1H, C*H*OH); 2.40 (*m*, 1H, C*H*NH); 1.80-1.96 (*m*, 2H); 1.60-1.66 (*m*, 2H); 1.09-1.21 (*m*, 4H); **^{13}C-NMR** (100 MHz, $CDCl_3$): 75.6, 57.5, 34.8, 34.0, 25.5, 25.0; **ESI-MS** (MeOH): positive ion mode: 116 (100, $[M+H]^+$)

(1S,2S)-2-((R)-1-phenylethylamino)cyclopentanol (243) and (1R,2R)-2-((R)-1-phenylethylamino)cyclopentanol (244)[75] 29.2 ml of a 2M solution of trimethylaluminium in heptane (58.31 mol, 1.0 eq.) were added slowly to 7.07 g (R)-(+)-methylbenzylamine (58.31 mol, 1.0 eq.) in 35 ml DCM at -5°C. After stirring for an additional hour at 0°C, 5.15 g cyclopenteneoxide (61.22 mol, 1.05 eq.) dissolved in 35 ml DCM were added over a period of 30 minutes to the cold solution and let stir for 3 h at 0°C and 18 h at r.t. The white suspension was then cooled to 0°C and 10.3 g NaF were added. 3.3 ml water were added very carefully and the solution was stirred for 90 minutes at r.t. After filtration over Celite and washing with DCM, the organic phase was dried over K_2CO_3 and concentrated. The crude product was purified by column chromatography (SiO_2, Hx/EtOAc/Et_3N 1:1:0.1), yielding 2.91 g **244** (31% yield) and 2.73 g **243** (29% yield) as white solids.

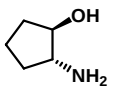




(1R,2R): **TLC** (SiO_2, Hx/EtOAc/Et_3N 1:1:0.1): R_f = 0.29 ; **^{1}H-NMR** (400 MHz, DMSO-d_6): 7.21-7.33 (*m*, 4H, H_{ar}); 7.10-7.15 (*m*, 1H, H_{ar}); 4.41 (*d*, *J* = 4.1, 1H, OH); 3.72-3.84 (*m*, 2H, PhC*H*(CH_3)NH and C*H*OH); 2.58-2.62 (*m*, 1H, C*H*NH); 1.75-1.82 (*m*, 1H); 1.54-1.62 (*m*, 1H); 1.45-1.51 (*m*, 2H); 1.29-1.38 (*m*, 1H); 1.20 (*d*, *J* = 6.6, 3H, CH_3); 1.01-1.11 (*m*, 1H); **^{13}C-NMR** (100 MHz, DMSO-d_6): 146.6, 128.9, 127.3, 127.0, 79.1, 65.4, 57.3, 33.0, 31.5, 24.6, 20.9; **ESI-MS** (MeOH): positive ion mode: 206 (100, $[M+H]^+$)

(1S,2S): **TLC** (SiO_2, Hx/EtOAc/Et_3N 1:1:0.1): R_f = 0.22 ; **^{1}H-NMR** (400 MHz, DMSO-d_6): 7.22-7.32 (*m*, 4H, H_{ar}); 7.11-7.18 (*m*, 1H, H_{ar}); 4.43 (*d*, *J* = 4.0, 1H, OH); 3.70 (*q*, *J* = 6.6, 1H, PhC*H*(CH_3)NH); 3.59-3.64 (*m*, 1H, C*H*OH); 2.42-2.54 (*m*, 1H, C*H*NH); 1.68-1.75 (*m*, 2H); 1.42-1.58 (*m*, 2H); 1.21-1.34 (*m*, 2H); 1.22 (*d*, *J* = 6.6, 3H, CH_3); **^{13}C-NMR** (100 MHz, DMSO-d_6): 146.8, 129.0, 127.3, 127.2, 77.9, 64.1, 56.3, 33.1, 30.0, 25.7, 21.1; **ESI-MS** (MeOH): positive ion mode: 206 (100, $[M+H]^+$)

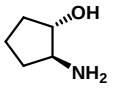
(1R,2R)-2-aminocyclopentanol (117)[75] 0.35 g **244** (1.80 mmol) were dissolved in



15 ml MeOH and stirred for 4 h under a hydrogen atmosphere in the presence of 0.30 g Pd/C. The mixture was filtrated over Celite and basic alox, yielding 0.14 g **117** (87% yield) as a yellow oil.

TLC (SiO_2, EtOAc/MeOH/NH_4OH 2:1:0.05): R_f = 0.13; **^{1}H-NMR** (400 MHz, $CDCl_3$): 3.50-3.53 (*m*, 1H, C*H*OH); 2.70-2.74 (*m*, *1*H, C*H*NH); 1.77-1.84 (*m*, 2H); 1.52-1.56 (*m*, 2H); 1.31-1.37 (*m*, 1H); 1.11-1.19 (*m*, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): 79.8, 60.3, 32.6, 32.3, 20.8; **ESI-MS** (MeOH): positive ion mode: 124 (100, $[M+H]^+$)

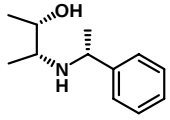
(1S,2S)-2-aminocyclopentanol (116)[75] 0.50 g **243** (2.59 mmol) were dissolved in

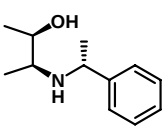


20 ml MeOH and stirred for 4 h under a hydrogen atmosphere in the presence of 0.34 g Pd/C. The mixture was filtrated over Celite and basic alox, yielding 0.19 g **116** (84% yield) as a yellow oil.

TLC (SiO_2, EtOAc/MeOH/NH_4OH 2:1:0.05): R_f = 0.13; **^{1}H-NMR** (400 MHz, $CDCl_3$): 3.50-3.53 (*m*, 1H, C*H*OH); 2.70-2.74 (*m*, *1*H, C*H*NH); 1.77-1.84 (*m*, 2H); 1.52-1.56 (*m*, 2H); 1.31-1.37 (*m*, 1H); 1.11-1.19 (*m*, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): 79.8, 60.3, 32.6, 32.3, 20.8; **ESI-MS** (MeOH): positive ion mode: 124 (100, $[M+H]^+$)

(2S,3R)-3-((R)-1-phenylethylamino)butan-2-ol (110) and (2R,3S)-3-((R)-1-phenylethylamino)butan-2-ol (111)[75] 13.8 ml of a 2M solution of trimethylaluminium in heptane (27.50 mol, 1.0 eq.) were added slowly to 3.34 g (R)-(+)-methylbenzylamine (27.50 mol, 1.0 eq.) in 15 ml DCM at -5°C. After stirring for an additional hour at 0°C, 2.01 g trans-epoxybutane (28.90 mol, 1.05 eq.) dissolved in 15 ml DCM were added over a period of 30 minutes to the cold solution and let stir for 3 h at 0°C and 40 h at r.t. The white suspension was then cooled to 0°C and 4.8 g NaF were added. 3.0 ml water were added very carefully and the solution was stirred for 90 minutes at r.t. After filtration over Celite and washing with DCM, the organic phase



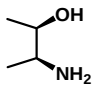


was dried over K_2CO_3 and concentrated. The crude product was purified by column chromatography (SiO_2, Hx/EtOAc/Et_3N 2:1:0.075), yielding 2.05 g **111** (37% yield) and 1.34 g **110** (24% yield) as white solids.

(2S,3R): **TLC** (SiO_2, Hx/EtOAc/Et_3N 1:1:0.16): R_f = 0.33; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.20-7.38 (*m*, 5H, H_{ar}); 3.85-3.95 (*m*, 1H, PhC*H*(CH_3)NH); 3.48-3.54 (*m*, 1H, C*H*OH); 2.49-2.56 (*m*, 1H, C*H*NH); 1.36 (*d*, *J* = 6.6, 3H, PhCHC*H*$_3$); 1.02 (*d*, *J* = 6.3, 3H, PhCH(C*H*$_3$)NH); 0.98 (*d*, *J* = 6.6, 3H, C*H*$_3$CHOH); **^{13}C-NMR** (100 MHz, $CDCl_3$):146.1, 128.9, 127.4, 127.0, 69.1, 55.8, 55.4, 25.5, 18.0, 14.8

(2R,3S): **TLC** (SiO_2, Hx/EtOAc/Et_3N 1:1:0.16): R_f = 0.38; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.18-7.42 (*m*, 5H, H_{ar}); 3.74-3.91 (*m*, 2H, PhC*H*(CH_3)NH and C*H*OH); 2.51-2.54 (*m*, 1H, C*H*NH); 1.33 (*d*, *J* = 6.8, 3H, PhCH(C*H*$_3$)NH); 1.02 (*d*, *J* = 6.3, 3H, C*H*$_3$CHNH); 0.88 (*d*, *J* = 6.6, 3H, C*H*$_3$CHOH); **^{13}C-NMR** (100 MHz, $CDCl_3$): 146.2, 129.0, 127.4, 126.9, 66.5, 55.3, 54.7, 25.0, 18.2, 15.1

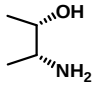
(2R,3S)-3-aminobutan-2-ol (113)[75] 0.60 g **111** (3.11 mmol) were dissolved in 30 ml



MeOH and stirred for 3 days under a hydrogen atmosphere in the presence of 0.15 g Pd/C. The mixture was filtrated over Celite and basic alox, yielding 0.14 g **113** (51% yield) as a yellow oil.

TLC (SiO_2, Hx/EtOAc/Et_3N 2:1:0.05): R_f = 0.07; **^{1}H-NMR** (400 MHz, $CDCl_3$): 3.64-3.66 (*m*, 1H, C*H*OH); 2.94-2.96 (*m*, 1H, C*H*NH); 1.10 (*d*, *J* = 6.3, 3H, C*H*$_3$CHOH); 1.01 (*d*, *J* = 6.6, 3H, C*H*$_3$CHNH); **^{13}C-NMR** (100 MHz, $CDCl_3$): 71.0, 51.5, 17.9, 17.8 ; **ESI-MS** (MeOH): positive ion mode: 90 (100, $[M+H]^+$)

(2S,3R)-3-aminobutan-2-ol (112)[75] 1.12 g **110** (5.70 mmol) were dissolved in 45 ml

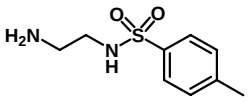


MeOH and stirred for 3 days under a hydrogen atmosphere in the presence of 0.28 g Pd/C. The mixture was filtrated over Celite and basic alox, yielding 0.34 g **112** (66% yield) as a yellow oil.

TLC (SiO_2, Hx/EtOAc/Et_3N 2:1:0.05): R_f = 0.07; **^{1}H-NMR** (400 MHz, $CDCl_3$): 3.64-3.66 (*m*, 1H, C*H*OH); 2.94-2.96 (*m*, 1H, C*H*NH); 1.10 (*d*, *J* = 6.3, 3H, C*H*$_3$CHOH); 1.01 (*d*, *J* = 6.6, 3H, C*H*$_3$CHNH); **^{13}C-NMR** (100 MHz, $CDCl_3$): 71.0, 51.5, 17.9, 17.8 ; **ESI-MS** (MeOH): positive ion mode: 90 (100, $[M+H]^+$)

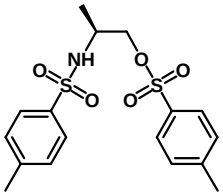
5.2.1.2 Monotosylated Diamines

N-tosylethane-1,2-diamine (157)[77] 10.00 g ethane-1,2-diamine **155** (0.17 mol, 3.0 eq.) were dissolved in 20 ml of benzene. 10.57 g tosylchloride **156** (0.06 mol, 1.0 eq.) dissolved in 40 ml of benzene were added dropwise under vigorous stirring. The yellowish precipitate was filtered off and stirred in 25 ml 1M HCl. After filtration, the white crystals were dissolved in another 25 ml 1M HCl and filtrated. The filtrate was basified with 1M NaOH precipitation of white crystals. After filtration and washing with ice-water one gained 3.11 g of **157** (8.5 % yield) as white crystals.



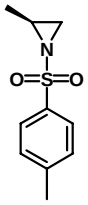
TLC (SiO_2, Hx/TBME 1:1): R_f = 0.11; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.75 (*d*, *J* = 8.3, 2H, H_{ar}); 7.31 (*d*, *J* = 8.3, 2H, H_{ar}); 2.96 (*t*, *J* = 5.1, 2H); 2.79 (*t*, *J* = 5.1, 2H); 2.43 (*s*, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 143.8, 137.3, 130.1, 127.5, 45.8, 41.2, 21.9; **ESI-MS** (MeOH): positive ion mode: 215 (75, $[M+H]^+$); 237 (100, $[M+Na]^+$); 429 (26, $[2M+H]^+$); 451 (54, $[2M+Na]^+$)

(S)-2-(tosylamino)propyl-4-methylbenzenesulfonat (160)[79] 2.08 g (S)-2-amino-1-propanol **159** (27.70 mmol, 1.0 eq.) were dissolved in 7.5 ml of pyridine. 10.54 g tosylchloride (55.30 mmol, 2.0 eq.) dissolved in 30 ml of pyridine were added dropwise over a period of 30 minutes at 0°C. After stirring for an additional hour at 0°C, the solution was allowed to come to r.t. and stirred for 18 h. The pyridine was evaporated under reduced pressure, the brownish residue dissolved in 75 ml of water and extracted three times with TBME. The combined organic phases were washed with 4 x 50 ml 5%-H_2SO_4, 50 ml sat. $CuSO_4$, water, sat. $NaHCO_3$ and brine. After drying over Na_2SO_4, the crude product was purified by column chromatography (SiO_2, Hx/EtOAc 3:1) yielding 6.82 g **160** (64% yield) as white crystals.



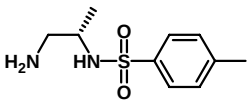
TLC (SiO_2, Hx/TBME 3:1): R_f = 0.21; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.70 (*m*, 4H, H_{ar}); 7.36 (*d*, *J* = 8.1, 2H, H_{ar}); 7.28 (*d*, *J* = 8.1, 2H, H_{ar}); 4.67 (*d*, *J* = 8.1, 1H, NH); 3.92 (*m*, 1H, CH_2OH); 3.84 (*m*, 1H, CH_2OH); 3.53 (*m*, 1H, C*H*NH); 2.47 (*s*, 3H, ArCH_3); 2.42 (*s*, 3H, ArCH_3); 1.08 (*d*, *J* = 6.8, 3H, CH_3); **ESI-MS** (MeOH): positive ion mode: 406 (100, $[M+Na]^+$); 789 (68, $[2M+Na]^+$)

(S)-2-methyl-1-tosylaziridine (161)[79] 0.22 g KOH (10.98 mmol, 3.0 eq.) dissolved in 3 ml of MeOH was added over a period of 15 minutes to a solution of 1.40 g **160** (3.66 mmol, 1.0 eq.) in 15 ml of MeOH. The solution was stirred for 30 min, before quenching with 10 ml of water. The aqueous phase was extracted three times with TBME, the combined organic phases washed with sat. ammonium chloride, water, sat. $NaHCO_3$ and brine. After drying over Na_2SO_4 the solvent was evaporated and the crude product purified by column chromatography (SiO_2, Hx/EtOAc 3:1), yielding 0.62 g **161** (80% yield) as white crystals.



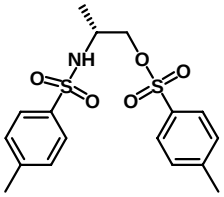
TLC (SiO_2, Hx/TBME 3:1): R_f = 0.41; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.82 (*d*, *J* = 8.3, 2H, H_{ar}); 7.34 (*d*, *J* = 8.3, 2H, H_{ar}); 2.82 (*m*, 1H, C*H*NH); 2.61 (*d*, *J* = 7.1, 1H, CH_2NH); 2.45 (*s*, 3H, ArCH_3); 2.02 (*d*, *J* = 4.6, 1H, CH_2NH); 1.26 (*d*, *J* = 5.6, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 144.8, 135.8, 130.1, 128.2, 36.3, 35.1, 22.0, 17.2; **ESI-MS** (MeOH): positive ion mode: 234 (79, [*M*+Na]$^+$); 445 (100, [2*M*+Na]$^+$)

(S)-N-2-tosylpropane-1,2-diamine (162) 2.60 g **161** (12.04 mmol) dissolved in 50 ml of MeOH were added to 160 ml of a saturated solution of ammonia in MeOH at 0°C over a period of 2 h. The mixture was then stirred at r.t. overnight. The ammonia was removed by bubbling nitrogen through the solution and the solvent under reduced pressure. The crude product was recrystallized three times in toluene, to yield 2.33 g **162** (83% yield, ee was shown to be 99% (S) by mosher amidation) as white crystals.



TLC (SiO_2, 2:1 Hx/TBME): R_f = 0; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.77 (*d*, *J* = 8.3, 2H, H_{ar}); 7.30 (*d*, *J* = 8.3, 2H, H_{ar}); 5.00 (broad, 1H, NH); 3.20 (*m*, 1H, C*H*NH); 2.68 (*dxd*, *J* = 4.3, 10.0, 1H, CH_2NH$_2$); 2.50 (*dxd*, *J* = 6.8, 12.1, 1H, CH_2NH$_2$); 2.43 (*s*, 3H, ArCH_3); 1.03 (*d*, *J* = 6.8, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 143.7, 138.2, 130.1, 127.5, 51.9, 47.4, 21.9, 19.4; **ESI-MS** (MeOH): positive ion mode: 229 (100, [*M*+H]$^+$); 457 (15, [2*M*+H]$^+$); **EA**: calculated for $C_{10}H_{16}N_2O_2S$: C 52.61, H 7.06, N 12.27, O 14.02; found: C 52.68, H 6.94, N 12.06, O 13.83

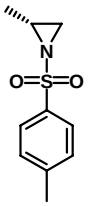
(R)-2-(tosylamino)propyl-4-methylbenzenesulfonate (245)[79] 1.04 g (R)-2-amino-1-propanol (13.82 mmol, 1.0 eq.) was dissolved in 3.8 ml of pyridine. 5.27 g tosylchloride (27.66 mmol, 2.0 eq.) dissolved in 15 ml of pyridine was added dropwise over a period of 30 minutes at 0°C. After stirring for an additional hour at 0°C, the solution was



allowed to come to r.t. and stirred for 18 h. The pyridine was evaporated under reduced pressure, the brownish residue dissolved in 75 ml of water and extracted three times with TBME. The combined organic phases were washed with 4 x 25 ml 5%-H_2SO_4, 25 ml sat. $CuSO_4$, water, sat. $NaHCO_3$ and brine. After drying over Na_2SO_4, the crude product was purified by column chromatography (SiO_2, Hx/EtOAc 3:1) yielding 6.82 g **245** (80% yield) as white crystals.

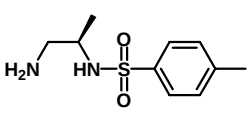
TLC (SiO_2, Hx/TBME 3:1): R_f = 0.21; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.70 (*m*, 4H, H_{ar}); 7.36 (*d*, *J* = 8.1, 2H, H_{ar}); 7.28 (*d*, *J* = 8.1, 2H, H_{ar}); 4.67 (*d*, *J* = 8.1, 1H, NH); 3.92 (*m*, 1H, C*H*$_2$OH); 3.84 (*m*, 1H, C*H*$_2$OH); 3.53 (*m*, 1H, C*H*NH); 2.47 (*s*, 3H, $ArCH_3$); 2.42 (*s*, 3H, $ArCH_3$); 1.08 (*d*, *J* = 6.8, 3H, CH_3); **ESI-MS** (MeOH): positive ion mode: 406 (100, [*M*+Na]$^+$); 789 (68, [2*M*+Na]$^+$)

(R)-2-methyl-1-tosylaziridine (246)[79] 1.90 g KOH (33.16 mmol, 3.0 eq.) dissolved in 9 ml of MeOH was added over a period of 15 minutes to a solution of 4.23 g **245** (11.08 mmol, 1.0 eq.) in 45 ml of MeOH. The solution was stirred for 30 min, before quenching with 10 ml of water. The aqueous phase was extracted three times with TBME, the combined organic phases washed with sat. ammonium chloride, water, sat. $NaHCO_3$ and brine. After drying over Na_2SO_4 the solvent was evaporated and the crude product purified by column chromatography (SiO_2, Hx/EtOAc 3:1), yielding 1.14 g **246** (47% yield) as white crystals.



TLC (SiO_2, Hx/TBME 3:1): R_f = 0.41; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.82 (*d*, *J* = 8.3, 2H, H_{ar}); 7.34 (*d*, *J* = 8.3, 2H, H_{ar}); 2.82 (*m*, 1H, C*H*NH); 2.61 (*d*, *J* = 7.1, 1H, C*H*$_2$NH); 2.45 (*s*, 3H, $ArCH_3$); 2.02 (*d*, *J* = 4.6, 1H, C*H*$_2$NH); 1.26 (*d*, *J* = 5.6, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 144.8, 135.8, 130.1, 128.2, 36.3, 35.1, 22.0, 17.2; **ESI-MS** (MeOH): positive ion mode: 234 (79, [*M*+Na]$^+$); 445 (100, [2*M*+Na]$^+$)

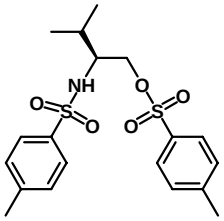
(R)-N-2-tosylpropane-1,2-diamine (164) 1.14 g **246** (5.02 mmol) dissolved in 24 ml of MeOH was added to 70 ml of a saturated solution of ammonia in MeOH at 0°C over a period of 2 h. The mixture was then stirred at r.t. overnight. The ammonia was removed by bubbling nitrogen through the solution and the solvent under reduced pressure. The crude product was recrystallized three times in toluene, to yield 0.99 g **164** (81% yield, ee was shown to be 99% (R) by mosher amidation) as white crystals.



TLC (SiO_2, 2:1 Hx/TBME): R_f = 0; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.77 (*d*, *J* = 8.3, 2H, H_{ar}); 7.30 (*d*, *J* = 8.3, 2H, H_{ar}); 5.0 (broad, 1H, NH); 3.20 (*m*, 1H, C*H*NH); 2.68 (*dxd*,

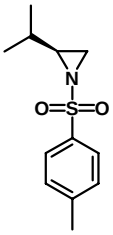
J = 4.3, 4.5, 1H, C*H*$_2$NH$_2$); 2.50 (*dxd*, *J* = 6.8, 7.1, 1H, C*H*$_2$NH$_2$); 2.43 (*s*, 3H, ArCH$_3$); 1.03 (*d*, *J* = 6.8, 3H, CH$_3$); **^{13}C-NMR** (100 MHz, CDCl$_3$): 143.7, 138.2, 130.1, 127.5, 51.9, 47.4, 21.9, 19.4; **ESI-MS** (MeOH): positive ion mode: 229 (100, [*M*+H]$^+$); 457 (15, [2*M*+H]$^+$); **EA**: calculated for $C_{10}H_{16}N_2O_2S$: C 52.61, H 7.06, N 12.27, O 14.02; found: C 52.69, H 6.96, N 12.08, O 13.82

(S)-3-methyl-2-(tosylamino)butyl-4-methylbenzenesulfonate (247)[79] 1.50 g (S)-2-amino-3-methylbutan-1-ol (14.54 mmol, 1.0 eq.) was dissolved in 4.0 ml of pyridine. 3.77 g tosylchloride (29.08 mmol, 2.0 eq.) dissolved in 15 ml of pyridine was added dropwise over a period of 30 minutes at 0°C. After stirring for an additional hour at 0°C, the solution was allowed to come to r.t. and stirred for 18 h. The pyridine was evaporated under reduced pressure, the brownish residue dissolved in 75 ml of water and extracted three times with TBME. The combined organic phases were washed with 4 x 50 ml 5%-H_2SO_4, 50 ml sat. $CuSO_4$, water, sat. $NaHCO_3$ and brine. After drying over Na_2SO_4, the crude product was purified by column chromatography (SiO_2, Hx/EtOAc 2:1) yielding 3.62 g **247** (61% yield) as white crystals.



TLC (SiO_2, Hx/TBME 3:1): R_f = 0.42; **^{1}H-NMR** (400 MHz, CDCl$_3$): 7.72 (*d*, *J* = 8.1, 2H, H$_{ar}$); 7.68 (*d*, *J* = 8.0, 2H, H$_{ar}$); 7.35 (*d*, *J* = 8.1, 2H, H$_{ar}$); 7.25 (*d*, *J* = 8.0, 2H, H$_{ar}$); 4.80 (*d*, *J* = 8.1, 1H, NH); 3.99 (*m*, 1H, C*H*$_2$OH); 3.78 (*m*, 1H, C*H*$_2$OH); 3.15 (*m*, 1H, C*H*NH); 2.46 (*s*, 3H, ArCH$_3$); 2.41 (*s*, 3H, ArCH$_3$); 1.38 (*hp*, *J* = 6.8, 1H, CH); 0.83 (*d*, *J* = 6.8, 3H, CH$_3$); 0.72 (*d*, *J* = 6.8, 3H, CH$_3$); **ESI-MS** (MeOH): positive ion mode: 412 (90, [*M*+H]$^+$); 434 (100, [*M*+Na]$^+$)

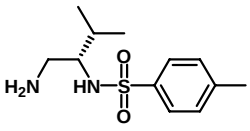
(S)-2-isopropyl-1-tosylaziridine (248)[79] 0.81 g KOH (12.78 mmol, 3.0 eq.) dissolved in 8 ml of MeOH was added over a period of 15 minutes to a solution of 1.75 g **247** (4.26 mmol, 1.0 eq.) in 40 ml of MeOH. The solution was stirred for 30 min, before quenching with 10 ml of water. The aqueous phase was extracted three times with TBME, the combined organic phases washed with sat. ammonium chloride, water, sat. $NaHCO_3$ and brine. After drying over Na_2SO_4 the solvent was evaporated and the crude product purified by column chromatography (SiO_2, Hx/EtOAc 3:1), yielding solid 0.97 g **248** (95% yield).



TLC (SiO_2, Hx/TBME 3:1): R_f = 0.52; **^{1}H-NMR** (400 MHz, CDCl$_3$): 7.85 (*d*, *J* = 12.8, 2H, H$_{ar}$); 7.33 (*d*, *J* = 12.8, 2H, H$_{ar}$); 2.62 (*d*, *J* = 11.2, 1H, C*H*NH); 2.52 (*m*, 1H,

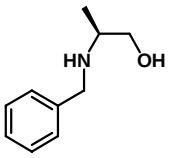
CH_2NH); 2.44 (*s*, 3H, ArCH_3); 2.10 (*d*, *J* = 7.5, 1H, CH_2NH); 1.40 (*hp*, *J* = 11.2 , 1H, CH); 0.90 (*d*, *J* = 11.0, 3H, CH_3); 0.79 (*d*, *J* = 11.0, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 144.8, 135.5, 130.0, 128.5, 46.7, 33.1, 30.5, 22.1, 20.0, 19.5; **ESI-MS** (MeOH): positive ion mode: 262 (100, [*M*+Na]$^+$); 501 (51, [2*M*+Na]$^+$)

(S)-3-methyl-N-2-tosylbutane-1,2-diamine (165) 0.97 g **248** (4.06 mmol) dissolved in 18 ml of MeOH was added to 50 ml of a saturated solution of ammonia in MeOH at 0°C over a period of 2 h. The mixture was then stirred at r.t. overnight. The ammonia was removed by bubbling nitrogen through the solution and the solvent under reduced pressure. The crude product was washed with 50 ml hexane, to yield 0.90 g **165** (87% yield, ee was shown to be 99% (S) by mosher amidation) as white crystals.



TLC (SiO_2, 2:1 Hx/TBME): R_f = 0; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.76 (*d*, *J* = 8.4, 2H, H_{ar}); 7.29 (*d*, *J* = 8.4, 2H, H_{ar}); 4.98 (broad, 1H, NH); 2.94 (*m*, 1H, C*H*NH); 2.65 (*dxd*, *J* = 6.1, 13.1, 1H, CH_2NH_2); 2.55 (*dxd*, *J* = 4.6, 13.2, 1H, CH_2NH_2); 2.42 (*s*, 3H, ArCH_3); 1.75 (*hp*, *J* = 6.6, 1H, CH); 0.74-0.83 (*m*, 6H, 2xCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 143.6, 138.6, 130.0, 127.5, 61.4, 42.6, 30.3, 21.9, 19.1, 18.9; **ESI-MS** (MeOH): positive ion mode: 257 (100, [*M*+H]$^+$)

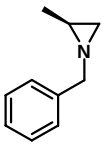
(S)-2-(benzylamino)propan-1-ol (249)[80] 1.04 g (S)-2-aminopropan-1-ol (13.83 mmol, 1.0 eq.) and 1.55 ml benzaldehyde **171** (15.21 mmol, 1.1 eq) were refluxed in 16 ml of toluene with a Dean-Stark Condenser for 5 h. After evaporation of the solvent, the resulting yellowish oil was dissolved in 15 ml of EtOH and cooled down to 0°C. 1.30 g sodium boronhydride (34.57 mmol, 2.5 eq.) were added and the mixture acidified to pH 2 with 3M HCl. After stirring for 14 h at r.t., water was removed at the rotavap, the residue dissolved in 30 ml 1M HCl and five times extracted with 20 ml of DCM. The aqueous phase was basified to pH 13 with 1M NaOH and extracted five times with DCM. The combined organic phases were dried over Na_2SO_4 and purified by column chromatography (alox neutral, DCM/Hx 1:1) yielding 1.83 g **249** (80% yield) as a colourless oil.



TLC (alox neutral, 1:1 DCM/Hx): R_f = 0.32 ; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.23-7.38 (*m*, 5H, H_{ar}); 3.84 (*d, J* = 13.0, 1H, CH_2Ph); 3.71 (*d, J* = 13.0, 1H, CH_2Ph); 3.55 (*dxd*, *J* = 4.0, 10.6, 1H, CH_2OH); 3.23 (*dxd*, *J* = 7.0, 10.6, 1H, CH_2OH); 2.71 (*m*, 1H,

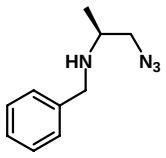
C*H*NH); 1.10 (*d*, *J* = 6.5, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 140.5, 128.7, 128.3, 127.3, 65.7, 53.9, 51.3, 17.4

(S)-1-benzyl-2-methylaziridine (250)[80] 1.83 g **249** (11.08 mmol, 1.0 eq.) and 4.36 g triphenylphosine (16.62 mmol, 1.5 eq.) were dissolved in 30 ml diethylether. 3.44 ml DIAD (16.62 mmol, 1.5 eq.) were added dropwise over a period of 45 minutes at a temperature between 5-10°C and then stirred at r.t. over night. The red solution was filtered and washed with 30 ml ether/hexane (1:1). The filtrate was extracted twice with 20 ml 1M HCl and the aqueous phase basified to pH 13 with 5M NaOH. After extracting five times with ether, the combined organic phases were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product purified by column chromatography (alox neutral, DCM/Hx 1:1) yielding 0.86 g **250** (47% yield) as a colourless oil.



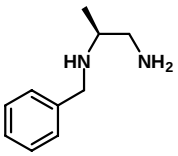
TLC (alox neutral, 1:1 DCM/Hx): R_f = 0.19; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.27-7.38 (*m*, 5H, H_{ar}); 3.48 (*d, J* = 13.6, 1H, CH_2Ph); 3.43 (*d, J* = 13.6, 1H, CH_2Ph); 1.61 (*d*, *J* = 3.6, 1H, CH_2OH); 1.54 (*m*, 1H, CH_2OH); 1.42 (*d*, *J* = 3.6, 1H, C*H*NH); 1.23 (*d*, *J* = 5.5, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 139.7, 128.5, 128.0, 127.0, 64.9, 35.2, 35.0, 18.5

(S)-1-azido-N-benzylpropan-2-amine (251)[81] 0.38 ml trimethylsilyl azide (2.72 mmol, 2.0 eq.) and 0.20 g **250** (1.36 mmol, 1.0 eq.) were refluxed in 5 ml of acetonitril for 5 days. The red solution was adjusted to pH 1 with 1M HCl and stirred for 1 h. After the solution was basified to pH 9 with $NaHCO_3$, the aqueous solution was extracted three times with DCM. The combined organic phases were dried over Na_2SO_4. The solvent was evaporated and the crude product purified by column chromatography (SiO_2, EtOAc/Hx 3:1) yielding 0.40 g **251** (27% yield) as a colourless oil.



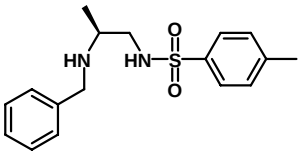
TLC (SiO_2, EtOAc/Hx 3:1): R_f = 0.40; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.24-7.33 (*m*, 5H, H_{ar}); 3.83 (*d, J* = 13.0, 1H, CH_2Ph); 3.73 (*d, J* = 13.6, 1H, CH_2Ph); 3.33 (*dxd*, *J* = 6.4, 12.1, 1H, CH_2OH); 3.21 (*dxd*, *J* = 4.8, 12.1, 1H, CH_2OH); 1.54 (*broad*, 1H, NH); 2.89 (*m*, 1H, C*H*NH); 1.17 (*d*, *J* = 6.4, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 140.2, 128.7, 128.6, 128.3, 56.8, 52.2, 51.4, 18.5

(S)-N-2-benzylpropane-1,2-diamine (252)[81] 560 mg **251** (2.96 mmol, 1.0 eq.) were dissolved in 5 ml diethylether. 90 mg $LiAlH_4$ (2.37 mmol, 0.8 eq.) were added slowly and the mixture stirred for 3 h at r.t. The reaction was quenched with sat. $NaHCO_3$, extracted three times with 20 ml ether and dried over Na_2SO_4. 232 mg **252** (47% yield) were obtained after evaporation of the solvent and used without further purification.



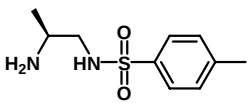
TLC (SiO_2, EtOAc/Hx 3:1): R_f = 0; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.18-7.34 (*m*, 5H, H_{ar}); 3.87 (*d, J* = 13.1, 1H, C*H*$_2$Ph); 3.73 (*d, J* = 12.9, 1H, C*H*$_2$Ph); 2.52-2.77 (*m*, 3H, 2xCH_2 and CH); 1.05 (*m*, *J* = 6.6, 3H, C*H*$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 140.9, 128.6, 128.3, 127.0, 54.6, 51.5, 47.6, 18.5; **ESI-MS** (MeOH): positive ion mode: 165 (100, $[M+H]^+$)

(S)-N-(2-(benzylamino)propyl)-4-methylbenzenesulfonamide (253) 0.27 g **156** (1.41 mmol, 1.0 eq.) diluted in 5 ml DCM were slowly added to a solution containing 0.23 g **252** (1.41 mmol, 1.0 eq.) and 0.20 ml triethylamine (1.41 mmol, 1.0 eq.) in 15 ml DCM at 0°C. After stirring for 2.5 h at r.t., the solvent was removed and the crude product purified by column chromatography (SiO_2, DCM/MeOH/Et_3N 100:5:1) yielding 0.39 g **253** (77% yield) as a white powder.



TLC (SiO_2, DCM/MeOH/Et_3N 100:5:1): R_f = 0.37; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.71 (*d*, *J* = 6.7, 2H, H_{ar}); 7.23-7.32 (*m,* 7H, H_{ar}); 3.67 (*d, J* = 13.0, 1H, C*H*$_2$Ph); 3.54 (*d, J* = 13.0, 1H, C*H*$_2$Ph); 2.98 (*dxd*, *J* = 3.8, 11.9, 1H, C*H*$_2$OH); 2.77 (*m*, 1H, C*H*NH); 2.70 (*dxd*, *J* = 6.9, 11.8, 1H, C*H*$_2$OH); 2.47 (*s*, 3H, ArCH_3); 1.06 (*d*, *J* = 6.3, 3H, CH_3)

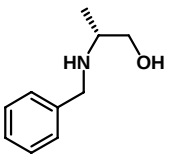
(S)-N-(2-aminopropyl)-4-methylbenzenesulfonamide (177) 0.12 g **253** (0.36 mmol) was dissolved in 3 ml MeOH and stirred for 12 h in the presence of 0.35 g Pd/C under a hydrogen atmosphere. After filtration over Celite and evaporation of the solvent, the crude product was purified by column chromatography (basic alox, DCM/MeOH 100:5), yielding 0.48 g **177** (60% yield) as a yellow oil.



TLC (alox basic, DCM/MeOH 100:5): R_f = 0.30; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.71 (*d*, *J* = 8.4, 2H, H_{ar}); 7.27 (*d*, *J* = 7.9, 2H, H_{ar}); 2.96 (*m,* 1H, C*H*NH_2); 2.89 (*dxd*, *J* = 4.1, 12.5, 1H, CH_2); 2.60 (*dxd*, *J* = 4.3, 12.6, 1H, CH_2); 2.77 (*m*, 2H, C*H*$_2$NH); 1.00 (*d*, *J* = 6.4, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 143.4, 137.1, 129.8, 127.1, 50.8,

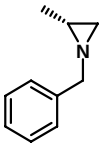
46.4, 21.6, 21.5; **ESI-MS** (MeOH): positive ion mode: 229 (65, $[M+H]^+$); 251 (81, $[M+Na]^+$); 457 (38, $[2M+H]^+$); 479 (100, $[2M+Na]^+$); negative ion mode: 227 (100, M^-)

(R)-2-(benzylamino)propan-1-ol (172)[80] 2.08 g (R)-2-aminopropan-1-ol (27.66 mmol, 1.0 eq.) and 3.10 ml benzaldehyde (30.42 mmol, 1.1 eq) were refluxed in 30 ml of toluene with a Dean-Stark Condenser for 5 h. After evaporation of the solvent, the resulting yellowish oil was dissolved in 30 ml of EtOH and cooled down to 0°C. 2.60 g sodium boronhydride (69.14 mmol, 2.5 eq.) was added and the mixture acidified to pH 2 with 3M HCl. After stirring for 14 h at r.t., water was removed at the rotavap, the residue dissolved in 30 ml 1M HCl and five times extracted with 20 ml of DCM. The aqueous phase was basified to pH 13 with 1M NaOH and extracted five times with DCM. The combined organic phase were dried over Na_2SO_4 and purified by column chromatography (alox neutral, DCM/Hx 1:1) yielding 3.95 g **172** (86% yield) as a colourless oil.



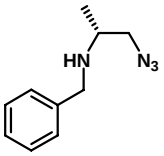
TLC (alox neutral, 1:1 DCM/Hx): R_f = 0.32 ; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.23-7.38 (*m*, 5H, H_{ar}); 3.84 (*d, J* = 13.0, 1H, CH_2Ph); 3.71 (*d, J* = 13.0, 1H, CH_2Ph); 3.55 (*dxd*, *J* = 4.0, 10.6, 1H, CH_2OH); 3.23 (*dxd*, *J* = 7.0, 10.6, 1H, CH_2OH); 2.71 (*m*, 1H, C*H*NH); 1.10 (*d*, *J* = 6.5, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 140.5, 128.7, 128.3, 127.3, 65.7, 53.9, 51.3, 17.4

(R)-1-benzyl-2-methylaziridine (173)[80] 3.95 g **172** (23.90 mmol, 1.0 eq.) and 9.40 g triphenylphosine (35.85 mmol, 1.5 eq.) were dissolved in 60 ml diethylether. 7.63 ml DIAD (35.85 mmol, 1.5 eq.) were added dropwise over a period of 45 minutes at a temperature between 5-10°C and then stirred at r.t. over night. The red solution was filtered and washed with 50 ml ether/hexane (1:1). The filtrate was extracted twice with 40 ml 1M HCl and the aqueous phase basified to pH 13 with 5M NaOH. After extracting five times with ether, the combined organic phases were dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product purified by column chromatography (alox neutral, DCM/Hx 1:1) yielding 1.73 g **173** (50% yield) as a colourless oil.



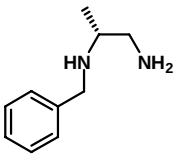
TLC (alox neutral, 1:1 DCM/Hx): R_f = 0.19; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.27-7.38 (*m*, 5H, H_{ar}); 3.48 (*d, J* = 13.6, 1H, CH_2Ph); 3.43 (*d, J* = 13.6, 1H, CH_2Ph); 1.61 (*d*, *J* = 3.6, 1H, CH_2OH); 1.54 (*m*, 1H, CH_2OH); 1.42 (*d*, *J* = 3.6, 1H, C*H*NH); 1.23 (*d*, *J* = 5.5, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 139.7, 128.5, 128.0, 127.0, 64.9, 35.2, 35.0, 18.5

(R)-1-azido-N-benzylpropan-2-amine (174)[81] 11.29 ml trimethylsilyl azide (82.32 mmol, 3.0 eq.) and 4.00 g **173** (27.12 mmol, 1.0 eq.) were refluxed in 5 ml of acetonitrile for 4 days. The red solution was adjusted to pH 1 with 1M HCl and stirred for 1 h. After the solution was basified to pH 9 with $NaHCO_3$, the aqueous solution was extracted three times with DCM. The combined organic phases dried over Na_2SO_4. The solvent was evaporated and the crude product purified by column chromatography (SiO_2, EtOAc/Hx 3:1) yielding 1.29 g **174** (33% yield) as a colourless oil.



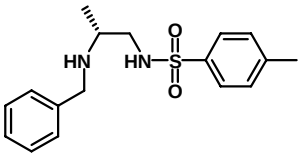
TLC (SiO_2, EtOAc/Hx 3:1): R_f = 0.40; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.24-7.33 (*m*, 5H, H_{ar}); 3.83 (*d, J* = 13.0, 1H, C*H*$_2$Ph); 3.73 (*d, J* = 13.6, 1H, C*H*$_2$Ph); 3.33 (*dxd*, *J* = 6.4, 12.1, 1H, C*H*$_2$OH); 3.21 (*dxd*, *J* = 4.8, 12.1, 1H, C*H*$_2$OH); 1.54 (*broad*, 1H, NH); 2.89 (*m*, 1H, C*H*NH); 1.17 (*d*, *J* = 6.4, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 140.2, 128.7, 128.6, 128.3, 56.8, 52.2, 51.4, 18.5

(R)-N-2-benzylpropane-1,2-diamine (175)[81] 1.29 g **174** (6.79 mmol, 1.0 eq.) were dissolved in 10 ml diethylether. 0.21 g $LiAlH_4$ (5.43 mmol, 0.8 eq.) were added slowly and the mixture stirred for 3 h at r.t. The reaction was quenched with sat. $NaHCO_3$, extracted three times with 20 ml ether and dried over Na_2SO_4. 0.39 g **175** (35% yield) were obtained after evaporation of the solvent and used without further purification.



TLC (SiO_2, EtOAc/Hx 3:1): R_f = 0; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.18-7.34 (*m*, 5H, H_{ar}); 3.87 (*d, J* = 13.1, 1H, C*H*$_2$Ph); 3.73 (*d, J* = 12.9, 1H, C*H*$_2$Ph); 2.52-2.77 (*m*, 3H, 2xCH_2 and CH); 1.05 (*m*, *J* = 6.6, 3H, C*H*$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 140.9, 128.6, 128.3, 127.0, 54.6, 51.5, 47.6, 18.5; **ESI-MS** (MeOH): positive ion mode: 165 (100, $[M+H]^+$)

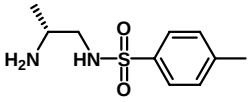
(R)-N-(2-(benzylamino)propyl)-4-methylbenzenesulfonamide (176) 0.45 g **156** (2.35 mmol, 1.0 eq.) diluted in 5 ml DCM were slowly added to a solution containing 0.39 g **175** (2.35 mmol, 1.0 eq.) and 0.32 ml triethylamine (2.35 mmol, 1.0 eq.) in 15 ml DCM at 0°C. After stirring for 2.5 h at r.t., the solvent was removed and the crude product purified by column chromatography (SiO_2, DCM/MeOH/Et_3N 100:5:1) yielding 0.39 g **176** (77% yield) as a white powder.



TLC (SiO_2, DCM/MeOH/Et_3N 100:5:1): R_f = 0.37; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.71 (*d*, *J* = 6.7, 2H, H_{ar}); 7.23-7.32 (*m,* 7H, H_{ar}); 3.67 (*d, J* = 13.0, 1H, C*H*$_2$Ph); 3.54 (*d,*

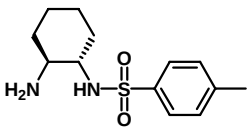
J = 13.0, 1H, C*H*$_2$Ph); 2.98 (*dxd*, *J* = 3.8, 11.9, 1H, C*H*$_2$OH); 2.77 (*m*, 1H, C*H*NH); 2.70 (*dxd*, *J* = 6.9, 11.8, 1H, C*H*$_2$OH); 2.47 (*s*, 3H, ArCH$_3$); 1.06 (*d*, *J* = 6.3, 3H, CH$_3$)

(R)-N-(2-aminopropyl)-4-methylbenzenesulfonamide (169) 0.12 g **176** (0.36 mmol) was dissolved in 3 ml MeOH and stirred for 12 h in the presence of 0.35 g Pd/C under a hydrogen atmosphere. After filtration over Celite and evaporation of the solvent, the crude product was purified by column chromatography (basic alox, DCM/MeOH 100:5), yielding 0.48 g **169** (60% yield) as a yellow oil.



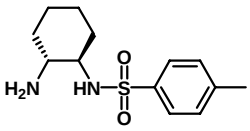
TLC (alox basic, DCM/MeOH 100:5): R_f = 0.30; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.71 (*d*, *J* = 8.4, 2H, H_{ar}); 7.27 (*d*, *J* = 7.9, 2H, H_{ar}); 2.96 (*m,* 1H, C*H*NH$_2$); 2.89 (*dxd*, *J* = 4.1, 12.5, 1H, CH$_2$); 2.60 (*dxd*, *J* = 4.3, 12.6, 1H, CH$_2$); 1.00 (*d*, *J* = 6.4, 3H, CH$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 143.4, 137.1, 129.8, 127.1, 50.8, 46.4, 21.56, 21.55; **ESI-MS** (MeOH): positive ion mode: 229 (65, [*M*+H]$^+$); 251 (81, [*M*+Na]$^+$); 457 (38, [2*M*+H]$^+$); 479 (100, [2*M*+Na]$^+$); negative ion mode: 227 (100, *M*$^-$)

(1S,2S)-N-tosylcyclohexane-1,2-diamine (254)[82] 500 mg (S,S)-cyclohexane-1,2-diamine (4.38 mmol, 1.5 eq.), 661 mg L-tartrate (4.38 mmol, 1.5 eq.), 5.78 ml of 2M NaOH and 0.81 ml triethylamine were dissolved in 42 ml DCM and cooled down to 0°C. Then 0.56 g tosylchloride (2.91 mmol, 0.66 eq.) dissolved in 29 ml DCM were added over a period of 30 minutes. The mixture was stirred at r.t over night. The reaction mixture was washed three times with 50 ml 2M HCl. The aqueous phase was basified with 1M NaOH to pH 9, extracted three times with DCM and dried over Na_2SO_4. One obtained 0.71 g **254** (60% yield) as white crystals.



TLC (alox basic): R_f = 0.22; **1H-NMR** (500 MHz, $CDCl_3$): 7.77 (*d*, J = 8.3, 2H, H_{ar}); 7.28 (*d*, J = 7.9, 2H, H_{ar}); 2.64 (*dxt*, J = 6.5, 10.2, 1H, C*H*NHTs); 2.37-2.41 (*m*, 4H ArCH$_3$ and C*H*NH$_2$); 1.93 (*m*, 1H, CH$_2$); 1.75 (*m*, 1H, CH$_2$); 1.57-1.63 (*m*, 2H, CH$_2$); 1.05-1.19 (*m*, 4H, CH$_2$); **13C-NMR** (126 MHz, $CDCl_3$): 143.4, 138.0, 129.8, 127.2, 60.4, 54.9, 35.5, 32.7, 25.0, 24.9, 21.7; **ESI-MS** (MeOH): positive ion mode: 269 (100, [*M*+H]$^+$); 291 (33, [*M*+Na]+); 537 (77, [2*M*+H]$^+$); 559 (95, [2*M*+Na]+); negative ion mode: 267 (100, *M*-)

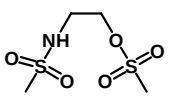
(1R,2R)-N-tosylcyclohexane-1,2-diamine (255)[82] 0.50 g (R,R)-cyclohexane-1,2-diamine (4.38 mmol, 1.5 eq.), 0.66 g L-tartrate (4.38 mmol, 1.5 eq.), 5.78 ml of 2M NaOH and 0.81 ml triethylamine were dissolved in 42 ml DCM and cooled down to 0°C. Then 0.56 g tosylchloride (2.91 mmol, 0.66 eq.) dissolved in 29 ml DCM were added over a period of 30 minutes. The mixture was stirred at r.t over night. The reaction mixture was washed three times with 50 ml 2M HCl. The aqueous phase was basified with 1M NaOH to pH 9, extracted three times with DCM and dried over Na_2SO_4. One obtained 0.68 g **255** (58% yield) as white crystals.



TLC (alox basic): R_f = 0.21; **1H-NMR** (500 MHz, $CDCl_3$): 7.76 (*d*, J = 8.2, 2H, H_{ar}); 7.30 (*d*, J = 8.0, 2H, H_{ar}); 2.60 (*m*, 1H, C*H*NH_2); 2.42 (*s*, 3H CH_3); 2.33 (*dxt*, J = 4.1, 10.5, 1H, C*H*NHTs); 1.91 (*m*, 1H, CH_2); 1.83 (*m*, 1H, CH_2); 1.60 (*m*, 2H, CH_2); 1.05-1.25 (*m*, 4H, CH_2); **13C-NMR** (126 MHz, $CDCl_3$): 143.7, 138.2, 130.1, 127.5, 60.8, 55.3, 36.1, 33.1, 25.3, 25.2, 22.0; ; **ESI-MS** (MeOH): positive ion mode: 269 (100, $[M+H]^+$); 291 (24, [*M*+Na]+); 537 (66, $[2M+H]^+$); 559 (90, [2M+Na]+); negative ion mode: 267 (100, *M*-)

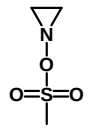
5.2.1.3 Monomesyltaed Diamines

2-(methylsulfonamido)ethylmethanesulfonate (256)[79] 8.39 ml mesityl chloride (108.06 mmol, 2.2 eq.) were added dropwise over a period of 90 minutes to a solution of 3.00 g aminoethanol (49.12 mmol, 1.0 eq.) and 13.69 ml triethylamine (98.23 mmol, 2.0 eq.) in 300 DCM at -20°C. After stirring for 14 h at -20°C, the cold solution was washed twice with 45 ml 0.1M HCl and once with 60 ml sat. $NaHCO_3$, and then dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product purified by column chromatography (SiO_2, EtOAc/Hx 5:1), yielding 3.74 g of **256** (35% yield) as white crystals.



TLC (SiO_2, EtOAc/Hx 5:1): R_f = 0.25; **^{1}H-NMR** (400 MHz, $CDCl_3$): 5.11 (*s,* 1H, NH); 4.36 (*m,* 2H, CH_2OMs); 3.50 (*m,* 2H, CH_2NHMs); 3.09 (*s*, 3H, OSO_2CH_3); 3.02 (*s*, 3H, $NHSO_2CH_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 69.2, 42.8, 41.4, 38.0

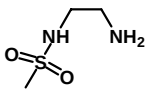
1-(methylsulfonyl)aziridine (257)[79] 3.72 g **256** (17.20 mmol, 1.0 eq.) dissolved in



60 ml THF were added dropwise to a suspension of 0.62 g sodium hydride (25.80 mmol, 1.5 eq.) in 25 ml THF at r.t. and then stirred for 3 h. After quenching with 12 ml EtOH and 25 ml water, the mixture was diluted with 70 ml brine and 90 ml ether. The aqueous phase was extracted twice with ether and the combined organic phases dried over Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography (SiO_2, EtOAc/Hx 3:2), yielding 1.66 g **257** (80% yield) as a colourless liquid.

TLC (SiO_2, EtOAc/Hx 3:2): R_f = 0.29; **^{1}H-NMR** (400 MHz, $CDCl_3$): 3.51-3.56 (*m*, 3H, CH_2); 3.25-3.31 (*m*, 1H, CH_2); 3.08 (*s*, 3H, $NHSO_2CH_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): 39.8, 27.2

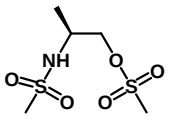
N-(2-aminoethyl)methanesulfonamide (183) 0.98 g **257** (8.06 mmol) dissolved in



60 ml MeOH were added over a period of 6 h to a saturated solution of ammonia in 120 ml MeOH and stirred for 14 h at r.t. After evaporation of the solvent, the crude product was purified by column chromatography (basic alox, DCM/MeOH 5:1), yielding 1.00 g **183** (90% yield) as a yellow oil.

TLC (basic alox, DCM/MeOH 5:1): R_f = 0.19; **^{1}H-NMR** (400 MHz, CD_3CN): 3.14 (*t*, *J* = 2H, CH_2); 2.97 (*s*, 3H, CH_3); 2.72 (*t*, *J* = 6.8, 2H, CH_2); **^{13}C-NMR** (100 MHz, CD_3CN): 46.4, 41.9, 39.3; **ESI-MS** (MeOH): positive ion mode: 139 (28, $[M+H]^+$); 161 (100, $[M+Na]^+$)

(S)-1-(methylsulfonamido)propan-2-yl-methanesulfonate (258)[79] 4.72 ml mesityl

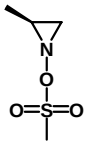


chloride (60.92 mmol, 2.2 eq.) were added dropwise over a period of 90 minutes to a solution of 2.08 g (S)-alaninol (27.70 mmol, 1.0 eq.) and 7.72 ml triethylamine (55.40 mmol, 2.0 eq.) in 175 DCM at -20°C. After stirring for 14 h at -20°C, the cold solution was washed twice with 15 ml 0.1M HCl and once with 20 ml sat. $NaHCO_3$, and then dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product purified by column chromatography (SiO_2, EtOAc/Hx 4:1), yielding 3.13 g of **258** (47% yield) as white crystals.

TLC (SiO_2, EtOAc/Hx 4:1): R_f = 0.27; **^{1}H-NMR** (400 MHz, $CDCl_3$): 4.76 (*d, J* = 8.1, 1H, NH); 4.26 (*dxd*, *J* = 4.3, 10.4, 1H, CH_2OMs); 4.16 (*dxd*, *J* = 5.6, 10.5, 1H, CH_2OMs); 3.86 (*m*, 1H, CHNHMs); 3.08 (*s*, 3H, OSO_2CH_3); 3.03 (*s*, 3H, $NHSO_2CH_3$);

1.33 (*d*, *J* = 6.8, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 72.4, 48.8, 42.0, 37.4, 18.4; **ESI-MS** (MeOH): positive ion mode: 254 (100, $[M+Na]^+$); 485 (62, $[2M+Na]^+$)

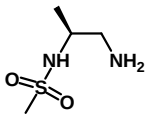
(S)-2-methyl-1-(methylsulfonyl)aziridine (259)[79] 1.00 g **258** (4.33 mmol, 1.0 eq.)



dissolved in 16 ml THF were added dropwise to a suspension of 0.16 g sodium hydride (6.49 mmol, 1.5 eq.) in 6 ml THF at r.t. and then stirred for 3 h. After quenching with 4 ml EtOH and 10 ml water, the mixture was diluted with 20 ml brine and 30 ml ether. The aqueous phase was extracted twice with ether and the combined organic phases dried over Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography (SiO_2, EtOAc/Hx 1:1), yielding 0.46 g **259** (77% yield) as a colourless liquid.

TLC (SiO_2, EtOAc/Hx 1:1): R_f = 0.40; **^{1}H-NMR** (400 MHz, $CDCl_3$): 3.06 (*s*, 3H, $NHSO_2CH_3$); 2.82 (*m*, 1H, CH); 2.60 (*d, J* = 7.1, 1H, CH_2); 2.08 (*d, J* = 4.5, 1H, CH_2); 1.35 (*d*, *J* = 5.8, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 40.1, 35.6, 34.7, 17.3

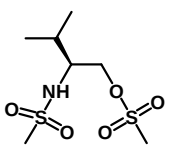
(S)-N-(1-aminopropan-2-yl)methanesulfonamide (184) 0.46 g **259** (3.40 mmol)



dissolved in 180 ml MeOH were added over a period of 9 h to a saturated solution of ammonia in 500 ml MeOH and stirred for 14 h at r.t. After evaporation of the solvent, the crude product was purified by column chromatography (basic alox, DCM/MeOH 5:1), yielding 0.41 g **184** (88% yield) as a yellow oil.

TLC (basic alox, DCM/MeOH 5:1): R_f = 0.19; **^{1}H-NMR** (400 MHz, $CDCl_3$): 3.45 (*m*, 1H, CH); 3.00 (*s*, 3H, $NHSO_2CH_3$); 2.87 (*dxd*, *J* = 4.3, 12.9, 1H, CH_2); 2.62 (*dxd*, *J* = 6.8, 13.0, 1H, CH_2); 1.23 (*d*, *J* = 9.8, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 52.2, 47.7, 42.4, 19.9; **ESI-MS** (MeOH): positive ion mode: 153 (100, $[M+H]^+$); 175 (71, $[M+Na]^+$)

(S)-3-methyl-1-(methylsulfonamido)butan-2-yl-methanesulfonate (260)[79] 0.87 ml

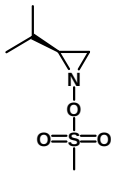


mesityl chloride (11.22 mmol, 2.2 eq.) were added dropwise over a period of 90 minutes to a solution of 0.53 g (S)-valinol (5.10 mmol, 1.0 eq.) and 1.42 ml triethylamine (10.21 mmol, 2.0 eq.) in 40 DCM at -20°C. After stirring for 14 h at -20°C, the cold solution was washed twice with 10 ml 0.1M HCl and once with 20 ml sat. $NaHCO_3$, and then dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product purified by

column chromatography (SiO_2, EtOAc/Hx 4:1), yielding 0.81 g of **260** (61% yield) as white crystals.

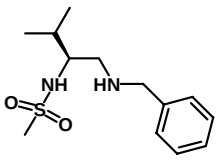
TLC (SiO_2, EtOAc/Hx 2:1): R_f = 0.43; **^{1}H-NMR** (400 MHz, $CDCl_3$): 4.65 (*d, J* = 8.8, 1H, NH); 4.25-4.33 (*m,* 2H, C*H*$_2$OMs); 3.47 (*m*, 1H, C*H*NHMs); 3.08 (*s*, 3H, OSO_2CH_3); 3.04 (*s*, 3H, $NHSO_2CH_3$); 1.95 (*m*, 1H, C*H*); 1.01-1.03 (*m*, 6H, 2xCH_3);**^{13}C-NMR** (100 MHz, $CDCl_3$): 70.3, 58.8, 42.4, 37.9, 30.1, 19.6, 18.8

(S)-2-isopropyl-1-(methylsulfonyl)aziridine (261)[79] 0.80 g **260** (3.09 mmol, 1.0 eq.) dissolved in 15 ml THF were added dropwise to a suspension of 0.11 g sodium hydride (4.63 mmol, 1.5 eq.) in 5 ml THF at r.t. and then stirred for 3 h. After quenching with 4 ml EtOH and 10 ml water, the mixture was diluted with 20 ml brine and 30 ml ether. The aqueous phase was extracted twice with ether and the combined organic phases dried over Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography (SiO_2, EtOAc/Hx 1:1), yielding 0.46 g **261** (91% yield) as a colourless liquid.



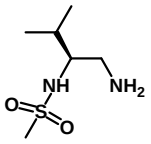
TLC (SiO_2, EtOAc/Hx 3:1): R_f = 0.51; **^{1}H-NMR** (400 MHz, $CDCl_3$): 3.06 (*s*, 3H, $NHSO_2CH_3$); 2.54-2.59 (*m*, 2H, CH_2); 2.14 (*d, J* = 4.3, 1H, C*H*NSO_2); 1.56 (*m*, 1H, C*H*); 1.06 (*d*, *J* = 6.6, 3H, CH_3); 1.00 (*d*, *J* = 6.6, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 46.0, 39.9, 32.7, 30.5, 20.2, 19.5

(S)-N-(1-(benzylamino)-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (262) 0.15 g **261** (0.92 mmol, 1.0 eq.) dissolved in 5 ml MeOH was added over a period of 7 h to a solution of 1.00 ml benzylamine (9.20 mmol, 10 eq.) in 1 ml MeOH. After stirring for 14 h, the solvent was removed at the rotavap and excess benzylamine by distillation (115°C, 28 mbar). The crude product was purified by column chromatography (SiO_2, DCM/MeOH 6:1), yielding 0.21 g **262** (85% yield) as a white solid.



TLC (SiO_2, DCM/MeOH 6:1): R_f = 0.47; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.25-7.37 (*m*, 5H, H_{ar}); 3.79 (*s*, 2H, PhC*H*$_2$); 3.21-3.25 (m, 1H, C*H*NSO_2); 2.91 (*s*, 3H, $NHSO_2CH_3$); 2.71-2.74 (*m*, 2H, CH_2); 1.58 (*m*, 1H, CH); 0.95 (*d*, *J* = 6.8, 3H, CH_3); 0.93 (*d*, *J* = 6.8, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 140.1, 128.8, 128.6, 127.1, 59.4, 53.9, 49.5, 41.4, 30.1, 19.7; **ESI-MS** (MeOH): positive ion mode: 271 (100, $[M+H]^+$); 293 (30, $[M+Na]^+$)

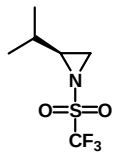
(S)-N-(1-amino-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (185) 0.36 g **262** (1.33 mmol) was dissolved in 4 ml MeOH and stirred for 1 h under a hydrogen atmosphere in the presence of 0.05 g Pd/C. After evaporation of the solvent, the product was filtered over Celite, yielding 0.22 g **185** (94%) and used without further purification.



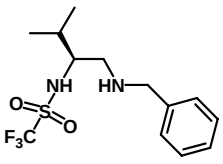
TLC (SiO_2, DCM/MeOH 6:1): R_f = 0.09; **^{1}H-NMR** (400 MHz, $CDCl_3$): 3.48 (m, 1H, C*H*NSO_2CH_3); 3.02 (*s*, 3H, $NHSO_2CH_3$); 2.80-2.85 (*m*, 2H, CH_2); 1.86 (*m*, 1H, CH); 0.97 (*d*, *J* = 6.8, 6H, 2xCH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 57.1, 42.4, 41.0, 30.0, 17.9, 17,7; **ESI-MS** (MeOH): positive ion mode: 181 (51, $[M+H]^+$); 203 (69, $[M+Na]^+$); 361 (41, $[2M+H]^+$); 383 (100, $[2M+Na]^+$); negative ion mode: 179 (100, M^-)

5.2.1.4 Monotriflated Diamines

(S)-2-isopropyl-1-(trifluoromethylsulfonyl)aziridine (190)[79] 3.60 ml triflicanhydride (21.32 mmol, 2.2 eq.) were added at -78°C over a period of 1 h to a solution containing 1.0 g (L)-valinol **189** (9.69 mmol, 1.0 eq.) and 2.70 ml triethylamine (19.39 mmol, 2.0 eq.) in 40 ml of DCM. The solution was then stirred for 3 h at -40°C, 12 h at -20°C and 2 h at r.t. The red solution was then diluted with 40 ml DCM and successively washed with 0.1 M HCl and sat. Na_2CO_3. The solvent was removed after drying over Na_2SO_4, yielding 2.02 g **190** (96% yield) as white crystals. The crude product was used without further purification.



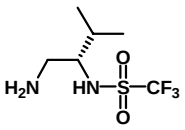
(S)-N-(2-(benzylamino)-3-methylbutyl)trifluoromethanesulfonamide (263) 0.70 g **190** (3.23 mmol, 1.0 eq.) were dissolved in 3 ml MeOH. 2.84 ml benzylamine (26.00 mmol, 8.0 eq.) were added at 0°C over a period of 20 minutes and the solution was then stirred at r.t. for 4 days. Excess of benzylamine was removed by distillation (77°C, 6 mbar). The crude product was purified by column chromatography (SiO_2, gradient starting with 100% Hx to Hx/EtOAc 1:1), yielding 0.51 g **263** (50% yield) as a colourless oil.



TLC (SiO_2, Hx/EtOAc 5:1): R_f = 0.46; **^{1}H-NMR** (400 MHz, CD_3CN): 7.26-7.35 (*m,* 5H, H_{ar}); 3.80 (*s,* 2H, CH_2Ph); 3.33 (*m*, 1H, C*H*NHTf); 2.90 (*dxd*, *J* = 7.2, 19.3, 1H, CH_2); 2.69 (*dxd*, *J* = 4.8, 12.9, 1H, CH_2); 1.89 (*m*, 1H, C*H*$(CH_3)_2$); 0.92 (*d*, *J* = 10.2, 6H, 2x

CH_3); **^{13}C-NMR** (100 MHz, CD_3CN): 139.8, 129.0, 128.5, 127.8, 120.1, 61.1, 54.4, 49.3, 30.8, 19.4, 19.0; **^{19}F-NMR** (376 MHz, CD_3CN): -78.4 (*s*, 3F); **ESI-MS** (MeOH): positive ion mode: 325 (100, $[M+H]^+$); 347 (28, $[M+Na]^+$)

(S)-N-(2-amino-3-methylbutyl)trifluoromethanesulfonamide (195) 80 mg **263**

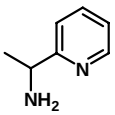


(0.25 mmol) was dissolved in 5 ml MeOH and stirred for 3 h in the presence of 0.20 g Pd/C under a hydrogen atmosphere. Filtration over Celite and evaporation of the solvent, yielded 59 mg **195** (99% yield) as white crystals.

TLC (alox basic, DCM/MeOH 100:5): R_f = 0.11; **^{1}H-NMR** (400 MHz, CD_3CN): 3.17 (*m,* 1H, C*H*NHTf); 2.85 (*dxd*, *J* = 6.4, 19.7, 1H, CH_2); 2.60 (*dxd*, *J* = 10.6, 19.7, 1H, CH_2); 2.77 (*m*, 1H, C*H*NH); 1.85 (*m*, 1H, C*H*$(CH_3)_2$); 0.92 (*d*, *J* = 10.2, 6H, 2xCH_3); **^{13}C-NMR** (100 MHz, CD_3CN): 149.7, 57.1, 40.2, 31.1, 17.9; **^{19}F-NMR** (376 MHz, CD_3CN): -79.0 (*s*, 3F); **ESI-MS** (MeOH): positive ion mode: 235 (100, $[M+H]^+$); negative ion mode: 233 (100, M^-); 489 (35, $[2M+Na]^-$)

5.2.1.5 α-Pycolyl Amines

1-(pyridin-2-yl)ethanamine (199)[84] A solution of 2-acetylpyridine (25.00 g, 0.21

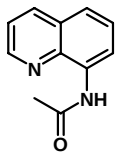


mol, 1.0 eq.) and hydroxylamine hydrochloride (16.48 g, 0.24 mol, 1.15 eq.) in 100 ml of pyridine was heated to reflux for 6 h. After removing the solvent on a rotary evaporator, 400 ml of water was added, resulting in precipitation of the oxime in the form of white crystals which were isolated by vacuum filtration. The filtrate was extracted three times with 100 ml of TBME. The white solid was dissolved in TBME, combined with the extracts and dried over Na_2SO_4. After evaporation of the solvent, the crude product (25.85 g, 0.19 mol, 1.0 eq.) was dissolved in 345 ml of 95% EtOH. 230 ml acetic acid was added to the solution. 233 g zinc dust (3.56 mol, 19.0 eq.) was added in 10 g increments over 2 h. The reaction mixture was stirred with an overhead mechanical stirrer for 12 h. The mixture was filtered, and the filtrate was concentrated under vacuum. Several portions of water were added and evaporated to remove acetic acid. The mixture was then basified with saturated aqueous KOH solution until a brown/yellow oil appeared on the surface of the mixture. The mixture was extracted with TBME, and the combined fractions were dried over Na_2SO_4. After removal of the solvent, the crude product

was distilled using a Kugelrohr apparatus, yielding 16.67 g **190** (66% yield over two steps).

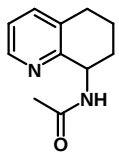
bp: 50°C at 0.08 mbar; **^{1}H-NMR** (500 MHz, $CDCl_3$): 8.54 (*m*, 1H, H_{ar}); 7.64 (*m*, 1H, H_{ar}) 7.29 (*m*, 1H, H_{ar}); 7.15 (*m*, 1H, H_{ar}); 4.14 (*qxd*, *J* = 5.2, 2.6, 1H, CH); 1.42 (*d*, *J* = 6.7, 3H, CH_3); **^{13}C-NMR** (126 MHz, $CDCl_3$): 165.8, 149.2, 136.6, 121.8, 120.1, 52.5, 24.5; **ESI-MS** (MeOH): positive ion mode: 123 (100, $[M+H]^+$); 145 (32, $[M+Na]^+$)

N-(quinolin-8-yl)acetamide (264)[86] 2.00 g quinolin-8-amine **203** (13.87 mmol, 1.0 eq.), 1.56 g acetic anhydride (15.26 mmol, 1.1 eq.), 1.54 g triethylamine (15.26 mmol, 1.1 eq.) and 0.34 g DMAP (2.77 mmol, 0.2 eq.) were stirred in 25 ml of DCM for 2 h. The mixture was washed with sat. NH_4Cl and extracted two times with DCM. The combined organic phases were dried over Na_2SO_4. The crude product was purified by column chromatography (SiO_2, DCM/MeOH 50:1) yielding 1.77 g **264** (69% yield) as white crystals.



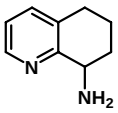
TLC (SiO_2, DCM/MeOH 50:1): R_f = 0.30; **^{1}H-NMR** (500 MHz, $CDCl_3$): 9.77 (broad, 1H, NH); 8.74-8.80 (*m*, 2H, H_{ar}); 8.16 (*m*, 1H, H_{ar}); 7.41-7.56 (*m*, 3H, H_{ar}); 2.36 (*s*, 3H, CH_3); **^{13}C-NMR** (126 MHz, $CDCl_3$): 169.0, 148.2, 138.3, 136.5, 134.6, 128.0, 127.5, 121.7, 121.6, 116.5, 25.3

N-(5,6,7,8-tetrahydroquinolin-8-yl)acetamide (204)[86] 1.77 g **264** (9.51 mmol, 1.0 eq.) and 0.11 g PtO_2 (0.48 mmol, 0.05 eq.) were dissolved in 30 ml of trifluoroacetic acid and stirred at 60°C under a hydrogen atmosphere for 3.5 h. After filtration of the catalyst, the filtrate was basified to pH 10 with 1M KOH, extracted three times with DCM and dried over Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography (basic alox, DCM:MeOH 9:1) yielding 1.02 g of **204** (57% yield) as a white solid.



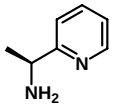
TLC (basic alox, DCM/MeOH 100:1): R_f = 0.22; **^{1}H-NMR** (500 MHz, $CDCl_3$): 8.40 (*m*, 1H, H_{ar}); 7.42 (*m*, 1H, H_{ar}); 7.14 (*m*, 1H, H_{ar}); 6.51 (broad, 1H, NH); 4.87 (*m*, 1H, C*H*NH); 2.81 (*m*, 2H); 2.55 (*m*, 1H); 2.07 (*s*, 3H, CH_3); 1.89 (*m*, 2H); 1.64 (*m*, 1H); **^{13}C-NMR** (126 MHz, $CDCl_3$): 170.6, 155.4, 147.0, 137.3, 133.2, 122.6, 51.3, 29.5, 28.3, 23.9, 20.0; **ESI-MS** (MeOH): positive ion mode: 213 (49, $[M+Na]^+$); 403 (100, $[2M+Na]^+$)

5,6,7,8-tetrahydroquinolin-8-amine (205)[85] 1.02 g **204** (5.40 mmol) were refluxed for 2 h in 15 ml of 6M HCl. The mixture was cooled down and basified to pH 10 with 1M KOH, extracted three times with DCM and dried over Na_2SO_4. Resulting amine **205** was reacted with lipase without further purification.



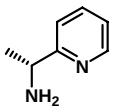
TLC (basic alox, DCM/MeOH 9:1): R_f = 0.44; **^{1}H-NMR** (500 MHz, $CDCl_3$): 8.39 (*d*, *J* = 4.2, 1H, H_{ar}); 7.35 (*d*, *J* = 7.7, 1H, H_{ar}); 7.05 (*m*, 1H, H_{ar}); 3.99 (*t*, *J* = 7.6, 1H, C*H*NH_2); 2.82 (*m*, 2H); 2.18 (*m*, 1H); 1.94 (*m*, 1H);, 1.85 (*m*, 1H); 1.70 (*m*, 1H); **^{13}C-NMR** (126 MHz, $CDCl_3$): 159.7, 147.2, 136.9, 131.7, 121.8, 51.5, 32.1, 29.1, 20.1

(S)-1-(pyridin-2-yl)ethanamine (201)[85] 2.00 g **205** (16.38 mmol, 1.0 eq.) and 0.60 g CALB (30% in weight) were stirred in 46 ml of EtOAc (479.90 mmol, 29.0 eq.) at 60°C for 7 h. After filtration and washing with EtOAc, the solvent was removed under vacuum and the crude product applied to column chromatography (basic alox, gradient starting with 100% DCM to DCM/MeOH 9:1) yielding 0.66 g of the (S)-amine **201** (eluting second, ee = 99%, determined by Mosher amidation) and 0.74 g of the (R)-amide **200** (eluting first).



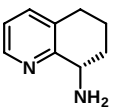
TLC (basic alox, DCM/MeOH 100:1): R_f = 0.17; **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.54 (*d*, *J* = 7.6, 1H, H_{ar}); 7.66 (*m*, 1H, H_{ar}); 7.62 (*m*, 1H, H_{ar}); 7.26 (*m*, 1H, H_{ar}); 4.14 (*q*, *J* = 6.8, 1H, CH); 1.42 (*d*, *J* = 6.6, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 166.2, 149.5, 137.0, 122.2, 120.5, 52.9, 24.9

(R)-1-(pyridin-2-yl)ethanamine (202)[85] 0.74 g **200** were refluxed in 17 ml of 6M HCl for 2 h. The solution was basified with 1M KOH to pH 12, extracted three times with DCM and dried over Na_2SO_4. After evaporation of the solvent, the crude product was filtrated over a small basic alox column to yield 0.33 g of the (R)-amine **202** (ee = 97%, determined by Mosher amidation).



TLC (basic alox, DCM/MeOH 100:1): R_f = 0.17; **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.54 (*d*, *J* = 7.6, 1H, H_{ar}); 7.66 (*m*, 1H, H_{ar}); 7.62 (*m*, 1H, H_{ar}); 7.26 (*m*, 1H, H_{ar}); 4.14 (*q*, *J* = 6.8, 1H, CH); 1.42 (*d*, *J* = 6.6, 3H, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): 166.2, 149.5, 137.0, 122.2, 120.5, 52.9, 24.9

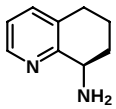
(S)-5,6,7,8-tetrahydroquinolin-8-amine (207)[85] 0.90 g **205** (6.15 mmol, 1.0 eq.) and 0.28 g CALB (30% in weight) were stirred in a mixture of 2.36 ml EtOAc and 15.18 ml of i-PrOH at 60°C for 4 h. After filtration and washing



with EtOAc, the solvent was removed under vacuum and the crude product applied to column chromatography (basic alox, gradient starting with 100% DCM to DCM/MeOH 12:1) yielding 0.24 g of the (S)-amine **207** (eluting second, ee = 93%, determined by Mosher amidation) and 0.31 g of the (R)-amide **265** (eluting first).

TLC (basic alox, DCM/MeOH 100:1): R_f = 0.19 ; **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.38 (*d*, *J* = 4.0, 1H, H_{ar}); 7.35 (*m*, 1H, H_{ar}); 7.04 (*m*, 1H, H_{ar}); 3.99 (*m*, 1H, C*H*NH_2); 2.75 (*m*, 2H); 2.24 (*m*, 1H); 1.95 (*m*, 1H); 1.59 (*m*, 2H)

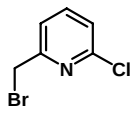
(R)-5,6,7,8-tetrahydroquinolin-8-amine (206)[85] 0.31 g **265** were refluxed in 17 ml of 6M HCl for 2 h. The solution was basified with 1M KOH to pH 12, extracted three times with DCM and dried over Na_2SO_4. After evaporation of the solvent, the crude product was filtrated over a small basic alox column to yield 0.22 g of the (R)-amine **206** (ee = 94%, determined by Mosher amidation).



TLC (basic alox, DCM/MeOH 100:1): R_f = 0.19; **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.38 (*d*, *J* = 4.0, 1H, H_{ar}); 7.35 (*m*, 1H, H_{ar}); 7.04 (*m*, 1H, H_{ar}); 3.99 (*m*, 1H, C*H*NH_2); 2.75 (*m*, 2H); 2.24 (*m*, 1H); 1.95 (*m*, 1H); 1.59 (*m*, 2H)

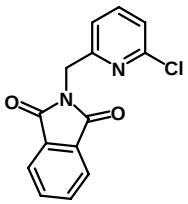
5.2.1.6 Chlorinated and Fluorinated Pyridylamines

2-(bromomethyl)-6-chloropyridine (214)[87] 2.61 ml (23.60 mmol, 1.0 eq.) **213** and 5.88 g (33.04 mmol, 1.4 eq.) NBS were refluxed overnight in 50 ml CCl_4 in the presence of 0.38 g (2.34 mmol, 0.1 eq.) of AIBN. The suspension was filtered and the solvent removed at reduced pressure. Remaining starting material was distilled off the solution with a Kugelrohr (1013 mbar, 87°C). The residue was purified by column chromatography (SiO_2, gradient: starting with Hx/EtOAc 100:0 to Hx/EtOAc 10:1) to yield 1.36 g of compound **214** (28% yield) as a colourless liquid.



TLC (SiO_2, Hx/EtOAc 10:1): R_f = 0.44; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.50 (*m*, 1H, H_{ar}); 7.46 (*d*, 1H, H_{ar}); 7.23 (*d*, 1H, H_{ar}); 4.48 (*s*, 2H, CH_2Br)

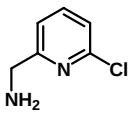
2-((6-chloropyridin-2-yl)methyl)isoindoline-1,3-dione (266)[87] A suspension of



1.36 g **214** (8.69 mmol, 1.0 eq.), 1.69 g isoindoline-1,3-dione (9.13 mmol, 1.05 eq.) and 3.60 g potassium carbonate (dried for four hours at high vacuum at 80°C; 26.07 mmol, 3.0 eq.) in 110 ml of acetonitrile was refluxed for 2 hours. The solvent was removed after filtration. The residue was dissolved in 50 ml DCM/H_2O 1:1. The organic phase was separated and dried over Na_2SO_4. The crude product was purified by column chromatography (SiO_2, Hx/EtOAc 2:1) to yield 1.48 g **266** (82% yield) as a white solid.

TLC (SiO_2, Hx/EtOAc 2:1): R_f = 0.39; **mp**: 152-153°C; **^{1}H-NMR** (500 MHz, $CDCl_3$): 7.89 (*m*, 2H, H_{ar}); 7.75 (*m*, 2H, H_{ar}); 7.59 (*t*, *J* = 7.7, 1H, H_{ar}); 7.21 (*d*, *J* = 8.0, 1H, H_{ar}); 7.13 (*d*, *J* = 7.9, 1H, H_{ar}); 4.98 (*s*, 2H, CH_2); **^{13}C-NMR** (126 MHz, $CDCl_3$): 168.1, 156.5, 151.4, 139.5, 134.4, 132.2, 123.8, 123.4, 119.7, 42.7; **IR** (KBr): 3070w, 2932w, 1713s; **ESI-MS** (MeOH): positive ion mode: 295 (100, $[M+H]^+$); **EA**: calculated for $C_{14}H_9N_2O_2Cl$: C 61.66, H 3.33, N 10.27, O 11.73; found: C 61.67, H 3.42, N 10.16, O not detectable

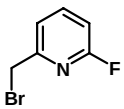
(6-chloropyridin-2-yl)methanamine (212)[87] A solution of 1.43 g **266** (5.35 mmol,



1.0 eq.) and 620 mg hydrazine monohydrate (12.31 mmol, 2.3 eq.) was stirred in 50 ml MeOH at 60°C for 12 hours. The solution was filtered and MeOH removed at reduced pressure. The residue was dissolved in DCM, washed three times with 1M NaOH and dried over Na_2SO_4. 563 mg of a colourless oil (74% yield) were used without further purification.

TLC (basic Alox, DCM/MeOH 20:1): R_f = 0.55; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.58 (*t*, *J* = 7.6, 1H, H_{ar}); 7.19 (*m*, 2H, H_{ar}); 3.91 (*s*, 2H, CH_2); 1.63 (broad, 2H, NH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$): 163.3, 151.1, 139.3, 122.4, 119.7, 47.5; **IR** (KBr): 3364w, 3287w, 1585s, 1582s, 1435m, 1312m, 1165m, 1134m; **ESI-MS** (MeOH): positive ion mode: 143 (100, $[M+H]^+$); 165 (33, $[M+Na]^+$)

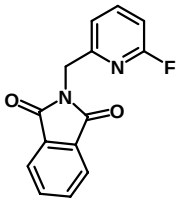
2-(bromomethyl)-6-fluoropyridine (267)[87] 2.79 ml (27.00 mmol, 1.0 eq.) 6-



fluoropyridine and 6.73 g (37.80 mmol, 1.4 eq.) NBS were refluxed overnight in 50 ml CCl_4 in the presence of 0.44 g (2.70 mmol, 0.1 eq.) AIBN. After filtration and removal of the solvent, the residue was dissolved

in 50 ml toluene/water (1:1), extracted four times with toluene and dried over Na_2SO_4. After removal of toluene, the crude product (a 2:1 mixture of mono- and dibromo product, checked by ^{1}H-NMR) was used without further purification.

2-((6-fluoropyridin-2-yl)methyl)isoindoline-1,3-dione (268)[87] A suspension of



3.27 g **267** (17.21 mmol, 1.0 eq.), 3.35 g isoindoline-1,3-dione (18.07 mmol, 1.05 eq.) and 6.14 g potassium carbonate (dried for four hours at high vacuum at 80°C; 54.63 mmol, 2.6 eq.) in 180 ml of acetonitrile was refluxed for 2 hours. The solvent was removed after filtration. The residue was dissolved in 50 ml DCM/H_2O 1:1. The organic phase was separated and dried over Na_2SO_4. The crude product was purified by column chromatography (SiO_2, Hx/EtOAc 2:1) to yield 1.77 g **268** (40% yield; two steps) as a white solid.

TLC (SiO_2, Hx/EtOAc 2:1): R_f = 0.28; **mp**: 154-155°C; **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.89 (*m*, 2H, H_{ar}); 7.74 (*m*, 3H, H_{ar}); 7.13 (*m*, 1H, H_{ar}); 6.80 (*m*, 1H, H_{ar}); 4.94 (*s*, 2H, CH_2); **^{13}C-NMR** (100 MHz, $CDCl_3$): 168.3, 163.2, 162.5, 154.9, 134.6, 132.5, 124.0, 118.9, 108.7, 42.4; **^{19}F-NMR** (376 MHz, $CDCl_3$): -67.7 (*s*, 1F); **IR** (KBr): 3464w, 3078w, 2932w, 1767s, 1705s, 1605s, 1574s, 1420s, 1389s, 1119m; **ESI-MS** (MeOH): positive ion mode: 257 (100, $[M+H]^+$); 279 (64, $[M+Na]^+$); **EA**: calculated for $C_{14}H_9N_2O_2F$: C 65.62, H 3.54, N 10.93, O 12.49; found: C 65.54, H 3.64, N 10.85, O not detectable

(6-fluoropyridin-2-yl)methanamine (215)[87] A solution of 1.77 g **268** (6.91 mmol,

1.0 eq.) and 0.80 g hydrazinemonohydrate (15.89 mmol, 2.3 eq.) were stirred in 50 ml MeOH at 60°C for 12 hours. The solution was filtered and MeOH removed at reduced pressure. The residue was dissolved in DCM, washed three times with 1M NaOH and dried over Na_2SO_4. 0.69 g of a colourless oil (80% yield) was used without further purification.

TLC (basic Alox, DCM/MeOH 20:1): R_f = 0.32; **^{1}H-NMR** (500 MHz, $CDCl_3$): 7.72 (*m*, 1H, H_{ar}); 7.15 (*m*, 1H, H_{ar}); 6.77 (*m*, 1H, H_{ar}); 3.90 (*s*, 2H, CH_2); **^{13}C-NMR** (126 MHz, $CDCl_3$): 165.0, 161.7, 141.9, 118.6, 107.7, 47.5; **^{19}F-NMR** (376 MHz, $CDCl_3$): - 68.9 (*s*, 1F); **IR** (KBr): 3364br, 2917w, 2854w, 2361m, 1605s, 1574s, 1443s, 1265s, 1219s; **ESI-MS** (MeOH): positive ion mode: 127 (100, $[M+H]^+$); 149 (58, $[M+Na]^+$); 233 (10, $[2M-F]^+$); 275 (8, $[2M+Na]^+$)

5.2.2 Synthesis of Substrates for Catalysis

5.2.2.1 Synthesis of racemic Alcohols

Aromatic and aliphatic alcohols were synthezised with the following procedure: 1.0 eq. of ketone were dissolved in diethylether and stirred for 30 minutes in the presence of 0.5 eq. $LiAlH_4$. The mixture was quenched with 1M HCl. The organic phase was washed with water, dried over Na_2SO_4 and purified by column chromatography (SiO_2, hexane/EtOAc). The purity was checked by ^{1}H-NMR and GC.

5.2.2.2 Synthesis of Diketones

4-bromo-2-methylbut-1-ene (143) 11.60 ml methanesulfonyl chloride (0.15 mol, 1.5 eq.) dissolved in 50 ml DCM was slowly added to a mixture of 8.50 g 3-methyl-3-buten-1-ol **142** (0.10 mol, 1.0 eq.) and 21.00 ml triethylamine (0.15 mol, 1.5 eq.) in 200 ml DCM at 0°C. The mixture was stirred for additional 30 minutes at r.t. before quenching with sat. NH_4Cl. The organic phase was washed with 3 x 100 ml NH_4Cl, 100 ml brine and dried over Na_2SO_4. The solvent was removed in the dark to protect decomposition. The obtained yellowish oil was dissolved in 125 ml THF, 17.00 g lithium bromide (0.20 mol, 2.0 eq.) were added. The suspension was refluxed overnight, quenched with 100 ml water, washed with brine and dried over Na_2SO_4. One obtained 6.77 g **143** (47% yield, 2 steps) as a white solid.

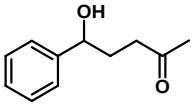
^{1}H-NMR (500 MHz, $CDCl_3$): 4.87 (*s*, 1H, $CH_2CH_2CH(CH_2)CH_3$); 4.65 (*s*, 1H, $CH_2CH_2CH(CH_2)CH_3$); 3.44 (*t*, *J* = 7.1, 2H, CH_2); 2.57 (*t*, *J* = 7.1, 2H, CH_2); 1.73 (*s*, 3H, CH_3)

4-methyl-1-phenylpent-4-en-1-ol (144) 0.28 g magnesium (11.00 mmol, 1.0 eq.) and 1/20 of 1.70 g **143** (11.00 mmol, 1.0 eq.) were suspended in 3 ml THF. The reaction vessel was heated with an air gun till the suspension got dingy. The remaining 19/20 **143** were added and refluxed for 30 minutes. The mixture was cooled down to r.t. and 0.93 ml benzaldehyde (9.00 mmol, 0.8 eq.) dissolved in 1 ml THF were added. The mixture was refluxed for 1 h before quenching carefully with water and 6M HCl. The organic phase was washed with sat. $NaHCO_3$ and dried over

Na_2SO_4. The crude product was purified by column chromatography (SiO_2, Hx/EtOAc 8:1) yielding 1.27 g **144** (66% yield) as a colourless oil.

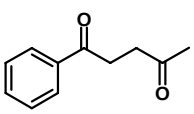
TLC (SiO_2, Hx/EtOAc 8:1): R_f = 0.19; **^{1}H-NMR** (500 MHz, $CDCl_3$): 7.28-7.35 (*m*, 5H, H_{ar}); 4.74 (*s*, 1H, $CH_2CH_2CH(CH_2)CH_3$); 4.71 (*s*, 1H, $CH_2CH_2CH(CH_2)CH_3$); 4.69 (*dxd*, *J* = 4.4, 6.2, 1H, C*H*OH); 2.14 (*m*, 1H, $CH(OH)CH_2CH_2$); 2.05 (*m*, 1H, $CH(OH)CH_2CH_2$); 1.95 (*m*, 1H, $CH(OH)CH_2CH_2$); 1.86 (*m*, 1H, $CH(OH)CH_2CH_2$); 1.73 (*s*, 3H, CH_3); **^{13}C-NMR** (126 MHz, $CDCl_3$): 145.6, 144.8, 128.6, 127.7, 126.0, 110.3, 74.4, 37.0, 34.1, 22.7; **IR** (NaCl): 3397br, 2956w, 2936w, 2908w, 2888w, 1721s; **EA**: calculated for $C_{12}H_{16}O$: C 81.77, H 9.15, O 9.08; found: C 81.44, H 9.15, O 9.26

5-hydroxy-5-phenylpentan-2-one (138) 1.28 g **144** (7.27 mmol, 1.0 eq.) were dissolved in 5 ml DCM and cooled down to -78°C. Ozone was bubbled through the solution till it turned blue (5 minutes). The bubbling was continued for 10 minutes. The remaining ozone was replaced by nitrogen, 2.29 g triphenylphosphine (8.72 mmol, 1.5 eq.) were added and the solution allowed to reach r.t. After removal of the solvent, the crude product was purified by column chromatography (SiO_2, Hx/EtOAc 1:1), yielding 0.93 g **138** (72% yield) as a colourless oil.



TLC (SiO_2, Hx/EtOAc 1:1): R_f = 0.28; **^{1}H-NMR** (500 MHz, $CDCl_3$): 7.28-7.34 (*m*, 5H, H_{ar}); 4.73 (*m*, 1H, C*H*OH); 2.56 (*t*, *J* = 7.3, 2H, CH_2CO); 2.44 (*broad*, 1H, OH); 2.14 (*s*, 3H, CH_3); 2.03 (*m*, 2H, $CH(OH)CH_2$); **^{13}C-NMR** (126 MHz, $CDCl_3$): 209.6, 144.4, 128.6, 127.7, 125.8, 73.6, 40.0, 32.7, 30.2; **IR** (NaCl): 3355br, 3074w, 3028w, 2934w, 2858w, 2560w, 1714m, 1648m, 1452m; **EA**: calculated for $C_{11}H_{14}O_2$: C 74.13, H 7.92, O 17.95; found: C 73.79, H 7.97, O 18.50

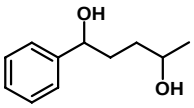
1-phenylpentane-1,4-dione (139) 0.25 g **138** (1.40 mmol, 1.0 eq.) and 0.25 g manganese(IV) oxide (2.88 mmol, 2.06 eq., dried at 250°C for 12 h) were refluxed in 25 ml DCM for 12 h. Remaining manganese salts were filtered off and the crude product was purified by column chromatography (SiO_2, Hx/EtOAc 3:1) yielding 0.13 g **139** (51% yield) as a colourless oil.



TLC (SiO_2, Hx/EtOAc 3:1): R_f = 0.24; **^{1}H-NMR** (500 MHz, $CDCl_3$): 7.97 (*d*, *J* = 7.1, 1H, H_{ar}); 7.57 (*m*, 2H, H_{ar}); 7.46 (*m*, 2H, H_{ar}); 3.28 (*t*, *J* = 6.1, 2H, $PhCOCH_2$); 2.88 (*t*, *J* = 6.0, 2H, CH_2COCH_3); 2.27 (*s*, 3H, CH_3); **^{13}C-NMR** (126 MHz, $CDCl_3$): 207.5,

198.7, 136.7, 133.3, 128.7, 128.2, 37.2, 32.5, 30.2; **IR** (NaCl): 3393br, 3065w, 3030w, 2936w, 2365w, 2339w, 1715m, 1685m, 1648m, 1449;

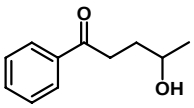
1-phenylpentane-1,4-diol (140) 138 (1.96 mmol, 1.0 eq.) and 0.05 g $LiAlH_4$ were



stirred for 2 h in 4 ml THF at r.t. The mixture was quenched with water and 1M HCl, extracted three times with TBME and dried over Na_2SO_4. The crude product was purified by column chromatography (SiO_2, Hx/TBME 4:5), yielding 0.21 g **140** (60% yield) as a colourless oil.

TLC (SiO_2, Hx/EtOAc 4:5): R_f = 0.22; **^{1}H-NMR** (500 MHz, $CDCl_3$): 7.27-7.34 (*m*, 5H, H_{ar}); 4.71 (*m*, 1H, PhC*H*OH); 3.86 (*m*, 1H, C*H*(OH)HCH_3); 1.83-1.91 (*m*, 2H, PhCH(OH)C*H*$_2$); 1.56-1.66 (*m*, 3H, C*H*$_2$CHOHCH_3 and OH); 1.19 (*d*, *J* = 6.6, 3H, C*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$): 144.9, 128.6, 127.7, 125.9, 74.7, 68.3, 36.1, 35.3, 23.8; **IR** (NaCl): 3355br, 3074w, 3028w, 2934w, 2858w, 2560w, 1714m, 1648m, 1452m; **EA**: calculated for $C_{11}H_{16}O_2$: C 73.30, H 8.95, O 17.75; found: C 72.50, H 9.07, O 18.27

4-hydroxy-1-phenylpentan-1-one (141) 122 mg **140** 1-phenylpentane-1,4-diol (0.68



mmol, 1.0 eq.) and 118 mg manganese(IV) oxide (1.35 mmol, 2.0 eq.) were refluxed in 5 ml toluene for 6 h. After filtration over Celite, the organic phase was dried over Na_2SO_4. The crude product was purified by column chromatography (SiO_2, Hx/TBME 7:6), yielding 73 mg **141** (62% yield) as a colourless oil.

TLC (SiO_2, Hx/EtOAc 7:6): R_f = 0.26; **^{1}H-NMR** (500 MHz, $CDCl_3$): 7.98 (*m*, 2H, H_{ar}); 7.56 (*m*, 1H, H_{ar}); 7.46 (*m*, 2H, H_{ar}); 3.89 (*m*, 1H, C*H*OH); 3.15 (*m*, 2H, PhCOC*H*$_2$); 1,92-2.14 (*m*, 1H, C*H*$_2$CH(OH)CH_3); 1.81-1.91 (*m*, 2H, C*H*$_2$CH(OH)CH_3 and OH); 1.25 (*d*, *J* = 6.2, 3H, C*H*$_3$); **^{13}C-NMR** (126 MHz, $CDCl_3$): 200.9, 137.0, 133.3, 128.7, 128.2, 67.7, 35.1, 33.2, 24.0; **IR** (NaCl): 3390br, 3087w, 2939w, 2360w, 2342w

5.2.3 Synthesis of Cyclodextrins modified on Primary Face

General procedures for the linkage of side chains to the primary face of β-Cyclodextrin:

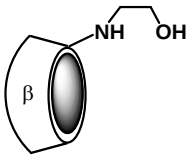
Procedure A: Between 10 and 80 eq. of the amine and 1.0 eq. of mono-6-deoxy-6-(*O*-tosyl)-β-cyclodextrin **68** were stirred at 80°C for 12 h, neat or in the presence of small amounts DMF (0.1-1.0 ml). DMF was removed under reduced pressure and the resulting yellowish oil dissolved in very little warm water. This solution was then poured into 15-150 ml of acetone (depending on the reaction scale). The precipitate was filtered off and washed with acetone.
Procedure B: Between 2 and 15 eq. of the amine and 1.0 eq. of mono-6-deoxy-6-(*O*-tosyl)-β-cyclodextrin **68** or mono-6-deoxy-(6-iodo)-β-cyclodextrin were dissolved in 0.75 ml DMSO and stirred in a closed vessel in the microwave at 70-100°C (constant power 75-150 Watt). Reaction times varied between 1 and 4 hours. After removal of DMSO, the yellowish residue was treated as described below.

General procedure for the purification of modified Cyclodextrins:

Method A (recrystallization): Some modified cyclodextrins could be obtained in a reasonable pure form after 1-3 recrystallizations in water. This method is limited to reactions performed with more than 100 mg of mono-6-deoxy-6-(*O*-tosyl)-β-cyclodextrin. Recrystallizations with smaller amounts led to unsatisfying yields.
Method B (**reprecipitation)**: The crystals obtained from the first precipitation were dissolved again in very little water and precipitated in an excess of acetone. This procedure was repeated 1-3 times. The precipitate can be washed with either acetone or small amounts of ice cold water.
Method C (by chromatography): Modified cyclodextrins can be purified by reversed phase chromatography (silica gel 100 C-18) using water or a mixture of water and MeOH as eluent. Ion exchange resin (CG-50) can also be used to purify modified cyclodextrins, using water as eluent.

5.2.3.1 Linkage of Amino alcohols[71]

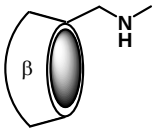
mono-6-deoxy-6-[N-2-hydroxyethyl]-6-amino-β-cyclodextrin (β-CD-AE) (79)



Following general procedure A, 394 mg **68** (0.31 mmol, 1.0 eq.) were stirred in 1.40 ml aminoethanol (21.40 mmol, 70 eq.) for 12 h at 70°C. After two precipitations in acetone and one recrystallization in water, one obtained 193 mg of pure **79** (53% yield) as white crystals.

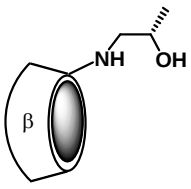
TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.26; **mp**: decomposition >275°C; **[α]** (c (H_2O)= 0.63 M): +130°; **^{1}H-NMR** (500 MHz, D_2O): 5.07 (*m*, 7H, 7xH_1); 3.81-3.99 (*m*, 26H, 7xH_3, 7xH_5 and 12xH_6); 3.53-3.75 (*m*, 15H, 7xH_2, 6xH_4 and $NHCH_2CH_2OH$); 3.44 (*dxd*, *J* = 9.6, 9.6, 1H, H_4); 3.08 (*m*, 1H, H_6); 2.84 (*m*, 1H, H_6); 2.74 (*m*, 2H, $NHCH_2CH_2OH$); **ESI-MS** (MeOH): positive ion mode: 588.5 (67, $[M+Na]^{2+}$); 1179 (100, $[M+H]^+$); 1201 (72, $[M+Na]^+$)

mono-6-deoxy-6-[N-methyl]-6-amino-β-cyclodextrin (269) Following general procedure B, 30 mg **68** (0.02 mmol, 1.0 eq.) and 0.15 ml of 8M methyl amine in EtOH (1.16 mmol, 50 eq.) were stirred in 0.75 ml DMF in the microwave for 4 h at 90 °C. After removal of DMF and one precipitation in acetone, one obtained 16 mg of pure **269** (61% yield) as white crystals.



TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.22; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, DMSO): 5.61-5.80 (*m*, 14H); 4.82 (*s*, 8H); 4.43 (*m*, 6H); 3.51-3.74 (*m*, 28H); 2.26 (*m*, 3H, CH_3); **ESI-MS** (MeOH): positive ion mode: 1149 (100, [*M*+H)

mono-6-deoxy-6-[N-(2,2-(S)-methyl-hydroxyethyl)]-6-amino-β-cyclodextrin (β-CD-SAP) (92)



Following general procedure A, 265 mg **68** (0.20 mmol, 1.0 eq.) were stirred in 1.18 g (S)-1-aminopropan-2-ol (15.72 mmol, 81 eq.) for 12 h at 70°C. After one precipitation in acetone and one recrystallization in water, one obtained 140 mg of pure **92** (59% yield) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.24; **mp**: decomposition >275°C; **[α]** (c (H_2O)= 0.32 M): +136°; **^{1}H-NMR** (400 MHz, D_2O): 5.02 (*m*, 7H, 7xH_1); 3.87-3.94 (*m*, 8H, 7xH_3 and $NHCH_2CH(CH_3)OH$); 3.76-3.85 (*m*, 19H, 7xH_5 and 12xH_6); 3.48-3.63 (*m*, 13H, 7xH_2 and 6xH_4); 3.38 (*dxd*, *J* = 9.6, 9.6, 1H, H_4); 3.02 (*d*,

J = 10.9, 1H, H_6); 2.81 (*m*, 1H, H_6); 2.56 (*m*, 2H, NHC*H*$_2$CH(CH_3)OH); 1.09 (*d*, *J* = 6.3, 3H, C*H*$_3$); **ESI-MS** (MeOH): positive ion mode: 607.5 (85, [*M*+Na]$^{2+}$); 1193 (100, [*M*+H]$^+$); 1215 (78, [*M*+Na]$^+$)

mono-6-deoxy-6-[N-(2,2-(R)-methyl-hydroxyethyl)]-6-amino-β-cyclodextrin (β-CD-RAP) (91) Following general procedure A, 215 mg **68** (0.17 mmol, 1.0 eq.) were stirred in 1.00 g (R)-1-aminopropan-2-ol (13.30 mmol, 81 eq.) for 12 h at 70°C. After three precipitations in acetone one obtained 91 mg of pure **91** (46% yield) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.26; **mp**: decomposition >275°C; **[α]** (c (H_2O)= 0.23 M): +158°; **^{1}H-NMR** (400 MHz, D_2O): 5.01 (*m*, 7H, 7xH_1); 3.72-3.94 (*m*, 27H, 7xH_3, 7xH_5, 12xH_6 and NHCH_2C*H*(CH_3)OH); 3.46-3.58 (*m*, 13H, 7xH_2 and 6xH_4); 3.38 (*dxd*, *J* = 9.4, 9.4, 1H, H_4); 3.05 (*d*, *J* = 12.9, 1H, H_6); 2.72 (*m*, 1H, H_6); 2.51 (*m*, 2H, NHC*H*$_2$CH(CH_3)OH); 1.03 (*d*, *J* = 6.3, 3H, C*H*$_3$); **ESI-MS** (MeOH): positive ion mode: 607.5 (83, [*M*+Na]$^{2+}$); 1193 (100, [*M*+H]$^+$); 1215 (77, [*M*+Na]$^+$)

mono-6-deoxy-6-[N-(1-(R)-methyl-2-hydroxyethyl)]-6-amino-β-cyclodextrin (β-CD-AR) (90) Following general procedure A, 171 mg **68** (0.13 mmol, 1.0 eq.) were stirred in 0.86 ml (R)-alaninol (10.83 mmol, 81 eq.) for 12 h at 70°C. After one precipitation in acetone and one recrystallization in water, one obtained 93 mg of pure **90** (60% yield) as white crystals.

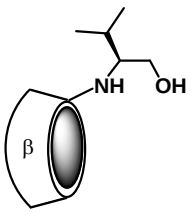
TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.19; **mp**: decomposition >275°C; **^{1}H-NMR** (400 MHz, D_2O): 5.06 (*d*, *J* = 3.8, 1H, H_1); 5.00 (*m*, 6H, 6xH_1); 3.75-3.95 (*m*, 26H, 7xH_3, 7xH_5, 12xH_6); 3.51-3.64 (*m*, 13H, 7xH_2 and 6xH_4); 3.35-3.45 (*m*, 3H, H_4 and NHCH(CH_3)C*H*$_2$OH); 3.16 (*m*, 1H, H_6); 2.63-2.80 (*m*, 2H, H_6 and NHC*H*(CH_3)CH_2OH); 0.98 (*d*, *J* = 6.6, 3H, C*H*$_3$); **ESI-MS** (MeOH): positive ion mode: 607.5 (77, [*M*+Na]$^{2+}$); 1193 (100, [*M*+H]$^+$); 1215 (77, [*M*+Na]$^+$)

mono-6-deoxy-6-[N-(1-(S)-methyl-2-hydroxyethyl)]-6-amino-β-cyclodextrin (β-CD-AS) (89) Following general procedure A, 198 mg **68** (0.15 mmol, 1.0 eq.) were stirred in 1.0 ml (S)-alaninol (12.54 mmol, 81 eq.) for 12 h at 70°C. After one precipitation in acetone and one recrystallization

in water, one obtained 102 mg of pure **89** (57% yield) as white crystals.

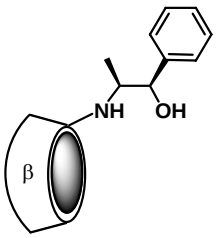
TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.21; **mp**: decomposition >275°C; **^{1}H-NMR** (400 MHz, D_2O): 5.08 (*d*, *J* = 3.8, 1H, H_1); 5.01 (*m*, 6H, 6xH_1); 3.75-3.95 (*m*, 26H, 7xH_3, 7xH_5, 12xH_6); 3.48-3.61 (*m*, 13H, 7xH_2 and 6xH_4); 3.38-3.46 (*m*, 3H, H_4 and and NHCH(CH_3)C*H_2*OH); 2.75-3.05 (*m*, 3H, 2xH_6 and NHC*H*(CH_3)CH_2OH); 1.00 (*d*, *J* = 6.6, 3H, C*H_3*); **ESI-MS** (MeOH): positive ion mode: 607.5 (80, [*M*+Na]$^{2+}$); 1193 (100, [*M*+H]$^+$); 1215 (75, [*M*+Na]$^+$)

mono-6-deoxy-6-[N-(1-(S)-isopropyl-2-hydroxyethyl)]-6-amino-β-cyclodextrin β-CD-VAS) (124) Following general procedure A, 156 mg **68** (0.12 mmol, 1.0 eq.) were stirred in 1.00 ml (S)-valinol (9.69 mmol, 81 eq.) for 12 h at 70°C. After one precipitation in acetone and one recrystallization in water, one obtained 72 mg of pure **124** (52% yield) as white crystals.



TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.21; **mp**: decomposition >275°C; **^{1}H-NMR** (400 MHz, D_2O): 5.08 (*d*, *J* = 3.8, 1H, H_1); 5.00 (*m*, 6H, 6xH_1); 3.67-3.96 (*m*, 26H, 7xH_3, 7xH_5, 12xH_6); 3.42-3.63 (*m*, 15H, 7xH_2 and 6xH_4 and NHCH(CH(CH_3)$_2$)C*H_2*OH); 3.31-3.39 (*dxd*, J = 9.4, 9.4, 1H, H_4); 3.06 (*m*, 1H, H_6); 2.75 (*m*, 1H, H_6); 2.51 (*m*, 1H, NHC*H*(CH(CH_3)$_2$)CH_2OH); 1.81 (*m*, 1H, NHCH(C*H*(CH_3)$_2$)CH_2OH); 0.89 (*d*, *J* = 7.1, 3H, C*H_3*); 0.82 (*d*, *J* = 7.0, 3H, C*H_3*); **ESI-MS** (MeOH): positive ion mode: 621.5 (100, [*M*+Na]$^{2+}$); 1220 (41, [*M*+H]$^+$); 1242 (18, [*M*+Na]$^+$)

mono-6-deoxy-6-[N-(1-(S)-methyl-2,2-(R)-phenyl-hydroxyethyl)]-6-amino-β-cyclodextrin (123) Following general procedure A, 198 mg **68** (0.15 mmol, 1.0 eq.) were stirred in 1.00 ml L-norephedrin (12.51 mmol, 81 eq.) for 12 h at 70°C. After three precipitations in acetone, the crystals were washed with very little ice cold water. One obtained 51 mg of pure **123** (26% yield) as white crystals.



TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.20; **mp**: decomposition >275°C; **^{1}H-NMR** (400 MHz, D_2O): 7.28-7.39 (*m*, 3H, H_{ar}); 7.18-7.26 (*m*, 2H, H_{ar}); 4.95-5.07 (*m*, 7H, 7xH_1); 4.51 (*m*, 1H, NHCH(CH_3)C*H*(Ph)OH); 3.47-3.99 (*m*, 39H, 7xH_2, 7xH_3, 6xH_4, 7xH_5, 12xH_6); 3.28 (*m*, 1H, H_4); 2.72-2.90 (*m*, 3H, 2xH_6 and

NHC*H*(CH_3)CH(Ph)OH); 1.09 (*d*, *J* = 6.6, 3H, CH_3); **ESI-MS** (MeOH): positive ion mode: 646 (95, [*M*+Na]$^{2+}$); 1268 (100, [*M*+H]$^{+}$); 1290 (60, [*M*+Na]$^{+}$)

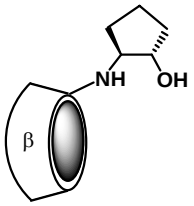
mono-6-deoxy-6-[N-(1-(R)-methyl-2,2-(S)-phenyl-hydroxyethyl)]-6-amino-β-cyclodextrin (122) Following general procedure A, 198 mg **68** (0.15 mmol, 1.0 eq.) were stirred in 1.00 ml D-norephedrin (12.51 mmol, 81 eq.) for 12 h at 70°C. After two precipitations in acetone and one recrystallization in water, one obtained 68 mg of pure **122** (36% yield) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.21; **mp**: decomposition >275°C; **^{1}H-NMR** (400 MHz, D_2O): 7.28-7.39 (*m*, 3H, H_{ar}); 7.18-7.26 (*m*, 2H, H_{ar}); 4.97-5.08 (*m*, 7H, 7xH_1); 4.47 (*m*, 1H, NHCH(CH_3)C*H*(Ph)OH); 3.45-3.96 (*m*, 39H, 7xH_2, 7xH_3, 6xH_4, 7xH_5, 12xH_6); 3.25 (*m*, 1H, H_4); 2.70-2.87 (*m*, 3H, 2xH_6 and NHC*H*(CH_3)CH(Ph)OH); 1.06 (*d*, *J* = 6.6, 3H, CH_3); **ESI-MS** (MeOH): positive ion mode: 646 (93, [*M*+Na]$^{2+}$); 1268 (100, [*M*+H]$^{+}$); 1290 (63, [*M*+Na]$^{+}$)

mono-6-deoxy-6-[N-(1-(R)-2,2-(R)-hydroxy-cyclopentyl)]-6-amino-β-cyclodextrin (119) Following general Procedure A, 127 mg **68** (0.10 mmol, 1.0 eq.) were stirred in 500 mg **117** (4.95 mmol, 50 eq.) for 12 h at 70°C. After one precipitation in acetone, the crude product was purified by reversed phase chromatography using water as eluent. One obtained 36 mg of pure **119** (30% yield) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.23; **mp**: decomposition >275°C; **^{1}H-NMR** (400 MHz, D_2O): 5.01-5.08 (*m*, 7H, 7xH_1); 3.70-3.97 (*m*, 27H, 7xH_3, 7xH_5, 12xH_6 and CH_2C*H*OH); 3.50-3.63 (*m*, 13H, 7xH_2 and 6xH_4); 3.34-3.43 (*m*, 1H, H_4); 3.12-3.21 (*m*, 1H, H_6); 2.87-3.06 (*m*, 2H, H_6 and NHC*H*CH_2); 2.01-2.10 (*m*, 1H, NHCHCH_2CH_2C*H*$_2$CHOH); 1.90-1.99 (*m*, 1H, NHCHC*H*$_2$CH_2CH_2CHOH); 1.63-1.72 (*m*, 2H, NHCHCH_2C*H*$_2$CH_2CHOH); 1.50-1.59 (*m*, 1H, NHCHCH_2CH_2C*H*$_2$CHOH); 1.32-1.47 (*m*, 1H, NHCHC*H*$_2$CH_2CH_2CHOH); **ESI-MS** (MeOH): positive ion mode: 1218 (100, [*M*+H]$^{+}$)

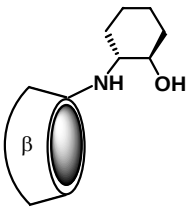
mono-6-deoxy-6-[N-(1-(S)-2,2-(S)-hydroxy-cyclopentyl)]-6-amino-β-cyclodextrin



(127) Following general Procedure A, 50 mg **68** (0.04 mmol, 1.0 eq.) were stirred in 194 mg **116** (1.93 mmol, 50 eq.) for 12 h at 70°C. After one precipitation in acetone, the crude product was purified by reversed phase chromatography using water as eluent. One obtained 17 mg of pure **127** (36% yield) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.23; **mp**: decomposition >275°C; **^{1}H-NMR** (600 MHz, D_2O): 5.09 (*m*, 1H, H_1); 5.01-5.06 (*m*, 6H, 6xH_1); 3.71-3.98 (*m*, 27H, 7xH_3, 7xH_5, 12xH_6 and CH_2CHOH); 3.51-3.64 (*m*, 13H, 7xH_2 and 6xH_4); 3.36-3.43 (*m*, 1H, H_4); 3.00-3.05 (*m*, 1H, H_6); 2.91-2.97 (*m*, 1H, NHC*H*CH_2); 2.77-2.84 (*m*, 1H, H_6); 1.87-1.98 (*m*, 2H, NHCHC*H*$_2$$CH_2CH_2CHOH$ and $NHCHCH_2CH_2C$*H*$_2$$CHOH$); 1.60-1.68 (*m*, 2H, $NHCHCH_2C$*H*$_2$$CH_2CHOH$); 1.43-1.50 (*m*, 1H, $NHCHCH_2CH_2C$*H*$_2$$CHOH$); 1.28-1.36 (*m*, 1H, NHCHC*H*$_2$$CH_2CH_2CHOH$); **ESI-MS** (MeOH): positive ion mode: 1218 (100, [*M*+H]$^+$)

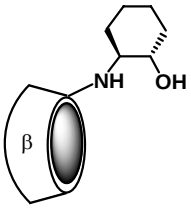
mono-6-deoxy-6-[N-(1-(R)-2,2-(R)-hydroxy-cyclohexyl)]-6-amino-β-cyclodextrin



(120) Following general procedure A, 75 mg **117** (0.06 mmol, 1.0 eq.) were stirred in 337 mg **115** (2.91 mmol, 50 eq.) for 12 h at 70°C. After one precipitation in acetone and one recrystallization in water, one obtained 32 mg of pure **120** (43% yield) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.20; **mp**: decomposition >275°C; **^{1}H-NMR** (400 MHz, D_2O): 5.01-5.10 (*m*, 7H, 7xH_1); 3.21-4.02 (*m*, 41H, 7xH_2, 7xH_3, 7xH_4, 7xH_5, 12xH_6 and CH_2CHOH); 2.90-3.00 (*m*, 1H, H_6); 2.68-2.82 (*m*, 1H, NHC*H*CH_2); 2.27-2.37 (*m*, 1H, H_6); 1.72-1.95 (*m*, 2H, NHCHC*H*$_2$$CH_2CH_2CH_2CHOH$ and $NHCHCH_2CH_2CH_2C$*H*$_2$$CHOH$) 1.41-1.62 (*m*, 2H, NHCHC*H*$_2$$CH_2CH_2CH_2CHOH$ and $NHCHCH_2CH_2CH_2C$*H*$_2$$CHOH$); 0.98-1.32 (*m*, 4H, $NHCHCH_2C$*H*$_2$$C$*H*$_2$$CH_2CHOH$); **ESI-MS** (MeOH): positive ion mode: 1232 (100, [*M*+H]$^+$)

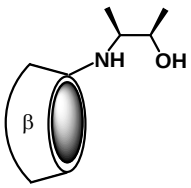
mono-6-deoxy-6-[N-(1-(S)-2,2-(S)-hydroxy-cyclohexyl)]-6-amino-β-cyclodextrin



(126) Following general procedure A, 43 mg **68** (0.03 mmol, 1.0 eq.) were stirred in 310 mg **114** (2.69 mmol, 80 eq.) for 12 h at 70°C. After one precipitation, the crude product was purified by reversed phase chromatography using water as eluent. One obtained 18 mg of pure **126** (44% yield) as white crystals.

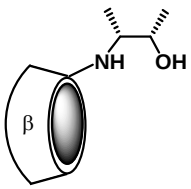
TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.18; **mp**: decomposition >275°C; **^{1}H-NMR** (400 MHz, D_2O): 5.01-5.09 (*m*, 7H, 7xH_1); 3.80-3.98 (*m*, 27H, 7xH_3, 7xH_5, 12xH_6 and CH_2CHOH); 3.50-3.67 (*m*, 13H, 7xH_2 and 6xH_4); 3.38-3.47 (*m*, 1H, H_4); 3.24-3.33 (*m*, 1H, H_6); 2.54-2.64 (*m*, 1H, NHC*H*CH_2); 2.37-2.47 (*m*, 1H, H_6); 1.86.1.98 (*m*, 2H, NHCHC*H*$_2$$CH_2CH_2CH_2$CHOH and NHCHC$H_2CH_2CH_2CH_2$C*H*$_2$CHOH) 1.61-1.74 (*m*, 2H, NHCHC*H*$_2$$CH_2CH_2CH_2$CHOH and NHCHC$H_2CH_2CH_2CH_2$C*H*$_2$CHOH); 1.13-1.33 (*m*, 3H, 1xNHCHCH_2C*H*$_2$$CH_2CH_2$CHOH and 2xNHCHC$H_2CH_2$C*H*$_2$$CH_2$CHOH); 1.02-1.11 (*m*, 1H, NHCHCH_2C*H*$_2$$CH_2CH_2$CHOH); **ESI-MS** (MeOH): positive ion mode: 1232 (100, $[M+H]^+$)

mono-6-deoxy-6-[N-(1-(S)-methyl-2,2-(R)-methyl-hydroxyethyl)]-6-amino-β-cyclodextrin (β-CD-RSDM) (125) Following general Procedure A, 51 mg **68** (0.04 mmol, 1.0 eq.) and 280 mg **111** (3.14 mmol, 80 eq.) were stirred in 0.5 ml DMF for 12 h at 70°C. After three precipitations in acetone and washing with very little ice cold water, one obtained 34 mg of pure **125** (73% yield) as white crystals.



TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.21; **mp**: decomposition >275°C; **^{1}H-NMR** (400 MHz, D_2O): 5.01-5.09 (*m*, 7H, 7xH_1); 3.73-3.97 (*m*, 26H, 7xH_3, 7xH_5, 12xH_6); 3.51-3.67 (*m*, 14H, 7xH_2, 6xH_4 and C*H*(CH_3)OH); 3.37-3.46 (*m*, 1H, H_4); 2.98-3.06 (*m*, 1H, H_6); 2.79-2.87 (*m*, 1H, NHC*H*(CH_3)CH(CH_3)OH); 2.62-2.73 (*m*, 1H, H_6); 1.13 (*d*, *J* = 6.7, 3H, CH(C*H*$_3$)OH); 0.97 (*d*, *J* = 6.7, 3H, NHCH(C*H*$_3$)); **ESI-MS** (MeOH): positive ion mode: 1206 (100, $[M+H]^+$)

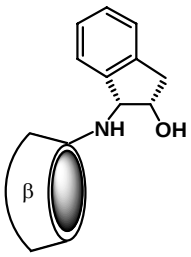
mono-6-deoxy-6-[N-(1-(R)-methyl-2,2-(S)-methyl-hydroxyethyl)]-6-amino-β-cyclodextrin (β-CD-SRDM) (118) Following general Procedure A, 121 mg **68** (0.09 mmol, 1.0 eq.) and 335 mg **110** (3.76 mmol, 40 eq.) were stirred at 70°C for 12 h. After two precipitations in acetone and washing with very little ice cold water, one obtained 21 mg of pure



118 (19% yield) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.22; **mp**: decomposition >275°C; **^{1}H-NMR** (400 MHz, D_2O): 5.01-5.09 (*m*, 7H, 7xH_1); 3.75-4.04 (*m*, 26H, 7xH_3, 7xH_5, 12xH_6); 3.52-3.71 (*m*, 14H, 7xH_2, 6xH_4 and C*H*(CH_3)OH); 3.42-3.51 (*m*, 1H, H_4); 3.14-3.23 (*m*, 1H, H_6); 2.65-2.79 (*m*, 2H, H_6 and NHC*H*(CH_3)CH(CH_3)OH); 1.14 (*d*, *J* = 6.5, 3H, CH(C*H*$_3$)OH); 1.01 (*d*, *J* = 6.3, 3H, NHCH(C*H*$_3$)); **ESI-MS** (MeOH): positive ion mode: 1206 (100, [*M*+H]$^+$)

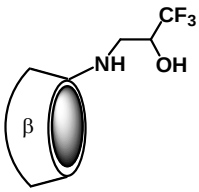
mono-6-deoxy-6-[N-(1-(R)-2,2-(S)-hydroxy-indanyl)]-6-amino-β-cyclodextrin



(121) Following general Procedure B, 50 mg **68** (0.04 mmol, 1 eq.) and 60 mg (1R,2S)-1-amino-2,3-dihydro-1H-inden-2-ol (0.40 mmol, 10 eq.) were dissolved in 0.75 ml DMSO. The mixture was stirred in the microwave for 4 h at 80°C (90 Watt). After two precipitations in acetone, one obtained 16 mg of pure **121** (32% yield) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.18; **mp**: decomposition >275°C; **^{1}H-NMR** (400 MHz, D_2O): 7.23-7.43 (*m*, 4H, H_{ar}); 5.02-5.11 (*m*, 7H, 7xH_1); 3.52-4.02 (*m*, 43H, 7xH_2, 7xH_3, 6xH_4 7xH_5, 12xH_6, NHC*H*, C*H*OH and PhC*H*$_2$); 3.45-3.51 (*m*, 1H, H_4); 2.90-3.13 (*m*, 2H, 2xH_6); **ESI-MS** (MeOH): positive ion mode: 1266 (96, [*M*+H]$^+$); 1288 (100, [*M*+Na]$^+$)

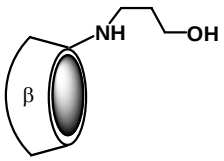
mono-6-deoxy-6-[N-(2,2-trifluoromethyl-hydroxyethyl)]-6-amino-β-cyclodextrin



(129) Following general Procedure B, 75 mg **68** (0.06 mmol, 1 eq.) and 38 mg 1,1,1-trifluoro-3-amino-2-propanol (0.29 mmol, 5 eq.) were dissolved in 0.75 ml DMSO. The mixture was stirred in the microwave for 4 h at 80°C (120 Watt). After two precipitations in acetone, the crude product was purified over IRA-68 ion exchange resin using water as eluent. One obtained 37 mg of pure **129** (49% yield) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.22; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O): 5.40 (*m*, 1H, 1xH_1); 5.02-5.10 (*m*, 6H, 6xH_1); 3.75-4.00 (*m*, 26H, 7xH_3, 7xH_5 and 12xH_6); 3.52-3.67 (*m*, 14H, 7xH_2 and 6xH_4 and and NHCH_2C*H*(CF_3)OH); 3.38-3-45 (*m*, 1H, H_4); 2.72-3.12 (*m*, 4H, 2xH_6 and NHC*H*$_2$CH(CF_3)OH); **^{19}F-NMR** (376 MHz, D_2O): -79.80, -79.87; **ESI-MS** (MeOH): positive ion mode: 1247 (91, [*M*+H]$^+$); 1269 (100, [*M*+Na]$^+$)

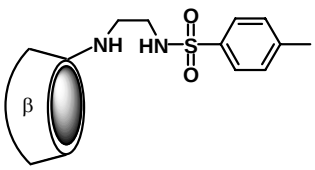
mono-6-deoxy-6-[N-3-hydroxypropyl)]-6-amino-β-cyclodextrin (128) Following general Procedure A 107 mg **68** (0.08 mmol, 1.0 eq.) and 500 mg 3-amino-1-propanol (6.66 mmol, 80 eq.) were stirred at 70°C for 12 h. After three precipitations in acetone and washing with very little ice cold water, one obtained 34 mg of pure **128** (35% yield) as white crystals.



TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.22; **mp**: decomposition >275°C; **^{1}H-NMR** (400 MHz, D_2O): 5.02-5.09 (*m*, 7H, 7xH_1); 3.77-3.98 (*m*, 26H, 7xH_3, 7xH_5 and 12xH_6); 3.50-3.70 (*m*, 15H, 7xH_2, 6xH_4 and $NHCH_2CH_2CH_2OH$); 3.40 (*dxd*, *J* = 9.6, 9.6, 1H, H_4); 3.06 (*m*, 1H, H_6); 2.82-2.91 (*m*, 1H, $NHCH_2CH_2CH_2OH$); 2.67 (*m*, 1H, H_6); 2.51-2.60 (*m*, 2H, $NHCH_2CH_2CH_2OH$ and $NHCH_2CH_2CH_2OH$); 1.67-1.78 (*m*, 1H, $NHCH_2CH_2CH_2OH$); **ESI-MS** (MeOH): positive ion mode: 1192 (100, $[M+H]^+$); negative ion mode: 1190 (100, M^-);

5.2.3.2 Linkage of Monotosylated-, Monomesylated- and Monotriflated Diamines

mono-6-deoxy-6-[N-2-tosylsulfonamidoethyl]-6-amino-β-cyclodextrin (β-CD-MTDA) (154) Following general Procedure A, 113 mg **68** (0.09 mmol, 1.0 eq.) and 1.5 g **157** (7.02 mmol, 80 eq.) were stirred in 1.0 ml DMF for 12 h at 70°C. After two precipitations in acetone and washing with very little ice cold water, one obtained 54 mg of pure **154** (47% yield) as white crystals.



TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.17; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O, 315K): 7.78 (*d*, *J* = 8.2, 2H, H_{ar}); 7.65 (*d*, *J* = 8.0, 2H, H_{ar}); 5.24 (*d*, *J* = 3.5, 1H, H_1); 5.22 (*d*, *J* = 3.6, 1H, H_1); 5.17 (*d*, *J* = 3.5, 1H, H_1); 5.14 (*d*, *J* = 3.3, 1H, H_1); 5.09 (*d*, *J* = 3.6, 1H, H_1); 5.02-5.07 (*m*, 2H, 2xH_1); 3.60-4.14 (*m*, 38H, 7xH_2, 7xH_3, 6xH_4, 6xH_5 and 12xH_6); 3.53 (*m*, 1H); 3.26-3.31 (*m*, 1H, H_4); 3.18-3.25 (*m*, 1H, H_5); 3.11-3.18 (*m*, 1H, CH_2NHTs); 3.01-3.09 (*m*, 1H, CH_2NHTs); 2.81-2.88 (*m*, 1H, H_6); 2.72-2.81 (*m*, 1H, H_6); 2.67 (*s*, 3H, $TsCH_3$); 2.52-2.61 (*m*, 1H, $NHCH_2$); 2.37-2.47 (*m*, 1H, $NHCH_2$); **ESI-MS** (MeOH): positive ion mode: 688.5 (77, $[M+Na]^{2+}$); 1332 (15, $[M+H]^+$); 1354 (100, $[M+Na]^+$)

mono-6-deoxy-6-[N-(2,2-(S)-methyl-tosylsulfonamidoethyl)]-6-amino-β-cyclodextrin (166) Following general Procedure A, 50 mg **68** (0.04 mmol, 1.0 eq.) and 700 mg **162** (3.07 mmol, 80 eq.) were stirred in 0.7 ml DMF for 12 h at 70°C. After three precipitations in acetone and one recrystallization in water, one obtained 14 mg of pure **166** (26% yield) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.19; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O): 7.53 (*d*, *J* = 6.7, 2H, H_{ar}); 7.40 (*d*, *J* = 6.3, 2H, H_{ar}); 5.00 (*d*, *J* = 2.8, 1H, H_1); 4.98 (*d*, *J* = 3.0, 1H, H_1); 4.92 (*d*, *J* = 2.9, 1H, H_1); 4.90 (*d*, *J* = 3.0, 1H, H_1); 4.80-4.84 (*m*, 3H, 3xH_1); 3.26-3.96 (*m*, 37H, 7xH_2, 7xH_3, 6xH_4, 6xH_5 and 12xH_6); 3.13-3.19 (*m*, 1H, C*H*(CH_3)NHTs); 2.92-3.05 (*m*, 2H, H_5 and H_4); 2.49-2.57 (*m*, 2H, 2xH_6); 2.57 (*s*, 3H, TsCH_3); 1.90-1.98 (*m*, 2H, NHC*H_2*); 1.05 (*d*, *J* = 5.3, 3H, C*H_3*); **ESI-MS** (MeOH): positive ion mode: 695 (34, $[M+Na]^{2+}$); 1345 (100, $[M+H]^+$); negative ion mode: 671 (55, M^{2-}); 1343 (100, M^-)

mono-6-deoxy-6-[N-(2,2-(R)-methyl-tosylsulfonamidoethyl)]-6-amino-β-cyclodextrin (167) Following general Procedure A, 68 mg **162** (0.05 mmol, 1.0 eq.) and 960 mg **164** (4.21 mmol, 80 eq.) were stirred in 0.9 ml DMF for 12 h at 70°C. After three precipitations in acetone, one obtained 47 mg of pure **167** (66% yield) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.21; **mp**: decomposition >275°C; **^{1}H-NMR** (400 MHz, D_2O): 7.55 (*d*, *J* = 8.2, 2H, H_{ar}); 7.43 (*d*, *J* = 8.2, 2H, H_{ar}); 4.98-5.02 (*m*, 2H, 2xH_1); 4.95 (*d*, *J* = 3.6, 1H, H_1); 4.89 (*d*, *J* = 3.5, 1H, H_1); 4.85 (*d*, *J* = 3.6, 1H, H_1); 4.81 (*d*, *J* = 3.3, 1H, H_1); 4.77 (*d*, *J* = 3.0, 1H, H_1); 3.35-3.95 (*m*, 37H, 7xH_2, 7xH_3, 6xH_4, 6xH_5 and 12xH_6); 3.13-3.19 (*m*, 1H, C*H*(CH_3)NHTs); 2.91-3-09 (*m*, 2H); 2.78-2-85 (*s*, 1H); 2.35-2.53 (*m*, 5H, TsCH_3 and 2xH_6); 2.18-2.32 (*m*, 2H, NHC*H_2*); 1.09 (*d*, *J* = 6.5, 3H, C*H_3*); **ESI-MS** (MeOH): positive ion mode: 673 (82, $[M+H]^{2+}$); 1345 (100, $[M+H]^+$) 1367 (67, $[M+Na]^+$); negative ion mode: 671 (19, M^{2-}); 1343 (100, M^-)

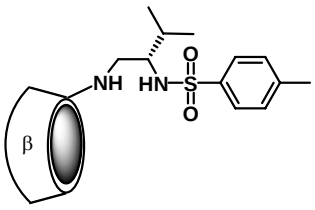
mono-6-deoxy-6-[N-(1-(R)-methyl-2-tosylsulfonamidoethyl)]-6-amino-β-cyclodextrin (178) Following general Procedure B, 54 mg **68** (0.04 mmol, 1.0 eq.) and 48 mg **169** (0.21 mmol, 5.0 eq.) were dissolved in 0.75 ml DMSO. The mixture was stirred in the microwave for 3 h at 85°C (120 Watt). After one precipitation in acetone, the crude product was purified over IRA-68 ion exchange resin using water as eluent. One obtained 18 mg of pure **178** (32% yield) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.18; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O): 7.69 (*d*, *J* = 8.2, 2H, H_{ar}); 7.51 (*d*, *J* = 8.2, 2H, H_{ar}); 4.90-5.09 (*m*, 7H, 7xH_1); 3.72-4.02 (*m*, 26H, 7xH_3, 7xH_5, and 12xH_6); 3.50-3.70 (*m*, 14H, 7xH_2, 7xH_4); 3.12-3.18 (*m*, 1H); 2.80-3.00 (*m*, 2H); 2.54 (*s*, 3H, $TsCH_3$); 2.40-2.44 (*m*, 2H); 1.03 (*d*, *J* = 6.6, 3H, CH_3); **ESI-MS** (MeOH): positive ion mode: 1345 (100, $[M+H]^+$); negative ion mode: 1343 (100, M^-)

mono-6-deoxy-6-[N-(1-(S)-methyl-2-tosylsulfonamidoethyl)]-6-amino-β-cyclodextrin (179) Following general Procedure B, 36 mg **68** (0.03 mmol, 1.0 eq.) and 33 mg **177** (0.24 mmol, 5.0 eq.) were dissolved in 0.75 ml DMSO. The mixture was stirred in the microwave for 3 h at 85°C (120 Watt). After one precipitation in acetone, the crude product was purified over IRA-68 ion exchange resin using water as eluent. One obtained 20 mg of pure **179** (53% yield) as white crystals.

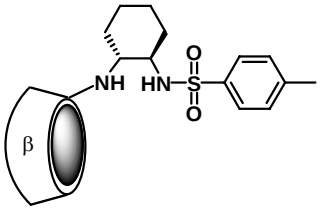
TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.20; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O): 7.54 (*d*, *J* = 8.2, 2H, H_{ar}); 7.42 (*d*, *J* = 8.2, 2H, H_{ar}); 4.81-5.03 (*m*, 7H, 7xH_1); 3.62-3.93 (*m*, 26H, 7xH_3, 7xH_5, and 12xH_6); 3.36-3.57 (*m*, 14H, 7xH_2, 7xH_4); 3.28-3.34 (*m*, 1H); 3.01-3.08 (*m*, 1H); 2.90-2.97 (*m*, 1H); 2.47-2.76 (*m*, 3H); 2.42 (*s*, 3H, $TsCH_3$); 0.88 (*d*, *J* = 6.5, 3H, C*H*$_3$); **ESI-MS** (MeOH): positive ion mode: 1345 (100, $[M+H]^+$); 1367 (83, $[M+Na]^+$); negative ion mode: 1343 (100, M^-)

mono-6-deoxy-6-[N-(2,2-(S)-isopropyl-tosylsulfonamidoethyl)]-6-amino-β-cyclodextrin (168) Following general Procedure A, 47 mg **68** (0.04 mmol, 1.0 eq.) and 750 mg **165** (2.93 mmol, 80 eq.) were stirred in 0.7 ml DMF for 12 h. After two precipitations in acetone and washing with very little ice cold water, one obtained 25 mg of pure **168** (50% yield) as white crystals.

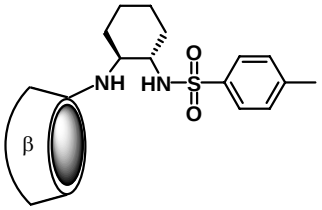


TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.20; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O): 7.53 (*d*, *J* = 8.2, 2H, H_{ar}); 7.39 (*d*, *J* = 8.1, 2H, H_{ar}); 5.02 (*d*, *J* = 3.4, 1H, H_1); 4.94-4.98 (*m*, 2H, 2xH_1); 4.88 (*d*, *J* = 3.5, 1H, H_1); 4.85 (*d*, *J* = 3.3, 1H, H_1); 4.82 (*d*, *J* = 3.7, 1H, H_1); 4.80 (*d*, *J* = 2.7, 1H, H_1); 3.32-4.02 (*m*, 37H, 6xH_2, 7xH_3, 6xH_4, 6xH_5 and 12xH_6); 3.23-3.28 (*m*, 1H); 3.15-3.20 (*m*, 1H, H_2); 3.00-3.09 (*m*, 2H, NHCH_2 and H_4); 2.90-2.95 (*m*, 1H, H_5); 2.45-2.53 (*m*, 2H, 2xH_6); 2.43 (*s*, 3H, $TsCH_3$); 2.12-2.22 (*m*, 1H, NHCH_2); 1.73-1.77 (*m*, 1H, C*H*$(CH_3)_2$); 1.57-1.63 (*m*, 1H, C*H*NHTs); 0.85 (*d*, *J* = 6.7, 3H, CH_3); 0.63 (*d*, *J* = 6.9, 3H, CH_3); **ESI-MS** (MeOH): positive ion mode: 1373 (50, $[M+H]^+$); 1395 (100, $[M+Na]^+$); negative ion mode: 1371 (100, M^-)

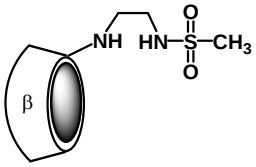
mono-6-deoxy-6-[N-(1-(R)-2,2-(R)-tosylsulfonamido-cyclohexyl)]-6-amino-β-cyclodextrin (181) Following general Procedure A, 106 mg **68** (0.09 mmol, 1.0 eq.) and 683 mg **255** (2.54 mmol, 30 eq.) were stirred in 0.5 ml DMF for 12 h. After three precipitations in acetone and washing with very little ice cold water, one obtained 63 mg of pure **181** (54% yield) as white crystals.



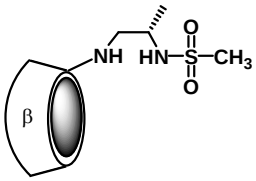
TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.20; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O): 7.66 (*d*, *J* = 8.2, 2H, H_{ar}); 7.50 (*d*, *J* = 8.2, 2H, H_{ar}); 5.07-5.10 (*m*, 2H, 2xH_1); 5.05 (*d*, *J* = 3.3, 1H, H_1); 5.02 (*d*, *J* = 3.5, 1H, H_1); 4.95-4.98 (*m*, 2H, 2xH_1); 4.92 (*d*, *J* = 3.3, 1H, H_1); 3.45-4.10 (*m*, 40H, 7xH_2, 7xH_3, 7xH_4, 7xH_5 and 12xH_6); 3.10-3.20 (*m*, 2H, 2xH_6); 2.76-2.88 (*m*, 1H, NHC*H*); 2.76-2.88 (*m*, 1H, C*H*NHTs); 2.43 (*s*, 3H, $TsCH_3$); 1.86-1.98 (*m*, 1H, cyclohexane ring); 1.73-1-85 (*m*, 1H, cyclohexane ring); 1.53-1.65 (*m*, 2H, cyclohexane ring); 1.42-1.53 (*m*, 1H, cyclohexane ring); 1.27-1.42 (*m*, 3H, cyclohexane ring); **ESI-MS** (MeOH): positive ion mode: 1407 (100, $[M+Na]^+$); negative ion mode: 1383 (100, M^-)

mono-6-deoxy-6-[N-(1-(S)-2,2-(S)-tosylsulfonamido-cyclohexyl)]-6-amino-β-cyclodextrin (180)  Following general Procedure A, 74 mg **68** (0.06 mmol, 1.0 eq.) and 480 mg **254** (1.79 mmol, 30 eq.) were stirred in 0.5 ml DMF for 12 h. After three precipitations in acetone and washing with very little ice cold water, one obtained 36 mg of pure **180** (44% yield) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.18; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O): 7.65 (*d*, *J* = 8.1, 2H, H_{ar}); 7.48 (*d*, *J* = 8.2, 2H, H_{ar}); 4.91-5.10 (*m*, 7H, 7xH_1); 3.41-4.11 (*m*, 40H, 7xH_2, 7xH_3, 7xH_4, 7xH_5 and 12xH_6); 3.10-3.30 (*broad*, 3H, 2xH_6 NHC*H*); 2.45-2.52 (*m*, 4H, TsCH_3 and C*H*NHTs); 1.51-1.81 (*m*, 4H, cyclohexane ring); 1.12-1.41 (*m*, 4H, cyclohexane ring); **ESI-MS** (MeOH): positive ion mode: 1407 (100, [*M*+Na]$^+$); negative ion mode: 1383 (100, M^-)

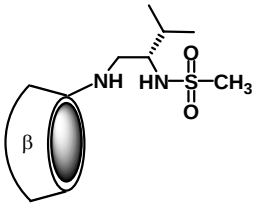
mono-6-deoxy-6-[N-methylsulfonamidoethyl)]-6-amino-β-cyclodextrin (186)  Following general Procedure B, 70 mg **68** (0.05 mmol, 1.0 eq.) and 60 mg **183** (0.44 mmol, 8.0 eq.) were dissolved in 0.75 ml DMSO. The mixture was stirred in the microwave for 2 h at 85°C (90 Watt). After one precipitation in acetone, the crude product was purified over IRA-68 ion exchange resin using water as eluent. One obtained 37 mg of pure **186** (40% yield) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.21; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O): 5.01-5.10 (*m*, 7H, 7xH_1); 3.79-4.01 (*m*, 26H, 7xH_3, 7xH_5 and 12xH_6); 3.53-3.68 (*m*, 13H, 7xH_2 and 6xH_4); 3.38-3.42 (*m*, 1H, H_4); 3.17-3.23 (*m*, 2H, *C*H_2Ms); 3.04-3.12 (*m*, 4H, H_6 and MsCH_3); 2.75-2.85 (*m*, 3H, H_6 and 2xNHCH_2); **ESI-MS** (MeOH): positive ion mode: 1255 (100, [*M*+H]$^+$); 1277 (57, [*M*+Na]$^+$); negative mode: 1253 (100, M^-)

mono-6-deoxy-6-[N-(2,2-(S)-methyl-methylsulfonamidoethyl)]-6-amino-β-cyclodextrin (187)  Following general Procedure B, 125 mg **68** (0.09 mmol, 1.0 eq.) and 74 mg **184** (0.49 mmol, 5.0 eq.) were dissolved in 0.75 ml DMSO. The mixture was stirred in the microwave for 2h at 85°C (100 Watt). After one precipitation in acetone, the crude product was purified over IRA-68 ion exchange resin using water as eluent. One obtained 86 mg of pure **187** (70% yield) as white crystals.

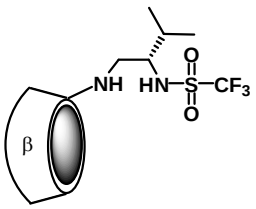
TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.22; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O): 4.99-5.09 (*m*, 7H, 7xH_1); 3.77-4.00 (*m*, 26H, 7xH_3, 7xH_5 and 12xH_6); 3.51-3.69 (*m*, 13H, 7xH_2 and 6xH_4); 3.38-3.43 (*m*, 1H, H_4); 3.17-3.23 (*m*, 2H, *CH*Ms); 3.04-3.12 (*m*, 4H, H_6 and $MsCH_3$); 2.75-2.85 (*m*, 3H, H_6 and 2xNHC*H_2*); 0.88 (*d*, *J* = 6.5, 3H, C*H_3*) **ESI-MS** (MeOH): positive ion mode: 1269 (100, [*M*+H]$^+$); 1291 (60, [*M*+Na]$^+$)

mono-6-deoxy-6-[N-(2,2-(S)-isopropyl-methylsulfonamidoethyl)]-6-amino-β-cyclodextrin (188) Following general Procedure B, 59 mg **68** (0.04 mmol, 1.0 eq.) and 66 mg **185** (0.37 mmol, 8.0 eq.) were dissolved in 0.75 ml DMSO. The mixture was stirred in the microwave for 2 h at 80°C (90 Watt). After one precipitation in acetone, the crude product was purified over IRA-68 ion exchange resin using water as eluent. One obtained 27 mg of pure **188** (47% yield) as white crystals.



TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.20; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O): 5.00-5.10 (*m*, 7H, 7xH_1); 3.50-4.20 (*m*, 41H, 7xH_2, 7xH_3, 6xH_4, 7xH_5 and 14xH_6); 3.41-3.47 (*m*, 1H, H_4); 3.16 (*s*, 3H, $MsCH_3$); 3.01-3.15 (*broad*, 2H, *CH*Ms); 2.10-2.20 (*m*, 2H, NHC*H_2*); 1.82-1.91 (*m*, 1H, C*H*(CH_3)$_2$); 0.90-1.01 (*m*, 6H, 2xC*H_3*); **ESI-MS** (MeOH): positive ion mode: 1295 (100, [*M*+H]$^+$); negative mode: 1297 (100, M$^-$)

mono-6-deoxy-6-[N-(2,2-(S)-isopropyl-trifluoromethylsulfonamidoethyl)]-6-amino-β-cyclodextrin (196) Following general Procedure B, 59 mg **68** (0.05 mmol, 1.0 eq.), 222 mg **195** (0.95 mmol, 20 eq.) and 0.18 ml ethyldiisopropylamine (1.04 mmol, 22 eq.) were dissolved in 0.75 ml DMSO. The mixture was stirred in the microwave for 3 h at 85°C (100 Watt). After two precipitations in acetone, one obtained 34 mg of pure **196** (53% yield) as white crystals.



TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.17; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O): 5.03-5.10 (*m*, 7H, 7xH_1); 4.17-4.26 (*m*, 1H, H_5); 3.70-4.05 (*m*, 25H, 7xH_3, 6xH_5 and 12xH_6); 3.52-3.69 (*m*, 14H, 7xH_2, 6xH_4 and 1xH_6); 3.44-3.51 (*m*, 1H, H_4); 3.20-3.27 (*m*, 2H, H_6 and *CH*NHMs); 3.04-3.12 (*m*, 1H, NHC*H*); 2.87-2.93 (*m*, 1H, NHC*H*); 1.70-1.77 (*m*, 1H, C*H*(CH_3)$_2$); 0.86-0.97 (*m*, 6H,

2xCH_3); **ESI-MS** (MeOH): positive ion mode: 1373 (100, [*M*+Na]$^+$); negative mode: 1349 (100, M$^-$)

5.2.3.3 Linkage of α-Pycolyl Amines

mono-6-deoxy-6-[N-(N-2-pyridyl)-methyl]-6-amino-β-cyclodextrin (β-CD-ampy) (198) Following general Procedure A, 170 mg **68** (0.14 mmol, 1.0 eq.) and 0.46 ml pyridin-2-ylmethanamine **197** (4.37 mmol, 30 eq.) were stirred for 12 h. After three precipitations in acetone, one obtained 80 mg of pure **198** (48% yield) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.20; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O): 8.49 (*d*, *J* = 4.6, 1H, $H6_{py}$); 7.87 (*dxt*, *J* = 1.8, 7.8, 1H, $H4_{py}$); 7.44 (*d*, *J* = 7.8, 1H, $H3_{py}$); 7.41 (*dxd*, *J* = 5.2, 7.2, 1H, $H5_{py}$); 5.04-5.12 (*m*, 7H, 7xH_1); 3.74-4.02 (*m*, 28H, 7xH_3, 7xH_5,12xH_6 and NHCH_2); 3.54-3.70 (*m*, 13H, 7xH_2 and 6xH_4); 3.36-3.42 (*m*, 1H, H_4); 3.00-3.07 (*m*, 1H, H_6); 2.82-2.91 (*m*, 1H, H_6); **ESI-MS** (MeOH): positive ion mode: 1225 (100, [*M*+H]$^+$)

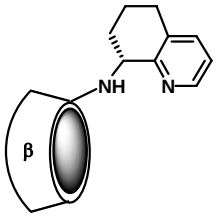
mono-6-deoxy-6-[N-(1-(R)-methyl-pyridylmethyl]-6-amino-β-cyclodextrin (208) Following general Procedure A, 80 mg **68** (0.06 mmol, 1.0 eq.) and 236 mg **202** (1.93 mmol, 30 eq.) were stirred in 0.2 ml DMF for 12 h at 70°C. After three precipitations in acetone, one obtained 51 mg of pure **208** (64% yield) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.22; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O): 8.45 (*d*, *J* = 4.7, 1H, $H6_{py}$); 7.80 (*dxt*, *J* = 1.5, 7.9, 1H, $H4_{py}$); 7.33-7.39 (*m*, 2H, $H3_{py}$ and $H5_{py}$); 4.95-5.05 (*m*, 7H, 7xH_1); 3.40-3.98 (*m*, 40H, 7xH_2, 7xH_3, 6xH_4, 7xH_5, 12xH_6 and NHC*H*); 3.22-3.30 (*m*, 1H, H_4); 2.70-2.90 (*broad*, 2H, 2xH_6); 1.31 (*d*, *J* = 5.9, 3H, CH_3); **ESI-MS** (MeOH): positive ion mode: 1239 (66, [*M*+H]$^+$); 1261 (100, [*M*+Na]$^+$)

mono-6-deoxy-6-[N-(1-(S)-methyl-pyridylmethyl]-6-amino-β-cyclodextrin (209) Following general Procedure A, 52 mg **68** (0.04 mmol, 1.0 eq.) and 151 mg **201** (1.23 mmol, 30 eq.) were stirred in 0.2 ml DMF for 12 h at 70°C. After three precipitations in acetone, one obtained 21 mg of pure **209** (41% yield) as white crystals.

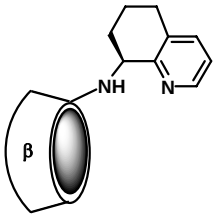
TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.22; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O): 8.50 (*d*, *J* = 4.7, 1H, $H6_{py}$); 7.90 (*dxt*, *J* = 1.7, 7.8, 1H, $H4_{py}$); 7.33-7.41 (*m*, 2H, $H3_{py}$ and $H5_{py}$); 4.92-5.12 (*m*, 7H, 7xH_1); 3.40-4.05 (*m*, 39H, 7xH_2, 7xH_3, 6xH_4, 6xH_5, 12xH_6 and NHC*H*); 3.22-3.37 (*m*, 2H, H_4 and H_5); 2.50-2.90 (*broad*, 2H, 2xH_6); 1.33 (*d*, *J* = 6.0, 3H, CH_3); **ESI-MS** (MeOH): positive ion mode: 1261 (100, [*M*+Na]$^+$); negative ion mode: 1237 (100, *M*$^-$)

mono-6-deoxy-6-[N-(1-(R)-5,6,7,8-tetrahydroquinolin-8-amine)]-6-deoxy-β-cyclodextrin (210) Following general Procedure A, 56 mg **68** (0.05 mmol, 1.0 eq.) and 200 mg **206** (1.36 mmol, 30 eq.) were stirred in 0.2 ml DMF for 12 h at 70°C. After three precipitations in acetone, one obtained 22 mg of pure **210** (39% yield) as white crystals.



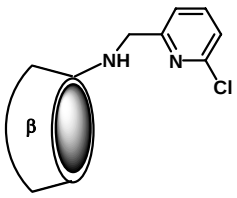
TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.22; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O): 8.23 (*d*, *J* = 4.9, 1H, $H6_{py}$); 7.48 (*d*, *J* = 7.9, 1H, $H4_{py}$); 7.14 (*dxd*, *J* = 4.9, 7.9, 1H, $H5_{py}$); 4.97-5.09 (*m*, 7H, 7xH_1); 3.36-3.99 (*m*, 39H, 7xH_2, 7xH_3, 6xH_4, 6xH_5, 12xH_6 and NHC*H*); 3.27-3.33 (*m*, 1H, H_4); 3.02-3.08 (*d*, *J* = 11.4, 1H, H_5); 2.60-2.71 (*m*, 3H, 2xH_6 and NHCHCH$_2$CH$_2$C*H*$_2$C$_{ar}$); 2.41-2.48 (*m*, 1H, NHCHCH$_2$CH$_2$C*H*$_2$C$_{ar}$); 1.98-2.07 (*m*, 1H, NHCHC*H*$_2$CH$_2$CH$_2$C$_{ar}$); 1.75-1.85 (*m*, 1H, NHCHC*H*$_2$CH$_2$CH$_2$C$_{ar}$); 1.98-2.07 (*m*, 2H, NHCHCH$_2$C*H*$_2$CH$_2$C$_{ar}$); **ESI-MS** (MeOH): positive ion mode: 1265 (100, [*M*+H]$^+$); 1287 (100, [*M*+Na]$^+$); negative ion mode: 1263 (100, *M*$^-$)

mono-6-deoxy-6-[N-(1-(S)-5,6,7,8-tetrahydroquinolin-8-amine)]-6-deoxy-β-cyclodextrin (211) Following general Procedure A, 67 mg **68** (0.05 mmol, 1.0 eq.) and 238 mg **207** (1.62 mmol, 30 eq.) were stirred in 0.2 ml DMF for 12 h at 70°C. After three precipitations in acetone, one obtained 35 mg of pure **211** (51% yield) as white crystals.



TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.22; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O): 8.39 (*d*, *J* = 4.6, 1H, $H6_{py}$); 7.64 (*m*, 1H, $H4_{py}$); 7.33 (*dxd*, *J* = 4.9, 7.9, 1H, $H5_{py}$); 4.99-5.11 (*m*, 7H, 7xH_1); 3.50-4.02 (*m*, 39H, 7xH_2, 7xH_3, 6xH_4, 6xH_5, 12xH_6 and NHC*H*); 3.39-3.48 (*m*, 1H, H_4); 3.20-3.29 (*m*, 1H, H_5); 2.65-3.00 (*m*, 4H, 2xH_6 and NHCHCH$_2$CH$_2$C*H*$_2$C$_{ar}$); 2.13-2.22 (*m*, 1H, NHCHC*H*$_2$CH$_2$CH$_2$C$_{ar}$); 1.89-2.01 (*m*, 1H, NHCHC*H*$_2$CH$_2$CH$_2$C$_{ar}$); 1.70-1.85 (*m*, 2H, NHCHCH$_2$C*H*$_2$CH$_2$C$_{ar}$); **ESI-MS** (MeOH): positive ion mode: 1265 (100, [*M*+H]$^+$)

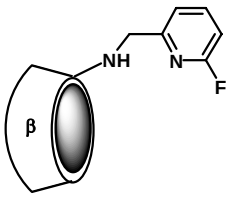
mono-6-deoxy-6-[N-(3-chloro-N-2-pyridyl)-methyl]-6-amino-β-cyclodextrin (216)



Following general Procedure A, 75 mg **68** (0.06 mmol, 1.0 eq.) and 258 mg **212** (1.81 mmol, 30 eq.) were stirred in 0.2 ml DMF for 12 h at 70°C. After three precipitations in acetone, one obtained 35 mg of pure **216** (51% yield) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.23; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O): 7.87 (*t*, *J* = 7.9, 1H, $H4_{py}$); 7.37-7.42 (*m*, 2H, $H3_{py}$ and $H5_{py}$); 4.95-5.10 (*m*, 7H, 7xH_1); 3.45-4.10 (*m*, 40H, 7xH_2, 7xH_3, 6xH_4, 6xH_5, 12xH_6 and NHCH_2); 3.32-3.39 (*m*, 2H, H_4 and H_5); 2.80-3.13 (*broad*, 2H, 2xH_6); **ESI-MS** (MeOH): positive ion mode: 1259 (18, $[M+Na]^+$); 1281 (100, $[M+Na]^+$);

mono-6-deoxy-6-[N-(3-fluoro-N-2-pyridyl)-methyl]-6-amino-β-cyclodextrin (217)

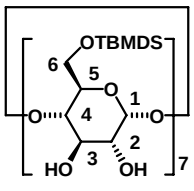


Following general Procedure A, 103 mg **68** (0.08 mmol, 1.0 eq.) and 260 mg **215** (2.06 mmol, 25 eq.) were stirred in 0.5 ml DMF for 12 h at 70°C. After one precipitation in acetone, the crude product was purified by reversed phase chromatography using water as eluent. One obtained 25 mg of pure **217** (25% yield) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O 7:7:5:4): R_f = 0.21; **mp**: decomposition >275°C; **^{1}H-NMR** (500 MHz, D_2O): 8.03 (*dxd*, *J* = 7.9, 8.0, 1H, $H4_{py}$); 7.39 (*dxd*, *J* = 1.9, 7.7, 1H, $H3_{py}$); 7.14 (*dxd*, *J* = 1.6, 8.2, 1H, $H5_{py}$); 5.00-5.14 (*m*, 7H, 7xH_1); 3.48-4.02 (*m*, 42H, 7xH_2, 7xH_3, 6xH_4, 6xH_5, 14xH_6 and NHCH_2); 3.39-3.45 (*m*, 2H, H_4 and H_5); **ESI-MS** (MeOH): positive ion mode: 645.5 (81, $[M+Na]^{2+}$); 1243 (67, $[M+H]^+$); 1265 (67, $[M+Na]^+$); negative mode: 620 (75, M^{2-}); 1241 (100 M^-)

5.2.4 Synthesis of Cyclodextrin modified on Secondary Face[65]

heptakis(6-*O-tert.*-butyldimethylsilyl)-β-CD (218) To a solution of dry β-CD **52**

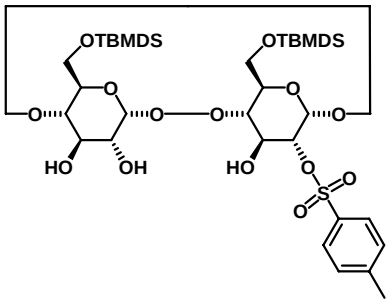


(1.00 g, 0.88 mmol) in dry pyridine (20 ml) was added the solution of TBDMSCl (1.19 g, 7.50 mmol) in 10 ml pyridine dropwise over a period of 90 minutes at 0°C. The reaction mixture was stirred at room temperature for 20 h and then poured into ice-water and stirred vigorously for 10 minutes. The resulting precipitate was filtered, washed with ice-water and dissolved in ethyl acetate. The organic solution was washed with 1M HCl,

saturated $NaHCO_3$, brine and dried over Na_2SO_4. The resulting crude product was purified by column chromatography (SiO_2, EtOAc/EtOH/H_2O = 50:4:2) yielding 1.31 g **218** (77% yield) as a white solid.

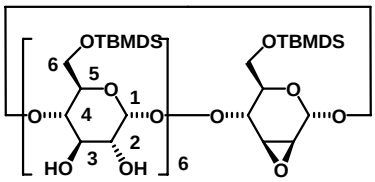
TLC (SiO_2, EtOAc/EtOH/H_2O = 50:7:4): R_f = 0.38; **^{1}H-NMR** (400 MHz, Toluene-D_8): 7.25 (*s*, 7H, C(3)-O*H*), 5.83 (*s*, 7H, C(2)-O*H*), 4.93 (*d*, *J* = 3.3, 7H, C(1)-H), 4.31 (*t*, *J* = 9.1, 7H, C(3)-H), 4.07 (*dxd*, *J* = 11.0, 3.0, 7H, C(6)-H), 3.88 (*d*, *J* = 11, 7H, C(6)-H), 3.78 (*d*, *J* = 9.5, 7H, C(5)-H), 3.72 (*dxd*, *J* = 9.6, 3.5, 7H, C(2)-H), 3.63 (*t*, *J* = 9.1, 7H, C(4)-H), 1.02 (*s*, 63H, C*H*$_3$C), 0.2-0.18 (42H, C*H*$_3$Si); **^{13}C-NMR** (100 MHz, Toluene-D_8): 102.8 (C(1)), 82.69 (C(4)), 74.36 (C(2)), 74.13 (C(3)), 73.02 (C(5)), 62.49 (C(6)), 26.26 (*C*H$_3$C), 18.71 (CH$_3$*C*), -4.66 (*C*H$_3$Si), -4.84 (*C*H$_3$Si); **ESI-MS** (CH_2Cl_2/MeOH): positive ion mode: 989.7 (67, [*M*+2Na]$^{2+}$); 1956.1 (100, [*M*+Na]$^+$)

mono(2-*O*-tosyl) heptakis(6-*O*-*tert.*-butyldimethylsilyl)-β-CD (71) 5.50 g **218** (2.84 mmol, 1.0 eq.) were dissolved in 35 ml THF. After addition of 114 mg NaH (2.84 mmol, 1.0 eq., 60% suspension in oil), the mixture was stirred at 50°C for 2 h. 635 mg 1-tosyl-1,2,4-triazole (2.84 mmol, 1.0 eq.) dissolved in 20 ml THF were added over a period of 4 h at r.t. The mixture was stirred for 12 h at r.t. THF was removed under reduced pressure and the residue dissolved in EtOAc. The organic phase was washed with water, 1M HCl, brine, saturated $NaHCO_3$, and dried over Na_2SO_4. The resulting crude product was purified by column chromatography (SiO_2, EtOAc/EtOH/H_2O = 50:5:1.5) yielding 1.72 g **71** (29% yield) as a white solid.



TLC (SiO_2, EtOAc/EtOH/H_2O = 50:7:4): R_f = 0.45; **^{1}H-NMR** (500 MHz, Toluene-D_8): 8.18 (*d*, *J* = 10.1, 2H, H_{ar}); 7.08-7.18 (2H, H_{ar} hidden by solvent); 6.98-7.06 (*s*, 1H, C(3)-O*H*); 6.84 (*s*, 1H, C(3)-O*H*); 6.68 (*s*, 1H, C(3)-O*H*); 6.50 (*s*, 1H, C(3)-O*H*); 5.92 (*s*, 1H, C(2)-O*H*); 5.83 (*s*, 1H, C(2)-O*H*); 5.66 (*s*, 1H, C(2)-O*H*); 5.59 (broad, 1H, C(2)-O*H*); (*m*, 2H, C(2)-O*H*); 5.42 (*s*, 1H, C(2)-O*H*); 5.08 (*s*, 1H, H_1); 4.94 (*s*, 5H, H_1); 4.80 (*s*, 1H, H_1); 4.55-4.67 (*m*, 3H); 4.47-4.54 (*m*, 1H, H_2); 3.59-4.41 (m, 43H); 3.38-3.50 (*broad*, 1H, H_2); 3.09 (*t*, *J* = 6.8, 1H, H_4); 2.16 (*s*, 3H, CH_3); 0.91-1.15 (*m*, 63H, C*H*$_3$C), 0.11-0.29 (*m*, 42H, C*H*$_3$Si); **ESI-MS** (CH_2Cl_2/MeOH): positive ion mode: 1067 (14, [*M*+2Na]$^{2+}$); 2110 (100, [*M*+Na]$^+$); negative ion mode: 2087 (100, *M*$^-$)

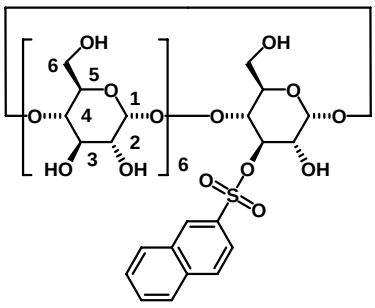
mono-manno-(2^A,3^A-anhydro) heptakis(6-*O-tert.*-butyldimethylsilyl)-β-CD (70)



2.20 **71** (1.05 mmol, 1.0 eq.) and 79 mg sodium ethylate (1.16 mmol, 1.1 eq.) were refluxed in 10 ml EtOH for 16 h. The reaction mixture was poured into 25 ml icewater and filtered. The resulting crude product was purified by column chromatography (SiO_2, ethyl acetate/EtOH/H_2O = 50:4:2) yielding 1.72 g **70** (83% yield) as a white solid.

TLC (SiO_2, EtOAc/EtOH/H_2O = 50:4:2): R_f = 0.38; **^{1}H-NMR** (400 MHz, $CDCl_3$): 6.61-6.63 (*m*, 2H); 6.57 (*s*, 1H); 6.32 (*s*, 1H); 6.24 (*s*, 1H); 5.30 (*s*, 1H); 5.25 (*s*, 1H); 5.20 (*s*, 2H, H_1); 5.17 (*s*, 1H); 4.97-4.99 (*m*, 2H); 4.89-4.92 (*m*, 5H); 4.37 (d, *J* = 9.9, 1H, H_6); 3.51-4.00 (*m*, 42 H); 3.37 (*d*, *J* = 3.3, 1H, H_3); 3.19 (*d*, *J* = 3.3, 1H, H_2); 0.87 (*m*, 63H, C*H*$_3$C), 0.03 (*m*, 42H, C*H*$_3$Si); **^{13}C-NMR** (126 MHz, $CDCl_3$): 102.3, 102.3, 102.1, 102.0, 101.4, 99.4, 96.3, 81.9, 81.5, 81.4, 80.8, 78.4, 77.4, 73.8, 73.7, 73.7, 73.6, 73.6, 73.5, 72.9, 72.7, 72.6, 72.6, 72.4, 72.3, 72.0, 69.9, 68.6, 64.0, 62.0, 61.7, 61.6, 61.6, 61.4, 53.2, 49.2, 26.0, 18.4-18.6, (-5.0)-(-4.9); **ESI-MS** (CH_2Cl_2/MeOH): positive ion mode: 1938 (100, [*M*+Na]$^+$); negative ion mode: 1915 (100, *M*$^-$)

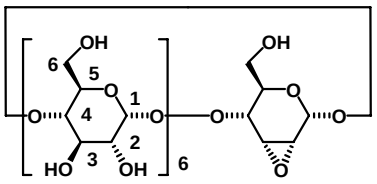
mono-3-(*O*-naphtyl)-β-CD (227) 3.50 g β-Cyclodextrin **52** (3.10 mmol, 1.0 eq.) were



dissolved in 50 ml 30% aqueous acetonitrile and adjusted to pH 12 with 2M NaOH. 3.5 g β-naphtalenesulfonyl chloride **226** (15.43 mmol, 5.0 eq.) were added and stirred at 40°C till the pH value dropped down to 8. After filtration, the filtrate was purified by RP-18 chromatography (gradient: 150 ml water only to 20% acetonitril), yielding 250 mg **227** (yield 6%) as a white powder.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O = 7:7:5:4): R_f = 0.56; **^{1}H-NMR** (500 MHz, D_2O): 8.59 (*s*, 1H); 8.20 (*d*, *J* = 9.0, 1H); 8.10 (*m*, 1H); 8.01 (*d*, *J* = 7.6, 1H); 7.95 (*d*, *J* = 7.6, 1H); 7.70-7.81 (*m*, 2H); 4.88-5.11 (*m*, 7H, 7xH_1); 4.02-4.17 (*m*, 2H); 3.62-4.00 (*m*, 38H); 3.27-3.40 (*m*, 2H); **ESI-MS** (MeOH): positive ion mode: 1347 (100, [*M*+Na]$^+$); negative ion mode: 1323 (100, *M*$^-$)

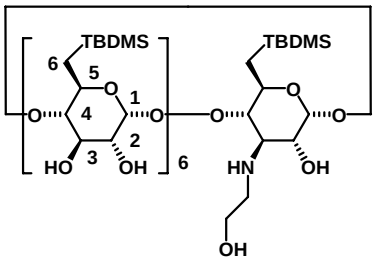
mono-allo-(2^A,3^A-anhydro) heptakis(6-*O-tert.*-butyldimethylsilyl)-β-CD (228) 250 mg **227** (0.19 mmol) were stirred in 25 ml water containing 62 mg K_2CO_3 for 4 h at r.t. The solution was neutralized using 1M HCl and purified by RP-18 chromatography (gradient: 150 ml water only to 5% acetonitril), yielding 193 mg **228** (yield 93%) as a white powder.



TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O = 7:7:5:4): R_f = 0.12; **^{1}H-NMR** (500 MHz, D_2O): 5.33 (*d*, *J* =3.4, 1H, H_1); 5.01-5.10 (*m*, 6H, 6xH_1); 4.09-4.14 (*dxd*, *J* = 1.9, 9.4, 1H); 3.55-4.02 (*m*, 41H); **ESI-MS** (MeOH): positive ion mode: 1139 (100, [*M*+Na]$^+$); negative ion mode: 1115 (100, *M*$^-$)

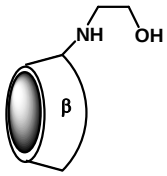
5.2.4.1 Linkage of Amino alcohols, Monotosylated Diamines, α-Pycolyl Amines and Alkyl Amines

mono-3-deoxy-3-[N-2-hydroxyethyl] heptakis(6-O-*tert.*-butyldimethylsilyl)-3-amino-β-CD (219). 145 mg **70** (0.08 mmol, 1.0 eq.) and 0.11 ml aminoethanol **79** (1.98 mmol, 25 eq.) were refluxed for 3 h in 1.0 ml ethanol. The solvent was removed at reduced pressure, the residue dissolved in DCM and washed with water. The organic phase was dried over Na_2SO_4 and purified by column chromatography (SiO_2, EtOAc/EtOH/H_2O = 50:7:4), yielding 90 mg **219** (yield 60%) as white crystals.



TLC (SiO_2, EtOAc/EtOH/H_2O = 50:7:4 R_f = 0.21; **^{1}H-NMR** (500 MHz, $CDCl_3$): 4.86-4.94 (*m*, 5H, 5xH_1); 4.82 (*d*, *J* = 3.6, 1H, H_1); 4.50 (*d*, *J* = 7.3, 1H, H_1); 3.43-4.13 (*m*, 43 H); 2.70-2.78 (*m*, 2H, NHCH_2 and H_3); 2.67 (*m*, 1H, NHCH_2); 0.88 (*m*, 63H, CH_3C), 0.01 (*m*, 42H, CH_3Si); **^{13}C-NMR** (126 MHz, $CDCl_3$): 105.7, 103.0, 102.7, 102.5, 102.1, 101.6, 82.2, 81.7, 81.5, 81.4, 80.9, 80.5, 78.4, 74.6, 74.3, 74.1, 74.0, 73.9, 73.8, 73.7, 72.6, 72.5, 72.0, 71.5, 62.0, 61.8, 61.7, 61.6, 60.9, 60.6, 26.2, 26.1, 26.0, 25.9, 18.5, 18.4, 18.1, -4.8, -4.9, -5.0, -5.1, -5.3; **ESI-MS** (MeOH): positive ion mode: 1978 (68, [*M*+H]$^+$); 1988.5 (48, [2*M*+Na]$^+$); 2000 (100, [*M*+Na]$^+$); negative ion mode: 1946 (100, *M*$^-$)

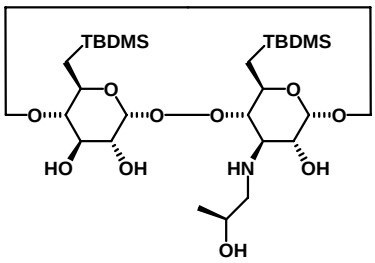
mono-3-deoxy-3-[N-2-hydroxyethyl]-3-amino-β-cyclodextrin (β-CD-AE-2F) (220)



77 mg **219** (0.04 mmol, 1.0 eq.) and 51 mg ammonium fluoride (1.38 mmol, 35 eq.) were refluxed in 2 ml MeOH for 2 h. After removal of the solvent, the crude product was purified by RP-18 chromatography (gradient: water only to 25% MeOH), yielding 34 mg **220** (yield 73%) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O = 7:7:5:4): R_f = 0.21; **^{1}H-NMR** (500 MHz, D_2O): 5.18 (*d*, *J* = 4.0, 1H, H_1); 5.15 (*d*, *J* = 3.9, 1H, H_1); 5.11 (*d*, *J* = 3.9, 1H, H_1); 5.01-5.07 (*m*, 4H, 4xH_1); 4.34 (*m*, 1H, H_4); 4.30 (*m*, 1H, H_5); 3.50-4.02 (*m*, 42H, 7xH_2, 7xH_3, 6xH_4, 6xH_5, 14xH_6 and $NHCH_2C\mathit{H}_2OH$); 3.30-3.42 (*m*, 2H, $NHC\mathit{H}_2CH_2OH$); **ESI-MS** (MeOH): positive ion mode: 1178 (100, $[M+H]^+$)

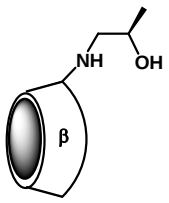
mono-3-deoxy-3-[N-(2,2-(R)-methyl-hydroxyethyl)] heptakis(6-O-*tert*.-butyldimethylsilyl)-3-amino-β-CD (270)



150 mg **70** (0.08 mmol, 1.0 eq.) and 29 mg (R)-1-aminopropan-2-ol (0.40 mmol, 5 eq.) were refluxed for 3 h in 1.0 ml ethanol. The solvent was removed at reduced pressure, the residue dissolved in DCM and washed with water. The organic phase was dried over Na_2SO_4 and purified by column chromatography (SiO_2, EtOAc/EtOH/H_2O = 6:1:0.6), yielding 117 mg **270** (yield 75%) as white crystals.

TLC (SiO_2, EtOAc/EtOH/H_2O = 50:7:4) R_f = 0.13; **^{1}H-NMR** (500 MHz, $CDCl_3$): 4.85-4.94 (*m*, 5H, 5xH_1); 4.83 (*d*, *J* = 3.9, 1H, H_1); 4.49 (*d*, *J* = 7.3, 1H, H_1); 3.53-4.18 (*m*, 39 H); 3.38-3.51 (*m*, 2 H); 2.85-2.92 (*m*, 1H); 2.45-2.65 (*m*, 3H, H_3 and 2x$NHC\mathit{H}_2$); 1.12 (*d*, *J* = 6.2, 3H, CH_3); 0.80-0.90 (*m*, 63H, $C\mathit{H}_3C$), 0.00-0.10 (*m*, 42H, $C\mathit{H}_3Si$); **^{13}C-NMR** (126 MHz, $CDCl_3$): 105.6, 103.1, 102.9, 102.6, 102.3, 101.8, 101.2, 83.2, 81.9, 81.7, 81.5, 80.8, 80.6, 80.2, 74.4, 74.3, 74.0, 73.7, 73.4, 71.8, 71.5, 65.3, 62.2, 62.0, 61.8, 61.7, 61.6, 59.8, 55.6, 25.9-26.2, 18.1-20.6, (-5.0)-(-4.8) **ESI-MS** (MeOH): positive ion mode: 2014 (100, $[M+Na]^+$); negative ion mode: 1990 (100, M^-)

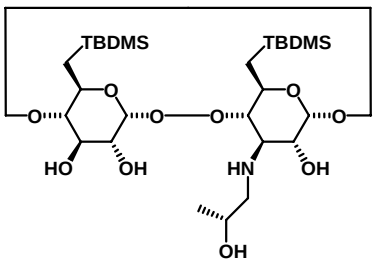
mono-3-deoxy-3-[N-(2,2-(R)-methyl-hydroxyethyl)]-3-amino-β-CD (224) 104 mg



270 (0.05 mmol, 1.0 eq.) and 0.47 ml of 1M TBAF in THF (0.47 mmol, 9.0 eq.) were refluxed in 2 ml THF for 4 h. After removal of the solvent, the crude product was dissolved in 2 ml water and extracted 5 times with chloroform. The aqueous phase was purified by CG-50 ion exchange chromatography (water), yielding 26 mg **224** (yield 56%) as white crystals.

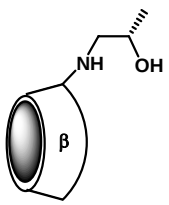
TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O = 7:7:5:4): R_f = 0.20; **^{1}H-NMR** (500 MHz, D_2O): 5.19 (*d*, *J* = 4.1, 1H, H_1); 5.16 (*d*, *J* = 3.8, 1H, H_1); 5.12 (*d*, *J* = 3.9, 1H, H_1); 5.02-5.10 (*m*, 4H, 4xH_1); 4.36 (*m*, 1H, H_4); 4.30 (*m*, 1H, H_5); 4.15 (*m*, 1H, C*H*(CH_3)OH); 3.51-4.05 (*m*, 40H, 7xH_2, 7xH_3, 6xH_4, 6xH_5, 14xH_6); 3.38-3.44 (*m*, 1H, NHC*H*$_2$CH(CH_3)OH); 3.06-3.16 (*m*, 1H, NHC*H*$_2$CH(CH_3)OH); **ESI-MS** (MeOH): positive ion mode: 1192 (100, [*M*+H]$^+$)

mono-3-deoxy-3-[N-(2,2-(S)-methyl-hydroxyethyl)] heptakis(6-O-*tert*.-butyldimethylsilyl)-3-amino-β-CD (271) 175 mg **70** (0.09 mmol, 1.0 eq.) and 69 mg (R)-1-aminopropan-2-ol (0.90 mmol, 10 eq.) were refluxed for 3 h in 1.0 ml ethanol. The solvent was removed at reduced pressure, the residue dissolved in DCM and washed with water. The organic phase was dried over Na_2SO_4 and purified by column chromatography (SiO_2, EtOAc/EtOH/H_2O = 6:1:0.6), yielding 140 mg **271** (yield 77%) as white crystals.



TLC (SiO_2, EtOAc/EtOH/H_2O = 50:7:4) R_f = 0.12; **^{1}H-NMR** (500 MHz, $CDCl_3$): 4.85-4.95 (*m*, 5H, 5xH_1); 4.84 (*d*, *J* = 3.8, 1H, H_1); 4.50 (*d*, *J* = 7.2, 1H, H_1); 3.54-4.18 (*m*, 39 H); 3.38-3.51 (*m*, 2H); 2.86-2.94 (*m*, 1H); 2.47-2.66 (*m*, 3H, H_3 and 2xNHC*H*$_2$); 1.12 (*d*, *J* = 6.3, 3H, CH_3); 0.82-0.90 (*m*, 63H, C*H*$_3$C), 0.01-0.11 (*m*, 42H, C*H*$_3$Si); **ESI-MS** (MeOH): positive ion mode: 2014 (100, [*M*+Na]$^+$); negative ion mode: 1990 (100, *M*$^-$)

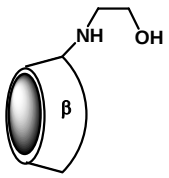
mono-3-deoxy-3-[N-(2,2-(S)-methyl-hydroxyethyl)]-3-amino-β-CD (223) 128 mg



271 (0.06 mmol, 1.0 eq.) and 0.64 ml of 1M TBAF in THF (0.64 mmol, 10 eq.) were refluxed in 2 ml THF for 4 h. After removal of the solvent, the crude product was dissolved in 2 ml water and extracted 5 times with chloroform. The aqueous phase was purified by CG-50 ion

exchange chromatography (water), yielding 42 mg **223** (yield 55%) as white crystals. **TLC** (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O = 7:7:5:4): R_f = 0.20; **^{1}H-NMR** (500 MHz, D_2O): 5.20 (*d*, *J* = 4.1, 1H, H_1); 5.17 (*d*, *J* = 3.8, 1H, H_1); 5.13 (*d*, *J* = 3.9, 1H, H_1); 5.04-5.11 (*m*, 4H, 4xH_1); 4.38 (*m*, 1H, H_4); 4.33 (*m*, 1H, H_5); 4.17 (*m*, 1H, C*H*(CH_3)OH); 3.53-4.07 (*m*, 40H, 7xH_2, 7xH_3, 6xH_4, 6xH_5, 14xH_6); 3.40-3.45 (*m*, 1H, NHC*H*$_2$CH(CH_3)OH); 3.08-3.17 (*m*, 1H, NHC*H*$_2$CH(CH_3)OH); **ESI-MS** (MeOH): positive ion mode: 1192 (100, [*M*+H]$^+$); positive ion mode: 1190 (100, *M*$^-$)

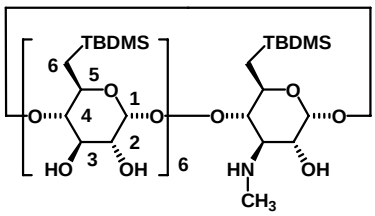
mono-3-deoxy-3-[N-2-hydroxyethyl]-3-amino-β-cyclodextrin (all glucose) (225)



100 mg **228** (0.09 mmol, 1.0 eq.) and 0.1 ml aminoethanol (1.80 mmol, 20 eq.) were stirred in 1 ml DMF for 12 h at 85°C. After removal of the solvent, the crude product was precipitated in acetone, filtarted and finally purified by RP-18 chromatography (2%-gradient: water only to 35% MeOH), yielding 34 mg **228** (yield 34%) as white crystals.

TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O = 7:7:5:4): R_f = 0.17; **ESI-MS** (MeOH): positive ion mode: 1178 (100, [*M*+H]$^+$); positive ion mode: 1176 (100, *M*$^-$)

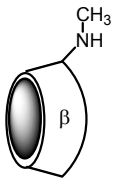
mono-3-deoxy-3-[N-methyl] heptakis(6-O-*tert*.-butyldimethylsilyl)-3-amino-β-CD (272)



118 mg **70** (0.06 mmol, 1.0 eq.) and 0.23 ml of 8M methyl amine in EtOH (1.85 mmol, 30 eq.) were stirred in 0.75 ml EtOH in the microwave for 6 h at 82 °C. After removal of solvent and excess methyl amine, the residue was dissolved in DCM and washed with water. The organic phase was dried over Na_2SO_4 and purified by column chromatography (SiO_2, EtOAc/EtOH/H_2O/Et_3N = 50:7:4:0.6), yielding 77 mg **272** (yield 64%) as white crystals.

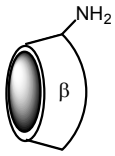
TLC (SiO_2, EtOAc/EtOH/H_2O/Et_3N = 50:7:4:0.6) R_f = 0.17; **^{1}H-NMR** (500 MHz, $CDCl_3$): 4.85-4.94 (*m*, 5H, 5xH_1); 4.81 (*d*, *J* = 3.6, 1H, H_1); 4.48 (*d*, *J* = 7.3, 1H, H_1); 3.40-4.16 (*m*, 40 H); 3.01-3.09 (*m*, 1H); 2.60-2.67 (*m*, 1H) 2.38 (*broad*, 3H, CH_3); 0.84-0.90 (*m*, 63H, C*H*$_3$C), 0.01-0.05 (*m*, 42H, C*H*$_3$Si); **ESI-MS** (MeOH): positive ion mode: 1948 (100, [*M*+H]$^+$)

mono-3-deoxy-3-[N-methyl]-3-amino-β-CD (232) 77 mg **272** (0.04 mmol, 1.0 eq.) and 51 mg ammonium fluoride (1.38 mmol, 35 eq.) were refluxed in 2 ml MeOH for 2 h. After removal of the solvent, the crude product was purified by RP-18 chromatography (gradient: water only to 25% MeOH in 30 ml fractions), yielding 34 mg **232** (yield 73%) as white crystals.



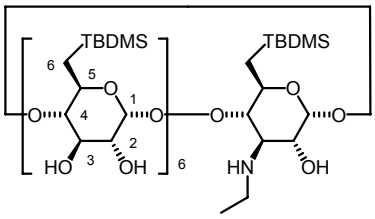
TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O = 7:7:5:4): R_f = 0.15; **^{1}H-NMR** (500 MHz, D_2O): 5.12-5.18 (*m*, 2H, 2xH_1); 5.01-5.08 (*m*, 4H, 4xH_1); 4.89 (*d*, *J* = 6.9, 1H, H_1); 4.36 (*m*, 1H, H_5); 4.17 (*m*, 1H, H_4); 3.52-4.02 (*m*, 39H, 7xH_2, 6xH_3, 6xH_4, 6xH_5, and 14xH_6); 3.02 (*broad*, 1H, H_3); 2.51 (s, 3H, CH_3); **ESI-MS** (MeOH): positive ion mode: 585.5 (32, $[M+H]^{2+}$); 1148 (100, $[M+H]^+$); 1170 (48, $[M+Na]^+$)

mono-3-deoxy-3-amino-β-CD (235) 60 mg mono-3-deoxy heptakis(6-O-*tert*.-butyldimethylsilyl)-3-amino-β-CD (0.03 mmol, 1.0 eq.) and 40 mg ammonium fluoride (1.01 mmol, 35 eq.) were refluxed in 2 ml MeOH for 2 h. After removal of the solvent, the crude product was purified by RP-18 chromatography (gradient: water only to 25% MeOH in 30 ml fractions), yielding 19 mg **235** (yield 54%) as white crystals.



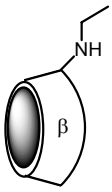
TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O = 7:7:5:4): R_f = 0.09; **^{1}H-NMR** (500 MHz, D_2O): 5.15-5.18 (*m*, 2H, 2xH_1); 5.01-5.09 (*m*, 4H, 4xH_1); 4.87 (*d*, *J* = 6.7, 1H, H_1); 4.25 (*m*, 1H, H_5); 3.51-4.01 (*m*, 40H, 7xH_2, 6xH_3, 7xH_4, 6xH_5, and 14xH_6); 3.17 (*m*, 1H, H_3); **ESI-MS** (MeOH): 1134 (51, $[M+H]^+$); 1156 (100, $[M+Na]^+$)

mono-3-deoxy-3-[N-ethyl)] heptakis(6-O-*tert*.-butyldimethylsilyl)-3-amino-β-CD (273) 62 mg **70** (0.04 mmol, 1.0 eq.) and 0.04 ml ethylamine (0.47 mmol, 15 eq.) were stirred in 1.0 ml EtOH for 12 h in microwave tube. After removal of solvent, the residue was dissolved in DCM and washed with water. The organic phase was dried over Na_2SO_4 and purified by column chromatography (SiO_2, EtOAc/EtOH/H_2O = 50:7:4), yielding 39 mg **273** (yield 48%) as white crystals.



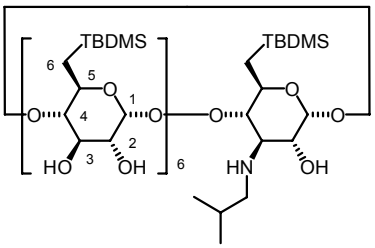
TLC (SiO_2, EtOAc/EtOH/H_2O/Et_3N = 50:7:4:0.6) R_f = 0.15; **^{1}H-NMR** (500 MHz, $CDCl_3$): 4.84-4.95 (*m*, 6H, 6xH_1); 4.58-4.63 (*broad*, 1H, H_1); 3.40-4.18 (*m*, 42 H); 2.62 (*m*, 1H); 2.46 (*q*, *J* = 7.3, 2H, NC$H_2$$CH_3$); 1.39 (*t*, *J* = 7.3, 3H, NCH_2CH_3); 0.84-0.90 (*m*, 63H, CH_3C), 0.01-0.09 (*m*, 42H, CH_3Si); **ESI-MS** (MeOH): positive ion mode: 1962 (100, $[M+H]^+$); 1984 (16, $[M+Na]^+$)

mono-3-deoxy-3-[N-ethyl)]-3-amino-β-CD (236) 39 mg **273** (0.02 mmol, 1.0 eq.) and 26 mg ammonium fluoride (0.700 mmol, 35 eq.) were refluxed in 2 ml MeOH for 2 h. After removal of the solvent, the crude product was purified by RP-18 chromatography (gradient: water only to 25% MeOH in 30 ml fractions), yielding 21 mg **236** (yield 90%) as white crystals.



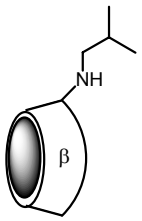
TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O = 7:7:5:4): R_f = 0.20; **^{1}H-NMR** (500 MHz, D_2O): 5.00-5.17 (*m*, 6H, 6xH_1); 5.01 (*d*, *J* = 6.7, 1H, H_1); 4.38 (*m*, 1H, H_5); 3.56-4.00 (*m*, 40H, 7xH_2, 6xH_3, 7xH_4, 6xH_5, 14xH_6); 2.98 (*m*, 1H, H3); 2.81 (*m*, 1H, NHC*H_2*CH_3); 2.65 (*m*, 1H, NHC*H_2*CH_3); 0.98 (*t*, 3H, $NHCH_2CH_3$); **ESI-MS** (MeOH): positive ion mode: 593 (98, $[M+Na]^{2+}$); 1162 (100, $[M+H]^+$); 1184 (63, $[M+Na]^+$)

mono-3-deoxy-3-[N-(2-methylpropyl)] heptakis(6-O-*tert*.-butyldimethylsilyl)-3-amino-β-CD (274) 60 mg **70** (0.03 mmol, 1.0 eq.) and 0.05 ml isobutylamine (0.47 mmol, 15 eq.) were refluxed in 1.0 ml EtOH for 12 h. After removal of solvent, the residue was dissolved in DCM and washed with water. The organic phase was dried over Na_2SO_4 and purified by column chromatography (SiO_2, EtOAc/EtOH/H_2O = 50:7:4), yielding 53 mg **274** (yield 86%) as white crystals.



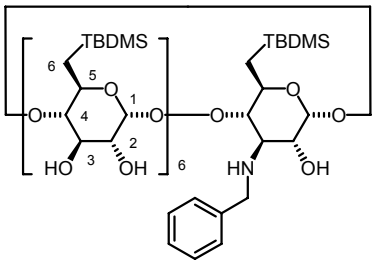
TLC (SiO_2, EtOAc/EtOH/H_2O = 50:7:4) R_f = 0.17; **^{1}H-NMR** (500 MHz, $CDCl_3$): 4.85-4.94 (*m*, 5H, 5xH_1); 4.79 (*d*, *J* = 3.7, 1H, H_1); 4.45 (*d*, *J* = 7.4, 1H, H_1); 3.48-4.20 (*m*, 42 H); 3.35-3.42 (*m*, 1H); 2.62 (*m*, 1H); 2.46 (d, *J* = 6.4, 2H, C*H_2*$CH(CH_3)_2$); 1.67 (*broad*, 1H, C*H*$(CH_3)_2$) 0.93 (*d*, *J* = 6.4, 6H, 2xCH_3); 0.84-0.90 (*m*, 63H, C*H_3*C), 0.01-0.06 (*m*, 42H, C*H_3*Si); **^{13}C-NMR** (126 MHz, $CDCl_3$): 105.5, 103.4, 103.0, 102.6, 102.4, 101.9, 101.4, 83.4, 81.9, 81.8, 81.7, 81.2, 80.9, 74.3, 74.1, 74.0, 73.9, 73.8, 73.6, 73.5, 73.4, 72.6, 72.5, 71.8, 71.7, 62.3, 61.9, 61.8, 61.6, 61.4, 58.6, 55.0, 25.9-26.8, 20.9, 20.4, 18.5, 18.4, 18.1, (-5.0)-(-4.8); **ESI-MS** (MeOH): positive ion mode: 2012 (100, $[M+Na]^+$)

mono-3-deoxy-3-[N-(2-methylpropyl)]-3-amino-β-CD (237) 53 mg **274** (0.03 mmol, 1.0 eq.) and 0.21 ml of 1M TBAF in THF (0.21 mmol, 8 eq.) were refluxed in 2 ml THF for 4 h. After removal of the solvent, the crude product was dissolved in 2 ml water and extracted 5 times with chloroform. The aqueous phase was purified by CG-50 ion exchange chromatography (water), yielding 16 mg **237** (yield 50%) as white crystals.



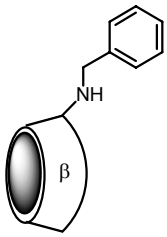
TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O = 7:7:5:4): R_f = 0.22; **^{1}H-NMR** (500 MHz, D_2O): 5.17 (*d*, *J* = 4.0, 1H, H_1); 5.14 (*d*, *J* = 3.8, 1H, H_1); 5.10 (*d*, *J* = 3.9, 1H, H_1); 5.04-5.07 (*m*, 2H, 2xH_1); 5.03 (*d*, *J* = 3.4, 1H, H_1); 5.00 (*d*, *J* = 6.7, 1H, H_1); 4.35 (*m*, 2H, H_4 and H_5); 3.53-4.01 (*m*, 40H, 7xH_2, 7xH_3, 6xH_4, 6xH_5, 14xH_6); 3.01-3.12 (*m*, 2H, NHC*H*$_2$CH(CH_3)$_2$); 2.02-2.11 (*m*, 1H, NHCH$_2$C*H*(CH_3)$_2$); 1.00 (*d*, *J* = 6.4, 6H, 2xCH_3); **ESI-MS** (MeOH): positive ion mode: 1190 (100, [*M*+H]$^+$)

mono-3-deoxy-3-[N-benzyl] heptakis(6-O-*tert*.-butyldimethylsilyl)-3-amino-β-CD (275) 60 mg **70** (0.03 mmol, 1.0 eq.) and 0.05 ml benzylamine (0.47 mmol, 15 eq.) were refluxed in 1.0 ml EtOH for 12 h. After removal of the solvent, the residue was dissolved in DCM and washed with water. The organic phase was dried over Na_2SO_4 and purified by column chromatography (SiO_2, EtOAc/EtOH/H_2O = 50:7:4), yielding 55 mg **275** (yield 88%) as white crystals.



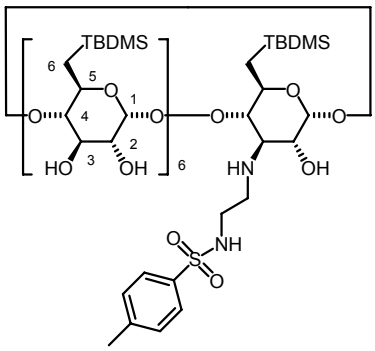
TLC (SiO_2, EtOAc/EtOH/H_2O = 50:7:4) R_f = 0.54; **^{1}H-NMR** (500 MHz, $CDCl_3$): 7.35-7.38 (*m*, 2H, H_{ar}); 7.28-7.32 (*m*, 2H, H_{ar}); 7.21-7.25 (*m*, 1H, H_{ar}); 4.78-4.88 (*m*, 6H, 6xH_1); 4.40 (*d*, *J* = 7.4, 1H, H_1); 3.38-4.15 (*m*, 43 H); 2.73 (*dxd*, J = 2.0, 10.8, 1H); 0.84-0.89 (*m*, 63H, C*H*$_3$C), 0.02-0.06 (*m*, 42H, C*H*$_3$Si); **^{13}C-NMR** (126 MHz, $CDCl_3$): 139.2, 128.7, 128.6, 127.3, 105.5, 103.4, 103.0, 102.6, 102.4, 101.9, 101.4, 83.3, 81.9, 81.8, 81.6, 81.2, 80.8, 78.1, 77.8, 74.4, 74.1, 73.9, 73.8, 73.6, 73.5, 73.4, 72.6, 72.5, 71.8, 62.2, 62.0, 61.8, 61.6, 58.9, 51.4, 26.0-26.2, 18.4-18.5, (-5.1)-(-4.8); **ESI-MS** (MeOH): positive ion mode: 2047 (100, [*M*+Na]$^+$)

mono-3-deoxy-3-[N-benzyl]-3-amino-β-CD (238) 55 mg **275** (0.03 mmol, 1.0 eq.) and 0.22 ml of 1M TBAF in THF (0.22 mmol, 8 eq.) were refluxed in 2 ml THF for 4 h. After removal of the solvent, the crude product was dissolved in 2 ml water and extracted 5 times with chloroform. The aqueous phase was purified by CG-50 ion exchange chromatography (water), yielding 12 mg **238** (yield 36%) as white crystals.



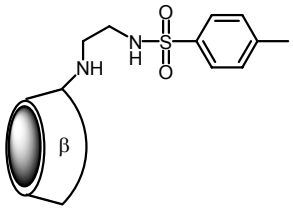
TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O = 7:7:5:4): R_f = 0.23; **^{1}H-NMR** (500 MHz, D_2O): 7.48-7.54 (*m*, 5H, H_{ar}); 5.17 (*d*, *J* = 4.2, 1H, H_1); 5.15 (*d*, *J* = 4.0, 1H, H_1); 5.12 (*d*, *J* = 3.7, 1H, H_1); 5.05-5.07 (*m*, 2H, 2xH_1); 5.03 (*d*, *J* = 3.6, 1H, H_1); 4.97 (*d*, *J* = 6.6, 1H, H_1); 4.56 (*d*, *J* = 13.0, 1H, NHCH_2Ph); 4.37 (*d*, *J* = 13.0, 1H, NHCH_2Ph); 4.30-4.36 (*d*, 2H, H_4 and H_5); 3.52-4.01 (*m*, 40H, 7xH_2, 7xH_3, 6xH_4, 6xH_5, 14xH_6); **ESI-MS** (MeOH): positive ion mode: 1225 (100, [*M*+H]$^+$)

mono-3-deoxy-3-[N-2-tosylsulfonamidoethyl] heptakis(6-O-*tert*.-butyldimethylsilyl)-3-amino-β-CD (276) 350 mg **70** (0.18 mmol, 1.0 eq.) and 391 mg **154** (1.83 mmol, 10 eq.) were refluxed in 3.0 ml EtOH for 12 h. After removal of the solvent, the residue was dissolved in DCM and washed with water. The organic phase was dried over Na_2SO_4 and purified by column chromatography (SiO_2, EtOAc/EtOH/H_2O = 50:7:4), yielding 350 mg **276** (yield 95%) as white crystals.



TLC (SiO_2, EtOAc/EtOH/H_2O = 50:8:5) R_f = 0.23; **^{1}H-NMR** (500 MHz, $CDCl_3$): 7.73 (*d*, *J* = 7.6, 2H, H_{ar}); 7.28 (*d*, *J* = 7.6, 2H, H_{ar}); 4.87-4.92 (*m*, 5H, 5xH_1); 4.72 (*broad*, 1H, H_1); 4.48 (*broad*, 1H, H_1); 3.48-4.12 (*m*, 41H); 3.42 (*t*, *J* = 9.2, 1H); 3.05 (*broad*, 2H); 2.73 (*broad*, 2H); 2.50 (*s*, 3H, ArCH_3); 0.84-0.89 (*m*, 63H, CH_3C), 0.02-0.06 (*m*, 42H, CH_3Si); **^{13}C-NMR** (126 MHz, $CDCl_3$): 129.9, 127.2, 105.3, 101.3-102.8, 80.4-82.5, 71.9-73.8, 61.5-61.9, 47.4, 43.1, 42.6, 29.7, 26.0-26.2, 21.7, 18.3-18.4, (-5.1)-(-4.8); **ESI-MS** (MeOH): positive ion mode: 2153 (100, [*M*+Na]$^+$); negative ion mode: 2129 (100, [*M*+Na]$^-$);

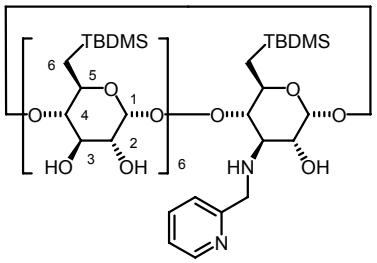
mono-3-deoxy-3-[N-2-tosylsulfonamidoethyl]-3-amino-β-CD (230) 318 mg **276**



(0.15 mmol, 1.0 eq.) and 1.49 ml of 1M TBAF in THF (1.49 mmol, 10 eq.) were refluxed in 2 ml THF for 4 h. After removal of the solvent, the crude product was dissolved in 2 ml water and extracted 5 times with chloroform. The aqueous phase was purified by CG-50 ion exchange chromatography (water), yielding 153 mg **230** (yield 77%) as white crystals.

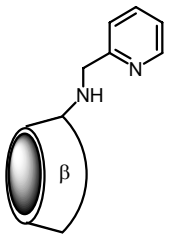
TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O = 7:7:5:4): R_f = 0.21; **^{1}H-NMR** (500 MHz, D_2O): 7.78 (*d*, *J* = 8.0, 2H, H_{ar}); 7.56 (*d*, *J* = 6.8, 2H, H_{ar}); 5.15 (*d*, *J* = 3.9, 1H, H_1); 5.11 (*d*, *J* = 3.6, 1H, H_1); 5.08 (*d*, *J* = 3.6, 1H, H_1); 5.05 (*m*, 1H, H_1); 5.03 (*d*, *J* = 3.6, 1H, H_1); 5.00 (*d*, *J* = 3.8, 1H, H_1); 4.94 (*m,*, 1H, H_1); 4.35-4.45 (*m*, 2H, H_4 and H_5); 3.35-4.13 (*m*, 42H, 7xH_2, 7xH_3, 6xH_4, 6xH_5, 14xH_6 and CH_2NHTs); 3.20-3.33 (*m*, 2H, CH_2NH); 2.51 (*s*, 3H, CH_3); **ESI-MS** (MeOH): positive ion mode: 676.5 (20, [*M*+Na]$^{2+}$); 1331 (100, [*M*+H]$^+$); 1353 (17, [*M*+Na]$^+$); negative ion mode: 664 (18, M^{2-}); 1329 (100, M^-); 1365 (29, [*M*+Na]$^-$);

mono-3-deoxy-3-[N-(N-2-pyridyl)-methyl] heptakis(6-O-*tert*.-butyldimethylsilyl)-3-amino-β-CD (277) 200 mg **70** (0.10 mmol, 1.0 eq.) and 0.11 ml pyridin-2-ylmethanamine **197** (1.04 mmol, 10 eq.) were refluxed in 2.5 ml EtOH for 12 h. After removal of the solvent, the residue was dissolved in DCM and washed with water. The organic phase was dried over Na_2SO_4 and purified by column chromatography (SiO_2, EtOAc/EtOH/H_2O = 50:8:4), yielding 60 mg **277** (yield 29%) as white crystals.



TLC (SiO_2, EtOAc/EtOH/H_2O = 50:8:4) R_f = 0.05; **ESI-MS** (MeOH): positive ion mode: 2025 (31, [*M*+H]$^+$); 2047 (100, [*M*+Na]$^+$); negative ion mode: 2023 (100, M^-);

mono-3-deoxy-3-[N-(N-2-pyridyl)-methyl]-3-amino-β-CD (231) 43 mg **277** (0.02 mmol, 1.0 eq.) and 28 mg ammonium fluoride (0.74 mmol, 35 eq.) were refluxed in 1 ml MeOH for 2 h. After removal of the solvent, the crude product was purified by RP-18 chromatography (gradient: water only to 40% MeOH in 30 ml fractions), yielding 16 mg **231** (yield 62%) as white crystals.



TLC (SiO_2, EtOAc/i-PrOH/NH_4OH/H_2O = 7:7:5:4): R_f = 0.18; **^{1}H-NMR** (500 MHz, D_2O): 8.57 (*d*, *J* = 4.4, 1H, $H6_{py}$); 7.92 (*dxt*, *J* = 1.5, 7.6, 1H, $H4_{py}$); 7.53 (*d*, *J* = 3.9, 1H, $H3_{py}$); 7.92 (*m*, 1H, $H5_{py}$); 5.12-5.17 (*m*, 2H, $2xH_1$); 5.10 (*d*, *J* = 3.8, 1H, H_1); 5.02-5.08 (*m*, 3H, $3xH_1$); 4.94 (*d*, *J* = 6.7, 1H, H_1); 4.22-4.45 (*m*, 4H); 3.53-4.04 (*m*, 38H); 3.40-3.51 (*broad*, 1H); **ESI-MS** (MeOH): positive ion mode: 1226 (100, $[M+H]^+$); 1248 (10, $[M+Na]^+$)

5.2.5 Catalysis: Conditions and Separation of Enantiomers

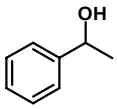
5.2.5.1 Catalysis Conditions

The ligand (0.0050 mmol) was dissolved in H_2O or H_2O/DMF (3:1, 0.25 mL), $[RuCl_2(C_6H_6)]_2$ (0.0025 mmol) was added, and the resulting mixture was stirred for 1 h at room temperature. Sodium formate (0.500 mmol) was then added, and after further stirring for 10 minutes the ketone (0.050 mmol) was injected. The reaction was then stirred for 12-72 hours at room temperature or at 50°C. Then 1.0 ml water was added, the mixture extracted three times with hexane (2 mL), the combined hexane extracts were washed with water (6 mL) and dried over Na_2SO_4. The yields were analyzed by nonchiral GC on a *Supelcowax* column. The *ee* values of the products were determined by chiral HPLC, chiral GC or ^{1}H-NMR/^{19}F-NMR spectroscopic studies of the corresponding Mosher esters. The absolute configuration of the stereocentre was determined by optical rotation or mosher correlation model.

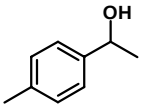
For the synthesis of racemic alcohols: see 5.2.2.1

5.2.5.2 Alcohols Separated by chiral HPLC:

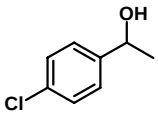
Following substrates were separated on the same Chiracel OD-H column from *Daicel*. Conditions: 0.5 ml/min, 25°C, UV 220 nm.



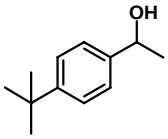
1-phenylethanol (278): HPLC (heptane/i-PrOH 95:5): 15.0 min (R-isomer); 18.0 min (S-isomer)



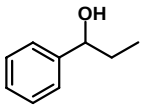
1-*p*-tolylethanol (279): HPLC (heptane/i-PrOH 97:3): 21.0 min (S-isomer); 22.6 min (R-isomer)



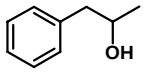
1-(4-chlorophenyl)ethanol (150): HPLC (heptane/i-PrOH 95:5): 14.6 min (S-isomer); 16.0 min (R-isomer)



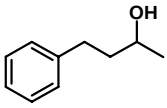
1-(4-*tert*.-butylphenyl)ethanol (280): HPLC (heptane/i-PrOH 95:5): 11.2 min (R-isomer); 12.1 min (S-isomer)



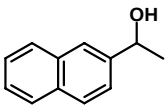
1-phenylpropan-1-ol (281): HPLC (heptane/i-PrOH 95:5): 14.8 min (R-isomer); 15.7 min (S-isomer)



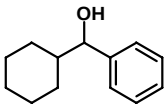
1-phenylpropan-2-ol (282): HPLC (heptane/i-PrOH 95:5): 13.2 min (S-isomer); 14.4 min (R-isomer)



4-phenylbutan-2-ol (283): HPLC (heptane/i-PrOH 97:3): 15.8 min (R-isomer); 22.3 min (S-isomer)

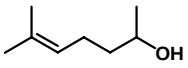


1-(naphthalen-2-yl)ethanol (284): HPLC (heptane/i-PrOH 97:3): 27.8 min (S-isomer); 30.2 min (R-isomer)

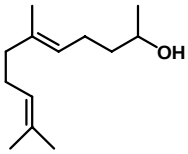


cyclohexyl(phenyl)methanol (285): HPLC (heptane/i-PrOH 97:3): 27.8 min (S-isomer); 30.2 min (R-isomer)

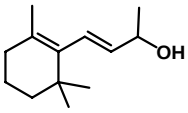
5.2.5.3 Alcohols Separated by chiral GC:



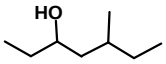
6-methylhept-5-en-2-ol (286): GC (Hydrodex 3-β-P, 25 m, 0.25 mm, from 100°C to 110°C, 0.2°C/min): 32 min (S-isomer), 35 min (R-isomer)



(E)-6,10-dimethylundeca-5,9-dien-2-ol (287): GC (Hydrodex 3-β-P, 25 m, 0.25 mm, from 100°C to 119°C, 0.2°C/min): 75 min (S-isomer), 77 min (R-isomer)



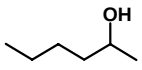
(E)-4-(2,6,6-trimethylcyclohex-1-enyl)but-3-en-2-ol (288): GC (Hydrodex 3-β-P, 25 m, 0.25 mm, from 100°C to 120°C, 0.2°C/min): 64.9 min (S-isomer); 65.7 min (R-isomer)



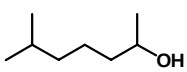
6-methylheptan-2-ol (289): (Hydrodex 3-β-P, 25 m, 0.25 mm, from 100°C to 115°C, 0.2°C/min): 67.9 min (S-isomer); 69.9 min (R-isomer)

5.2.5.4 Alcohols Separated by Esterification with Moshersubstrate:

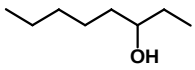
general procedure: The catalysis was quenched with water (1 ml) and extracted with TBME (3x2 ml). The organic phase was dried over Na_2SO_4 and the alcohol separated from the rest of the ketone (kieselgel, hexane/TBME 3:1). The alcohol was stirred with (R)-(+)-α-methoxy-α-trifluoromethylphenylacetyl-chloride in 0.25 ml of pyridine for 30 min. After quenching with 1 ml of water the solution was extracted three times with 2 ml of TBME, the organic phase dried over Na_2SO_4 and purified over kieselgel (hexane/TBME 10:1) to get the pure mosher ester, which was analyzed by ^{1}H-NMR (OCH_3 of ester)/^{19}F-NMR (CF_3 of ester):



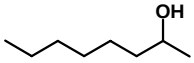
hexan-2-ol (290): ^{19}F-NMR (376 MHz, $CDCl_3$): -72.57 (S-isomer, -72.62 (R-isomer)



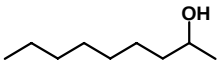
6-methylheptan-2-ol (291): ^{19}F-NMR (376 MHz, $CDCl_3$):-72.55 (S-isomer), -72.59 (R-isomer)



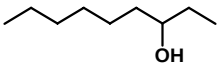
octan-3-ol (292): **^{19}F-NMR** (376 MHz, $CDCl_3$): -72.41 (S-isomer), -72.48 (R-isomer)



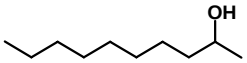
octan-2-ol (293): **^{1}H-NMR** (400 MHz, $CDCl_3$): 3.58 (S-isomer), 3.60 (R-isomer); **^{19}F-NMR** (376 MHz, $CDCl_3$): -72.57 (S-isomer), -72.62 (R-isomer)



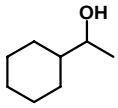
nonan-2-ol (294): **^{19}F-NMR** (376 MHz, $CDCl_3$): -72.56 (S-isomer), -72.62 (R-isomer)



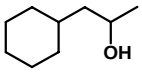
nonan-3-ol (295): **^{19}F-NMR** (376 MHz, $CDCl_3$): -72.41 (S-isomer), -72.48 (R-isomer)



decan-2-ol (296): **^{1}H-NMR** (400 MHz, $CDCl_3$): 3.57 (R-isomer), 3.55 (S-isomer); **^{19}F-NMR** (376 MHz, $CDCl_3$): -72 56 (S-isomer), -72.62 (R-isomer)

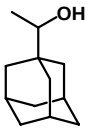


1-cyclohexylethanol (297): **^{1}H-NMR** (400 MHz, $CDCl_3$): 3.60 (S-isomer), 3.57 (R-isomer); **^{19}F-NMR** (376 MHz, $CDCl_3$): -72.47 (S-isomer), -72.51 (R-isomer)



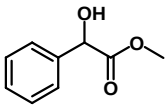
1-cyclohexylpropan-2-ol (298): **^{1}H-NMR** (400 MHz, $CDCl_3$): 3.58 (R-isomer), 3.55 (S-isomer); **^{19}F-NMR** (376 MHz, $CDCl_3$): -72 43 (S-isomer), -72.58 (R-isomer)

The optical purity of **1-(1-adamyntyl)ethanol (299)** was determined by comparison of the intensities of the methyl doublet in the ^{1}H-NMR (1.08 ppm for the S-isomer and 1.10 ppm for the R-isomer) by using the chiral solvent reagent (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) (*JACS*, *112*, **1990**, 4441-4447)

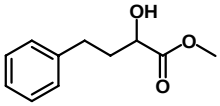


5.2.5.5 Separation of Keto Esters

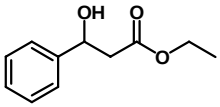
All keto esters were separated on the same Chiracel OD-H column as most of the aromatic ketones



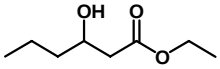
methyl 2-hydroxy-2-phenylacetate (300): HPLC (heptane/i-PrOH 95:5): 14.6 min (S-isomer); 24.7 min (R-isomer)



methyl 2-hydroxy-4-phenylbutanoate (301): HPLC (heptane/i-PrOH 90:10): 12.1 min (R-isomer); 17.2 min (S-isomer)



ethyl 3-hydroxy-3-phenylpropanoate (302): HPLC (heptane/i-PrOH 90:10): 14.0 min (R-isomer); 17.2 min (S-isomer)



ethyl 3-hydroxyhexanoate (303): HPLC (heptane/i-PrOH 75:25): 7.0 min (R-isomer); 7.8 min (S-isomer)

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10/2003-10/2004	Roche Research Foundation MBA Fellowship Programme
02/2007	Camille- und Henry Dreyfus Prize (University of Basel)

Publications:

2004 A. Schlatter, M. K. Kundu, and Wolf-D. Woggon. *Angewandte Chem. Int. Ed.* **2004**, *43*, 6731-74. Enantioselective Reduction of Aromatic and Aliphatic Ketones Catalyzed by Ruthenium Complexes Attached to β-Cyclodextrin

2007 A publication with a secondary face modified β-Cyclodextrin-based catalyst is submitted to *Angewandte Chem. Int. Ed.*

Presentations:

October 2005 Oral Presentation at the EPFL in Lausanne (Switzerland) on the occasion of the Fall Meeting of the Swiss Chemical Society with the title: Enantioselective Reduction of Aromatic and Aliphatic Ketones Catalyzed by Ruthenium Complexes Attached to β-Cyclodextrin

January 2006 Oral Presentation at the University of Freiburg i. Br. (Germany) on the occasion of “Graduiertenkolleg” (International Research Training Group "Catalysts and Catalytic Reactions for Organic Synthesis) with the title: Enantioselective Reduction of Aromatic and Aliphatic Ketones Catalyzed by Ruthenium Complexes Attached to β-Cyclodextrin

2003-2005 Posterpresentations: Regio Symposium 2003, Falkau (Germany), Swiss Fall Meeting 2004, Zürich (Switzerland), Regiosymposium 2005, Sornetan (Switzerland), Supramolecular Spring School 2005, Murten (Switzerland)

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Alain Schlatter
Basel, 2007

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, dass ich meine Dissertation selbständig und nur mit den angegebenen Hilfsmitteln angefertigt habe. Ich erkläre ausserdem, dass ich diese Dissertation an keiner anderen Fakultät eingereicht habe.

Basel, den 02. Mai. 2007

Alain Schlatter