Doctoral Dissertation 2005
Department of Organic Chemistry
Stockholm University

Abstract

The ability of amino acids to form nucleophilic enamines with aldehydes and ketones has been used in the development of asymmetric *α*-oxidation reactions with electrophilic oxidizing agents. Singlet molecular oxygen has for the first time been asymmetrically incorporated into aldehydes and ketones, and the products were isolated as their corresponding diols in good yields and *ee*'s. Organocatalytic *α*-oxidations of cyclic ketones with iodosobenzene and *N*-sulfonyloxaziridine were also possible and furnished after reduction the product diols in generally low yields and in low to good *ee*'s. Amino acids have also been shown to catalyze the formation of carbohydrates by sequential aldol reactions. For example, proline and hydroxy proline mediate a highly selective trimerization of *α*-benzyloxyacetaldehyde into allose, which was obtained in >99 % *ee*. Non-linear effect studies of this reaction revealed the largest permanent nonlinear effect observed in a proline-catalyzed reaction to date. Moreover, polyketides were also assembled in a similar fashion by an amino acid-catalyzed one-pot reaction, and was successful for the trimerization of propionaldehyde. However, the sequential cross aldol reactions suffered from lower selectivity. This problem was overcome by the development of a two-step synthesis that enabled the formation of a range of polyketides with excellent selectivities from a variety of aldehydes. The method furnishes the polyketides via the shortest route reported and in comparable product yields to most multi-step synthesis. All polyketides were isolated as single diastereomers with >99 % *ee*. Based on the observed amino acid-catalysis, it seems possible that amino acids might have taken part in the prebiotic formation of tetroses and hexose.

ISBN 91-7155-035-6
Akademitryck AB

Tillägnas mina östgötar

Papers included in the thesis

The thesis is based on the following papers, referred to in the text by their Roman numerals **I-VI**:

I. **The Direct Amino Acid-Catalyzed Asymmetric Incorporation of Molecular Oxygen to Organic Compounds.** Córdova, A.; Sundén, H.; Engqvist, M.; Casas, J. *J. Am. Chem. Soc.* **2004**, *126*, 8914

II. **Direct Amino Acid-Catalyzed Asymmetric *α*-Oxidation of Ketones with Molecular Oxygen.** Sundén, H.; Engqvist, M.; Casas, J.; Córdova, A. *Angew. Chem.* **2004**, *116*, 6694

III. **Direct Organoctalytic Asymmetric *α*-Oxidation of Ketones with Iodosobenzene and *N*-sulfonyloxaziridine.** Engqvist, M.; Casas, J.; Sundén, H.; Ibrahem, I.; Córdova, A. *Tetrahedron Letters* **2005**, *46*, 2053

IV. **Conceivable Origins of Homochirality in the Amino Acid-Catalyzed Neogenesis of Sugars.** Córdova, A.; Engqvist, M.; Ibrahem, I.; Casas, J.; Sundén, H. *Chem. Comm.* **2005**, Adv. article

V. **Direct Amino Acid-Catalyzed Asymmetric Synthesis of Polyketide Sugars.** Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Córdova, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1343

VI. **Amino Acid-Catalyzed Neogenesis of Carbohydrates: A Plausible Ancient Transformation.** Córdova, A.; Ibrahem, I.; Casas, J.; Sundén, H.; Engqvist, M.; Reyes, E. *Chem. Eur. J.* **2005** in press.

List of abbreviations

AcOH	Acetic acid
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphtyl
DKR	Dynamic kinetic resolution
DMF	*N*,*N*-dimethyl formamide
DMSO	Dimethyl sulfoxide
d.r	Diastereomeric ratio
DYKAT	Dynamic kinetic asymmetric transformation
ee	Enantiomeric excess
ent	Enantiomer
EtOAc	Ethyl acetate
GC	Gas chromatography
HPLC	High-performance liquid chromatography
hv	light
m-CPBA	*meta*-chloroperbenzoic acid
MeOH	Methanol
n.d	Not determined
NMP	*N*-methyl pyrrolidinone
PhIO	Iodosobenzene
PMP	*para*-methoxyphenyl
rt	Room temperature
$^1O_2$	Singlet molecular oxygen
TFE	Trifluoroethanol
THF	Tetrahydrofuran
TPP	*meso*-tetraphenylporphine
TS	Transition state

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1 Introduction

1.1 Catalysis in general

Catalysis in general is to enhance the rate of one or more steps in a reaction by the substoichiometric use of a catalyst which is normally unchanged throughout the reaction. The catalyst can't shift the equilibrium of a reaction but it increases the reaction rate by providing an additional faster pathway of lower activation energy for the reaction.

Catalytic processes have been operating on earth for a long time, plausibly taking part in the molecular evolution of life by catalyzing the formation of prebiotic building blocks, such as sugars, and later on through the catalytic work of enzymes in living organisms. The catalysis of organic reactions is today an important research field in many aspects for chemists in industry and in the academia. Catalysis is employed, for example, in the industrial production of commodity- and fine-chemicals.[1] Catalysis is also used for environmental reasons, to avoid undesired by-products like exhaust gases.

1.2 Classes of catalysis

Catalysis is often divided into two fields, heterogeneous and homogeneous catalysis. In the former the catalyst is not present in the same phase as the reactant and product. The reaction takes place at the surface of the catalyst where the reactants first have to be adsorbed, recombined into products, and desorbed. In homogeneous catalysis, the catalyst operates in the same phase as the products and reactants. The reactions will in the case of organometallic catalysts take place at the metal as it serves as an organizational center and activator for the substrate or reagent or both. Homogeneous catalysis also covers acid- , base- and nonorganometallic catalysis.

1.3 Different types of catalysts

The various catalysts encountered in the literature or in laboratories are often thought of as belonging to a certain category of catalysts. The main categories are the following:

Metal-catalysts comprise a large group of catalysts that can be divided into catalysts for use in either heterogeneous- or homogeneous catalysis. Chiral transition metal complexes are an important class of catalysts. The complexes gains their chirality from the various ligands coordinated to the metal. Catalysts of this class have attracted considerable interest over the last decades, especially in the field of asymmetric synthesis. Enzymes are high molar mass polypeptides that catalyze a wide variety of reactions in living organisms. Enzymes are usually restricted to only work with one or a few substrates and the reactions take place at an active site within the enzyme.

Organocatalysts are organic molecules that catalyze reactions. A commonly occurring class of organocatalysts is amino acids or their derivatives, and they are often more stable than enzymes and some of the organometallic catalysts. Alkaloids have been and are still being

used as catalysts. Organocatalysis will be discussed more in detail below. Lewis acids are another class of catalysts that are found in many reactions. Lewis acids are compounds that can accept an electron pair from another molecule to form an adduct. This adduct when formed with an intended acceptor molecule will be activated by the decrease in electron density towards nucleophiles.[2]

1.4 Chirality

The history of chirality and stereochemistry dates back to the beginning of the 19th century when French scientists studied hemihedral quartz crystals and found that they could induce the polarization of light. In 1848, Louis Pasteur resolved and separated the enantiomeric pair of tartaric acid from its sodium ammonium salt. Today, we define chirality in an object as the property of not being superimposable on its mirror image and lack of refractional symmetry. Such an object and its mirror image are called enantiomers.

1.5 Enantiomerically pure or enriched compounds and their importance

Enantiomerically pure compounds are of great importance because today it is widely accepted that nature is chiral and the biological activity of different enantiomers will differ. This becomes clear when considering taste and smell. For example the enantiomers of limonene have a smell of either lemon or orange and the enantiomers of aspargine taste either bitter or sweet (Figure 1:1).

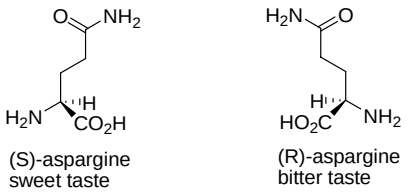


Figure 1:1. The two enantiomers of aspargine.

The different smell of the enantiomers is a result of the stereogenic interactions in the receptors in the mouth and nose as these are chiral. Problems arise when a desired compound is not enantiomerically pure or enriched enough, so that undesired side effects could occur. One early example that highlighted the different reactivities of enantiomers was when the sedative thalidomide (Neurosedyn) caused some ten thousand fetal abnormalities in the beginning of the 1960's. Since that time the level of control in clinical testing has become more rigorous. This has also had an impact on organic chemistry in the sense that more resources have been put into R&D in both academia and industry where organic chemists are directing the development of methods to obtain a single enantiomer of the products. In chemistry, a 1:1 mixture of enantiomers is called a racemate and when this is shifted in favor of any of the enantiomers it is expressed as the enantiomeric excess, *ee*, of that enantiomer and it is defined as $ee=([S]-[R])/([S]+[R])\text{x}100\%$.

1.6 Sources of enantiomerically pure or enriched compounds

Having understood the importance of good access to substances of high enantiomerical purity for use in synthesis or other applications, the question of where they can be obtained arises. There are three main strategies for obtaining enantiomerically pure or enriched compounds. One can turn to nature, the chiral pool, and utilize the variety of naturally occurring optically active substances such as carbohydrates, alkaloids, terpenes and amino acids. The limitations of the chiral pool are the few classes of compounds available and that usually only one enantiomer is abundant. For different reasons some compounds are not accessible as enantiopure, but in what can be called enantioenriched form, i.e. when one enantiomer predominates over the other. A commonly used method in the preparation of enantiomerically pure substances is to resolve racemates. The racemates can be either isolated from nature or prepared synthetically. The classic way of resolving racemates of amines and carboxylic acids is by formation of their diastereomeric salts with a resolving agent. Tartaric acid and strychnine serve as examples of such agents used in resolution processes. The yield of such a resolution can obviously not exceed 50 % but this disadvantage can in some cases be overcome by recycling the undesired enantiomer by racemization. There is also a method called kinetic resolution that is based on the different reaction rates of the enantiomers and the chiral reagent or catalyst. The formed diastereomers have different energy in their transition states (TS) and consequently different reaction rates. A kinetic resolution must be monitored and stopped when the highest *ee* of the product is obtained. If the reaction goes to completion, both enantiomers will have reacted and the product will be racemic (0 % *ee*).

An extension to the kinetic resolution is the use of a catalyst that continuously will racemize the build up of the slow reacting enantiomer as the fast reacting enantiomer is turned in to product. This method is called dynamic kinetic resolution (DKR) and it will convert the racemic compound to an enantiomerically pure product by continuously racemizing the slow reacting enantiomer to the faster reacting one. A more recent development in the field of kinetic resolution is dynamic kinetic asymmetric transformation (DYKAT). In a DYKAT reaction, the diastereomers are epimerized catalytically and one of the enantiomers is reacted with greater rate than the others with the chiral catalyst.[3]

1.7 Asymmetric synthesis

The area in which chemists strive to develop methodology to perform transformations that will turn an achiral substrate into an optically active product is called asymmetric synthesis. Within this area of chemistry, there exists a set of available methods that can be separated by the way in which the chirality is transferred. The use of chiral auxiliaries means that the substrate is coupled with a chiral substance that force it to undergo reactions in a stereoselective way. The chiral auxiliary can be removed once the desired stereocenter in the compound is introduced.

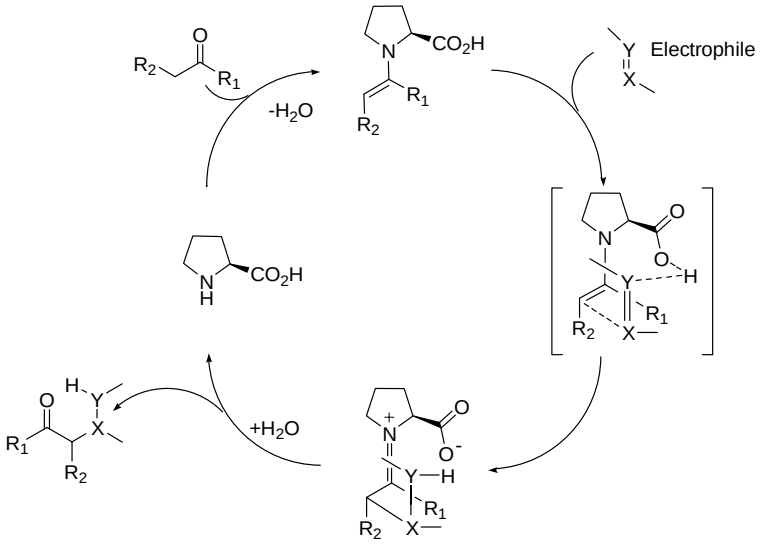
A prochiral substrate can be treated with a chiral reagent that brings about a transformation in an enantioselective way. Both these methods, the use of chiral auxiliaries or chiral reagents, can be expensive as they require at least one equivalent of the chirality transferring agent and some sort of recovery procedure for recycling purposes. Performing a reaction in the presence of a chiral catalyst is another way of introducing asymmetry into a synthesized compound as the prochiral substrate and the reagent react in the chiral environment of the catalyst. The catalyst is not affected by the reaction and is ready to catalyze the next transformation with a new substrate molecule. The catalytic cycle goes on until the reaction is complete or the catalyst becomes inactive due to catalyst poisoning.

1.8 Nonlinear effects and asymmetric amplification in asymmetric synthesis

When performing catalytic asymmetric reactions, the *ee* of the catalyst should be the upper limit for the *ee* in the product. The observed *ee* in the product is sometimes far higher or lower than the *ee* of catalyst. Making a plot of different catalyst *ee*'s versus obtained product *ee*'s from a set of reactions can reveal such a nonlinear relationship between catalyst and product. This relationship is called a nonlinear effect and it can be used as a tool for elucidating reaction-mechanisms. For example it can be used to predict if one or more catalyst molecules are present in the TS. The origin of the effect is due to diastereomeric interactions between a chiral enantiopure catalyst and the enantiomers or diastereomers of the reactant. The diastereomers will be of different energy in their TS and that difference causes the enantiodifferation and the chiral amplification, expressed as a higher *ee* in the product than in the actual catalyst.[4]

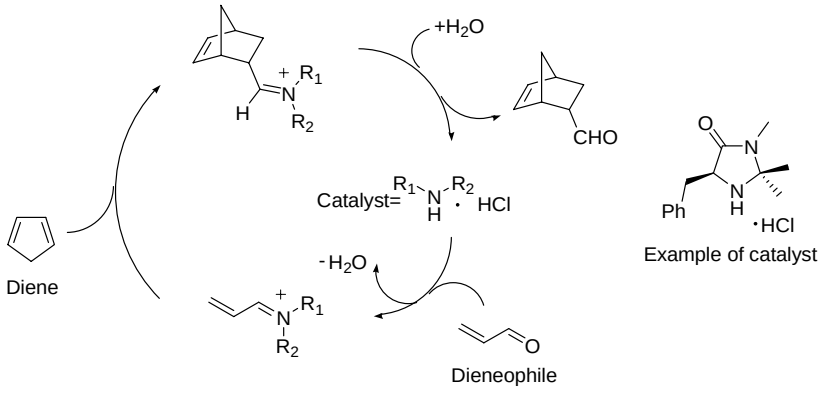
1.9 Organocatalysts in asymmetric synthesis

Until some years ago it was more or less accepted that enzymes and chiral transition metal complexes were among the most efficient catalysts for asymmetric catalysis. Lately there has been progress made with the use of organic compounds as catalysts for a variety of reactions.[5] The use of organocatalysts is however not new in chemistry. The first asymmetric catalysts were in fact organocatalysts. Despite their sometimes modest results in the beginning they have started to catch up with the achievements reached with transition metal catalysts during the last decades. One particular class of organocatalysts is amino acids and their derivatives. Several of the amino acid-catalyzed reactions follow the enamine catalytic cycle in which the donor molecule is activated by transformation to a nucleophilic enamine which can add to a variety of π-electrophiles (Scheme 1:1). This is the reaction mechanism by which we have based our work on in the following chapters. Hydrogen bondactivation and Brönsted acids have also been used with success in organocatalytic reactions.[6]



Scheme 1:1. L-proline-mediated enamine catalytic cycle.

Another mechanism found in organocatalysis is one in which the acceptor molecule is turned into an iminium salt and in that way activates the corresponding carbonyl compound for other reagents.[7] The organocatalyzed Diels Alder reaction can serve as an example (Scheme 1:2).[7]



Scheme 1:2. Diels Alder reaction mediated by an organocatalyst that conducts the reaction via formation of an iminium salt with the dieneophile.

1.10 Organocatalysts

L-proline has been, and still is one of the leading organocatalysts.[8, 5] The reason for its widespread use and successful performance in many reactions has been attributed to its secondary amine functionality which results in a higher pKa value compared to the other natural amino acids often tested as catalyst. In addition it also has higher nucleophilicity and readily forms enamines or iminium ions with carbonyl functionalities and Michael acceptors. The higher nucleophilicity can however cause problems. Many partial steps in amine

catalyzed reactions are equilibrium reactions and a catalyst of higher nucleophilicity can react in a number of ways in equilibrated reactions with present electrophiles. This possible problem is usually circumvented by a high catalyst loading. Proline-catalyzed reactions have also been noted for a very high enantioselectivity. This has been explained by the formation of highly organized transitionstates by extensive hydrogen bonding in which the carboxylic group of proline plays a vital part. The carboxylic acid or the secondary amine functionality is also responsible for the proton transfer in the transition state, which is important for the charge stabilization during the C-C bond formation. The bifunctionality of possessing a nucleophilic part and a group with proton donating ability is common among the organocatalysts as this activates both acceptor and donor. Proline is of course not the only catalyst used but it can serve as a general example of a catalyst displaying these valuable properties. Other classes of catalysts are alkaloids, oligopeptides, amines, amino acids, amino acid derivatives, organic acids, organic acid derivatives and amino alcohols. Most of them are bifunctional.

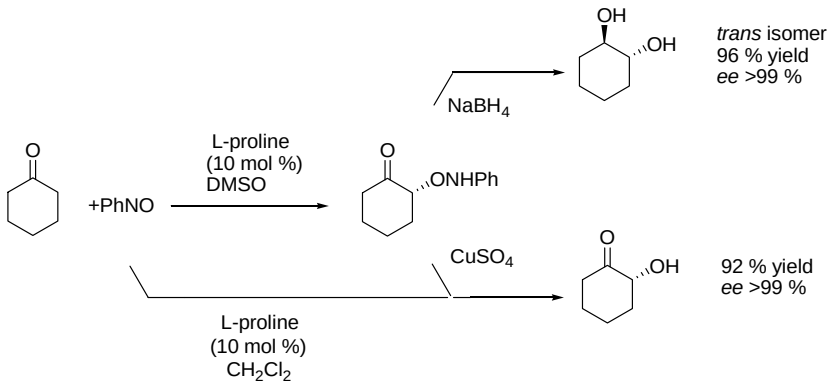
2 *α*-Oxidations of ketones and aldehydes [I, II, III]

2.1 Introduction

A goal within organic chemistry is to find and develop new catalytic and stereoselective routes to optically active compounds from inexpensive and readily available starting materials. The *α*-hydroxy carbonyl moiety is a frequently encountered structural feature in many natural products that could be of pharmaceutical or biological importance.[9] Developing methods to introduce this moiety in a stereoselective way would therefore be of interest to chemists working with pharmaceutical chemistry or total synthesis.

2.2 Existing methodology for obtaining *α*-hydroxy carbonyl compounds

The asymmetric *α*-oxidation of carbonyl compounds has been a challenge for chemists for a long time. The older methods involve substitutionreactions on optically active carbonyl compounds[10] and different reductions of dicarbonyl compounds.[11] Two oxidative approaches have also been reported. The first reaction, the Rubottom reaction, is an oxidation of a preformed silyl enolate with *m*-CPBA[12] or *N*-sulfonyloxaziridine.[13] The second method is the direct oxidation of metal enolates using dioxygen[14] or dibenzyl peroxycarbonate.[15] Despite the effort put in to this research, it was not until recently that a more efficient asymmetric catalytic system was developed based on AgX/BINAP complexes by Yamamoto and co-workers that could perform *α*-oxidation of activated tin enolates with nitrosobenzene as the electrophile.[16] In 2003, the first direct amino acid catalyzed *α*-aminoxylation of unmodified ketones using nitrosobenzene as an oxidant was developed by our group and others.[17] This method produces *α*-hydroxy-ketones in good yields and with high enantioselectivity (Scheme 2:1).



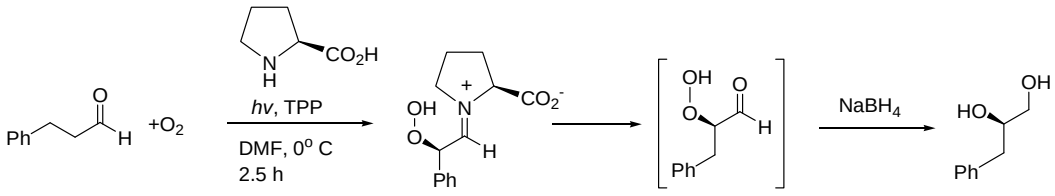
Scheme 2:1. L-proline catalyzed *α*-aminoxylation of cyclohexanone with nitrosobenzene.

2.3 *α*-Hydroxylations using singlet oxygen

Molecular oxygen is an oxidant that can be used in some reactions, although it is not reactive enough for all substrates as it exists in its triplet state ($^3O_2$). Molecular oxygen can however be transferred to its more reactive singlet state ($^1O_2$) by exposure to light in the presence of photosensitizers, or it can be generated chemically.[18] The more reactive and electrophilic nature of $^1O_2$ have resulted in its use as an oxygen source in some synthetic applications, such as in the preparation of allylic hydroperoxids analogous to the "ene" reaction and in the generation of cyclic peroxides via Diels-Alder-like reactions.[19] Singlet oxygen also plays a role in some biochemical processes in organisms, and it is responsible for the development of a few diseases and biocatalytical oxidations.[20] Taking the electrophilic nature of singlet oxygen into account it seemed desirable to develop a method to asymmetrically incorporate it into organic compounds. Since asymmetric *α*-oxidation of ketones had been accomplished by the use of proline-derived enamine addition to the electrophilic oxygen in nitrosobenzene, we reasoned that an enamine approach to trap the singlet oxygen should work. The enamines could be generated from either aldehydes or ketones. No previous work of catalytic asymmetric incorporation of singlet molecular oxygen had been reported, possibly because photo-chemists believed it would be hard to react $^1O_2$ in an enantioselective way.

2.4 The direct catalytic asymmetric incorporation of $^1O_2$ to aldehydes[I]

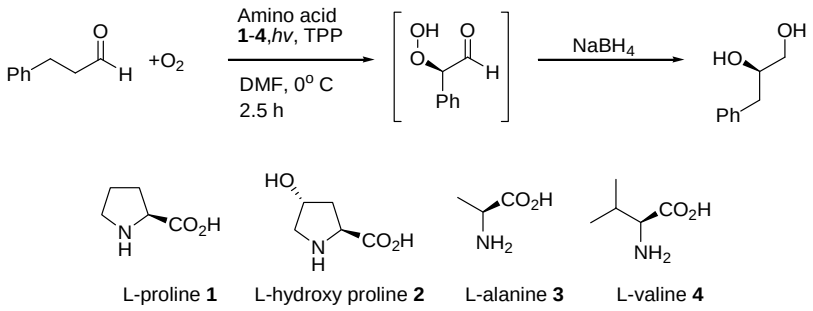
In an initial test to verify or discard the hypothesis that amino acid-derived enamines could add to $^1O_2$, 3-phenyl propionaldehyde was exposed to light in the presence of tetraphenylprophine (TPP) and L-proline (20 mol %) in DMF. The expected *α*-peroxyaldehyde intermediate was not isolated, instead an excess of $NaBH_4$ was added with methanol and the corresponding diol was isolated (Scheme 2:2).



Scheme 2:2. The initial attempt to trap $^1O_2$ with a L-proline-derived enamine.

L-proline was not the only amino acid screened for this reaction but it turned out to be the most effective of the amino acids tested in the asymmetric *α*-oxidation of 3-phenyl propionaldehyde (Table 2:1). At that time, no further search for better catalysts was conducted.

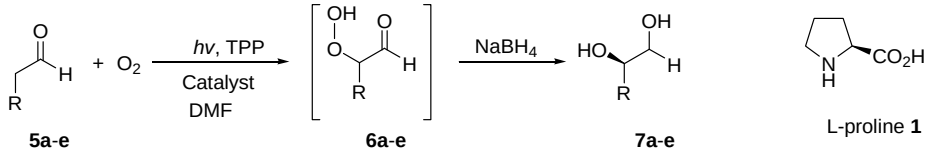
Table 2:1. The screening of amino acids as catalysts for the asymmetric α-oxidation of 3-phenyl propionaldehyde and the catalysts tested, **1**-**4**.



Entry	Catalyst	*ee* (%)
1	**1**	48
2	**2**	6
3	**3**	7
4	**4**	6

Having identified L-proline as the best catalyst so far, it was tested in a set of reactions with different aldehydes, **5a**-**e**. L-proline catalyzed the reactions and provided, after *in situ* reduction of the intermediates **6a**-**e** with $NaBH_4$ the optically active diols **7a**-**e** in high yields with modest *ee*'s (Table 2:2). Exchanging L for D-proline afforded the opposite enantiomer of the diol without affecting the yield or asymmetric induction (entry 5, Table 2:2).

Table 2:2. Results from L-proline catalyzed asymmetric incorporation of $^1O_2$ to aldehydes.[a]

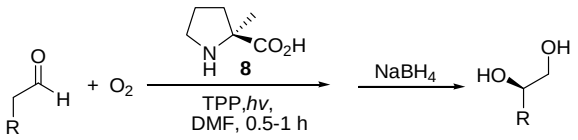


Entry	Catalyst	Aldehyde	R	Diol	Temp. (°C)	Yield (%)[b]	*ee* (%)[c]
1	**1**	**5a**	Bn	**7a**	27	45	22
2	**1**	**5a**	Bn	**7a**	-5	91	48
3	**1**	**5b**	Ph	**7b**	-20	92	24
4	**1**	**5c**	^{i}Pr	**7c**	-5	95	42
5	*ent*-**1**	**5c**	^{i}Pr	**7c**	-5	93	41
6	**1**	**5d**	Pe	**7d**	-5	91	16
7	**1**	**5e**	Bu	**7e**	-5	92	22

[a] In a typical experiment, the amino acid (20 mol %) was stirred in the solvent (5 mL) for 20 minutes followed by addition of TPP (5 mol %) and the aldehyde (1 mmol). The reaction was initiated and performed by letting a continuous flow of molecular oxygen or air through the reaction for 0.5-3 h in the presence of visible light from a 250 W high-pressure sodium lamp. [b] Isolated yield of diols **7a**-**7e** after silica-gel column chromatography. [c] Determined by chiral-phase HPLC or GC. The racemic diols derived by D, L-proline catalysis were used as reference materials. The absolute configuration was determined by comparison with commercially available diols and/or literature data.

Due to the modest *ee*'s obtained with proline, our attention shifted towards unnatural amino acids. Two *α*-substituted proline derivatives were found having a methyl and a benzyl group, respectively. L-*α*-methyl proline, **8**, demonstrated very good catalyst abilities and catalyzed the asymmetric incorporation of $^1O_2$ with the best enantioselectivity (Table 2:3). The diols **7a-7e** were obtained in good yields with up to 66 % *ee*. The *α*-benzyl-proline catalyst furnished a product *ee* of 18 % in 40 % yield. Further tests with L-*α*-methyl proline showed that the catalyst loading could be reduced to 10 mol % without affecting the reaction's efficiency. An explanation for the improved enantioselectivity of catalyst **8** could be due to a more favored enamine conformation.

Table 2:3. Results showing the importance of the *α*-methyl group in L-*α*-methyl proline for the enantioselectivity in the *α*-oxidation of aldehydes .[a]



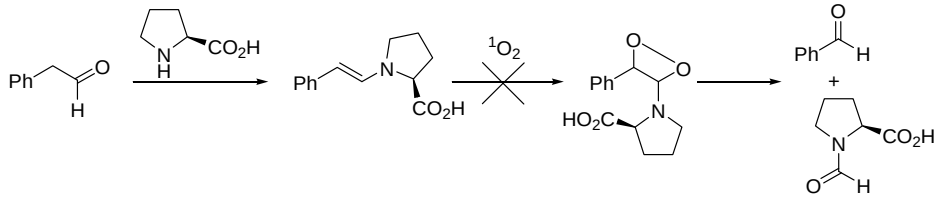
Entry	Aldehyde	R	Diol	Yield (%)[b]	*ee* (%)[c]
1	**5a**	Bn	**7a**	77	66
2	**5a**	Bn	**7a**	72[d]	66
3	**5c**	^{i}Pr	**7c**	75	57
4	**5d**	Pe	**7d**	77	54
5	**5e**	Bu	**7e**	73	57

[a] In a typical experiment, the amino acid (20 mol %) was stirred in the DMF (1 mL) for 20 minutes followed by addition of TPP (5 mol %) and the aldehyde (1 mmol) at 0 °C. The reaction was initiated and performed by letting a continuous flow of molecular oxygen or air through the reaction for 0.5-3 h in the presence of visible light from a 250 W high-pressure sodium lamp. [b] Isolated yield after silica-gel column chromatography. [c] Determined by chiral-phase HPLC or GC. [d] The reaction was performed with air as the oxygen source.

2.5 Proposed mechanism / TS for the asymmetric incorporation of $^1O_2$ to aldehydes

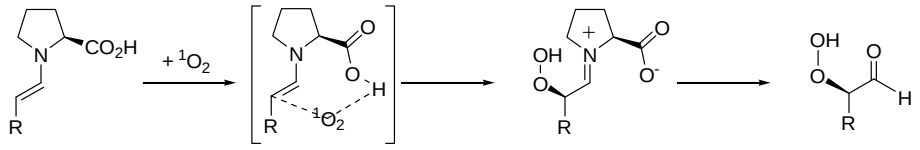
The *α*-hydroxylation of aldehydes with $^1O_2$ is supposed to proceed via a catalytical enamine mechanism similar to the above-mentioned catalytic cycle (Scheme 1:1). This was supported by the observation that no diol product could be isolated unless the reaction was performed in the presence of a catalyst able to form an enamine with the substrate. The enamine is thought to add to the electrophilic singlet oxygen and the addition should occur on the face of the enamine that has the directing and proton donating group. The protonation should result in a *α*-hydroperoxide aldehyde, from which the corresponding diol is obtainable after reduction with $NaBH_4$. In order to prove that $^1O_2$ was the electrophile and not $^3O_2$, L-proline catalyzed reactions were performed on some aldehyde substrates in the presence of triethylphosphite

using $^3O_2$ as the oxidant. Since no diol products were obtained, it proved that $^1O_2$ and not $^3O_2$ is the fastest reacting electrophile.[21] To prove the presence of *α*-hydroperoxide intermediate, 2-phenyl acetaldehyde was oxidized under the same conditions as the other substrates and reduced. During the reaction no benzaldehyde was detected and the reduction furnished a high yield of the desired diol product. These observations indicate that 1, 2-addition of $^1O_2$ to the enamine does not take place, as that should result in a dioxetane intermediate that can decompose into benzaldehyde and *N*-formylated L-proline (Scheme 2:3).[22]



Scheme 2:3. Control reaction to prove the presence of the *α*-hydroperoxide intermediate. If a dioxetane intermediate is formed, benzaldehyde should be detected as a decomposition product.

We propose that the enamine adds to the electrophilic $^1O_2$ and that the carboxylic acid proton is responsible for the enantiodifferentiation in the TS between the two faces of the enamine. The $^1O_2$ is in this way predominantly guided to the *si*-face (Scheme 2:4).



Scheme 2:4. Singlet oxygen adds to the *si*-face of the L-proline derived enamine as directed by the carboxylic acid proton.

2.6 Results and discussion of the direct catalytic asymmetric incorporation of $^1O_2$ to ketones [II]

Having established an experimental procedure for amino acid-catalyzed asymmetric α-oxidation of aldehydes, we began to examine ketones as substrates. We reasoned that they would show similar reactivity as the aldehydes. The synthetic plan was to perform the α-oxidation in the same way as we previously had done with the aldehydes and then reduce the formed α-peroxy ketone to the corresponding diol with $NaBH_4$. Cyclohexanone **9a** was chosen as the standard substrate for our initial catalyst and solvent screens. The first reaction was set up with L-proline as catalyst and performed in DMSO (scheme 2:4).

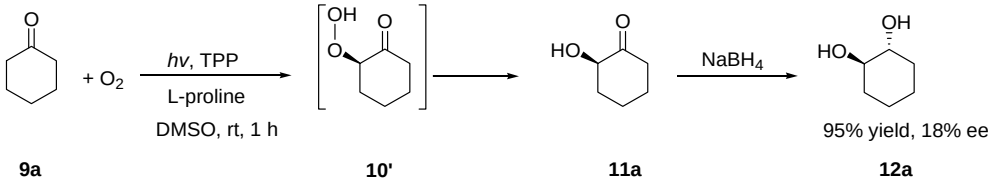
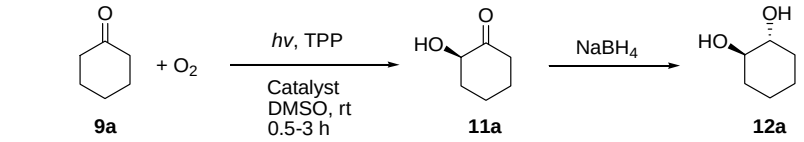


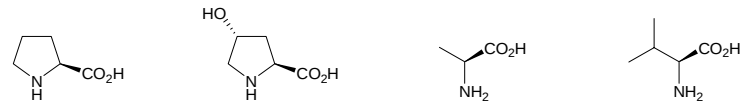
Figure 2:4. α-oxidation of cyclohexanone with $^1O_2$.

The initially generated α-peroxy ketone **10'** could not be found in the reaction mixture, instead α-hydroxy ketone **11a** was found as its dimer. It is likely that **11a** was also present as higher oligomeric products. That was not investigated further. The *in situ* reduction with $NaBH_4$ furnished diol **12b**. During the catalyst screen several amino acids and amino acid derivatives proved to mediate the reaction with good efficiency (Table 2:4). Alanine and valine displayed the highest stereoselectivity of the amino acid catalysts tested. The D-amino acids afforded the opposite enantiomer compared to the reaction catalyzed by L-amino acids and in similar yields. In addition, amino alcohols, dipeptides and amino acid derivatives also catalyzed the asymmetric incorporation of molecular oxygen to ketones with similar efficiency as the amino acids. Glycin and ethanolamine also showed catalytic activity and afforded the α-hydroxylated product in high yield providing an inexpensive way to racemic α-hydroxy compounds.

Table 2:4. Amino acid-catalyzed introduction of $^1O_2$ to **9a**.[a]



9a **11a** **12a**



L-proline **1** L-4-hydroxy proline **2** L-alanine **3** L-valine **4**

L-α-methyl proline **8** L-α-methyl valine **10** L-α-phenyl glycine **11** L-phenyl alanine **12**

L-threonine **13** L-phenylalinol **14** **15** 5-pyrrolidine-2-yltetrazole **16**

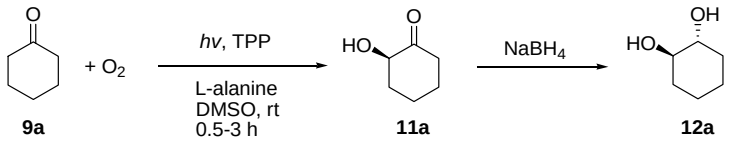
Entry	Catalyst	Product	Yield (%)[b]	*ee* (%)[c]
1	**3**	*ent*-**12a**	93	56
2	*ent*-**3**	**12a**	88	57
3	**4**	*ent*-**12a**	78	49
4	*ent*-**4**	**12a**	77	48
5	**1**	**12a**	95	18
6	*ent*-**1**	*ent*-**12a**	93	16
7	**2**	**12a**	88	11
8	**8**	**12a**	20	48
9	**10**	*ent*-**12a**	15	6
10	**11**	*ent*-**12a**	70	20
11	**12**	*ent*-**12a**	89	38
12	*ent*-**11**	**12a**	71	21
13	**13**	*ent*-**12a**	20	10
14	**14**	*ent*-**12a**	67	<2
15	**15**	**12a**	62	11
16	Glycine	**12a**	85	-
17	Ethanol amine	**12a**	81	-
18	**16**	**12a**	97	<5

[a] To a vial containing TPP (1 mol %) and a catalytic amount of amino acid (30 mol %) in DMSO (1 mL) was added cyclohexanone (1 mmol). A continuous flow of O_2 or air was led through the vial containing the reaction mixture which was exposed to visible light by a 250 W high-pressure sodium lamp. The reaction was quenched either by addition of brine followed be extraction with EtOAc to furnish α-hydroxy-ketone **11a** or by in situ reduction of with $NaBH_4$ to afford the corresponding optically active crude diol **12a**, which was isolated by column chromatography. [b] Isolated yield after silica-gel column chromatography of the pure **12a** furnished after reduction of **11a**. [c] Determined by chiral-phase GC analyses. The racemic product derived by glycine catalysis was used as reference material. The absolute configuration was determined by comparison with commercially available diols and literature data.

In contrast to the best catalysts for aldehydes, the amino acid-catalyzed *α*-hydroxylation of cyclohexanone worked best with amino acids possessing primary amine functionality. L-alanine provided the best *ee* of **9a** in very high yield. Having gained some information on what kind of catalysts that worked best with cyclohexanone we turned our attention the effect of solvent on the outcome of the reaction. A solvent screen was conducted and the L-alanine-catalyzed oxidation of cyclohexanone was performed in 11 different solvents.

The best solvents for the amino acid-catalyzed *α*-hydroxylation of cyclohexanone were found to be dimethylsulfoxide (DMSO), *N*-methyl pyrrolidone (NMP) and *N*,*N*-dimethylformamide (DMF). In DMSO, the L-alanine-catalyzed reaction reached the highest conversion and the products their highest *ee*'s. In contrast, L-alanine only produced trace amounts of **9b** in methanol (MeOH), trifluoroethanol (TFE) and chloroform ($CHCl_3$) (Table 2:5).

Table 2:5. Solvent screen of the L-alanine catalyzed incorporation of $^1O_2$ to cyclohexanone.[a]

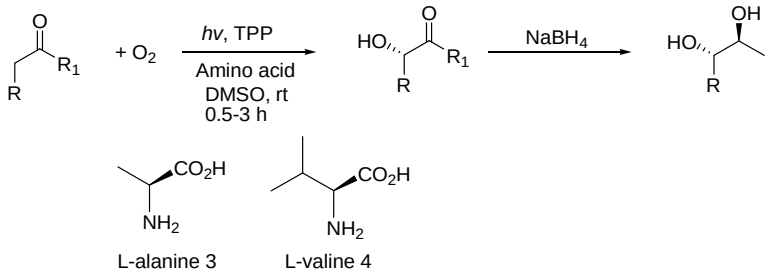


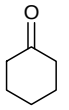
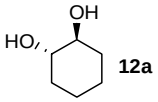
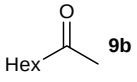
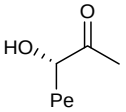
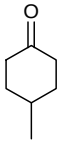
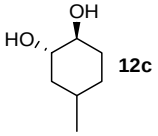
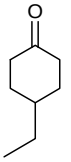
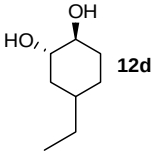
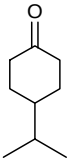
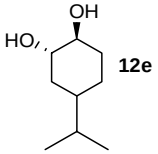
Entry	Solvent	Temp. (°C)	Yield (%)[b]	*ee* (%)[c]
1	MeOH	rt	traces	n.d
2	DMSO	40	79	55
3	DMSO	rt	93	56
4	DMSO	0 → rt	80	48
5	DMSO[d]	rt	82[d]	56[d]
6	NMP	rt	86	48
7	DMF	rt	82	49
8	TFE	rt	traces	n.d
9	Phosphate buffer[e]	rt	80[e]	18[e]
10	Water[e]	rt	77[e]	19[e]
11	$CHCl_3$	rt	traces	n.d

[a] To a vial containing TPP (1 mol %) and a catalytic amount of L-alanine (20 mol %) in solvent (1 mL) was added cyclohexanone (1 mmol). A continuous flow of O_2 or air was led through the reaction mixture which was exposed to visible light by a 250 W high-pressure sodium lamp. The reaction was quenched either by addition of brine followed be extraction with EtOAc to furnish *α*-hydroxy-ketone *ent*-**11a** or by in situ reduction of with $NaBH_4$ to afford the corresponding optically active crude diol *ent*-**12a**, which were isolated by column chromatography. [b] Isolated yield after silica-gel column chromatography of the pure *ent*-**12a** furnished after reduction of *ent*-**11a**. [c] Determined by chiral-phase GC analyses. [d] Reaction performed with air as the O_2 provider. [e] TPP (1 mol %) was used as the sensitizer and 40 Vol % DMSO.

At this point we investigated the effectiveness of the method for substituted cyclohexanones and linear ketones. Consequently, L-alanine- and L-valine-catalyzed oxidation of some 4-alkyl substituted cyclohexanones and 2-octanone were performed (Table 2:6).

Table 2:6. Amino acid-catalyzed incorporation of $^1O_2$ to ketones.[a]



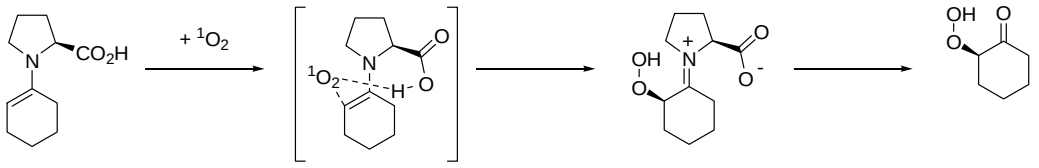
Entry	Ketone	Product	Catalyst	Yield (%)[b]	*ee* (%)[c]
1	 **9a**	 **12a**	**4**	50	28
2	 **9b**	 **12b**	**3**	93	56
3	 **9c**	 **12c**	**4**	75	69
4	**9c**	**12c**	**3**	67	72
5	 **9d**	 **12d**	**3**	61[d]	60
6	 **9e**	 **12e**	**3**	58[d]	52

[a] To a vial containing TPP (1 mol %) and a catalytic amount of L-amino acid (20 mol %) in DMSO or NMP (1 mL) was ketone added (1 mmol). A continuous flow of O_2 or air was led through the reaction mixture which was exposed to visible light by a 250 W high-pressure sodium lamp. The reaction was quenched either by addition of brine followed be extraction with EtOAc to furnish α-hydroxy-ketones **11a-e** or by in situ reduction with $NaBH_4$ to afford the corresponding optically active crude diols, **12a-e** which were isolated by column chromatography. [b] Isolated yield after silica-gel column chromatography of the diol **12a-e**.[c] Determined by chiral-phase GC analyses. The racemic products were derived by glycine or D, L-proline catalysis and were used as reference materials. [d] Reaction performed in NMP.

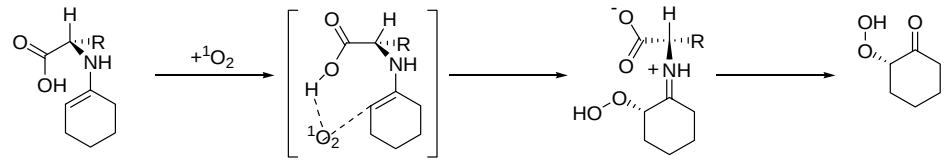
2.7 Proposed mechanism / TS for the incorporation of $^1O_2$ to ketones

The mechanism for the enamine catalyzed incorporation of $^1O_2$ to ketones probably follows the same suggested mechanism as for the same reaction with aldehydes. The electrophilic singlet state molecular oxygen is bound to the face of the enamine which bears the proton donating and stereo directing group. In the case with L-proline, the oxidation takes place on the *si*-face of the enamine as directed by the carboxylic acid group (Scheme 2:4).

The linear amino acids with primary amine functionality, operates in a similar way as the cyclic catalysts. The difference can be thought of as that the stereodirecting carboxylic acid group is being bent backwards over to the *re*-face of the enamine from where it will direct and finally protonate the incoming singlet state molecular oxygen (Scheme 2:5). The *ee*'s are not very high for any of the trials, even though the product yields are high for some catalysts. That suggests a possible singlet oxygen addition but with alternative protonation paths without any directing role of the proton source.



Scheme 2:4. Plausible mechanism and TS for the incorporation of $^1O_2$ on the *si*-face of the L-proline-derived enamine by the guidance of the carboxylic acid proton.



Scheme 2:5. A plausible mechanism and TS for the incorporation of $^1O_2$ on the *re*-face of a linear amino acid-derived enamine by the guidance of the carboxylic acid proton.

2.8 General conclusions from the asymmetric incorporation of $^1O_2$ in to aldehydes and ketones

The α-oxidation of aldehydes and ketones with $^1O_2$ is a method that can be simply accomplished and furnish the α–hydroxylated products in good yields and with modest to good *ee*'s. In the oxidation of aldehydes, the best results are achieved in DMF and for ketones DMSO proved to be superior to the others. Polar protic solvents like MeOH and TFE only produced trace amounts of α-hydroxylated ketones and with poor *ee*. Oxidation of both aldehydes and ketones could be accomplished in phosphate buffer. Ketones could also be oxidized in a DMSO/water mixture (4:6). From this it is clear that a polar aprotic solvent is the best while the polar protic solvents, with the exception of water, in some way prevent the oxidation.

2.8.1 Conclusions on the α-oxidation of aldehydes with $^1O_2$

From the initial catalyst screen for aldehyde substrates it was clear that the linear amino acids catalyzed the reaction but with very poor enantioselectivity compared to the cyclic ones. Proline furnished the α-hydroxylated product with in 48 % *ee*. Using α-methyl proline as catalyst, enhanced the *ee* in the isolated product which was obtained in high yield, although

not as high as the conversions reached with L-proline. The expanded substrate screen showed that α-methyl proline mediated the reaction with similar enantioselectivity (57-66 %) for the various aldehydes and the products were isolated in good yields (72-77 %). The reason for the methyl substituents enantioselectivity enhancing effect could arise from a more favored enamine conformation and the possibility that it also to some extent may prevent attack of the oxygen on the *re*-face of the enamine. The blocking of the *re*-face of the enamine was something we expected to see in the reaction with the α-benzyl proline mediated reaction but it turned out to be a poorer catalyst than proline. The conversion of aldehydes in the reactions catalyzed by linear amino acids was not determined but the *ee*'s in the isolated products were nearly racemic and therefore they were not further investigated. The poor catalyst performance by the non cyclic amino acids could be due to unfavored enamine conformations.

2.8.2 Conclusions on the α-oxidation of ketones with $^1O_2$

In the α-oxidation of ketones with $^1O_2$, many more catalysts were tested than with the aldehydes and the trend was somewhat different. Some of the cyclic amino acids (**1**, **2** and **16**) provided the products in high yields (95 %, 88 % and 97 %) but with poor *ee*'s (18 %, 11 % and <5 %). α-methyl proline displayed a higher asymmetric induction, 48 %, at the expense of conversion which only reached 20 %. The importance of the α-methyl group for obtaining high *ee*'s is evident but it also reduces conversion in the reaction with cyclic ketones. The linear amino acids on the other hand showed product yields comparable to the best obtained from the cyclic amino acids but with *ee*'s up to 57 %. Of the catalysts screened, alanine was the best, providing a very high product yield with the highest *ee*. Interestingly, catalyzing the reaction with valine **4**, which only differs from alanine **3** in terms of two methyl groups, keeps the yield of the product in the same range but the *ee* is reduced with ~10 %. This point in the direction that the bulk of the alkyl groups in the linear amino acids can't be of any size. The optimal being a methyl so far. The introduction of a α-methyl group in valine **10** did not improve yield or *ee* in any way. The product from the L-α–methyl valine was isolated in 15 % yield and with 6 % *ee*. Further studies and mechanistic understanding may enable the enantioselectivity in the reaction to reach the levels as the amino acid-catalyzed α-aminoxylation reaction displays.

2.9 Non proton-guided $^1O_2$ incorporation to aldehydes and ketones, a possible background reaction and concentration dependence

In our model for the amino acid-catalyzed incorporation of $^1O_2$ we have considered the oxygen molecule as an electrophile in its singlet state. The results clearly show that to be true when reacted with different enamines as the α-hydroxylated products are isolated. It does not however provide much information on in what manner the reaction takes place. My hypothesis is that the addition can proceed by at least two routes. In one possible reaction, the

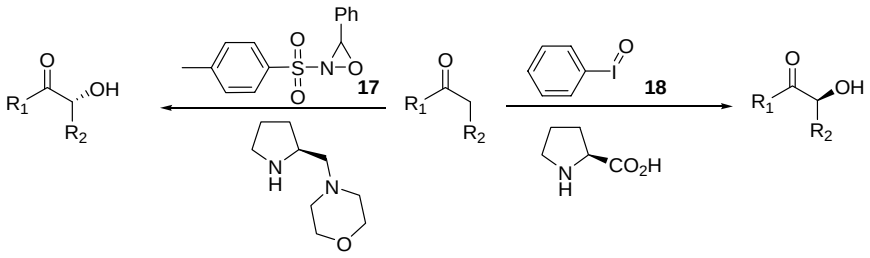
incoming electrophilic $^1O_2$ molecule is first hydrogen bonded by the carboxylic proton of the catalyst residue in the enamine. This bonding would dictate to which face of the enamine the addition will take place. This is supported by the presence of enantiomeric excess in the products.

The other possible route of $^1O_2$ addition proceeds in a non-proton guided fashion. The enamine simply attacks the electrophilic singlet oxygen and so reacts without any influence of enantioselectivity. This is a possible background reaction and this could be pronounced in a reaction where the concentration of singlet oxygen exceeds that of the enamine. Even if the carboxylic proton would be hydrogenbonded to an oxygen molecule, the enamine part could still react with another singlet oxygen molecule, thus contributing to the conversion of substrate but effecting *ee* negatively. Since these reactions are performed with little knowledge of the actual concentrations of the reactants, it would be of interest to control and keep the concentration of singlet oxygen low throughout the reaction. This would hopefully lead to an enhanced *ee* in the products as the probability of the suspected background reaction would decrease.

2.10 *α*-Hydroxylations of ketones with iodosobenzene and *N*-sulfonyloxaziridine as oxidants [III]

2.11 Introduction

The successful approach with amino acid-catalyzed *α*-hydroxylations of ketones with $^1O_2$ led us to test a set of other electrophilic oxidants we reasoned could be interesting in an enamine reaction. Among the oxidants tested on cyclohexanone with L-proline as catalyst in DMSO, *N*-sulfonyloxaziridine **17** and iodosobenzene, **18**, furnished the corresponding *α*-hydroxylated ketone (Scheme 2:6).



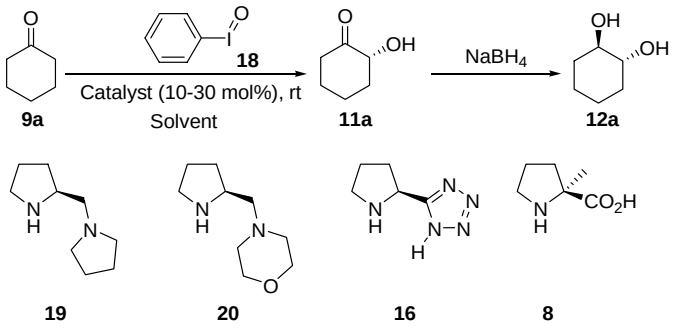
Sheme 2:6. Organocatalytic *α*-oxidation of ketones with iodosobenzene or *N*-sulfonyloxaziridine.

The initial results were expanded with a screening of other possible catalysts and solvents for iodosobenzene (PhIO) and *N*-sulfonyloxaziridine.

2.12 Results and discussion for *α*-hydroxylations of cyclohexanone using PhIO

L-proline proved to be the best catalyst for PhIO in DMSO providing the highest product *ee* and yield while the other catalysts only furnished trace amounts of diol (Table 2:7).

Table 2:7. Organocatalytic *α*-oxidation of cyclohexanone with iodosobenzene.[a]



Entry	Catalyst	Solvent	Yield (%)[b]	*ee* (%)[c]
1	**1**	DMSO	27(32)[d]	67(65)[d]
2	**19**	DMSO	traces	n.d
3	**20**	DMSO	traces	n.d
4	**16**	DMSO	traces	<5
5	**8**	DMSO	10	<5
6	**1**	DMF	29	77
7	**1**	CH_3CN	traces	5
8	**1**	DMF	22[e]	70[e]
9	**1**	Dioxane	10	50
10	**1**	$CHCl_3$	traces	n.d

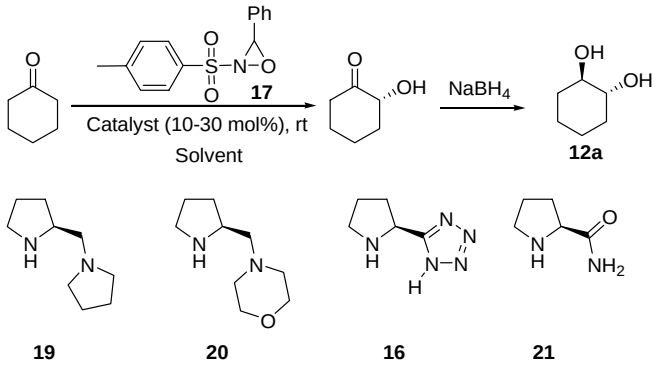
[a] To ketone **9a** (3 mmol) in 4 mL of organic solvent in the presence of organic catalyst (10-30 mol %) was added **18** (1 mmol). After stirring for 16-24 h at room temperature the reaction was quenched either by addition of brine followed be extraction with EtOAc to furnish *α*-hydroxy-ketone **11a** or by *in situ* reduction with excess $NaBH_4$ (15 mmol) at 0 ºC to afford the corresponding optically active crude diol **12a**. [b] Yield of the isolated pure diol **12a**. [c] The ee of *trans*-**12a** as determined by chiral-phase GC analyses. [d] 10 equiv of **9a** was used. [e] Reaction run at 0 ºC.

By conducting the reaction in DMF the enantioselectivity was improved, but decreasing the reaction temperature resulted in a lower *ee*.

2.13 Results and discussion for the *α*-hydroxylation of cyclohexanone using *N*-sulfonyloxaziridine

From the catalyst screen it became clear that the L-proline gave the highest *ee* and the tetrazole ring containing catalyst **16** furnished the highest conversion (Table 2:8).

Table 2:8. Organocatalytic *α*-oxidation of cyclohexanone with *N*-sulfonyloxaziridine.[a]



Entry	Catalyst	Solvent	Product	Yield (%)[b]	*ee* (%)[c]
1	**1**	DMSO	**12a**	44	29
2	**19**	DMSO	*ent*-**12a**	35	39
3	**20**	DMSO	*ent*-**12a**	traces	10
4	**16**	DMSO	**12a**	69	17
5	**21**	DMSO	**12a**	traces	0
6	**19**·AcOH(0.3equiv.)	DMSO	*ent*-**12a**	traces	n.d
7	**19**·TFA(0.3 equiv.)	DMSO	*ent*-**12a**	50	33
8	**19**	THF	*ent*-**12a**	46	37
9	**19**	THF	*ent*-**12a**	11[d]	15[d]
10	**20**	THF	*ent*-**12a**	29	52
11	**20**	$CHCl_3$	*ent*-**12a**	44	45

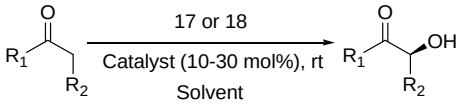
[a] To ketone **12** (3 mmol) in 4 mL of organic solvent in the presence of catalyst (10-30 mol %) was added **17** (1 mmol). After stirring for 16-24 h at room temperature the reaction was quenched either by addition of brine followed by extraction with EtOAc to furnish *α*-hydroxy-ketone **11a** or by *in situ* reduction with excess $NaBH_4$ (15 mmol) at 0 ºC to afford the corresponding optically active crude diol **12a**. [b] Yield of isolated pure diol **12a**. [c] The *ee* of *trans*-**12a** as determined by chiral-phase GC analyses. [d] The reactions were run at 0 ºC.

Substoichiometric amounts of acid were added to two reactions to see if it would affect *ee* and yield as it had been reported to do in diamine catalyzed reactions. The results with acid as additive to the diamine **19** catalyzed reaction increased the conversion but did not improve the *ee* (entry 5). From the solvent screen it was concluded that the best solvent for the diamine catalysts were THF and $CHCl_3$ as both increased the *ee* and furnished the hydroxylated product in yields of 29 and 44 %. In order to explore the possibility of increasing the hydrophobic interaction between catalyst and substrate a test was conducted with water added to the solvent and the yield of the product was increased but the *ee* was to some extent reduced.

2.14 Asymmetric amino-catalyzed *α*-hydroxylations of cyclic ketones with PhIO and *N*-sulfonyloxaziridine

All the reactions with *N*-sulphonyloxaziridine **17** and PhIO **18** had been performed with cyclohexanone **9a** as substrate and that was later expanded with a set of 4-alkyl substituted cyclohexanones **9b-e** that were tested in the amino acid-catalyzed oxidation with $^1O_2$ (Table 2:9).

Table 2:9. Organocatalytic *α*-oxidation of ketones with *N*-sulfonyloxaziridine and PhIO.



Entry	Catalyst	Ketone	Oxidant	Solvent	Product	Yield (%)[a]	*ee* (%)[b]
1	**1**	**9a**	**18**	DMF	**12a**	29	77
2	**1**	**9c**	**18**	DMSO	**12c**	20	70
3	**1**	**9c**	**18**	DMF	**12c**	22	68
4	**1**	**9d**	**18**	DMSO	**12d**	21	65
5	**1**	**9b**	**18**	DMSO	**12b**	10	n.d
6	**20**	**9a**	**17**	THF	**12a**	29	52
7	**20**	**9c**	**17**	THF	**12c**	28	63
8	**20**	**9d**	**17**	THF	**12d**	27	34

[a] Yield of isolated pure diols. [b] The *ee* of *trans*-diol products determined by chiral-phase GC analyses.

The L-proline catalyzed *α*-hydroxylations preceded smoothly using PhIO as oxidant, furnishing the *α*-hydroxy ketones in low yields but with ee's ranging from 65-77%. 2-Octanone was not as easily oxidized and furnished the product in the lowest yield of all the ketones. No other linear ketones were tested as the conversion of 2-octanone was so low and we did not expect other linear ketones to be different. The assumption that other linear ketones would react with similar low conversion was not followed up and investigated.

The corresponding reaction using *N*-sulfonyloxaziridine as oxidant and diamine **20** as catalyst in THF furnished the *α*-hydroxy ketones in similar yields and in lower *ee*. 2-octanone was also tested as substrate in the reaction and it only afforded little more than traces of product. The low yields could be due to decomposition of the electrophiles. This was however not investigated further. The cyclic substrates were the best for the oxidants tested under these conditions. The product yields from the substituted ketones were lower than the yield from cyclohexanone and the ee's dropped with increasing size of the substituent. 2-Octanone was a poor substrate for the *α*-oxidations under the conditions employed.

2.15 Proposed mechanism / TS for the α-hydroxylation of cyclohexanone with PhIO and *N*-sulfonyloxaziridine

The *α*-oxidation of ketones with PhIO or *N*-sulfonyloxaziridine was catalyzed by either amino acids or diamine catalysts. The stereochemistry of the products differed between the two types of catalysts and was determined by comparison with the previously reported *trans*-diol **12a** product from the singlet oxygen oxidation of **9a**. A possible explanation for the difference can be drawn from the suggested transitions states for the L-proline and diamine catalyzed oxidation of cyclohexanone with PhIO and *N*-sulfonyloxaziridine (Figure 2:7). The stereochemical outcome of the L-proline catalyzed reaction is explained by the *re*-facial attack on the catalytically generated enamine by the oxygen of PhIO (TS **I**), or by *N*-sulfonyloxaziridine (TS **II**), which is protonated by the acid moiety of L-proline to furnish the *α*-hydroxylated ketone **11a**. This is in accordance with the previously reported results on proline catalyzed *α*-oxidations with nitrosobenzene and $^1O_2$. The stereochemical outcome of the diamine catalyzed reaction is opposite to the proline catalyzed reaction. In this case, *si*-facial attack on the enamine by the oxygen of *N*-sulfonyloxaziridine occurs (TS **III**) and yields *α*-hydroxy ketone *ent*-**12b**. This transition state is thought to be favored due to hydrophobic interactions.[23]

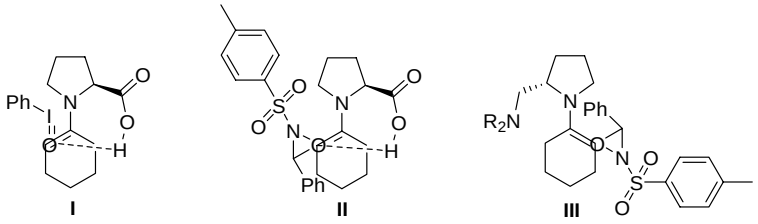


Figure 2:7. The proposed transition states **I-III**. TS **I** and **II** show the plausible TS for the L-proline-catalyzed *α*-hydroxylation of cyclohexanone with PhIO (**I**) and *N*-sulfonyloxaziridine (**II).** TS (**III**) is the plausible TS for the diamine-catalyzed *α*-hydroxylation of cyclohexanone with *N*-sulfonyloxaziridine.

2.16 Conclusions on the *α*-oxidation of ketones with PhIO and *N*-sulfonyloxaziridine

2.16.1 Conclusions on the *α*-oxidation of ketones with PhIO

The *α*-oxidations of ketones with PhIO or *N*-sulfonyloxaziridine both gave better results in polar solvents. For the oxidations with PhIO, DMF was the solvent that gave the product in highest yield and with the highest *ee*. The nature of the catalysts also had an influence of the conversions and *ee*'s. L-proline catalyzed the reaction best while the diamine catalysts **19** and **20** only furnished trace amounts of the product. This suggests a hydrogenbond activation of the PhIO by the L-proline derived enamine which would decrease electron density at the PhIO oxygen and make it more susceptible to attack by the enamine.

The diamine catalysts **19** and **20** furnish very little product. This may be due to their inability to activate PhIO by hydrogen bonding as they lack the required proton. Giving an explanation for the behavior of catalysts **8** and **16** is not as easy, as they both have protons available for hydrogen bonding to PhIO, so other factors must affect the outcome as well. From the $^1O_2$ experiments we know that **16** readily formed the enamine with cyclohexanone, as does **8** to a lesser extent. Possibly, the enamines the catalysts **8** and **16** form adopts conformations that are not favored for the entry of PhIO. The *α*-oxidation of the 4-alkyl substituted cyclohexanones showed that the product *ee*'s decreased with increasing bulk of the substituent.

2.16.2 Conclusions on the *α*-oxidation of ketones with *N*-sulfonyloxaziridine

L-proline furnishes the *α*-hydroxylated cyclohexanone in DMSO in higher yield when *N*-sulfonyloxaziridine is used compared to PhIO. Furthermore, the diamine **19** could be used with *N*-sulfonyloxaziridine as an electrophile, rather than PhIO. This suggests that the *N*-sulfonyloxaziridine is more reactive than PhIO. The results from the addition of acid to the reactions are harder to explain. Acetic acid (AcOH) nearly stopped the catalysis while trifluoro acetic acid (TFA) enhanced the product yield. The increase of product in the latter case could be due to acid assistance in the enamine formation. The small effect on *ee* may be a result of activation of the oxidant by protonation and nonselective reaction with the enamine, which would explain the increased yield and relatively unaffected *ee* in the product. Changing solvent to THF for catalyst **19** furnished the product in higher yield and similar *ee* as when the reaction was performed in DMSO. While catalyst **20** performed poorly in DMSO, in $CHCl_3$ and THF, its performance was improved. In $CHCl_3$ the product yield reached 44 % with an *ee* of 45 %. In THF we obtained the highest product *ee* for *N*-sulfonyloxaziridine oxidation of cyclohexanone. This could be because both THF and $CHCl_3$ are less polar solvents than DMSO and thus force the enamine and oxidant closer to each other in the transition state and furnish a more enantioselective oxidation. Catalyst **16** was very effective and furnished the highest product yields, unfortunately in low *ee*. Catalyst **21** was under the conditions tested, the poorest catalyst of the ones we tested, as very little product could be detected. In general it would be interesting to test some of the catalysts again in other solvents. Specifically, it would be interesting to try catalyst **16** in THF and catalyst **19** in $CHCl_3$. The trend when applying the *N*-sulfonyloxaziridine in *α*-oxidation of the 4-alkyl substituted cyclohexanones revealed that the best *ee* was obtained when the substituent was an ethyl group. This might be because the enamine adopts a configuration that enhances the enantiodifferantiation in which the ethyl group plays a vital role. The product *ee* is reduced when the alkyl substituent is changed to the more bulky isopropyl group. Unfortunately we did not run the reaction with the 4-methyl substituted cyclohexanone, as that may give some information on whether an even smaller substituent would affect the selectivity more.

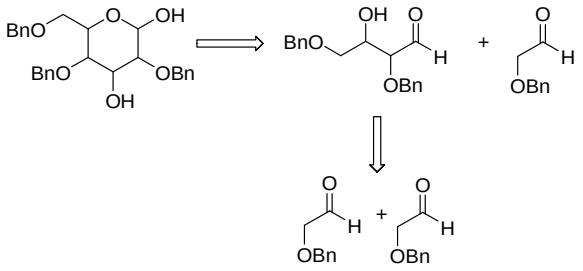
3 Amino acid-catalyzed neogenesis of carbohydrates [V, VI]

3.1 Introduction

A question that crossed our minds when we developed the $^1O_2$ oxidation of aldehydes was whether amino acids also could catalyze the formation of hexoses from glycoaldehydes. Under prebiotic conditions, it is considered that amino acids were responsible for the formation of tetroses out of glycoaldehydes, and it is reasonable to suspect that amino acids could catalyze the formation of hexoses as well. This interesting aspect of amino acid catalysis was investigated with the hope of finding a short route to hexoses.

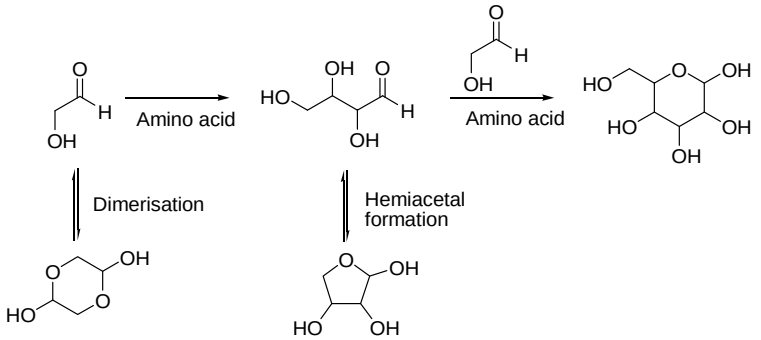
3.2 Strategy for the synthesis of hexoses

A retrosynthetic analysis of a hexose indicates that an amino acid-catalyzed trimerisation of a suitable glycoaldehyde is a possibility. The reaction would proceed by two sequential aldol reactions to furnish a benzylated hexose as the product (Scheme 3:1).



Scheme 3:1. Retrosynthetic analysis of a benzylated hexose.

The reason for using a protected glycoaldehyde was to prevent the possibilities for undesired cyclizations. If the alcohol functionality would be unprotected in *O*-benzyloxy acetaldehyde it could possibly form a dimer and the tetrose intermediate could also cyclize and form a hemiacetal (Scheme 3:2). Both these cyclisations would lower the yield of the hexose. Benzyl groups were chosen to protect the alcohol oxygens as they should be easily removed by hydrogenolysis. Debenzylation would also leave the hexose open for peracetylation prior to GC analysis.

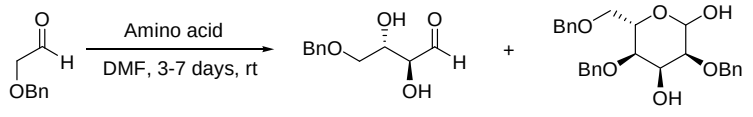


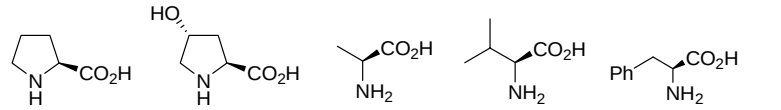
Scheme 3:2. The possible cyclisations that can occur if performing the reaction with unprotected alcohol functionality.

3.3 Results and discussion

An initial trimerisation test of *O*-benzyloxyacetaldehyde **22** was performed with L-4-hydroxyproline as a catalyst in DMF. The reaction furnished both the tetrose **23** and 2, 4, 6-tri-*O*-benzyl-allose **24** in 28 % yield as a single diastereomer with >99 % *ee* and showed that it was possible to make a natural benzyl-protected hexose in a one step reaction. This encouraged further investigation of more amino acids as possible catalysts for this reaction (Table 3:1).

Table 3:1. One-pot amino acid-catalyzed trimerization of *O*-benzyloxyacetaldehyde.





Entry	Catalyst	Tetrose	Yield(%)[a]	d.r	*ee*(%)[b]	Hexose	Yield(%)[c]	*ee*(%)[d]
1	*ent*-**3**	**23**	62	2:1	86	**24**	traces	n.d
2	*ent*-**4**	**23**	51	2:1	80	**24**	traces	n.d
3	**2**	**23**	62	5:1	97	**24**	28	>99
4	**3**	*ent*-**23**	67	2:1	88	*ent*-**24**	traces	n.d
5	**4**	*ent*-**23**	52	2:1	81	*ent*-**24**	traces	n.d
6	**12**	*ent*-**23**	55	2:1	71	*ent*-**24**	traces	n.d
7	**1**	**23**	51[e]	4:1[e]	98[e]	**24**	41[e]	>99[e]
8	*ent*-**1**	*ent*-**23**	50[e]	4:1[e]	98[e]	*ent*-**24**	40[e]	>99[e]
9	**1**	**23**	71[f]	4:1[f]	98[f]	**24**	26[f]	>99[f]
10	**1**	**23**	64[g]	4:1[g]	98[g]	**24**	24[g]	>99[g]

[a] Isolated yield after silica-gel column chromatography. [b] Diastereoselectivity (d.r) was determined by ^{1}H NMR of the crude product. [c] The *ee* of **40** was determined by chiral-phase HPLC analyses. [d] The *ee* of hexose **24** was determined by chiral-phase GC analyses of the peracetylated hexose. Racemic hexose **24** was obtained by D,L-proline-catalysis. [e] 4 days reaction time. [f] 2 days reaction time. [g] Reaction performed in DMSO.

All of the amino acids tested mediated the reaction and the formation of 1, 2-di-*O*-benzyl-erythrose **23**. The primary amino acids provided the tetrose but with lower *ee* than the cyclic amino acids. They also only furnished traces of hexoses. The cyclic amino acids, **1** and **2,** on the other hand gave 2, 4, 6-tri-*O*-benzyl-allose, **24**, as a single diastereomer in 41% and 28% yield with >99% *ee*. The yields of the hexoses are comparable to most conventional multi-step syntheses. In addition to being the shortest known synthetic route to a hexose, the aldol additions take place in a highly selective way with almost complete control over the four stereocenters created in the reaction.

3.4 Non-linear effect in the L-proline catalyzed cross aldol-assembly of hexoses

The origin of the homochirality of natural amino acids and sugars have intrigued and interested researchers for decades.[24] The evolution of high asymmetry from a diminutive imbalance of enantiomers was suggested and given a theoretical explanation more than half a century ago. This has led to the speculation that amino acid may have operated as catalysts for the evolution of biological homochirality. Amino acids with a slight enantiomeric excess that could have started such a process has been found in carbonaceous meteorites.[25] These extraterrestrial amino acids have been found with up to 9 % *ee* and it is speculated that amino acids of such low optical activity might have initiated the asymmetric neogenesis of hexose carbohydrates on earth. The synthesis of hexose carbohydrates have since been catalyzed by enzymes for millions of years.[26] It is also speculated that the amino acid catalysis was a possible route to the development of biological homochirality.[27] The asymmetric amplification of sugars is directly connected to the evolution of homochiral RNA synthesis, as well as to the selective chiral amino-acylation, which is the first step in the asymmetric protein synthesis.[28, 29] The confirmation that amino acids catalyzed the formation of benzylated allose from **22** and with good enantioselectivity paved the way for the investigation on the influence the catalysts' *ee*'s would have on the *ee*'s in the formed hexoses. Since the L- proline-catalyzed reaction furnished **24** with the highest yield, we decided to perform 7 L- proline-catalyzed reactions with varying catalyst *ee*. From all the reactions, **24** was isolated, it's *ee* determined, and plotted *versus* the catalyst *ee* (Figure 3:1). The obtained curve clearly shows a non-linear relationship between the *ee* of the catalyst and that of the obtained hexose **24**.

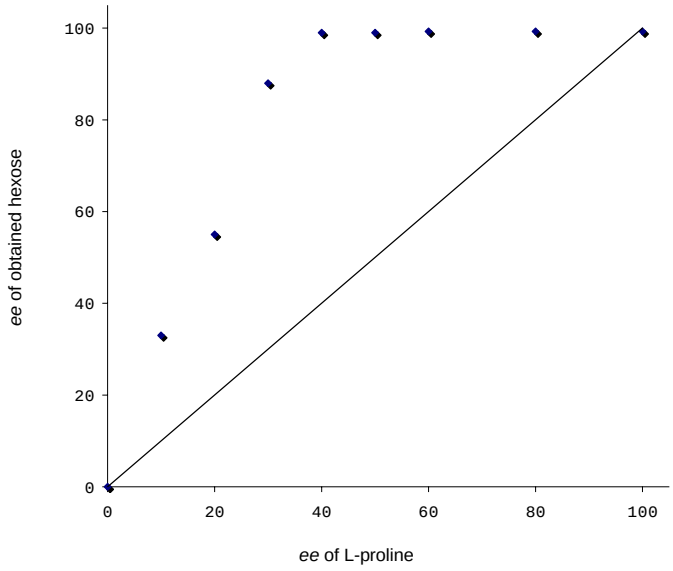
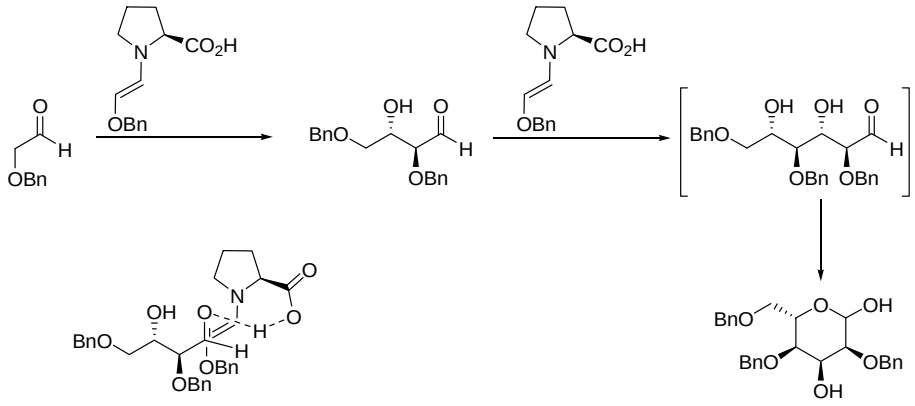


Figure 3:1. The graph shows the non-linear relationship between the *ee* of the amino acid catalyst and the *ee* of the product hexose **24**.

The *ee* of the sugar did not decrease drastically until the *ee* of the catalyst was below 40%. L-proline with an *ee* of 30 % furnished the sugar **24** with 85 % *ee*. Using L-proline with a 10% *ee* resulted in 33 % *ee* in hexose **24**. Catalyzing the reaction with D-proline of high optical purity (>99% *ee*) resulted in the formation of the enantiomer of **24**. Catalyzing the reaction with racemic D, L-proline gave no *ee* in the formed hexose. These results demonstrate that the configuration of the catalyst determine the configuration of the product hexose. The significant non-linear effect found between the *ee* of L-proline and the formed hexose is the largest reported permanent non-linear effect found for a proline catalyzed reaction up to date.[30, 31] At the moment we can not give an explanation for the observed asymmetric amplification that takes place in the reaction. Experiments are however planned that should give the information needed to explain the observed non-linear effect. Measuring the *ee* of the formed tetrose intermediate should tell us whether the asymmetric amplification takes place in the first or second step of the hexose formation.

3.5 Mechanism

The amino acid-catalyzed formation of hexoses is a sequential one-pot direct catalytic asymmetric aldol reaction, where the initially formed erythrose derivative undergoes a second enamine-catalyzed aldol reaction to furnish the hexose with excellent diastereo- and enantioselectivity (Scheme 3:3).



Scheme 3:3. The amino acid-catalyzed one-step synthesis of allose and the plausible TS in the second aldol addition step.

The stereoselectivity of the erythrose is set in the first aldol addition step and dictated by the catalytic enamine intermediate, which is formed between the amino acid and the glycoladehyde donor.[32, 33] Next, the erythrose adds to the *re*-face of the catalytic enamine intermediate and allose is formed. The rate of the second *anti*-selective aldol reaction is significantly slower than the initial aldol addition, which is established by the higher amount of erythrose intermediate formed compared to allose. Hence, the hexose formation is the rate-

determining step. Furthermore, the tetrose intermediate is less stable than the final hexose. The *ee* of the tetrose decreased with longer reaction times, and this will also be investigated further. No decrease in hexose *ee* caused by longer reaction times was found. Therefore, one can believe that the interactions between non-enantiomerically pure proline and the tetrose intermediate are important for the amplification of asymmetry in the sequential aldol additions.

3.6 Conclusions

We have shown with this work that amino acids catalyze the formation of tetroses and, more importantly hexoses from a glycoaldehyde precursor. The tetrose-forming first step is faster than the formation of the hexose as the tetrose is present in higher amount than the isolated hexose. The amino acid-catalyzed formation of allose is conducted with very high selectivity and the product *ee* is >99 %. The very pronounced non-linear effect observed when altering the catalysts' *ee* will be investigated by measuring the tetrose intermediate's *ee* as a function of catalyst *ee*. That information should tell us if the asymmetric amplification takes place in the first or second step and help us explain the observed results. We think the asymmetric amplification caused by quite low catalyst *ee*'s is intriguing as it is suggested that amino acids were responsible for the formation of tetroses and hexoses during the prebiotic era on earth. It further suggests that the amino acids may have played a part in the development of biomolecular homochirality in nature, as suggested by the fact that nearly all organisms use L-amino acids for protein synthesis and D-sugars for RNA- and DNA formation. Our experiments support this, as we observed that two L-amino acids catalyze the formation of a D-sugar and that the sugars' *ee*'s became higher than that of the catalyst in our experiments. Meteorites containing amino acids with low optical purity have been found and brought forth as support for this theory. The interesting question is then from where did an *ee* in the amino acids originate. In answer to this there is a not unchallenged theory of L-amino acids being more stable than their D-counterparts.[34]

4 Asymmetric synthesis of functionalized deoxysugars [IV, VI]

4.1 Introduction

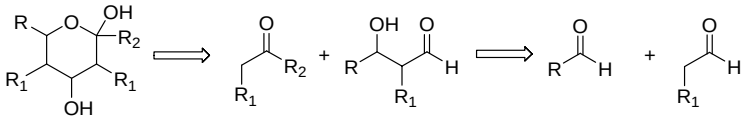
The directed asymmetric assembly of simple achiral building blocks into stereochemically complex molecules like carbohydrates and polypeptides has long been accomplished by enzymes in nature.[35] The interest in glycobiology and the search for new antibiotics has led to increased activity in developing reactions and methods for the synthesis of sugars and polyketides.[36]

4.2 Existing methodology for obtaining polyketide-sugars

Among the methods available, the aldol reaction is a well established approach in carbohydrate and triketide-synthesis.[37, 38] It usually requires protective group strategies and subsequent reduction–oxidation which adds synthetic steps. In particular, chiral auxiliaries like Evans' oxazolidinones have been successfully applied in aldol reactions.

4.3 Direct amino acid-catalyzed asymmetric synthesis of polyketide-sugars

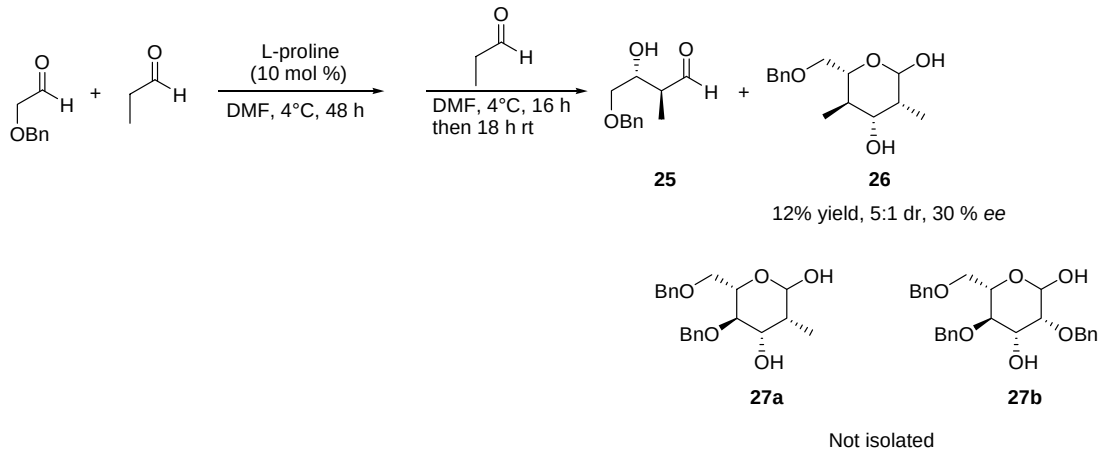
The use of enamine catalysis has enabled the first step of the sequential direct cross-aldol reaction with high stereoselectivity.[39] To date, only enzymes have been able to catalyze sequential one-pot direct aldol reactions with high stereoselectivity.[40] Also, no reaction or catalyst is reported to have achieved both the first and the second aldol step to obtain hexoses with high enantioselectivity. The first attempts on one-pot catalytic sequential aldol reactions furnished nearly racemic triketide sugars.[39f, g] A synthetic strategy, based on retrosynthetic analysis of a polyketide sugars, was found to be an amino acid-catalyzed iterative two-step aldol reaction (Scheme 4:1).



Scheme 4:1. Retrosynthesis of a polyketide sugar.

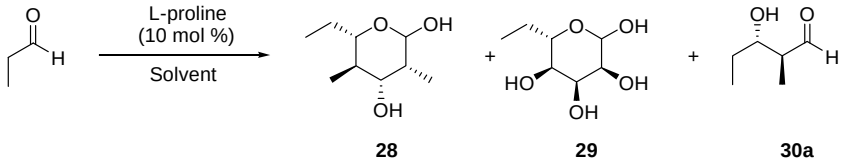
4.4 The one-pot synthesis of polyketide sugars

The first reaction performed to investigate our idea of synthesizing polyketide sugars in a sequential one-pot fashion by amino acid catalysis was the addition of propoionaldehyde to the formed aldol-adduct from *O*-benzyloxy-acetaldehyde and propionaldehyde **25** (Scheme 4:2). The first proline-catalyzed step was performed at 4°C for 48 h and the second addition and reaction at 4°C for 16 h. From this reaction polyketide **26** was isolated in 12 % yield and in 30 % *ee*. The other two possible sugars (**27a**, **27b)** were not found in the reaction which indicates a highly chemoselective sequential aldol-reaction.



Scheme 4:2. The synthesis of sugar **26** in a highly chemoselective sequential one-pot reaction.

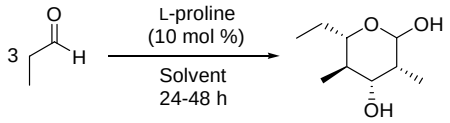
The proline-catalyzed trimerization of propionaldehyde was also investigated and polyketide sugar **28** was isolated along traces of **29** and unreacted **30a** (Scheme 4:3).



Scheme 4:3. Proline-catalyzed trimerization of propionaldehyde.

A screen of reaction conditions was conducted for the trimerization of propionaldehyde (Table 4:1). All the reactions furnished polyketide **28** in varying amounts and *ee*'s along with traces of **29** and propionalaldehyde dimer **30a**. The development of a new method (entry 6) enabled us to isolate **28** as the major diastereomer in 31 % yield and 85 % *ee*.

Table 4:1. Table showing some of the conditions tested for the trimerization of propionaldehyde.

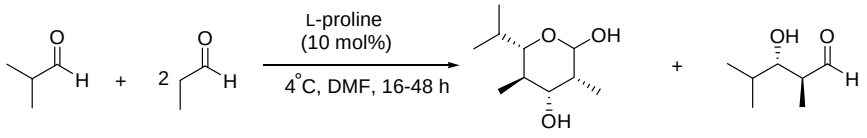


28

Entry	Solvent	Conditions	Yield (%)[a]	*ee* (%)
1	DMF	rt[c]	22	33
2	DMF	rt[d]	50	11
3	CH_3CN	rt	16	12
4	DMF	4°C	11	48
5	DMF	A[e]	17	40
6	DMF	B[f]	31	85
7	DMF	C[g]	12	71
8	1,4-dioxane	rt	16	18

[a]Isolated yield. [b] The *ee* of hexose **28** was determined by chiral-phase GC analyses. [c] 24 h reaction time. [d] 72h reaction time. [e] To a reaction mixture of L-proline in DMF was added slowly propionaldehyde at 4 ºC over 16 h and then stirring at room temperature for 24 h. [f] See experimental section in paper VI. [g] To a reaction mixture of L-proline and racemic **30a** (1 mmol) in DMF was added slowly propionaldehyde (2 mmol) at 4º C over 16 h and then stirring at room temperature for 24 h.

The amino acid-catalyzed asymmetric one-pot procedure for the synthesis of **28** was not equally successful when applied in the synthesis of **31**, which was obtained as a single diastereomer in 33 % yield and in low *ee* (Scheme 4:4). The cross-aldol adduct **32** was also isolated. The synthesis of **28** via trimerization of propionaldehyde had been most successful and the cross aldol reaction to obtain **31** furnished the product in similar yield. However, the *ee* was low, and this initiated some further questions on what controls the stereoselectivity in the reaction.



31 Isolated in 33 % yield and with *ee* < 12 %

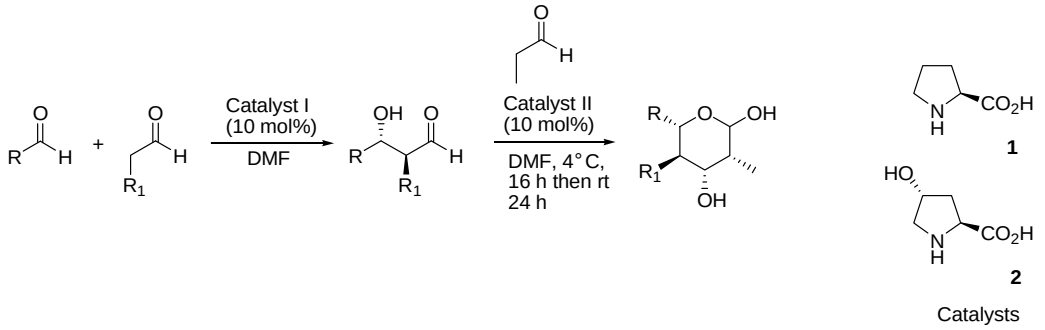
32

Scheme 4:4. Amino acid-catalyzed one-pot synthesis of polyketide **31**.

4.5 The two step synthesis of polyketide sugars

From the one-pot proline-catalyzed sequential direct aldol reactions one thing was evident, the reactions in general suffered from low product *ee*. The poor stereoselectivity in the one-pot reactions could be due to a missmatch relationship between the L-proline derived enamine and the L-proline mediated cross aldol adduct from the first step. From molecular modeling it was concluded that a D-proline derived enamine would attack the cross aldol adduct in a more enantioselective way. Hence, a new procedure was adopted. The L-proline derived cross aldol adduct was isolated prior to the D-proline-catalyzed second aldol step. Applying this method in the synthesis of hexose **28** led to a product yield of 29 % and *ee* of 99 %. We interpreted this result as a conformation that obtaining polyketide sugars with high *ee*'s necessitates a two step procedure as the stereochemical demands change between the two aldol steps. The newly developed two-step approach for the synthesis of polyketide sugars could be performed with a variety of alehydes and polyketide sugars **28**, **31**, and **33**-**35** were formed in the highly diastereo- and enantioselective two-step reaction. The remarkable selectivity in the reaction allows the product to be isolated as only one enantiomer out of a possible 16 stereoisomers. The products were isolated in yields ranging from 15-42 % and *ee*'s >99 % (Table 4:2).

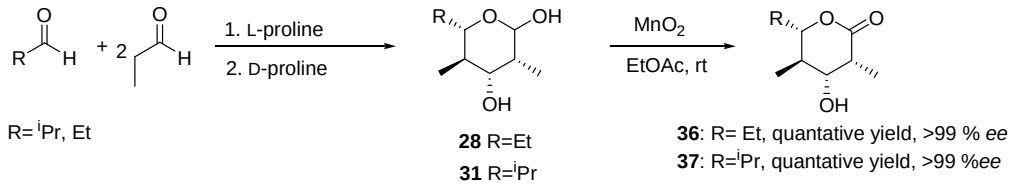
Table 4:2. The two step amino acid-catalyzed asymmetric synthesis of polyketide sugars.



Entry	R	R_1	Catalyst I	Catalyst II	Sugar	Yield (%)[a]	*ee* (%)[b]
1	$BnOCH_2$	OBn	**1**	*ent*-**1**	**35a**	39[c]	>99
2	$BnOCH_2$	OBn	*ent*-**1**	**1**	*ent*-**35a**	38[c]	>99
3	$BnOCH_2$	Me	**1**	*ent*-**1**	**35b**	30[d]	>99
4	$BnOCH_2$	Me	*ent*-**1**	**1**	*ent*-**35b**	29[d]	>99
5	Et	Me	**1**	*ent*-**1**	**28**	29[d]	99
6	^{i}Pr	Me	**1**	*ent*-**1**	**31**	42[d]	>99
7	^{i}Pr	Me	*ent*-**1**	**1**	*ent*-**31**	40[d]	>99
8	Et	Me	*ent*-**1**	**2**[c]	*ent*-**28**	30[d]	>99
9	^{i}Pr	Me	*ent*-**1**	**2**[c]	*ent*-**31**	15[d]	>99
10	^{i}Bu	Me	**1**	*ent*-**1**	**33**	24[d]	>99
11	c-hex	Me	**1**	*ent*-**1**	**34**	41[d]	>99

[a] Isolated overall yield of the hexoses based on the two-steps. [b] Determined by chiral-phase GC analyses of the peracetylated products and compared to racemic standards generated by D, L-proline catalysis. [c] 30 mol % hydroxy-proline was used. [d] The overall combined yield of a 10:1 diastereomer mixture (*anti*:*syn*).

Apart from being the shortest known synthetic route to polyketide sugars, the advantage of the method is that the intermediate is isolated and there is a possibility of changing catalyst prior to the second aldol step. For our entry 1, *ee* was brought above 99 % by exchanging catalyst *ent*-**1** to **2** in the second step. The yields of the sugars formed by this method were comparable or higher than most multi-step synthesis. Starting the iterative aldol reactions with D-proline as catalyst furnished the opposite enantiomer of the hexoses without affecting the stereoselectivity in the reaction. The hexoses were quantitatively converted into δ-lactones by oxidation with MnO_2 in EtOAc. For example, lactones **36** and **37** were prepared in three steps in >99% *ee* (Scheme 4:5).



Scheme 4:5. Amino acid-catalyzed enantioselective synthesis of δ-lactones **36** and **37**.

Thus, the two-step aldol strategy opens up a novel route to enantiomerically pure δ-lactones from simple aldehydes. This type of compounds was previously synthesized in 11 steps by using Evans type aldol-reactions. The absolute configurations of sugars in table 4:1 have been assigned based on the crystal structure of the α-anomer of sugar **31** (Figure 4:1).

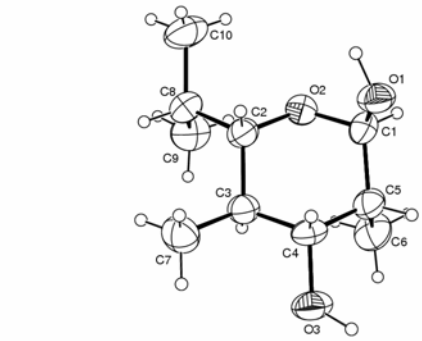
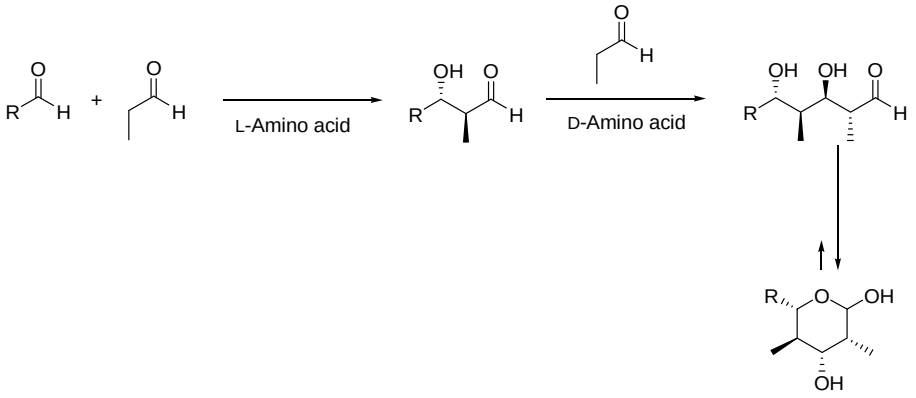


Figure 4:1. The crystal structure of the α-anomer of sugar **31**.

The crystal structure reveals that the previously suggested relative configuration of triketide sugar **31** was incorrect.[27f] The hexose **31** obtained by proline-catalysis has a mannopyranoside configuration and not the previously believed gulopyranoside configuration.[31f]

4.6 Mechanism of the two-step asymmetric amino acid-catalyzed assembly of polyketide sugars

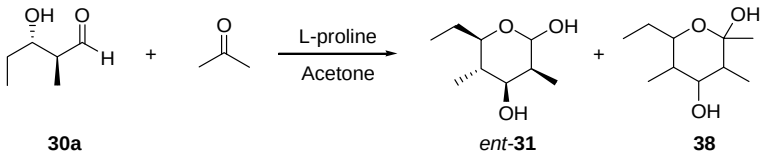
The initial formation of the *β*-hydroxyaldehyde proceeds by a *re*-facial attack on the acceptor aldehyde by the L-proline-derived enamine, which is in accordance with previous reported proline-catalyzed aldol reactions with aldehydes.[31] Next, the D-proline-catalyzed aldol addition proceeds in a highly *anti*-selective fashion with the *anti*-*β*-hydroxyaldehyde isomer to form the L-mannose structural motif. The sequential L- and D-proline catalysis furnished L-hexoses. Accordingly, the observed stereochemistry of the hexoses can be readily explained (Scheme 4:6)



Scheme 4:6. The two-step amino acid-catalyzed route to polyketide sugars.

4.7 Mechanism of the one-pot asymmetric amino acid-catalyzed assembly of polyketide sugars

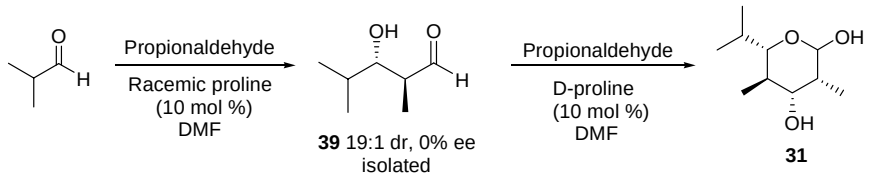
In an investigation on the possibility of performing a sequential L-proline-catalyzed cross-aldol reaction between the L-selfaldol adduct from propionaldehyde and acetone to form polyketide **38**, the L-selfaldol adduct **30a** (4:1 d.r, 99% *ee*) was formed in acetone by L-proline catalysis (Scheme 4:7). Not much acetone addition occurred in the reaction and only traces of polyketide **38** was isolated, however some *ent*-**31** was formed in the reaction and isolated. The remaining selfaldol adduct was nearly racemic (<10 % *ee*) and this suggested that L-proline must be responsible for the racemisation of L-*β*-hydroxy-aldehyde **30a** by a *retro*-aldol reaction. The formed D-*β*-hydroxy-aldehyde **30b** then underwent a selective L-proline-catalyzed cross-aldol reaction and formed polyketide *ent*-**31** in 17 % yield and 71 % *ee*.



Scheme 4:7. L-proline-catalyzed attempt to form the cross-aldol polyketide **31**.

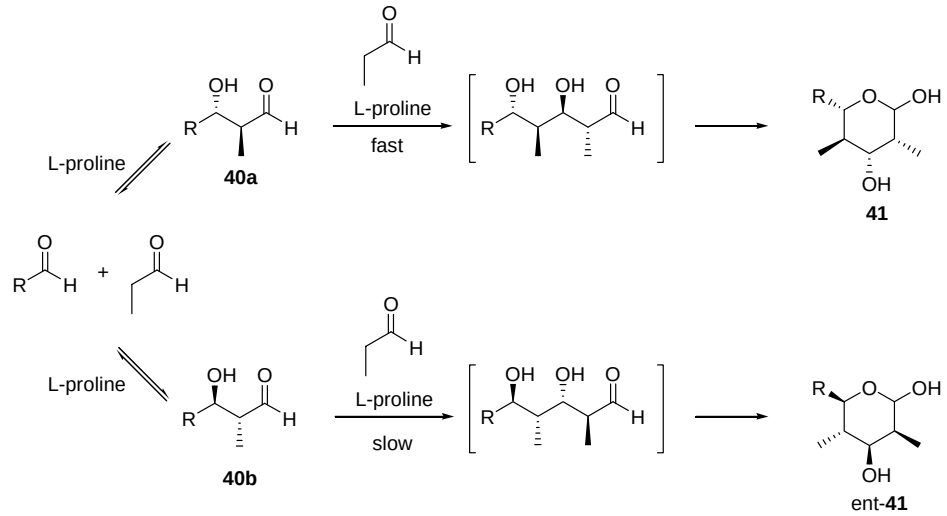
This clearly demonstrates that L-proline can interact not only with the donor aldehyde but with the *β*-hydroxy-aldehyde intermediates and cause racemization. From experiments with the racemic form of *β*-hydroxy-aldehyde **30a** it was demonstrated that amino acids catalyzed the formation of polyketides with high enantioselectivity.

To establish whether proline is able to discriminate between the two enantiomers of *anti*-*β*-hydroxy-aldehydes in sequential cross-aldol reactions, the proline-catalyzed *anti*-selective propionaldehyde addition to racemic *anti*-*β*-hydroxy aldehyde **39** was investigated (Scheme 4:8).



Scheme 4:8. A two-step synthesis of a polyketide hexose. The first step is catalyzed by racemic proline and the second with enantiomerically pure D-proline

When propionaldehyde was reacted with the racemic aldol adduct **39** in the presence of a catalytic amount of D-proline, the reaction proceeded with excellent selectivity and polyketide hexose **31** was isolated in 28 % yield with >19:1 d.r and 95 % *ee* together with remaining acceptor aldehyde with <5 % *ee*. From those experiments and by the absolute configuration of the isolated D-polyketide sugars it was assumed that the amino acids racemizes the L-*β*-hydroxy-aldehyde, **40a**, and in a subsequent highly selective cross-aldol reaction forms **40b** that in turn undergoes a slow L-proline-catalyzed cross-aldol reaction and forms *ent*-**41** (Scheme 4:9).



Scheme 4:9. The plausible mechanism for the L-proline-catalyzed one–pot synthesis of polyketides **41** and *ent*-**41**.

The L-proline catalyzed one-pot synthesis of polyketides furnished corresponding D-hexoses which is opposite to the absolute configuration of the hexoses produced in the two-step L- and D-proline-catalyzed way. We conclude that amino acids catalyze dynamic, kinetic asymmetric transformations (DYKAT).[3]

4.8 Conclusions on the synthesis of polyketide sugars

The experiments demonstrate that amino acids catalyze the formation of polyketide sugars. The polyketides can be assembled in a sequential one-pot reaction or in our newly developed two-step procedure, which proceeds with very high chemo-, diastereo- and enantioselectivity. The iterative method furnishes polyketides with *ee*'s above 99 % for several aldehydes and the yield is higher with this method than compared to the one-pot sequential version. Future use and application of this methodology should be of great value to chemists working with the synthesis of natural products, functionalized sugars or isotope labeling. The isolation of the *β*-hydroxy intermediate allows for change of catalyst prior to the second step. Screening of catalysts for the second step would probably assure a high *ee* in the product. Both the one-pot and the iterative procedure owe their good performance to amino acid catalyzed DYKAT.[3] In the DYKAT process, the amino acid racemizes the *β*-hydroxy intermediate by *retro*-aldol mechanisms and the amino acid reacts faster with one of the diastereomers thus giving the high *ee*'s we found in the polyketide sugars. The deoxysugars obtained from these methods have free hydroxyl groups at C1 and C3 which allows for further manipulations, like introduction of protective groups and di- or polysaccharide couplings.

5 Summery and outlook

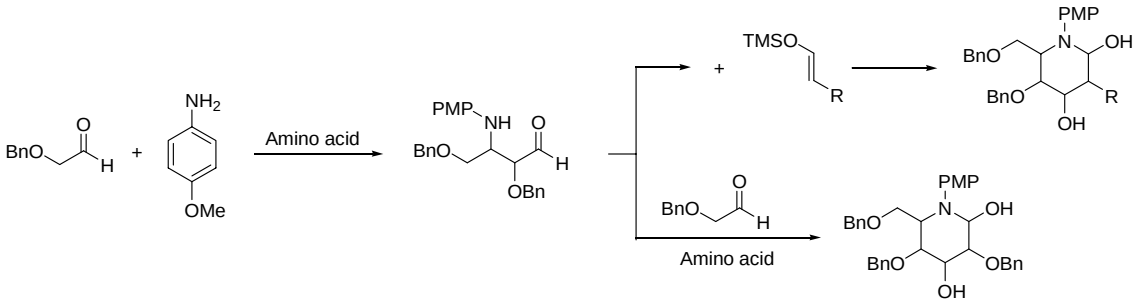
Organocatalysis is a rapidly growing area in synthetic chemistry and the set of reactions that can be performed catalytically by low molar mass organic compounds are expanding. In this work, we have demonstrated for the first time that amino acids can catalyze *α*-oxidation of aldehydes and ketones with $^1O_2$ to furnish *α*-hydroxy carbonyls with good *ee*'s and in good yield for many substrates. Still, the method needs development and further studies to improve the enantioselectivity and conversion. The catalysts can be modified as well as the reaction conditions and if optimized, it would be an attractive approach to chiral *α*-hydroxy carbonyl compounds as molecular oxygen and enantiopure amino acids are relatively cheap. The general high tolerance of the reaction also makes it attractive and easy to perform. The other oxidants we screened for the same transformation also furnished *α*-oxidation of ketones in moderate *ee*'s and product yields. We believe that these oxidants in addition to being more expensive also are more sensitive to the reaction conditions than the corresponding singlet oxygen route. A more extensive investigation of the catalysts to determine and optimize their design for use in both the iodosobenzene- and *N*-sulphonyloxaziridine reactions would be desirable. Such an investigation should provide valuable knowledge on what parameters enhance enantioselectivity and conversion.

Continuing our work on amino acid-catalysis made us investigate the possibilities of assembling hexoses from a protected glycoaldehyde. This was fully possible and in a one-pot sequential reaction the cyclic amino acids catalyzed the trimerization of *O*-benzyloxyacetaldehyde to 2, 4, 6-*O*-benzylallose, which was obtained as a single diastereomer in >99 % *ee*. The linear amino acids only produced traces of hexose sugar while proline and hyroxyproline catalyzed the formation of the hexose with *ee*'s >99 % and in similar yields compared to the multi-step methods otherwise used for their preparation. The tetrose intermediate was formed in substantial amounts by all the amino acids tested. During the experiments on amino acid-catalyzed hexose formation we began investigating the relationship between the *ee*'s of the catalysts and the product hexoses. The tests revealed a significant non-linear relationship. Further study is needed to understand these results, and this will involve an investigation on the *ee* of the tetrose compared to the *ee* of the catalyst. With those results it will be easier to speculate on the mechanism responsible for the interesting asymmetric amplification that is considerable even at low catalyst *ee*'s.

In our attempt to expand the scope of the amino acid-catalyzed hexose synthesis, we became interested in assembling polyketide sugars and the direct amino acid-catalyzed sequential one-pot synthesis was developed. After optimization of the conditions it furnished the trimerization product of propanal in good yield and a very high *ee*. The problems we experienced in the cross aldol reactions in the one-pot synthesis were solved as we developed a new two step procedure. The two step procedure, which is the shortest reported route to

polyketides and deoxysugars, have opened the way for polyketide- and deoxysugars synthesis with a remarkably high stereoselectivity and with good product yields. All aldehydes we tested could be transformed into polyketides or deoxysugars with *ee*'s >99 % with the exchange of catalyst between the steps.

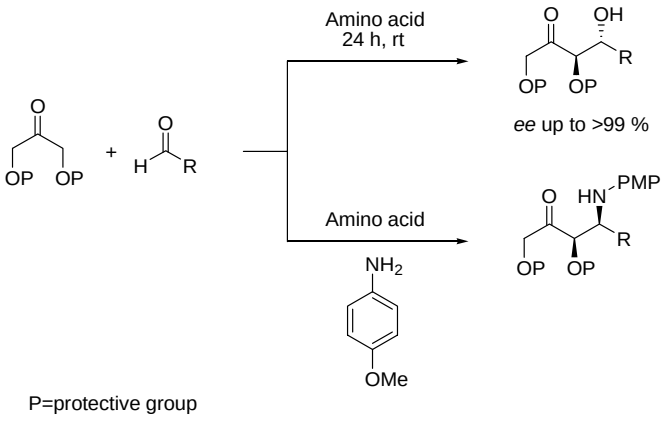
Amino sugars is an interesting substance-class that we would like to develop preparative methodology for as they are of medicinal interest and we think they can be obtained with some modifications to our existing methodology for carbohydrate synthesis (Scheme 5:1).



Scheme 5:1. Our considered routes for synthesis of amino sugars.

Our suggested approaches are based on a Mannich product which could either be treated with an enolate to form the amino sugar or by letting the Mannich product undergo an amino acid-catalyzed aldol reaction that would possibly furnish the amino sugar.[41]

We recently accomplished an amino acid-catalyzed one-step enantioselective synthesis of ketosugars (Scheme 5:2). This would further open up the area for *de novo* synthesis of carbohydrates.



Scheme 5:2. The synthesis of ketosugars and the corresponding amino derivatives.

Acknowledgements

I would like to thank the following persons for their direct influence on the making of this thesis:

My supervisor Armando Córdova for accepting me in to his research group and for all the help and guidance provided during this intensive year.

Jan-Erling Bäckvall, Adolf Gogoll and Lars Engman for giving me the opportunity to finish my education in Stockholm.

The department of organic chemistry in Uppsala for extended financial support.

Susan Schofer for taking the time correcting the language in the thesis.

The people I've had the pleasure to work with in the Armando Córdova group and all you other people from the organic chemistry department at Stockholm University that have made this a year to remember.

The people in the Pher Andersson group in Uppsala, thanks for all your help and the party invitations, I never left you, did I?

I would like to thank the following persons for their substantial support during the year in matters not directly connected to the work, however not less important:

Magnus Emilsson, Cecilia Ericsson, Niclas Sandström, Maria Arvidsson, Joakim Thörn, Linda Anderzon, Pedro Pihno, Christian Hedberg, Klas Källström, Joachim and John Östlund.

My family, friends and östgötarna.

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