STEREOCONTROL IN TANDEM REACTION SEQUENCES UNDER HYDROFORMYLATION CONDITIONS

Dissertation

zur

Erlangung des akademischen Grades eines

Doktors der Naturwissenschaften

(Dr. rer. nat.)

des Fachbereichs Chemie der Universität Dortmund

vorgelegt von

Serghei Chercheja

aus Chisinau (Republik Moldau)

Dortmund, 2007

1. Gutachter: Prof. Dr. Peter Eilbracht

2. Gutachter: Prof. Dr. Alois Fürstner

Tag der mündlichen Prüfung: 6. Nobember 2007

The following work took place in the time from October 2004 until September 2007 at the Faculty of Chemistry, University of Dortmund, under supervision of Prof. Dr. Peter Eilbracht.

The work on this thesis has been an inspiring, often exciting, sometimes challenging, but always interesting experience. It has been made possible by many other people, who have supported me.

First of all, I would like to express my deepest sense of gratitude to my supervisor Prof. Dr. Peter Eilbracht for his patient guidance, encouragement and excellent advice throughout this study.

My sincere thanks are due to the official referees, Prof. Dr. Alois Fürstner and Prof. Dr. Peter Eilbracht for their detailed review, constructive criticism and excellent advice during the preparation of this thesis. I would also like to thank the other member of my PhD committee Dr. Horst Hillgärtner who monitored my work and took effort in reading and providing me with valuable comments on earlier versions of this thesis. I would like to thank Prof. Dr. Bernd Plietker for the help with the chiral HPLC experiments and Prof. Dr. Burkhard Costissela for the help with NMR experiments.

I am grateful to the present and former members of the Eilbracht and Schmidt workgroups for their support and their comradeship: Prof Dr. B. Schmidt, Y. Berezhanskyy, K. Tuz (Kot), N. Mészáros, T. Rothenbücher, M. A. Subhani, B. Bondzic, A. Bokelmann, M. Gatys, J. Liebich, Dr. I. Kownacki, Z. Krausova (Alexandrová), Dr. A. Kovalchuk, Dr. F. Koc, Dr. G. Angelovski, J. Saadi, S. Bernardi, Dr. P. Linnepe (Köhling), Dr. K.-S. Müller, Dr. P. Osinski, Dr. S. Ricken, L. Okoro, A. Farwick, Dr. N. Susnjar, Dr. V. K. Srivastava, Dr. S. Nave, K. Weber, J. Krimmel, B. Appel, Y. Ali, Dr. M. Beigi, K. Dogan, T. Dyczczak, R. Lawniczek, Dr. S. Nadakudity, J. Schmidt, U. Vogel, A. Marek, R. Sivek and R. Keder.

Finally, I owe special gratitude to my parents Mihai and Nina Chercheja for continuous and unconditional support.

Index of abbreviations and symbols

abs.	absolute, dry
Ac	acetyl
acac	acetylacetonato
bp	boiling point
br	broad
Bu	butyl
Cy	cyclohexyl
d	doublet (NMR)
dd	doublet of doublets (NMR)
ddd	doublet of a doublet of doublets (NMR)
δ	delta (NMR)
DMF	dimethylformamide
DMAP	4-dimethylaminopyridine
dq	doublet of quartets (NMR)
dr	diastereomeric ratio
dt	doublet of triplets (NMR)
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
FAB	fast-atom bombardment mass spectroscopy
GC	gas chromatography
HPLC	high performance liquid chromatography
Hz	Hertz
i-	iso
J	NMR coupling constant
m	multiplet (NMR)
M^+	molecular peak
MNP	N-methylpyrrolidone

mp	melting point
n-	normal
NMR	nuclear magnetic resonance spectroscopy
p	total pressure
Ph	phenyl
PMP	p-methoxyphenyl
ppm	parts per million (NMR)
Pr	propyl
q	quartet (NMR)
rac	racemic
rt	room temperature
s	singlet (NMR)
t	time, triplet (NMR)
THF	tetrahydrofuran
Thr	threonine
Ts	tosyl

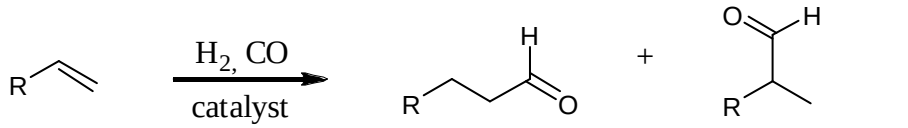
Table of contents

1 INTRODUCTION

1.1 Hydroformylation.

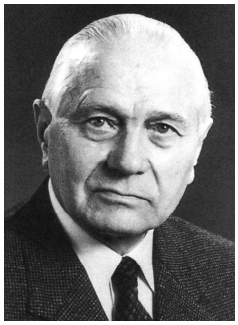
Hydroformylation, is the formal addition of a formyl group (CHO) and a hydrogen atom to a carbon-carbon double bond to yield linear and branched aldehydes having one more carbon atom than the original compound (Scheme 1).

Scheme 1. Hydroformylation reaction.



linear or normal (n) branched or iso (i)

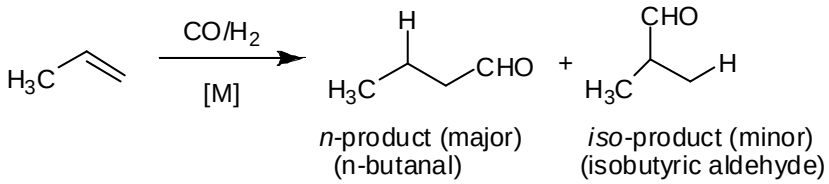
Hydroformylation was discovered by German chemist Otto Roelen in 1938 during the investigation of the origin of oxygenated products occurring in cobalt catalysed Fischer-Tropsch reactions. He observed that ethylene, H_2 and CO were converted into propanal, and at higher pressures, diethyl ketone. These findings marked the beginning of hydroformylation. He called this process "Oxo synthesis".[1] Nowadays, hydroformylation is one of the largest industrially applied processes, which is based on homogeneous catalysis. Most of the seven million tons of aldehydes produced annually by this process are hydrogenated to alcohols, oxidised to carboxylic acids or converted via aldol addition to condensation products. Esterification of the alcohols with phthalic anhydride produces dialkyl phthalate plasticizers that are primarily used for polyvinyl chloride plastics. Detergents and surfactants make up the next largest category, followed by solvents, lubricants, and chemical intermediates.



Otto Roelen (1897-1993)

The most important hydroformylation process on industrial scale, propene hydroformylation (Scheme 2), provides about 75% of all oxo chemicals consumed in the world.[2]

Scheme 2. Industrial synthesis of butanal from propene.



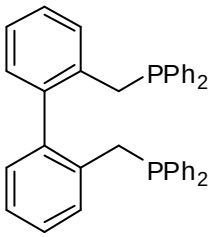
In addition to this industrial aspect, the hydroformylation represents an ideal atom economic CC-bond forming reaction with unique opportunities for application in target-oriented organic synthesis, provided that selectivity and stereoselectivity in the course of the reaction can be controlled.[3] The double bond does not react with a large set of reagents and conditions. This inertness allows this functionality to be carried through a number of steps in a synthetic sequence, until the one carbon chain elongation via hydroformylation is desired. However, despite these advantages and contrary to its industrial importance, the hydroformylation has not been frequently used in organic synthesis yet. This is due to the difficulty to control selectivity throughout the course of the hydroformylation reaction.[3, 4]

Roelen's original research into hydroformylation involved the use of cobalt salts that, under H_2/CO pressure, produced $HCo(CO)_4$ as the precursor. In 1966 Osborn, Young and Wilkinson reported that Rh(I)-PPh_3 complexes were active and highly regioselective hydroformylation catalysts for 1-alkenes, even at ambient conditions.[5] Although Slaugh and Mullineaux had filed a patent in 1961 that mentioned Rh/phosphine combinations for hydroformylation, it was Wilkinson's work that really initiated serious interest in rhodium phosphine hydroformylation catalysts.[5-8] The initial catalyst system was derived from Wilkinson's catalyst, $RhCl(PPh_3)_3$. Nowadays, $HRh(CO)(PPh_3)_3$ and

$Rh(acac)(CO)_2$ (acac = acetoacetonate) are two commonly used starting materials for hydroformylation catalysts.

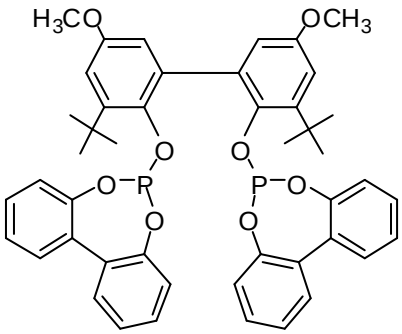
Eastman Kodak Company patented in 1987 first highly n-selective Rh-catalyst.[9] At present the best catalysts to achieve high levels of *n*-selectivity are those rhodium catalysts derived from the bidentate ligands BISBI,[10] BIPHEPHOS[11, 12] and XANTPHOS[13, 14] (Scheme 3).

Scheme 3. Ligands for regioselective hydroformylation of terminal alkenes.[3]



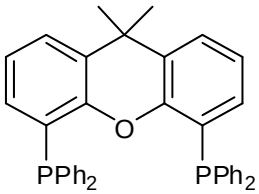
BISBI **1**

linear : branched
66 : 1 for 1-hexene



BIPHEPHOS **2**

linear : branched
> 40 : 1 for a wide range of functionalized alkenes



XANTPHOS **3**

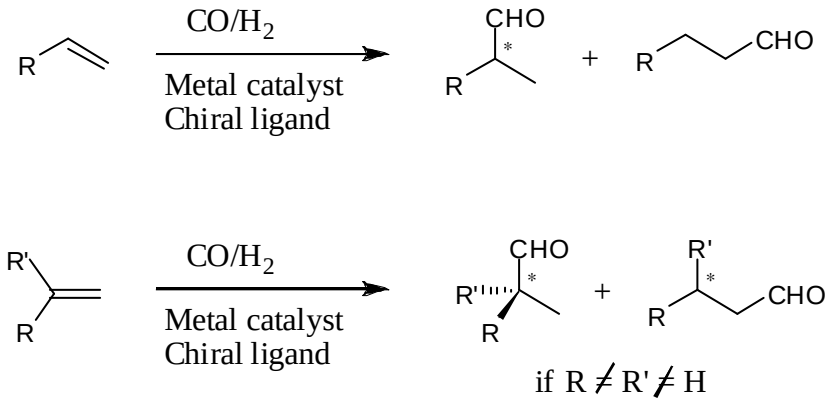
linear : branched
53 : 1 for 1-octene

1.2 Asymmetric hydroformylation

Asymmetric hydroformylation is a powerful technique for the construction of chiral aldehydes that can be further transformed into chiral acids, alcohols and amines. However, unlike its achiral counterpart, asymmetric hydroformylation has not been practiced on a commercial scale. There are several reasons why this promising technology has not previously been commercialised. The substrate scope for any single ligand is limited, effective simultaneous control of both regio- and enantioselectivity is difficult and high selectivities are normally observed at low temperatures, where the reaction rates are low.

For mono-substituted olefins, the branched product is chiral and the linear product achiral (Scheme 4).

Scheme 4. Asymmetric hydroformylation.

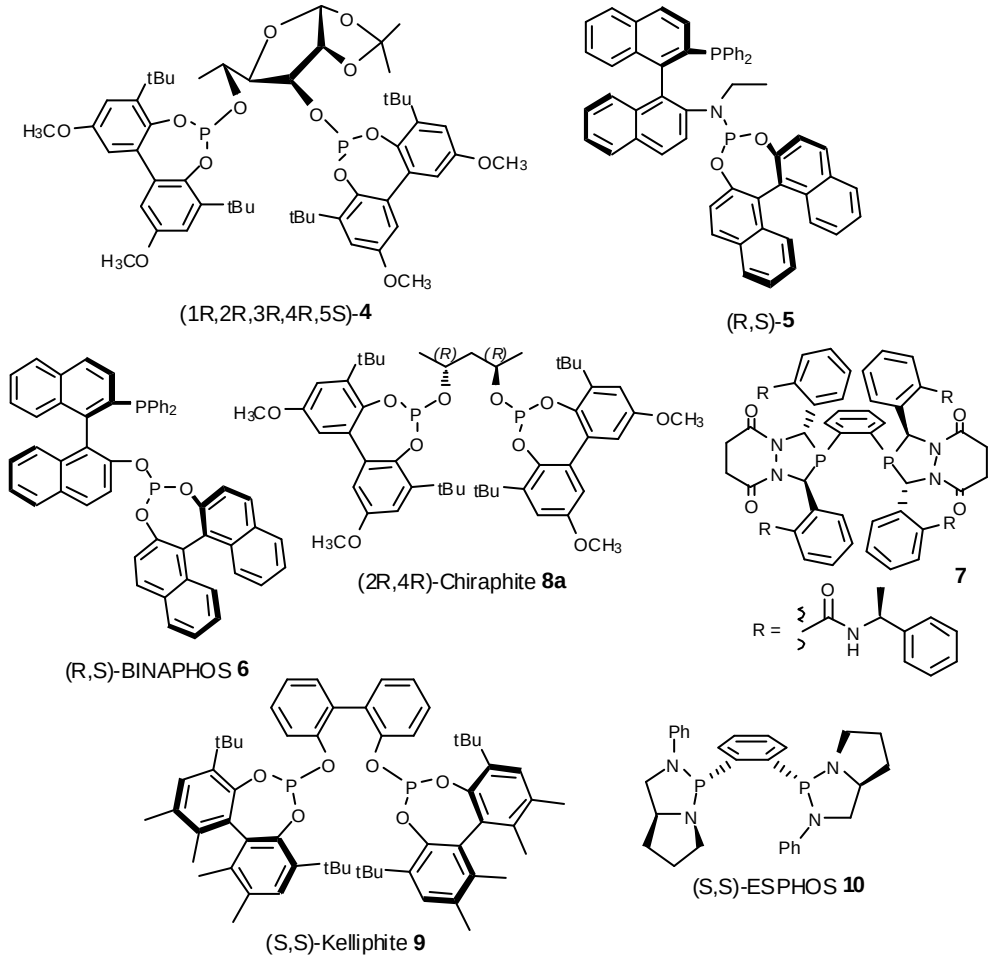


In the case of non-symmetric 1,1' or 1,2-disubstituted olefins, both product regioisomers are chiral. The formidable challenge for asymmetric hydroformylation catalysts is to control the branched to linear (*b:l*) ratio or regioselectivity, the ee and the chemoselectivity (e.g. versus hydrogenation) for a desired product, while also achieving economic catalyst loadings and suitable reaction times.

Many chiral phosphorus ligands have been evaluated with regard to induce enantioselectivity in the course of the hydroformylation reaction, but only a few ligand systems have been described in the literature for the highly efficient asymmetric hydroformylation. The best ligands to date include Chiraphite,[15, 16] sugar-based systems from Claver **4**,[17] Kelliphite,[18, 19] ESPHOS,[20] BINAPHOS[21] and the P,N-bidentate phosphite **(R,S)-5**[22] (Scheme 5). These ligands are used with rhodium or platinum-tin metal precursors to provide the active catalyst *in situ*.

Literature data for these ligands suggest that **6** is generally the most useful. Styrene, vinyl acetate, and allyl cyanide undergo hydroformylation with generally high enantioselectivities (94, 92, and 69%, respectively), modest *branched:linear* ratios (7.3:1, 6.2:1 and 2.2:1, respectively) and modest turnover frequencies (ca. 200 h^{-1} for all substrates) under reaction conditions of 60 – 70°C and ca. 10 atm of 1:1 CO/H_2.[21]

Scheme 5. Phosphorus ligands used in asymmetric hydroformylation reactions.



Ligand (R,S)-**5** which is prepared starting from chiral NOBIN (2-amino-2'-hydroxy-1,1'-binaphtyl) shows excellent enantioselectivities (up to 99% ee) in asymmetric hydroformylation of styrene derivatives and vinyl acetate (up to 96% ee).[22] Bis-3,4-diazaphospholane **7** demonstrates effective control of regio- and enantioselectivities for styrene (82% ee, *b*:*l* = 6.6), vinyl acetate (96% ee, *b*:*l* = 37) and allyl cyanide (87% ee, *b*:*l* = 4.1).[23] Ligands **4**, **8a**, **9** and **10**, in contrast, have more specialised utility. The ESPHOS ligand **10** is highly selective for vinyl acetate (ee = 90%, *b*:*l* = 16 : 1), but exhibits low enantioselectivity for styrene.[20] (2R,4R)-Chiraphite **8a** and (1R,2R,3R,4R,5S)-**4** are effective for styrene in the temperature range of 20 – 35°C, yielding enantioslectivities of 76% and 89%, respectively, with very high regioslectivity control (*b*:*l* = 47:1 and 49:1, respectively).[15-17] Kelliphite **9** is particularly well

suited for hydroformylation of allyl cyanide (ee = 75%, *b*:*l* = 56:1) at low temperature.

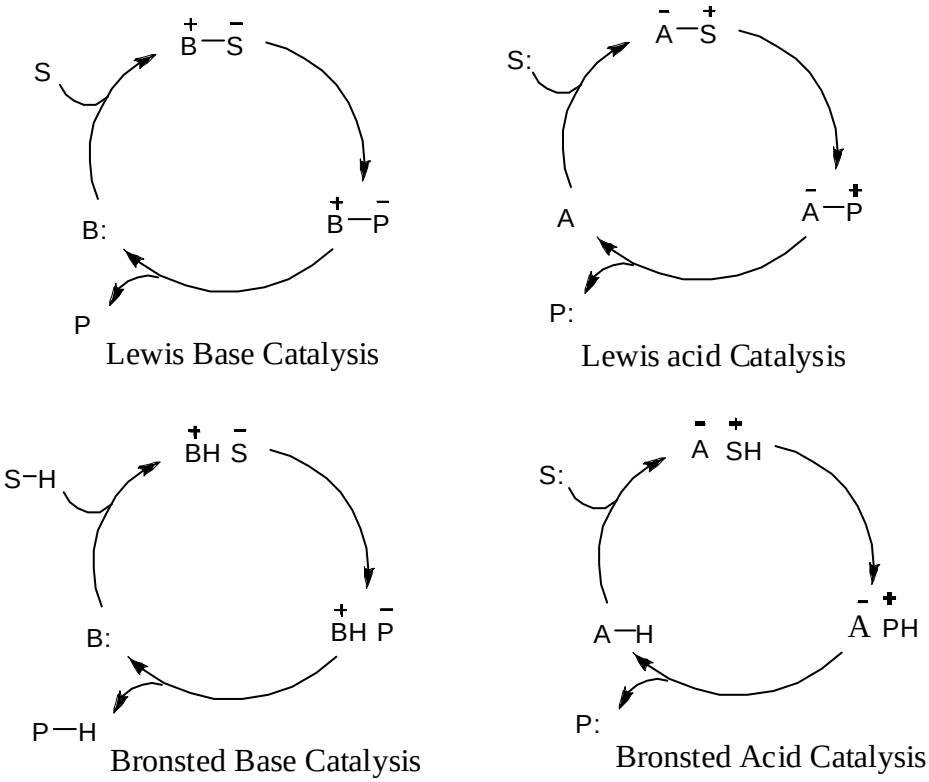
1.3 Asymmetric organocatalysis

1.3.1 Introduction

Until recently, the catalysts employed for the enantioselective synthesis of organic compounds fell almost exclusively into two general categories: transition metal catalysis and enzymatic transformations. Recently a third approach to the catalytic production of enantiomerically pure organic compounds has emerged – organocatalysis.[24] Organocatalysts are purely "organic" molecules, composed of carbon, hydrogen, nitrogen, sulphur and phosphorus. Organocatalysts have several advantages. They are usually robust, non-toxic, inexpensive and readily available. Because of their inertness toward moisture and oxygen, inert atmosphere, low temperatures, absolute solvents, etc, are, in many instances, not required.

List recently introduced a system of classification of organocatalytic reactions based on the mechanism of catalysis.[25] Most but not all organocatalysts can be broadly classified as Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids. The corresponding (simplified) catalytic cycles are shown in Scheme 6. Accordingly, Lewis base catalysts (B:) initiate the catalytic cycle *via* nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and then releases the product (P) and the catalyst for further turnover. Lewis acid catalysts (A) activate nucleophilic substrates (S:) in a similar manner. Brønsted base and acid catalytic cycles are initiated *via* a (partial) deprotonation or protonation, respectively.

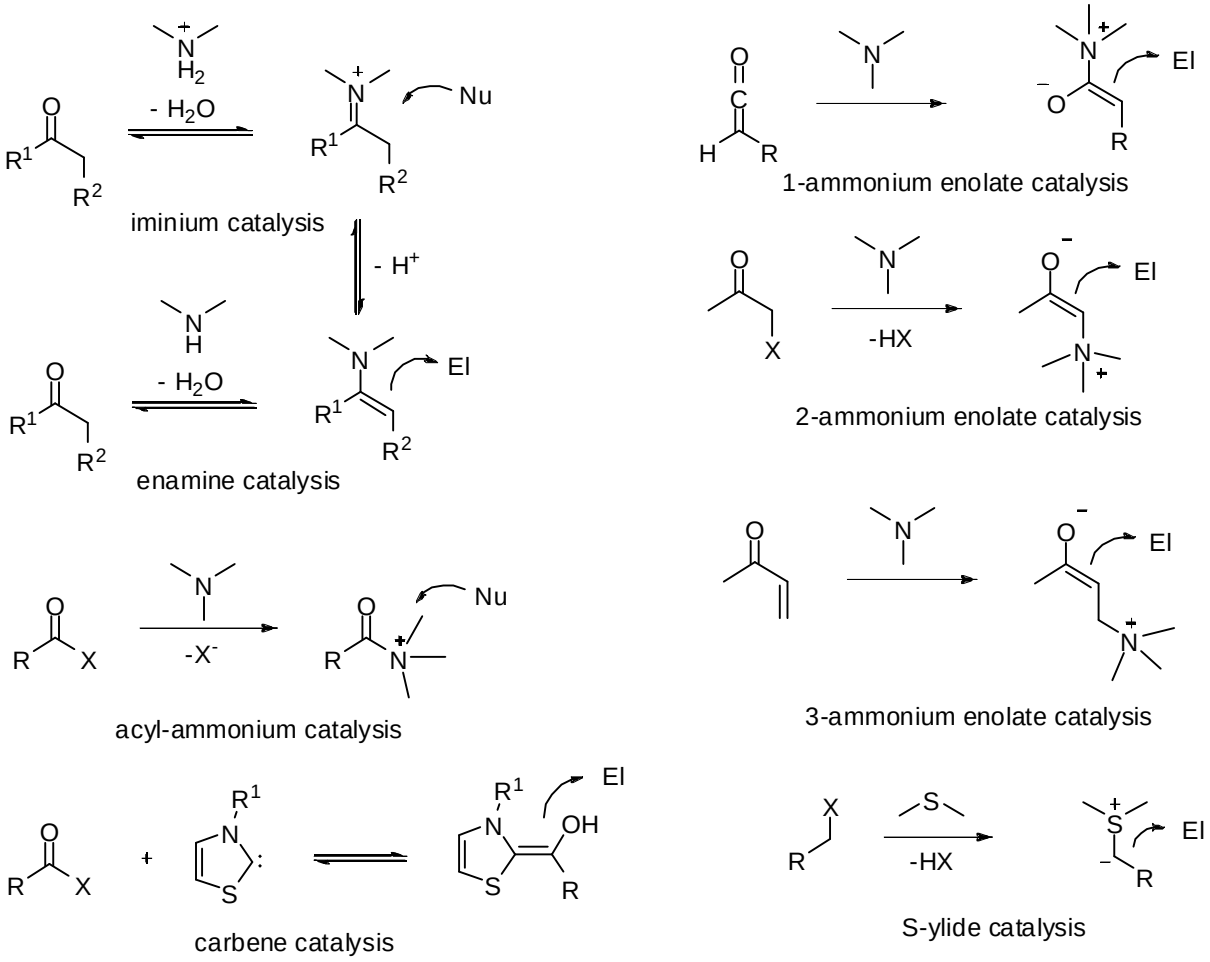
Scheme 6. Organocatalytic cycles.



The majority of organocatalysts are N-, C-, O-, P-, and S-based Lewis bases that operate through diverse mechanisms and convert the substrates either into activated nucleophiles or electrophiles. Typical reactive intermediates are iminium ions, enamines, acyl ammonium ions, 1-, 2-, or 3-ammonium enolates, *etc*. (Scheme 7).[25]

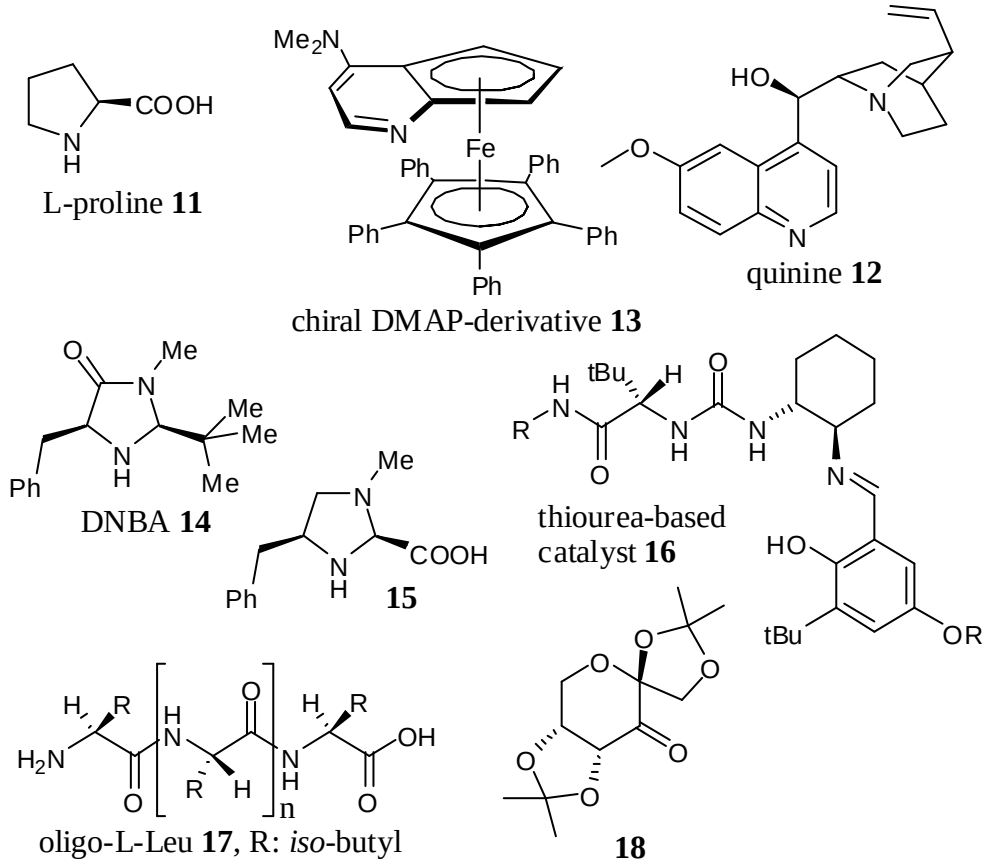
A selection of typical organocatalysts is shown in Scheme 8.[24] Proline **11**, a chiral-pool compound that catalyses aldol and related reactions by iminium ion or enamine pathways, is a prototypical example.[24, 26] The same is true for cinchona alkaloids. For instance, quinine **12**, has been abundantly used as a chiral base[27] or as a chiral nucleophilic catalyst.[28] The planar chiral DMAP-ferrocene derivative **13** introduced by Fu[29, 30] is extremely selective in several nucleophilic catalyses. Although it contains iron atom it is regarded an organocatalyst because its “active site” is the pyridine nitrogen atom.

Scheme 7. Examples of Lewis base organocatalysis.



For Mukaiyama-Michael reaction MacMillan group applied organocatalyst DNBA **14.**[31] Organocatalyst **15** is used in asymmetric Michael addition[32] and in malonate addition[33]. Chiral thiourea **16** introduced by Jacobsen et al.[34] have enabled excellent enantioselectivity in hydrocyanation of imines. Peptides, such as oligo-L-Leucine **17** have found use in the asymmetric epoxidation of enones. The chiral ketone **18** introduced by Shi[35] et al. is derived from D-fructose and catalyses the asymmetric epoxidation of a wide range of olefins with persulfate as the oxygen source. With the exception of the planar chiral DMAP derivative **13** all the organocatalysts shown in Scheme 8 are either chiral-pool compounds themselves, or they are derived from these readily available sources of chirality by means of a few synthetic steps.

Scheme 8. A selection of typical organocatalysts.



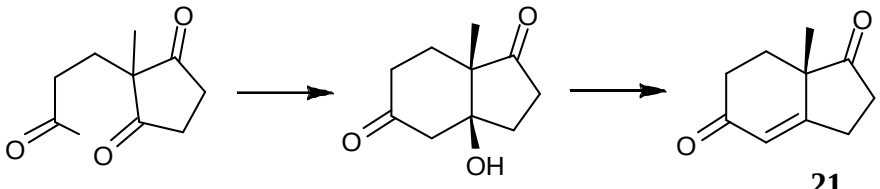
1.3.2 Organocatalysed enantioselective aldol reactions

Control of stereochemistry during aldol addition reactions has attracted considerable interest over the last decades, as the aldol reaction is one of the most powerful and versatile methods in modern carbonyl chemistry.[36, 37] This transformation can create up to two adjacent stereocenters upon joining of a nucleophilic carbonyl donor and an electrophilic carbonyl acceptor. Intensive effort has been invested to develop asymmetric aldol reactions. Several approaches have been taken to address diastereo- and enantioselection issues. Non-catalytic asymmetric aldol reactions usually involve the use of stoichiometric amounts of chiral auxiliaries,[38, 39] while the catalytic enantioselective versions of this reaction include chiral Lewis acid-catalysed and chiral Lewis base-catalysed aldol reactions.[40-43] However, the former approach suffers from the necessity of additional steps to install and remove the chiral auxiliary, while the latter two methods typically require pre-activation of the

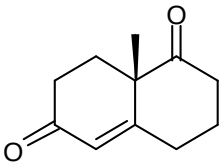
donor to a more reactive species, such as silyl enol ether, ketene silyl acetal, or alkyl enol ether. Searches for more convenient and efficient methods using more accessible, small organic molecule as catalysts are being actively carried out.

In the early 1970's, L-proline-catalysed intramolecular aldol cyclisations were explored in the synthesis of optically pure starting materials for the C, D rings of steroids.[44] Hajos and Parrish isolated the hydrindane dione **21** in an early proline-catalysed intramolecular aldol cyclisation (Scheme 9).

Scheme 9. L-proline-catalysed Hajos-Parrish-Eder-Sauer-Wiechert reaction

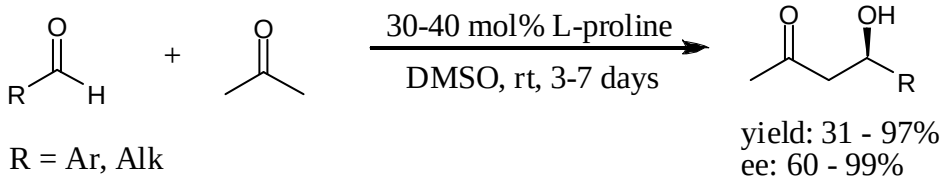


Experiments using 3 mol% L-proline in DMF gave 96.5:3.5 enantiomeric ratio (er) of aldol product **20** after 20 hours.[44] Despite these encouraging results, which were reported in 1974, the field did not expand, and it was not until the 1990's that a serious interest in proline as a catalyst was rekindled. Barbas and co-workers were interested in catalysed intramolecular Robinson annulations when they started studying past syntheses of the Wieland-Miescher ketone **22**.[45] In 2000, they described the first intermolecular direct asymmetric aldol reaction catalysed with proline.[46] Large excesses of acetone donors were used to suppress undesired self-condensation of aldehydes. In the presence of 30-40 mol% of proline catalysts, the cross aldol reactions proceeded smoothly at room temperature giving moderate to good yields and enantioselectivities (Scheme 10).



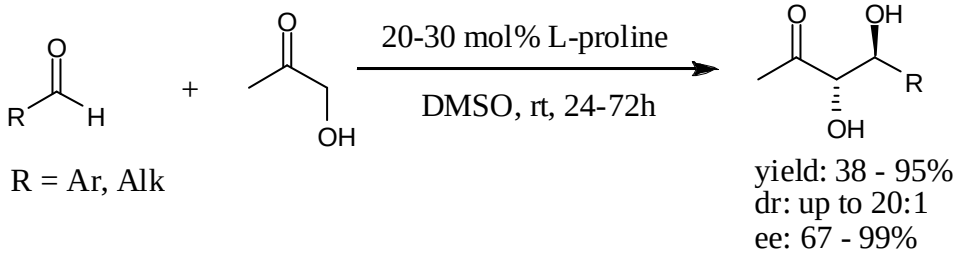
Wieland-Miescher ketone **22**

Scheme 10. Proline-catalysed aldol reactions with acetone.



Proline also can catalyse the direct aldol reaction between hydroxyacetone and various aldehydes with good regio- and stereoselectivities (Scheme 11).[47]

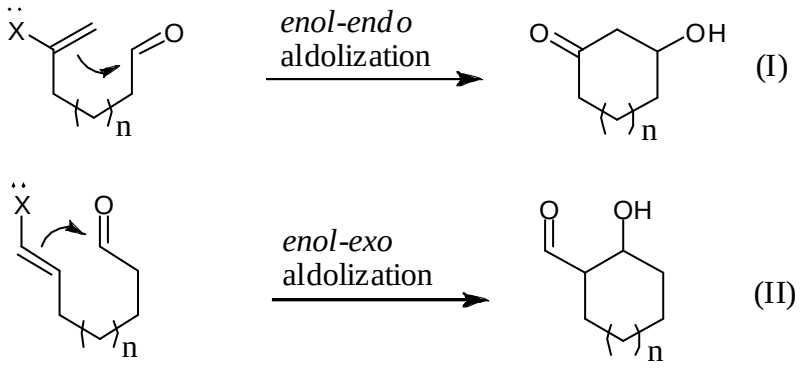
Scheme 11. Proline-catalysed aldol reactions with hydroxyacetone.



Besides acetone and hydroxyacetone, other ketones can generally be used including cyclopentanone and cyclohexanone.

L-Proline can also catalyse *enol-endo*-aldolisations and *enol-exo*-aldolisations (Scheme 12).

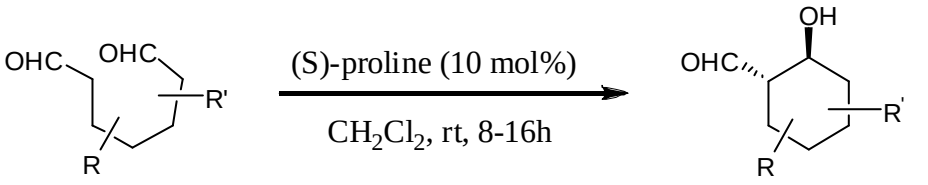
Scheme 12. *Enol-endo*- and *enol-exo*-aldolisations.



Recently a highly enantioselective proline-catalysed *enol-exo* aldolisation of dicarbonyl compounds was reported by List.[48] This reaction provides β-hydroxycyclohexane carbonyl derivatives that are of potential widespread usage in target-oriented synthesis. Various pentane-1,5-dialdehydes were converted to

the corresponding cyclic aldols in high yields and excellent diastereo- and enantioselectivities (Scheme 13).

Scheme 13. Proline-catalysed *enol-exo* aldolisations of dicarbonyl compounds. Yields refer to diols obtained after *in situ* $NaBH_4$ reduction.[48]



R = Alk

yield: 74 - 95%
dr: up to 20 : 1
ee: 97 - 99%

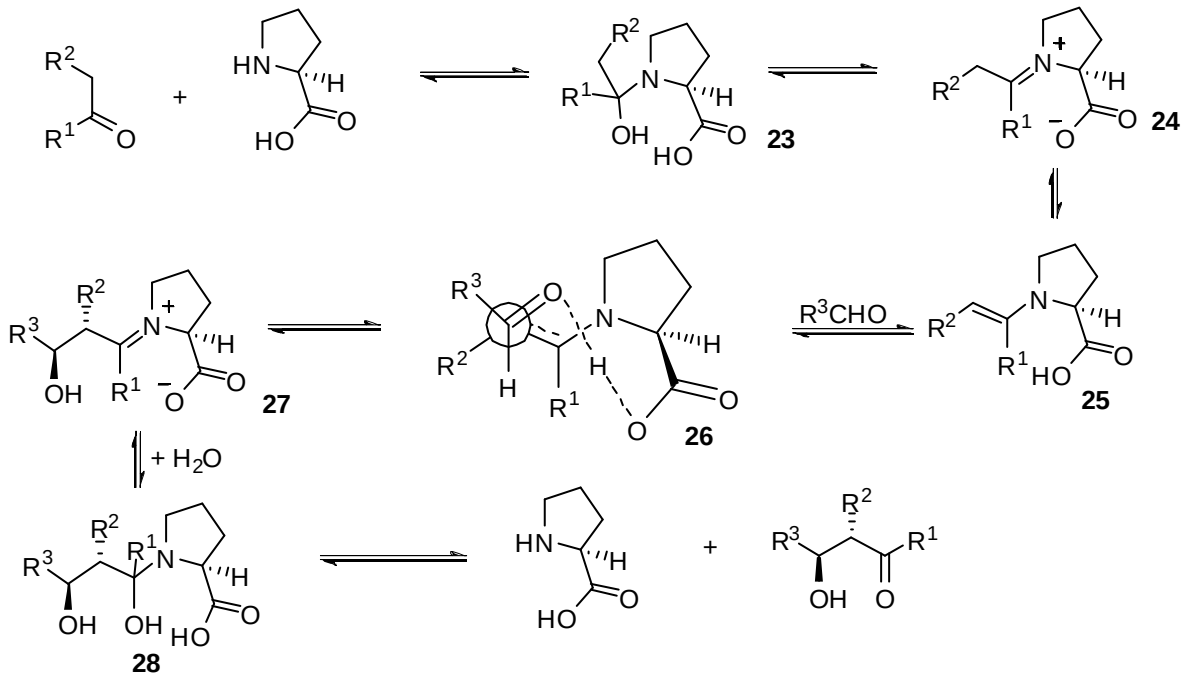
This anti-diastereoselective proline-catalysed *enol-exo* aldolisation nicely complements alternative methodologies such as the highly enantio- and syn-diastereoselective Baker's yeast reduction of β-keto esters.[49, 50] An advantage of the aldolisation methodology is that both enantiomeric products can be accessed simply by using either (S)- or (R)-proline, whereas the biocatalysis route is limited to products of a single absolute configuration.

1.3.3 Mechanism of the proline-catalysed aldol reaction

Initially, only limited mechanistic information was available on the proline-catalysed intermolecular aldol reaction. List[26] proposed an enamine catalysis mechanism involving carbinolamine **23**, iminium ion **24**, and enamine **25** intermediates, which is essentially identical to the accepted mechanism of class I aldolases (Scheme 14).

The carboxylic acid is proposed to act as a general-purpose Brønsted cocatalyst, replacing the several acid/base functional groups involved in the aldolase mechanism. In the transition state of the carbon-carbon bond formation List proposed protonation of the acceptor carbonyl group by the carboxylic acid, which is anti with respect to the (*E*)-enamine double bond.

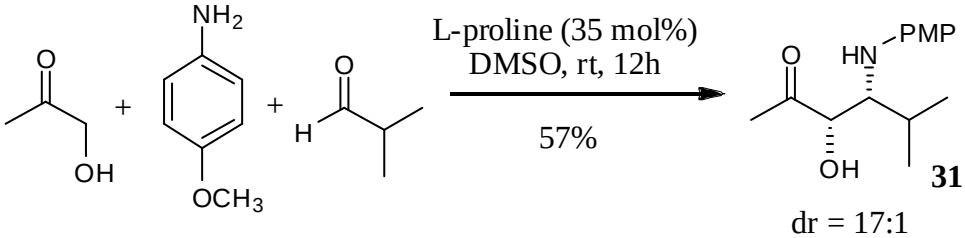
Scheme 14. Proposed mechanism of the proline-catalysed intermolecular aldol reaction.



1.3.4 Organocatalysed enantioselective Mannich reactions

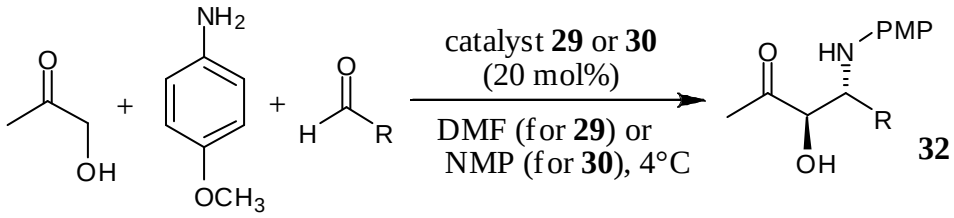
A large variety of natural products and drugs are nitrogen-containing molecules. Asymmetric Mannich and Mannich-type reactions are important carbon-carbon bond forming reactions that provide access to enantiomerically enriched β-amino carbonyl derivatives. The most desired versions are direct catalytic reactions that afford the syn- and anti-products with high diastereo- and enantioselectivities.[51, 52] Methods that use unmodified aldehydes and ketones are more atom-economical than those that require preactivation of carbonyl compounds, such as preformation of silyl enol ethers. For Mannich or Mannich-type reactions involving unmodified aldehydes and ketones, both syn-[53-57] and anti-selective[58-63] methods that afford products with high enantioselectivity have been reported; for example, L-proline, L-tryptophane **29** and o-tBu-L-Thr **30** have been used as catalysts (Schemes 15 and 16).

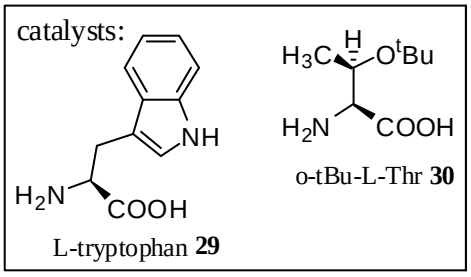
Scheme 15. syn-Mannich reaction catalysed by L-proline.



dr = 17:1
ee =65%

Scheme 16. anti-Mannich reactions catalysed by **29** and **30**.



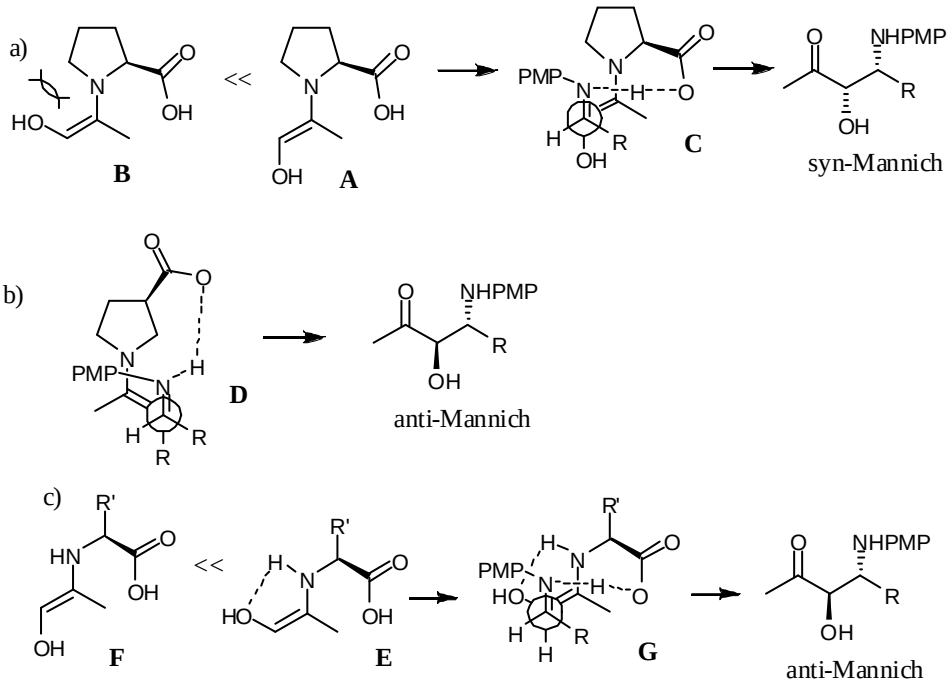


R = p-$NO_2C_6H_4$, a) cat. **29**, yield = 95%, syn/anti 12:1, ee = 95% b) cat. **30**, yield = 85%, syn/anti 15:1, ee = 98%

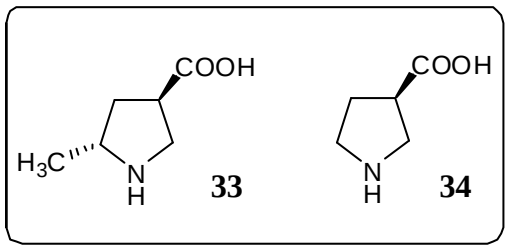
In the reactions of α-hydroxyketones with L-proline, products form *via* a reaction involving an *(E)*-enamine **A** for Mannich-type reaction. With pyrrolidine-derived catalysts or secondary amines, *(E)*-enamine intermediates predominate because of steric interactions in *(Z)*-enamine **B**. The stereochemistry of the product can be explained by transition state **C** because the *si* face of the *(E)*-enamine reacts (Scheme 17).

To selectively form anti-Mannich products in reactions involving alkyl aldehydes and alkanone-derived nucleophiles other organocatalyst has to be used such as (3R,5R)-5-methyl-3-pyrrolidinecarboxylic acid **33**, (R)-3-pyrrolidinecarboxylic acid (R-β-proline) **34**, L-tryptophan **29** or o-tBu-L-Thr **30** (Schemes 16 and 18).

Scheme 17. Transition states of organocatalysed syn- and anti-Mannich reactions.



Scheme 18. Organocatalysts for anti-Mannich or anti Mannich-type reactions.



With these catalysts, reactions proceed through transition state **D** or **E**, and the reaction face of the *(E)*-enamine is reversed from that of the (L)-proline-catalysed reaction (Scheme 17b,c)

1.4 Tandem catalysis

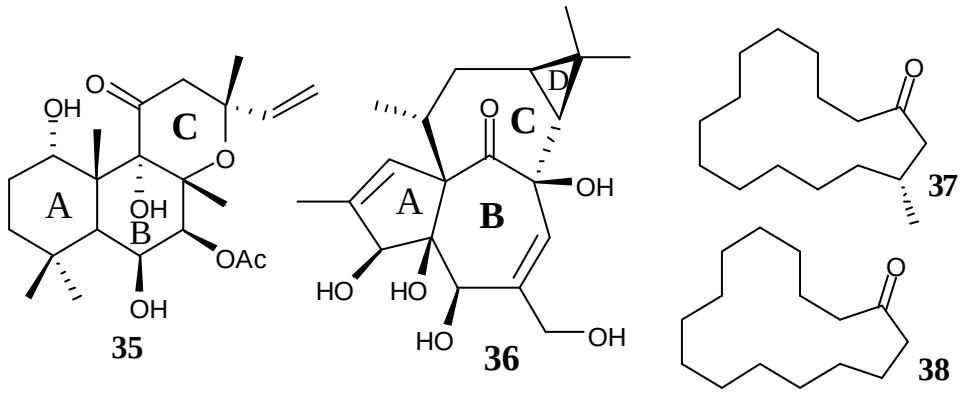
The term “tandem catalysis” has been used in the literature to include synthetic strategies that involve the sequential use of catalytic reactions with minimum workup, or change in conditions.[64]

“Tandem catalysis" constitutes a significant challenge for synthetic chemists and presents a number of opportunities to improve chemical

transformations. Multiple catalysts operating simultaneously could circumvent the time and yield losses associated with the isolation and purification of intermediates in multistep sequences. Generating harmful chemicals *in situ*, followed by incorporation into safer, more stable and larger molecular structures, would eliminate the inherent dangers associated with transportation of chemicals over long distances.[64-66]

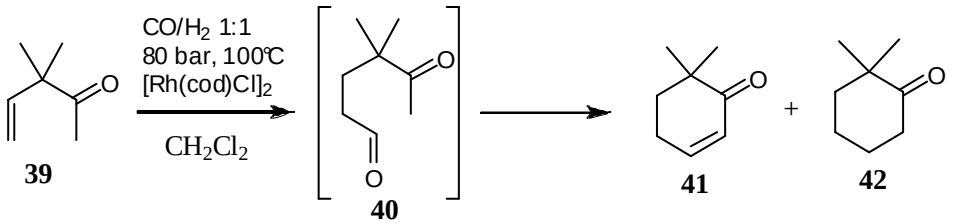
In recent years, in our group some efforts have been made to combine hydroformylation with a consecutive aldol reaction in a one-pot sequence. This strategy potentially can be applied in the construction of a series of natural molecules like forskolin **35,** ingenol **36, (-)**-muscone **37** and exaltone **38**, etc.

Scheme 19. Potential targets for sequential hydroformylation/aldol reactions.



In 1999 our group reported a Rh(I)-complex-catalysed tandem hydroformylation/aldol reactions of a β,γ-unsaturated ketone **39** in a one-pot procedure to give various cyclisation products (Scheme 20).[67]

Scheme 20. Reported hydroformylation and <u>intramolecular</u> cross aldol reactions.

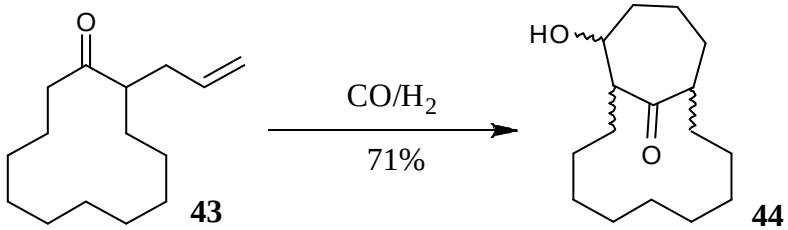


+ 10 mol% p-TsOH, 20h	58%	7%
+ 10 mol% p-TsOH, 42h	-	97%

In order to catalyse aldol condensation of the intermediate δ-keto aldehyde **40** under the hydroformylation conditions, catalytical amounts of p-toluenesulphonic acid were used.[67]

Later on, Fresu used tandem hydroformylation/aldol reactions for preparation of fifteen-membered rings, which can be used as building blocks for construction of natural macrocyclic musks (e.g. (-)-Muscone **37**, Exaltone **38,** etc). Fresu reported sequential hydroformylation / aldol reactions of 2-allylcyclododecanone (Scheme 21).[68]

Scheme 21. Reported sequential hydroformylation / aldol addition of 2-allyl-cyclododecanone.

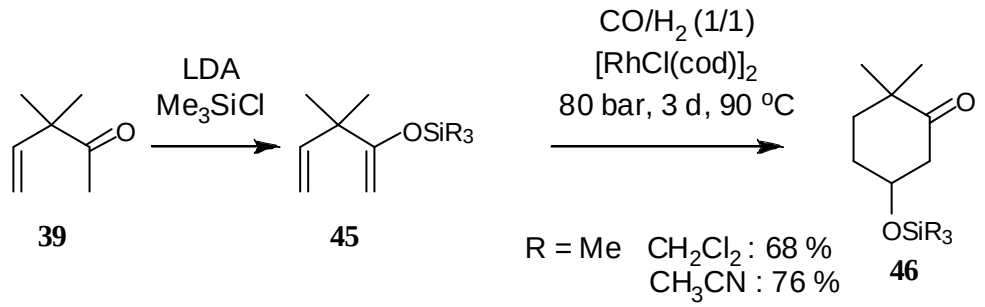


conditions: $Rh(acac)(CO)_2$, BIPHEPHOS, TsOH, 10/10 bar CO/H_2, 100°C, 3d

Bicyclic compound **44** was obtained in 71% yield as a mixture of two diastereoisomers (11:1 ratio) that could not be completely separated and assigned.

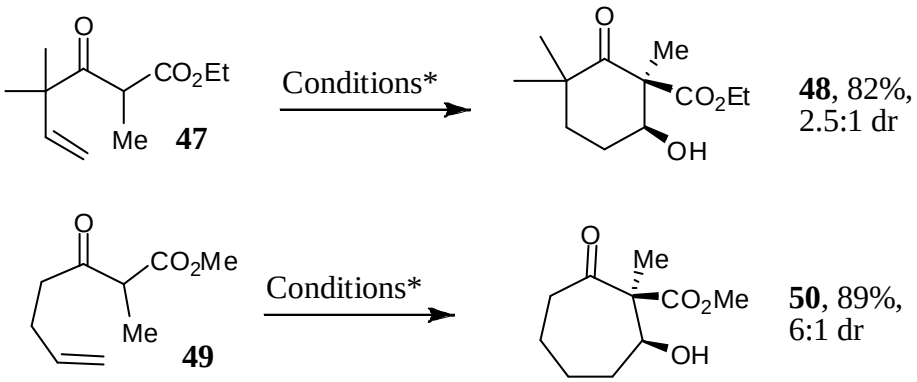
In 2000 Hollmann and Eilbracht reported the tandem hydroformylation and aldol addition of silyl enol ether of type **45** bearing remote olefinic functionalities to give β-silyloxy substituted cyclic ketones of type **46** (Scheme 22).[69] Complete transfer of the silyl fragment under hydroformylation condition was observed.

Scheme 22. Reported sequential intramolecular hydroformylation/aldol addition of the silyl enol ethers.



Also by our group was developed a new, mild enolboration / hydroformylation / aldol addition cascade reaction that allows for the regio- and diastereoselective construction of carbocycles bearing highly-functionalised quaternary carbon centers (Scheme 23).[70]

Scheme 23. Reported enolboration / hydroformylation / aldol addition cascade of ketoesters **47** and **49**.



Conditions: 1.05 eq. Cy_2BCl, 1.05 eq. Et_3N, 0°C, 0.9 mol% $Rh(acac)(CO)_2$, 1.8 mol% XANTPHOS, 16h, 60 bar CO/H_2, 80°C.

Ketoester **47** was exposed to standard conditions for stereoselective *E*(O)-enolboration prior to a regioselective n-hydroformylation in the presence of XANTPHOS ligand to afford after oxidative workup the desired cyclisation product ethyl 6-hydroxy-1,3,3-trimethyl-2-oxo-cyclohexane-carboxylate **48** in 82% isolated yield as a 2.5:1 mixture of diastereoisomers.[71] Starting from **49** resulted in the formation of the 7-membered ring of methyl 2-hydroxy-1-methyl-

7-oxocycloheptane-carboxylate **50** as the sole product in 89% yield as a 6:1 mixture of diastereoisomers. These aldol products are potentially useful as stereodefined building blocks, offering in one step direct access to the A-ring system of forskolin and the central B-ring of ingenol, respectively.

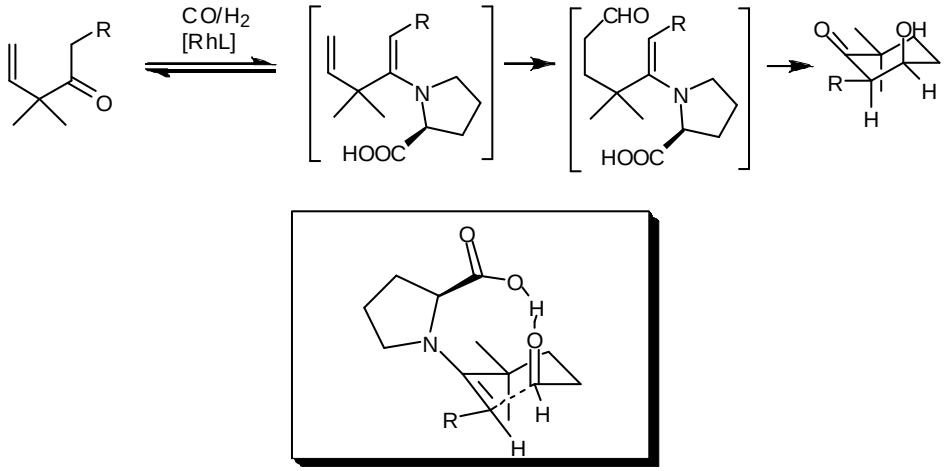
2 THEORY

2.1 Tandem metal- and organocatalysis in sequential hydroformylation and enantioselective aldol reactions

2.1.1 Sequential hydroformylation and enantioselective intramolecular aldol reactions

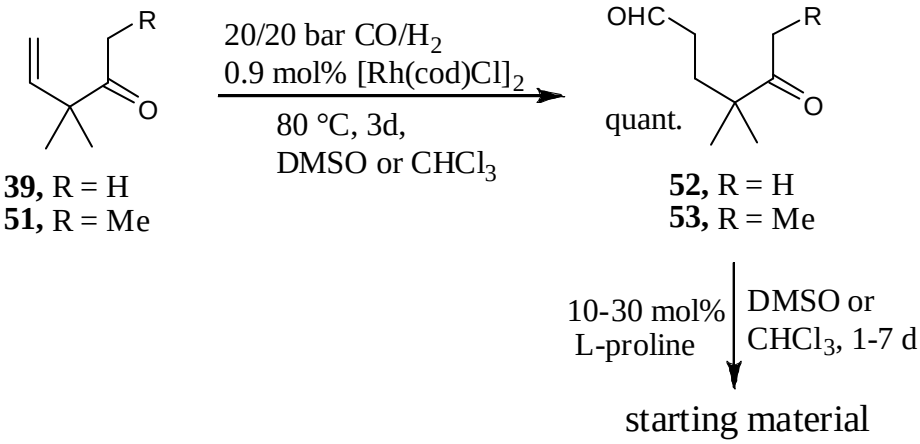
One of the main problems in aldol addition step under hydroformylation conditions is control of stereochemistry. Several methods can be used to overcome this problem (eg Mukaiyama-aldol addition, boron-enolate method, chiral auxiliaries etc.). Our initial strategy was the use of L-proline as a chiral organocatalyst in sequential hydroformylation/aldol addition reaction (Scheme 24). It seemed very promising when one considers the prospect of simply adding a catalytic amount of a chiral catalyst and performing the hydroformylation reaction with no additional constraints. Also beneficial is the fact that L-proline can be recovered by simple filtration. Workup and purification are also simplified since no auxiliaries or protecting groups are used.

Scheme 24. The concept of sequential hydroformylation/L-proline catalysed aldol addition.



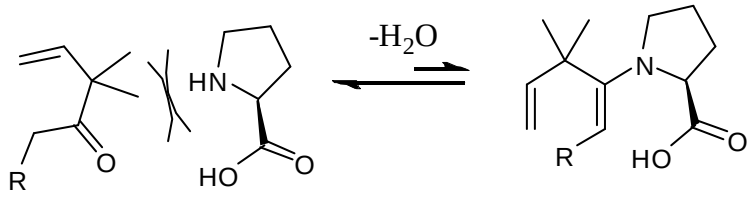
The first attempt to use this strategy was done by Keränen. Unsaturated ketones **39** and **51** were hydroformylated and then isolated aldehydes were stirred with L-proline in different solvents (Scheme 25).[72]

Scheme 25. Attempted stepwise hydroformylation and intramolecular aldol addition of unsaturated ketones.



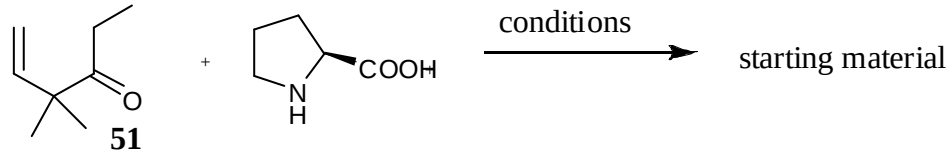
According to reported results, no aldol reaction was observed even after 7 days of stirring at room temperature. Keränen speculated that this lack of reactivity is due to steric factors prohibiting the formation of the proline-enamine necessary to accomplish the intramolecular aldol addition (Scheme 26).[72]

Scheme 26. Steric hindrance in the formation of proline-enamines from ketones bearing α-quaternary centers.



To overcome this problem we attempted to synthesise and to isolate a proline enamine of unsaturated ketone **51** (Scheme 27).

Scheme 27. Attempts to synthesise a proline enamine.

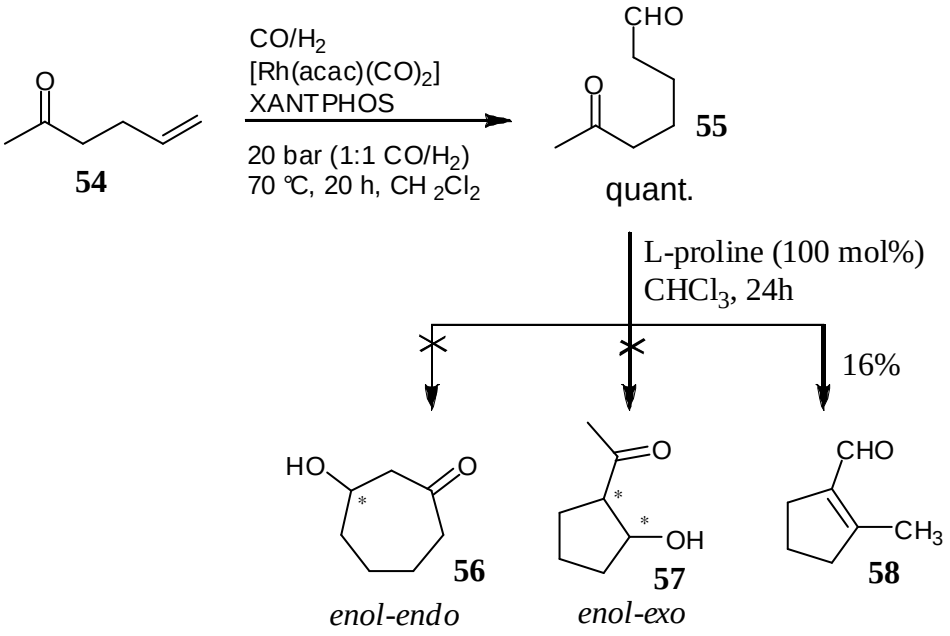


conditions: 1. $TiCl_4$, rt, hexane
2. TsOH, toluene, reflux, Dean-Stark trap
3. $MgSO_4$, Et_2O

Unfortunately, all three methods applied[73, 74] resulted only in the recovery of L-proline and unreacted ketone (Scheme 27). This is probably due to the low stability of L-proline derived enamines.

After our first attempts failed we performed stepwise regioselective hydroformylation and L-proline catalysed enantioselective aldol reaction on ketone not in possession of an α-quaternary carbon such as hex-5-en-2-one **54** (Scheme 28).

Scheme 28. Stepwise hydroformylation and aldol reaction of hex-5-en-2-one **54**.



Hydroformylation of the double bond with XANTPHOS modified Rh-catalyst gave aldehyde **55** in quantitative yield. Signals for *iso*-aldehyde were not

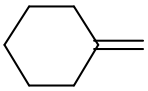
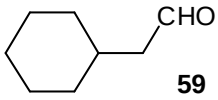
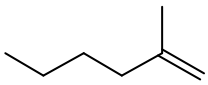
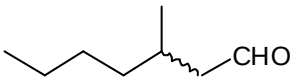
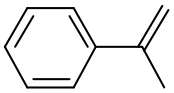
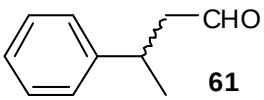
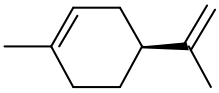
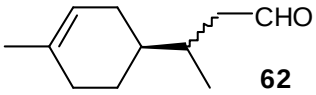
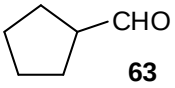
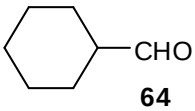
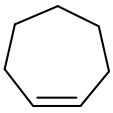
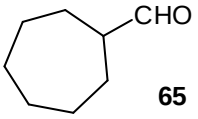
observed in ^{1}H NMR spectrum. Surprisingly, after stirring of aldehyde **55** with 100 mol% of L-proline in chloroform instead of expected aldol product **57,** was isolated condensation product **58**. This means that L-proline interacts preferably with the aldehyde group, but not with the keto-group of compound **51**.

2.1.2 Sequential hydroformylation and enantioselective intermolecular aldol reactions

After the combination of hydroformylation with proline catalysed intramolecular aldol reaction failed, we decided to focus our efforts on the combination of hydroformylation with intermolecular aldol addition.

In order to find the best candidates for this tandem reaction an alkene screening was done. Hydroformylation reactions were performed at 60°C with triphenylphosphine modified Rh-catalyst using acetone as a solvent (Table 1).
As shown in Table 1, methylenecyclohexane, 2-methylhex-1-ene, α-methylstyrene and cyclohexene are poor or moderately converted (2 - 47%) to the respective aldehydes under given conditions (Table 1, entries 1, 2, 3 and 6). The best conversions (87 – 99%) were obtained for S-(-)-limonene, cycloheptene and cyclopentene. These results suggest that these olefins should be suitable candidates for tandem reaction.

Table 1. Olefin screening for hydroformylation sequence using Ph_3P modified rhodium catalyst.[a]

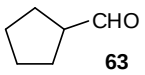
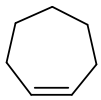
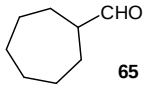
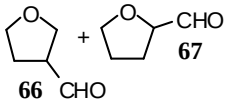
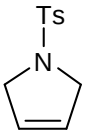
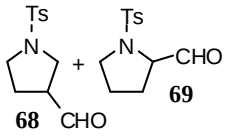
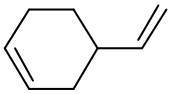
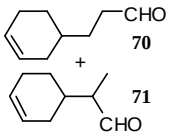
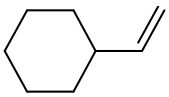
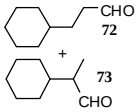
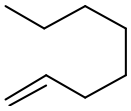
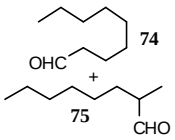
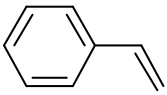
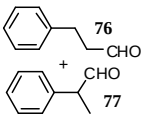
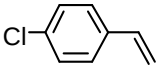
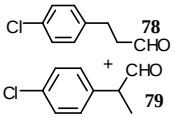
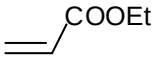
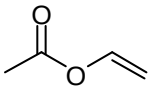
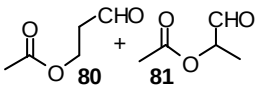
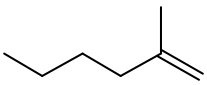
entry	olefin	product	olefin conversion (%)[b]	aldehyde yield (%)[b]
1		 **59**	47	47
2		 **60**	24	24
3		 **61**	14	14
4		 **62**	> 99	> 99
5		 **63**	87	87
6		 **64**	2	2
7		 **65**	89	89

[a]20/20 bar CO/H_2, 2 mol% Ph_3P, 0.5 mol% $Rh(acac)(CO)_2$, 60°C, 48h, acetone.

[b]Determined by GC using an internal standard.

In order to find milder conditions for hydroformylation of potential olefin substrates, triphenyl phosphite modified Rh-catalyst was tested. According to previous investigations[75] cyclopentene and 4-vinylcyclohexane were fully converted to respective aldehydes at 40°C, 1 bar CO/H_2, using $P(OPh)_3$ modified rhodium catalyst. We performed hydroformylation of several substrates under similar conditions, using 20/20 bar CO/H_2 and acetone as a solvent.

Table 2. Olefin screening for hydroformylation sequence using $P(OPh)_3$ modified rhodium catalyst.[a]

entry	olefin	product	alkene conv. (%)[b]	aldehyde yield (%)[b]	*l*:*b* ratio[b]
1		 **63**	> 99	> 99	-
2		 **65**	> 99	> 99	-
3		 **66** **67**	> 99	> 99	95 : 5[c]*
4		 **68** **69**	incomplete[c]	nd	3 : 1[c]*
5		 **70** **71**	> 99	> 99	3 : 1
6		 **72** **73**	> 99	> 99	3.2 : 1
7		 **74** **75**	> 99	> 99	1.4 : 1
8		 **76** **77**	> 99	> 99	5 : 95
9		 **78** **79**	> 99	> 99	4 : 96
10		intractable mixture	nd	nd	nd
11		 **80** **81**	> 99	> 99	7 : 93
12		intractable mixture	incomplete[c]	nd	nd

[a]20/20 bar CO/H_2, 2 mol% $P(OPh)_3$, 0.5 mol% $Rh(acac)(CO)_2$, 40°C, 72h, acetone.

[b]Determined by GC using an internal standard.

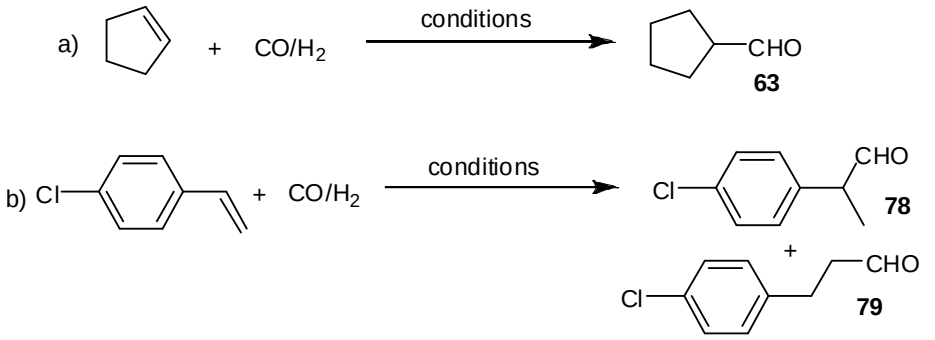
[c]Determined by ^1H NMR. nd – not determined. *3-aldehyde/2-aldehyde ratio.

As shown in Table 2, cyclic olefins such as cyclopentene and cycloheptene were fully converted to respective aldehydes under given conditions. 2,5-Dihydrofuran and 1-tosyl-2,5-dihydro-1H-pyrrole gave a mixture of aldehydes with a predominance of 3-aldehyde (Table 2, entries 3 and 4). In contrast with the data reported in the literature,[75] for 4-vinylcyclohex-1-ene, vinylcyclohexane and oct-1-ene, poor to moderate *l:b* selectivities were obtained with slight predominance of linear aldehyde (Table 2, entries 5, 6 and 7). As it was expected, styrene, 4-chlorostyrene, and vinyl acetate were converted with excellent regioselectivities to the respective *iso*-aldehydes. Ethyl acrylate and 2-methylhex-1-ene gave an intractable mixture of compounds. From the screening results cyclopentene was selected as a first model olefin in order to avoid the regioselectivity problems of hydroformylation and aldol reactions.

In control experiments possible negative interactions between Rh-catalyst and organocatalyst were tested in the hydroformylation of cyclopentene and 4-chlorostyrene in the presence of L-proline (Table 3).

As shown in Table 3, hydroformylation of olefins with triphenylphosphite modified rhodium catalyst both in the presence and in the absence of L-proline, takes place with excellent conversions and yields (> 99%). No self-aldolisation of the aldehydes **63** and **78**, **79** is observed (Table 3, entries 3, 4, 7 and 8). The unmodified Rh-catalyst under the same conditions gives full conversion of cyclopentene but incomplete conversion of 4-chlorostyrene (Table 3, entries 1, 2, 5, and 6). According to GC and ^{1}H NMR analyses of crude mixtures during the hydroformylation reaction only aldehydes are formed. Under the conditions given in Table 3, aldehyde **78** is generated with excellent regioselectivities (up to 99:1 branched/linear ratio), but shows no optical activity. Thus L-proline does not influence the stereochemistry of the hydroformylation step.

Table 3. Hydroformylation reactions both in the presence and in the absence of L-proline.



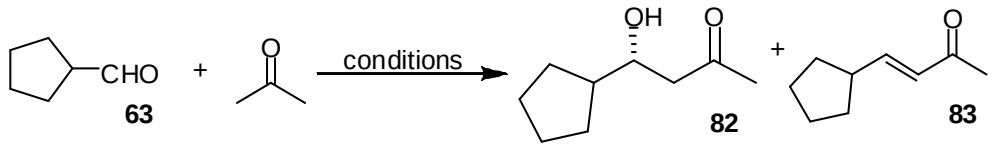
entry	conditions[a]	substrate	conv. (%)[b]	ald. yield (%)[b]	*b:l* ratio[b]
1	$Rh(acac)(CO)_2$, acetone	cyclopentene	> 99	> 99	-
2	$Rh(acac)(CO)_2$, acetone	4-chlorostyrene	49	49	97:3
3	$Rh(acac)(CO)_2$, $P(OPh)_3$, acetone	cyclopentene	> 99	> 99	-
4	$Rh(acac)(CO)_2$, $P(OPh)_3$, acetone	4-chlorostyrene	> 99	> 99	98:2
5	$Rh(acac)(CO)_2$, L-proline, CH_2Cl_2	cyclopentene	> 99	> 99	-
6	$Rh(acac)(CO)_2$, L-proline, CH_2Cl_2	4-chlorostyrene	75	75	97:3
7	$Rh(acac)(CO)_2$, $P(OPh)_3$, L-proline, CH_2Cl_2	cyclopentene	> 99	> 99	-
8	$Rh(acac)(CO)_2$, $P(OPh)_3$, L-proline, CH_2Cl_2	4-chlorostyrene	> 99	> 99	99:1

[a]20/20 bar CO/H_2, 40°C, 72h.

[b]Determined by GC using an internal standard.

Next we have investigated whether rhodium catalysts are compatible with organocatalysed enantioselective aldol reactions, and performed test aldol reactions with preformed aldehyde **63** both under atmospheric pressure and under hydroformylation conditions (Table 4). For the determination of results direct GC analysis was impossible. After injection of crude reaction mixture aldol product **82** partially self-decomposed with generation of aldehyde **63**, therefore determination of the aldehyde conversion was based on isolated unreacted aldehyde.

Table 4. Aldol reactions in the presence of Rh-catalysts both under atmospheric pressure and under hydroformylation conditions.



entry	conditions[a]	temp. (℃)	time (h)	aldehyde conv.(%)[b]	yield (%)[c] **82**	**83**	ee (%)[d] **82**
1	L-proline, acetone	25	24	87	30	5	80
2	Rh(acac)$(CO)_2$, L-proline, acetone	25	24	93	27	3	71
3	Rh(acac)$(CO)_2$, $P(OPh)_3$, L-proline, acetone	25	24	88	38	12	78
4	20/20 bar CO/H_2, Rh(acac)$(CO)_2$, $P(OPh)_3$, L-proline, acetone	25	24	41	19	< 1	81
5	20/20 bar CO/H_2, Rh(acac)$(CO)_2$, $P(OPh)_3$, L-proline, acetone	40	24	88	62	< 1	81
6	20/20 bar CO/H_2, Rh(acac)$(CO)_2$, $P(OPh)_3$, L-proline, acetone	40	48	96	65	< 1	79
7	20/20 bar CO/H_2, Rh(acac)$(CO)_2$, $P(OPh)_3$, L-proline, acetone	40	72	97	63	< 1	78

[a]See experimental section for details.

[b]Based on isolated unreacted aldehyde.

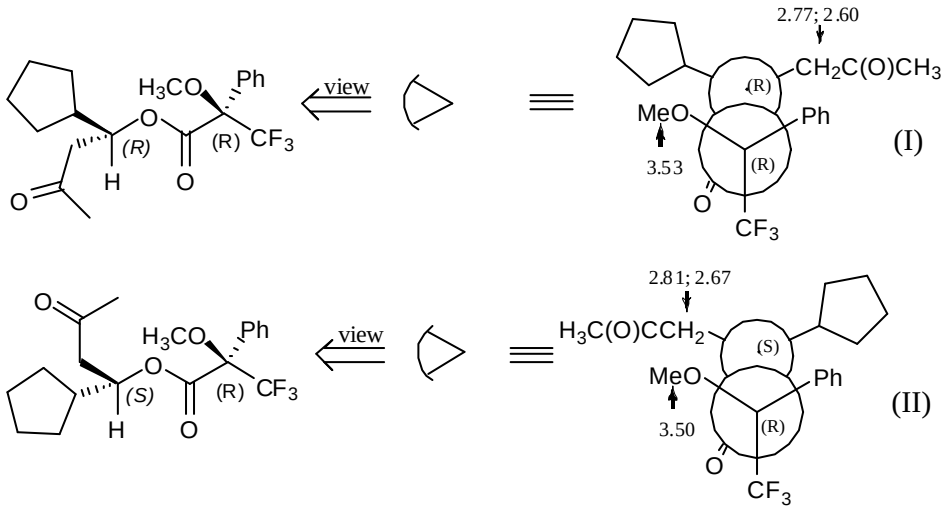
[c]Based on isolated product.

[d]Determined by chiral HPLC.

As shown in Table 4, under atmospheric pressure at room temperature the presence of rhodium complexes only marginally affects the conversion of aldehyde **63** (Table 4, entries 2 and 3). In contrast, at room temperature under hydroformylation conditions, a decrease of aldehyde conversion and suppression of the elimination to product **83** are observed (Table 4, entry 4). 96% of aldehyde **63** are converted within 48h, at 40 °C, under hydroformylation conditions (Table 4, entry 6). Enantioselectivity is not affected by the pressure and presence of rhodium catalysts. The absolute stereochemistry of the β-hydroxy group of the aldol adduct **82** being (R) was determined by Mosher's method (Scheme 29).[76]

For this aldol product **82** was converted into the two diastereomeric MTPA ester derivatives *via* reaction with the S-(+)-acid chloride of MTPA in the presence of pyridine. Structures (I) and (II) illustrate Mosher's model for correlating NMR shifts and absolute stereochemistry of MTPA esters. The substituent which eclipses the phenyl ring in such a Newman projection is always upfield.[76]

Scheme 29. MTPA ester derivatives of aldol product **82** (^{1}H NMR, 500 MHz, $CDCl_3$).



For effective tandem catalysis a range of phosphorus ligands (Figure 1) was tested for sequential hydroformylation and enantioselective aldol reactions of cyclopentene and acetone. The results are summarised in Table 5.

Figure 1. Phosphorus ligands tested.

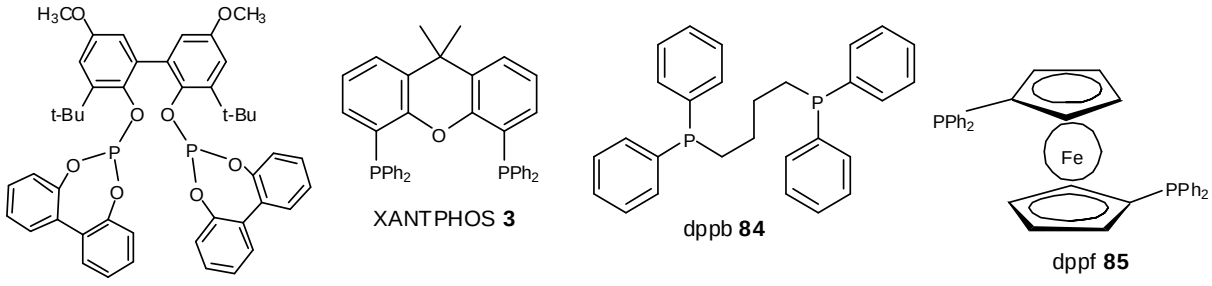
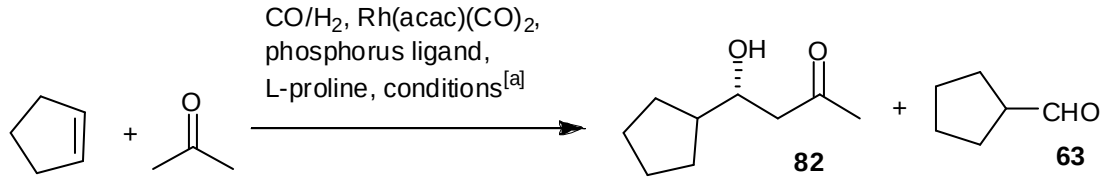


Table 5. Phosphorus ligand screening for sequential hydroformylation/enantioselective aldol reactions.



entry	ligand	reaction time (h)	alkene conv. (%)[b]	isolat. yield (%)[c] **82**	**63**	ee (%)[d] **82**
1	none	72	none	-	-	-
2	PPh_3	72	89	46	8	74
3	XANTPHOS	72	none	-	-	-
4	dppb	72	10	3	nd	65
5	dppf	72	17	7	3	72
6	BIPHEPHOS	72	> 99	72	7	82
7	$P(OPh)_3$	72	> 99	76	6	75
8	$P(OPh)_3$	48	95	70	8	81
9	$P(OPh)_3$	24	54	18	15	80

[a]0.5 mol% $Rh(acac)(CO)_2$, 2 mol% phosphorus ligand, 30 mol% L-proline, 20/20 bar CO/H_2, 40 °C, acetone.

[b]Determined by GC using an internal standard.

[c]Based on isolated product.

[d]Determined by chiral HPLC.

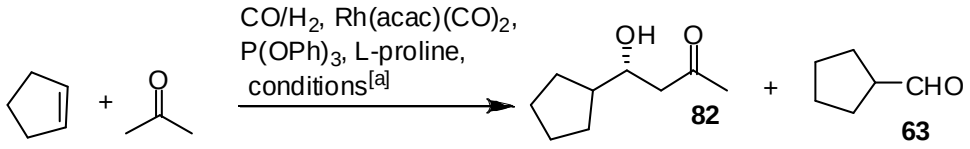
nd = not determined.

Surprisingly, the catalytic system with unmodified rhodium catalyst gave no conversion of the olefin (Table 5, entry 1). The steric and electronic properties of ligands drastically influence the rate of the hydroformylation reaction sequence. Rh-catalyst modified with non-bulky PPh_3 ligand gave good conversion (89%) of the olefin after three days of reaction (Table 5, entry 2). Diphosphine ligands lowered the activity of the corresponding Rh-catalysts as a result the olefin is not converted with XANTPHOS, and poor conversion is

observed with dppb and dppf ligands under given condition *(vide supra)*, although good stereoselectivities (65-72% ee) of the aldol product **82** were obtained (Table 5, entries 3, 4 and 5). Triphenyl phosphite and BIPHEPHOS show a significant advantage over all other phosphorus ligands tested. After 72 hours the olefin is fully converted under hydroformylation conditions and the aldol product **82** is formed with good enantioselectivities (Table 5, entries 6 and 7). Usually phosphites give more active catalysts than phosphines. This is mainly based on electronic factors. The phosphite ligands as stronger electron π-acceptor induce faster replacement of a carbonyl ligand by the alkene substrate, resulting in higher reaction rates.[75, 77]

As hydroformylation and aldol reactions are extremely sensitive to the reaction conditions, various CO and H_2 partial pressures were studied to ascertain pressure effects on tandem hydroformylation/enantioselective aldol reactions. The reactions of cyclopentene and acetone were performed at 10/10, 20/20, 30/30, 40/40 and 70/10 bar pressures of CO/H_2 (Table 6).

Table 6. Influence of CO and H_2 partial pressures on sequential hydroformylation/enantioselective aldol reactions.



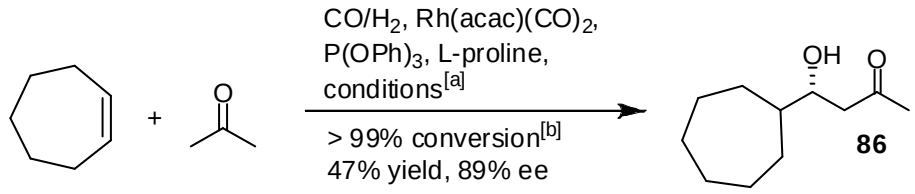
entry	P_{CO} (bar)	P_{H2} (bar)	alkene conversion (%)[b]	isolated yield (%) **82**	**63**	ee (%)[c] **82**
1	10	10	> 99	51	8	74
2	20	20	> 99	76	6	75
3	30	30	> 99	70	9	73
4	40	40	> 99	48	3	81
5	70	10	> 99	23	5	78

[a]0.5 mol% $Rh(acac)(CO)_2$, 2 mol% $P(OPh)_3$, 30 mol% L-proline, 40 °C, 72 hours, acetone.
[b]Determined by GC using an internal standard.
[c]Determined by chiral HPLC.

Reactions at 10/10, 20/20, 30/30 and 40/40 bar gas pressures provided medium to good yields (48 – 76%) of the desired compound **82** (Table 6, entries 1, 2, 3 and 4). In contrast with **104a,b** *(vide infra)*, at 70/10 bar CO/H_2, a drastic decrease in yields of the aldol product **82** (23%) was observed. Noteworthy, varying the total pressure from 20 to 80 bar has only small effects on the enantioselectivities (73-81 % ee).

Using similar conditions cycloheptene on conversion by sequential hydroformylation and enantioselective aldol reactions, gives the aldol product **86** in 47% yield with 89% ee (Scheme 30). The absolute configuration of compound **86** was assigned by analogy with compound **82**.

Scheme 30. Sequential hydroformylation/enantioselective aldol reactions of cycloheptene and acetone.



[a]20/20 bar CO/H_2, 0.5 mol% $Rh(acac)(CO)_2$, 2 mol% $P(OPh)_3$, 30 mol% L-proline, 40 °C, 72 h, acetone.

[b]Determined by GC using an internal standard.

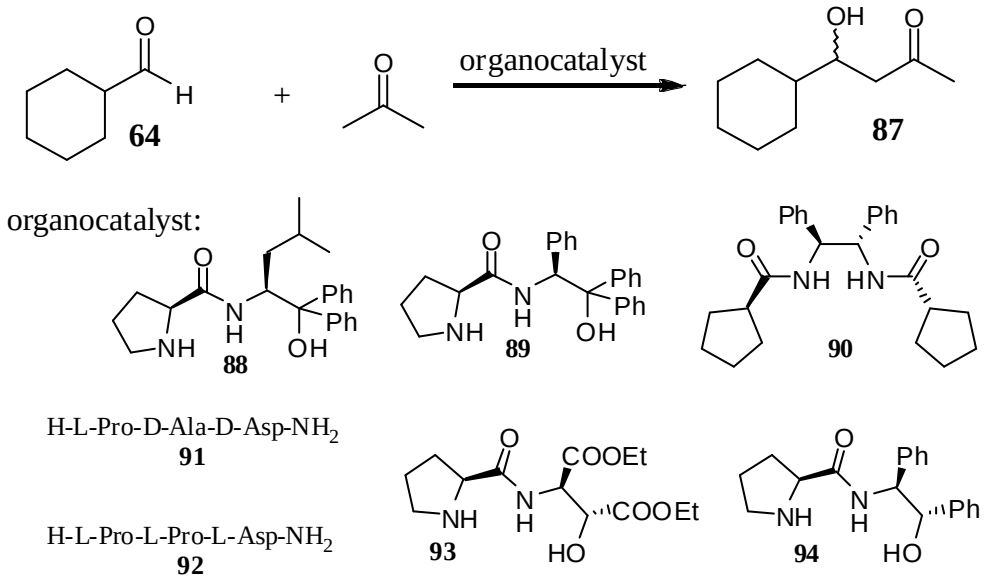
2.1.3 Intermolecular aldol reactions catalysed by organocatalysts other than L-proline

Although L-proline showed good enantioselectivities in sequential hydroformylation and aldol reactions (65-89% ee), we decided to test other organocatalysts in hope to find more active and selective catalyst for aldol reaction.

Usually for the asymmetric aldol addition new reported organocatalysts are evaluated in reactions between aromatic aldehydes (such as benzaldehyde or p-substituted benzaldehydes) and ketones. Since in hydroformylation always

enolizable aldehydes are formed, we were interested in organocatalysts that catalise asymmetric aldol reaction between such aldehydes and ketones.

Scheme 31. Reported aldol reaction between cyclohexanecarbaldehyde and acetone catalysed by different organocatalysts.



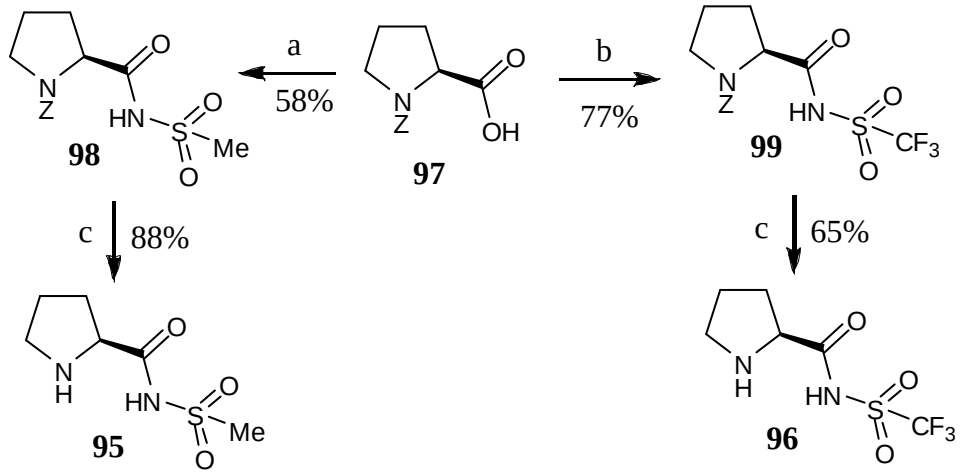
New L-proline based chiral organic molecules having a *gem*-diphenyl group **88** and **89** were recently reported to give excellent enantioselectivities (up to 99% ee) in the direct aldol reactions.[78] In contrast with L-proline these organic compounds can be used with low catalyst loading (up to 5 mol%). Also a C_2-symmetric bisprolinamide **90**[79] with two prolinamide moieties has been found to be an excellent catalyst for direct aldol reaction with more than doubled reactivity and better asymmetric induction than its monoprolinamide counterpart. Gong et al. reported that L-proline amides derived from chiral β-amino alcohols that bear strong electron-withdrawing groups exhibit high catalytic activities and enantioselectivities in direct aldol reactions of a wide range of aldehydes with acetone and butanone, to give the β-hydroxy ketones with very high enantioselectivities ranging from 96% to > 99% ee.[80] Peptides **91** and **92** containing a secondary amine and a carboxylic acid in a specific orientation to each other also are highly efficient catalysts for asymmetric aldol reactions.[81] Their activity is considerably higher compared to that of proline.

The enatioselectivity of the peptidic catalysts can be changed from (R)- to (S)-selectivity by simple modifications of the secondary structure. Unfortunately reported catalysts **88**, **90**, **93** and **94** gave high enantioselectivities at relatively low temperatures, between (–40)°C and 0°C. At such low temperatures hydroformylation rates usually are very low, therefore these catalysts cannot be used in our tandem reactions.

It was found that linear aminoacids L-valine, L-alanine and L-serine as well as several acylsulfonamides (e.g. **95)** catalyse asymmetric aldol reaction between unmodified ketones and aldehydes with excellent stereocontrol.[82, 83] In some cases addition of 1 equivalent of water accelerated the reaction speed.[84] The carboxylic acid proton in proline plays a critical role in enhancing the reactivity and stereoselectivity of proline based catalyst.[85, 86] In contrast, L-prolinamide is known to be ineffective in catalysing reactions.[85] The acidity of NH protons in L-prolinamide is much less than that of a carboxyl group in proline and, as a result the significant difference in catalytic activity between this two substances is likely due to their different acidity. We hypothesised that increasing the acidity of the NH amide protons would lead to a significant enhancement in the catalytic activity of L-proline. It is known that pK_a of trifluoromethane-sulfonamide in water is 6.3, which is comparable to that of acetic acid (pK_a of 4.76).[87-89] However, in DMSO, trifluoromethane-sulfonamide has an even greater acidity (pK_a of 9.7) than that of acetic acid (pK_a 12.3).[87-89] With these observations in mind, we envisioned that incorporation of trifluoromethane-sulfonamide moiety into a pyrrolidine system would create a new amine-sulfonamide bifunctional organocatalyst that could function in the same way as proline in catalysing organic reactions.

The synthesis of acylsulfonamides **95** and **96** were conducted according to the procedure published by Ley's group and invlolved the coupling of Z-L-proline **97** with the relevant sulfonamide (Scheme 32).[90]

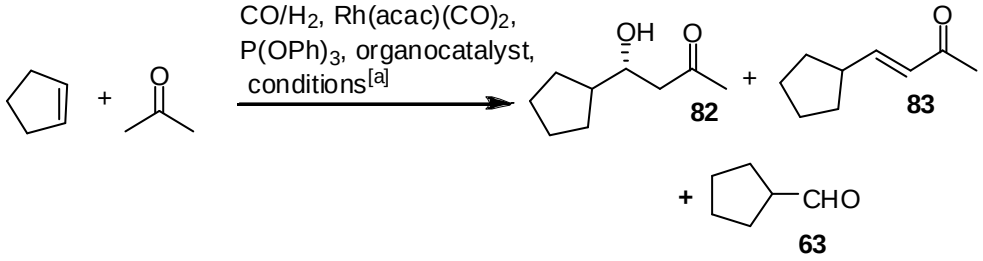
Scheme 32. Synthesis of acylsulfonamides **95** and **96**.

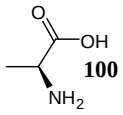
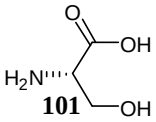
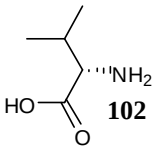
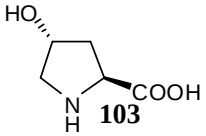
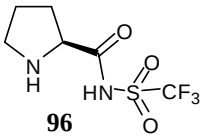
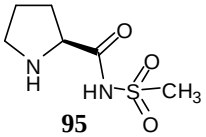


Reagents and conditions: [a] methanesulfoamide, EDCI, DMAP, CH_2Cl_2, rt, 48h. [b] trifluoromethanesulfonamide, EDCI, DMAP, CH_2Cl_2, rt, 48h. [c] 10% Pd/C, H_2, MeOH, rt, 20h.

Both catalysts were obtaind in good overall yields and together with a range of amino acids were tested in sequential hydroformylation/enantioselective aldol addition of cyclopentene and acetone (Table 7). Perhaps the most important observation is that the cyclopentene was fully converted in the presence of all organocatalysts. L-Alanine **100,** L-serine **101,** L-valine **102** and trans-4-hydroxy-L-proline **103** did not convert aldehyde **63** to aldol product **82** (Table 7, entries 1, 2, 3 and 5). Addition of one equivalent of water to L-valine in order to improve catalyst turnover via faster hydrolysis of the intermidiates of the enamine catalytic cycle, as well as the suppression of catalyst inhibition gave no expected effect (Table 7, entry 4).[26, 82, 91, 92] Surprisingly, acylsulfonamide **96** instead of aldol addition reaction catalysed Mannich-type elimination reaction. Organocatalyst **95** gave moderate yield and enantioselectivity of the aldol product **82** (Table 7, entry 7). The results of the organocatalyst screening revealed that all tested organocatalysts showed inferior activities and enantioselectivities in comparison with proline.

Table 7. Sequential hydroformylation/enantioselective aldol reactions of cyclopentene and acetone in the presence of different organocatalysts.



entry	organocatalyst	alkene conv. (%)[b]	yield (%) **82**[c]	**83**[c]	**63**[b]	ee (%)[d] **82**
1	 **100**	> 99	nd	-	> 95	nd
2	 **101**	> 99	nd	-	> 95	nd
3	 **102**	> 99	nd	-	> 95	nd
4	**102** + 1eq. H_2O	> 99	nd	-	> 95	nd
5	 **103**	> 99	nd	-	> 95	nd
6	 **96**	> 99	-	36	58[c]	-
7	 **95**	> 99	43	nd	32[c]	47

[a]20/20 bar CO/H_2, 0.5 mol% $Rh(acac)(CO)_2$, 2 mol% $P(OPh)_3$, 30 mol% organocatalyst, 40 °C, 72 h, acetone.

[b]Determined by GC using an internal standard.

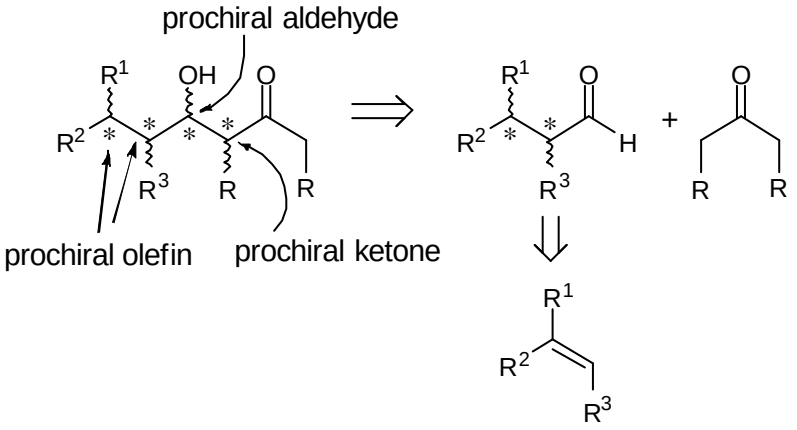
[c]Based on isolated product.

[d]Determined by chiral HPLC.

nd - not determined or not detected

Up to now, olefins and ketones explored in the sequential hydroformylation and enantioselective aldol reactions were not prochiral. For further studies prochiral olefins and/or prochiral ketones were considered since additional stereogenic centres are formed (Scheme 33).

Scheme 33. Origin of stereogenic centres in sequential hydroformylation/enantioselective aldol reactions.



At first, for the reaction between prochiral 4-chlorostyrene and acetone, pressure experiments were performed using 40 and 80 bar total gas pressures (Table 8). The absolute stereochemistry of the β-hydroxy group of the aldol adduct **104a** again was determined by Mosher's method.[76] The relative configurations of compunds **104a,b** were assigned by analogy with the known racemic compounds **105a,b** (*vide infra*).[93]

Scheme 34. The absolute configuration determination of aldol product **104a**.

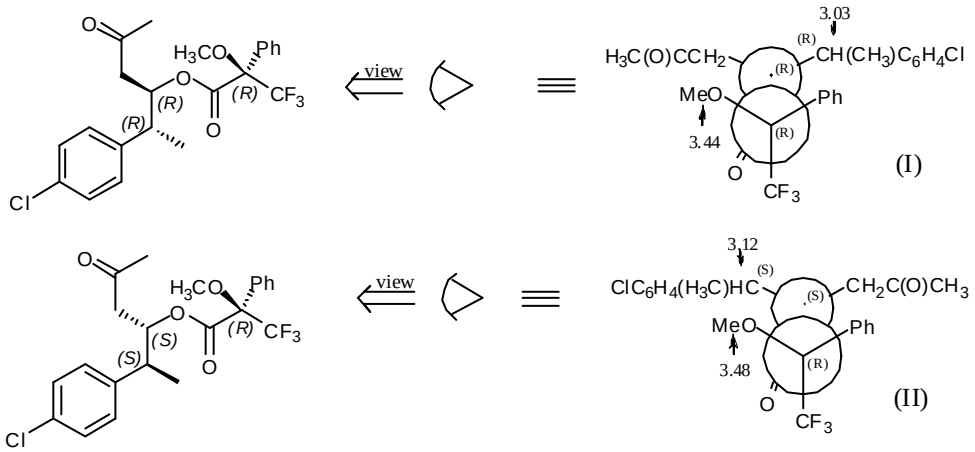
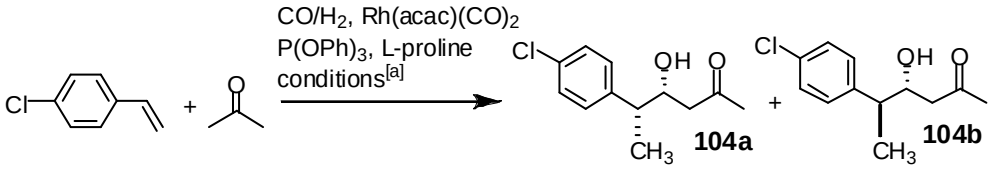


Table 8. Influence of CO and H_2 partial pressures on sequential hydroformylation/enantioselective aldol reactions.



entry	P_{CO} (bar)	P_{H2} (bar)	alkene conversion(%)[b]	yield (%)[c] **104a**+**104b**	d.r.[d] (syn : anti)	ee (%)[e] **104a**	**104b**
1	20	20	> 99	89	1.5 : 1	72	> 99
2	40	40	> 99	85	1.5 : 1	76	> 99
3	70	10	> 99	89	1.5 : 1	77	> 99

[a]0.5 mol% $Rh(acac)(CO)_2$, 2 mol% $P(OPh)_3$, 30 mol% L-proline, 40 °C, 72 hours, acetone.

[b]Determined by GC using an internal standard.

[c]Based on isolated product.

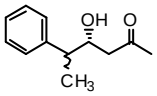
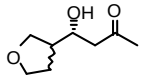
[d]Determined by ^1H NMR analyses.

[e]Determined by chiral HPLC.

As shown in Table 8, here, no significant influence of pressure on yields, enantio- and diastereoselectivities was observed. The two major stereoisomers obtained, have the same configuration at the carbon bonded to the hydroxy group and opposite configurations at the carbons bearing the methyl group. Here diastereoselectivities are not expected to be high since the hydroformylation step gives a racemate even in the presence of L-proline (see Table 3, entries 6 and 8), whereas the organocatalyst stereoselectively catalyses the aldol step towards the same configuration at the β-hydroxy group of both diastereoisomers.

Despite the findings that best enantioselectivities were obtained at 80 bar total pressure, 20/20 bar CO/H_2 was selected as the milder reaction conditions for all further studies with styrene and 2,5-dihydrofuran as prochiral olefins (Table 9).

Table 9. Sequential hydroformylation/enantioselective aldol reactions of prochiral alkenes with $P(OPh)_3$ modified rhodium catalyst.[a]

entry	substrate	ketone = solvent	product	ol. conv. (%)[b]	yield (%)[c]	syn:anti[d]	ee (%)[e]
1			 **105a**-syn **105b**-anti	> 99	83	1.5 : 1	72 (for syn) > 99 (for anti)
2			 **106a**-syn **106b**-anti	> 99	71	1 : 1	71 (for syn) 71 (for anti)

[a]0.5 mol% $Rh(acac)(CO)_2$, 20/20 bar CO/H_2, 2 mol% $P(OPh)_3$, 30 mol% L-proline, 40 °C, 72 hours.

[b]Determined by GC using an internal standard.

[c]Based on isolated product.

[d]Determined by ^1H NMR analyses.

[e]Determined by chiral HPLC.

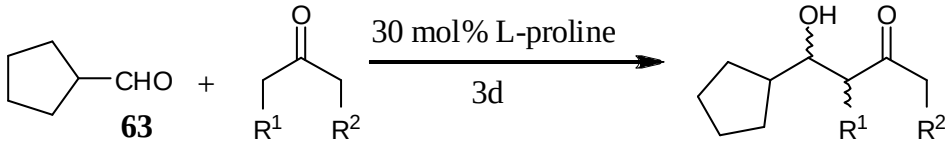
Styrene, as another prochiral olefin, gave identical results as compared to 4-chlorostyrene. In the reaction of prochiral 2,5-dihydrofuran and acetone enantioselectivities of 71% were observed, but no diastereoselectivity.

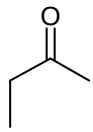
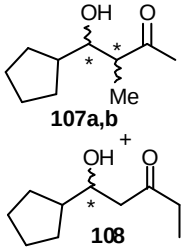
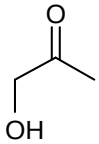
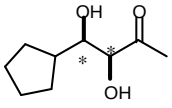
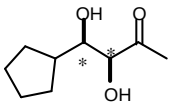
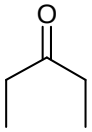
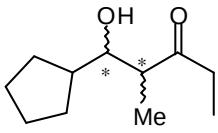
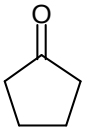
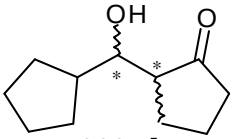
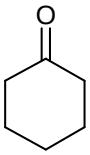
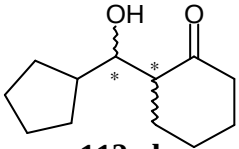
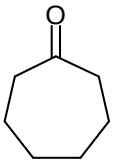
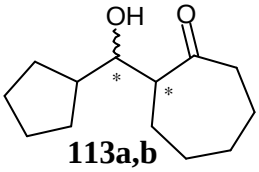
In contrast to tandem reactions, where cyclopentene was a substrate (see Table 4), the determination of styrene and 4-chlorostyrene conversions was possible by direct GC analysis. After injection of a crude reaction mixture, in GC spectra no signs of self-decomposition of aldol products **104** and **105** were observed.

Pro-chiral ketons can also be applied to sequential hydroformylation and enantioselective aldol reactions. According to the literature L-proline catalyses aldol reaction between aldehydes and prochiral ketones such as butanone, hydroxyacetone, pentan-3-one, cyclopentanone, cyclohexanone and cycloheptanone with good to excellent yields and enantioselectivities.[85, 90, 91, 94, 95] All these ketones were screened for aldol reaction under the condition from

Table 10, using cyclopentanecarbaldehyde as an aldehyde component and L-proline as an organocatalyst.

Table 10. Investigation of ketone scope.

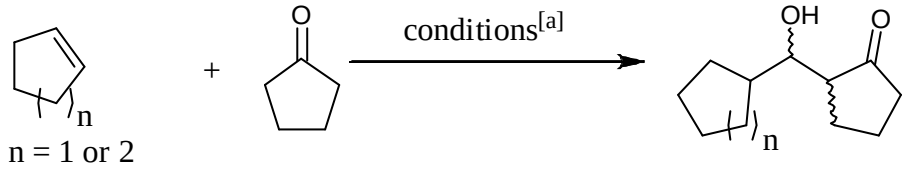


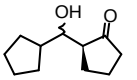
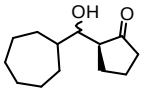
entry	ketone = solvent	product	aldehyde conversion[a]
1		 **107a,b** + **108**	none
2		 **109a,b**	none
3	hydroxyacetone/ CH_2Cl_2 1:3	 **109a,b**	none
4		 **110a,b**	none
5		 **111a,b**	50-80 %
6		 **112a,b**	none
7		 **113a,b**	none

[a]Determined by ^{1}H NMR analyses

Surprisingly under given conditions only cyclopentanone afforded an aldol product. Therefore just cyclopentanone was used further as a ketone component in sequential hydroformylation and aldol reactions (Table 11).

Table 11. Sequential hydroformylation/enantioselective aldol reactions of cyclic olefins and a prochiral ketone.



entry	substrate	ketone = solvent	product	ol. conv. (%)[b]	yield (%)[c]	syn:anti[b]	ee (%)[d]
1			 **111a**-syn **111b**-anti	> 99	59	1 : 2.7	95[e] (for syn) 96 (for anti)
2			 **114a**-syn **114b**-anti	> 99	76	1 : 1.9	83 (for syn) 85 (for anti)

[a]0.5 mol% $Rh(acac)(CO)_2$, 20/20 bar CO/H_2, 2 mol% $P(OPh)_3$, 30 mol% L-proline, 40 °C, 72 hours.

[b]Determined by ^1H NMR analyses.

[c]Based on isolated product.

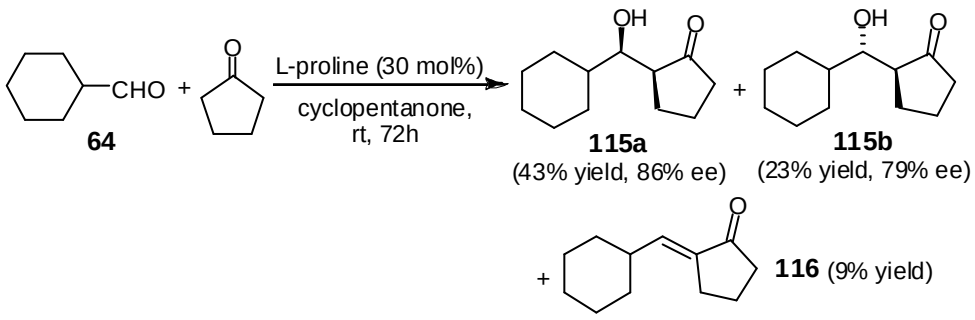
[d]Determined by chiral HPLC.

[e]Determined by Mosher's method.

As shown in Table 11, with non-prochiral cyclic alkenes and prochiral cyclopentanone very good yields and enantioselectivities, but low diastereoselectivities, were obtained.

In order to determine the relative and absolute configurations of compounds **111a,b** and **114a,b** a control room temperature experiment was performed with cyclohexanecarbaldehyde and cyclopentanone in the presence of L-proline (Scheme 35).

Scheme 35. L-proline-catalysed asymmetric aldol reaction of cyclohexanecarbaldehyde and cyclopentanone.



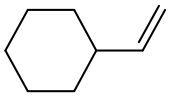
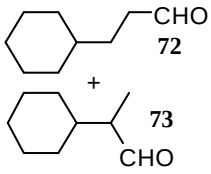
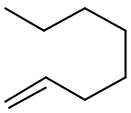
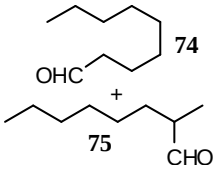
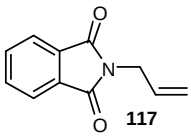
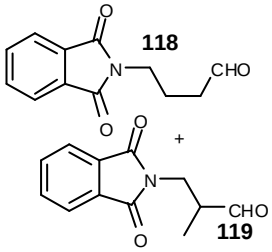
The assignment was based on the comparison of spectral data known for racemic compounds **115a,b**[96] and the results obtained in the reaction of cyclohexanone with benzaldehyde.[95] In all cases the absolute configuration at the β-hydroxy group is not identical for the syn/anti diastereomers (Table 11 and Scheme 35). Noteworthy, with cyclohexanecarbaldehyde (Scheme 35) the syn:anti ratio is reversed as compared to the tandem reactions with cyclic olefins and cyclopentanone described above (Table 11). This shows a surprising sensitivity of the diastereoselectivity towards substrate structure and reaction conditions. Thus, for further investigations of syn:anti diastereoselectivities various parameters have to be explored.

2.1.4 Sequential hydroformylation and aldol reactions of α-non-branched aldehydes

In order to combine hydroformylation and enantioselective aldol reactions of α-non-branched aldehydes, regioselectivity of hydroformylation sequence has to be controlled. For this reason a bulky phosphite ligand BIPHEPHOS was employed. According to the literature this phosphite exhibits excellent regioselectivities for a wide range of functionalised olefins.[97] Usually in order to have better regioselectivities relatively low pressures and high temperatures have to be used.[77] Vinylcyclohexane, oct-1-ene and 2-allylisoindoline-1,3-dione

117 were chosen as model substrates and were hydroformylated at 10/10 bar CO/H_2 and 50°C (Table 12).

Table 12. Olefin screening for regioselective hydroformylation sequence using BIPHEPHOS-modified rhodium catalyst.[a]

entry	olefin	product	alkene conv. (%)[b]	aldehyde yield (%)[b]	*l:b* ratio[b]
1		 **72** + **73**	> 99	> 99	20 : 1
2		 **74** + **75**	> 99	> 99	20 : 1
3	 **117**	 **118** + **119**	> 99[c]	nd	33 : 1[c]

[a]10/10 bar CO/H_2, 2 mol% BIPHEPHOS, 0.5 mol% $Rh(acac)(CO)_2$ 50°C, 72h, acetone.

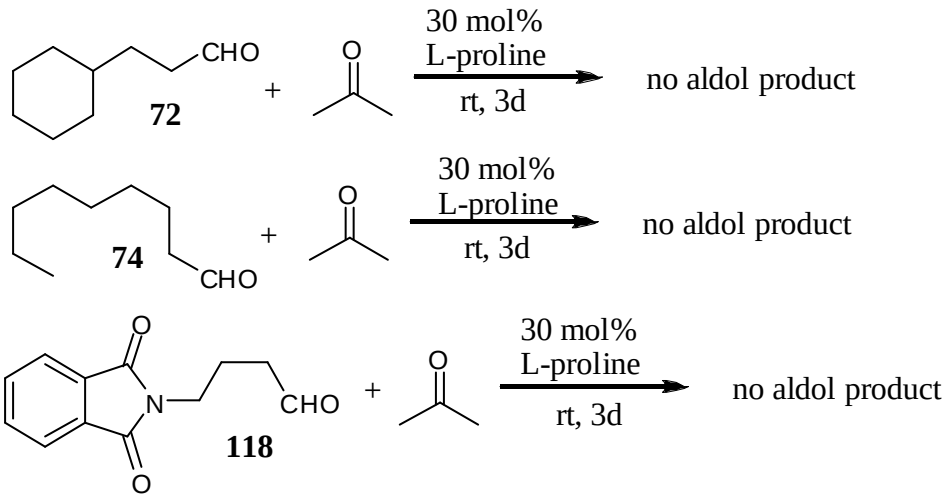
[b]Determined by GC using an internal standard.

[c]Determined by ^1H NMR.

nd – not determined

All subtrates were fully converted with BIPHEPHOS modified Rh-catalyst and gave excellent regioselectivities, up to 33:1 ratio *linear:branched* aldehydes. Then, L-proline was added to the solution of these aldehydes in acetone (Scheme 36).

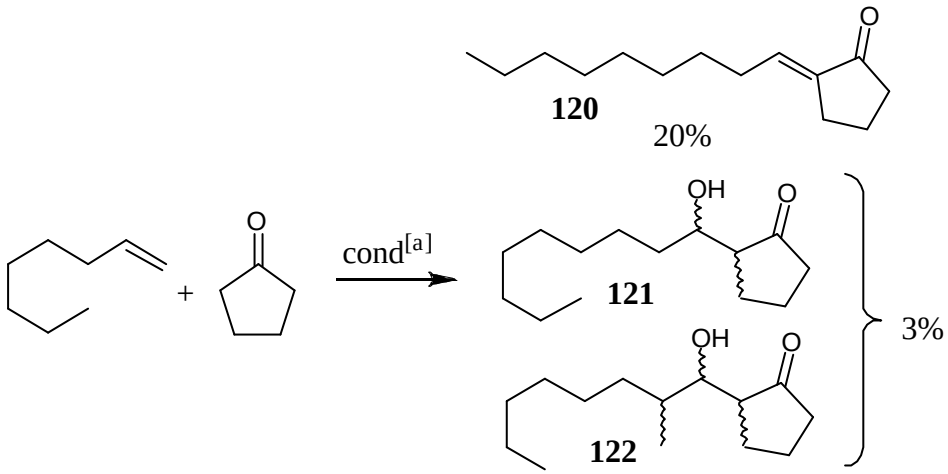
Scheme 36. L-proline-catalysed aldol reaction between acetone and α-non-branched aldehydes.



Surprisingly, after three days of stirring in all cases no aldol products were observed. It is known from the literature that in some cases L-proline do not catalyse aldol reactions between acetone and α-non-branched aldehydes.[95]

On the other hand, according to Yamasaki undecanal reacts with cyclopentanone in the presence of L-proline with good yields and excellent enantioselectivities.[98] We envisioned that changing the ketone component from acetone to cyclopentanone would allow L-proline to catalyse aldol reaction between a α-non-branched aldehyde and a cyclic ketone. For this reason we applied oct-1-ene to sequential hydroformylation/aldol reactions in cyclopentanone as the solvent (Scheme 37). Unfortunately only the elimination product **120** and traces of desired aldol **121** could be isolated after reaction.

Scheme 37. Sequential hydroformylation/enantioselective aldol reactions of oct-1-ene.[a]



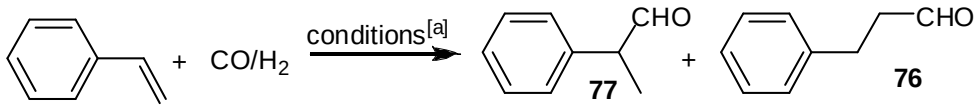
[a]10/10 bar CO/H_2, 2 mol% BIPHEPHOS, 0.5 mol% $Rh(acac)(CO)_2$, 30 mol% L-proline, 50°C, 72h, acetone.

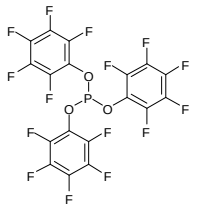
2.1.5 Room temperature hydroformylation

Since L-proline-catalysed aldol reactions usually are performed at room temperature we decided to investigate the effect of lowering temperature on yields, enantio- and diastereoselectivities of the sequential hydroformylation/enantioselective aldol reactions. At first, we performed a ligand screening in order to find the most active catalyst at room temperature. Hydroformylation of styrene in acetone was chosen as a model reaction (Table 13).

According to GC analysis, unmodified, triphenyl phosphite- and perfluoro-triphenyl phosphite-modified Rh-catalysts gave fastest hydroformylation catalysts (Table 13, entries 1, 4 and 7). Since sequential hydroformylation / aldol reactions do not proceed with unmodified Rh-catalysts (see Table 5, entry 1) triphenylphosphite ligand was selected for all further studies.

Table 13. Phosphorus ligand screening for room temperature hydroformylation.



entry	ligand	olefin conv. (%)[b]	aldehyde yield (%)[b]	*b:l* ratio[b]
1	none	32	32	77 : 23
2	PPh_3	5	5	96 : 4
3	BIPHEPHOS	3	3	96 : 4
4	$P(OPh)_3$	16	16	92 : 8
5	dppe	0	0	-
6	dppb	0	0	-
7		12	12	96 : 4

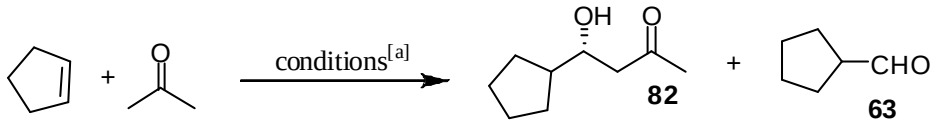
[a]0.5 mol% $Rh(acac)(CO)_2$, 20/20 bar CO/H_2, 2 mol% phosphorus ligand, 25°C, 24h, acetone.
[b]Determined by GC using an internal standard.

2.1.6 Room temperature sequential hydroformylation/aldol reactions

On the basis of our previous screenings (Table 8), room temperature sequential hydroformylation and enantioselective aldol reactions of cyclopentene and acetone were performed at 20/20 and 70/10 bar CO/H_2 gas pressures (Table 14).

As shown in Table 14, after 72 h cyclopentene was almost fully converted both at 20/20 and 70/10 bar CO/H_2. According to the GC analysis and yields of isolated products at 20/20 bar CO/H_2 aldol addition is considerably slower than hydroformylation (Table 14, entries 1 and 2). At 70/10 bar CO/H_2 a decrease in aldol yield was observed (Table 14, entry 3).

Table 14. Room temperature sequential hydroformylation/enantioselective aldol reactions of cyclopentene and acetone.



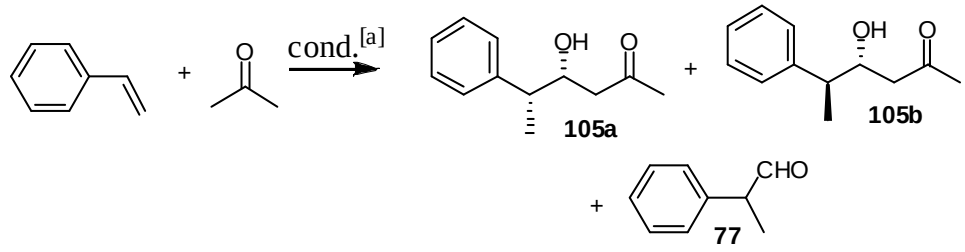
entry	P_{CO}	P_{H2}	time (h)	olefin conv. (%)[b]	isolated yield (%) **82**	isolated yield (%) **63**	ee **82** (%)[c]
1	20	20	72	94	33	18	83
2	20	20	120	94	45	6	82
3	70	10	72	93	18	8	82

[a]0.5 mol% $Rh(acac)(CO)_2$, 2 mol% $P(OPh)_3$, 30 mol% L-proline, 25°C, acetone.
[b]Determined by GC using an internal standard.
[c]Determined by chiral HPLC.

Next, in order to investigate how the decrease of reaction temperature influences yields, diastereo- and enantioselectivities of sequential hydroformylation and enantioselective aldol addition, reaction of prochiral styrene and acetone was performed (Table 15).

The results from Table 15 indicate that olefin conversion is drastically influenced by pressure. Styrene is almost fully converted at 20/20 bar CO/H_2 after 3 days reaction, however at 70/10 bar CO/H_2 according to GC analysis only 43% of alkene is converted. Diastereo- and enantioselectivities are not influenced by pressure and are slightly higher than in reaction performed at 40°C (see Table 9, entry 1).

Table 15. Room temperature sequential hydroformylation/enantioselective aldol reactions of styrene and acetone.



entry	P_{CO}	P_{H2}	olefin conv. (%)[b]	isolated yield (%) **105a,b**	**77**	syn:anti[c]	ee (%)[d]
1	20	20	96	75	5	1.8 : 1	79 (for syn) > 99 (for anti)
2	70	10	43	12	11	1.8 : 1	80 (for syn) > 99 (for anti)

[a]0.5 mol% $Rh(acac)(CO)_2$, 2 mol% $P(OPh)_3$, 30 mol% L-proline, 25°C, 72h, acetone.

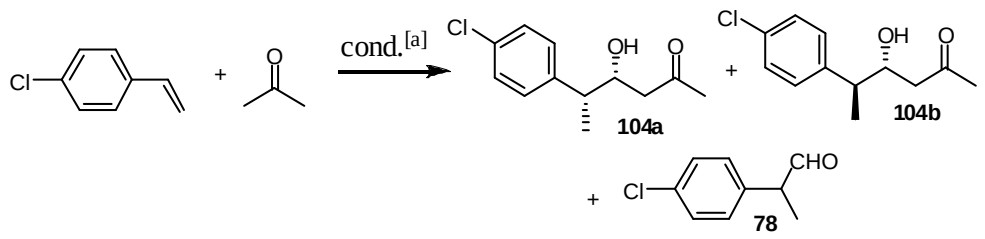
[b]Determined by GC using an internal standard.

[c]Determined by ^1H NMR analyses.

[d]Determined by chiral HPLC.

4-Chlorostyrene was also applied to room temperature sequential hydroformylation and enantioselective aldol reactions (Table 16). Again a drastic decrease in olefin conversion at 70/10 bar CO/H_2 was observed. Diastereo- and enantio-selectivities are similar with the results obtained at 40°C.

Table 16. Room temperature sequential hydroformylation/enantioselective aldol reactions of 4-chlorostyrene and acetone.



entry	P_{CO}	P_{H2}	olefin conv. (%)[b]	isolated yield (%) **104a,b**	isolated yield (%) **78**	syn:anti[c]	ee (%)[d]
1	20	20	97	82	2	1.6 : 1	75 (for syn) > 99 (for anti)
2	70	10	51	32	14	1.6 : 1	71 (for syn) > 99 (for anti)

[a]0.5 mol% $Rh(acac)(CO)_2$, 2 mol% $P(OPh)_3$, 30 mol% L-proline, 25°C, 72h, acetone.

[b]Determined by GC using an internal standard.

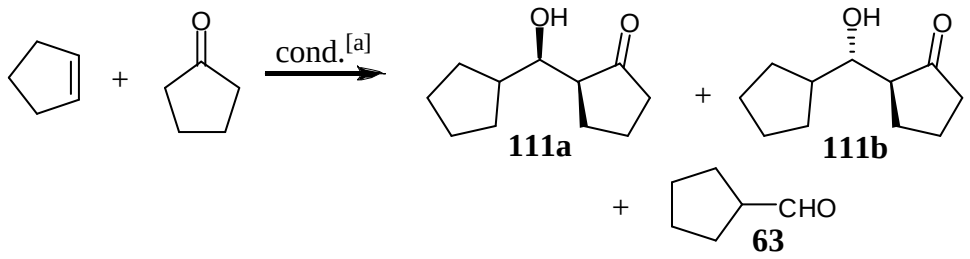
[c]Determined by ^1H NMR analyses.

[d]Determined by chiral HPLC.

Next, reaction of cyclopentene and prochiral cyclopentanone was investigated (Table 17).

Again at 70/10 bar CO/H_2 a drastic decrease in yields of aldol products was observed. 20/20 bar CO/H_2 gave a slightly higher conversion of olefin than 70/10 bar CO/H_2. No effect of pressure on enantioselectivities was observed.

Table 17. Room temperature sequential hydroformylation/enantioselective aldol reactions of cyclopentene and cyclopentanone.



entry	P_{CO}	P_{H2}	olefin conv. (%)[b]	isolated yield (%) **111a,b**	isolated yield (%) **63**	syn:anti[c]	ee (%)[d]
1	20	20	98	61	< 1	1 : 1.1	nd (for syn) 96 (for anti)
2	70	10	92	11	< 1	1 : 1.1	nd (for syn) 96 (for anti)

[a]0.5 mol% $Rh(acac)(CO)_2$, 2 mol% $P(OPh)_3$, 30 mol% L-proline, 25°C, 72h, acetone.

[b]Determined by GC using an internal standard.

[c]Determined by ^1H NMR analyses.

[d]Determined by chiral HPLC.

nd – not dermined

2.1.7 Summary

In summary, we have achieved to introduce enantioselectivity into the hydroformylation/aldol addition sequence. Scope, optimisation and application of this sequence have been described herein. Our methodology is operationally simple, gives good chemical yields and provides the products in high optical yields. We found that $P(OPh)_3$ modified Rh-catalyst and L-proline are the best catalysts for our tandem reaction. Possible negative interactions between hydroformylation catalyst (Rh-catalyst) and aldol addition catalyst (L-proline) were not observed. Also sequential hydroformylation / intra- or inter-molecular aldol addition of alkenes that generate α-non-branched aldehydes were explored. In these cases L-proline did not catalyse efficiently aldol step. Conducting

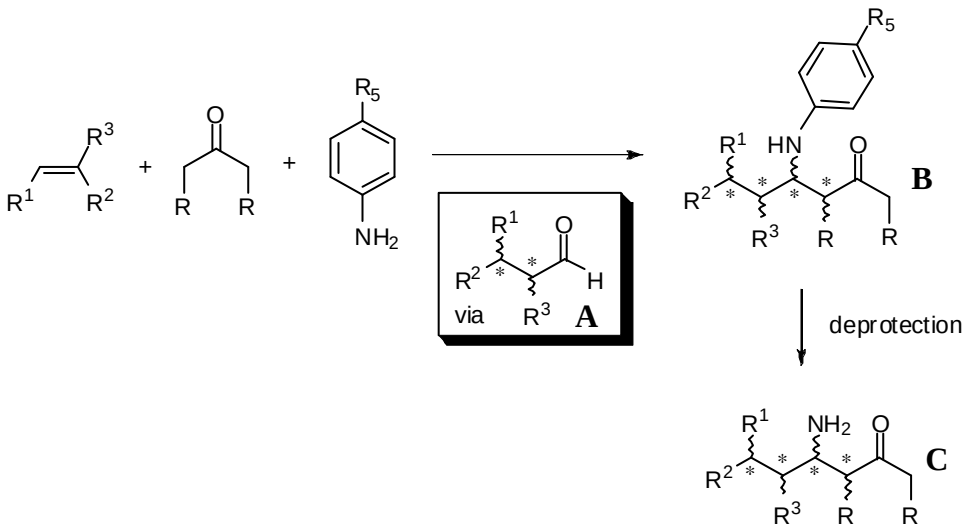
tandem reaction at room temperature (instead of 40°C) proved to be less efficient because of slow L-proline catalysed aldol addition.

2.2 Tandem metal- and organocatalysis in sequential hydroformylation and enantioselective Mannich reactions

2.2.1 First experiments

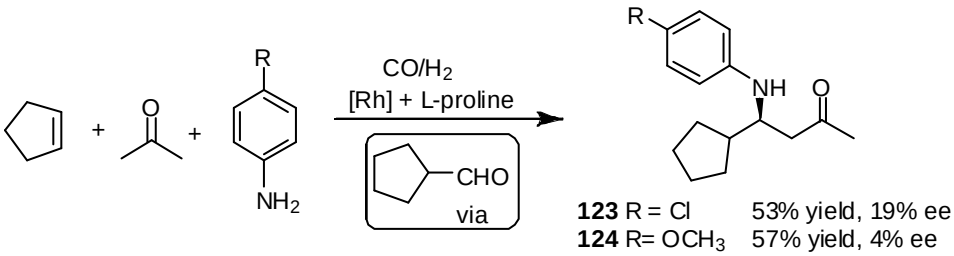
On the basis of our previous results concerning the combination of hydroformylation and stereoselective aldol reactions we became interested in whether we can combine metal catalysed enantioselective hydroformylation and organocatalysed enantioselective Mannich reactions in a tandem reaction sequence. In this transformation three components an alkene, a ketone and an amine are converted to a β-amino-ketone (**B**) in one pot procedure, generating up to four new stereocenters (Scheme 38).

Scheme 38. Tandem metal- and organocatalysis in sequential hydroformylation and enantioselective Mannich reactions.



At first, we performed sequential hydroformylation and enantioselective Mannich reactions under conditions that were found to be optimal for sequential hydroformylation and enantioselective aldol reactions. Cyclopentene, acetone and aromatic amine (p-anisidine or p-chloroaniline) were converted to β-amino-ketones **123** and **124** in the presence of Rh-catalyst and L-proline (Scheme 39).

Scheme 39. Sequential hydroformylation and enantioselective Mannich reactions.

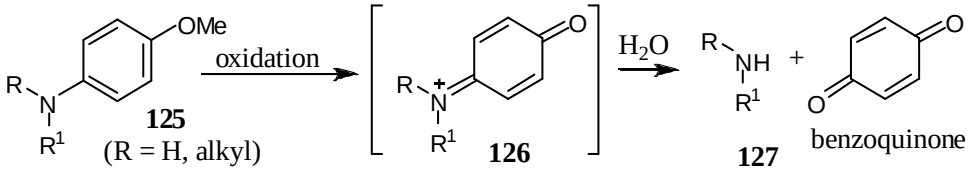


Conditions: 0.5 mol% $Rh(acac)(CO)_2$, 2 mol% $P(OPh)_3$, 30 mol% L-proline, 20/20 bar CO/H_2 , 40°C, 3d, acetone

Desired Mannich products were obtained with medium to good yields (53-57%), but modest enantioslectivities were observed. The absolute configuration of compunds **123** and **124** were assigned by analogy with the known β-amino ketones obtained in L-proline catalysed Mannich reaction.[55, 57, 110] It is important to note that absolute stereochemistry of the new stereogenic center is opposite to that which we have observed for the corresponding aldol reactions using the same catalyst.

When p-anisidine is used as an amine component, p-methoxyphenyl function of the β-amino-ketone (**B)** can be removed under oxidative conditions affording free amino group (Scheme 40).[111, 112]

Scheme 40. Deprotection of PMP-protected amines.



2.2.2 Summary

In conclusion, for the first time Rh-catalysed hydroformylation was combined with enantioselective proline-catalysed Mannich reactions. Our methodology does not require separate preactivation of substrates and can be performed on a multigram scale under operationally simple conditions. One more important features of this transformation is that inexpensive catalyst proline is available in both enantiomeric forms and can be recovered from the reaction mixture via filtration. At the moment the limitation of our methodology is poor optical yields, therefore more investigation on the solvent, substrate and amine scope has to be done.

2.3 Enantioselective sequential hydroformylation and aldol addition

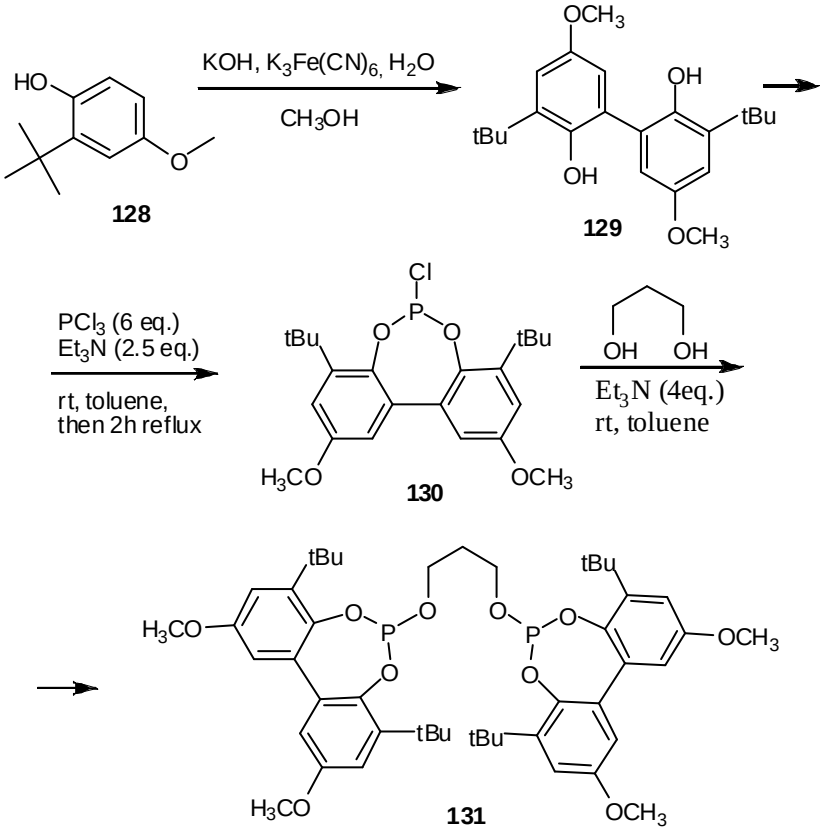
2.3.1 Enantioselective hydroformylation of styrene

In order to combine enantioselective hydroformylation with enantioselective aldol addition, styrene was chosen as a model substrate. In 1995 Piet W.N.M van Leeuwen's group reported both good regio- and enantioselectivities obtained with diphosphite ligands in the Rh-catalysed hydroformylation of styrene.[99] Enantioselectivities up to 76% at 50% conversion have been obtained with Chiraphite modified Rh-catalyst using relatively mild reaction conditions (25-40°C, 9 bar of CO/H_2 1:1 pressure, toluene).

2.3.2 Synthesis of Chiraphite ligands

Chiraphite ligands were prepared according to the van Leeuwen procedure (Scheme 41).[99]

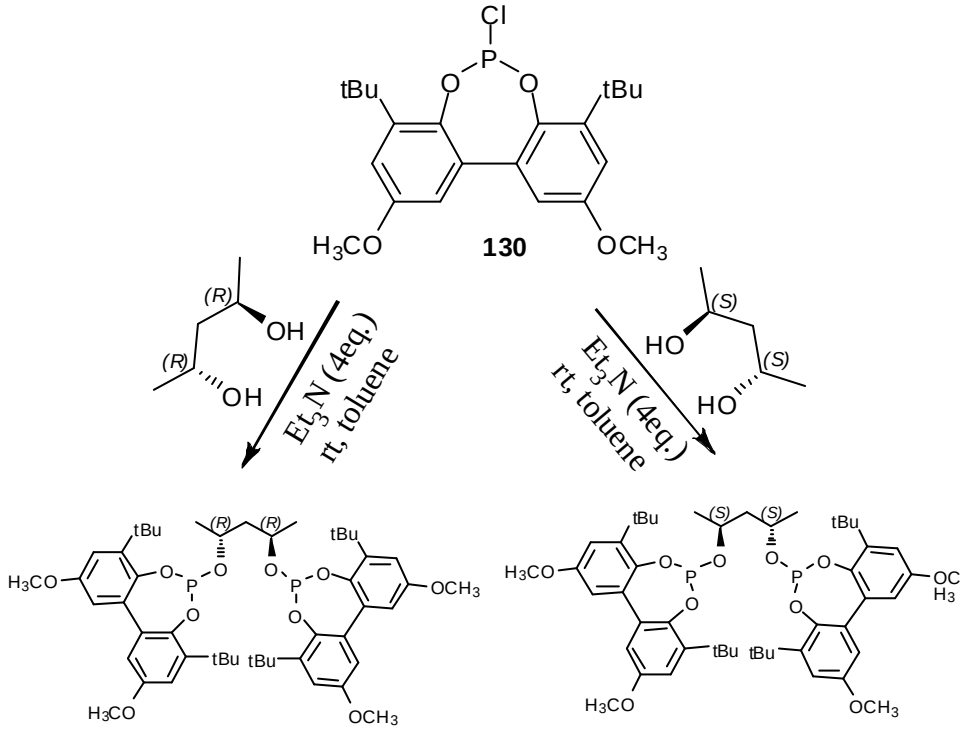
Scheme 41. Synthesis of new diphosphite ligand based on pentane–2,4-diol.



At first, 2,2'-dihydroxy-3,3'-di-tert-butyl-5,5'-dimethoxy-1,1'-biphenyl **129** was prepared in high yield from 2-tert-butyl-4-methoxyphenol following the literature procedure.[100] Treatment of **129** with PCl_3 in the presence of Et_3N gave phosphorochloridite **130**, which was further used without purification. In order to avoid losing of relatively expensive (2R,4R)-pentane-2,4-diol or (2S,4S)-pentane-2,4-diol, compound **130** was treated with propane–1,3-diol affording new phosphorus ligand **131** in moderate yield (28%).

Next, phosphorochloridite **130** was reacted with (2R,4R)-pentane-2,4-diol or (2S,4S)-pentane-2,4-diol in the presence of Et_3N affording (2R,4R)-Chiraphite **8a** or (2S,4S)-Chiraphite **8b** respectively in moderate yields (25-30%) (Scheme 42).

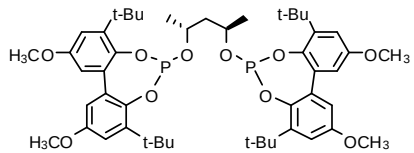
Scheme 42. Synthesis of (2R,4R)-Chiraphite and (2S,4S)-Chiraphite ligands.



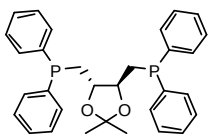
(2R,4R)-Chiraphite **8a** (2S,4S)-Chiraphite **8b**

Since tandem hydroformylation/aldol addition of styrene and acetone is performed at 40°C a series of chiral phosphorus ligands (Scheme 43) was evaluated in enantioselective hydroformylation of styrene at this temperature (Table 18).

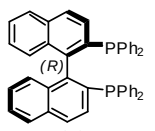
Scheme 43. Chiral phosphorus ligands used in enantioselective hydroformylation.



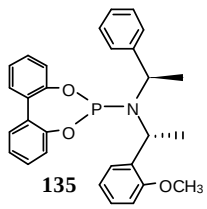
(2R,4R)-Chiraphite **8a**



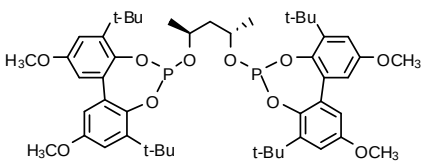
(+) DIOP **132a**



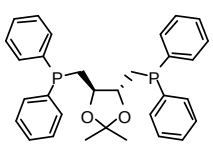
R-(+)-BINAP **133**



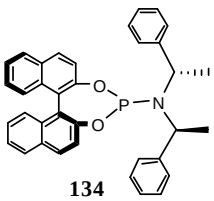
135



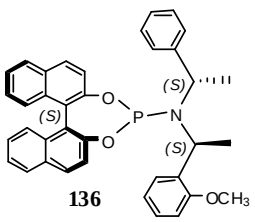
(2S,4S)-Chiraphite **8b**



(-) DIOP **132b**

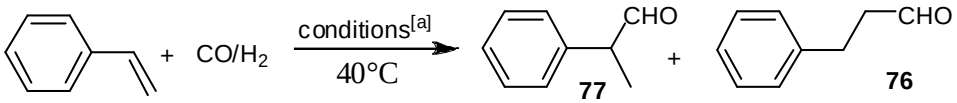


134



136

Table 18. Ligand screening for enantioselective hydroformylation reaction.



entry	ligand	reaction time (h)	P_{CO} (bar)	P_{H2} (bar)	conv. (%)[c]	ald. yield (%)[c]	b:l ratio[c]	ee (%)[c]
1[b]	(2R,4R)-Chiraphite	24	20	20	52	52	98:2	19 (S)
2	"	24	10	10	80	80	98:2	74 (S)
3	"	24	20	20	53	53	97:3	60 (S)
4	"	24	40	40	66	66	91:9	73 (S)
5	"	72	20	20	> 99	> 99	96:4	62 (S)
6	"	72	40	40	> 99	> 99	97:3	45 (S)
7	(2S,4S)-Chiraphite	24	10	10	75	75	96:4	40 (R)
8	"	24	20	20	48	48	94:6	59 (R)
9	"	24	40	40	52	52	85:15	63 (R)
10	"	72	20	20	> 99	> 99	96:4	62 (R)
11	"	72	40	40	84	84	96:4	53 (R)
12	(-)-DIOP	72	40	40	> 99	> 99	97:3	0
13	(+)-DIOP	24	20	20	42	42	97:3	0
14	"	72	40	40	> 99	> 99	97:3	0
15	BINAP	24	20	20	none	none	-	-
16	**66**	24	20	20	68	68	96:4	0
17	**67**	24	20	20	> 99	> 99	96:4	0
18	**68**	24	20	20	93	93	96:4	0

[a]0.5 mol% $Rh(acac)(CO)_2$, 2 mol% phosphorus ligand, 40°C, acetone.

[b]0.25 mol% $Rh(acac)(CO)_2$, 0.31 mol% phosphorus ligand, 40°C, toluene.

[c]Determined by GC using an internal standard.

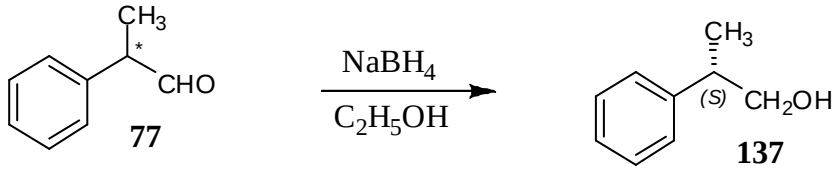
At first, we performed a test enantioselective hydroformylation of styrene at 20/20 bar CO/H_2 with not-preformed catalyst (Table 18, entry 1). In contrast with van Leeuwen's results (98% conv, 94:6 b:l and 67% ee of **62**)[99] we obtained 2-phenylpropanal in only 19% ee at 53% conversion of styrene. In order to increase the enantioselectivity of reaction, we increased two times the concentration of Chiraphite modified Rh-catalyst and we used acetone instead of

toluene. Pleasingly, enantioselectivities have grown to 59-60% ee (Table 18, entries 3 and 8). As enantioselective hydroformylation is extremely sensitive to the reaction conditions, various CO and H_2 partial pressures were studied to ascertain pressure effects. The stereoselective formation of 2-phenylpropanal was performed at 10/10, 20/20, and 40/40 bar pressures of CO/H_2 (Table 18). The best results 74% ee for (S)-2-phenylpropanal and 63% for (R)-2-phenylpropanal were obtained at 10/10 and 40/40 bar CO/H_2 respectively (Table 18, entries 2 and 9). Since L-proline-catalysed aldol reaction between 2-phenylpropanal and acetone requires 3 days of stirring, the time of enantioselective hydroformylation of styrene was increased from 24h to 72h. Noteworthy, at 20/20 bar CO/H_2 after 72h of hydroformylation no decrease in enantioselectivity was observed (Table 18, entries 3 and 5). Thus, Chiraphite-modified Rh-catalyst do not racemise *iso*-aldehyde **77**.

It is reported in the literature that Rh-catalysts modified with DIOP **132** and BINAP **133** provide low ees (12 –25 %) in hydroformylation of styrene in toluene at 65°C.[101] However, we expected that lowering temperature to 40°C and performing the hydroformylation in acetone would have some beneficial effect on enatioselectivities. Unfortunately no asymmetric induction was observed with these ligands (Table 18, entries 12, 13, 14 and 15). Moreover, BINAP-modified Rh-catalyst gave no conversion of styrene after 24 hours. Also no enantioselectivity was observed when Rh-catalyst was modified with chiral phosphoramidite ligands **134**, **135** and **136**.

In order to determine the right configuration of *iso*-aldehyde obtained in hydroformylation of styrene with (2R,4R)-Chiraphite-modified Rh-catalyst, 2-phenylpropanal was reduced with $NaBH_4$ in the presence of ethanol (Scheme 44).

Scheme 44. Reduction of 2-phenylpropanal to 2-phenylpropanol.

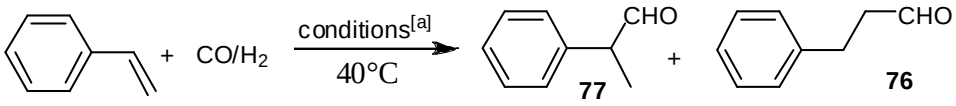


from reaction catalysed by (2R,4R)-Chiraphite-modified Rh-catalyst

Absolute configuration of obtained 2-phenylpropanol was determined by comparison of the retention time with that of optically pure (R)-(+)-2-phenylpropanol which is commercially available.

Next we investigated whether presence of 30 mol% of proline has some effect on enantioselective hydroformylation of styrene (Table 19).

Table 19. Enantioselective hydroformylation both in the presense and in the absence of proline.



en.	ligand	organocatalyst	conv. (%)[b]	ald. yield (%)[b]	b:l ratio[b]	ee **77** (%)[b]
1	(2S,4S)-Chiraphite	none	53	53	96 : 4	61 (R)
2	(2S,4S)-Chiraphite	L-proline	46	46	96 : 4	32 (R)
3	(2S,4S)-Chiraphite	D-proline	68	68	96 : 4	14 (R)

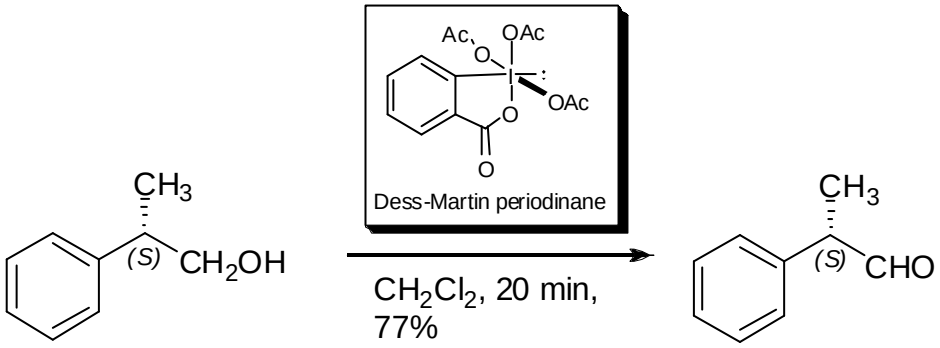
[a]40/40 bar CO/H_2, 0.5 mol% $Rh(acac)(CO)_2$, 2 mol% (2S,4S)-Chiraphite, 30 mol% organocatalyst, 40°C, 24h, CH_2Cl_2.

[b]Determined by GC using an internal standard.

The reaction was performed both in the presence and in the absence of organocatalyst in dichlormethane at 40°C. A substantial decrease in enantioselectivities was observed when L-proline and D-proline were added to the reaction mixture (Table 19, entries 2 and 3). Probably this is due to racemisation of formed hydratropaldehyde. Practically no influence on reaction conversion and reaction regioselectivity was detected.

In order to investigate whether proline is responsible for racemisation of aldehyde **77,** enantioenriched (S)-2-phenylpropanal (96% ee) was synthesised from enantiopure (S)-2-phenylpropanol using a Dess-Martin oxidation (Scheme 45)

Scheme 45. Synthesis of (S)-2-phenylpropanal by Dess-Martin oxidation of (S)-2-phenylpropanol.

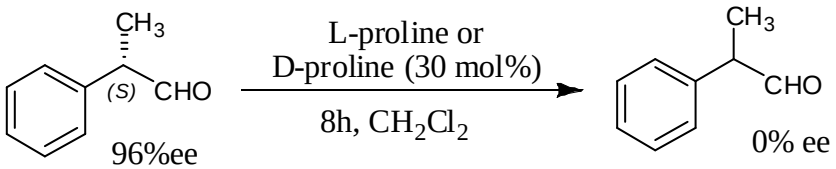


(S)-137 (<98%ee) **(S)-77 (96%ee)**

Among a variety of oxidizing reagents that were tested in the literature (Swern oxidation,[103] tetra-n-butylammonium per-ruthenate (TPAP),[104] chromium trioxide/Celite[105]), it appeared that the only reagent to give **(S)-77** in good chemical yield and almost without loss of enantiomeric excess is the Dess-Martin periodinane.[102, 106, 107]

After we obtained compound **77** as the S-enantiomer we have stirred the aldehyde in one flask with L-proline and in another with D-proline in dichlormethane at room temperature (Scheme 46).

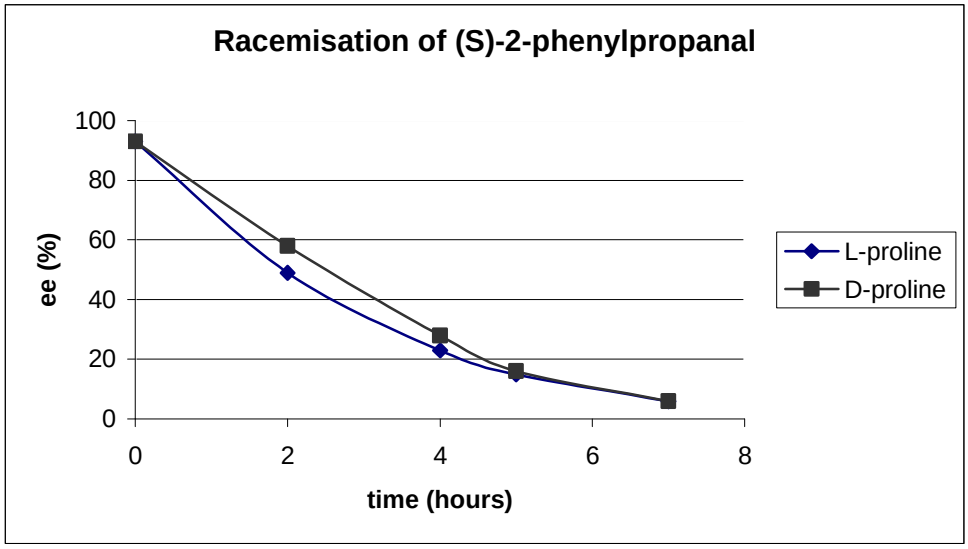
Scheme 46. Control reactions between (S)-2-phenylpropanal and proline.



(S)-77 **(rac)-77**

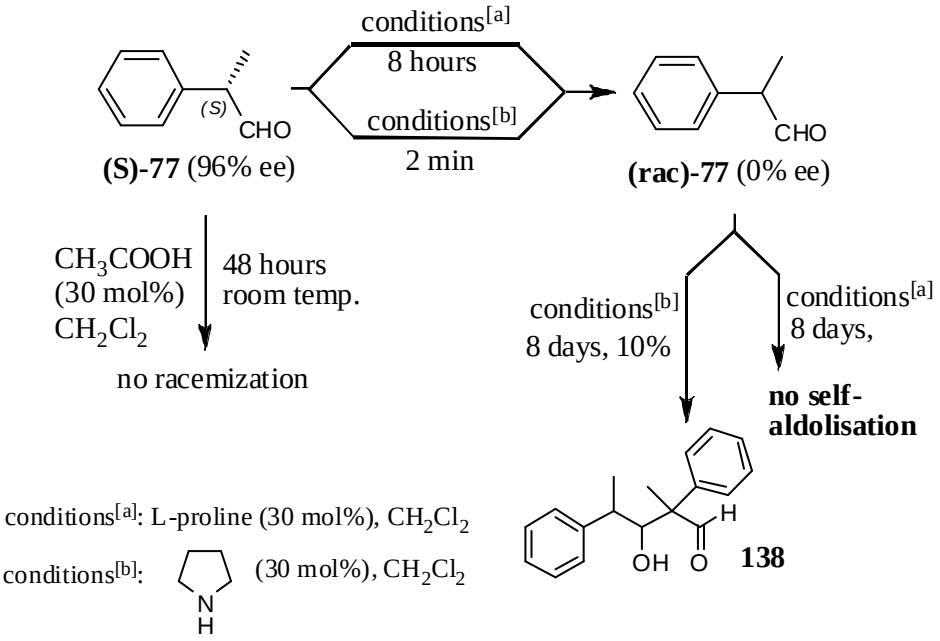
We observed slow racemisation of aldehyde in the presence of both L-proline and D-proline. Hydratropaldehyde was fully racemised within 8 hours at room temperature in both cases (Scheme 47).

Scheme 47. Racemisation of (S)-2-phenylpropanal in the presence of L-proline or D-proline.



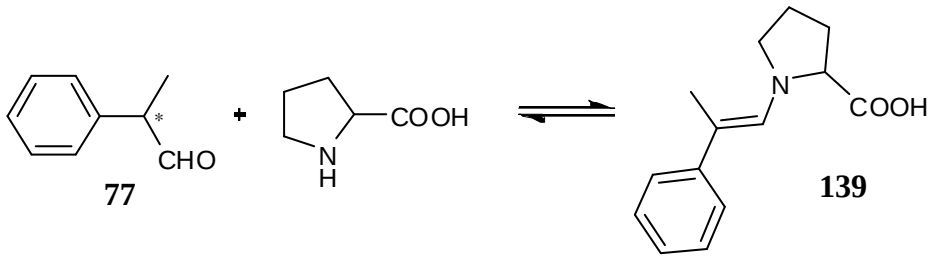
In order to investigate what part of the proline is responsible for racemisation of (S)-2-phenylpropanal we performed two control experiments. In one flask aldehyde **(S)-77** was stirred with 30 mol% of pyrrolidine in CH_2Cl_2, in second flask with 30 mol% of acetic acid in CH_2Cl_2 (Scheme 48).

Scheme 48. (S)-2-Phenylpropanal racemisation and self-aldolisation under acidic or basic conditions.



Acetic acid did not racemise aldehyde **(S)-77** even after 48 hours of stirring at room temperature. In contrast, pyrrolidine racemises aldehyde within 2 minutes. If stirring continues after 8 days in the presence of pyrrolidine aldehyde partially self-condensate to aldol product **138**. Since pyrrolidine part of proline is responsible for racemisation probably racemisation is due to formation of enamine **139** (Scheme 49).

Scheme 49. Formation of enamine **139** from hydratropaldehyde and proline.



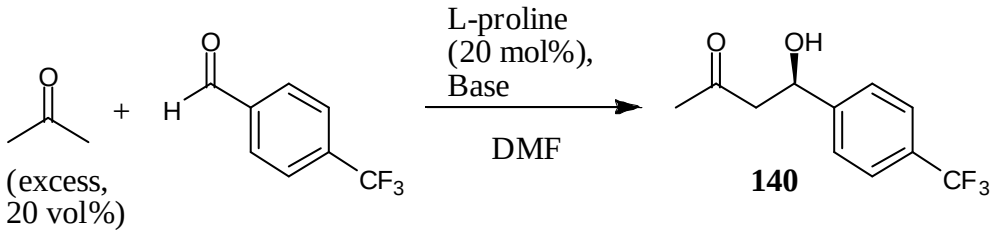
In order to have better asymmetric induction, aldol reaction has to be faster than aldehyde racemisation. In order to know which reaction is faster racemisation or aldol reaction we investigated proline-catalysed aldol reaction between 2-

phenylpropanal and acetone at room temperature. Also we were wondering whether we could increase the rate of the aldol reaction using some additives.

2.3.3 Effects of additives on the proline-catalysed aldol reactions

Recently several groups have tried to find additives that can improve enantioselectivity or accelerate the L-proline-catalysed aldol reaction. Pihko demonstrated that water has an accelerating effect on proline-catalysed ketone-aldehyde aldol reactions.[91, 108] This allows the use of stoichiometric amounts of both ketone and the aldehyde acceptor, thereby improving the overall economy of the process. In addition, aldol reactions with an excess of ketone are also improved by the addition of water. Also Pihko group studied the effect of base on the proline-catalysed aldol reaction between 4-trifluorobenzaldehyde and acetone (Scheme 50)

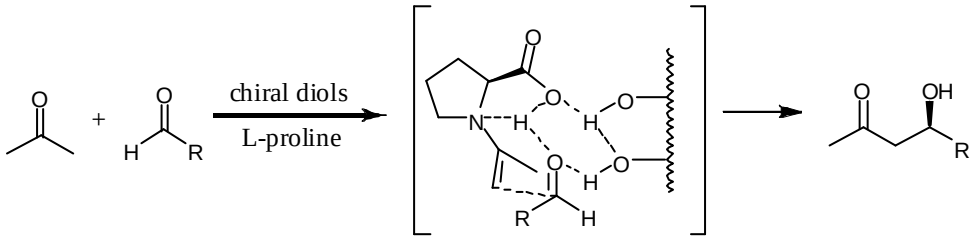
Scheme 50. L-proline-catalysed aldol reaction between acetone and p-trifluoromethylbenzaldehyde.



According to their results N,N-dimethylaniline, N-methylmorpholine, triethylamine, and dimethylamine did not exert any beneficial effect on the reaction rate. For the same reaction the effect of acids as additives was studied.[108] Acetic acid had a slight retarding effect on the reaction whereas trifluoroacetic acid, a stronger acid, brought the reaction to a complete halt. The enantioselectivity of the reaction was not affected by acetic acid.

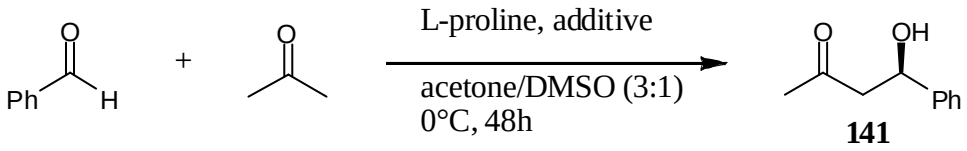
C_2-symmetric chiral diols have been examined as additives by Shan and Zhou in the L-proline catalysed direct aldol reaction (Scheme 51).[109]

Scheme 51. L-Proline-catalysed aldol reaction assisted by chiral diols.



On the basis of their results authors attributed the chiral induction in the aldol reaction to the chirality of L-proline, and probably, the role of additives is only enhancing chiral inductive ability of L-proline by the formation of a chiral supramolecular system through hydrogen-bonding interactions (Scheme 51).[109] They observed a significant improvement in enantioselectivity, conversion and yield, using 1 mol% of (S)-BINOL as an additive (Scheme 52).

Scheme 52. Screening of the additives on the direct aldol reaction.



141

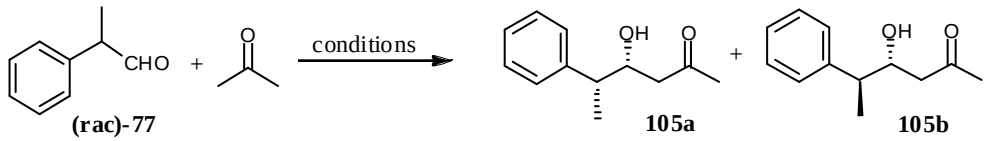
1. no additive - 60% conv., 43% yield, 72% ee
2. (R)-BINOL - 93% conv., 52% yield, 91% ee
3. (S)-BINOL - 76% con., 52% yield, 94% ee
4. rac-BINOL - 72% conv., 50% yield, 76% ee

In the reaction between benzaldehyde and acetone the enantioselectivity of reaction using additives was increased to 94% ee compared with the original 72% ee in which no additive was used (Scheme 52).[109]

In our tandem reaction is not desirable to use strong base as an additive since it can cause fast racemisation of formed hydrotropaldehyde. We supposed that C_2-symmetric chiral diols would be a suitable additive for our system.

To clarify the additive effect on the aldol reaction three parallel reactions were performed; a) without additive b) with 3 mol% of (S)-BINOL and c) with 3 mol% of (R)-BINOL (Scheme 53).

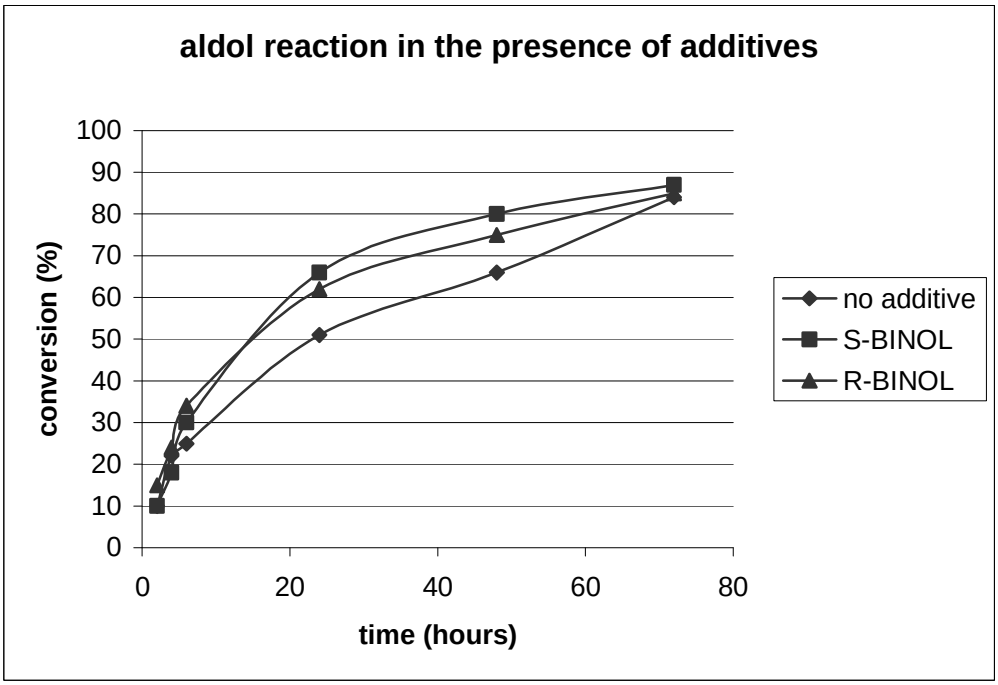
Scheme 53. L-proline-catalysed aldol reaction between hydrotropaldehyde and acetone.



(rac)-77 **105a** **105b**

syn/anti 1.9 : 1
(after 72h)

conditions:
a) L-proline, acetone
b) L-proline (30 mol%), (S)-BINOL (3 mol%), acetone
c) L-proline (30 mol%), (R)-BINOL (3 mol%), acetone

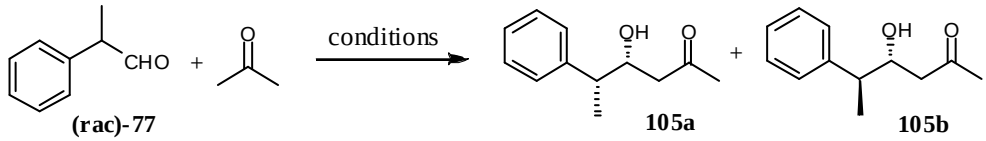


+

In contrast with reported effects of chiral diol additives on proline-catalysed aldol reaction,[109] 3 mol % of S-BINOL and R-BINOL gave no variation of enantioselectivity and diastereoselectivity in reaction between hydrotropaldehyde and acetone. After 72 hours in all three reactions diastereomeric ratio was 1.9:1 in the favor of syn diastereomer. When using S-BINOL or R-BINOL as an additive just a slight increase of aldol reaction speed as compared with reaction without additive was observed.

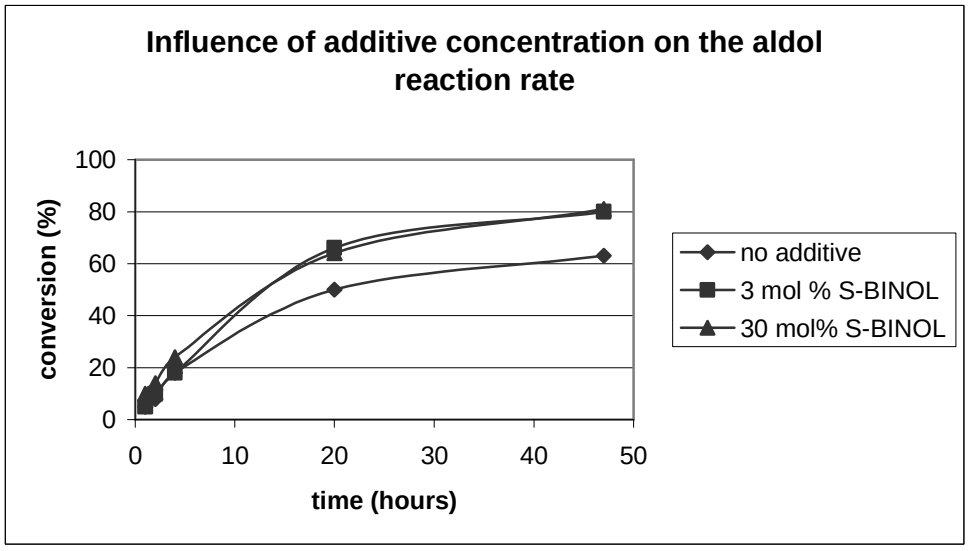
It was hoped that increasing concentration of additive would further increase the rate of aldol reactions (Scheme 54).

Scheme 54. Influence of (S)-BINOL concentration on the aldol reaction rate.



(rac)-77 **105a** **105b**

conditions:
a) L-proline (30 mol%), acetone
b) L-proline (30 mol%), (S)-BINOL (3 mol%), acetone
c) L-proline (30 mol%), (S)-BINOL (30 mol%), acetone



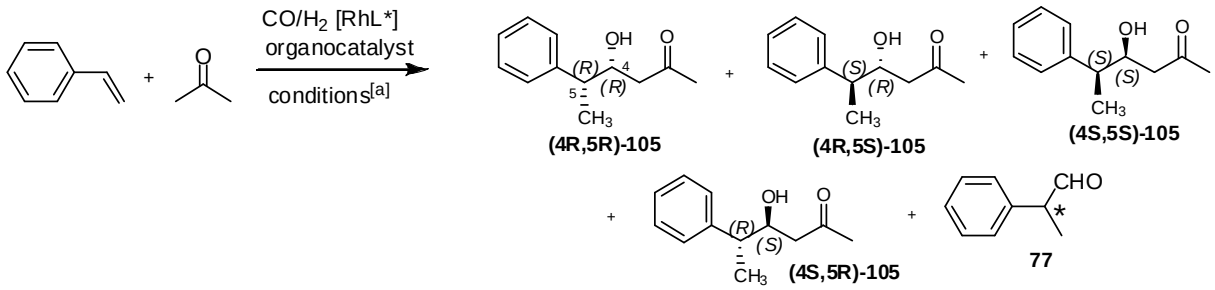
However, according to GC analyses 3 mol% and 30 mol% of (S)-BINOL gave similar results, thus increasing of additive concentration had no expected effect.

We envisaged that using a tandem reaction would allow us ta have an excellent asymmetric induction in aldol reaction. Since according to our previuos investigations at 40°C hydroformylation usually is slower than aldol reaction we expected the aldehyde formed, would fast be converted to aldol product without racemisation.

At first, standard conditions for tandem hydroformylation/enantioselective aldol reactions were used to convert styrene and acetone into aldol products. Since best conversion and enantioselectivities for hydroformylation of styrene

were obtained with Chiraphite ligands at 40/40 bar CO/H_2 (Table 18, entries 4 and 9) this pressure was used in initial tandem experiments (Table 20).

Table 20. Enantioselective sequential hydroformylation and aldol reactions at 40/40 bar CO/H_2.



en.	ligand	orgncat.	conv.[b]	yield[c]	syn:anti[d]	yield of **105** (ee) %[e]				ee **77** (%)[b]
						4R,5R	**4R,5S**	**4S,5S**	**4S,5R**	
1	2S,4S-Chiraphite	L-proline	88	65	2.5 : 1	66 (85)	27 (87)	5 (-)	2(-)	5 (R)
2	2S,4S-Chiraphite	D-proline	85	66	1.3 : 1	7 (-)	(-) -	50 (76)	43 (98)	9 (R)
3	2R,4R-Chiraphite	L-proline	83	63	1.3 : 1	49 (72)	43 (98)	8 (-)	(-) -	8 (S)
4	2R,4R-Chiraphite	D-proline	85	65	2.5 : 1	5 (-)	2 (-)	66 (87)	27 (89)	3 (S)
5	$P(OPh)_3$	L-proline	99	83	1.5 : 1	53 (76)	40 (99)	7 (-)	- (-)	0

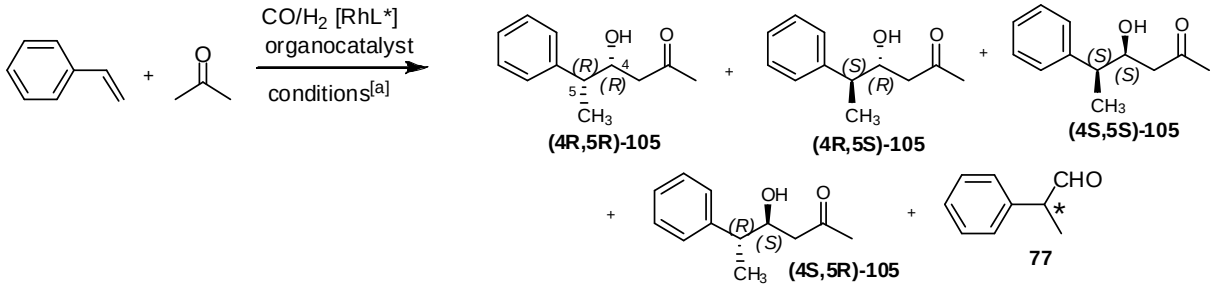
[a]40/40 bar CO/H_2, 0.5 mol% $Rh(acac)(CO)_2$, 2 mol% phosphorus ligand, 30 mol% organocatalyst, 40°C, 72h, acetone.
[b]Determined by GC using an internal standard.
[c]Based on isolated product.
[d]Determined by ^1H NMR analyses.
[e]Determined by chiral HPLC.

According to GC analyses after 72 hours Chiraphite modified Rh-catalysts gave 83-85% of styrene conversion (Table 20, entries 1-4). Noteworthy, with $P(OPh)_3$ modified Rh-catalyst styrene is fully converted within the same period of time. This means that Chiraphite ligands give slower hydroformylation catalyst in comparison with $P(OPh)_3$ modified Rh-catalyst (Table 20, entry 5). Enantioselective sequential hydroformylation and aldol addition provides an interesting example of a double asymmetric induction. (2R,4R)-Chiraphite/L-proline and (2S,4S)-Chiraphite/D-proline couples represent a mismatched pair of catalysts. (2S,4S)-Chiraphite/L-proline and (2R,4R)-Chiraphite/D-proline a matched pair of catalysts for induction of diastereoselectivity (Table 20, entries 1-4). For better understanding of phenomena happened in tandem reactions for every pair of catalysts we calculated distribution of aldol products and from this

distribution we calculated ratio of stereocentres bearing Ph and OH groups. (Schemes 55-59). For matched pair of catalysts ((2S,4S)-Chiraphite/L-proline and (2R,4R)-Chiraphite/D-proline) at 40/40 bar CO/H_2 some asymmetric induction from aldehyde to aldol products occurs. This can be seen from the ratio of stereocentres bearing Ph group (Scheme 58 and 61). Noteworthy this ratio in sequential enantioselective hydroformylation/aldol addition is smaller than in enantioselective hydroformylation under the same conditions. This is probably due to slow racemisation of formed aldehyde by organocatalyst. Completely different picture is for mismatched pair of catalysts ((2S,4S)-Chiraphite/D-proline and (2R,4R)-Chiraphite/L-proline) (see Schemes 56 and 57). In this case calculated ratio of stereocentres bearing Ph group is 1:1 suggesting that racemisation of the formed aldehyde by proline is faster than sequential aldol reaction.

In order to increase asymmetric induction from aldehyde to aldol products it is necessary to adjust the hydroformylation rate to the rate of proline-catalysed aldol addition in such a way that no accumulation of the aldehyde during the reaction is facilitated. In order to slow down speed of hydroformylation reaction we lowered the pressure from 40/40 to 20/20 bar syngas (Table 21).

Table 21. Tandem metal- and organocatalysis in enantioselective sequential hydroformylation and aldol reactions at 20/20 bar CO/H_2.



en.	ligand	orgncat.	conv.[b]	yield[c]	syn:anti[d]	yield of **105** (ee) %[e]				ee **77** (%)[b]
						4R,5R	**4R,5S**	**4S,5S**	**4S,5R**	
1	2S,4S-Chiraphite	L-proline	69	53	3 : 1	69 (84)	22.5 (80)	6 (-)	2.5 (-)	nd
2	2R,4R-Chiraphite	L-proline	45	31	1 : 1.2	34 (50)	54 (99)	11 (-)	1 (-)	nd
3	$P(OPh)_3$	L-proline	99	83	1.5 : 1	52 (72)	40 (99)	8 (-)	- (-)	nd

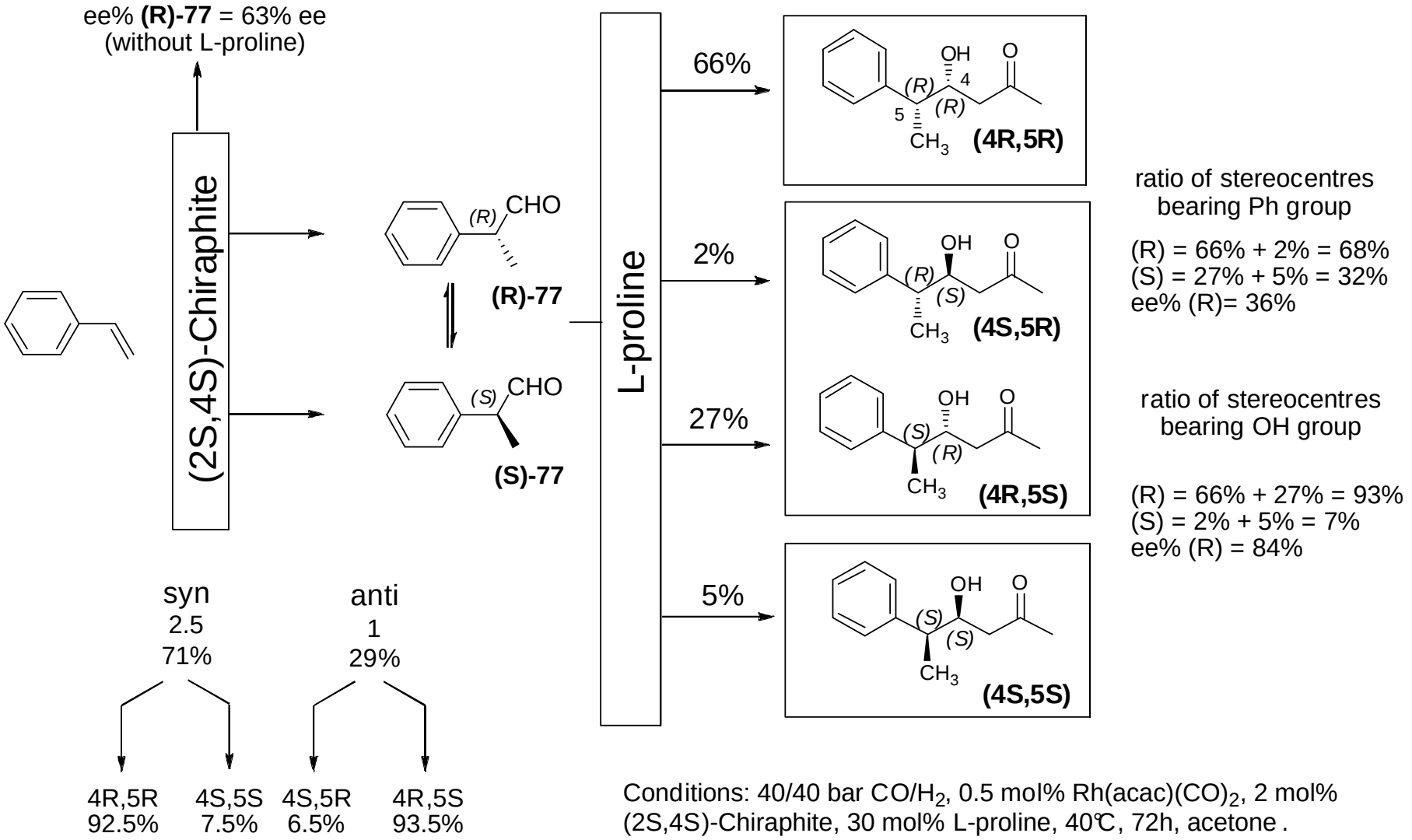
[a]20/20 bar CO/H_2, 0.5 mol% $Rh(acac)(CO)_2$, 2 mol% phosphorus ligand, 30 mol% organocatalyst, 40°C, 72h, acetone.
[b]Determined by GC using an internal standard.
[c]Based on isolated product.
[d]Determined by ^1H NMR analyses.
[e]Determined by chiral HPLC.

Pleasingly, at 20/20 bar CO/H_2 (in contrast with 40/40) even with mismatched pair of catalysts occurs asymmetric induction from aldehyde to aldol products (Scheme 61). The results indicate that formation of aldehyde is relatively slow; therefore aldehyde is immediately converted to aldol product. As transfer of chiral information is not full, from 60% ee to 30% ee (see Scheme 61), aldol reaction probably is not fast enough to fully suppress racemisation of formed hydrotropaldehyde by organocatalyst.

Again, in contrast to mismatched case, matched pair of catalyst (2S,4S-Chiraphite gave better transfer of chiral information (Scheme 60). This is probably due to faster aldol addition in matched case in comparison with mismatched case.

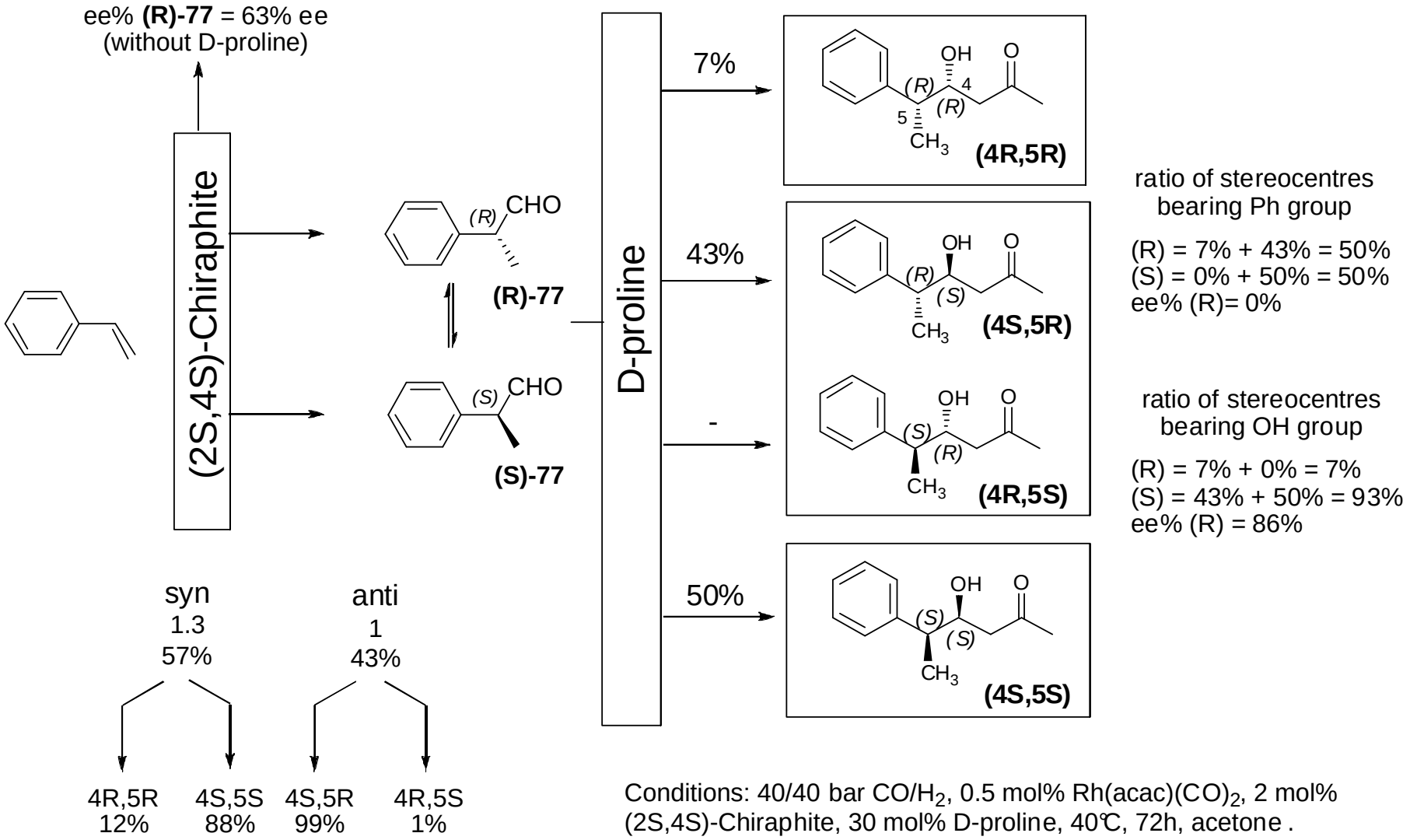
The different conversions of styrene for matched and mismatched pair of catalysts at 20/20 bar CO/H_2 (Table 21, entries 1 and 2) are due to differences in conditions used. These reactions were not performed in the same autoclave; therefore some parrameters (e.g. pressure) could vary.

Scheme 55. Enantioselective sequential hydroformylation and aldol reactions at **40/40** bar CO/H_2



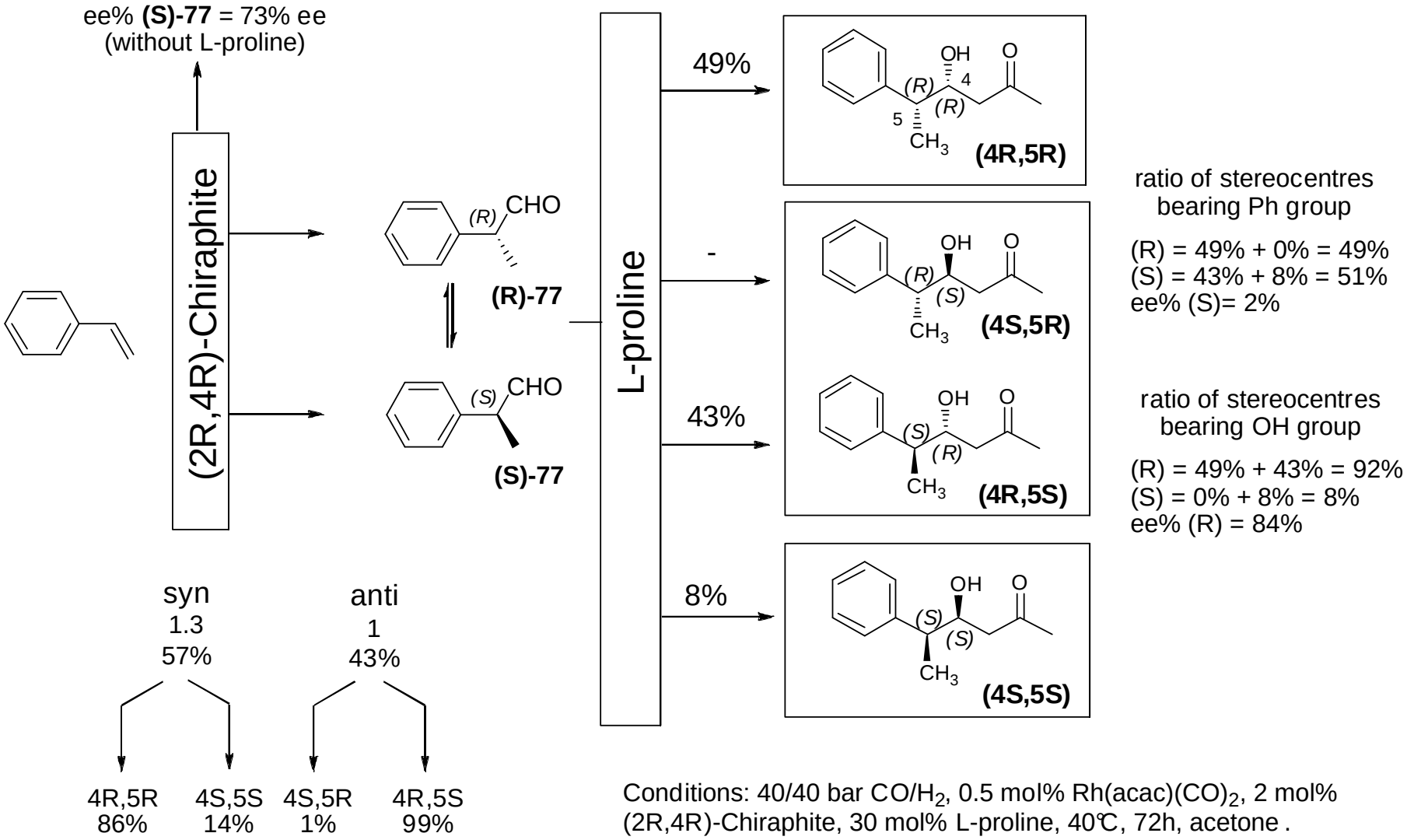
Conditions: 40/40 bar CO/H_2, 0.5 mol% $Rh(acac)(CO)_2$, 2 mol% (2S,4S)-Chiraphite, 30 mol% L-proline, 40℃, 72h, acetone .

Scheme 56. Enantioselective sequential hydroformylation and aldol reactions at **40/40** bar CO/H_2



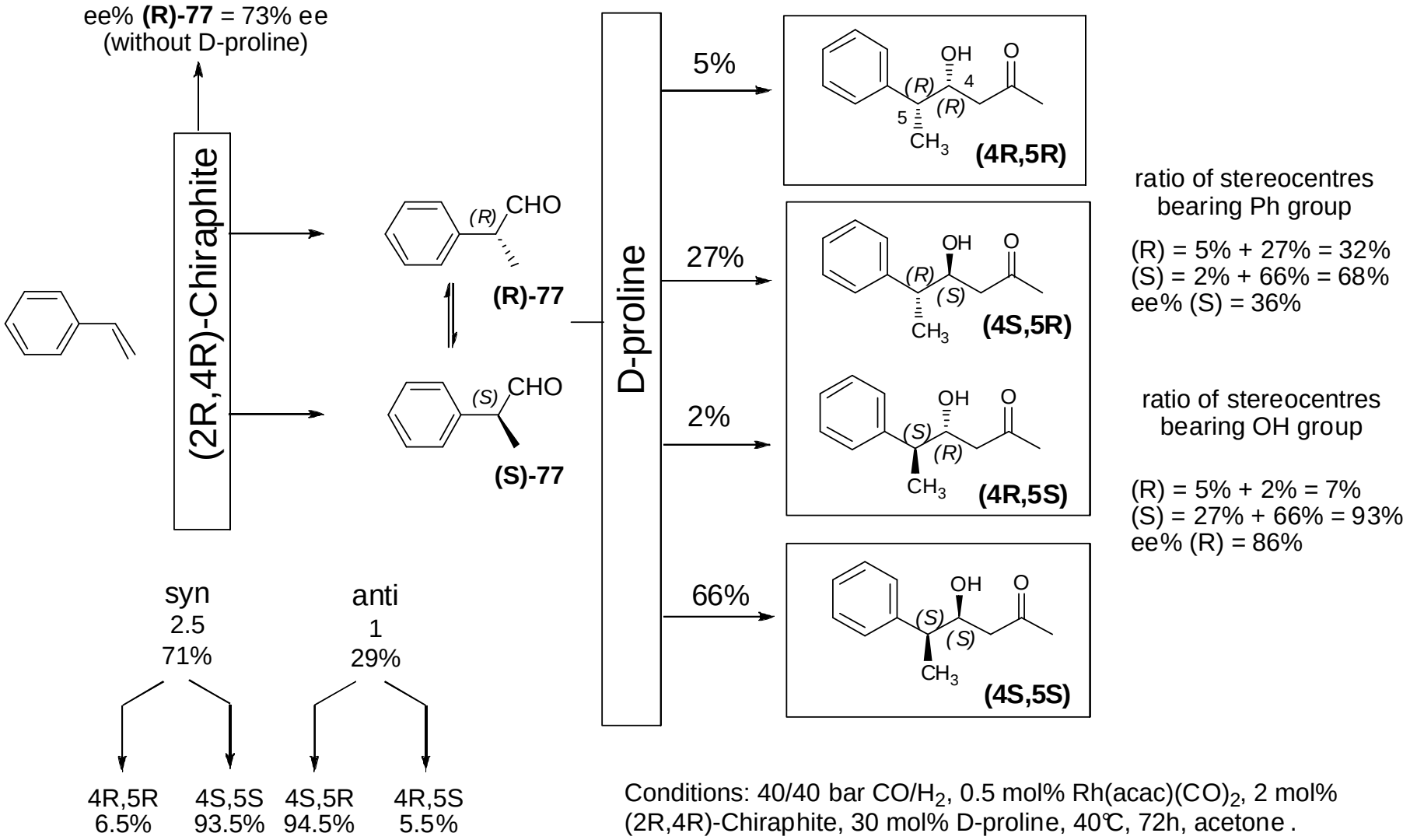
Conditions: 40/40 bar CO/H_2, 0.5 mol% $Rh(acac)(CO)_2$, 2 mol% (2S,4S)-Chiraphite, 30 mol% D-proline, 40℃, 72h, acetone .

Scheme 57. Enantioselective sequential hydroformylation and aldol reactions at **40/40** bar CO/H_2



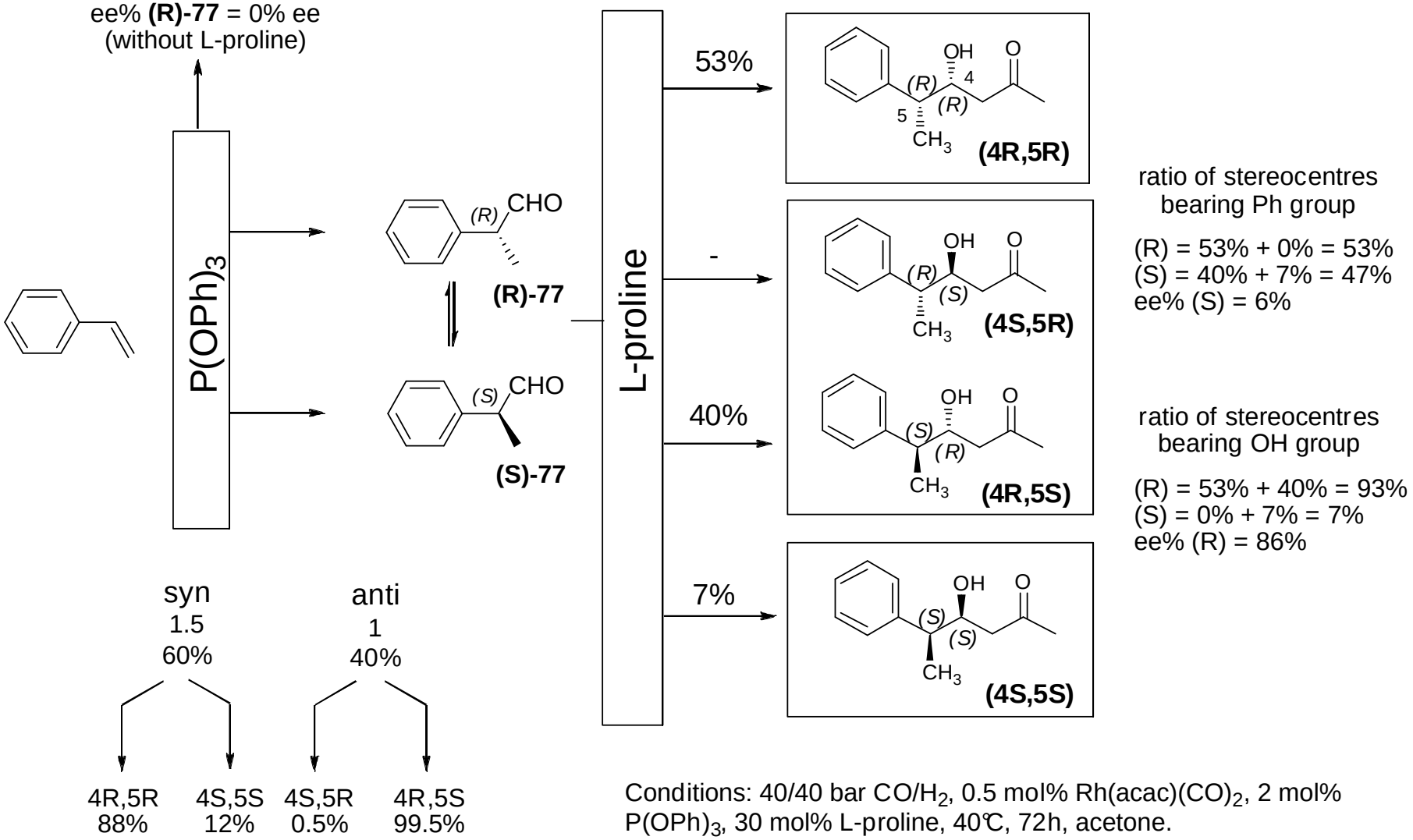
Conditions: 40/40 bar CO/H_2, 0.5 mol% $Rh(acac)(CO)_2$, 2 mol% (2R,4R)-Chiraphite, 30 mol% L-proline, 40℃, 72h, acetone .

Scheme 58. Enantioselective sequential hydroformylation and aldol reactions at **40/40** bar CO/H_2



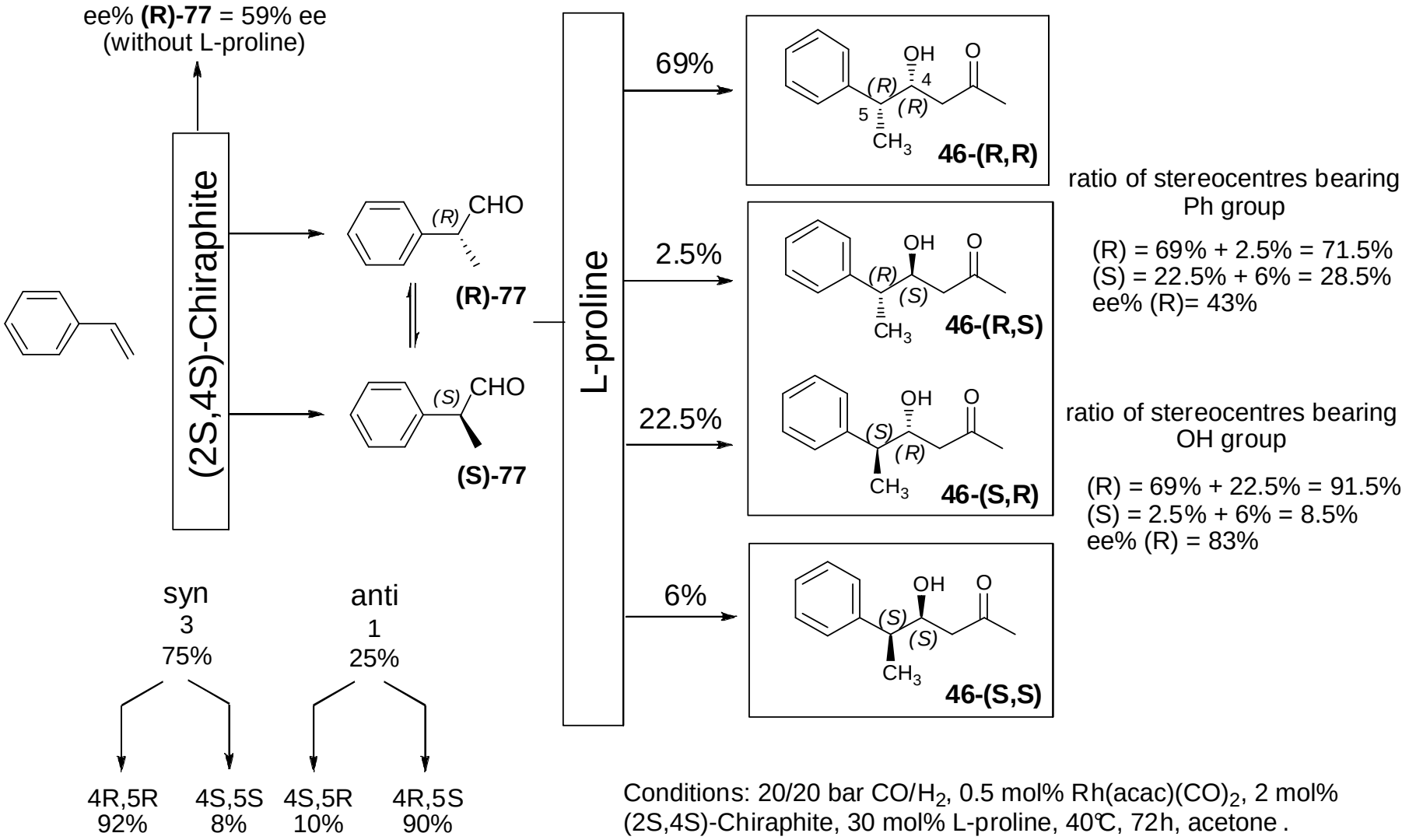
Conditions: 40/40 bar CO/H_2, 0.5 mol% $Rh(acac)(CO)_2$, 2 mol% (2R,4R)-Chiraphite, 30 mol% D-proline, 40℃, 72h, acetone .

Scheme 59. Enantioselective sequential hydroformylation and aldol reactions at **40/40** bar CO/H_2



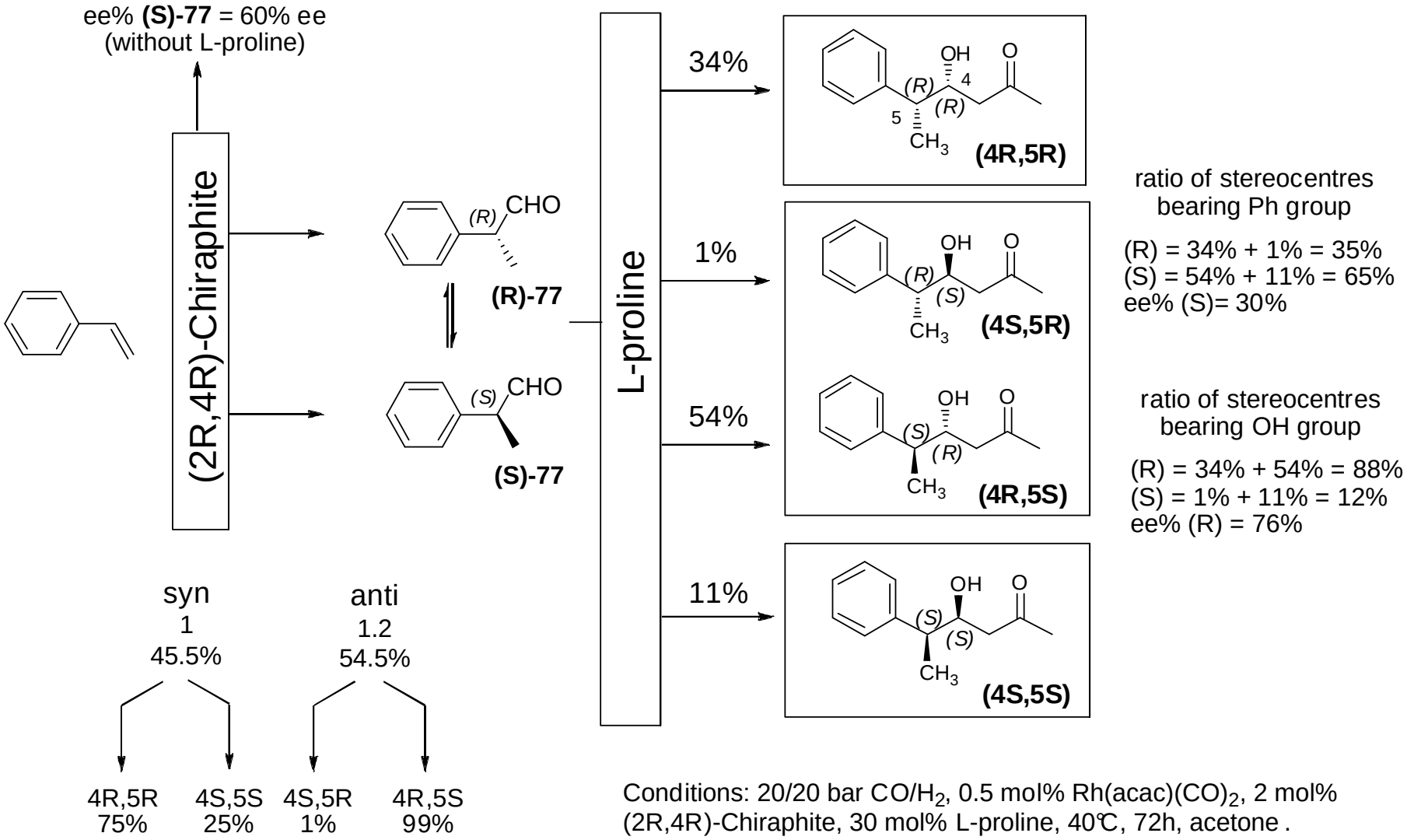
Conditions: 40/40 bar CO/H_2, 0.5 mol% $Rh(acac)(CO)_2$, 2 mol% $P(OPh)_3$, 30 mol% L-proline, 40℃, 72h, acetone.

Scheme 60. Enantioselective sequential hydroformylation and aldol reactions at **20/20** bar CO/H_2



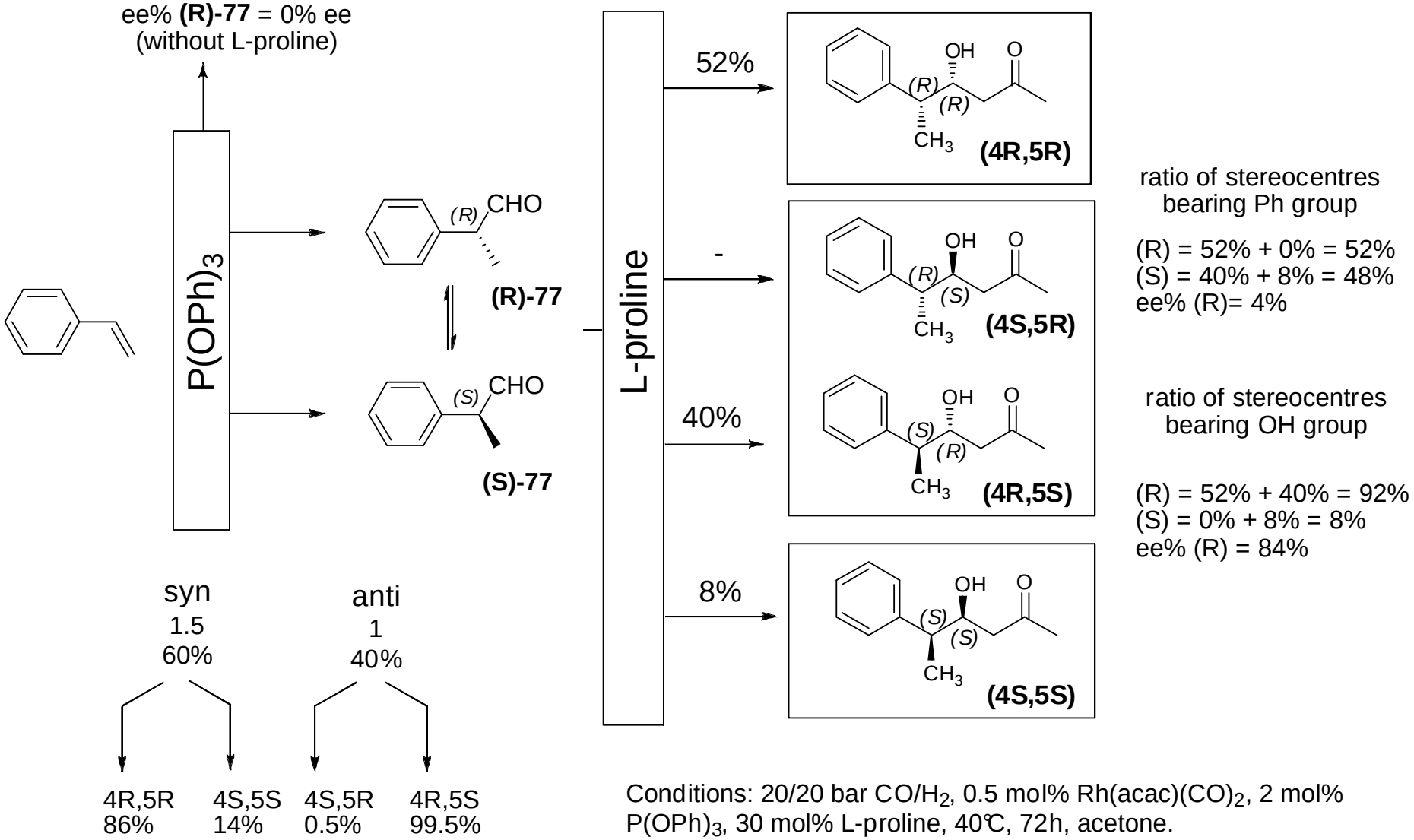
Conditions: 20/20 bar CO/H_2, 0.5 mol% $Rh(acac)(CO)_2$, 2 mol% (2S,4S)-Chiraphite, 30 mol% L-proline, 40℃, 72h, acetone .

Scheme 61. Enantioselective sequential hydroformylation and aldol reactions at **20/20** bar CO/H_2



Conditions: 20/20 bar CO/H_2, 0.5 mol% $Rh(acac)(CO)_2$, 2 mol% (2R,4R)-Chiraphite, 30 mol% L-proline, 40℃, 72h, acetone .

Scheme 62. Enantioselective sequential hydroformylation and aldol reactions at **20/20** bar CO/H_2



Conditions: 20/20 bar CO/H_2, 0.5 mol% $Rh(acac)(CO)_2$, 2 mol% $P(OPh)_3$, 30 mol% L-proline, 40℃, 72h, acetone.

Also styrene was applied to enantioselective sequential hydroformylatio/aldol addition at 20/20 bar CO/H_2 in the presence of 3 mol% or 30 mol% of (S)-BINOL. No influence of additive on conversion, enantio- and diastereoselectivities of tandem reaction was observed.

2.3.4 Summary

In conclusion, we successfully combined an enantioselective Rh-catalysed hydroformylation reaction with a proline-catalysed stereoselective aldol reaction in a tandem reaction sequence. Unfortunately due to racemisation of the formed aldehyde asymmetric induction asymmetric induction from aldehyde to aldol products is moderate. Addition of additives did not have any effect on the outcome of reaction. To solve this problem it is necessary either to prevent aldehyde racemisation (e.g. to apply other organocatalysts) or to decrease the hydroformylation rate and increase the rate of aldol reaction.

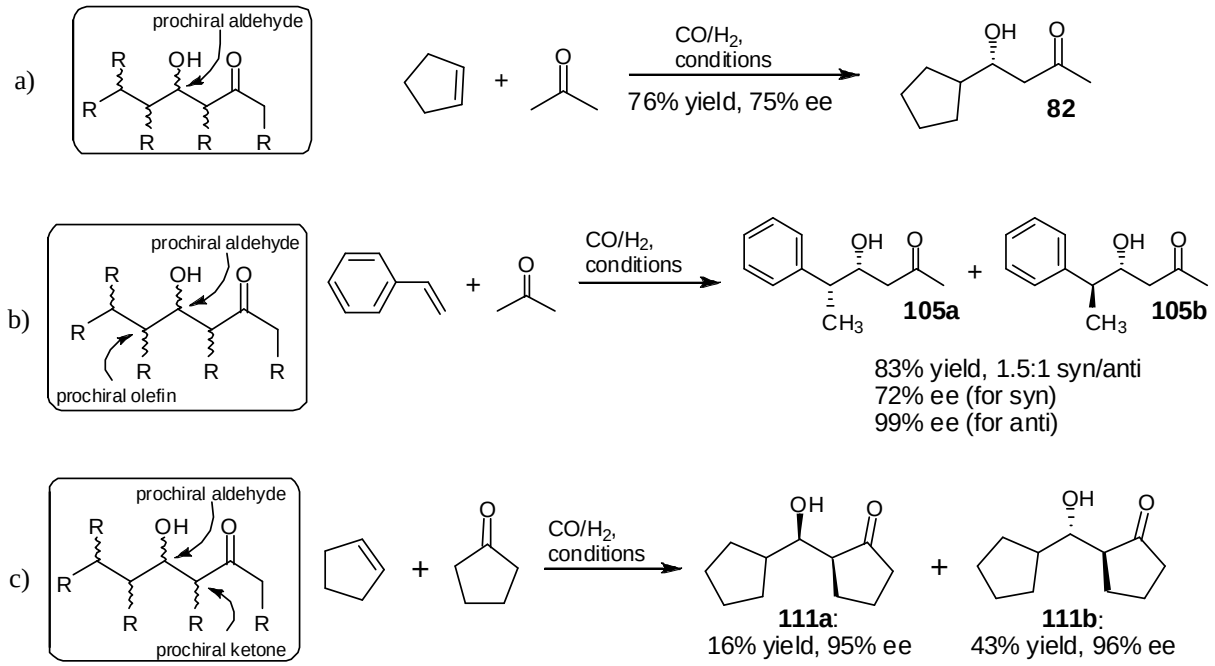
3 CONCLUSIONS AND OUTLOOK

A study designed to combine metal- and organocatalysis in order to control stereochemical outcome of hydroformylation/aldol addition and hydroformylation/Mannich reaction sequences has been undertaken. At first sequential hydroformylation and intramolecular aldol addition was studied. In order to apply this method to the production of forskolin A-ring analogs in an enantioselective fashion various unsaturated ketones were synthesised. Sequential and stepwise hydroformylation and aldol addition reactions were carried out. However, it was found that L-proline did not catalyse cyclisation of formed ketoaldehydes. In contrast with intramolecular, L-proline-catalysed intermolecular aldol addition proceeds in good yields and enatioselectivities. Much optimisation of the sequential hydroformylation and intermolecular aldol addition was carried out. A range of phosphorus ligands and organocatalysts was tested for this tandem reaction. Triphenyl phosphite and L-proline showed a significant advantage over all other catalysts tested. Also various CO and H_2 partial pressures were studied to ascertain pressure effects on tandem hydroformylation and enantioselective aldol reactions. Usually variation of pressure had no effect on yields, enantio- and diastereoselectivities of aldol addition. However, in case of cyclopentene at 70/10 bar CO/H_2 a drastic decrease in yield was observed. Also we investigated whether rhodium catalysts are compatible with organocatalysts in our tandem reaction. No potentially negative interactions were found.

Our new methodology has been applied to several substrates. Three possibilities were considered (see Scheme 63):

a) not prochiral olefin and not prochiral ketone
b) prochiral olefin and not prochiral ketone
c) not prochiral olefin and prochiral ketone

Scheme 63. Origin of stereogenic centers in sequential hydroformylation and enantioselective aldol reactions.



Conditions: $Rh(acac)(CO)_2$, 20/20 CO/H_2, $P(OPh)_3$, L-proline, 48 h

It could be demonstrated that organocatalysis of aldol reactions even under hydroformylation conditions occurs with high enantioselectivities, although the usually observed[95] diastereoselectivities are still to be optimised.

After we successfully combined hydroformylation and enantioselective aldol reactions we decided to extend our studies. We attempted to combine Rh-catalysed hydroformylation with proline-catalysed enantioselective Mannich reactions. A simple one-pot three-component reaction procedure consisting of alkene, acetone and an aromatic amine in the presence of Rh- and organocatalysts provided the corresponding β-aminoketones with good yields (53 - 57%), but poor ees (4-19%). In the literature usually observed ees for L-proline-catalysed enantioselective Mannich reactions are in the range of 50 – 90% ee.[54, 55, 110] Therefore, several parameters have to be explored in order to increase the stereocontrol of our tandem reaction. For instance interaction between Rh- and organocatalyst has to be further investigated. Also will be beneficial to perform our tandem reaction stepwise, in order to find which parameter is responsible for such low enantioselectivities. In order to broaden

the scope of our transformation, after optimal conditions are found, other more complicated substrates (inclusive prochiral alkenes and prochiral ketones) can be applied to our new methodology.

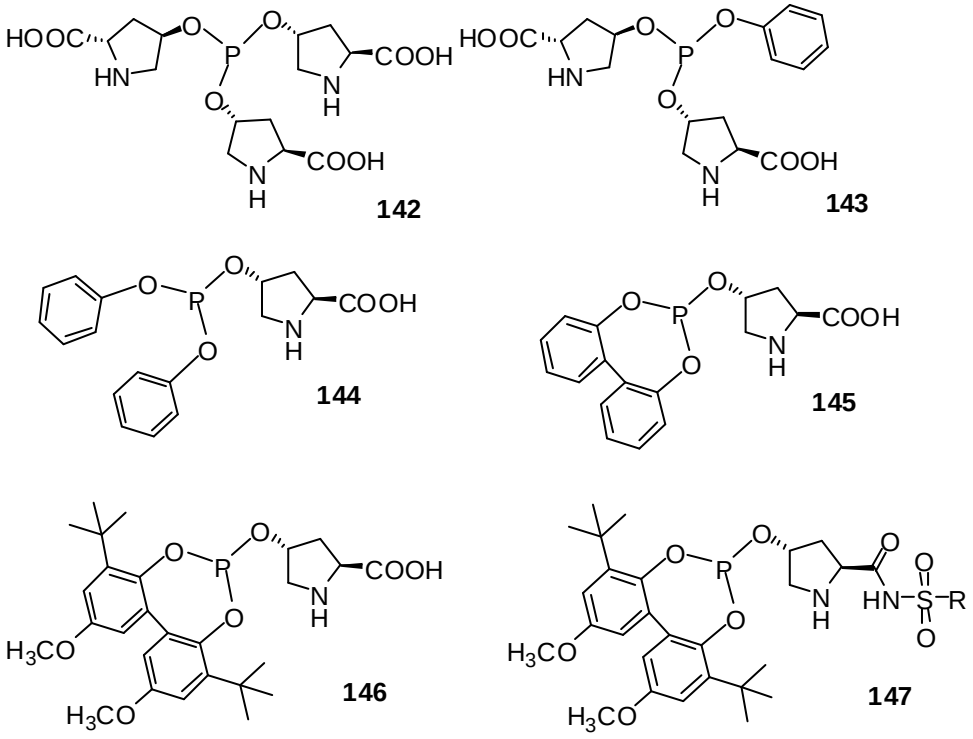
Especially challenging was combination of enantioselective hydroformylation and enantioselective aldol reactions in a tandem reaction sequence. Enantioselective sequential hydroformylation and aldol addition of styrene and acetone was chosen as a model reaction. Chiraphite modified Rh-complexes and proline were found to be the best catalysts for this tandem reaction. We expected that aldehyde generated from the olefin unit would react immediately with acetone allowing an asymmetric induction from aldehyde to aldol unit. However this requires correct adjustment of the enantioselective hydroformylation rate to the rate of proline-catalysed aldol addition, since accumulation of the aldehyde will facilitate racemisation of that component. A pressure screening revealed that at 20/20 bar CO/H_2 the transfer of chirality is not complete, but better than at 40/40 bar CO/H_2. This is due to lowering of stationary aldehyde concentration in consequence of decrease of hydroformylation rate. In order to prevent aldehyde racemisation further optimisations have to be done. One possible solution will be increase of aldol reaction speed by using additives. Also other chiral phosphorus ligands (e.g. BINAPHOS) and other organocatalysts have to be tested in order to increase enantioselectivities of hydroformylation and aldol steps respectively.

Noteworthy, enantioselective sequential hydroformylation and aldol addition provides an interesting example of a double asymmetric induction. (2R,4R)-Chiraphite/L-proline and (2S,4S)-Chiraphite/D-proline couples represent a mismatched pair of catalysts. (2S,4S)-Chiraphite/L-proline and (2R,4R)-Chiraphite/D-proline a matched pair of catalysts for induction of diastereoselectivity.

So far, for our tandem reaction we used two different catalysts: one (phosphorus modified Rh-catalyst) to catalyse hydroformylation reaction and

another (proline) to catalyse aldol addition reaction. One of the extension of our methodology can be synthesis and application of multifunctional catalysts bearing both organocatalyst and phosphite moieties (Scheme 64).

Scheme 64. Multifunctional catalyst that can be used in tandem reactions.

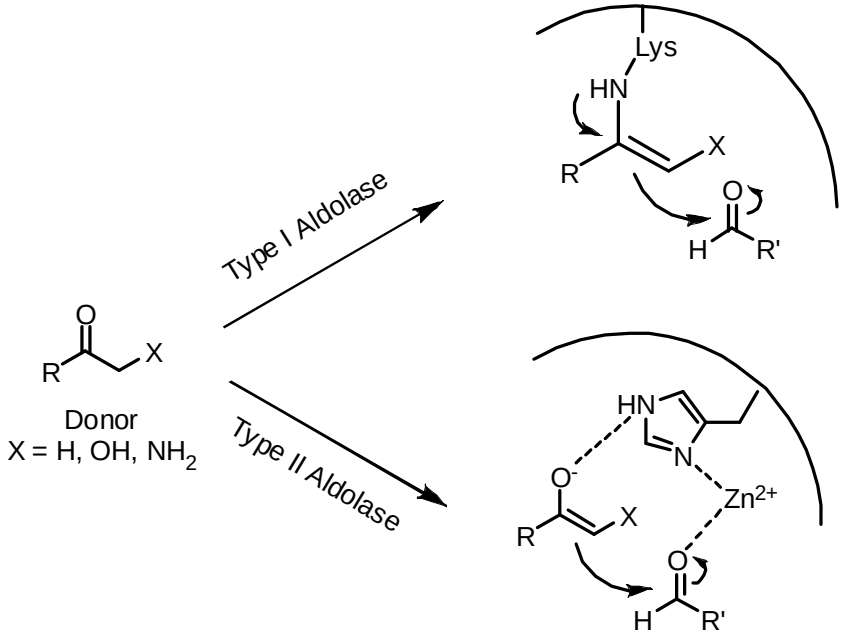


These catalysts offer many advantages over monofunctional catalysts including ease of separation, facility of reuse, and even the ability for multifunctionality.

An alternative strategy to control stereochemistry during aldol sequence in tandem reaction can be an enzyme-catalysed aldol reaction. One of the main attractions for the use of enzymes is their ability to perform reactions in a stereoselective way. Nature has developed two classes of aldolases for direct aldol reactions, in which an unmodified ketone donor is added to an aldehyde acceptor.[113] Class I aldolases activate the ketone donor via the formation of a Schiff base intermediate with a lysine residue in the active site. Class II aldolases contain an active site Zn^{2+} cofactor that facilitates the enolate

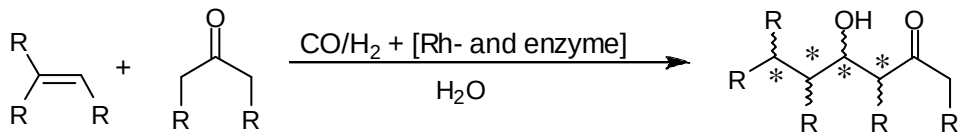
formation by coordinating to the carbonyl oxygen of the ketone donor (Scheme 65).

Scheme 65. General Mechanisms for Class I and Class II aldolases.[113]



It would be very promising whether is possible to combine metal-catalysis (e.g hydroformylation) with enzyme catalysis (e.g. enantioselective aldol reactions) in a tandem reaction sequence (Scheme 66).

Scheme 66. Sequential hydroformylation / enzyme-catalysed enantioselective aldol addition.

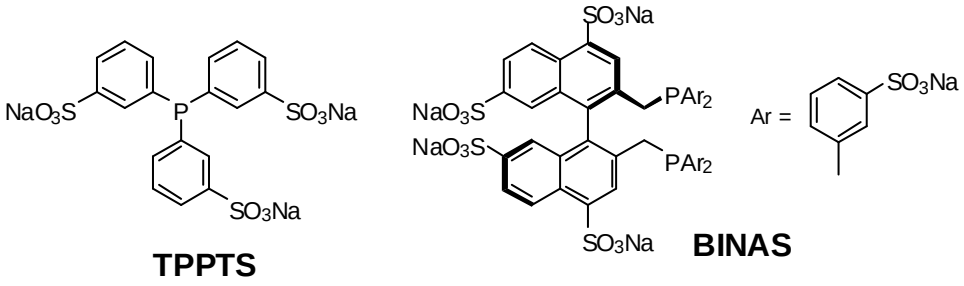


The use of enzymes has several advantages over chemical methods.[113] Because of the mild conditions in enzymatic reactions and the regioselectivity displayed by enzymes, protective group chemistry can be reduced to a minimum. Since most enzymes operate at room temperature in aqueous solution around pH 7, their reactions are often compatible with each other. This makes it

possible to combine several enzymes in a one-pot, multistep reaction sequence. Their use in aqueous solution and their biodegradability make enzymes also an excellent environmentally acceptable option. The high regio- and stereoselectivity and catalytic efficiency make enzymes especially useful for the synthesis of complex, highly functionalised molecules like carbohydrates.

According to our previous studies (see Chapter 2.1.6) sequential hydroformylation and aldol reaction can be performed even at room temperature (working temperature of enzymes). Since most enzymes require aqueous solution water-soluble catalysts for hydroformylation have to be used. The rhodium complex of water-soluble ligand TPPTS [tri(m-sulfonyl)triphenylphosphine trisodium salt), used by Kuntz and Cornils, can be one of candidates.[114] Its properties are very similar to the parent compound triphenylphosphine.

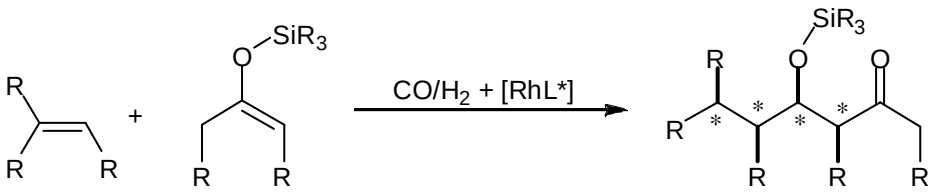
Scheme 67. Water-soluble ligands used in hydroformylation.



Besides the TPPTS-system a number of other sulfonated phosphines can be tested. Among them are systems, which are derived from biphenyl (e.g. BINAS = sulfonated NAPHOS, sulfonation grade between six and eight). Rhodium-BINAS is the most active and selective water-soluble hydroformylation catalyst, therefore it would be clearly the ligand of choice.[115] Although enzymes are efficient in catalysing aldol reactions, their applications in organic synthesis are still restricted owing to the long reaction times for largescale reactions and the relatively high price.

Another attempt to bring asymmetric induction into tandem reactions can be combination of enantioselective Rh-catalysed hydroformylation with an enantioselective Rh-catalysed Mukaiyama aldol addition (Scheme 68).

Scheme 68. Enantioselective sequential hydroformylation/Mukaiyama aldol addition.



In this tandem reaction it would be possible to affect two processes, hydroformylation and aldol addition, through the use of a single chiral Rh-catalyst. Initiall experiments done in our group have shown that not-enantioselective variant of such a tandem reaction can be applied with success for a wide range of unsaturated substrates, however enantioselective variant still has to be investigated.

4 ZUSAMMENFASSUNG

Eine Untersuchung ,angelegt , um Metall- und Organokatalyse zu kombinieren und den stereochemischen Verlauf von Hydroformylierung/Aldoladdition und Hydroformylierung/Mannich-Reaktion Sequenzen zu steuern, wurde durchgeführt. Zunächst wurde die sequentielle Hydroformylierung und intramolekulare Aldoladdition untersucht. Um diese Methode zur enantioselektiven Herstellung von Forskolin A-Ringanaloga anzuwenden, wurden verschiedene ungesättigte Ketone synthetisiert. Die sequentielle und stufenweise Hydroformylierung und Aldoladditions-Reaktionen wurden durchgeführt. Es stellte sich jedoch heraus das L-Prolin nicht die Cyclisierungen der gebildeten Ketoaldehyde katalysiert. Im Gegensatz zu L-Prolin katalysierten, intramolekularen Aldoladditionen laufen intermolekulare Aldoladditionen mit L-Prolin in guten Ausbeuten und Enantioselektivitäten ab. Es wurden viele Optimisierungen der sequentiellen Hydroformylierung und intermolekularen Aldoladdition-Reaktion durchgeführt. Eine Auswahl an Phosphorliganden und Organokatalysatoren wurde für diese Tandemreaktion erprobt. Triphenylphosphit und L-Prolin zeigten einen wesentlichen Vorteilen gegenüber allen anderen erprobten Katalysatoren. Ausserdem wurden verschiedene CO und H_2 Partialdrücke untersucht um Druckeffekte auf die Tandem Hydroformylierung und enantioselektive Aldoladditions-Reaktion zu bestimmen. Gewöhnlich hat die Veränderung des Drucks keinen Einfluss auf die Ausbeute und Enantio- bzw. Diastereoselektivität der Aldoladdition. Im Fall des Cyclopentens wurde jedoch eine drastische Abnahme der Ausbeute bei 70/10 bar CO/H_2 beobachtet. Ebenso wurde untersucht ob der Rhodiumkatalysator mit dem Organokatalysator in der Tandemreaktion kompatibel ist. Eine möglicherweise negative Wechselwirkung wurde nicht gefunden.

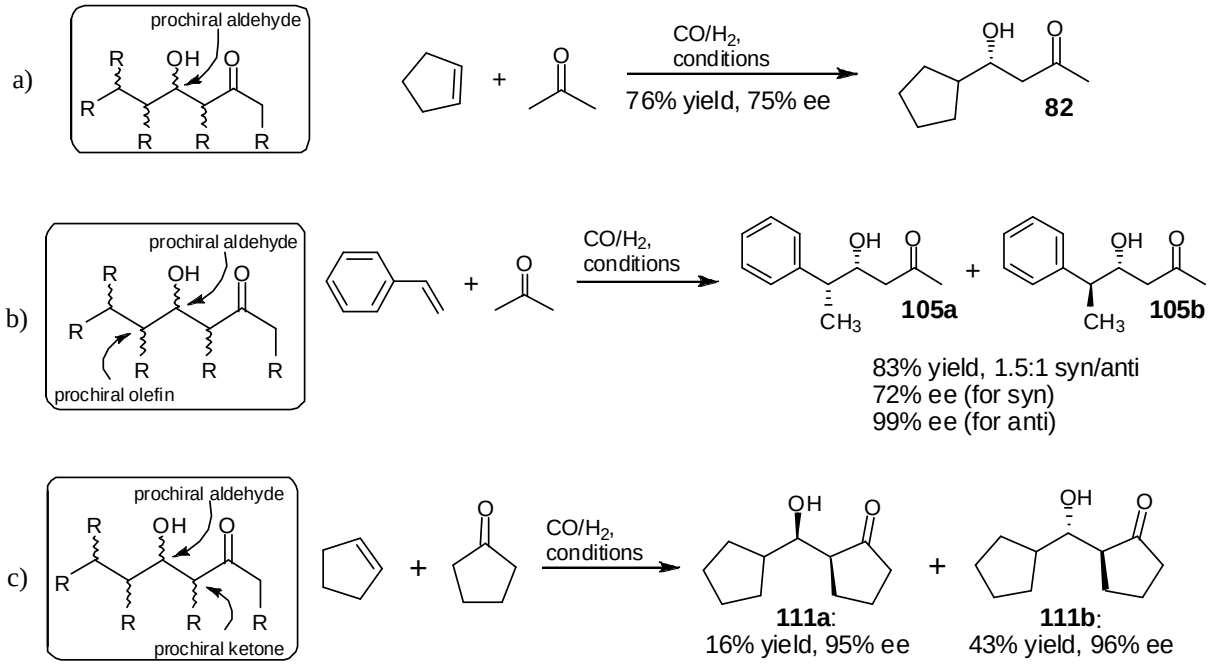
Die neue Methode wurde für verschiedene Substrate verwendet. Drei Möglichkeiten wurden betrachtet (s. Schema 69):

a) nicht-prochirales Olefin und nicht-prochirales Keton

b) prochirales Olefin und nicht-prochirales Keton

c) nicht-prochirales Olefin und prochirales Keton

Schema 69. Herkunft des stereogenen Zentrums in sequentiellen Hydroformylierung und enantioselektiven Aldoladditions-Reaktionen.



Conditions: $Rh(acac)(CO)_2$, 20/20 CO/H_2, $P(OPh)_3$, L-proline, 48 h

Es konnte gezeigt werden, dass die Organokatalyse der Aldolreaktion selbst unter Hydroformylierungsbedingungen mit hohen Enantioselektivitäten erfolgt, wenngleich die beobachteten Diastereoselektivitäten noch zu optimisieren sind. Nachdem wir die Hydroformylierung und enantioselektive Aldoladditions-Reaktion erfolgreich miteinander kombiniert haben, beschlossen wir die Untersuchungen auszuweiten. Wir versuchten die Rhodium-katalysierte Hydroformylierung mit der Prolin-katalysierten enantioselektiven Mannich-Reaktion zu kombinieren. Eine einfache Eintopf-Dreikomponenten Reaktionsdurchführung bestehend aus Alken, Aceton und einem aromatischen Amin in Gegenwart von Rhodium- und Organokatalysator lieferte das entsprechende β-Aminoketon mit guten Ausbeuten (53 - 57%), aber schlechten ee´s (4 – 19%). In der Literatur werden für die L-Prolin-katalysierte Mannich-

Reaktion üblicherweise ee im Bereich von 50 – 90% beobachtet.[54, 55, 110] Daher müssen verschiedene Parameter untersucht werden um die stereochemische Kontrolle der Tandemreaktion zu erhöhen. Beispielsweise muss die Wechselwirkung zwischen Rhodium und Organokatalysator weiter untersucht werden. Ausserdem wird es vorteilhaft sein die Tandemreaktion stufenweise durchzuführen, um die Parameter die für die geringen Enantioselektivitäten verantwortlich sind zu finden. Nachdem die optimalen Bedingungen gefunden wurden, können komplexere Substrate (inklusive prochirale Alkene und prochirale Ketone) mit der neuen Methode verwendet werden, um den Anwendungsbereich auszuweiten.

Besonders herausfordernd war die Kombination von enantioselektiver Hydroformylierung und enantioselektiver Aldol-Reaktion in einer Tandem Reaktionssequenz. Die enantioselektive, sequentielle Hydroformylierung und Aldoladdition von Styrol und Aceton wurde als Modelreaktion ausgewählt. Der beste Katalysator für diese Tandemreaktion war der Chiraphite-Rhodium modifizierte Komplex und Prolin. Wir erwarteten das der vom Olefin gebildete Aldehyd sofort mit Aceton reagiert und eine asymmetrische Induktion vom Aldehyd zum Aldol ermöglicht. Dies erfordert jedoch die genaue Anpassung der enantioselektiven Hydroformylierungsgeschwindigkeit und der Geschwindigkeit der Prolin-katalysierten Aldoladdition, da die Akkumulation des Aldehyds die Racemisierung und Homodimerisierung dieser Komponente fördert. Ein Druck Screening zeigte, das bei 20/20 bar CO/H_2 die asymmetrische Induktion nicht komplett, aber besser als bei 40/40 bar CO/H_2 ist. Das ist auf Grund der geringen stationären Aldehydkonzentration die Konsequenz der verringerten Hydroformylierungsgeschwindigkeit. Weitere Optimisierungen müssen gemacht werden um die Aldehyd Racemisierung zu unterdrücken. Eine mögliche Lösung wäre die Erhöhung der Reaktionsgeschwindigkeit der Aldolreaktion durch Verwendung von Additiven. Ausserdem müssen andere Phosphorliganden (z. B. BINAPHOS) und andere Organokatalysatoren erprobt werden um die

Enantioselektivitäten der Hydroformylierung bzw. der Aldolschritte zu erhöhen. Bemerkenswerterweise bietet die enantioselektive, sequentielle Hydroformylierung und Aldolreaktion ein interessantes Beispiel für eine doppelte, asymmetrische Induktion. Das (2R,4R)-Chiraphite/L-Prolin) und (2S,4S)-Chiraphite/D-Prolin Paar bilden ein mismatched-pair des Katalysators. (2S,4S)-Chiraphite/L-Prolin und (2R,4R)-Chirapite/D-Prolin bilden ein matched-pair des Katalysators für Induktion von Diastereoselektivität.

5 EXPERIMENTAL

5.1 General Remarks

Hydroformylation experiments were carried out in a BERGHOF HR-200 high pressure reactor with magnetic stirring and electrical heating. The inside part of the cover was made from Teflon® to protect the solution from direct contact with the stainless steel. All reactions were carried out in freshly distilled solvents. Dichloromethane and triethylamine were distilled from calcium hydride. All phosphorus ligands, except BIPHEPHOS, are commercially available. BIPHEPHOS was synthesised according to the literature procedure.[12] Commercial reagents were used as received. Organic solutions were concentrated under reduced pressure on a rotary evaporator. Column chromatography was carried out using MN Kieselgel 60 (0.063 – 0.2 mm/70-230 mesh). TLC was performed on Merck Silicagel 60 F_{254} plates. Visualizasion of the developed chromatograms was performed by ultraviolet irradiation (254 nm) or by anisaldehyde stain. Melting points were performed on a Büchi® melting point apparatus, and are uncorrected. For gas chromatographic analyses, Carlo Erba HRGC Mega2 Series MFC 800 chromatograph with a Carlo Erba EL 580 flame-ionisation detector (FID) was used. Separations were performed on the column CHROMPACK DB-1701 (25 m x 0.32 mm x 1.0 μm). ^{1}H NMR spectra were recorded on a Bruker 400 and Bruker 500 spectrometers, with residual proton signal of the deuterated solvent as the internal reference (δ_H=7.26 ppm for $CDCl_3$ and δ_H=7.15 ppm for C_6D_6). ^{13}C NMR spectra were recorded on the same spectrometers and referenced to solvent signals (δ_c=77 ppm for $CDCl_3$ and δ_c=128.02 ppm for C_6D_6). Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz). The proton spectra are reported as follows δ/ppm (multiplicity, number of protons, coupling constant J/Hz). DEPT135 and two dimensional (COSY, HMQC, HMBC) NMR spectroscopy were used where appropriate, to aid the assignment

of signals in the ^{1}H and ^{13}C NMR spectra. IR spectra were recorded on an Impact 400 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from University of Dortmund Mass Spectral facility. Elemental analyses were carried out in the Laboratory of Elemental Analyses at the University of Dortmund. Optical rotations were measured on a Perkin Elmer 341 polarimeter. Semi-preparative HPLC was performed using a SUPELCOSIL^{TM} LC-SI 5 μm (25 cm x 21.2 mm) column. Analytical HPLC was performed on a Hewlett-Packard 1050 Series chromatographs using a CHIRALCEL OD (250 x 4.6 mm), CHIRALCEL OJ (250 x 4.6 mm) and CHRALPAK AD (250 x 4.6 mm) columns as noted.

5.2 Working methods

Method A: *Hydroformylation*. To a solution of $Rh(acac)(CO)_2$ (5 mg, 0.019 mmol, 0.005 eq.) in 5 ml of solvent in a vial, was added phosphorus ligand (0.078 mmol, 0.02 eq.). The solution was stirred with magnetic stirrer for 5 min and then charged with olefin (3.8 mmol, 1 eq.) and dodecane (199 mg, 1.17 mmol, 0.3 eq.). The vial was transferred to the autoclave, pressurised and heated. After the reaction was completed, the autoclave was cooled down to room temperature, depressurised, flushed with argon and opened to obtain a sample for GC analysis.

Method B: *Sequential hydroformylation and enantioselective aldol reactions.* To a solution of $Rh(acac)(CO)_2$ (5 mg, 0.019 mmol, 0.005 eq.) in 5 ml of ketone in a vial, was added phosphorus ligand (0.078 mmol, 0.02 eq.). The solution was stirred with magnetic stirrer for 5 min and then charged with alkene (3.8 mmol, 1 eq.), dodecane (199 mg, 1.17 mmol, 0.3 eq.) and organocatalyst (1.17 mmol, 0.3 eq.). The vial was transferred to the autoclave, pressurised and heated to 40 °C. After the reaction was completed, the autoclave was cooled down to room temperature, depressurised, flushed with argon and opened to obtain a sample

for GC analysis. Then the reaction mixture was filtered through a column filled with silica gel. Additionally the column was washed with 50 mL of diethyl ether. The filtrate was concentrated *in vacuo* and the crude product was purified by column chromatography.

Method C: *Enantioselective hydroformylation.* To a solution of $Rh(acac)(CO)_2$ (2 mg, 0.0077 mmol, 0.005 eq.) in 3 ml of solvent in a vial, was added chiral phosphorus ligand (0.019 mmol, 0.0125 eq.). The solution was stirred with magnetic stirrer for 5 min and then charged with styrene (158 mg, 1.52 mmol, 1 eq.) and dodecane (78 mg, 0.456 mmol, 0.3 eq.). The vial was transferred to the autoclave, pressurised and heated to 40 °C. After the reaction was completed, the autoclave was cooled down to room temperature, depressurised, flushed with argon and opened to obtain a sample for GC analysis. GC conditions: carrier gas 50 kPa He, temperature program of 100°C for 5 min, then 4°C/min to 160°C and 20°C/min to 200°C; retention times: 8.69 min for styrene, 16.26 min for dodecane, 18.02 min for (R)-2-phenylpropanal, 18.28 min for (S)-2-phenylpropanal and 21.8 min for 3-phenylpropanal.

Method D: *Enantioselective sequential hydroformylation and aldol addition.* To a solution of $Rh(acac)(CO)_2$ (2 mg, 0.0077 mmol, 0.005 eq.) in 3 ml of ketone in a vial, was added Chiraphite (17 mg, 0.019 mmol, 0.0125 eq.). The solution was stirred with magnetic stirrer for 5 min and then charged with styrene (158 mg, 1.52 mmol, 1 eq.), dodecane (78 mg, 0.456 mmol, 0.3 eq.) and proline (53 mg, 0.456 mmol, 0.3 eq.). The vial was transferred to the autoclave, pressurised and heated to 40 °C. After the reaction was completed, the autoclave was cooled down to room temperature, depressurised, flushed with argon and opened to obtain a sample for GC analysis. Then the reaction mixture was filtered through a column filled with silica gel. Additionally the column was washed with 50 mL

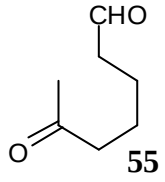
of diethyl ether. The filtrate was concentrated *in vacuo* and the crude product was purified by column chromatography.

Method E: *Sequential hydroformylation and enantioselective Mannich reactions.* To a solution of $Rh(acac)(CO)_2$ (5 mg, 0.019 mmol, 0.005 eq.) in 5 ml of ketone in a vial, was added $P(OPh)_3$ (24 mg, 0.078 mmol, 0.02 eq.). The solution was stirred with magnetic stirrer for 5 min and then charged with alkene (3.8 mmol, 1 eq.), amine (4.18 mmol, 1.1 eq.), dodecane (199 mg, 1.17 mmol, 0.3 eq.) and L-proline (131 mg, 1.17 mmol, 0.3 eq.). The vial was transferred to the autoclave, pressurised and heated to 40 °C. After the reaction was completed, the autoclave was cooled down to room temperature, depressurised, flushed with argon and opened to obtain a sample for GC analysis. Then the reaction mixture was filtered through a column filled with silica gel. Additionally the column was washed with 50 mL of diethyl ether. The filtrate was concentrated *in vacuo* and the crude product was purified by column chromatography.

Method F. *Preparation of MTPA Derivatives (Mosher's Method).* The reaction was carried out in a dry schlenk tube fitted with a rubber septum. The reagents were injected via syringe into the tube in the following order: Et_3N (300 µl, 220 mg), DMAP (1 mg, 0.01 mmol), S-(+)-MTPA-Cl (MTPA = α-methoxy-α-trifluoro-methylphenylacetic acid) (35 mg, 26 µl, 0.14 mmol), CH_2Cl_2 (300 µl) and the substrate aldol (0.10 mmol). After 24 hours of stirring, the mixture was diluted with diethyl ether, washed (cold dilute HCl, cold saturated $NaHCO_3$ and brine), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was further purified by column chromatography.

5.3 Syntheses

Preparation of 6-oxoheptanal (55).



55

$C_7H_{12}O_2$
Mol. Wt.: 128,17

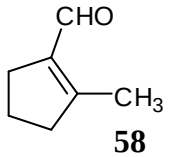
Amounts:	383 mg	3.9 mmol (1 eq.)	hex-5-en-2-one
	5 mg	0.019 mmol (0.005 eq.)	$Rh(acac)(CO)_2$
	33 mg	0.057 mmol (0.015 eq.)	XANTPHOS

Procedure: Method A; using 5 mL CH_2Cl_2, 10/10 bar CO/H_2, 70 °C, 72h

Yield: 504 mg **55** (>99%) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) 9.74 (t, 1H); 2.46 – 2.43 (m, 4H); 2.12 (s, 3H); 1.60 – 1.58 (m, 4H).

Preparation of 2-methylcyclopent-1-enecarbaldehyde (58).



58

$C_7H_{10}O$
Mol. Wt.: 110,15

To a solution of 6-oxoheptanal (200 mg, 1.56 mmol) in 3 ml $CHCl_3$ in a flask, was added L-proline (179 mg, 1.56 mmol). The suspension was stirred for 24h. Then, the reaction mixture was filtered and the filtrate concentrated under vacuum. The crude product was purified by column chromatography (hexane/acetone 10:1.5) to afford the title compound as a colourless oil (yield: 27 mg, 16%). ^{1}H NMR (400 MHz, $CDCl_3$) 10.00 (s, 1H); 2.57 – 2.54 (m, 4H); 2.14 (s, 3H), 1.87 – 1.83 (m, 2H). ^{13}C NMR (100 MHz) 189.63, 42.35, 31.57, 22.66, 15.73.

Olefin screening for hydroformylation sequence using Ph_3P modified rhodium catalyst (Table 1).

Amounts:		3.9 mmol (1 eq.)	olefin
	5 mg	0.019 mmol (0.005 eq.)	$Rh(acac)(CO)_2$
	20 mg	0.078 mmol (0.02 eq.)	PPh_3
	199 mg	1.17 mmol (0.3 eq.)	dodecane

Procedure: Method A; using 5 mL acetone, 20/20 bar CO/H_2, 60 °C, 72h

Yield: Determined by GC using an internal standard.

Olefin screening for hydroformylation sequence using $P(OPh)_3$ modified rhodium catalyst (Table 2).

Amounts:		3.9 mmol (1 eq.)	olefin
	5 mg	0.019 mmol (0.005 eq.)	$Rh(acac)(CO)_2$
	24 mg	0.078 mmol (0.02 eq.)	$P(OPh)_3$
	199 mg	1.17 mmol (0.3 eq.)	dodecane

Procedure: Method A; using 5 mL acetone, 20/20 bar CO/H_2, 40 °C, 72h

Yield: Determined by GC using an internal standard.

Hydroformylation reactions in the presence of L-proline (Table 3, entries 7 and 8).

Amounts:		3.9 mmol (1 eq.)	olefin
	5 mg	0.019 mmol (0.005 eq.)	$Rh(acac)(CO)_2$
	24 mg	0.078 mmol (0.02 eq.)	$P(OPh)_3$
	199 mg	1.17 mmol (0.3 eq.)	dodecane
	135 mg	1.17 mmol (0.3 eq.)	L-proline

Procedure: Method A; using 5 mL CH_2Cl_2, 20/20 bar CO/H_2, 40 °C, 72h

Yield: Determined by GC using an internal standard. Cyclopentene products: carrier gas 40 kPa He, temperature program of 30°C for 10 min, then 15°C/min to 260°C; retention times: 4.57 min for

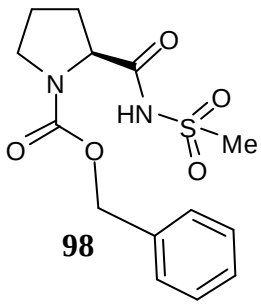
cyclopentene, 17.60 min for cyclopentanecarbaldehyde, 21.23 min for dodecane. 4-Chlorostyrene products: carrier gas 65 kPa He, temperature program of 35°C for 10 min, then 10°C/min to 260°C; retention times: 21.63 min for 4-chlorostyrene, 22.27 min for dodecane, 26.47 min for aldehyde **78** (branched regioisomer), 27.86 min for aldehyde **79** (linear regioisomer).

Aldol reaction in the presence of Rh-catalysts under atmospheric pressure (Table 4, entry 3). To a solution of $Rh(acac)(CO)_2$ (5 mg, 0.019 mmol, 0.005 eq.) in 5 ml of acetone in a flask, was added $P(OPh)_3$ (24 mg, 0.078 mmol, 0.02 eq.). The solution was stirred with magnetic stirrer for 5 min and then charged with cyclopentanecarbaldehyde (373 mg, 3.8 mmol, 1 eq.) and L-proline (131 mg, 1.17 mmol, 0.3 eq.). The resulting mixture was stirred at room temperature for 24 hours. Then, the reaction mixture was filtered through a column filled with silica gel. Additionally the column was washed with 50 mL of diethyl ether. The filtrate was concentrated *in vacuo* (compounds **63** and **83** are volatile, not recommended to use pressure less than 200 mbar at 40 °C) and the crude product was purified by column chromatography (MTBE/cyclohexane 1:4) to give unreacted cyclopentanecarbaldehyde (yield: 36 mg, 12%), (Z)-4-cyclopentylbut-3-en-2-one 4 (R_f = 0.68) as a pale yellow oil (yield: 51 mg, 12%) and (R)-4-cyclopentyl-4-hydroxybutan-2-one 3 (R_f = 0.34) as a pale yellow oil (yield: 178 mg, 38%). HPLC: CHIRALPAK AD, n-heptane/i-PrOH, 98.2:1.8, 1.0 $mL \cdot min^{-1}$, 280 nm, ee = 78%: t_R (major) = 19.0 min; t_R (minor) = 20.5 min.

Aldol reaction in the presence of Rh-catalyst under hydroformylation conditions (Table 4, entry 6). To a solution of $Rh(acac)(CO)_2$ (5 mg, 0.019 mmol, 0.005 eq.) in 5 ml of acetone in a vial, was added $P(OPh)_3$ (24 mg, 0.078 mmol, 0.02 eq.). The solution was stirred with magnetic stirrer for 5 min and then charged with cyclopentanecarbaldehyde (373 mg, 3.8 mmol, 1 eq.) and L-

proline (131 mg, 1.17 mmol, 0.3 eq.). The vial was transferred to the autoclave, pressurised to 20/20 bar CO/H_2 and heated to 40 °C. After the reaction was completed, the autoclave was cooled down to room temperature, depressurised, flushed with argon and opened. The reaction mixture was filtered through a column filled with silica gel. Additionally the column was washed with 50 mL of diethyl ether. The filtrate was concentrated *in vacuo* (compounds **63** and **83** are volatile, not recommended to use pressure less than 200 mbar at 40 °C) and the crude product was purified by column chromatography (MTBE/cyclohexane 1:4) to give unreacted cyclopentanecarbaldehyde (yield: 12 mg, 4%) and (R)-4-cyclopentyl-4-hydroxybutan-2-one 3 (R_f = 0.34) as a pale yellow oil (yield: 396 mg, 65%). HPLC: CHIRALPAK AD, n-heptane/i-PrOH, 98.2:1.8, 1.0 mL·min^{-1}, 280 nm, ee = 79%: t_R (major) = 19.0 min; t_R (minor) = 20.5 min.

(S)-2-Methanesulfonylaminocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester (98).



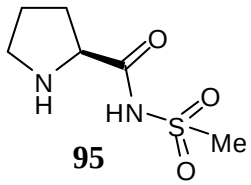
98

$C_{14}H_{18}N_2O_5S$
Mol. Wt.: 326,37

To a stirred solution of Z-L-proline (5.00 g, 20.1 mmol, 1 eq.) in dichlorometane (150 mL) were added methanesulfonamide (2.10 g, 22.1 mmol, 1.1 eq.), DMAP (380 mg, 3.11 mmol, 0.15 eq.) and EDCI (3.85 g, 20.1 mmol, 1 eq.) respectively. The resulting mixture was stirred at room temperature for 2 days. The reaction was concentrated to half the volume *in vacuo* and the resulting mixture was partitioned between EtOAc (250 mL) and 1M aqueous HCl (100mL). The organic layer was washed with half-saturated brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (dichlormethane/EtOAc, 7 : 3) to give the title compound as a clear colourless residue (yield: 3.79 g, 58%). ^{1}H NMR (500 MHz $CDCl_3$, 10.08 (broad s., 1H); 7.36 (m, 5H); 5.21 (d, 1H, J = 12.2 Hz); 5.15 (d, 1H, J = 12.2

Hz); 4.36 (m, 1H); 3.46 (m, 2H); 3.25 (s, 3H); 2.46 (s, 1H); 1.94 (m, 3H), in accord with the literature data.[90]

(S)-N-(methylsulfonyl)pyrrolidine-2-carboxamide (95).

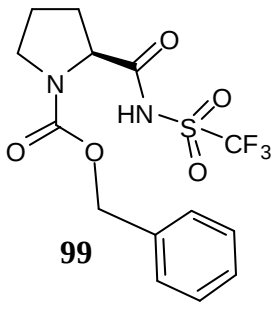


95

$C_6H_{12}N_2O_3S$
Mol. Wt.: 192,24

To a solution of (S)-2-methanesulfonylaminocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester **98** (1.00 g, 3.06 mmol, 1 eq.) in MeOH (100 mL) was added 10%Pd/C (180 mg). The mixture was stirred at room temperature for 20h under an atmosphere of hydrogen. The reaction was filtered through Celite® and 1cm of silica gel, and the filtrate was concentrated *in vacuo* to give a white solid. The crude product was purified by flash column chromatography (CH_2Cl_2/MeOH 8:2) to give the title compound as a white solid (yield: 517 mg, 88%). ^{1}H NMR (500 MHz, CD_3OD) 4.02 (dd, 1H, J = 6.5, 8.5 Hz); 3.41 – 3.36 (m, 1H); 3.27 – 3.24 (m, 1H); 3.00 (s, 3H); 2.37 – 2.29 (m, 1H); 2.15 – 2.09 (m, 1H); 2.02 – 1.96 (m, 2H), in accord with the literature data.[90]

(S)-benzyl 2-(trifluoromethylsulfonylcarbamoyl)pyrrolidine-1-carboxylate (99).



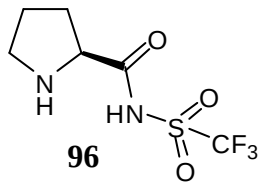
99

$C_{14}H_{15}F_3N_2O_5S$
Mol. Wt.: 380,34

To a stirred solution of z-L-proline (4 g, 16.0 mmol) in 125 ml DCM were added trifluoromethanesulfonamide (2.62 g, 17.6 mmol), DMAP (294 mg, 2.4 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) (2.48g, 16.0 mmol). The resulting mixture was stirred at room temperature for 4 days. The reaction was concentrated to half volume *in vacuo* and was partioned between 250 ml EtOAc and 100 ml 1.5 M HCl. The organic phase was washed with 50 ml half-saturated brine, dried with $MgSO_4$ and concentrated *in vacuo* to afford the title compound (yield: 5.17g, 77%) as a colourless residue. ^{1}H NMR (400 MHz, $CDCl_3$) 7.38 (m, 5H); 5.21 (m, 2H, 12.4 Hz); 5.19 (d, 1H, J = 12.4 Hz); 4.42 (d,

1H, J = 6.8 Hz); 3.56 – 3.48 (m, 1H); 3.47 – 3.38 (m, 1H); 2.58 – 2.49 (m, 1H); 1.95 – 1.89 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 24.3, 26.4, 47.3, 61.3, 68.6, 128.2, 128.5, 128.6. LRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{16}F_3N_2O_5S$) requires m/z 381.0, found m/z 381.1. HRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{16}F_3N_2O_5S$) requires m/z 381,0732, found m/z 381.0752.

(S)-N-(trifluoromethylsulfonyl)pyrrolidine-2-carboxamide (96).



96

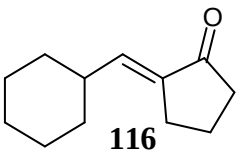
$C_6H_9F_3N_2O_3S$
Mol. Wt.: 246,21

(S)-benzyl 2-(trifluoromethylsulfonylcarbamoyl)pyrrolidine-1-carboxylate **99** (4.73g, 12.4 mmol) was dissolved in 250 ml MeOH and stirred with 2 g Pd/C for 20 hours under an atmosphere of hydrogen. The solution was filtered through Celite® and 1cm of silica gel and the filtrate was concentrated *in vacuo* to give a white solid. The crude product was purified by recrystallisation from MeOH to give the title compound (yield: 1.97 g, 65%) as fine white crystals. ^{1}H NMR (400 MHz, DMSO-d^6) 8.69 (br. s., 1H); (t, 1H, J = 6.8 Hz); 3.19 – 3.16 (m, 1H); 3.13 – 3.08 (m, 1H); 2.21 – 2.16 (m, 1H); 1.90 – 1.79 (m, 3H). LRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_6H_{10}F_3N_2O_3S$) requires m/z 247,0364, found m/z 247.0. HRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_6H_{10}F_3N_2O_3S$) requires m/z 247,0364, found m/z 247,0395.

L-Proline-catalysed asymmetric aldol reaction of cyclohexanecarbaldehyde and cyclopentanone (Scheme 35). To a stirred suspension of L-proline (126 mg, 1 mmol, 0.3 eq.) in 5 ml of cyclopentanone was added cyclohexanecarbaldehyde (300 mg, 3.65 mmol, 1 eq.). The resulting mixture was stirred at room temperature for 72 hours. Then, the reaction mixture was filtered through a column filled with silica gel. Additionally the column was washed with 50 mL of diethyl ether. The filtrate was concentrated *in vacuo* and

the crude product was purified by column chromatography (EtOAc/cyclohexane 1:4) to afford compounds **116**,[96] **115a**[96] and **115**b.

(*E*)-2-(cyclohexylmethylene)cyclopentanone (116). R_f = 0.50 (yield: 43 mg, 9%). ^{1}H NMR (400 MHz, $CDCl_3$) 6.37 (td, 1H, J = 6.0, 2.5 Hz); 2.58 (dt, 2H, J = 7.2, 2.5 Hz); 2.30 (t, 2H, J = 7.8 Hz); 2.19 – 2.10 (m, 1H); 1.94 – 1.89 (m, 2H); 1.75 – 1.61 (m, 5H); 1.32 – 1.10 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) 19.8, 25.4, 25.7, 26.5, 31.6, 38.5, 38.7, 135.2, 140.9, 207.9, in accord with the literature data.[96]

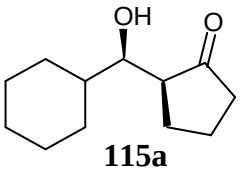


116

$C_{12}H_{18}O$
Mol. Wt.: 178,27

(S)-2-((R)-cyclohexyl(hydroxy)methyl)cyclopentanone (115a).

R_f = 0.31 (yield: 225 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) 3.98 (br. s, 1H); 3.51 (dd, 1H, J = 9.0, 1.9 Hz); 2.40 – 1.10 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) 20.6, 25.0, 26.4, 26.6, 30.0, 38.4, 40.9, 51.3, 76.0, 224.9, in accord with the literature data.[96] ^{1}H NMR (400 MHz, C_6D_6) 4.29 (br. s, 1H); 3.37 (dd, 1H, J = 9.1, 2.5 Hz); 1.88 – 0.80 (m, 18H). ^{13}C NMR (100 MHz, C_6D_6) 20.5, 25.2, 26.3, 26.8, 26.9, 27.1, 30.5, 38.1, 41.3, 51.1, 76.1, 223.6. $[\alpha]^{20}_D$ -112.8 (c 1.00, n-heptane) HPLC: CHIRALPAK AD, n-heptane/i-PrOH, 95:5, 1.0 mL·min^{-1}, 280 nm, ee = 86%: t_R (major) = 11.1 min; t_R (minor) = 9.7 min.

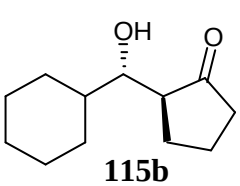


115a

$C_{12}H_{20}O_2$
Mol. Wt.: 196,29

(S)-2-((S)-cyclohexyl(hydroxy)methyl)cyclopentanone (115b).

R_f = 0.13 (yield: 120 mg, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) 3.79 (dd, 1H, J = 9.0, 2.4 Hz); 2.33 – 0.82 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) 20.6, 22.4, 25.7, 26.0, 26.2, 29.0, 29.5, 39.0, 41.2, 52.1, 73.9, 222.3. ^{1}H NMR (400 MHz, C_6D_6) 3.80 (dd, 1H, J = 8.8, 1.8 Hz); 2.06 – 0.66 (m, 18H). ^{13}C NMR (100 MHz, C_6D_6) 20.8, 22.6, 26.2, 26.4, 26.7, 29.3, 29.7, 38.9, 41.8, 52.0, 74.0,



115b

$C_{12}H_{20}O_2$
Mol. Wt.: 196,29

220.2. $[\alpha]^{20}_{D}$ +115.5 (c 1.00, n-heptane) HPLC: CHIRALCEL OD-H, n-heptane/i-PrOH, 98:2, 1.0 mL·min^{-1}, 280 nm, ee = 79%: t_R (major) = 12.3 min; t_R (minor) = 9.6 min.

Regioselective hydroformylation using BIPHEPHOS-modified rhodium catalyst (Table 12).

Amounts:		3.9 mmol (1 eq.)	olefin
	5 mg	0.019 mmol (0.005 eq.)	$Rh(acac)(CO)_2$
	61 mg	0.078 mmol (0.02 eq.)	BIPHEPHOS
	199 mg	1.17 mmol (0.3 eq.)	dodecane

Procedure: Method A; using 5 mL acetone, 10/10 bar CO/H_2, 50 °C, 72h

Yield: Determined by GC using an internal standard.

Sequential hydroformylation and aldol reactions of oct-1-ene (Scheme 37).

Amounts:	438 mg	3.9 mmol (1 eq.)	oct-1-ene
	5 mg	0.019 mmol (0.005 eq.)	$Rh(acac)(CO)_2$
	61 mg	0.078 mmol (0.02 eq.)	BIPHEPHOS
	131 mg	1.14 mmol (0.3 eq.)	L-proline
	199 mg	1.17 mmol (0.3 eq.)	dodecane

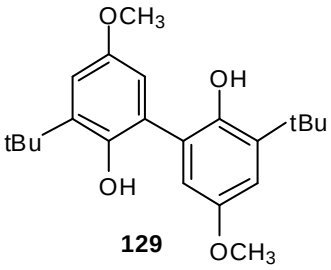
Procedure: Method B; using 5 mL cyclopentanone, 10/10 bar CO/H_2, 50 °C, 72h

Yield: Elimination product **120** was obtained in 20% yield. Also traces of aldol products **121** and **122** were isolated.

3,3'-di-tert-butyl-5,5'-dimethoxybiphenyl-2,2'-diol (129).

This compound was prepared according to a literature procedure.[100] A solution of 3-tert-butyl-4-hydroxyanisole (10 g, 0.055 mol) in methanol (300 mL) was prepared and a solution of KOH (11.07 g, 0.19 mol) and $K_3Fe(CN)_6$ (18.3 g, 0.055 mol) in water (300 mL) was added dropwise over 1 h at room

temperature. The mixture was stirred for 2 hours before the addition of 200 mL of water. The suspension was extracted with 500 mL of ethyl acetate twice. The aqueous solution was extracted with 150 mL of ether and the organic phases were combined and washed with 200 mL of saturated brine.

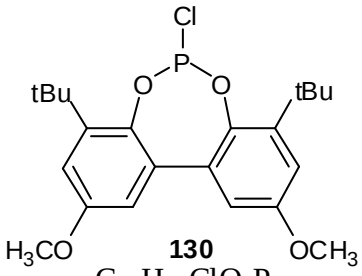


129

$C_{22}H_{30}O_4$
Mol. Wt.: 358,47

The organic phase was dried over $MgSO_4$. Removal of the solvents under vacuum afforded a light brown solid. Washing with n-hexane resulted in an off-white powder (yield: 19.60 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) 6,96 (d, 2H, J = 3 Hz); 6,63 (d, 2H, 3 Hz); 3,77 (s, 6H); 1,43 (s, 18H). ^{13}C NMR (100 MHz, C6D6) 153.4, 146.1, 139.2, 123.5, 115.5, 112.0, 56.0, 35.4, 29.7 in accord with the literature data.[100]

4,8-di-tert-butyl-6-chloro-2,10-dimethoxy-dibenzo[d,f][1,3,2]dioxa-phosphepine (130). This compound was prepared according to the literature procedure.[99] 3,3'-Di-tert-butyl-5,5'-dimethoxy-biphen-yl-2,2'-diol **129** (1.79g 5.0 mmol), was dissolved in toluene (20 mL) and pyridine (10 mmol, 0.81 mL). This solution was added dropwise to a cooled solution (0°C) of PCl_3 (0.52 mL, 6.0 mmol) and pyridine (0.81 mL, 10 mmol). The reaction mixture was stirried for 2h at reflux temperature. The solvent and excess of PCl_3 were removed under vacuum and compound **130** obtained *in situ* was dissolved in toluene and use in next step without purification. ^{31}P NMR (81 MHz) 173.9 ppm.



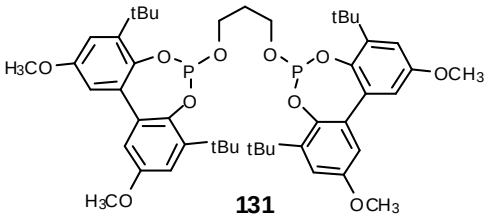
130

$C_{22}H_{28}ClO_4P$
Mol. Wt.: 422,88

1,3-bis(4,8-di-tert-butyl-2,10-dimethoxydibenzo[d,f][1,3,2]dioxaphosphepin-6-yloxy)propane (131).

Compound **130** (5.0 mmol) was dissolved in toluene (10 cm^3) and pyridine (1.62 mL, 20 mmol). Propane-1,3-diol (152 mg, 2.0 mmol) was dissolved in toluene and added in 30 min to the solution of **130** at room temperature. The reaction

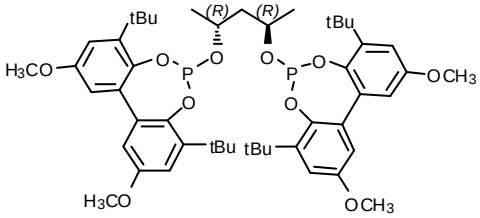
mixture was stirred overnight and the pyridine salts formed were filtered off. Evaporation of the solvent gave white foam, which was purified by chromatography (toluene/cyclohexane 4:1, silica gel deactivated with 1% Et_3N) to afford the title compound as a white powder (yield: 424 mg, 25%). ^{31}P NMR ($CDCl_3$, 81 MHz) 136.57 ppm. ^{1}H NMR (400 MHz, $CDCl_3$) 6.96 (d, 1H, J = 2.8 Hz); 6.69 (d, 2H, J = 2.8 Hz); 3.86 – 3.78 (m, 4H); 3.80 (s, 12H), 1.77 (p, 2H, J = 6.4 Hz); 1.42 (s, 36H). ^{13}C NMR (100 MHz, $CDCl_3$) 30.9, 32.4, 35.4, 55.7, 61.2, 112.8, 114,4, 133.51, 133.55, 142.3, 155.5



131

$C_{47}H_{62}O_{10}P_2$
Mol. Wt.: 848,94

6,6'-(2R,4R)-pentane-2,4-diylbis(oxy)bis(4,8-di-tert-butyl-2,10-dimethoxydibenzo[d,f][1,3,2]dioxaphosphepine) (8a).

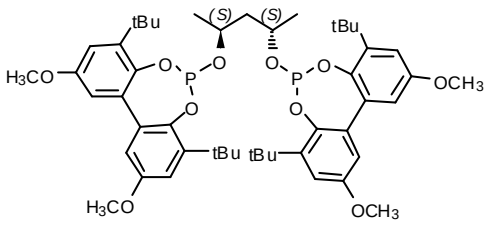


(2R,4R)-Chiraphite **8a**

$C_{49}H_{66}O_{10}P_2$
Mol. Wt.: 876,99

Compound **130** (5.0 mmol) was dissolved in toluene (10 mL) and pyridine (1.62 mL, 20 mmol). (2R,4R)-pentane-2,4-diol (208 mg, 2.0 mmol) was dissolved in toluene and added in 30 min to the solution of **130** at room temperature. The reaction mixture was stirred overnight and the pyridine salts formed were filtered off. Evaporation of the solvent gave white foam, which was purified by chromatography (toluene/cyclohexane 4:1, silica gel deactivated with 1% Et_3N) to afford the title compound as a white powder (yield: 350 mg, 20%). ^{31}P NMR (80 MHz, C_6D_6) 147.1 ppm, in accordance with the literature data.[99]

6,6'-(2S,4S)-pentane-2,4-diylbis(oxy)bis(4,8-di-tert-butyl-2,10-dimethoxydibenzo[d,f][1,3,2]dioxaphosphepine) (8b)



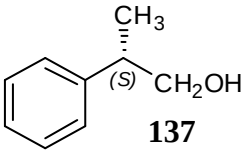
(2S,4S)-Chiraphite **8b**

$C_{49}H_{66}O_{10}P_2$

Mol. Wt.: 876,99

Compound **130** (5.0 mmol) was dissolved in toluene (10 mL) and pyridine (1.62 mL, 20 mmol). (2S,4S)-pentane-2,4-diol (208 mg, 2.0 mmol) was dissolved in toluene and added in 30 min to the solution of **130** at room temperature. The reaction mixture was stirred overnight and the pyridine salts formed were filtered off. Evaporation of the solvent gave white foam, which was purified by chromatography (toluene/cyclohexane 4:1, silica gel deactivated with 1% Et_3N) to afford the title compound as a white powder (yield: 350 mg, 20%). ^{31}P NMR (80 MHz, C_6D_6) 147.1 ppm, in accordance with the literature data.[99]

Reduction of (S)-2-phenylpropanal to S-2-phenylpropanol.



137

$C_9H_{12}O$

Mol. Wt.: 136,19

2-phenylpropanal (obtained using conditions from Table 18, entry 3) (134 mg, 1 mmol) was dissolved in ethanol (5 ml). Sodium tetrahydroborate (76 mg, 2 mmol) was added and the reaction mixture stirred for 90 min at room temperature. After quenching the mixture with water, it was extracted two times with ethyl acetate. The organic layers were combined and dried on magnesium sulfate. This reduced reaction mixture were analysed by GC. Absolute configuration of resulted 2-phenylpropanol **137** was assigned being (S) by comparison of the retention time with that of optically pure (R)-(+)-2-phenylpropanol which is commercially available. GC conditions: carrier gas 50 kPa He, temperature program of 100°C for 5 min, then 4°C/min to 160°C and 20°C/min to 200°C; retention times: 21.21 min for (R)-2-phenylpropanol and 21.47 min for (S)-2-phenylpropanol.

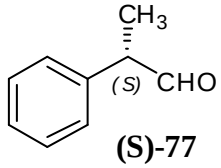
Enantioselective hydroformylation in the presence of L-proline (Table 19, entry 2).

Amounts:	158 mg	1.52 mmol (1 eq.)	styrene
	2 mg	0.0077 mmol (0.005 eq.)	$Rh(acac)(CO)_2$
	24 mg	0.019 mmol (0.0125 eq.)	(2S,4S)-Chiraphite
	78 mg	0.456 mmol (0.3 eq.)	dodecane
	53 mg	0.456 mmol (0.3 eq.)	L-proline

Procedure: Method C; using 3 mL CH_2Cl_2, 40/40 bar CO/H_2, 40 °C, 24h

Yield: Determined by GC using an internal standard.

Synthesis of (S)-2-phenylpropanal by Dess-Martin oxidation of (S)-2-phenylpropanol.



(S)-77

$C_9H_{10}O$

Mol. Wt.: 134,18

To a solution of (S)-2-phenylpropanol (1g, 7.3 mmol, 1 eq.) in dry dichloromethane (40 mL) was added the Dess-Martin periodinane (5.3 g, 12.4 mmol, 1.7 eq.) in one portion. The reaction was stirred for 20 min at room temperature. A buffer solution of $NaH_2PO_4/KHPO_4$ (25 mL) was added to the reaction flask and the mixture was stirred for 10 min. The reaction mixture was filtered through Celite and washed with dichloromethane. The solution was extracted with CH_2Cl_2 and dried over magnesium sulfate. The organic layer was filtered and evaporated to give a colourless liquid with a strong characteristic odour. The latter was diluted with pentane and filtered again over Celite. After evaporation of the solvent, the product was further used without purification. Spectral data are in accordance with the literature.[116] Chiral GC: 18.04 min (R)-isomer (minor), 18.35 min (S)-isomer (major), 93% ee of (S)-isomer.

Control reaction between enantioenriched (S)-2-phenylpropanal and L-proline (Scheme 46). To a solution of enantioenriched (93% ee) (S)-2-phenylpropanal (20 mg, 0.15 mmol, 1 eq.) in 1 ml of CH_2Cl_2 in a flask, was

added L-proline (5 mg, 0.045 mmol, 0.3 eq.). The solution was stirred with magnetic stirrer at room temperature for 8 days. A sample for GC analysis was taken every hour. According to GC analysis (S)-2-phenylpropanal was fully racemised within 8 hours. After 8 days reaction no self-aldolisation of the aldehyde was observed.

(S)-2-Phenylpropanal racemisation under acidic conditions (Scheme 48).

To a solution of enantioenriched (93% ee) (S)-2-phenylpropanal (40 mg, 0.3 mmol, 1 eq.) in 2 ml of CH_2Cl_2 in a flask, was added acetic acid (5 mg, 0.09 mmol, 0.3 eq.). The solution was stirred with magnetic stirrer at room temperature for 2 days. A sample for GC analysis was taken at first every hour and then every 24 hours. According to GC analysis (S)-2-phenylpropanal is not racemizing under acidic conditions.

(S)-2-Phenylpropanal racemisation and self-aldolisation under basic conditions (Scheme 48).

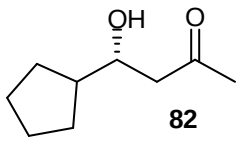
To a solution of enantioenriched (93% ee) (S)-2-phenylpropanal (40 mg, 0.3 mmol, 1 eq.) in 2 ml of CH_2Cl_2 in a flask, was added pyrrolidine (6.4 mg, 0.09 mmol, 0.3 eq.). The solution was stirred with magnetic stirrer at room temperature for 8 days. A sample for GC analysis was taken at first every hour and then every 24 hours. According to GC analysis (S)-2-phenylpropanal is racemizing under basic conditions within 2 minutes. After 8 days reaction self-aldolisation product **138** was isolated in 10% yield.

Influence of additives on the L-proline-catalysed aldol reaction between hydrotropaldehyde and acetone (Scheme 53).

To a solution of racemic 2-phenylpropanal (300 mg, 2.24 mmol, 1 eq.) in 10 ml of acetone in a flask, was added S-BINOL (19 mg, 0.067 mmol, 0.03 eq.) and L-proline (77 mg, 0.67 mmol, 0.3 eq.). The solution was stirred with magnetic

stirrer at room temperature for 72 hours. A sample for GC analysis was taken at first every hour and then every 24 hours.

(R)-4-Cyclopentyl-4-hydroxybutan-2-one (82) (Table 6, entry 4).

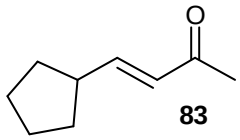


82

$C_9H_{16}O_2$
Mol. Wt.: 156,22

Purified using column chromatography (EtOAc/cyclohexane 1:4) to yield the title compound as a colourless oil (293 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) 3.84 – 3.79 (m, 1H); 2.96 (d, 1H, J = 3.2 Hz); 2.64 (dd, 1H, J = 17.6, 2.0 Hz); 2.52 (dd, 1H, J = 17.6, 9.6 Hz); 2.17 (s, 3H); 1.90 – 1.75 (m, 2H); 1.67 – 1.49 (m, 5H); 1.42 – 1.34 (m, 1H); 1.19 – 1.13 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) 25.4, 25.6, 28.7, 28.9, 30.7, 45.2, 49.0, 71.5, 210.2. HRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_9H_{17}O_2$) requires m/z 157.1229, found m/z 157.1155. Elemental analysis (%), calculated for $C_9H_{16}O_2$: C 69.19, H 10.32; found C 68.96, H 10.60. IR ν_{max} (film)/cm^{-1} 3435, 2952, 2868, 1709, 1360. $[\alpha]^{20}_D$ +45.7 (c 1.00, n-heptane). HPLC: CHIRALPAK AD, n-heptane/i-PrOH, 98.2:1.8, 1.0 mL·min^{-1}, 280 nm, ee = 81%: t_R (major) = 19.1 min; t_R (minor) = 20.7 min.

(Z)-4-Cyclopentylbut-3-en-2-one (83).

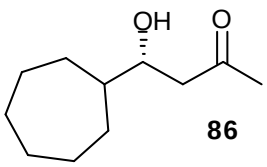


83

$C_9H_{14}O$
Mol. Wt.: 138,21

^{1}H NMR (400 MHz, $CDCl_3$) 6.76 (dd, 1H, J = 16.0, 8.0 Hz); 6.03 (d, 1H, J = 16.0 Hz); 2.61 – 2.54 (m, 1H); 2.30 (s, 3H); 1.89 – 1.21 (m, 8H), in accord with the literature data.[117]

(R)-4-Cycloheptyl-4-hydroxybutan-2-one (86).



86

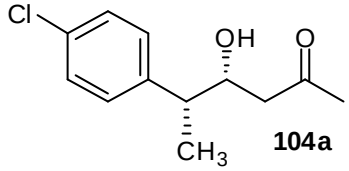
$C_{11}H_{20}O_2$
Mol. Wt.: 184,28

Purified using column chromatography (EtOAc/cyclohexane 1:4) to yield the title compound as a colourless oil (yield: 337 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) 3.91 – 3.87 (m, 1H); 2.92 (d, 1H, J = 2.8 Hz); 2.60 – 2.48 (m, 2H); 2.16 (s, 3H); 1.86 – 1.17 (m, 13H). ^{13}C NMR (100 MHz, $CDCl_3$)

26.7, 26.9, 28.2, 29.2, 29.8, 30.8, 44.1, 46.6, 71.8, 210.5. HRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{21}O_2$) requires m/z 185.1542, found m/z 185.1565. Elemental analysis (%), calculated for $C_{11}H_{20}O_2$: C 71.70, H 10.94; found C 71.46, H 11.10. IR ν_{max} (film)/cm^{-1} 3435, 2921, 2854, 1709, 1358. $[\alpha]^{20}_D$ +50.8 (c 1.00, n-heptane). HPLC: CHIRALPAK AD, n-heptane/i-PrOH, 98:2, 1.0 mL·min^{-1}, 280 nm, ee = 89%: t_R (major) = 15.7 min; t_R (minor) = 18.9 min.

5-(4-Chlorophenyl)-4-hydroxyhexan-2-one (104a,b) (Table 8, entry 1). Purified using column chromatography (EtOAc/cyclohexane 1:4) to yield the mixture of syn/anti diastereomers (1.5:1) of the title compound as a colourless oil (yield: 0.786 g, 89%). The diastereomers were separated on a semi-preparative HPLC column (EtOAc/cyclohexane 1:6).

(4R,5R)-5-(4-Chlorophenyl)-4-hydroxyhexan-2-one **104a**:



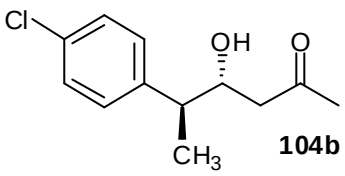
104a

$C_{12}H_{15}ClO_2$
Mol. Wt.: 226,70

^{1}H NMR (500 MHz, $CDCl_3$) 7.29 – 7.26 (m, 2H); 7.21 – 7.11 (m, 2H); 4.06 (dddd, 1H, J = 7.8, 5.8, 5.8, 3.8 Hz); 3.13 (d, 1H, J = 3.8 Hz); 2.73 (qd, 1H, J = 7.8, 7.0 Hz); 2.41 - 2.39 (m, 2H); 2.08 (s, 3H); 1.33 (d, 3H, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) 17.3, 30.8, 44.3, 47.4, 71.4, 128.4, 129.5, 132.3, 141.4, 209.4. HRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{16}ClO_2$) requires m/z 227,0839, found m/z 227.0822. Elemental analysis (%), calculated for $C_{12}H_{15}ClO_2$: C 63.58, H 6.67; found C 63.39, H 6.90. IR ν_{max} (film)/cm^{-1} 3464, 2964, 2927, 1711, 1492, 1411, 1360, 1091, 1012, 828. $[\alpha]^{20}_D$ +17.8 (c 1.60, n-heptane). HPLC: CHIRALPAK AD, n-heptane/i-PrOH, 98:2, 1.0 mL·min^{-1}, 230 nm, ee = 72%: t_R (major) = 16.0 min; t_R (minor) = 17.3 min.

(4R,5S)-5-(4-Chlorophenyl)-4-hydroxyhexan-2-one **104b**:

^{1}H NMR (500 MHz, $CDCl_3$) 7.30 – 7.26 (m, 2H); 7.21 – 7.18 (m, 2H); 4.17 (ddd, 1H, J = 9.2, 6.00, 2.8 Hz); 2.78 (qd, 1H, J = 7.2, 6.0 Hz); 2.58 (dd, 1H, J =



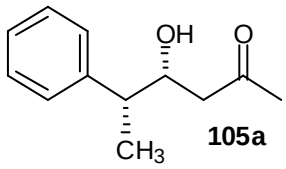
104b

$C_{12}H_{15}ClO_2$
Mol. Wt.: 226,70

17.3, 2.8 Hz); 2.43 (dd, 1H, J = 17.3, 9.2 Hz); 2.14 (s, 3H); 1.29 (d, 3H, J = 7.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) 17.3, 30.8, 44.3, 47.4, 71.4, 128.4, 129.5, 132.3, 141.4, 209.4. HRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{16}ClO_2$) requires m/z 227,0839, found m/z 227.0822. Elemental analysis (%), calculated for $C_{12}H_{15}ClO_2$: C 63.58, H 6.67; found C 63.45, H 6.90. IR ν_{max} (film)/cm^{-1} 3464, 2964, 2927, 1711, 1492, 1411, 1360, 1091, 1012, 828. $[\alpha]^{20}_D$ +45.4 (c 1.00, n-heptane). HPLC: CHIRALCEL OJ, n-heptane/i-PrOH, 97:3, 0.5 mL·min^{-1}, 230 nm, ee > 99%: t_R = 16.0 min.

4-Hydroxy-5-phenylhexan-2-one (105a,b). Purified using column chromatography (EtOAc/cyclohexane 1:4) to yield the mixture of syn/anti diastereomers (1.5:1) of the title compound as colourless oil (yield: 615 mg, 83%). Diastereomers were separated on a semi-preparative HPLC column (EtOAc/cyclohexane 1:6).

(4R,5R)-4-Hydroxy-5-phenylhexan-2-one **105a**: ^{1}H NMR (500 MHz, $CDCl_3$)

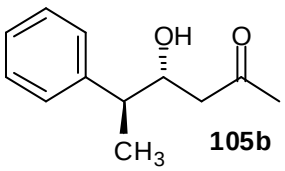


105a

$C_{12}H_{16}O_2$
Mol. Wt.: 192,25

7.32 – 7.29 (m, 2H); 7.24 – 7.16 (m, 3H); 4.09 (ddd, 1H, J = 7.9, 5.8, 5.8 Hz); 2.74 (qd, 1H, J = 7.9, 7.0 Hz); 2.42 - 2.40 (m, 2H); 2.07 (s, 3H); 1.36 (d, 3H, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) 17.6, 30.7, 45.4, 47.9, 72.1, 126.6, 127.6, 128.6, 143.8, 210.1, in accord with the literature data.[93] HRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{17}O_2$) requires m/z 193.1229, found m/z 193.1236. Elemental analysis (%), calculated for $C_{12}H_{16}O_2$: C 74.97, H 8.39; found C 74.48, H 8.50. IR ν_{max} (film)/cm^{-1} 3461, 2965, 1708, 1493, 1452, 1361, 1164, 702. $[\alpha]^{20}_D$ +13.8 (c 1.23, n-heptane). HPLC: CHIRALPAK AD, n-heptane/i-PrOH, 98:2, 1.0 mL·min^{-1}, 254 nm, ee = 72%: t_R (major) = 14.9 min; t_R (minor) = 15.8 min.

(4R,5S)-4-Hydroxy-5-phenylhexan-2-one **105b**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.34 - 7.31 (m, 2H); 7.26 – 7.22 (m, 3H); 4.20 (ddd, 1H, J = 9.3, 6.1, 2.6 Hz);

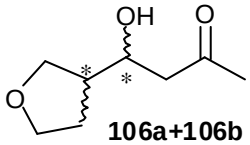


105b

$C_{12}H_{16}O_2$
Mol. Wt.: 192,25

2.82 (qd, J = 7.0, 6.1 Hz); 2.58 (dd, 1H, J = 17.2, 2.6 Hz); 2.47 (dd, 1H, J = 17.2, 9.3 Hz); 2.14 (s, 3H), 1.31 (d, 3H, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) 17.0, 30.8, 45.0, 47.3, 71.7, 126.6, 128.1, 128.4, 142.8, 209.4, in accord with the literature data.[93] HRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{17}O_2$) requires m/z 193.1229, found m/z 193.1236. Elemental analysis (%), calculated for $C_{12}H_{16}O_2$: C 74.97, H 8.39; found C 74.62, H 8.60. IR ν_{max} (film)/cm^{-1} 3461, 2965, 1708, 1493, 1452, 1361, 1164, 702. $[\alpha]^{20}_D$ +32.7 (c 1.97, n-heptane). HPLC: CHIRALCEL OJ, n-heptane/i-PrOH, 90:10, 1.0 mL·min^{-1}, 254 nm, ee > 99%: t_R = 13.4 min.

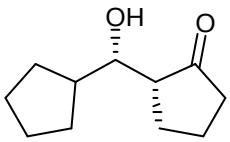
(syn+anti)-4-Hydroxy-4-(tetrahydrofuran-3-yl)butan-2-one (1:1 mixture, 106a,b). Purified using column chromatography (EtOAc) to yield a mixture of inseparable syn/anti diastereomers (1:1) of title compound as colourless oil (yield: 432 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) 3.97 – 3.67 (m, 9H); 3.51 – 3.48 (m, 1H); 2.67 (dd, 1H, J = 17.5, 2.0 Hz); 2.56 – 2.50 (m, 3H); 2.30 – 2.24 (m, 2H); 2.174 (s, 3H); 2.170 (s, 3H); 2.03 – 1.97 (m, 1H); 1.94 – 1.87 (m, 1H); 1.87 – 1.79 (m, 1H); 1.57 – 1.49 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) 28.1, 28.7, 30.7, 44.4, 48.4, 48.5, 68.0, 68.2, 68.8, 69.6, 70.5, 209.4, 209.5. HRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_8H_{15}O_3$) requires m/z 159,1021, found m/z 159.1014. Elemental analysis (%), calculated for $C_8H_{14}O_3$: C 60.74, H 8.92; found C 60.38, H 9.10. IR ν_{max} (film)/cm^{-1} 3411, 2936, 2873, 1709, 1361, 1066. CHIRALPAK AD, n-heptane/i-PrOH, 97:3, 1.0 mL·min^{-1}, 280 nm, ee = 71% (for I diastereomer), ee = 71% (for II diastereomer): t_R (major I) = 32.1 min; t_R (major II) = 34.3 min; t_R (minor I) = 36.6 min; t_R (minor II) = 41.6 min.



106a+106b

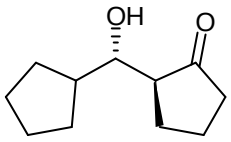
$C_8H_{12}O_3$
Mol. Wt.: 156,18

(S)-2-((R)-Cyclopentyl(hydroxy)methyl)cyclopentanone (111a). Purified using column chromatography (EtOAc/cyclohexane 1:4, R_f = 0.48) to yield the title compound as a colourless oil (yield: 112 mg, 16%). ^{1}H NMR (400 MHz, C_6D_6) 4.15 (dd, 1H, J = 1.8, 1.0 Hz); 3.49 (ddd, 1H, J = 8.4, 3.4, 1.8 Hz); 1.85 – 1.44 (m, 13H); 1.36 – 1.30 (m, 1H); 1.10 – 0.90 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) 20.7, 25.7, 25.8, 26.0, 27.1, 28.8, 38.7, 43.5, 53.3, 74.3, 224.2. HRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{19}O_2$) requires m/z 183,1385, found m/z 183.1374. Elemental analysis (%), calculated for $C_{11}H_{18}O_2$: C 72.49, H 9.95; found C 72.28, H 10.10. IR ν_{max} (film)/cm^{-1} 3496, 2952, 2867, 1720, 1405, 1159. $[\alpha]^{20}_D$ -119.0 (c 1.00, n-heptane).



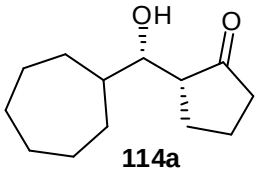
111a
$C_{11}H_{18}O_2$
Mol. Wt.: 182,26

(S)-2-((S)-Cyclopentyl(hydroxy)methyl)cyclopentanone (111b). Purified using column chromatography (EtOAc/cyclohexane 1:4, R_f = 0.25) to yield the title compound as a colourless oil (yield: 302 mg, 43%). ^{1}H NMR (400 MHz, C_6D_6) 3.88 (dd, 1H, J = 9.2, 2.0 Hz); 2.02 – 0.86 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) 20.6, 22.4, 25.4, 29.1, 29.9, 39.0, 44.2, 53.7, 74.0, 221.6. HRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{19}O_2$) requires m/z 183,1385, found m/z 183.1351. Elemental analysis (%), calculated for $C_{11}H_{18}O_2$: C 72.49, H 9.95; found C 72.21, H 10.20. IR ν_{max} (film)/cm^{-1} 3451, 2953, 2869, 1732, 1156. $[\alpha]^{20}_D$ +152.0 (c 1.00, n-heptane). HPLC: CHIRALCEL OD, n-heptane/i-PrOH, 90:10, 1.0 mL·min^{-1}, 280 nm, ee = 96%: t_R (major) = 5.4 min; t_R (minor) = 4.7 min.



111b
$C_{11}H_{18}O_2$
Mol. Wt.: 182,26

(S)-2-((R)-Cycloheptyl(hydroxy)methyl)cyclopentanone (114a). Purified using column chromatography (EtOAc/cyclohexane 1:4, R_f = 0.62) to yield the title compound as a colourless oil (yield: 211 mg, 26%). ^{1}H NMR (400 MHz, C_6D_6) 3.45 (dd, 1H, J = 9.2, 2.0 Hz); 1.90 – 1.10 (m, 18H); 1.10 – 0.97 (m, 1H);

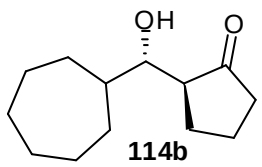


114a

$C_{13}H_{22}O_2$
Mol. Wt.: 210,31

0.90 – 0.79 (m, 1H). ^{13}C NMR (100 MHz, C_6D_6) 20.4, 26.4, 26.6, 27.4, 27.9, 28.9, 32.9, 38.0, 42.8, 51.6, 77.7, 223.6. HRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{23}O_2$) requires m/z 211,1698, found m/z 211.1675. Elemental analysis (%), calculated for $C_{13}H_{22}O_2$: C 74.24, H 10.54; found C 73.96, H 10.80. IR ν_{max} (film)/cm^{-1} 3498, 2923, 1712. $[\alpha]^{20}_D$ -90.3 (c 1.00, n-heptane). HPLC: CHIRALCEL OJ, n-heptane, 0.5 mL·min^{-1}, 280 nm, ee = 83%: t_R (major) = 19.4 min; t_R (minor) = 21.1 min.

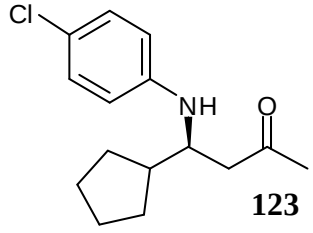
(S)-2-((S)-Cycloheptyl(hydroxy)methyl)cyclopentanone (114b). Purified using column chromatography (EtOAc/cyclohexane 1:4, R_f = 0.40) to yield the title compound as colourless crystals (yield: 406 mg, 50%). Mp 72 – 74 °C. ^{1}H NMR (400 MHz, C_6D_6) 3.87 (dd, 1H, J = 8.2, 1.8 Hz); 2.01 – 1.15 (m, 19H); 0.98 – 0.89 (m, 1H). ^{13}C NMR (100 MHz, C_6D_6) 20.8, 22.9, 26.6, 26.8, 28.8, 29.3, 29.6, 30.7, 38.8, 43.4, 52.3, 73.3, 219.8. HRMS (FAB+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{23}O_2$) requires m/z 211,1698, found m/z 211.1724. Elemental analysis (%), calculated for $C_{13}H_{22}O_2$: C 74.24, H 10.54; found C 74.05, H 10.70. IR ν_{max} (KBr)/cm^{-1} 3441, 2912, 1724. $[\alpha]^{20}_D$ +157.4 (c 1.00, n-heptane). HPLC: CHIRALPAK AD, n-heptane/i-PrOH, 98:2, 1.0 mL·min^{-1}, 280 nm, ee = 85%: t_R (major) = 28.5 min; t_R (minor) = 26.8 min.



114b

$C_{13}H_{22}O_2$
Mol. Wt.: 210,31

(S)-4-(4-Chlorophenylamino)-4-cyclopentylbutan-2-one (123). Purified using column chromatography (EtOAc/cyclohexane 1:4, R_f = 0.40) to yield the title compound as a brown oil (yield: 535 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) 7.08 – 7.06 (m, 2H); 6.53 – 6.51 (m, 2H); 3.76 (br. s., 1H); 3.70 – 3.64 (m, 1H); 2.67 (dd, 1H, J = 16.7, 5.1 Hz); 2.61 (dd, 1H, J = 16.7, 5.4 Hz); 2.12 (s, 3H); 2.11 – 2.02 (m, 1H);

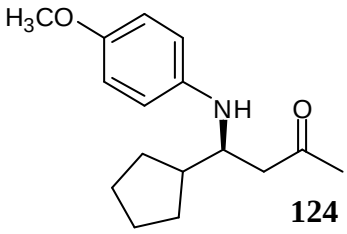


123

$C_{15}H_{20}ClNO$
Mol. Wt.: 265,78

1.82 – 1.48 (m, 6H); 1.28 – 1.16 (m, 2H). ESI-MS exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}ClNO$) requires m/z 266,13117, found m/z 266.13064. IR ν_{max} (film)/cm^{-1} 3386, 2952, 2866, 1708, 1598, 1500. $[\alpha]^{20}_D$ +7.5 (c 1.00, n-heptane). HPLC: CHIRALCEL OD-H, n-heptane/i-PrOH, 90:10, 1.0 mL·min^{-1}, 254 nm, ee = 19%: t_R (major) = 6.6 min; t_R (minor) = 5.4 min.

(S)-4-Cyclopentyl-4-(4-methoxyphenylamino)butan-2-one (124). Purified using column chromatography (EtOAc/cyclohexane 1:4, R_f = 0.40) to yield the title compound as a brown oil (yield: 566 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) 6.75 – 6.73 (m, 2H); 6.58 – 6.56 (m, 2H); 3.72 (s, 3H); 3.66 – 3.61 (m, 1H); 2.64 (dd, 1H, J = 19.1, 5.5 Hz); 2.60 (dd, 1H, J = 19.1, 5.5 Hz); 2.11 (s, 3H); 2.12 – 2.01 (m, 1H); 1.83 – 1.75 (m, 1H); 1.70 – 1.47 (m, 5H); 1.31 – 1.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) 25.30, 25.39, 29.63, 29.66, 31.0, 45.1, 46.9, 55.3, 55.6, 114.85, 141.72, 151.9, 208.6. ESI-MS exact mass calculated for $[M+H]^+$ ($C_{16}H_{24}NO_2$) requires m/z 262,18070, found m/z 262.17971. $[\alpha]^{20}_D$ +1.2 (c 1.00, n-heptane). HPLC: CHIRALCEL OJ, n-heptane/i-PrOH, 95:5, 1.0 mL·min^{-1}, 254 nm, ee = 4%: t_R (major) = 17.1 min; t_R (minor) = 15.4 min.



124

$C_{16}H_{23}NO_2$
Mol. Wt.: 261,36

6 LITERATURE

1. Roelen, O., German patent DE 849,548, 1938/1952, US Patent, 2.327.066, **1943**.
2. Weissermel, K.; Arpe, H.-J., *Industrielle Organische Chemie*. VCH: Weinheim, Germany: **1988**.
3. Breit, B., *Acc. Chem. Res.* **2003,** *36*, 264-275.
4. Breit, B.; Seiche, W., *Synthesis* **2001**, 1-36.
5. Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G., *J. Chem. Soc. A* **1966**, 1711-1732.
6. Evans, D. A.; Osborn, J. A.; Wilkinson, G., *J. Chem. Soc. A* **1968**, 3133 - 3142.
7. Brown, C. K.; Wilkinson, G., *J. Chem. Soc. A* **1970,** *17*, 2753-2764.
8. Wilkinson, G., *Bull. Soc. Chim. Fr*. **1968**, 5055-5058.
9. Devon, T. J.; Phillips, G. W.; Puckete, T. A.; Stavinoha, J. L.; Vanderbilt, J. J., *U.S. Patent 4,694,109*, **1987**; *Chem. Abstr*. **1988**, 108, 7890. **1987**.
10. Casey, C. P.; Whiteker, G. T.; Melville, M. G.; Petrovich, L. M.; Gavey, J. A.; Powell, D. R., *J. Am. Chem. Soc* **1992,** *114*, 5535-5543.
11. Billig, E.; Abatjoglou, A. G.; Bryant, D. R., *U.S. Patent 4,769,498* **1988**.
12. Cunny, G. D.; Buchwald, S. L., *J. Am. Chem. Soc* **1993,** *115*, 2066-2068.
13. Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, W. N. M. P.; Goubitz, K.; Fraanje, J., *Organometallics* **1995,** *14*, 3081-3089.
14. Kamer, P. C. J.; van Leeuwen, W. N. M. P.; Reek, J. N. H., *Acc. Chem. Res.* **2001,** *34*, 895-904.
15. Babin, J. E.; Whiteker, G. T., *Patent WO 93/03830* **1992**.
16. Whiteker, G. T.; Briggs, J. R.; Barner, B. A., *Catalysis of Organic Reactions*. New York, **2003**.
17. Dieguez, M.; Pamies, O.; Ruiz, A.; Castillon, S.; Claver, C., *Chem. Eur. J.* **2001,** *7*, 3086-3094.

18. Cobley, C. J.; Gardner, K.; Klosin, J.; Praquin, C.; Hill, C.; Whiteker, G. T.; Zanotti-Gerosa, A.; Petersen, J. L.; Abboud, K. A., *J. Org. Chem.* **2004,** *69*, 4031-4040.
19. Cobley, C. J.; Klosin, J.; Qin, C.; Whiteker, G. T., *Org. Lett.* **2004,** *6*, 3277-3280.
20. Breeden, S.; Cole-Hamilton, D. J.; Foster, D. F.; Schwarz, G. J.; Wills, M., *Angew. Chem. Int. Ed.* **2000,** *39*, 4106-4108.
21. Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H., *J. Am. Chem. Soc* **1997,** *119*, 4413-4423.
22. Yongjun, Y.; Xumu, Z., *J. Am. Chem. Soc* **2006,** *128*, 7198-7202.
23. Clark, T. P.; Clark, R. L.; Freed, S. L.; Klosin, J.; Abboud, K. A., *J. Am. Chem. Soc* **2005,** *127*, 5040-5042.
24. Berkessel, A.; Gröger, H., *Asymmetric Organocatalysis*. ***Wiley-VCH***, *Weinheim* **2005**.
25. Seayad, J.; List, B., *Org. Biomol. Chem.* **2005,** 3, 719-724.
26. List, B.; Hoang, L.; Martin, H. J., *Proc. Natl. Acad. Sci. U.S.A* **2004,** *101*, 5839.
27. Wynberg, H.; Staring, E. G. J., *J. Am. Chem. Soc* **1982,** 104, 166-168.
28. Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A., *J. Org. Chem.* **2000,** 65, (21), 6984-6991.
29. Fu, G. C.; Ruble, J. C.; Liang, J., *J. Org. Chem.* **1998,** 63, (10), 3154-3155.
30. Ruble, J. C.; Tweddel, J.; Fu, G. C., *J. Org. Chem.* **1998,** 63, (9), 2794-2795.
31. Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C., *J. Am. Chem. Soc* **2003,** 125, (5), 1192-1194.
32. Halland, N.; Hazell, R. G.; Jorgensen, K. A., *J. Org. Chem.* **2002,** 67, (24), 8331-8338.

33. Halland, N.; Aburel, P. S.; Jorgensen, K. A., *Angew. Chem. Int. Ed.* **2003,** 42, 661-665.
34. Jacobsen, E., *Angew. Chem.* **2002**, 1336.
35. Shu, L.; Wang, P.; Gan, Y.; Shi, Y., *Org. Lett.* **2003,** 5, (3), 293-296.
36. Palomo, C.; Oiarbide, M.; Garcia, J. M., *Chem. Soc. Rev.* **2004,** 33, 65.
37. Mahrwald, R., Modern Aldol Reactions. *Wiley-VCH, Weinheim* **2004**.
38. Kim, B. M.; Williams, S. F.; Masamune, S.; Trost, B. M.; Fleming, I., Comprehensive Organic Synthesis. *Pergamon Press: Oxford,* **1991,** 2, 239.
39. Heathcock, C. H., Asymmetric Synthesis. *Academic Press: New York* **1984,** 3, 111.
40. Nelson, S. G., *Tetrahedron: Asymmetry* **1998,** 9, 357.
41. Carreira, E. M., Catalytic Asymmetric Synthesis. *Wiley-VCH, Weinheim* **2000**.
42. Johnson, J. S.; Evans, D. A., *Acc. Chem. Res.* **2000,** 33, 432.
43. Denmark, S. E.; Stavenger, R. A., *Acc. Chem. Res.* **2000,** 33, 432.
44. Hajos, A. G.; Parrish, D. R., *J. Org. Chem.* **1974,** 39, 1615-1621.
45. Zhong, G.; Hoffmann, T.; Lerner, R. A.; Danishefsky, S.; Barbas III, C. F., *J. Am. Chem. Soc* **2000,** 122, 2395-2396.
46. List, B.; Lerner, R. A.; Barbas III, C. F., *J. Am. Chem. Soc* **2000,** *122*, 2395-2396.
47. Notz, W.; List, B., *J. Am. Chem. Soc* **2000,** 122, 7386.
48. Pidathala, C.; Hoang, L.; Vignola, N.; List, B., *angew. Chem. Int. Ed.* **2003,** 42, 2785-2788.
49. Bertau, M.; Bürli, M.; Hungerbühler, E.; Wagner, P., *Tetrahedron: Asymmetry* **2001,** 12, 2103-2107.
50. Spiliotis, V.; Papahatjis, D.; Ragoussis, N., *Tetrahedron Letters* **1990,** 31, 1615-1616.

51. Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M., *J. Am. Chem. Soc* **2004,** *126*, 8777-8785.
52. Kobyashi, S.; Ishitani, H.; Ueno, M., *J. Am. Chem. Soc* **1998,** *120*, 431-432.
53. Cobb, A. J. A.; Shaw, D. M.; Ley, S. V., *Synlett* **2004**, 558.
54. Notz, W.; Tanaka, F.; Watanabe, S.-i.; Naidu, S. C.; Turner, J. M.; Thayumanavan, R.; Barbas III, C. F., *J. Org. Chem.* **2003,** *68*, 9624.
55. List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J., *J. Am. Chem. Soc* **2002,** *124*, 827.
56. Pojarliev, P.; Biller, W. T.; Martin, H. J.; List, B., *Synlett* **2003,** *12*, 1903-1905.
57. List, B., *J. Am. Chem. Soc*. **2000,** *122*, 9336-9337.
58. Ramasastry, S. S. V.; Zhang, H.; Fujie, T.; Barbas III, C. F., *J. Am. Chem. Soc* **2007,** *129*, 288-289.
59. Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z., *J. Am. Chem. Soc* **2007,** (ASAP article).
60. Cordova, A.; Barbas III, C. F., *Tetrahedron Letters* **2002,** *43*, 7749.
61. Franzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjaersgaard, A.; Jorgensen, K. A., *J. Am. Chem. Soc* **2005,** *127*, 18296.
62. Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K., *J. Am. Chem. Soc* **2005,** *127*, 16408.
63. Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas III, C. F., *J. Am. Chem. Soc* **2006,** *128*, 1040.
64. Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C., *Chem. Rev.* **2005,** 105, 1001-1020.
65. Tietze, L. F., *Chem. Rev.* **1996,** 96, 115-136.
66. Lee, J. M.; Na, Y.; H., H.; Chang, S., *Chem. Soc. Rev.* **2004,** 33, 302-312.
67. Hollmann, C.; Eilbracht, P., *Tetrahedron Letters* **1999,** 40, 4313-4316.
68. Fresu, S., PhD Thesis **2004**.

69. Hollmann, C.; Eilbracht, P., *Tetrahedron* **2000,** 56, 1685-1692.
70. Keränen, M. D.; Eilbracht, P., *Org. Biomol. Chem.* **2004,** 2, 1688-690.
71. Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B., *J. Am. Chem. Soc* **1989,** 111, 3441.
72. Keränen, M., PhD Thesis, Dortmund 2004.
73. Tsai, C.-C.; Hsieh, I.-L.; Cheng, T.-T.; Tsai, P.-K.; Lin, K.-W.; Yan, T.-H., *Org. Lett.* **2006,** 11, 2261-2263.
74. Hayakawa, K.; Takewaki, M.; Fujimoto, I.; Kanematsu, K., *J. Org. Chem.* **1986,** 56, 5100-5105.
75. Trzeciak, A. M.; Ziolkowski, J. J., *J. Organomet. Chem.* **1994,** *479*, 213-216.
76. Dale, J. A.; Mosher, H. S., *J. Am. Chem. Soc* **1973,** *95*, 1667.
77. van Leeuwen, W. N. M. P.; Claver, C., Rhodium Catalyzed Hydroformylation. *Kluwer Academic Publisher* **2000,** Dordrecht.
78. Raj, M.; Ginotra, S. K.; Singh, V. K., *Org. Lett.* **2006,** 8, 4097-4099.
79. Samanta, S.; Liu, J.; Dodda, R.; Zhao, C.-G., *Org. Lett.* **2005,** 7, 5321-5323.
80. Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z., *J. Am. Chem. Soc* **2005,** 127, 9285-9289.
81. Krattiger, P.; Kovasy, R.; Revell, J. D.; Ivan, S.; Wennemers, H., *Org. Lett.* **2005,** 7, 1101-1103.
82. Cordova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.-W., *Chem. Commun.* **2005**, 3586-3588.
83. Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y., *Chem. Commun.* **2006**, 2801-2803.
84. Amedjkouh, M., *Tetrahedron: Asymmetry* **2005,** *16*, 1411-1414.
85. Sakthivel, K.; Notz, W.; Bui, T.; Barbas III, C. F., *J. Am. Chem. Soc* **2001,** *123*, 5260-5261.
86. Momiyama, N.; Torii, H.; Saito, S.; Yamamoto, H., *Proc. Natl. Acad. Sci. U.S.A* **2004,** 101, 5374-5378.

87. Bordwell, F. G., *Acc. Chem. Res.* **1988,** *21*, 456-463.
88. Bordwell, F. G.; Branca, G. C.; Hughes, D. L.; Olmstead, W. N., *J. Org. Chem.* **1980,** *41*, 3305-3313.
89. Bordwell, F. G.; Algrim, D. J., *J. Org. Chem.* **1976,** *41*, 2507-2508.
90. Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V., *Org. Biomol. Chem.* **2005,** *3*, 84-96.
91. Nyberg, A. I.; Usano, A.; Pihko, P., *Synlett* **2004**, 1891.
92. Ward, D. E.; Jheengut, V., *Tetrahedron Letters* **2004,** *45*, 8347.
93. Heathcock, C. H.; Flippin, L. A., *J. Am. Chem. Soc* **1983,** *105*, 1667.
94. Sekiguchi, Y.; Sasaoka, A.; Shimomoto, A.; Fujioka, S.; Kotsuki, H., *Synlett* **2003,** *11*, 1655-1658.
95. List, B.; Pojarliev, P.; Castello, C., *Org. Lett.* **2001,** *3*, 573-575.
96. Enholm, E. J.; Whitley, P. E.; Xie, Y., *J. Org. Chem.* **1996,** *61*, 5384.
97. Vogl, C.; Paetzold, E.; Fischer, C.; Kragl, U., *J. Mol. Catal.* **2005,** *232*, 41-44.
98. Sun, B.; Peng, L.; Chen, X.; Li, Y.; Li, Y.; Yamasaki, K., *Tetrahedron: Asymmetry* **2005,** *16*, 1305-1307.
99. Buisman, G. J. H.; Vos, E. J.; Kamer, P. C. J.; van Leeuwen, W. N. M. P., *J. Chem. Soc. Dalton. Trans.* **1995**, 409.
100. Butsugan, Y.; Muto, M.; Kawai, M.; Araki, S.; Murase, Y.; Saito, K., *J. Org. Chem.* **1989,** *54*, 4215.
101. Masdeu-Bulto, A. M.; Orejon, A.; Castellanos, A.; Castillon, S.; Claver, C., *Tetrahedron Asymmetry* **1996,** 7, 1829.
102. Botuha, C.; Haddad, M.; Larcheveque, M., *Tetrahedron: Asymmetry* **1998,** 9, 1929-1931.
103. Mancuso, A.; Swern, D., *Synthesis* **1981**, 165.
104. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D., *J. Chem. Soc., Chem. Commun.* **1987**, 1625.
105. Flatt, S. J.; Fleet, G. W. J.; Taylor, B. J., *Synthesis* **1979**, 815.

106. Dess, D. B.; Martin, J. C., *J. Am. Chem. Soc* **1991,** 113, 7277.
107. Ireland, R. E.; Liu, L. J., *J. Org. Chem.* **1993,** 58, 2899.
108. Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Kaavi, J. A., *Tetrahedron* **2006,** 62, 317-328.
109. Zhou, Y.; Shan, Z., *J. Org. Chem.* **2006,** 71, 9510-9512.
110. Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas III, C. F., *Tetrahedron Letters* **2001,** *42*, 199-201.
111. Verkade, J. M. M.; Hemert, L. J. C. v.; Quaedflieg, P. J. L. M.; Alsters, P. L.; Delft, F. L.; Rutjes, F. P. J. T., *Tetrahedron Letters* **2006,** *47*, 8109-8113.
112. Bravo, P.; Guidetti, M.; Viani, F.; Zanda, M.; Markovsky, A. L.; Sorochinsky, A. E.; Soloshonok, I. V.; Soloshonok, V. A., *Tetrahedron* **1998,** *54*, 12789-12806.
113. Gijsen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H., *Chem. Rev.* **1996,** 96, 443.
114. Kuntz, E. D., *CHEMTECH* **1987,** 17, 570.
115. Herrmann, W. A.; Kohlpainter, W. A., *J. Mol. Catal.* **1995,** 97, 65.
116. Corey, E. J.; Hannon, F. J.; Boaz, N. W., *Tetrahedron* **1989,** 45, 545.
117. Bhandal, H.; Howwel, A. R.; Patel, V. F.; Pattenden, D., *J. Chem. Soc., Perkin Trans. 1* **1990**, 2709.

Curriculum Vitae

Personal information

Name: Serghei Chercheja
Date of birth: 24.12.1979
Place of birth: Chisinau, Republic of Moldova
Familial status: single

Education

10/2004 - 9/2007	Ph.D., Faculty of Chemistry, University of Dortmund, Dortmund, Germany
10/2002 - 7/2003	M.Sc in Organic Chemistry, State University of Moldova, Chisinau, Republic of Moldova
9/1997 - 7/2002	Diploma of Licence in Organic Chemistry, State University of Moldova, Chisinau, Republic of Moldova

Scientific employment

Postdoctoral research fellow (10/2007)
University of St Andrews, St Andrews, UK. Advisor: Prof. Dr. Paul Kamer

Wissenschaftlicher Angestellter/Assistent, (10/2004 - 9/2007)
University of Dortmund, Germany. Advisor: Prof. Dr. Peter Eilbracht

Research assistant (7/2003 - 7/2004)
University of Evora, Portugal. Advisor: Prof. Dr. Anthony Joseph Burke

Research assistant (9/2002 - 7/2003)
State University of Moldova, Rep. of Moldova. Advisor Prof. Dr. Nicanor Barba

Memberships & affiliations

Associate Member of the Royal Society of Chemistry